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REVIEW

Pathogenesis of Respiratory Viral and Fungal Coinfections

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SUMMARY Individuals suffering from severe viral respiratory tract infections have recently emerged as "at risk" groups for developing invasive fungal infections. Influenza virus is one of the most common causes of acute lower respiratory tract infections worldwide. Fungal infections complicating influenza pneumonia are associated with increased disease severity and mortality, with invasive pulmonary aspergillosis being the most common manifestation. Strikingly, similar observations have been made during the current coronavirus disease 2019 (COVID-19) pandemic. The copathogenesis of respiratory viral and fungal coinfections is complex and involves a dynamic interplay between the host immune defenses and the virulence of the microbes involved that often results in failure to return to homeostasis. In this review, we discuss the main mechanisms underlying susceptibility to invasive fungal disease following respiratory viral infections. A comprehensive understanding of these interactions will aid the development of therapeutic modalities against newly identified targets to prevent and treat these emerging coinfections.

KEYWORDS SARS-CoV, antifungal immunity, aspergillosis, coinfection, copathogenesis, fungal pathogens, influenza, respiratory viruses

INTRODUCTION

Fungal infections are major causes of human morbidity and mortality. These infections range from superficial mucosal and dermal infections to life-threatening disseminated infections that can involve virtually any organ (1, 2). Opportunistic fungi, including *Aspergillus*, *Pneumocystis*, and *Cryptococcus*, can cause severe fungal infections in the lungs that can lead to invasive disease and dissemination to other tissues (3). Invasive fungal infections in the lungs, including invasive pulmonary aspergillosis (IPA), *Pneumocystis*

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pneumonia (PCP), and cryptococcosis, account for more than one million cases worldwide annually and primarily affect immunocompromised individuals, such as patients with HIV/AIDS, those with malignancies and undergoing bone marrow transplantations, and patients receiving immunosuppressive therapies (1, 3). Over the last decade, it has become evident that patients with severe viral respiratory tract infections are highly susceptible to developing a fungal coinfection, in particular pulmonary aspergillosis.

Lower respiratory tract infections cause nearly 4 million deaths annually, with influenza accounting for up to half a million of them (4). Severe bacterial pneumonia following influenza infection, most commonly caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae,* and *Streptococcus pyogenes*, is well recognized and known to increase disease severity and mortality in these patients (5–7). It is estimated that around 25% of all influenza-related deaths are associated with bacterial coinfections, particularly during seasonal outbreaks (8, 9). More recently, there is increased recognition of the importance of fungal coinfections, primarily caused by *Aspergillus*, in the severity and mortality of patients suffering from influenza (10, 11). Coinfections are well known complications in other respiratory viral diseases like severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), parainfluenza virus, cytomegalovirus (CMV), respiratory syncytial virus (RSV), rhinovirus, and adenovirus, although assessing their precise impact on disease severity and attributable mortality has proven difficult (12–20). Previous studies estimated that 25 to 30% of SARS survivors experienced secondary infections (21). In the current coronavirus disease 2019 (COVID-19) pandemic, early studies have suggested that 50% of patients who died due to COVID-19 experienced a secondary infection (22). Susceptibility to bacterial coinfections in influenza patients is thought to be attributed to damage and dysfunction of the epithelial barriers, inability to mount an effective primary immune response, and/or incapacity to develop disease tolerance to infection. Even though most of these mechanisms could be playing a role during fungal coinfections, a detailed understanding of the interactions between respiratory viruses and fungal pathogens is lacking. In this review, we evaluate what is currently understood about the immunopathological mechanisms underlying susceptibility to invasive fungal infections following severe viral pneumonia with an emphasis on influenza-associated pulmonary aspergillosis (IAPA) and COVID-19-associated pulmonary aspergillosis (CAPA).

FUNGAL COINFECTIONS IN RESPIRATORY VIRAL DISEASE

The realization that fungal coinfections complicate viral respiratory disease has only recently emerged. In retrospect, earlier case reports described the association of *Aspergillus* and influenza coinfection, but the significance was not appreciated (8). During the 2009 H1N1 pandemic, increasing numbers of cases with IAPA were described in the literature, resulting in proposed disease definitions and clinical management guidelines (10, 11). Furthermore, the recent update of the U.S. clinical practice guidelines regarding diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza has included fungal coinfection as a complication of influenza (10). Based on recent clinical observations and diagnostic test results in patients with IAPA, a new clinical algorithm has been proposed to better classify the certainty of the diagnosis of invasive *Aspergillus* disease (23–25). A similar pattern has been observed during the current COVID-19 pandemic, with hundreds of cases of fungal coinfections being described (26, 27). International efforts to better classify CAPA has also led to proposed novel disease definitions and research and clinical guidelines (2, 28, 29). The recognition that patients with severe viral pneumonia have an increased susceptibility to developing fungal coinfections asks for an analysis of the reported clinical epidemiology to provide insights into the clinical importance of fungal-viral coinfections. Underlying medical conditions resulting in lung injury, such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD), are considered independent risk factors for developing invasive fungal infections (30) and therefore are covered in this review.

Influenza and *Aspergillus*

Influenza viruses are classified into types A, B, C, and D based on genetic and antigenic differences (4). Influenza A viruses are predominantly responsible for seasonal annual epidemics, and they have caused a number of pandemics in humans (4, 31). Worldwide, 3 to 5 million people develop severe influenza infection, leading to up to half a million deaths every year. Of the hospitalized patients, 5 to 10% need admission to an intensive care unit (ICU). A feared complication is the development of acute respiratory distress syndrome (ARDS), which is associated with high mortality rates (32). The first report of pulmonary aspergillosis following influenza bronchopneumonia dates back to 1952 (33). After that, several clinical cases have been reported (34–38), but it was not until the 2009 H1N1 pandemic that the number of reports started to increase dramatically (24, 39). One of the first detailed descriptions of the association between influenza H1N1 and *Aspergillus* coinfection showed that 23% of critically ill patients with influenza admitted to the ICU developed IPA (39). A large number of other centers have reported comparable experiences, but the incidence of *Aspergillus*-influenza virus coinfection shows huge variation, with incidences reported between 7% and 32% (24, 32, 40–51). Despite such variations, a number of important observations have been made supporting the fact that fungal coinfections do play a significant role in the disease severity and outcome of influenza pneumonia. First, one of the larger clinical studies that included more than 400 patients admitted to the ICU over a period of 7 years identified influenza as an independent risk factor for the development of IPA (24). Second, pulmonary fungal coinfections outnumbered the cases of bacterial coinfection among influenza patients admitted to two ICUs in the Netherlands (16 versus 13 out of 45 patients, respectively) (32). Increased mortality rates of 51% to 66% have been reported in patients with IAPA compared to 15% to 28% in patients without and with bacterial coinfections (24, 49). Even though the majority of reported cases have been associated with influenza A virus, cases associated with influenza B virus have also been described (52, 53). In the last decade, novel avian influenza viruses have emerged in Asia associated with mortality rates of up to 50%. A study from China collected data from 335 patients with avian influenza H7N9 between 2013 and 2018, and 5.4% of those were diagnosed with IPA (54).

SARS-CoV and *Aspergillus*

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, has affected millions of people and caused more than four and a half million deaths worldwide by September 2021. About 5% of COVID-19 patients infected with SARS-CoV-2 require ICU management; these patients might be at high risk of developing secondary infections, including IPA (55–58). Reports from the previous SARS epidemic in 2003, caused by SARS-CoV-1, pointed to the occurrence of *Aspergillus* infection in those patients treated with corticosteroids for virus-induced inflammation (59–61); however, no systematic studies were performed to determine rates of incidence. During the current pandemic, secondary bacterial (22) and fungal coinfections, mainly due to *Aspergillus* spp. (Table 1), are increasingly being reported (62–97). Overall, hundreds of patients with CAPA have been reported from many countries in Europe, Asia, Australia, and America (27). As with IAPA, incidences exhibit great variability, with some studies reporting incidences of CAPA as low as 1% of ICU cases and others reporting extremely high incidences of up to 35% in ICU settings in Europe (56, 98–100). In a case series from the Netherlands, the mortality rate among patients with CAPA was 67% compared to 32% in patients with severe COVID-19 without signs of IPA (101). Importantly, in a recent prospective study from Germany, COVID-19 was independently associated with IPA (95). Some studies suggest that CAPA might be underdiagnosed due to difficulties obtaining respiratory samples. Concerns over aerosolization of respiratory secretions and the SARS-CoV-2 virus have restricted the number of invasive procedures performed, such as bronchoalveolar lavage (102, 103). Moreover, there are inherent difficulties in obtaining a clear diagnosis of *Aspergillus* infection, whereas others have suggested that the incidence of *Aspergillus* infection in COVID-19 patients is not as high as previously

TABLE 1 Large clinical studies (with 10 or more patients) reporting cases of CAPA[a]

Study (reference)	Country	Incidence [no. (%)]	Mortality [no. (%)]
Alanio et al., 2020 (56)	France	9/27 (33)	4/9 (44)
Bardi et al., 2021 (58)	Spain	4/140 (3)	NR
Bartoletti et al., 2020 (73)	Italy	30/108 (28)	13/30 (44)
Dupont et al., 2021 (86)	France	19/106 (18)	8/19 (42)
Falces-Romero et al., 2020 (71)	Spain	NR	7/10 (70)
Fekkar et al., 2020 (82)	France	7/145 (5)	4/7 (57)
Fu et al., 2020 (87)	China	1/101 (1)	NR
Gangneux et al., 2020 (28)	France	7/45 (16)	2/7 (29)
Garcia-Vidal et al., 2021 (88)	Spain	7/989 (0.7)	3/7 (43)
Helleberg et al., 2021 (85)	Denmark	2/25 (8)	2/2 (100)
Koehler et al., 2020 (98)	Germany	5/19 (26)	3/5 (60)
Lahmer et al., 2021 (95)	Germany	11/32 (34)	4/11 (36)
Lamoth et al., 2020 (69)	Switzerland	3/118 (3)	1/3 (33)
Machado et al., 2021 (89)	Spain	6/239 (2.5)	6/6 (100)
Nasir et al., 2020 (65)	Pakistan	5/23 (22)	3/5 (60)
Roman-Montes et al., 2021 (90)	Mexico	14/144 (10)	8/14 (57)
Rutsaert et al., 2020 (99)	Belgium	7/20 (35)	4/7 (57)
Segrelles-Calvo et al., 2021 (91)	Spain	7/215 (3)	5/7 (71)
van Arkel et al., 2020 (101)	The Netherlands	6/31 (19)	4/6 (67)
Van Biesen et al., 2020 (92)	The Netherlands	9/42 (21)	2/9 (22)
Velez Pintado et al., 2021 (96)	Mexico	16/83 (19)	5/16 (31)
Wang et al., 2020 (76)	China	8/104 (8)	NR
White et al., 2020 (2)	Wales	19/135 (14)	11/19 (58)
Yang et al., 2020 (75)	China	2/52 (4)	NR

[a]CAPA, COVID-19-associated invasive pulmonary aspergillosis; NR, not reported.

predicted (104–107). Whether these discrepancies are associated with the extent to which specific fungal diagnostic tests are employed is at present unclear.

SARS-CoV-2 and Mucormycosis

Recently, thousands of COVID-19-associated mucormycosis (CAM) cases have been reported in the literature, mostly from India (108, 109). Importantly, mucormycosis associated with influenza has also been described (110). Major risk factors include patients receiving systemic corticosteroid treatment or suffering from uncontrolled diabetes (111, 112). Hyperglycemia increases the expression of the glucose-regulated protein (GRP78), which acts as a receptor for the CotH protein kinase present in *Rhizopus* spores, helping the fungus to adhere and invade endothelial and nasal epithelial cells (113–115). In addition, beyond their immunosuppressive function, treatment with corticosteroids can cause diabetic ketoacidosis, further increasing susceptibility to CAM (116, 117). A recent review of the literature described that CAM exhibits a mortality of up to 49%, with rhino-orbital cerebral mucormycosis being the most common manifestation of the disease, followed by pulmonary mucormycosis (109). Notably, a significant proportion of surviving patients suffered life-changing morbidities, including loss of vision. Diagnosis of CAM is challenging, as the clinical and radiological signs of pulmonary and disseminated mucormycosis are nonspecific and may overlap with findings associated with COVID-19. Furthermore, mucormycosis is caused by a variety of Mucorales species (*Rhizopus arrhizus* is the predominant species in India), with some of them exhibiting poor susceptibility to antifungal therapy (118). Recently, the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) provided a comprehensive guideline of recommendations for the clinical management of CAM patients, including diagnosis, treatment, and prevention (119). Early recognition, better diagnostics, and more effective antifungals are required to improve the outcome of these patients, especially in low and middle-income countries.

Viral Respiratory Tract Infections and Other Fungi

Fungal coinfections complicating viral infections with pathogens other than *Aspergillus*

have also been reported. PCP caused by the fungal pathogen *Pneumocystis jirovecii* is the most common AIDS-defining disease, with up to half a million cases worldwide annually (3). Influenza complicated by PCP has been observed in HIV-infected patients (120–122). Therefore, influenza vaccination has been suggested as a prophylactic measure to reduce the risk of developing PCP secondary to influenza in HIV patients (123). Patients with deficiencies in adaptive immunity or individuals undergoing immunosuppression therapy are also at risk of developing PCP associated with influenza infection (124, 125). Recently, cases of COVID-19 and *Pneumocystis* coinfections have been reported (81, 126, 127), some of them associated with HIV comorbidity (79, 128–130). Since SARS-CoV-2 and PCP have common clinical and radiological features, coinfection with *Pneumocystis* is likely underappreciated in patients with SARS-CoV-2 (128, 131–138) and there are several clinical case studies reporting misdiagnosis (139, 140). *Cryptococcus* infections affect primarily immunocompromised hosts like HIV-infected individuals and solid organ transplant recipients. Infection starts in the lungs, and it can then disseminate into the central nervous system, causing meningitis that accounts for more than 200,000 cases worldwide annually (3). Only a few cases of influenza with concomitant cryptococcal infection have been reported in the literature (141–143), all of them with either the H1N1 or H7N9 strain (142). The scarcity of case studies could be a result of underdiagnosis, so special attention is needed in regions with a high prevalence of HIV/AIDS, including sub-Saharan Africa. *Candida auris* is a multidrug-resistant fungal pathogen classified as an "urgent threat" by the U.S. Centers for Disease Control and Prevention (CDC) due to its ability to cause life-threatening systemic infections in critically ill patients. Several outbreaks of *C. auris* infection in COVID-19 patients have been reported (144–149), in some cases associated with corticosteroid treatment (150–154). *C. auris* is difficult to identify by standard laboratory methods, which can lead to misidentification, causing outbreaks in health care settings often associated with high mortality. Therefore, advancing diagnostic methods is essential for early detection and control of this emerging pathogen.

COPATHOGENESIS OF RESPIRATORY VIRAL-FUNGAL COINFECTIONS

Immune responses against one pathogen can significantly influence immunity to a secondary nonidentical pathogen. This phenomenon, termed heterologous immunity, has been studied mainly in the context of viral infections and vaccines but could also play a role during viral-fungal coinfections (155, 156). Studies on the copathogenesis between viral and fungal coinfections are scarce, unlike studies regarding viral and bacterial coinfections. Most reports have attributed destruction of the airway epithelium and suppression of cellular immunity (including defective antigen-specific cytotoxic T lymphocyte responses and impaired phagocyte activities such as phagocytosis, production of cytokines, and reactive oxygen species [ROS], formation of neutrophil extracellular traps [NETs], and killing abilities) as the causes responsible for fungal coinfections (157–159). Several of the mechanisms that account for fungal susceptibility in individuals suffering from influenza could also be at play during SARS-CoV-2 infection, including the effects on tissue integrity and functionality and the dysregulation of immune responses and effector functions (160). Despite these similarities, the pathophysiology of SARS-CoV-2 infection is different from that of influenza at numerous levels, including viral tropism, viral replication, and incubation period as well as the effects on the host defense (161–165).

The outcome of host-pathogen interactions depends on numerous factors, including dose, route of infection, and virulence properties of the pathogen, as well as several host factors that include innate and adaptive immunity. Initiation of protective antiviral immunity depends on the recognition of viral RNA in the endosomal or cytosolic compartment by Toll-like receptor 3 (TLR3) and TLR7 or by retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) (RIG-I and melanoma differentiation-associated protein 5 [MDA5]), respectively. Viral recognition by innate immune cells, including dendritic cells (DCs) and macrophages, triggers a signaling cascade leading to both NF-κB-mediated induction of proinflammatory cytokines (interleukin 6 [IL-6], tumor necrosis

factor [TNF], IL-1), and IFN regulatory factor 3 (IRF3) and IRF7-mediated induction of type I (IFN-α and IFN-β) and type III (IFN-λ) interferons (IFNs). IFNs are crucial for effective antiviral immunity; for example, in epithelial cells, IFN signaling inhibits viral replication and orchestrates an effective adaptive antiviral immune response (4, 166, 167). Conversely, antifungal immunity strongly relies on C-type lectin receptors (CLRs) that play a key role in the recognition of fungal glucans, glycolipids, and glycoproteins by phagocytes (mainly macrophages and neutrophils) and in the activation of innate host defense mechanisms, including phagocytosis, respiratory burst, formation of NETs, autophagy, and chemokine and cytokine production (168). These mechanisms promote fungal killing but also influence activation of the adaptive immune system (169–173). Understanding how these mechanisms interact in a synergistic or antagonistic manner is fundamental to dissecting their roles during viral-fungal coinfections. In the next section, the major mechanisms that mediate susceptibility to fungal coinfections in individuals suffering from severe viral pneumonia are discussed: from innate immune mechanisms, including the role of the epithelium, phagocytes, and antigen-presenting cells (APCs), to T cell responses and adaptive humoral and cytotoxic responses.

Barrier Integrity

The respiratory epithelium is composed of a variety of cells, including a pseudostratified epithelium of ciliated and secretory cells lining the trachea and most proximal airways. A cuboidal epithelium lines the small airways, and squamous type I alveolar cells (involved in the process of gas exchange) and cuboid type II alveolar cells (which secrete pulmonary surfactant) form the alveoli (174). In healthy individuals, inhaled airborne fungal conidia are easily trapped in the mucus and eliminated mechanically by ciliated cells from the upper respiratory tract. However, due to their small size (2 to 3 μm), *Aspergillus* conidia (asexual spores) can reach the lower respiratory tract and interact with the airway epithelium, at either the bronchial or alveolar level (175). Upon reaching airway epithelial cells, fungal conidia are taken up and trafficked through the endosomal system, culminating with the formation of the phagolysosome by fusion of late phagosomes with lysosomes. This organelle has an acidic pH and contains many degradative enzymes that facilitate destruction and clearance of fungal conidia from the host. However, upon injury or disease (disrupting barrier integrity), conidia may escape this process and eventually germinate, facilitating tissue invasion (175). Different respiratory viruses preferentially bind and infect specific epithelial cells expressing specific receptors along the respiratory tract. For instance, cell entry of influenza virus is mediated by the binding of the viral hemagglutinin to terminal sialic acids that are attached via either an α2,3 or α2,6 linkage. Human influenza virus, such as H1N1, binds preferentially to α2,6-linked sialyloligosaccharide receptors, which predominate in nonciliated epithelial cells from the upper respiratory tract, whereas avian influenza virus, such as H5N1 and H7N9, binds to α2,3 linkages, which are more prevalent in ciliated epithelial cells from the lower respiratory tract (31, 176–179). Lower respiratory tract infection enables deep lung infection by other pathogens, including fungal pathogens. Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS-CoV and the new SARS-CoV-2 (180–184). Both SARS-CoV and SARS-CoV-2 primarily target type II pneumocytes, consistent with their ACE2 expression (161); however, SARS-CoV-2 replicates abundantly in upper respiratory epithelia and is efficiently transmitted (185, 186). Of note, SARS-CoV and SARS-CoV-2 can also infect alveolar macrophages that support viral replication (185, 187–189). Both influenza virus and SARS-CoV-2 can cause pneumonia, which occurs when infection and inflammation involve the alveoli and lung parenchyma. Therefore, productive viral infection of specific respiratory epithelial cells along the respiratory tract will determine the clinical symptoms as well as the susceptibility to fungal infections (179).

Respiratory viral infection causes multiple changes in the lungs that can weaken antifungal defenses, facilitating secondary fungal invasion. These effects can be grouped into three major aspects, including changes to the extracellular matrix components that facilitate adhesion, compromise of epithelial cytoskeletal machinery that modifies the dynamics of internalization, and damage of the epithelium that compromises barrier integrity (190).

Disruption of tracheal epithelial integrity after influenza infection affects the mechanical removal of subsequent pathogens, facilitating secondary infections (191, 192). In the more severe cases, damage to the epithelium can alter the surface display of numerous transmembrane proteins, exposing sites for fungal adherence in the tracheobronchial tree. For instance, injured cells or cells in an intermediate state of differentiation may express apical receptors such as $\alpha 5\beta 1$ integrin (expressed upon lung inflammation and injury to control cell migration during wound healing [193]), to which *Aspergillus fumigatus* can adhere (194, 195). Moreover, airway fibrinogenolysis and disruption of epithelial tight junctions by *Aspergillus*-secreted proteases such as alkaline protease 1 (Alp1) during and after germination can trigger allergic inflammation and further contribute to epithelial cell pathology in the context of coinfections (196–199). All of the above suggest that during influenza infection, the chronicity of the disease might determine susceptibility to secondary fungal infections. Lung tissue disruption during SARS-CoV-2 infection has also been shown to be an important factor in determining the severity of the disease, which likely contributes to susceptibility to coinfections (200, 201). Moreover, COVID-19-driven inflammation affects alveolar epithelial regeneration and induces the expansion of pathological fibroblasts that promote fibrosis and impair regeneration (202, 203). Of note, using a model of influenza infection, mice experiencing an acute inflammatory response with limited bystander tissue damage do not show susceptibility to a secondary bacterial infection (204). Whether the same holds true for secondary fungal infections is unknown.

Exposure of the substratum during severe viral pneumonia presents additional opportunities for fungal cells to adhere. In addition, changes in the airways during tissue damage and repair may provide adherence sites during recovery (205). During tissue remodeling, exposure of basement membrane and extracellular matrix components, such as fibronectin, laminin, or collagen, in areas of incomplete healing or where fibrin and fibrinogen deposition have taken place (observed during SARS-CoV-2 infection [206]) could facilitate fungal adhesion to the basal lamina (175, 207). All of the above might be significant in patients suffering from idiopathic pulmonary fibrosis, a condition characterized by the thickening and stiffening of the tissue surrounding the alveoli that shares several risk factors with COVID-19 (208) and has been independently associated with both influenza and *Aspergillus* infections (209, 210).

Several respiratory viruses, including influenza virus, can hijack the cytoskeletal system to their benefit in order to direct the cellular machinery to the production of viral particles. This could be particularly relevant during *Aspergillus* infections, since upregulation of several genes involved in cytoskeleton reorganization has been observed during *Aspergillus* infection (211, 212). Actin polymerization has been suggested to be crucial for internalization of conidia (213). In this context, *in vitro* studies have shown that *Aspergillus*-derived mycotoxins, such as gliotoxin, can promote actin cytoskeleton dynamics and internalization of *A. fumigatus* (214). Importantly, influenza infection alters the levels, structures, and functions of F-actin and microtubules in host cells (215). In addition, influenza infection downregulates the levels and/or activities of proteins involved in the regulation of F-actin and microtubule dynamics, such as Arp2/3 (involved in actin polymerization and the formation of branched actin networks) (216). Notably, components of the Arp2/3 complex have been shown to be upregulated in response to *Aspergillus* conidia and to mediate internalization of conidia (212). Another example is phospholipase D, which plays a fundamental role in lipid metabolism and cytoskeleton rearrangement and whose activity is stimulated following influenza infection (217). This enzyme mediates rapid endocytosis of the virus and at the same time can promote *A. fumigatus* internalization (218, 219). The complex interaction between influenza viruses and cytoskeleton components, including actin microfilaments, intermediate filaments, and microtubules, could therefore underlie mechanisms of susceptibility to fungal pathogens.

The epithelium is very important in orchestrating innate immune responses to both viral and fungal infections. The lung epithelium produces several soluble factors that form the first barrier of defense against fungal infections. Airway epithelial cells, particularly from the upper airways, secrete mucins that act as a barrier against fungal

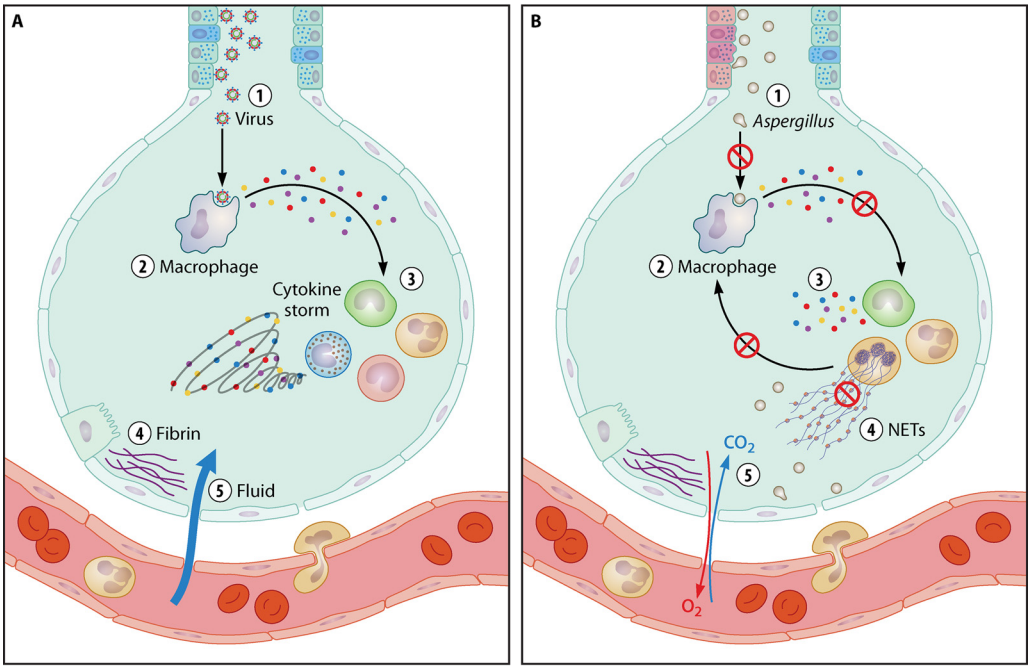

FIG 1 Progression of respiratory viral-fungal coinfections into the alveolar space determines disease severity. (A) Progression of a viral infection into the alveolar space. (1) The virus infects airway epithelium. (2) Alveolar macrophages recognize the virus and in response produce cytokines. (3) Cytokines attract more immune cells, including neutrophils and monocytes, which in turn produce more cytokines, creating a cycle of inflammation that damages the lung tissue. (4) Damage can further occur through the formation of fibrin and scar tissue. (5) Weakened blood vessels allow fluid to seep in and fill the lung cavities, leading to respiratory failure. (B) Progression of a fungal infection into the alveolar space following severe viral pneumonia. (1) When *Aspergillus* enters the airways, damaged epithelium facilitates adhesion of fungal conidia and subsequent invasion. (2) Phagocytosis, fungal killing, and cytokine production by alveolar macrophages are impaired. (3) Recruitment of neutrophils and their cross talk with macrophages are also affected. (4) Loss of neutrophils compromises their cytokine production and neutrophil extracellular trap (NET)-mediated fungal killing. (5) The release of fibrinous material can cause the obstruction of the small airways, decreasing oxygen and carbon dioxide diffusion capacities and creating a hypoxic milieu that changes *Aspergillus* virulence properties and the outcome of host-*Aspergillus* interaction. (This figure was created with BioRender.)

invasion. Binding of conidial lectins (FleA) to glycan moieties on gel-forming mucins (MUC5AC and MUC5B) allow them to become trapped within the mucus barrier, unable to reach the underlying epithelium and subsequently cleared from the airways by mucociliary clearance (220, 221). Surfactant proteins (SP-A and SP-D) and ficolins are involved in fungal opsonization and phagocytosis. Chemokines promote neutrophil recruitment and antimicrobial peptides (AMPs; including LL-37 and defensins) and are involved in fungal killing (222, 223). Influenza virus itself can interact with some of these glycosylated proteins, affecting their mode of action. For instance, neuraminidase helps the virus to gain access to airway epithelial cells by catalyzing the cleavage of sialic acids presented by decoy receptors, such as mucins (224–226). Fungal recognition through sialylated mucins is a critical step in the mucociliary clearance and macrophage killing that prevents *Aspergillus* pneumonia (220). SARS-CoV-2 can inhibit protein translation, which abolishes innate immune responses by the epithelium (i.e., IFN-dependent induction of IFN-stimulated genes) (227). Cross talk between alveolar epithelial cells and other immune cells, including DCs, is crucial for effective pathogen clearance and recovery from injury (Fig. 1) (228). Importantly, epithelial cells can control overinflammation by expressing anti-inflammatory mediators such as the tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase (229). Disruption of these immune-regulatory mechanisms as a result of viral infection could lead to uncontrolled exacerbated inflammation, increasing tissue damage, immunopathology, and susceptibility to fungal coinfections as mentioned above.

In severe cases of influenza, obstruction of the small airways caused by the

sloughing of cells and the release of fibrinous material into the airways leads to the decrease of oxygen and carbon dioxide diffusion capacities. This hypoxic milieu can significantly influence the course of *Aspergillus* infection by affecting fungal virulence and host immune responses (230) (Fig. 1). Importantly, oxygen tension has notable effects on the macroscopic and biofilm morphotypes of *Aspergillus fumigatus* (colony furrowing and percentage of vegetative nonconidiating mycelia), leading to increased host inflammation, rapid disease progression, and mortality in a murine model of invasive aspergillosis (231). *Aspergillus*-derived secondary metabolites (i.e., gliotoxin) can further contribute to increased localized and systemic hypoxia by inhibiting angiogenesis and tissue repair (232). Therefore, the metabolic adaptability of *Aspergillus* spp. to low-oxygen environments could be critical for the ability to cause infection following influenza (175, 233–235). Interestingly, hypoxia inducible factor 1α (HIF1α), a transcription factor that controls immune cell metabolism and function during hypoxic conditions, has been shown to be important in controlling influenza virus replication (236) and for protection against pulmonary *Aspergillus* infection (237). Beyond the epithelium, hypoxia contributes to endothelial cell activation with the release of several soluble mediators, including proinflammatory cytokines, platelet-activating factor, and adhesion molecules, all of which amplify tissue destruction and inflammation into the small airways (238).

Damage of alveolar integrity can enable fungal spores to reach blood vessels (Fig. 1). Recently, it was shown that a major receptor involved in sensing of *Aspergillus* 1,8-dihydroxynaphthalene (DHN)-melanin, named melanin-sensing lectin (MelLec), is highly expressed on endothelial cells that line the internal surfaces of vessels (239). Therefore, destruction of alveolar epithelial integrity could enable deep penetration of fungal conidia and invasion through MelLec-expressing endothelial cells. Compromised endothelial sensing of conidia through MelLec could also facilitate *Aspergillus* infection, as has been shown in murine models of infection (239).

Interferons

Type I and type III IFNs induce an IFN-stimulated gene signature that has the capacity to interfere with every step of viral replication (4, 166, 167). Besides their role during viral infections, IFNs play an essential role in driving antifungal responses in the lungs. Type I and type III IFNs are expressed with distinct kinetics during IPA, and both are essential for the activation of neutrophils (240, 241). Upon *Aspergillus* recognition, recruited monocytes (via CCR2) are an important early source of type I IFNs that induce optimal expression of IFN-λ. Type III IFN production by hematopoietic and nonhematopoietic cells at the mucosa acts on neutrophils to activate their antifungal response, including ROS production (240, 241). Controlled IFN signaling may be a crucial factor in determining whether secondary fungal infections are cleared at mucosal sites (5, 242, 243). Sustained uncontrolled IFN production can lead to tissue damage and immunopathology; e.g., type I IFNs cause lymphopenia (244), which has been associated with severe cases of influenza and SARS-CoV-2 infection, increasing susceptibility to secondary infections (245–253). Furthermore, not only type I but also type III IFNs can impair microbial control during coinfections (254, 255). Excessive or prolonged production of IFN-λ can interfere with lung repair during influenza recovery, which reduces epithelial proliferation and differentiation, increasing disease severity and susceptibility to coinfections (256, 257) (Fig. 2).

Type II IFNs can be detrimental during influenza infection (258, 259) and contribute to susceptibility to secondary bacterial infections by depleting alveolar macrophages and suppressing their phagocytic capacity (260–265). IFN-γ also impacts memory Th17 responses that attenuate bacterial clearance following influenza infection (266). Therefore, blocking IFN-γ has been exploited as a therapeutic strategy in several experimental models (267–269). However, type II IFNs might have a protective role during fungal coinfections. IFN-γ production by Th1 cells and invariant natural killer T (iNKT) cells (innate-like lymphocytes that express a conserved $\alpha\beta$ T-cell receptor [TCR] chain) is required for the activation of phagocytes (270) and restraining of inflammation

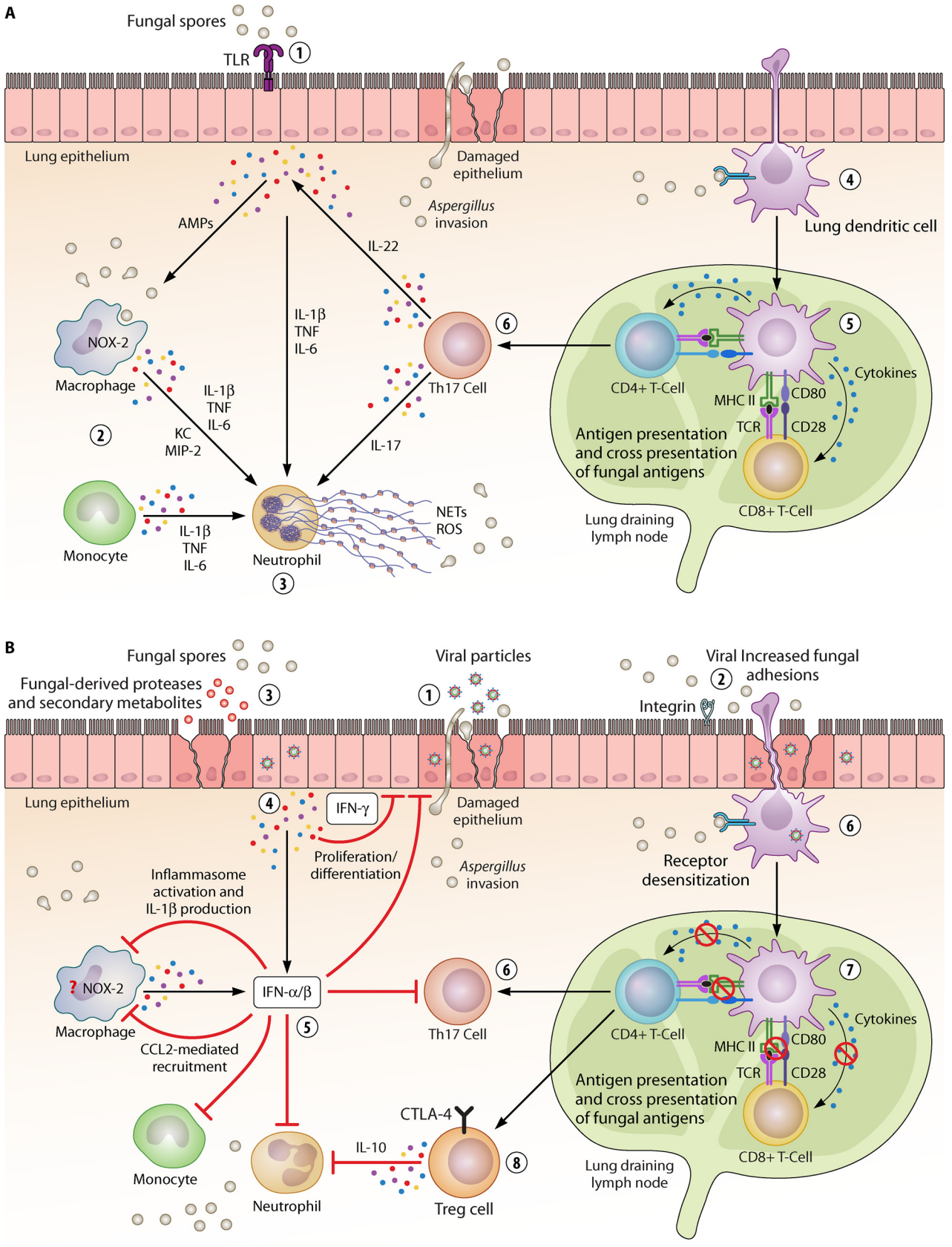

FIG 2 Interplay between cellular mechanisms underlying respiratory viral-fungal coinfections. (A) Effector cellular mechanisms against fungal infections. (1) Fungal recognition by the airway epithelium leads to the production of proinflammatory cytokines that can activate other immune

(Continued on next page)

during fungal clearance (271). Moreover, postinfluenza *Cryptococcus* coinfection has been associated with reduced levels of IFN-γ (272). Consequently, IFN-γ therapy has proven to be beneficial as an adjunctive therapy in patients with chronic granulomatous disease (CGD) (who are deficient in the NOX complex) and undergoing transplantation (273), but its beneficial effects during fungal coinfections remain to be investigated.

Understanding the immune response that underpins influenza and COVID-19 is important for identifying potential mechanisms of susceptibility to fungal coinfections. Both are characterized by a cytokine release syndrome; nevertheless, they exhibit distinct immune response profiles (253). In comparison to other highly pathogenic coronaviruses and common respiratory viruses, including influenza A virus, SARS-CoV-2 drives an imbalanced inflammatory response. Studies have shown that both SARS-CoV-2 and SARS-CoV infection drive a lower antiviral transcriptional response that is marked by low type I and III IFN levels and elevated chemokine expression, all of which might contribute to COVID-19 (274–280). Low levels of IFNs have been associated with the presence of autoantibodies against type I IFNs (281–285) or inborn errors in genes involved in the regulation of type I and type III IFN immunity (286). Conversely, other reports have shown upregulation of a type I IFN response in peripheral blood (287) that coexists with a proinflammatory TNF/IL-1β/IL-6-driven response in patients with COVID-19 compared to severe influenza patients (160, 250, 252). Similar results have been observed at mucosal sites (288–290). These discrepancies have been attributed to two differing outcomes (200, 291), with a delayed type I IFN response causing enhanced viral persistence and pathological inflammation but an early robust type I IFN response controlling viral replication that results in a mild disease (275, 280, 292–297). In this context, a type I IFN response is critical for the development of ARDS and increased lethality during severe SARS-CoV infection (275, 292, 298). More recently, studies have shown that the location where IFNs are being produced is also relevant. High levels of type III IFNs, and to a lesser extent type I IFNs, characterize the upper airways of patients with a mild pathology, while severe COVID-19 patients exhibit strong production of IFNs in the lower airways compared to subjects with other infectious or noninfectious lung pathologies (299, 300). This suggests that hyperinflammation and dysregulation of the IFN pathway are likely important factors that contribute to the development of fungal coinfections in COVID-19 patients.

Phagocytes and Effector Mechanisms

Effective elimination of pathogens relies on the recruitment and functions of several immune cells. These effector cells regulate important processes that are pivotal for controlling viral persistence and preventing fungal invasion. Impairment of phagocyte

FIG 2 Legend (Continued)
cells, including macrophages and neutrophils. (2) Monocytes and alveolar macrophages play pivotal roles during fungal infections, including phagocytosis and cytokine and chemokine production. (3) Neutrophils form neutrophil extracellular traps (NETs) and produce reactive oxygen species (ROS) that contribute to fungal killing. (4) Lung dendritic cells recognize, ingest, and kill *Aspergillus* conidia, acquire a fully mature state, and then migrate to draining lymph nodes. (5) Antigen presentation of fungus-derived peptides to naive $CD4^+$ and $CD8^+$ T cells occurs in the draining lymph nodes. (6) T cell activation leads to Th17 differentiation, which is pivotal for control of fungal infections at the airways. In particular, Th17 cells support neutrophil activation and the production of antimicrobial peptides (AMPs) by epithelial cells. (B) Mechanisms responsible for increased susceptibility to fungal infections in patients suffering severe viral pneumonia. (1 to 3) The lung epithelium undergoes different changes over the course of respiratory viral infections, including tissue disruption that facilitates secondary fungal invasion (1) and expression and/or exposure of receptors to which fungal pathogens can adhere (2). In addition, germinated fungal spores themselves release molecules with the potential to increase permeability and tissue damage, such as proteases and mycotoxins (3). (4) The airway epithelium produces type I and type III interferons (IFNs), which have a significant impact on antifungal immunity at different levels. (5) IFN-α/β are also produced by alveolar macrophages. IFNs reduce epithelial cell proliferation and differentiation, increasing susceptibility to coinfections. IFNs suppress monocyte, macrophage, and neutrophil recruitment and effector responses that are essential for fighting fungal infections. IFNs act as negative regulators of inflammasome activation in response to fungal pathogens, thus affecting fungal clearance. IFNs dampen Th17 responses, leading to attenuation of AMP production and neutrophil recruitment that are required for antifungal clearance. (6) Desensitization of pattern recognition receptors (PRRs), which are essential for fungal recognition and antifungal immunity, contributes to susceptibility to coinfections. (7) Viral infections also interfere with antigen-presenting cell functionalities, affecting the subsequent immune response to fungal antigens. For instance, viral infection affects antigen presentation through interference with any of the three signals required for T cell activation, namely, MHC presentation, expression of cosignaling molecules, and/or production of cytokines. (8) Regulatory T cells (Tregs) induced during the recovery and resolution phase of a viral infection persist for long enough to interfere with immunity (i.e., neutrophil functionalities) during subsequent fungal infections. Some questions remain, including the role of the NADPH oxidase 2 (NOX-2) complex in the context of viral-fungal coinfections. (This figure was created with BioRender.)

functions following influenza infection is among the most damaging consequences that increase susceptibility to secondary fungal infections (301). Neutrophils are one of the most important innate effector cells for the control of fungal infections. Humans suffering from neutropenia or neutrophil dysfunction exhibit a dramatic increase in susceptibility to major fungal pathogens, including *A. fumigatus* (168). This is particularly evident in CGD patients, whose neutrophils exhibit impaired fungal killing abilities (302). Suppressed neutrophil recruitment (due to reduced chemokine production) and dysfunction (reflected in impaired myeloperoxidase [MPO], ROS, and NET formation) during influenza virus infection increase susceptibility to secondary bacterial infection (303, 304) and contribute to the development of IPA (301, 305–308). Following influenza, IFN production and signaling through STAT1 impair neutrophil recruitment into the lungs and airways, augmenting fungal burdens (242, 301).

Monocytes and macrophages are key effector cells in controlling fungal infection through direct killing and the production of proinflammatory mediators (168). Influenza infection can result in depletion of alveolar macrophages and affect their functionalities, including inflammasome activation (263, 309, 310), thereby increasing disease severity and susceptibility to coinfections. Cross talk between neutrophils and monocytes/macrophages is important to combat respiratory infections, as neutrophils can drive macrophage inflammasome activation during respiratory viral infection (311–313) and can prevent macrophage depletion during *S. pneumoniae* coinfection (314). As macrophages are an important source of neutrophil chemoattractants, such as keratinocyte-derived cytokines (KC) and macrophage inflammatory protein-2 (MIP-2) (315), their depletion as seen in IAPA impairs neutrophil recruitment into the lungs (301). As described above, monocytes can trigger neutrophil activation and ROS production through type I IFN production (240, 241). Furthermore, both monocytes and neutrophils can control maturation and expansion of DCs in the lung, which in turn activates neutrophil oxidative burst, which is essential for host defense against *Aspergillus fumigatus* (316–318). This suggests that reduced numbers of neutrophils, monocytes, and macrophages in the lung tissue caused by influenza infection increases susceptibility to secondary fungal infections (Fig. 2).

Single-cell technologies employed on blood samples from severe COVID-19 patients have revealed defective monocyte activation and dysregulated myelopoiesis with release of immature dysfunctional neutrophils into the circulation (251, 252, 277, 287, 319–323). More recently, high-dimensional flow cytometry analyses have identified a redistribution of monocyte subsets toward intermediate monocytes (a transitional population between classical and nonclassical monocytes that exhibits a hyperinflammatory signature) and the appearance of monocytic myeloid-derived suppressor cell-like cells (324–326). Defective monocyte and neutrophil responses render these patients highly susceptible to invasive fungal infections. However, despite their protective role, excessive phagocyte activation and/or recruitment can also cause lung damage and immunopathology, leading to increased susceptibility to coinfections (168, 327–334). Elevated levels of plasma granulocyte-macrophage colony-stimulating factor (GM-CSF) are observed in fatal COVID-19 cases, but not in influenza cases, and may explain the excessive monocyte and neutrophil recruitment leading to tissue destruction (335). Furthermore, a substantial induction of monocyte/macrophage and neutrophil-associated chemokines has been observed in the lungs of patients with severe COVID-19 (201, 251, 289, 336–339). While mechanistic studies on CAPA and IAPA have not been undertaken with the same level of resolution, the impact of these inflammatory processes on fungal secondary infection is evident from an *in vivo* model of influenza and *Cryptococcus gattii* coinfection. Increased neutrophil and macrophage recruitment into the lungs during influenza infection predisposed mice to more severe lung damage and increased fungal burden in the brain, resulting in increased morbidity and mortality (272). In addition, viral infection has been shown to strongly augment macrophage expulsion of *Cryptococcus* via a nonlytic mechanism (vomocytosis) which could potentially influence cryptococcal dissemination in the host (340).

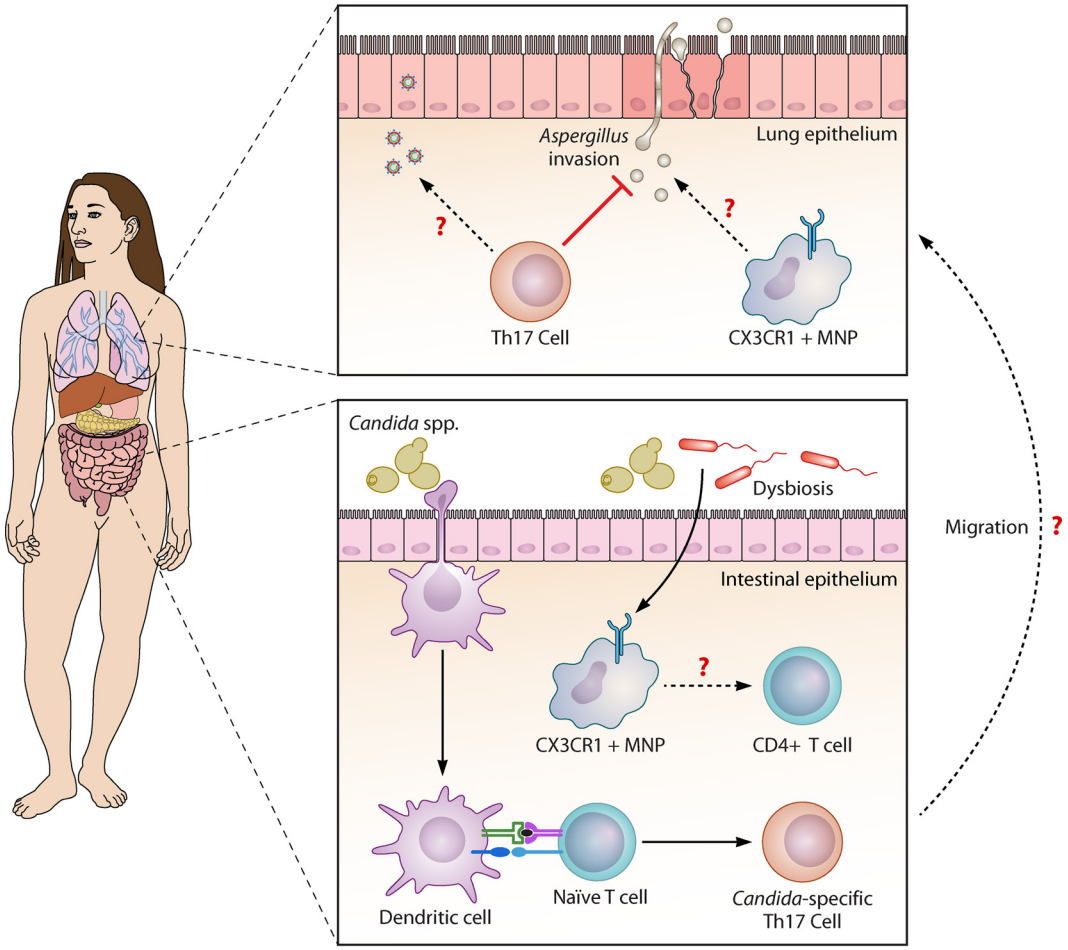

FIG 3 Gut-lung axis in the context of respiratory viral-fungal coinfections. The mycobiota plays a significant role in immunity and homeostasis in the intestine, which can influence immune responses at the airways. *C. albicans*-specific Th17 cells can confer protection against *Aspergillus* infection in the lungs. Importantly, intestinal microbial dysbiosis could affect functionalities of immune cells in the gut-lung axis, such as CX3CR1$^+$ mononuclear phagocytes (MNPs), which in turn could influence susceptibility to fungal coinfections. Additional important questions remained unanswered. For instance, do these immune responses develop locally or traffic from the gut, or both? If they do migrate, what is their route of migration? What signals control it? (This figure was created with BioRender.)

The mononuclear phagocyte system and, in particular, tissue-resident monocytes and macrophages expressing the fractalkine receptor CX3CR1 are important in controlling fungal growth and dissemination at different tissue locations in mice and humans (341, 342). In the context of influenza infection, CX3CR1$^+$ lung macrophages mediate pulmonary immune pathology and mortality through production of high levels of TNF and nitric oxide synthase 2 (NOS2) (343). However, under certain conditions, such as those involved in airway bacterial colonization, these cells could acquire an anti-inflammatory phenotype that controls influenza-mediated immunopathology (344, 345), suggesting that specific tissue environmental factors might affect the phenotype and function of these mononuclear phagocytes (MNPs). Importantly, CX3CR1$^+$ MNPs are essential in sensing intestinal microbial dysbiosis and in shaping immune responses in the airways during homeostasis and inflammation (346–350). For instance, fungal dysbiosis and colonization with specific fungi in the gut can exacerbate the development of allergic airway diseases through fungal sensing by gut-resident MNPs (346–355). Bacterial dysbiosis as a result of antibiotic use has been associated with augmented severity of influenza infection and increased risk of developing secondary infections (345, 356, 357). Influenza infection itself can cause intestinal dysbiosis that contributes to secondary infections through alterations of the killing activities of alveolar macrophages (345, 357, 358)

(Fig. 3). Alterations in the mycobiome have also been reported in COVID-19 patients (359), but whether this affects the functionalities of tissue-resident MNPs in a way comparable to that observed for influenza is unknown. Even though most of these mechanisms are still uncertain, these studies do suggest that MNPs could play a significant role in driving susceptibility to fungal coinfections in individuals suffering from severe viral pneumonia.

Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome plays a critical role in the innate immune antiviral response (313, 360, 361) and in shaping adaptive immune responses (360, 362–364). The NLRP3 inflammasome is activated by tissue/cellular damage in a two-step process that is dependent on microbial and host-derived signals. First, NF-κB signaling is induced (i.e., through activation of TLR or TNF receptor signaling), resulting in increased expression of pro-IL-1β and pro-IL-18. Next, signal two (i.e., potassium efflux, uric acid, and mitochondrial damage among others) leads to complex assembly, activation of caspase-1, and secretion of IL-1β and IL-18, causing the recruitment of monocytes, macrophages, and neutrophils to the site of infection (364). Influenza viruses (312, 313, 365–367), as well as most respiratory viruses, including SARS-CoV-2, activate the NLRP3 inflammasome using viroporins (virally encoded hydrophobic proteins that oligomerize in the membrane of host cells, leading to the formation of hydrophilic pores) (157, 368–370). Nevertheless, several influenza virus-derived components (i.e., nonstructural proteins NS1 and PB1-F2) can inhibit the inflammasome, causing viral pathogenicity and immunopathology and increasing the susceptibility to bacterial coinfections (366, 371–377). Additionally, during influenza-associated bacterial coinfection, IL-1 signaling plays a protective role by preventing alveolar macrophage depletion (314) and supporting Th17 immunity (378). Notably, type-I IFNs can act as negative regulators of IL-1β expression and inflammasome activation in response to fungal pathogens, thus affecting fungal clearance (379, 380). Inflammasome activation, through the polysaccharide galactosaminogalactan, is important for protective responses during fungal infection (381–386), such as neutrophil recruitment. Therefore, this mechanism might be playing a crucial role in facilitating IAPA (Fig. 2). Excessive inflammasome activation can lead to uncontrolled inflammation (202, 387, 388), facilitating bacterial coinfections (389, 390) and potentially fungal coinfections. Tight regulation of the inflammasome is important to avoid hyperinflammation and immunopathology that might increase susceptibility to IAPA and/or CAPA. The importance of a balanced regulation of the inflammasome has been shown in patients with cystic fibrosis or CGD suffering from inflammasome-driven immunopathology and at risk for developing invasive fungal infections (271, 383, 384).

One of the most important effector mechanisms in host defense against *A. fumigatus* is the NADPH oxidase (NOX) complex. This is highlighted by the increased susceptibility to IPA in patients with CGD (302, 391). Conversely, ROS production during viral infection, including influenza infection, promotes virus pathogenicity and immunopathology. Therefore, regulation of ROS production could constitute a synergistic copathogenesis mechanism during viral-fungal coinfections. Oxidative stress during influenza infection induces formation of oxidized phospholipids that can result in acute lung injury and cytokine production by lung macrophages through TLR4 signaling (392). In fact, inhibition of NOX2 reduced lung injury and dysfunction, as well as lowering influenza burdens, suggesting that NOX2-derived ROS production promotes viral infection (392–397). Single-stranded RNA viruses, such as influenza virus, activate NOX2 in endocytic compartments of alveolar macrophages, resulting in endosomal hydrogen peroxide generation, which suppresses antiviral and humoral signaling networks (398). These data correlate with studies in mice deficient in NOX2 and in CGD patients, who have elevated circulating type I IFNs and autoantibodies, supporting the notion that low levels of ROS result in an enhanced immune response to viruses (399, 400). Modulation of NOX2-derived ROS production during influenza infection increased susceptibility to bacterial infections (304, 401). A fine balance of NOX2 activity and ROS production is therefore required to control viral infections and to improve coinfection outcomes. However, more studies are required to better clarify their precise roles during fungal coinfections.

Emerging Cellular Players

Other immune cells are emerging as important players during IAPA and CAPA. For instance, NK cells are crucial for direct killing of fungal pathogens as well as controlling the fungicidal activity of other immune cells such as neutrophils (402). NK cell-depleted mice have increased susceptibility to fungal pathogens, including *A. fumigatus* (168). NK cell functions are impaired during influenza and SARS-CoV-2 infection (250, 251, 321, 328, 403–406), which has been linked with increased susceptibility to coinfections (407). Of note, recent studies have shown that asymptomatic COVID-19 patients or those who have recovered have elevated levels of NK cells, which was not observed in patients with severe COVID-19, suggesting an important role in controlling disease severity (321, 404, 408, 409). Furthermore, circulating NKT cell frequency (a subset that features characteristics of both T cells and NK cells) was identified as a predictive biomarker for patient outcome (322).

Platelets are also emerging as key mediators of immune responses. Thrombocytopenia often coincides with neutropenia in patients at high risk for developing IPA (410). Importantly, an increased platelet count has been suggested as one of the main predictors of coinfections in patients suffering from severe influenza (411) and recently has been associated with disease severity in COVID-19 patients (412, 413). Interestingly, platelets express ACE2, and *in vitro* exposure to SARS-CoV-2 potentiates platelet activation and aggregation (414), which might be an important mechanism leading to the vascular complications observed in COVID-19 patients and increasing susceptibility to coinfections.

Dendritic Cells and Antigen Presentation

There are two major types of DC lineages, myeloid conventional DCs (cDCs) and lymphoid plasmacytoid DCs (pDCs) which both arise from DC precursors. During influenza infection, pDCs are a major source of type I IFNs, causing the expansion of antigen-specific T cells (415–418). pDC-derived type I IFNs also inhibit viral replication in airway epithelial cells following SARS-CoV-2 infection (419–421). They play a nonredundant role in host defense against *Aspergillus* infection. Recognition of *Aspergillus* hyphae by pDCs results in the release of proinflammatory cytokines, including TNF and IFN-α, and the formation of extracellular traps (422–424). More recently, it was shown that recruitment of pDCs into the lungs activates neutrophil NADPH activity to promote clearance of inhaled conidia (316). Importantly, severe COVID-19 patients show gene expression signatures of apoptosis in pDCs that correlate with reduced pDC frequency (278, 405, 419, 421). Dysregulation of pDCs might contribute to depressed IFN signatures affecting susceptibility to fungal coinfections.

In contrast, cDCs are important players in antigen presentation and activation of T cells that underpin adaptive immune responses. Upon antigen recognition, uptake, and processing, DCs acquire a fully mature state and migrate to the draining lymph nodes, where they present antigen-derived peptides in the context of major histocompatibility complex (MHC) molecules to $CD8^+$ T cells or $CD4^+$ T cells (425). Impairments of DC functionalities following severe viral pneumonia can be classified as having short-lived and long-term effects. Short-lived effects are reversible as soon as the viral infection is cleared and include modulation of DC antigen presentation capabilities and interference with signaling pathways. It is well recognized that some viral pathogens, in particular DNA viruses such as herpesviruses, can interfere with the antigen presentation pathway (426, 427), while RNA viruses, including influenza virus, by an unknown mechanism seem to preferentially target the cross-presentation pathway (which occurs when exogenous antigens, normally loaded into major histocompatibility complex class II [MHC-II] molecules, are shuttled into the MHC-I pathway) (428–432) (Fig. 2). DCs are susceptible to SARS-CoV-2 infection, which attenuates the IFN response via viral antagonism of STAT1 phosphorylation (433). However, whether these mechanisms have implications during secondary fungal infections is unknown.

Heterologous immunity can significantly impact DC phenotype and the ability of DCs to activate optimal immune responses to fungi. For instance, desensitization of pattern recognition receptors (PRRs) (i.e., TLR2, TLR4, and TLR5) associated with

reduced chemokine production and NF-κB activation has been reported during viral infections (434, 435). *In vitro* studies have suggested that exposure to a viral infection affects DC cytokine production to a subsequent secondary challenge (436, 437). In addition, upregulation of inhibitory signals, such as CD200R, desensitizes APCs (DCs and macrophages), increasing their threshold of activation, a mechanism shown to contribute to bacterial coinfections (204) (Fig. 2). Nevertheless, in COVID-19 patients, CD200R expression was shown to be reduced in peripheral blood DCs, which could contribute to the expression of proinflammatory cytokines, tissue damage, disease severity, and mortality (324). More recently, it has been suggested that SARS-CoV-2 infection results in significantly reduced numbers of DCs, with functional impairment reflected in reduced maturation and cytokine production necessary to perform antigen presentation to activate T cells (324, 337, 438–441). Some of these long-lasting mechanisms could persist for weeks or even months after recovery, considerably increasing susceptibility to fungal coinfections. Remarkably, preexposure to *Pneumocystis* results in enhanced antigen processing, maturation, and trafficking abilities of DCs, which causes an accelerated influenza virus-specific primary immune response and viral clearance (442).

CLRs expressed by myeloid cells, including DCs and macrophages, are crucial for tailoring immune responses to pathogens. A recent study showed that several CLRs, including dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), liver/lymph node-specific intercellular adhesion molecule 3-grabbing integrin (L-SIGN), liver/lymph node sinusoidal endothelial cell C-type lectin (LSECtin), and macrophage galactose-type lectin (MGL), participate in SARS-CoV-2 recognition and induction of proinflammatory mediators (IL-1β, IL-8, CXCL10, CCL2, and CCL3) that correlate with disease severity (443, 444). DC-SIGN also mediates binding and internalization of *A. fumigatus* conidia by DCs (445), and it is expressed by alveolar macrophages in the lung (446). However, it is not clear whether DC-SIGN is required for activation of innate immune signaling or if it is involved in the initial stages of *Aspergillus* pulmonary infection and dissemination (446). Importantly, DC-SIGN polymorphisms are associated with the development of IPA, suggesting that it might be involved in the pathogenesis of this infection (447). Therefore, the potential convergence of CLR-driven innate and/or adaptive immune responses in the setting of SARS-CoV-2 and *Aspergillus* coinfection should be further explored, as it might influence copathogenesis and disease progression.

Resolution of lung inflammatory disease after influenza virus infection sets a different threshold for innate immune activation (204). This altered homeostasis could have a significant impact on the threshold of responsiveness to the next pathogen. Engagement of PRRs on the surface of APCs induces epigenetic functional reprogramming that affects their sensitivity to a second challenge, a process referred to as "trained immunity" (448). Even though myeloid cells are typically short-lived during inflammation, these phenomena can occur in bone marrow progenitors (448–452) and impact monocytes, macrophages, and DC populations during fungal infections (453). In particular, TNF production during invasive cryptococcosis induces a stable state of DC phenotypic programming (DC1/M1-like), rendering the DCs resistant to both antigen- and cytokine (IL-4)-induced alternative activation (DC2/M2-like). This reprogramming was also shown in bone marrow DC precursors and was demonstrated to be essential for Th1/Th17 immune protection (454). Interestingly, DC differentiation from bone marrow precursors is impaired during the course of a viral infection, leading to susceptibility to secondary infections (455, 456). In addition, recent studies have shown that DCs undergo a metabolic reprogramming early during influenza infections that results in significant changes in innate immune functions of DCs, including reduced motility and T cell activation (457). How long this reprogramming persists and whether it may impact fungal coinfections are unknown and will require more study.

Several functional studies have established the role for specific DC subsets (pDCs, cDCs, and inflammatory DCs) in immunity against influenza virus infection (458–462). However, we still know very little about the role of different pulmonary DC subsets during fungal infections (463). Therefore, substantially more work is needed to separate which subsets are needed at which phase of the response to prevent IAPA or CAPA.

T Cell Responses

$CD4^+$ T cells produce several antimicrobial soluble factors that control the spread of viral and fungal infections. They are also required for class switching of antibodies and for optimal $CD8^+$ T cell memory responses (4). The type I IFN response during influenza infection can directly affect adaptive immunity to fungi by dampening Th17 responses via the suppression of IL-23, a cytokine that is crucial for the expansion and maintenance of Th17 cells (464). Defective Th17 responses can lead to attenuation of the AMP production and neutrophil recruitment required for antifungal clearance (168, 465). This suggests that defective Th17 responses are a significant factor during IAPA, as has been shown during bacterial coinfections (464–467) (Fig. 2). Th1 responses are important in controlling systemic fungal dissemination (169), but they might be detrimental during respiratory fungal coinfections. STAT1 knockout (KO) mice, which have defective Th1 cell differentiation and increased Th17 immune activation, are less susceptible to coinfections than wild-type controls (467). Remarkably, it has been shown that COVID-19 patients with moderate disease displayed a progressive reduction of both antiviral (characterized by the dominance of the transcription factor T-bet and the expression of IFN-γ) and antifungal (orchestrated by the RORγt-induced cytokines IL-17 and IL-22) responses whereas patients with severe disease maintained these elevated responses throughout the course of the disease (200). This suggests that dysregulation of T cell responses could be an important factor that contributes to the development of fungal coinfections in COVID-19 patients.

Another important T cell population that plays a significant role during recovery and resolution of inflammation is $Foxp3^+$ regulatory T cells (Tregs). Influenza virus-specific Tregs can be detected for a prolonged time after viral clearance (468) and can reduce expansion of $CD4^+$ and $CD8^+$ effector T cells (469–471) while suppressing neutrophil-driven cytokine release into the airways, contributing to the resolution of disease (472). This Treg-mediated dampening of inflammation likely impacts immunity to subsequent infections such as *Aspergillus* infections (5). Indeed, Tregs can control immunity and tolerance to *Aspergillus* at different stages of the immune response (473, 474). However, early during infection, they might have a detrimental role by suppressing neutrophil functions through secretion of IL-10 and expression of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (which acts to inhibit T cell activation) (475) (Fig. 2). Tregs can also facilitate processes of tissue repair that can further sustain this anti-inflammatory state (306). Functional assessments of how the altered dynamics of T cell populations during viral infection affects antifungal capabilities could help to understand their role during fungal coinfections.

Adaptive Humoral and Cytotoxic Responses

B cell and $CD8^+$ T cell responses are critical for pathogen neutralization and clearance and play a major part in the memory response that prevents reinfection (4, 476, 477). Respiratory viral infections could influence susceptibility to subsequent fungal infections by targeting adaptive immune components at different levels, including cross-presentation, $CD8^+$ T cell activation, and B cell activation and antibody production. The contribution of $CD8^+$ T cells in host immunity against fungal infections in not well understood, and several studies have suggested that they might play a protective role in the setting of $CD4^+$ T cell deficiency (478–480). Studies have suggested that influenza viruses might interfere with the cross-presentation pathway (428–432). In particular, DCs that capture dead cells containing influenza virus are unable to activate $CD8^+$ T cell clones specific to cell-associated antigens of captured dead cells (431). Moreover, influenza virus-infected DCs exhibit impaired cross-presentation of influenza virus-derived and other exogenous antigens (430). Although it has not yet been demonstrated, these mechanisms could have significant implications during fungal coinfections.

The role of protective humoral immunity against fungal infections is not well defined, and it is still very controversial (481–485). Therefore, studies focusing on understanding the role of humoral immunity during viral and fungal coinfections are scarce. Of note, monoclonal antibodies targeting *Candida albicans* can confer protection against lethal

pulmonary infections by Gram-negative bacteria in mice (486), while *Pneumocystis* infection can protect mice against subsequent influenza infection due to the enhancement of the influenza virus-specific antibody response (487). Susceptibility mechanisms could include the activation of low-affinity cellular responses and/or production of nonneutralizing antibodies that could facilitate coinfections (488–490). Interestingly, meningeal IgA plasma cells that are dependent on the presence of gut commensals can confer protection against fungal invasion into the brain (484). Therefore, alteration of these fungus-specific antibodies could facilitate fungal dissemination during coinfections (Fig. 3).

Cross-Reactive Immunity

The immune response to a pathogen is greatly influenced by the individual's immune history (491, 492). Cross-reactivity of adaptive immune lymphocytes can either confer protection or drive susceptibility to subsequent infections. Heterologous immunity refers to the ability of one pathogen to modify the immune response to a related or unrelated pathogen that could boost or weaken protective immunity, break tolerance, or induce immunopathology (488). This phenomenon has been shown for closely related but also unrelated pathogens, including parasites, protozoa, bacteria, and viruses (493–495). Literature on heterologous immunity to fungi is limited. One study shows that a modified heat-labile bacterial toxin (LTK63) improved the immune response to subsequent infection with *Cryptococcus neoformans* by increasing pathogen-specific $CD8^+$ T cell and IgA responses in the nasal mucosa (496). Furthermore, segmented filamentous bacterial colonization during pulmonary *Aspergillus* infection augments antifungal Th17 immunity (172). Interestingly, heterologous immunity to a single, ubiquitous member of the fungal microbiota is fundamental for systemic induction of protective antifungal Th17 responses and immunopathology (355). In particular, the commensal *C. albicans* is the main inducer of Th17 responses in peripheral blood that later can be expanded in the lungs by cross-reactive airborne *A. fumigatus* (355). Further studies suggest that priming of these fungal cross-reactive T cells by gut commensal fungi and selective recruitment of these cells to the lungs may be important factors in the pathogenesis of inflammatory airway diseases (355, 497) (Fig. 3). Therefore, it is plausible that immune responses to commensal fungi may be altered during chronic viral infections, facilitating fungal coinfections. Interestingly, *C. albicans* colonization does not confer protection against influenza virus infection and rather exacerbates allergic airway inflammation susceptibility, indicating that fine-tuning of T cell responses is required to control immunity versus immunopathology (355, 497). In this context, "pathogenic" Th17/Th1 versus "anti-inflammatory" Th17/Treg mixed responses could play differential roles during influenza-associated coinfections (170).

FROM CLINICAL OBSERVATIONS TO COPATHOGENESIS

Clinical studies have shown a huge variation in the incidence of IAPA and CAPA. This variation in incidence might be explained by the interplay of a number of factors with the copathogenesis of respiratory viral and fungal coinfections, including differences in environmental and/or genetic factors, type of circulating viral strain, treatment modalities for the critical illness, and the use of and access to fungal diagnostic tools. Environmental conditions can modulate host immune responses, including mucociliary clearance, tissue repair functions, and innate immune defenses (498), as well as outbreaks of viral respiratory diseases by influencing virus stability and transmission rates (499–501). Seasonal fluctuations in airborne fungal spore levels have also been determined for different genera, with the dominant genera varying depending on geographical location (502–510). In some regions, seasonal variations in total airborne fungal counts have been shown to correlate with different environmental factors, including temperature, humidity, rainfall, and wind speed (502–507). Whereas most studies have suggested that *A. fumigatus* is present at low but persistent levels in the outdoor environment (502), there are possible geographical links that need to be more fully explored. A study from Brazil showed that *Aspergillus* spp. were among the dominant species found in both indoor and outdoor environments (506), while a study from the Netherlands found that *Aspergillus* was present all year round and prevailed in the autumn and winter months

(507). Interestingly, a study from Canada described a positive association between *Aspergillus* hyphal fragments and wind speed (504).

Genetic factors associated with increased susceptibility to influenza viral infection include genes involved with viral recognition and IFN signaling (*Ifitm3*, *Irf7*, *Ifnar1*, *Ifnl1*, *Stat1*, *Sfpta1*) (511). Another set of genes are associated with disease exacerbation during influenza infection, including genes involved in inflammation (*Par1*, *Tnfaip3*, *Nos2*, *Ptges2*, and *Ifi35*) and tissue homeostasis (*Epg5*, *Atg14*, and *Atg7*) (511). This is consistent with the idea of immunopathology contributing to disease severity and susceptibility to coinfections. Recent studies have identified several host factors critical for SARS-CoV-2 infection, including genes involved in cholesterol biosynthesis, autophagy, viral entry, and phosphatidylinositol biosynthesis, among others (512–517). Genes involved in fungal recognition and effector mechanisms (*Ptx3*, *Tlr4*, *clec7a*, *Clec1a*, *Plg*, *Cxcl10*, *Ifng*, *Il10*) are associated with increased susceptibility to invasive aspergillosis in patients undergoing hematopoietic stem cell transplant. A second set of genes (*S100b*, *Rage*, *Nod2*) are involved with hyperactivity of innate recognition pathways (518–520). These susceptibility mechanisms have also been reiterated in studies of other vulnerable populations, including patients with COPD, solid organ transplant recipients, and patients with hematological malignancies. Nevertheless, genetic studies are required to determine their role in a population of patients suffering from severe viral pneumonia.

Emergence of highly pathogenic viral strains increases susceptibility and modifies the kinetics of coinfections (521). Viral polymorphisms that alter the tropism of influenza viruses from the upper to the lower respiratory tract and facilitate bacterial coinfections (5) could potentially increase susceptibility to fungal coinfections. Major subtypes of influenza virus strains linked to IAPA include H1N1, H5N1, and H7N9. Influenza virus strain H5N1 increases the production of proinflammatory cytokines and enhances viral replication in the lung, causing immunopathology and pulmonary fibrosis (209, 376, 522–524), which are important contributing factors that drive secondary infections (168, 245, 327–334, 366, 371–377). In contrast, strain H7N9 can inhibit the inflammasome (372), an important effector mechanism against viral and fungal infections. In the case of CAPA, many novel SARS-CoV-2 variants which have different clinical effects are emerging. The B.1.1.7 (alpha, United Kingdom), B.1.351 (beta, South Africa), P.1 (gamma, Brazil), B.1.427/29 (epsilon, USA), and, most recently, B.1.617.2 (delta, India) variants have all shown to be highly transmissible, with some studies suggesting an association with higher mortality and escape from natural and vaccine-induced immunity (525–527). However, whether these novel variants are associated with increased susceptibility to fungal coinfections is unknown. Of note, some authors have suggested an association between the delta variant and the emergence of mucormycosis in India (528, 529); however, so far there are no specific data to support this hypothesis.

Treatment modalities for severely ill patients could also increase susceptibility to respiratory fungal coinfections following severe viral pneumonia. This includes the use of antibiotic, antiviral, and/or immunomodulatory treatment. For instance, the use of antibiotics to prevent secondary bacterial infection can cause dysbiosis, a condition that has been linked to increased severity during respiratory viral infections and susceptibility to secondary infections (345, 356, 357). The use of neuraminidase inhibitors has been suggested to increase susceptibility to fungal coinfections following influenza infection (44) and has been recently demonstrated to increase the susceptibility of mice to invasive aspergillosis (530). The use of the corticosteroid dexamethasone as an immunosuppressive drug to treat ARDS, which was shown to reduce mortality in seriously ill COVID-19 patients (531), is one of the major risk factors for developing CAPA and negatively affects immunity to *Aspergillus* (532–534). Several studies have reported a relationship between the use of steroidal immunosuppressant (corticosteroids) and the incidence of IPA in critically ill COVID-19 patients (56, 73, 82, 89, 535–539). A prospective study from ICUs in Wales showed that the use of high-dose systemic corticosteroids increased the likelihood of developing CAPA (16 out of 22 patients [72%] compared to 32 out of 57 patients without CAPA [56%]) (2). Similar findings were observed

in studies focused on patients with severe influenza (24, 540). However, some studies have found no association between the use of corticosteroids and the incidence of hospital-acquired fungal infections in patients with COVID-19 (541, 542), which has been suggested to be due to an early administration of low-dose corticosteroids for a short period (541). Importantly, in some of these studies, additional risk factors might be at play, including a history of chronic respiratory disease. Recent clinical trials have suggested that combining corticosteroids with anti-IL-6 treatment (tocilizumab) improves the outcomes in terms of morbidity and mortality in severe COVID-19 patients (543, 544). Nevertheless, COVID-19 patients receiving tocilizumab are reported to be at higher risk of developing CAPA (65, 69, 82, 545, 546). As IL-6 is essential for inducing protective Th17 responses (170–172) and controlling the effector functions of phagocytes (547), anti-IL-6 therapy increases the susceptibility for fungal infections. Earlier studies have documented an increased risk for developing bacterial and fungal infections in patients receiving tocilizumab in combination with corticosteroids for the treatment of rheumatoid arthritis (548). A retrospective study conducted in Chicago involving 111 COVID-19 patients found that those receiving tocilizumab had a higher risk of developing fungal infections and increased mortality (549). Strikingly, in a prospective study from Spain that includes 2,723 patients with COVID-19, all CAPA patients who received tocilizumab and corticosteroids had a fatal outcome (8 out of 8 patients) (89). Prospective monitoring of these patients is needed to shed light on whether tocilizumab negatively impacts the susceptibility to and outcome of respiratory fungal coinfections. Furthermore, metanalyses of retrospective studies could help to elucidate the role of immunosuppressive agents in predisposing COVID-19 patients to fungal coinfections.

The epidemiology of, and the mortality associated with, coinfections complicating viral respiratory tract infections is difficult to assess with confidence. This is partly due to the fact that diagnosis of sequential infections is challenging, as the primary pathogen is often no longer detectable by the time the secondary infection presents itself (550). Alternatively, if both infections present themselves at the same time, one could quickly override the other. Furthermore, the presence of a specific pathogen may be part of the airway commensal community rather than an indication of infection and disease (551). Therefore, the specific attribution of the primary viral infection and coinfections to mortality is complex to unravel. In comparison to bacterial coinfections in viral respiratory disease, differentiation of fungal colonization versus infection and disease is even more challenging. *Aspergillus* spp. are ubiquitous in the environment, and as a consequence, our airways are exposed on a daily basis to its spores (conidia). In immunocompetent healthy individuals, these spores are cleared without infection and disease, while in immunocompromised patients and those with chronic lung disease, spore inhalation can lead to pulmonary aspergillosis (235). Diagnosis of pulmonary aspergillosis is based on a combination of criteria that includes host factors, clinical and radiological features, and mycological studies (11, 552). However, cultures from respiratory samples do not differentiate colonization from disease, antigen testing in serum has a low specificity, and specific changes on chest imaging and invasive diagnostics (e.g., bronchoscopy) are often not feasible due to the critical clinical condition of the patient and the risk of aerosolization in cases of viral pneumonia. The absence of rapid, sensitive, and specific fungal diagnostic tools is a major challenge. Optimal availability of, access to, and implementation of fungal diagnostic tools in routine clinical care will affect incidences reported and provide a real insight into the clinical epidemiology and burden of disease.

FUTURE PERSPECTIVES

Viral-fungal coinfections are increasingly being recognized by the scientific and medical communities. The urgent need to obtain insight into the epidemiology, pathogenesis, and underlying immune mechanisms is driven by the additional mortality among patients with IAPA and CAPA (288). Comprehensive epidemiological data are

lacking, and therefore data from larger cohorts of patients are required to better assess the incidence, clinical features, and detailed characteristics of secondary fungal infections in influenza and COVID-19 patients, especially with the highly pathogenic emerging strains (553). Early diagnosis of fungal infection is critical for effective treatment. Current diagnostic methods lack sensitivity and specificity to differentiate colonization from infection and invasive disease. Systematic prospective studies that employ uniform diagnostic testing and criteria are urgently required to optimize the management of patients in the ICU, and first initiatives are been undertaken in this area (119, 133, 554, 555). Azole-resistant *A. fumigatus* causing infections in COVID-19 (556–558) and influenza (47, 559, 560) patients is emerging, highlighting the importance of early causative diagnosis and surveillance during antifungal therapy. Developing treatment modalities in which both the virus and the fungus are being targeted could also be proven useful. Using unbiased approaches, studies have identified several immunotypes in hospitalized COVID-19 patients that could predict clinical outcome and disease trajectory (200, 561, 562). Similar longitudinal studies could prove of value in identifying comparable profiles predicting the presence of fungal infections in these patients, which could have significant implications for therapeutic interventions.

Our understanding of how host-pathogen interactions are affected during polymicrobial infections is limited. We have summarized a number of immune pathways and mechanisms that may play a crucial role in the copathogenesis of viral and fungal lung infections. Interindividual heterogeneity of the immune system that is shaped by divergent exposure of immune cells to infections, vaccination, and lifestyle-related stimuli (diet, physical activity, and stress) will influence an individual's risk for acquiring fungal infections. Improved tools and models to study coinfections are needed to obtain better insight into the copathogenesis and immune pathways driving disease. Preliminary studies have shown a strong link between high viral replication and increased susceptibility to fungal coinfection, which suggest that the timing of coinfection is important in determining susceptibility and disease outcome (272). Influenza infection induces several long-lasting changes at molecular levels, as shown by transcriptome, proteome, and metabolome analyses, which could affect susceptibility to fungal infections (563). Studies with convalescent-phase samples from COVID-19 patients have suggested that the immune system does not fully recover after infection (250). As with postacute viral syndromes described in survivors of other SARS epidemics, there are increasing reports of persistent and prolonged effects after acute COVID-19 beyond 1 month from the onset of symptoms (564, 565). Long-term follow-up studies are needed to investigate the consequences on fungal immunity. Importantly, long-term metabolic dysregulation influences disease trajectory and immune response to COVID-19 (566–568) and might also affect susceptibility to secondary fungal infections. Host genetic factors such as polymorphisms in key immune receptors and signaling molecules involved in fungal sensing could also be playing a key role. Increasing our understanding of the copathogenesis of respiratory viral-fungal coinfections and the impact of the microbiomes in this interplay could help to develop better diagnostics and therapeutic modalities against newly identified targets.

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REFERENCES

1. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. 2012. Hidden killers: human fungal infections. Sci Transl Med 4:165rv13. https://doi.org/10.1126/scitranslmed.3004404.
2. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, Pandey M, Whitaker H, May A, Morgan M, Wise MP, Healy B, Blyth I, Price JS, Vale L, Posso R, Kronda J, Blackwood A, Rafferty H, Moffitt A, Tsitsopoulou A, Gaur S, Holmes T, Backx M. 2020. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis 73:e1634–e1644. https://doi.org/10.1093/cid/ciaa1298.
3. Bongomin F, Gago S, Oladele RO, Denning DW. 2017. Global and multinational prevalence of fungal diseases—estimate precision. J Fungi (Basel) 3:57. https://doi.org/10.3390/jof3040057.

4. Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, Palese P, Shaw ML, Treanor J, Webster RG, Garcia-Sastre A. 2018. Influenza. Nat Rev Dis Primers 4:3. https://doi.org/10.1038/s41572-018-0002-y.
5. McCullers JA. 2014. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol 12:252–262. https://doi.org/10.1038/nrmicro3231.
6. Morens DM, Taubenberger JK, Fauci AS. 2008. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 198:962–970. https://doi.org/10.1086/591708.
7. Collins SD. 1930. Influenza-pneumonia mortality in a group of about 95 cities in the United States, 1920–1929. Public Health Rep 45:361–406. https://doi.org/10.2307/4579562.
8. Shieh WJ, Blau DM, Denison AM, Deleon-Carnes M, Adem P, Bhatnagar J, Sumner J, Liu L, Patel M, Batten B, Greer P, Jones T, Smith C, Bartlett J, Montague J, White E, Rollin D, Gao R, Seales C, Jost H, Metcalfe M, Goldsmith CS, Humphrey C, Schmitz A, Drew C, Paddock C, Uyeki TM, Zaki SR. 2010. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 177:166–175. https://doi.org/10.2353/ajpath.2010.100115.
9. Centers for Disease Control and Prevention. 2009. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)—United States, May-August 2009. MMWR Morb Mortal Wkly Rep 58:1071–1074.
10. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT. 2019. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 68:895–902. https://doi.org/10.1093/cid/ciy874.
11. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, Caliendo AM, Castagnola E, Cruciani M, Cuenca-Estrella M, Decker CF, Desai SR, Fisher B, Harrison T, Heussel CP, Jensen HE, Kibbler CC, Kontoyiannis DP, Kullberg BJ, Lagrou K, Lamoth F, Lehrnbecher T, Loeffler J, Lortholary O, Maertens J, Marchetti O, Marr KA, Masur H, Meis JF, Morrisey CO, Nucci M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Racil Z, et al. 2020. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 71:1367–1376. https://doi.org/10.1093/cid/ciz1008.
12. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK. 2006. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax 61:611–615. https://doi.org/10.1136/thx.2005.048397.
13. Korppi M, Laurikainen K, Pietikainen M, Silvasti M. 1991. Antitussives in the treatment of acute transient cough in children. Acta Paediatr Scand 80:969–971. https://doi.org/10.1111/j.1651-2227.1991.tb11764.x.
14. Korppi M, Leinonen M, Makela PH, Launiala K. 1990. Bacterial involvement in parainfluenza virus infection in children. Scand J Infect Dis 22:307–312. https://doi.org/10.3109/00365549009027052.
15. Pitkaranta A, Roivainen M, Blomgren K, Peltola J, Kaijalainen T, Raty R, Ziegler T, Ronkko E, Hatakka K, Korpela R, Poussa T, Leinonen M, Hovi T. 2006. Presence of viral and bacterial pathogens in the nasopharynx of otitis-prone children. A prospective study. Int J Pediatr Otorhinolaryngol 70:647–654. https://doi.org/10.1016/j.ijporl.2005.08.018.
16. Gianella S, Letendre S. 2016. Cytomegalovirus and HIV: a dangerous pas de deux. J Infect Dis 214(Suppl 2):S67–S74. https://doi.org/10.1093/infdis/jiw217.
17. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, Peng Z, Pan H. 2020. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 127:104364. https://doi.org/10.1016/j.jcv.2020.104364.
18. Contou D, Claudinon A, Pajot O, Micaelo M, Longuet Flandre P, Dubert M, Cally R, Logre E, Fraisse M, Mentec H, Plantefeve G. 2020. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care 10:119. https://doi.org/10.1186/s13613-020-00736-x.
19. Bezerra PGM, Britto MCA, Correia JB, Duarte MDCMB, Fonceca AM, Rose K, Hopkins MJ, Cuevas LE, McNamara PS. 2011. Viral and atypical bacterial detection in acute respiratory infection in children under five years. PLoS One 6:e18928. https://doi.org/10.1371/journal.pone.0018928.
20. Johansson N, Kalin M, Hedlund J. 2011. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. Scand J Infect Dis 43:609–615. https://doi.org/10.3109/00365548.2011.570785.
21. Zahariadis G, Gooley TA, Ryall P, Hutchinson C, Latchford MI, Fearon MA, Jamieson FB, Richardson S, Kuschak T, Mederski B. 2006. Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: variable incidence of atypical bacteria coinfection based on diagnostic assays. Can Respir J 13:17–22. https://doi.org/10.1155/2006/862797.
22. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
23. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, Dimopoulos G, Paiva JA, Misset B, Rello J, Vandewoude K, Vogelaers D, AspICU Study Investigators. 2012. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 186:56–64. https://doi.org/10.1164/rccm.201111-1978OC.
24. Schauwvlieghe A, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, Lagrou K, Verweij PE, Van de Veerdonk FL, Gommers D, Spronk P, Bergmans D, Hoedemaekers A, Andrinopoulou ER, van den Berg C, Juffermans NP, Hodiamont CJ, Vonk AG, Depuydt P, Boelens J, Wauters J, Dutch-Belgian Mycosis Study Group. 2018. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 6:782–792. https://doi.org/10.1016/S2213-2600(18)30274-1.
25. Verweij PE, Rijnders BJA, Bruggemann RJM, Azoulay E, Bassetti M, Blot S, Calandra T, Clancy CJ, Cornely OA, Chiller T, Depuydt P, Giacobbe DR, Janssen NAF, Kullberg BJ, Lagrou K, Lass-Florl C, Lewis RE, Liu PW, Lortholary O, Maertens J, Martin-Loeches I, Nguyen MH, Patterson TF, Rogers TR, Schouten JA, Spriet I, Vanderbeke L, Wauters J, van de Veerdonk FL. 2020. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med 46:1524–1535. https://doi.org/10.1007/s00134-020-06091-6.
26. Hoenigl M. 2020. Invasive fungal disease complicating COVID-19: when it rains it spores. Clin Infect Dis 73:e1645–e1648. https://doi.org/10.1093/cid/ciaa1342.
27. Chong WH, Saha BK, Ananthakrishnan R, Chopra A. 2021. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection 49:591–605. https://doi.org/10.1007/s15010-021-01602-z.
28. Gangneux JP, Reizine F, Guegan H, Pinceaux K, Le Balch P, Prat E, Pelletier R, Belaz S, Le Souhaitier M, Le Tulzo Y, Seguin P, Lederlin M, Tadie JM, Robert-Gangneux F. 2020. Is the COVID-19 pandemic a good time to include Aspergillus molecular detection to categorize aspergillosis in ICU patients? A monocentric experience. J Fungi (Basel) 6:105. https://doi.org/10.3390/jof6030105.
29. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, Klimko N, Lass-Florl C, Oladele RO, Vinh DC, Zhu LP, Boll B, Bruggemann R, Gangneux JP, Perfect JR, Patterson TF, Persigehl T, Meis JF, Ostrosky-Zeichner L, White PL, Verweij PE, Cornely OA, European Confederation of Medical Mycology, International Society for Human Animal Mycology, Asia Fungal Working Group, INFOCUS LATAM/ISHAM Working Group, ISHAM Pan Africa Mycology Working Group, European Society for Clinical Microbiology, Infectious Diseases Fungal Infection Study Group, ESCMID Study Group for Infections in Critically Ill Patients, Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy, Medical Mycology Society of Nigeria, Medical Mycology Society of China Medicine Education Association, Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology, Association of Medical Microbiology, Infectious Disease Canada. 2020. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 21:e149–e162. https://doi.org/10.1016/S1473-3099(20)30847-1.
30. Xu L, Chen B, Wang F, Wei C, Liu H, Liu J, Herth FJF, Luo F. 2019. A higher rate of pulmonary fungal infection in chronic obstructive pulmonary disease patients with influenza in a large tertiary hospital. Respiration 98:391–400. https://doi.org/10.1159/000501410.
31. Paules C, Subbarao K. 2017. Influenza. Lancet 390:697–708. https://doi.org/10.1016/S0140-6736(17)30129-0.

32. Beumer MC, Koch RM, van Beuningen D, OudeLashof AM, van de Veerdonk FL, Kolwijck E, van der Hoeven JG, Bergmans DC, Hoedemaekers CWE. 2019. Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. J Crit Care 50:59–65. https://doi.org/10.1016/j.jcrc.2018.11.013.
33. Abbott JD, Fernando HV, Gurling K, Meade BW. 1952. Pulmonary aspergillosis following post-influenzal bronchopneumonia treated with antibiotics. Br Med J 1:523–525. https://doi.org/10.1136/bmj.1.4757.523.
34. Lewis M, Kallenbach J, Ruff P, Zaltzman M, Abramowitz J, Zwi S. 1985. Invasive pulmonary aspergillosis complicating influenza A pneumonia in a previously healthy patient. Chest 87:691–693. https://doi.org/10.1378/chest.87.5.691.
35. Fischer JJ, Walker DH. 1979. Invasive pulmonary aspergillosis associated with influenza. JAMA 241:1493–1494. https://doi.org/10.1001/jama.1979.03290400053024.
36. Horn CR, Wood NC, Hughes JA. 1983. Invasive aspergillosis following post-influenzal pneumonia. Br J Dis Chest 77:407–410. https://doi.org/10.1016/0007-0971(83)90078-5.
37. Jariwalla AG, Smith AP, Melville-Jones G. 1980. Necrotising aspergillosis complicating fulminating viral pneumonia. Thorax 35:215–216. https://doi.org/10.1136/thx.35.3.215.
38. McLeod DT, Milne LJ, Seaton A. 1982. Successful treatment of invasive pulmonary aspergillosis complicating influenza A. Br Med J (Clin Res Ed) 285:1166–1167. https://doi.org/10.1136/bmj.285.6349.1166-a.
39. Wauters J, Baar I, Meersseman P, Meersseman W, Dams K, De Paep R, Lagrou K, Wilmer A, Jorens P, Hermans G. 2012. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med 38:1761–1768. https://doi.org/10.1007/s00134-012-2673-2.
40. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB, Lim CM, Koh Y, Korean Society of Critical Care Medicine H1N1 Collaborative. 2011. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 183:1207–1214. https://doi.org/10.1164/rccm.201101-0110OC.
41. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J, ESICM H1N1 Registry Contributors. 2011. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med 37:272–283. https://doi.org/10.1007/s00134-010-2078-z.
42. Ku YH, Chao CM, Ou HF, Yu WL. 2020. Dynamic variation in occurrence of influenza A(H1N1)-associated invasive pulmonary aspergillosis in southern Taiwan. Clin Infect Dis 72:899–900. https://doi.org/10.1093/cid/ciaa404.
43. Schwartz IS, Friedman DZP, Zapernick L, Dingle TC, Lee N, Sligl W, Zelyas N, Smith SW. 2020. High rates of influenza-associated invasive pulmonary aspergillosis may not be universal: a retrospective cohort study from Alberta, Canada. Clin Infect Dis 71:1760–1763. https://doi.org/10.1093/cid/ciaa007.
44. Rijnders BJA, Schauwvlieghe A, Wauters J. 2020. Influenza-associated pulmonary aspergillosis: a local or global lethal combination? Clin Infect Dis 71:1764–1767. https://doi.org/10.1093/cid/ciaa010.
45. Martin-Loeches I, J Schultz M, Vincent J-L, Alvarez-Lerma F, Bos LD, Solé-Violán J, Torres A, Rodriguez A. 2017. Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 43:48–58. https://doi.org/10.1007/s00134-016-4578-y.
46. Rodriguez-Goncer I, Thomas S, Foden P, Richardson MD, Ashworth A, Barker J, Geraghty CG, Muldoon EG, Felton TW. 2018. Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. Eur J Clin Microbiol Infect Dis 37:1251–1257. https://doi.org/10.1007/s10096-018-3241-7.
47. van de Veerdonk FL, Kolwijck E, Lestrade PP, Hodiamont CJ, Rijnders BJ, van Paassen J, Haas PJ, Oliveira Dos Santos C, Kampinga GA, Bergmans DC, van Dijk K, de Haan AF, van Dissel J, van der Hoeven HG, Verweij PE, Dutch Mycoses Study Group. 2017. Influenza-associated aspergillosis in critically ill patients. Am J Respir Crit Care Med 196:524–527. https://doi.org/10.1164/rccm.201612-2540LE.
48. Huang L, Zhang N, Huang X, Xiong S, Feng Y, Zhang Y, Li M, Zhan Q. 2019. Invasive pulmonary aspergillosis in patients with influenza infection: a retrospective study and review of the literature. Clin Respir J 13:202–211. https://doi.org/10.1111/crj.12995.
49. Ku YH, Chan KS, Yang CC, Tan CK, Chuang YC, Yu WL. 2017. Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections. J Formos Med Assoc 116:660–670. https://doi.org/10.1016/j.jfma.2017.06.002.
50. Yu WL, Liu WL, Chan KS, Yang CC, Tan CK, Tsai CL, Chen CM, Chuang YC. 2018. High-level ambient particulate matter before influenza attack with increased incidence of Aspergillus antigenemia in Southern Taiwan, 2016. J Microbiol Immunol Infect 51:141–147. https://doi.org/10.1016/j.jmii.2016.09.001.
51. Waldeck F, Boroli F, Suh N, Wendel Garcia PD, Flury D, Notter J, Iten A, Kaiser L, Schrenzel J, Boggian K, Maggiorini M, Pugin J, Kleger GR, Albrich WC. 2020. Influenza-associated aspergillosis in critically-ill patients-a retrospective bicentric cohort study. Eur J Clin Microbiol Infect Dis 39:1915–1923. https://doi.org/10.1007/s10096-020-03923-7.
52. Shah MM, Hsiao EI, Kirsch CM, Gohil A, Narasimhan S, Stevens DA. 2018. Invasive pulmonary aspergillosis and influenza co-infection in immunocompetent hosts: case reports and review of the literature. Diagn Microbiol Infect Dis 91:147–152. https://doi.org/10.1016/j.diagmicrobio.2018.01.014.
53. Nulens EF, Bourgeois MJ, Reynders MB. 2017. Post-influenza aspergillosis, do not underestimate influenza B. Infect Drug Resist 10:61–67. https://doi.org/10.2147/IDR.S122390.
54. Zou P, Wang C, Zheng S, Guo F, Yang L, Zhang Y, Liu P, Shen Y, Wang Y, Zhang X, Tang L, Gao H, Li L. 2020. Invasive pulmonary aspergillosis in adults with avian influenza A (H7N9) pneumonia in China: a retrospective study. J Infect Dis 221:S193–S197. https://doi.org/10.1093/infdis/jiz682.
55. Clancy CJ, Nguyen MH. 2020. COVID-19, superinfections and antimicrobial development: what can we expect? Clin Infect Dis 71:2736–2743. https://doi.org/10.1093/cid/ciaa524.
56. Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. 2020. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med 8:e48–e49. https://doi.org/10.1016/S2213-2600(20)30237-X.
57. Lansbury L, Lim B, Baskaran V, Lim WS. 2020. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 81:266–275. https://doi.org/10.1016/j.jinf.2020.05.046.
58. Bardi T, Pintado V, Gomez-Rojo M, Escudero-Sanchez R, Azzam Lopez A, Diez-Remesal Y, Martinez Castro N, Ruiz-Garbajosa P, Pestana D. 2021. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis 40:495–502. https://doi.org/10.1007/s10096-020-04142-w.
59. Hwang DM, Chamberlain DW, Poutanen SM, Low DE, Asa SL, Butany J. 2005. Pulmonary pathology of severe acute respiratory syndrome in Toronto. Mod Pathol 18:1–10. https://doi.org/10.1038/modpathol.3800247.
60. Wu YP, Wei R, Verhoef J. 2003. Real time assay of Aspergillus should be used in SARS patients receiving corticosteroids. BMJ 327:1405. https://doi.org/10.1136/bmj.327.7428.1405.
61. Wang H, Ding Y, Li X, Yang L, Zhang W, Kang W. 2003. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. N Engl J Med 349:507–508. https://doi.org/10.1056/NEJM200307313490519.
62. Blaize M, Mayaux J, Nabet C, Lampros A, Marcelin AG, Thellier M, Piarroux R, Demoule A, Fekkar A. 2020. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. Emerg Infect Dis 26:1636–1637. https://doi.org/10.3201/eid2607.201603.
63. Prattes J, Valentin T, Hoenigl M, Talakic E, Reisinger AC, Eller P. 2020. Invasive pulmonary aspergillosis complicating COVID-19 in the ICU—a case report. Med Mycol Case Rep 31:2–5. https://doi.org/10.1016/j.mmcr.2020.05.001.
64. Antinori S, Rech R, Galimberti L, Castelli A, Angeli E, Fossali T, Bernasconi D, Covizzi A, Bonazzetti C, Torre A, Carsana L, Tonello C, Zerbi P, Nebuloni M. 2020. Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: a diagnostic challenge. Travel Med Infect Dis 38:101752. https://doi.org/10.1016/j.tmaid.2020.101752.
65. Nasir N, Farooqi J, Mahmood SF, Jabeen K. 2020. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: an observational study from Pakistan. Mycoses 63:766–770. https://doi.org/10.1111/myc.13135.
66. Lahmer T, Rasch S, Spinner C, Geisler F, Schmid RM, Huber W. 2020. Invasive pulmonary aspergillosis in severe coronavirus disease 2019 pneumonia. Clin Microbiol Infect 26:1428–1429. https://doi.org/10.1016/j.cmi.2020.05.032.
67. Sharma A, Hofmeyr A, Bansal A, Thakkar D, Lam L, Harrington Z, Bhonagiri D. 2020. COVID-19 associated pulmonary aspergillosis (CAPA): an Australian case report. Med Mycol Case Rep 31:6–10. https://doi.org/10.1016/j.mmcr.2020.06.002.

68. Schein F, Munoz-Pons H, Mahinc C, Grange R, Cathebras P, Flori P. 2020. Fatal aspergillosis complicating severe SARS-CoV-2 infection: a case report. J Mycol Med 30:101039. https://doi.org/10.1016/j.mycmed.2020.101039.
69. Lamoth F, Glampedakis E, Boillat-Blanco N, Oddo M, Pagani JL. 2020. Incidence of invasive pulmonary aspergillosis among critically ill COVID-19 patients. Clin Microbiol Infect 26:1706–1708. https://doi.org/10.1016/j.cmi.2020.07.010.
70. Fernandez NB, Caceres DH, Beer KD, Irrazabal C, Delgado G, Farias L, Chiller TM, Verweij PE, Stecher D. 2020. Ventilator-associated pneumonia involving Aspergillus flavus in a patient with coronavirus disease 2019 (COVID-19) from Argentina. Med Mycol Case Rep 31:19–23. https://doi.org/10.1016/j.mmcr.2020.07.001.
71. Falces-Romero I, Ruiz-Bastian M, Diaz-Pollan B, Maseda E, Garcia-Rodriguez J, SARS-CoV-2 Working Group. 4 August 2020. Isolation of Aspergillus spp. in respiratory samples of patients with COVID-19 in a Spanish tertiary care hospital. Mycoses https://doi.org/10.1111/myc.13155.
72. Haglund A, Christensen S, Kristensen L, Gertsen JB, Buus L, Lausch KR. 2020. Invasive pulmonary aspergillosis and hyperthermia in an immunocompetent patient with COVID-19. Med Mycol Case Rep 31:29–31. https://doi.org/10.1016/j.mmcr.2020.11.004.
73. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, Fornaro G, Tonetti T, Pizzilli G, Francalanci E, Giuntoli L, Rubin A, Moroni A, Ambretti S, Trapani F, Vatamanu O, Ranieri VM, Castelli A, Baiocchi M, Lewis R, Giannella M, Viale P, PREDICO Study Group. 28 July 2020. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clin Infect Dis https://doi.org/10.1093/cid/ciaa1065.
74. Bruno G, Fabrizio C, Buccoliero GB. 2020. COVID-19-associated pulmonary aspergillosis: adding insult to injury. Lancet Microbe 1:e106. https://doi.org/10.1016/S2666-5247(20)30063-X.
75. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. 2020. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 8:475–481. https://doi.org/10.1016/S2213-2600(20)30079-5.
76. Wang Z, Yang B, Li Q, Wen L, Zhang R. 2020. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 71:769–777. https://doi.org/10.1093/cid/ciaa272.
77. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S, Yazdanpanah Y. 2020. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 20:697–706. https://doi.org/10.1016/S1473-3099(20)30200-0.
78. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513. https://doi.org/10.1016/S0140-6736(20)30211-7.
79. Farinacci D, Ciccullo A, Borghetti A, Visconti E, Tamburrini E, Izzi IM, Cauda R, Di Giambenedetto S, Pallavicini F. 2020. People living with HIV in the COVID-19 era: a case report. AIDS Res Hum Retroviruses 37:253–254. https://doi.org/10.1089/AID.2020.0149.
80. Agrifoglio A, Cachafeiro L, Figueira JC, Anon JM, Garcia de Lorenzo A. 2020. Critically ill patients with COVID-19 and candidaemia: we must keep this in mind. J Mycol Med 30:101012. https://doi.org/10.1016/j.mycmed.2020.101012.
81. Cai S, Sun W, Li M, Dong L. 2020. A complex COVID-19 case with rheumatoid arthritis treated with tocilizumab. Clin Rheumatol 39:2797–2802. https://doi.org/10.1007/s10067-020-05234-w.
82. Fekkar A, Lampros A, Mayaux J, Poignon C, Demeret S, Constantin JM, Marcelin AG, Monsel A, Luyt CE, Blaize M. 2020. Occurrence of invasive pulmonary fungal infections in severe COVID-19 patients admitted to the ICU. Am J Respir Crit Care Med 203:307–317. https://doi.org/10.1164/rccm.202009-3400OC.
83. Salmanton-Garcia J, Sprute R, Stemler J, Bartoletti M, Dupont D, Valerio M, Garcia-Vidal C, Falces-Romero I, Machado M, de la Villa S, Schroeder M, Hoyo I, Hanses F, Ferreira-Paim K, Giacobbe DR, Meis JF, Gangneux JP, Rodriguez-Guardado A, Antinori S, Sal E, Malaj X, Seidel D, Cornely OA, Koehler P, FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group. 2021. COVID-19-associated pulmonary aspergillosis, March–August 2020. Emerg Infect Dis 27:1077–1086. https://doi.org/10.3201/eid2704.204895.
84. Warris A, Schwartz I. 2021. Editorial MMCR special issue "Covid-19 associated pulmonary aspergillosis." Med Mycol Case Rep 31:1. https://doi.org/10.1016/j.mmcr.2021.02.003.
85. Helleberg M, Steensen M, Arendrup MC. 2021. Invasive aspergillosis in patients with severe COVID-19 pneumonia. Clin Microbiol Infect 27:147–148. https://doi.org/10.1016/j.cmi.2020.07.047.
86. Dupont D, Menotti J, Turc J, Miossec C, Wallet F, Richard JC, Argaud L, Paulus S, Wallon M, Ader F, Persat F. 2021. Pulmonary aspergillosis in critically ill patients with coronavirus disease 2019 (COVID-19). Med Mycol 59:110–114. https://doi.org/10.1093/mmy/myaa078.
87. Fu Y, Yang Q, Xu M, Kong H, Chen H, Fu Y, Yao Y, Zhou H, Zhou J. 2020. Secondary bacterial infections in critical ill patients with coronavirus disease 2019. Open Forum Infect Dis 7:ofaa220. https://doi.org/10.1093/ofid/ofaa220.
88. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, Fernandez-Pittol M, Pitart C, Inciarte A, Bodro M, Morata L, Ambrosioni J, Grafia I, Meira F, Macaya I, Cardozo C, Casals C, Tellez A, Castro P, Marco F, Garcia F, Mensa J, Martinez JA, Soriano A, Group C-R, COVID-19 Researchers Group. 2021. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 27:83–88. https://doi.org/10.1016/j.cmi.2020.07.041.
89. Machado M, Valerio M, Alvarez-Uria A, Olmedo M, Veintimilla C, Padilla B, De la Villa S, Guinea J, Escribano P, Ruiz-Serrano MJ, Reigadas E, Alonso R, Guerrero JE, Hortal J, Bouza E, Munoz P, Group C-S, COVID-19 Study Group. 2021. Invasive pulmonary aspergillosis in the COVID-19 era: an expected new entity. Mycoses 64:132–143. https://doi.org/10.1111/myc.13213.
90. Roman-Montes CM, Martinez-Gamboa A, Diaz-Lomeli P, Cervantes-Sanchez A, Rangel-Cordero A, Sifuentes-Osornio J, Ponce-de-Leon A, Gonzalez-Lara MF. 2021. Accuracy of galactomannan testing on tracheal aspirates in COVID-19-associated pulmonary aspergillosis. Mycoses 64:364–371. https://doi.org/10.1111/myc.13216.
91. Segrelles-Calvo G, Araujo GRS, Llopis-Pastor E, Carrillo J, Hernandez-Hernandez M, Rey L, Rodriguez Melean N, Escribano I, Anton E, Zamarro C, Garcia-Salmones M, Frases S. 2021. Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. Mycoses 64:144–151. https://doi.org/10.1111/myc.13219.
92. Van Biesen S, Kwa D, Bosman RJ, Juffermans NP. 2020. Detection of invasive pulmonary aspergillosis in COVID-19 with non-directed bronchoalveolar lavage. Am J Respir Crit Care Med 202:1171–1173. https://doi.org/10.1164/rccm.202005-2018LE.
93. Nasri E, Shoaei P, Vakili B, Mirhendi H, Sadeghi S, Hajiahmadi S, Sadeghi A, Vaezi A, Badali H, Fakhim H. 2020. Fatal invasive pulmonary aspergillosis in COVID-19 patient with acute myeloid leukemia in Iran. Mycopathologia 185:1077–1084. https://doi.org/10.1007/s11046-020-00493-2.
94. Abdalla S, Almaslamani MA, Hashim SM, Ibrahim AS, Omrani AS. 2020. Fatal coronavirus disease 2019-associated pulmonary aspergillosis; a report of two cases and review of the literature. IDCases 22:e00935. https://doi.org/10.1016/j.idcr.2020.e00935.
95. Lahmer T, Kriescher S, Herner A, Rothe K, Spinner CD, Schneider J, Mayer U, Neuenhahn M, Hoffmann D, Geisler F, Heim M, Schneider G, Schmid RM, Huber W, Rasch S. 2021. Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: results from the prospective AspCOVID-19 study. PLoS One 16:e0238825. https://doi.org/10.1371/journal.pone.0238825.
96. Velez Pintado M, Camiro-Zuniga A, Aguilar Soto M, Cuenca D, Mercado M, Crabtree-Ramirez B, ARMIIStudy Group. 2021. COVID-19-associated invasive pulmonary aspergillosis in a tertiary care center in Mexico City. Med Mycol 59:828–833. https://doi.org/10.1093/mmy/myab009.
97. Rabagliati R, Rodriguez N, Nunez C, Huete A, Bravo S, Garcia P. 2021. COVID-19-associated mold infection in critically ill patients, Chile. Emerg Infect Dis 27:1454–1456. https://doi.org/10.3201/eid2705.204412.
98. Koehler P, Cornely OA, Bottiger BW, Dusse F, Eichenauer DA, Fuchs F, Hallek M, Jung N, Klein F, Persigehl T, Rybniker J, Kochanek M, Boll B, Shimabukuro-Vornhagen A. 2020. COVID-19 associated pulmonary aspergillosis. Mycoses 63:528–534. https://doi.org/10.1111/myc.13096.
99. Rutsaert L, Steinfort N, Van Hunsel T, Bomans P, Naesens R, Mertes H, Dits H, Van Regenmortel N. 2020. COVID-19-associated invasive pulmonary aspergillosis. Ann Intensive Care 10:71. https://doi.org/10.1186/s13613-020-00686-4.
100. Chong WH, Neu KP. 2021. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. J Hosp Infect 113:115–129. https://doi.org/10.1016/j.jhin.2021.04.012.

101. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. 2020. COVID-19 associated pulmonary aspergillosis. Am J Respir Crit Care Med 202:132–135. https://doi.org/10.1164/rccm.202004-1038LE.
102. Flikweert AW, Grootenboers M, Yick DCY, Du Mee AWF, van der Meer NJM, Rettig TCD, Kant MKM. 2020. Late histopathologic characteristics of critically ill COVID-19 patients: different phenotypes without evidence of invasive aspergillosis, a case series. J Crit Care 59:149–155. https://doi.org/10.1016/j.jcrc.2020.07.002.
103. Santana MF, Pivoto G, Alexandre MAA, Baia-da-Silva DC, Borba M, Val FA, Brito-Sousa JD, Melo GC, Monteiro WM, Souza JVB, Pinheiro SB, Ferreira LCL, Naveca FG, Nascimento VA, Corado ALG, Hajjar LA, Silva Neto JR, Siva GAV, Pasqualotto AC, Lacerda MVG. 2020. Confirmed invasive pulmonary aspergillosis and COVID-19: the value of postmortem findings to support antemortem management. Rev Soc Bras Med Trop 53:e20200401. https://doi.org/10.1590/0037-8682-0401-2020.
104. Boyd S, Martin-Loeches I. 2021. Rates of aspergillus co-infection in COVID patients in ICU not as high as previously reported. Clin Infect Dis 73:e1236–e1238. https://doi.org/10.1093/cid/ciab008.
105. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. 2020. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect 26:1395–1399. https://doi.org/10.1016/j.cmi.2020.06.025.
106. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. 2020. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 71:2459–2468. https://doi.org/10.1093/cid/ciaa530.
107. Razazi K, Arrestier R, Haudebourg AF, Benelli B, Carteaux G, Decousser JW, Fourati S, Woerther PL, Schlemmer F, Charles-Nelson A, Botterel F, de Prost N, Mekontso Dessap A. 2020. Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to coronavirus 19 disease. Crit Care 24:699. https://doi.org/10.1186/s13054-020-03417-0.
108. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, Puri GD, Chakrabarti A, Agarwal R. 2021. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia 186:289–298. https://doi.org/10.1007/s11046-021-00528-2.
109. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A, Lagrou K, Meis JF, Cornely OA, Perfect JR, White PL, Chakrabarti A, on behalf of ECMM and ISHAM Collaborators. 12 May 2021. The emergence of COVID-19 associated mucormycosis: analysis of cases from 18 countries. Lancet https://doi.org/10.2139/ssrn.3844587.
110. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, Salehi M, Tabari A, Mohammadi Ardehali M, Kord M, Roilides E, Rezaie S. 2021. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: a case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. Mycoses 64:798–808. https://doi.org/10.1111/myc.13256.
111. John TM, Jacob CN, Kontoyiannis DP. 2021. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi (Basel) 7:298. https://doi.org/10.3390/jof7040298.
112. Narayanan S, Chua JV, Baddley JW. 2021. COVID-19 associated mucormycosis (CAM): risk factors and mechanisms of disease. Clin Infect Dis 2021:ciab726. https://doi.org/10.1093/cid/ciab726.
113. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, Edwards JE, Jr, Filler SG, Ibrahim AS. 2010. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest 120:1914–1924. https://doi.org/10.1172/JCI42164.
114. Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, Edwards JE, Jr, Filler SG, Yeaman MR, Ibrahim AS. 2014. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest 124:237–250. https://doi.org/10.1172/JCI71349.
115. Sabirli R, Koseler A, Goren T, Turkcuer I, Kurt O. 2021. High GRP78 levels in Covid-19 infection: a case-control study. Life Sci 265:118781. https://doi.org/10.1016/j.lfs.2020.118781.
116. Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. 2021. Mucor in a viral land: a tale of two pathogens. Indian J Ophthalmol 69:244–252. https://doi.org/10.4103/ijo.IJO_3774_20.
117. Sarkar S, Gokhale T, Choudhury SS, Deb AK. 2021. COVID-19 and orbital mucormycosis. Indian J Ophthalmol 69:1002–1004. https://doi.org/10.4103/ijo.IJO_3763_20.
118. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, Savio J, Sethuraman N, Madan S, Shastri P, Thangaraju D, Marak R, Tadepalli K, Savaj P, Sunavala A, Gupta N, Singhal T, Muthu V, Chakrabarti A, Muco-Covi Network3. 2021. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 27:2349–2359. https://doi.org/10.3201/eid2709.210934.
119. Rudramurthy SM, Hoenigl M, Meis JF, Cornely OA, Muthu V, Gangneux JP, Perfect J, Chakrabarti A, ECMM and ISHAM. 2021. ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries. Mycoses 64:1028–1037. https://doi.org/10.1111/myc.13335.
120. van Kampen JJ, Bielefeld-Buss AJ, Ott A, Maaskant J, Faber HJ, Lutisan JG, Boucher CA. 2013. Case report: oseltamivir-induced resistant pandemic influenza A (H1N1) virus infection in a patient with AIDS and Pneumocystis jirovecii pneumonia. J Med Virol 85:941–943. https://doi.org/10.1002/jmv.23560.
121. Pulcini C, Hasseine L, Mondain V, Baudin G, Roger PM. 2012. Possible pandemic H1N1 influenza complicated by Pneumocystis jirovecii pneumonia in an HIV-infected patient. J Mycol Med 22:88–91. https://doi.org/10.1016/j.mycmed.2011.11.003.
122. Franconi I, Monari C, Tutone M, Ciusa G, Corradi L, Franceschini E, Meschiari M, Puzzolante C, Gennari W, Pecorari M, Guaraldi G, Mussini C. 2019. Pneumocystosis as a complication of H1N1 influenza A infection in an HIV-positive patient on effective cART. Open Forum Infect Dis 6:ofz105. https://doi.org/10.1093/ofid/ofz105.
123. Guerrero M, Kruger S, Saitoh A, Sorvillo F, Cheng KJ, French C, Beall G. 1999. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. AIDS 13:1971–1975. https://doi.org/10.1097/00002030-199910010-00021.
124. Burke J, Soubani AO. 2018. Influenza and Pneumocystis jirovecii pneumonia in an allogeneic hematopoietic stem cell transplantation recipient: coinfection or superinfection? Transpl Infect Dis 20:e12802. https://doi.org/10.1111/tid.12802.
125. Guigue N, Alanio A, Menotti J, Castro ND, Hamane S, Peyrony O, LeGoff J, Bretagne S. 2015. Utility of adding Pneumocystis jirovecii DNA detection in nasopharyngeal aspirates in immunocompromised adult patients with febrile pneumonia. Med Mycol 53:241–247. https://doi.org/10.1093/mmy/myu087.
126. Menon AA, Berg DD, Brea EJ, Deutsch AJ, Kidia KK, Thurber EG, Polsky SB, Yeh T, Duskin JA, Holliday AM, Gay EB, Fredenburgh LE. 2020. A case of COVID-19 and Pneumocystis jirovecii co-infection. Am J Respir Crit Care Med 202:136–138. https://doi.org/10.1164/rccm.202003-0766LE.
127. Viceconte G, Buonomo AR, Lanzardo A, Pinchera B, Zappulo E, Scotto R, Schiano Moriello N, Vargas M, Iacovazzo C, Servillo G, Gentile I, "Federico II" COVID-19 Team. 2021. Pneumocystis jirovecii pneumonia in an immunocompetent patient recovered from COVID-19. Infect Dis (Lond) 53:382–385. https://doi.org/10.1080/23744235.2021.1890331.
128. Coleman H, Snell LB, Simons R, Douthwaite ST, Lee MJ. 2020. Coronavirus disease 2019 and Pneumocystis jirovecii pneumonia: a diagnostic dilemma in HIV. AIDS 34:1258–1260. https://doi.org/10.1097/QAD.0000000000002571.
129. Mang S, Kaddu-Mulindwa D, Metz C, Becker A, Seiler F, Smola S, Massmann A, Becker SL, Papan C, Bals R, Lepper PM, Danziger G. 2020. Pneumocystis jirovecii pneumonia and severe acute respiratory syndrome coronavirus 2 coinfection in a patient with newly diagnosed HIV-1 infection. Clin Infect Dis 72:1487–1489. https://doi.org/10.1093/cid/ciaa906.
130. Bhat P, Noval M, Doub JB, Heil E. 2020. Concurrent COVID-19 and Pneumocystis jirovecii pneumonia in a severely immunocompromised 25-year-old patient. Int J Infect Dis 99:119–121. https://doi.org/10.1016/j.ijid.2020.07.061.
131. Coleman JJ, Manavi K, Marson EJ, Botkai AH, Sapey E. 2020. COVID-19: to be or not to be; that is the diagnostic question. Postgrad Med J 96:392–398. https://doi.org/10.1136/postgradmedj-2020-137979.
132. Choy CY, Wong CS. 2020. It's not all about COVID-19: pneumocystis pneumonia in the era of a respiratory outbreak. J Int AIDS Soc 23:e25533. https://doi.org/10.1002/jia2.25533.
133. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. 2020. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med 30:100971. https://doi.org/10.1016/j.mycmed.2020.100971.
134. Guo W, Wang M, Ming F, Tang W, Liang K. 10 August 2020. The diagnostic trap occurred in two COVID-19 cases combined pneumocystis pneumonia in patient with AIDS. Res Sq https://doi.org/10.21203/rs.3.rs-53350/v1.
135. Favot M, Collins L. 2020. Man with dyspnea. J Am Coll Emerg Physicians Open 1:1117–1118. https://doi.org/10.1002/emp2.12174.

136. Rigamonti E, Salera D, Gheorghiu AC, Fratila C, Gianella P. 2020. The many faces of interstitial pneumonia: a case of presumed SARS-CoV-2 infection. Swiss Med Wkly 150:w20312. https://doi.org/10.4414/smw.2020.20312.
137. Kelly S, Waters L, Cevik M, Collins S, Lewis J, Wu MS, Blanchard TJ, Geretti AM. 2020. Pneumocystis pneumonia, a COVID-19 mimic, reminds us of the importance of HIV testing in COVID-19. Clin Med (Lond) 20:590–592. https://doi.org/10.7861/clinmed.2020-0565.
138. Blanco JL, Ambrosioni J, Garcia F, Martinez E, Soriano A, Mallolas J, Miro JM, COVID-19 in HIV Investigators. 2020. COVID-19 in patients with HIV: clinical case series. Lancet HIV 7:e314–e316. https://doi.org/10.1016/S2352-3018(20)30111-9.
139. Metan G, Bozkurt I, Koc AN. 2011. Pneumocystis jiroveci pneumonia (PCP) misdiagnosed as pandemic influenza H1N1 in a renal transplant patient. Infez Med 19:182–184.
140. Cunha BA, Chawla K, Jimada I. 2019. HIV adult with fever and shortness of breath: influenza B misdiagnosed as Pneumocystis (carinii) jiroveci pneumonia (PCP). IDCases 17:e00543. https://doi.org/10.1016/j.idcr.2019.e00543.
141. Huang J, Li H, Lan C, Zou S, Zhang H, Wang X, Weng H. 2019. Concomitant severe influenza and cryptococcal infections: a case report and literature review. Medicine (Baltimore) 98:e15544. https://doi.org/10.1097/MD.0000000000015544.
142. Gupta A, Capoor MR, Gupta S, Sachdeva HC. 2015. Concomitant infections of influenza A H1N1 and disseminated cryptococcosis in an HIV seropositive patient. J Lab Physicians 7:134–136. https://doi.org/10.4103/0974-2727.163137.
143. Hosseinnezhad A, Rapose A. 2012. Cryptococccal meningoencephalitis after H1N1 influenza. BMJ Case Rep 2012:bcr1120115224. https://doi.org/10.1136/bcr.11.2011.5224.
144. Senok A, Alfaresi M, Khansaheb H, Nassar R, Hachim M, Al Suwaidi H, Almansoori M, Alqaydi F, Afaneh Z, Mohamed A, Qureshi S, Ali A, Alkhajeh A, Alsheikh-Ali A. 2021. Coinfections in patients hospitalized with COVID-19: a descriptive study from the United Arab Emirates. Infect Drug Resist 14:2289–2296. https://doi.org/10.2147/IDR.S314029.
145. Nobrega de Almeida J, Jr, Brandao IB, Francisco EC, de Almeida SLR, de Oliveira Dias P, Pereira FM, Santos Ferreira F, de Andrade TS, de Miranda Costa MM, de Souza Jordao RT, Meis JF, Colombo AL, Candida auris Brazilian Study Group. 2021. Axillary digital thermometers uplifted a multidrug-susceptible Candida auris outbreak among COVID-19 patients in Brazil. Mycoses 64:1062–1072. https://doi.org/10.1111/myc.13320.
146. Mulet Bayona JV, Tormo Palop N, Salvador Garcia C, Fuster Escriva B, Chanza Avino M, Ortega Garcia P, Gimeno Cardona C. 2021. Impact of the SARS-CoV-2 pandemic in candidaemia, invasive aspergillosis and antifungal consumption in a tertiary hospital. J Fungi (Basel) 7:440. https://doi.org/10.3390/jof7060440.
147. Magnasco L, Mikulska M, Giacobbe DR, Taramasso L, Vena A, Dentone C, Dettori S, Tutino S, Labate L, Di Pilato V, Crea F, Coppo E, Codda G, Robba C, Ball L, Patroniti N, Marchese A, Pelosi P, Bassetti M. 2021. Spread of carbapenem-resistant gram-negatives and Candida auris during the COVID-19 pandemic in critically ill patients: one step back in antimicrobial stewardship? Microorganisms 9:95. https://doi.org/10.3390/microorganisms9010095.
148. Di Pilato V, Codda G, Ball L, Giacobbe DR, Willison E, Mikulska M, Magnasco L, Crea F, Vena A, Pelosi P, Bassetti M, Marchese A. 2021. Molecular epidemiological investigation of a nosocomial cluster of C. auris: evidence of recent emergence in Italy and ease of transmission during the COVID-19 pandemic. J Fungi (Basel) 7:140. https://doi.org/10.3390/jof7020140.
149. Allaw F, Kara Zahreddine N, Ibrahim A, Tannous J, Taleb H, Bizri AR, Dbaibo G, Kanj SS. 2021. First Candida auris outbreak during a COVID-19 pandemic in a tertiary-care center in Lebanon. Pathogens 10:157. https://doi.org/10.3390/pathogens10020157.
150. Villanueva-Lozano H, Trevino-Rangel RJ, Gonzalez GM, Ramirez-Elizondo MT, Lara-Medrano R, Aleman-Bocanegra MC, Guajardo-Lara CE, Gaona-Chavez N, Castilleja-Leal F, Torre-Amione G, Martinez-Resendez MF. 2021. Outbreak of Candida auris infection in a COVID-19 hospital in Mexico. Clin Microbiol Infect 27:813–816. https://doi.org/10.1016/j.cmi.2020.12.030.
151. de Almeida JN, Jr, Francisco EC, Hagen F, Brandao IB, Pereira FM, Presta Dias PH, de Miranda Costa MM, de Souza Jordao RT, de Groot T, Colombo AL. 2021. Emergence of Candida auris in Brazil in a COVID-19 intensive care unit. J Fungi (Basel) 7:220. https://doi.org/10.3390/jof7030220.
152. Hanson BM, Dinh AQ, Tran TT, Arenas S, Pronty D, Gershengorn HB, Ferreira T, Arias CA, Shukla BS. 2021. Candida auris invasive infections during a COVID-19 case surge. Antimicrob Agents Chemother 65:e01146-21. https://doi.org/10.1128/AAC.01146-21.
153. Chowdhary A, Tarai B, Singh A, Sharma A. 2020. Multidrug-resistant Candida auris infections in critically ill coronavirus disease patients, India, April-July 2020. Emerg Infect Dis 26:2694–2696. https://doi.org/10.3201/eid2611.203504.
154. Rodriguez JY, Le Pape P, Lopez O, Esquea K, Labiosa AL, Alvarez-Moreno C. 2020. Candida auris: a latent threat to critically ill patients with COVID-19. Clin Infect Dis 2020:ciaa1595. https://doi.org/10.1093/cid/ciaa1595.
155. Messina NL, Zimmermann P, Curtis N. 2019. The impact of vaccines on heterologous adaptive immunity. Clin Microbiol Infect 25:1484–1493. https://doi.org/10.1016/j.cmi.2019.02.016.
156. Balz K, Trassl L, Hartel V, Nelson PP, Skevaki C. 2020. Virus-induced T cell-mediated heterologous immunity and vaccine development. Front Immunol 11:513. https://doi.org/10.3389/fimmu.2020.00513.
157. Arastehfar A, Carvalho A, van de Veerdonk FL, Jenks JD, Koehler P, Krause R, Cornely OA, D SP, Lass-Florl C, Hoenigl M. 2020. COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. J Fungi (Basel) 6:91. https://doi.org/10.3390/jof6020091.
158. Feldman C, Anderson R. 2021. The role of co-infections and secondary infections in patients with COVID-19. Pneumonia (Nathan) 13:5. https://doi.org/10.1186/s41479-021-00083-w.
159. Tavakoli M, Shokohi T, Lass Florl C, Hedayati MT, Hoenigl M. 2020. Immunological response to COVID-19 and its role as a predisposing factor in invasive aspergillosis. Curr Med Mycol 6:75–79. https://doi.org/10.18502/cmm.6.4.5442.
160. Lee JS, Park S, Jeong HW, Ahn JY, Choi SJ, Lee H, Choi B, Nam SK, Sa M, Kwon JS, Jeong SJ, Lee HK, Park SH, Park SH, Choi JY, Kim SH, Jung I, Shin EC. 2020. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. Sci Immunol 5:eabd1554. https://doi.org/10.1126/sciimmunol.abd1554.
161. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, Feldman J, Muus C, Wadsworth MH, 2nd, Kazer SW, Hughes TK, Doran B, Gatter GJ, Vukovic M, Taliaferro F, Mead BE, Guo Z, Wang JP, Gras D, Plaisant M, Ansari M, Angelidis I, Adler H, Sucre JMS, Taylor CJ, Lin B, Waghray A, Mitsialis V, Dwyer DF, Buchheit KM, Boyce JA, Barrett NA, Laidlaw TM, Carroll SL, Colonna L, Tkachev V, Peterson CW, Yu A, Zheng HB, Gideon HP, Winchell CG, Lin PL, Bingle CD, Snapper SB, Kropski JA, Theis FJ, HCA Lung Biological Network, et al. 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 181:1016–1035.e19. https://doi.org/10.1016/j.cell.2020.04.035.
162. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. 2020. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 172:577–582. https://doi.org/10.7326/M20-0504.
163. Vardhana SA, Wolchok JD. 2020. The many faces of the anti-COVID immune response. J Exp Med 217:e20200678. https://doi.org/10.1084/jem.20200678.
164. Flerlage T, Boyd DF, Meliopoulos V, Thomas PG, Schultz-Cherry S. 2021. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. Nat Rev Microbiol 19:425–441. https://doi.org/10.1038/s41579-021-00542-7.
165. Reizine F, Pinceaux K, Lederlin M, Autier B, Guegan H, Gacouin A, Luque-Paz D, Boglione-Kerrien C, Bacle A, Le Dare B, Launey Y, Lesouhaitier M, Painvin B, Camus C, Mansour A, Robert-Gangneux F, Belaz S, Le Tulzo Y, Tadie JM, Maamar A, Gangneux JP. 2021. Influenza- and COVID-19-associated pulmonary aspergillosis: are the pictures different? J Fungi (Basel) 7:388. https://doi.org/10.3390/jof7050388.
166. Iwasaki A. 2012. A virological view of innate immune recognition. Annu Rev Microbiol 66:177–196. https://doi.org/10.1146/annurev-micro-092611-150203.
167. Crotta S, Davidson S, Mahlakoiv T, Desmet CJ, Buckwalter MR, Albert ML, Staeheli P, Wack A. 2013. Type I and type III interferons drive redundant amplification loops to induce a transcriptional signature in influenza-infected airway epithelia. PLoS Pathog 9:e1003773. https://doi.org/10.1371/journal.ppat.1003773.
168. Salazar F, Brown GD. 2018. Antifungal innate immunity: a perspective from the last 10 years. J Innate Immun 10:373–397. https://doi.org/10.1159/000488539.
169. Rivera A, Ro G, Van Epps HL, Simpson T, Leiner I, Sant'Angelo DB, Pamer EG. 2006. Innate immune activation and CD4+ T cell priming during respiratory fungal infection. Immunity 25:665–675. https://doi.org/10.1016/j.immuni.2006.08.016.

170. Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M, Monticelli S, Lanzavecchia A, Sallusto F. 2012. Pathogen-induced human TH17 cells produce IFN-gamma or IL-10 and are regulated by IL-1beta. Nature 484:514–518. https://doi.org/10.1038/nature10957.
171. Zelante T, Wong AY, Ping TJ, Chen J, Sumatoh HR, Vigano E, Hong Bing Y, Lee B, Zolezzi F, Fric J, Newell EW, Mortellaro A, Poidinger M, Puccetti P, Ricciardi-Castagnoli P. 2015. CD103(+) dendritic cells control Th17 cell function in the lung. Cell Rep 12:1789–1801. https://doi.org/10.1016/j.celrep.2015.08.030.
172. McAleer JP, Nguyen NL, Chen K, Kumar P, Ricks DM, Binnie M, Armentrout RA, Pociask DA, Hein A, Yu A, Vikram A, Bibby K, Umesaki Y, Rivera A, Sheppard D, Ouyang W, Hooper LV, Kolls JK. 2016. Pulmonary Th17 antifungal immunity is regulated by the gut microbiome. J Immunol 197:97–107. https://doi.org/10.4049/jimmunol.1502566.
173. Speakman EA, Dambuza IM, Salazar F, Brown GD. 2020. T cell antifungal immunity and the role of C-type lectin receptors. Trends Immunol 41:61–76. https://doi.org/10.1016/j.it.2019.11.007.
174. Bustamante-Marin XM, Ostrowski LE. 2017. Cilia and mucociliary clearance. Cold Spring Harb Perspect Biol 9:a028241. https://doi.org/10.1101/cshperspect.a028241.
175. Croft CA, Culibrk L, Moore MM, Tebbutt SJ. 2016. Interactions of Aspergillus fumigatus conidia with airway epithelial cells: a critical review. Front Microbiol 7:472. https://doi.org/10.3389/fmicb.2016.00472.
176. Xiong X, Martin SR, Haire LF, Wharton SA, Daniels RS, Bennett MS, McCauley JW, Collins PJ, Walker PA, Skehel JJ, Gamblin SJ. 2013. Receptor binding by an H7N9 influenza virus from humans. Nature 499:496–499. https://doi.org/10.1038/nature12372.
177. van Riel D, Munster VJ, de Wit E, Rimmelzwaan GF, Fouchier RA, Osterhaus AD, Kuiken T. 2006. H5N1 virus attachment to lower respiratory tract. Science 312:399. https://doi.org/10.1126/science.1125548.
178. Nicholls JM, Chan MC, Chan WY, Wong HK, Cheung CY, Kwong DL, Wong MP, Chui WH, Poon LL, Tsao SW, Guan Y, Peiris JS. 2007. Tropism of avian influenza A (H5N1) in the upper and lower respiratory tract. Nat Med 13:147–149. https://doi.org/10.1038/nm1529.
179. Subbarao K, Mahanty S. 2020. Respiratory virus infections: understanding COVID-19. Immunity 52:905–909. https://doi.org/10.1016/j.immuni.2020.05.004.
180. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271–280.e8. https://doi.org/10.1016/j.cell.2020.02.052.
181. Kuhn JH, Li W, Choe H, Farzan M. 2004. Angiotensin-converting enzyme 2: a functional receptor for SARS coronavirus. Cell Mol Life Sci 61:2738–2743. https://doi.org/10.1007/s00018-004-4242-5.
182. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 581:215–220. https://doi.org/10.1038/s41586-020-2180-5.
183. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q, Zhou H, Yan J, Qi J. 2020. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 181:894–904.e9. https://doi.org/10.1016/j.cell.2020.03.045.
184. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. 2020. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367:1444–1448. https://doi.org/10.1126/science.abb2762.
185. V'Kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. 2020. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 19:155–170. https://doi.org/10.1038/s41579-020-00468-6.
186. Dou D, Revol R, Ostbye H, Wang H, Daniels R. 2018. Influenza A virus cell entry, replication, virion assembly and movement. Front Immunol 9:1581. https://doi.org/10.3389/fimmu.2018.01581.
187. Vanarsdall AL, Johnson DC. 2012. Human cytomegalovirus entry into cells. Curr Opin Virol 2:37–42. https://doi.org/10.1016/j.coviro.2012.01.001.
188. Bohmwald K, Espinoza JA, Pulgar RA, Jara EL, Kalergis AM. 2017. Functional impairment of mononuclear phagocyte system by the human respiratory syncytial virus. Front Immunol 8:1643. https://doi.org/10.3389/fimmu.2017.01643.
189. Grant RA, Morales-Nebreda L, Markov NS, Swaminathan S, Querrey M, Guzman ER, Abbott DA, Donnelly HK, Donayre A, Goldberg IA, Klug ZM, Borkowski N, Lu Z, Kihshen H, Politanska Y, Sichizya L, Kang M, Shilatifard A, Qi C, Lomasney JW, Argento AC, Kruser JM, Malsin ES, Pickens CO, Smith SB, Walter JM, Pawlowski AE, Schneider D, Nannapaneni P, Abdala-Valencia H, Bharat A, Gottardi CJ, Budinger GRS, Misharin AV, Singer BD, Wunderink RG, Investigators NSS, NU SCRIPT Study Investigators. 2021. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature 590:635–641. https://doi.org/10.1038/s41586-020-03148-w.
190. Herold S, Becker C, Ridge KM, Budinger GR. 2015. Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 45:1463–1478. https://doi.org/10.1183/09031936.00186214.
191. Pittet LA, Hall-Stoodley L, Rutkowski MR, Harmsen AG. 2010. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. Am J Respir Cell Mol Biol 42:450–460. https://doi.org/10.1165/rcmb.2007-0417OC.
192. Duez JM, Sixt N, Pechinot A. 2009. Influenza virus infection: don't forget the role of the mucociliary system! J Antimicrob Chemother 63:421–422. https://doi.org/10.1093/jac/dkn468.
193. Pilewski JM, Latoche JD, Arcasoy SM, Albelda SM. 1997. Expression of integrin cell adhesion receptors during human airway epithelial repair in vivo. Am J Physiol 273:L256–63. https://doi.org/10.1152/ajplung.1997.273.1.L256.
194. Puchelle E, Zahm JM, Tournier JM, Coraux C. 2006. Airway epithelial repair, regeneration, and remodeling after injury in chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:726–733. https://doi.org/10.1513/pats.200605-126SF.
195. Liu H, Lee MJ, Solis NV, Phan QT, Swidergall M, Ralph B, Ibrahim AS, Sheppard DC, Filler SG. 2016. Aspergillus fumigatus CalA binds to integrin alpha5beta1 and mediates host cell invasion. Nat Microbiol 2:16211. https://doi.org/10.1038/nmicrobiol.2016.211.
196. Wiesner DL, Merkhofer RM, Ober C, Kujoth GC, Niu M, Keller NP, Gern JE, Brockman-Schneider RA, Evans MD, Jackson DJ, Warner T, Jarjour NN, Esnault SJ, Feldman MB, Freeman M, Mou H, Vyas JM, Klein BS. 2020. Club cell TRPV4 serves as a damage sensor driving lung allergic inflammation. Cell Host Microbe 27:614–628.e6. https://doi.org/10.1016/j.chom.2020.02.006.
197. Millien VO, Lu W, Mak G, Yuan X, Knight JM, Porter P, Kheradmand F, Corry DB. 2014. Airway fibrinogenolysis and the initiation of allergic inflammation. Ann Am Thorac Soc 11(Suppl 5):S277–S283. https://doi.org/10.1513/AnnalsATS.201403-105AW.
198. Landers CT, Tung HY, Knight JM, Madison MC, Wu Y, Zeng Z, Porter PC, Rodriguez A, Flick MJ, Kheradmand F, Corry DB. 2019. Selective cleavage of fibrinogen by diverse proteinases initiates innate allergic and antifungal immunity through CD11b. J Biol Chem 294:8834–8847. https://doi.org/10.1074/jbc.RA118.006724.
199. Kogan TV, Jadoun J, Mittelman L, Hirschberg K, Osherov N. 2004. Involvement of secreted Aspergillus fumigatus proteases in disruption of the actin fiber cytoskeleton and loss of focal adhesion sites in infected A549 lung pneumocytes. J Infect Dis 189:1965–1973. https://doi.org/10.1086/420850.
200. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lapidus S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A, Yale IT, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaugh ND, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A, Yale IMPACT Team. 2020. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 584:463–469. https://doi.org/10.1038/s41586-020-2588-y.
201. Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, Debnath O, Thurmann L, Kurth F, Volker MT, Kazmierski J, Timmermann B, Twardziok S, Schneider S, Machleidt F, Muller-Redetzky H, Maier M, Krannich A, Schmidt S, Balzer F, Liebig J, Loske J, Suttorp N, Eils J, Ishaque N, Liebert UG, von Kalle C, Hocke A, Witzenrath M, Goffinet C, Drosten C, Laudi S, Lehmann I, Conrad C, Sander LE, Eils R. 2020. COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. Nat Biotechnol 38:970–979. https://doi.org/10.1038/s41587-020-0602-4.
202. Melms JC, Biermann J, Huang H, Wang Y, Nair A, Tagore S, Katsyv I, Rendeiro AF, Amin AD, Schapiro D, Frangieh CJ, Luoma AM, Filliol A, Fang Y, Ravichandran H, Clausi MG, Alba GA, Rogava M, Chen SW, Ho P, Montoro DT, Kornberg AE, Han AS, Bakhoum MF, Anandasabapathy N, Suarez-Farinas M, Bakhoum SF, Bram Y, Borczuk A, Guo XV, Lefkowitch JH, Marboe C, Lagana SM, Del Portillo A, Zorn E, Markowitz GS, Schwabe RF, Schwartz RE, Elemento O, Saqi A, Hibshoosh H, Que J, Izar B. 2021. A molecular single-cell lung atlas of lethal COVID-19. Nature 595:114–119. https://doi.org/10.1038/s41586-021-03569-1.

203. Delorey TM, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe A, Abbondanza D, Fleming SJ, Subramanian A, Montoro DT, Jagadeesh KA, Dey KK, Sen P, Slyper M, Pita-Juarez YH, Phillips D, Biermann J, Bloom-Ackermann Z, Barkas N, Ganna A, Gomez J, Melms JC, Katsyv I, Normandin E, Naderi P, Popov YV, Raju SS, Niezen S, Tsai LT, Siddle KJ, Sud M, Tran VM, Vellarikkal SK, Wang Y, Amir-Zilberstein L, Atri DS, Beechem J, Brook OR, Chen J, Divakar P, Dorceus P, Engreitz JM, Essene A, Fitzgerald DM, Fropf R, Gazal S, Gould J, Grzyb J, Harvey T, Hecht J, et al. 2021. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. Nature 595:107–113. https://doi.org/10.1038/s41586-021-03570-8.
204. Goulding J, Godlee A, Vekaria S, Hilty M, Snelgrove R, Hussell T. 2011. Lowering the threshold of lung innate immune cell activation alters susceptibility to secondary bacterial superinfection. J Infect Dis 204:1086–1094. https://doi.org/10.1093/infdis/jir467.
205. Sheppard DC. 2011. Molecular mechanism of Aspergillus fumigatus adherence to host constituents. Curr Opin Microbiol 14:375–379. https://doi.org/10.1016/j.mib.2011.07.006.
206. Stukalov A, Girault V, Grass V, Karayel O, Bergant V, Urban C, Haas DA, Huang Y, Oubraham L, Wang A, Hamad MS, Piras A, Hansen FM, Tanzer MC, Paron I, Zinzula L, Enghleitner T, Reinecke M, Lavacca TM, Ehmann R, Wolfel R, Jores J, Kuster B, Protzer U, Rad R, Ziebuhr J, Thiel V, Scaturro P, Mann M, Pichlmair A. 2021. Multilevel proteomics reveals host perturbations by SARS-CoV-2 and SARS-CoV. Nature 594:246–252. https://doi.org/10.1038/s41586-021-03493-4.
207. Bertuzzi M, Hayes GE, Icheoku UJ, van Rhijn N, Denning DW, Osherov N, Bignell EM. 2018. Anti-Aspergillus activities of the respiratory epithelium in health and disease. J Fungi (Basel) 4:8. https://doi.org/10.3390/jof4010008.
208. George PM, Wells AU, Jenkins RG. 2020. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med 8:807–815. https://doi.org/10.1016/S2213-2600(20)30225-3.
209. Qiao J, Zhang M, Bi J, Wang X, Deng G, He G, Luan Z, Lv N, Xu T, Zhao L. 2009. Pulmonary fibrosis induced by H5N1 viral infection in mice. Respir Res 10:107. https://doi.org/10.1186/1465-9921-10-107.
210. Liu C, Yang J, Lu Z. 2019. Idiopathic pulmonary fibrosis with chronic necrotizing pulmonary aspergillosis: a case report. Int J Clin Exp Pathol 12:2653–2656.
211. Gomez P, Hackett TL, Moore MM, Knight DA, Tebbutt SJ. 2010. Functional genomics of human bronchial epithelial cells directly interacting with conidia of Aspergillus fumigatus. BMC Genomics 11:358. https://doi.org/10.1186/1471-2164-11-358.
212. Chen F, Zhang C, Jia X, Wang S, Wang J, Chen Y, Zhao J, Tian S, Han X, Han L. 2015. Transcriptome profiles of human lung epithelial cells A549 interacting with Aspergillus fumigatus by RNA-Seq. PLoS One 10:e0135720. https://doi.org/10.1371/journal.pone.0135720.
213. Bertuzzi M, Schrettl M, Alcazar-Fuoli L, Cairns TC, Munoz A, Walker LA, Herbst S, Safari M, Cheverton AM, Chen D, Liu H, Saijo S, Fedorova ND, Armstrong-James D, Munro CA, Read ND, Filler SG, Espeso EA, Nierman WC, Haas H, Bignell EM. 2014. The pH-responsive PacC transcription factor of Aspergillus fumigatus governs epithelial entry and tissue invasion during pulmonary aspergillosis. PLoS Pathog 10:e1004413. https://doi.org/10.1371/journal.ppat.1004413.
214. Zhang C, Chen F, Liu X, Han X, Hu Y, Su X, Chen Y, Sun Y, Han L. 2019. Gliotoxin induces cofilin phosphorylation to promote actin cytoskeleton dynamics and internalization of Aspergillus fumigatus into type II human pneumocyte cells. Front Microbiol 10:1345. https://doi.org/10.3389/fmicb.2019.01345.
215. Bedi S, Ono A. 2019. Friend or foe: the role of the cytoskeleton in influenza A virus assembly. Viruses 11:46. https://doi.org/10.3390/v11010046.
216. Coombs KM, Berard A, Xu W, Krokhin O, Meng X, Cortens JP, Kobasa D, Wilkins J, Brown EG. 2010. Quantitative proteomic analyses of influenza virus-infected cultured human lung cells. J Virol 84:10888–10906. https://doi.org/10.1128/JVI.00431-10.
217. Oguin TH, III, Sharma S, Stuart AD, Duan S, Scott SA, Jones CK, Daniels JS, Lindsley CW, Thomas PG, Brown HA. 2014. Phospholipase D facilitates efficient entry of influenza virus, allowing escape from innate immune inhibition. J Biol Chem 289:25405–25417. https://doi.org/10.1074/jbc.M114.558817.
218. Jia X, Chen F, Pan W, Yu R, Tian S, Han G, Fang H, Wang S, Zhao J, Li X, Zheng D, Tao S, Liao W, Han X, Han L. 2014. Gliotoxin promotes Aspergillus fumigatus internalization into type II human pneumocyte A549 cells by inducing host phospholipase D activation. Microbes Infect 16:491–501. https://doi.org/10.1016/j.micinf.2014.03.001.
219. Han X, Yu R, Zhen D, Tao S, Schmidt M, Han L. 2011. beta-1,3-Glucan-induced host phospholipase D activation is involved in Aspergillus fumigatus internalization into type II human pneumocyte A549 cells. PLoS One 6:e21468. https://doi.org/10.1371/journal.pone.0021468.
220. Kerr SC, Fischer GJ, Sinha M, McCabe O, Palmer JM, Choera T, Lim FY, Wimmerova M, Carrington SD, Yuan S, Lowell CA, Oscarson S, Keller NP, Fahy JV. 2016. FleA expression in Aspergillus fumigatus is recognized by fucosylated structures on mucins and macrophages to prevent lung infection. PLoS Pathog 12:e1005555. https://doi.org/10.1371/journal.ppat.1005555.
221. Cowley AC, Thornton DJ, Denning DW, Horsley A. 2017. Aspergillosis and the role of mucins in cystic fibrosis. Pediatr Pulmonol 52:548–555. https://doi.org/10.1002/ppul.23618.
222. Ordonez SR, Veldhuizen EJA, van Eijk M, Haagsman HP. 2017. Role of soluble innate effector molecules in pulmonary defense against fungal pathogens. Front Microbiol 8:2098. https://doi.org/10.3389/fmicb.2017.02098.
223. Jhingran A, Kasahara S, Shepardson KM, Junecko BA, Heung LJ, Kumasaka DK, Knoblaugh SE, Lin X, Kazmierczak BI, Reinhart TA, Cramer RA, Hohl TM. 2015. Compartment-specific and sequential role of MyD88 and CARD9 in chemokine induction and innate defense during respiratory fungal infection. PLoS Pathog 11:e1004589. https://doi.org/10.1371/journal.ppat.1004589.
224. Cohen M, Zhang XQ, Senaati HP, Chen HW, Varki NM, Schooley RT, Gagneux P. 2013. Influenza A penetrates host mucus by cleaving sialic acids with neuraminidase. Virol J 10:321. https://doi.org/10.1186/1743-422X-10-321.
225. Yang X, Steukers L, Forier K, Xiong R, Braeckmans K, Van Reeth K, Nauwynck H. 2014. A beneficiary role for neuraminidase in influenza virus penetration through the respiratory mucus. PLoS One 9:e110026. https://doi.org/10.1371/journal.pone.0110026.
226. McAuley JL, Corcilius L, Tan HX, Payne RJ, McGuckin MA, Brown LE. 2017. The cell surface mucin MUC1 limits the severity of influenza A virus infection. Mucosal Immunol 10:1581–1593. https://doi.org/10.1038/mi.2017.16.
227. Hsu JC, Laurent-Rolle M, Pawlak JB, Wilen CB, Cresswell P. 2021. Translational shutdown and evasion of the innate immune response by SARS-CoV-2 NSP14 protein. Proc Natl Acad Sci U S A 118:e2101161118. https://doi.org/10.1073/pnas.2101161118.
228. Unkel B, Hoegner K, Clausen BE, Lewe-Schlosser P, Bodner J, Gattenloehner S, Janßen H, Seeger W, Lohmeyer J, Herold S. 2012. Alveolar epithelial cells orchestrate DC function in murine viral pneumonia. J Clin Invest 122:3652–3664. https://doi.org/10.1172/JCI62139.
229. de Luca A, Bozza S, Zelante T, Zagarella S, D'Angelo C, Perruccio K, Vacca C, Carvalho A, Cunha C, Aversa F, Romani L. 2010. Non-hematopoietic cells contribute to protective tolerance to Aspergillus fumigatus via a TRIF pathway converging on IDO. Cell Mol Immunol 7:459–470. https://doi.org/10.1038/cmi.2010.43.
230. Wezensky SJ, Cramer RA, Jr, 2011. Implications of hypoxic microenvironments during invasive aspergillosis. Med Mycol 49(Suppl 1):S120–S124. https://doi.org/10.3109/13693786.2010.495139.
231. Kowalski CH, Kerkaert JD, Liu KW, Bond MC, Hartmann R, Nadell CD, Stajich JE, Cramer RA. 2019. Fungal biofilm morphology impacts hypoxia fitness and disease progression. Nat Microbiol 4:2430–2441. https://doi.org/10.1038/s41564-019-0558-7.
232. Ben-Ami R, Lewis RE, Leventakos K, Kontoyiannis DP. 2009. Aspergillus fumigatus inhibits angiogenesis through the production of gliotoxin and other secondary metabolites. Blood 114:5393–5399. https://doi.org/10.1182/blood-2009-07-231209.
233. Shepardson KM, Ngo LY, Aimanianda V, Latge JP, Barker BM, Blosser SJ, Iwakura Y, Hohl TM, Cramer RA. 2013. Hypoxia enhances innate immune activation to Aspergillus fumigatus through cell wall modulation. Microbes Infect 15:259–269. https://doi.org/10.1016/j.micinf.2012.11.010.
234. Kowalski CH, Beattie SR, Fuller KK, McGurk EA, Tang YW, Hohl TM, Obar JJ, Cramer RA, Jr. 2016. Heterogeneity among isolates reveals that fitness in low oxygen correlates with Aspergillus fumigatus virulence. mBio 7:e01515-16. https://doi.org/10.1128/mBio.01515-16.
235. van de Veerdonk FL, Gresnigt MS, Romani L, Netea MG, Latge JP. 2017. Aspergillus fumigatus morphology and dynamic host interactions. Nat Rev Microbiol 15:661–674. https://doi.org/10.1038/nrmicro.2017.90.
236. Zhao C, Chen J, Cheng L, Xu K, Yang Y, Su X. 2020. Deficiency of HIF-1alpha enhances influenza A virus replication by promoting autophagy in alveolar type II epithelial cells. Emerg Microbes Infect 9:691–706. https://doi.org/10.1080/22221751.2020.1742585.

237. Shepardson KM, Jhingran A, Caffrey A, Obar JJ, Suratt BT, Berwin BL, Hohl TM, Cramer RA. 2014. Myeloid derived hypoxia inducible factor 1-alpha is required for protection against pulmonary Aspergillus fumigatus infection. PLoS Pathog 10:e1004378. https://doi.org/10.1371/journal.ppat.1004378.
238. Pinsky DJ, Naka Y, Liao H, Oz MC, Wagner DD, Mayadas TN, Johnson RC, Hynes RO, Heath M, Lawson CA, Stern DM. 1996. Hypoxia-induced exocytosis of endothelial cell Weibel-Palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. J Clin Invest 97:493–500. https://doi.org/10.1172/JCI118440.
239. Stappers MHT, Clark AE, Aimanianda V, Bidula S, Reid DM, Asamaphan P, Hardison SE, Dambuza IM, Valsecchi I, Kerscher B, Plato A, Wallace CA, Yuecel R, Hebecker B, da Gloria Teixeira Sousa M, Cunha C, Liu Y, Feizi T, Brakhage AA, Kwon-Chung KJ, Gow NAR, Zanda M, Piras M, Zanato C, Jaeger M, Netea MG, van de Veerdonk FL, Lacerda JF, Campos A, Carvalho A, Willment JA, Latge JP, Brown GD. 2018. Recognition of DHN-melanin by a C-type lectin receptor is required for immunity to Aspergillus. Nature 555:382–386. https://doi.org/10.1038/nature25974.
240. Espinosa V, Dutta O, McElrath C, Du P, Chang YJ, Cicciarelli B, Pitler A, Whitehead I, Obar JJ, Durbin JE, Kotenko SV, Rivera A. 2017. Type III interferon is a critical regulator of innate antifungal immunity. Sci Immunol 2:eaan5357. https://doi.org/10.1126/sciimmunol.aan5357.
241. Dutta O, Espinosa V, Wang K, Avina S, Rivera A. 2020. Dectin-1 promotes type I and III interferon expression to support optimal antifungal immunity in the lung. Front Cell Infect Microbiol 10:321. https://doi.org/10.3389/fcimb.2020.00321.
242. Shahangian A, Chow EK, Tian X, Kang JR, Ghaffari A, Liu SY, Belperio JA, Cheng G, Deng JC. 2009. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest 119:1910–1920. https://doi.org/10.1172/JCI35412.
243. Parker D. 2017. Impact of type I and III interferons on respiratory superinfections due to; Multidrug-resistant pathogens. J Infect Dis 215:S58–S63. https://doi.org/10.1093/infdis/jiw466.
244. Kamphuis E, Junt T, Waibler Z, Forster R, Kalinke U. 2006. Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. Blood 108:3253–3261. https://doi.org/10.1182/blood-2006-06-027599.
245. Galani IE, Triantafyllia V, Eleminiadou EE, Koltsida O, Stavropoulos A, Manioudaki M, Thanos D, Doyle SE, Kotenko SV, Thanopoulou K, Andreakos E. 2017. Interferon-lambda mediates non-redundant front-line antiviral protection against influenza virus infection without compromising host fitness. Immunity 46:875–890.e6. https://doi.org/10.1016/j.immuni.2017.04.025.
246. Bellelli V, d'Ettorre G, Celani L, Borrazzo C, Ceccarelli G, Venditti M. 2019. Clinical significance of lymphocytopenia in patients hospitalized with pneumonia caused by influenza virus. Crit Care 23:330. https://doi.org/10.1186/s13054-019-2608-1.
247. Gooskens J, Jonges M, Claas EC, Meijer A, Kroes AC. 2009. Prolonged influenza virus infection during lymphocytopenia and frequent detection of drug-resistant viruses. J Infect Dis 199:1435–1441. https://doi.org/10.1086/598684.
248. Lalueza A, Folgueira D, Diaz-Pedroche C, Hernandez-Jimenez P, Ayuso B, Castillo C, Laureiro J, Trujillo H, Torres M, Lumbreras C. 2019. Severe lymphopenia in hospitalized patients with influenza virus infection as a marker of a poor outcome. Infect Dis (Lond) 51:543–546. https://doi.org/10.1080/23744235.2019.1598572.
249. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. 2020. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 5:33. https://doi.org/10.1038/s41392-020-0148-4.
250. Zhang JY, Wang XM, Xing X, Xu Z, Zhang C, Song JW, Fan X, Xia P, Fu JL, Wang SY, Xu RN, Dai XP, Shi L, Huang L, Jiang TJ, Shi M, Zhang Y, Zumla A, Maeurer M, Bai F, Wang FS. 2020. Single-cell landscape of immunological responses in patients with COVID-19. Nat Immunol 21:1107–1118. https://doi.org/10.1038/s41590-020-0762-x.
251. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, Agyekum RS, Mathew D, Baxter AE, Vella LA, Kuthuru O, Apostolidis SA, Bershaw L, Dougherty J, Greenplate AR, Pattekar A, Kim J, Han N, Gouma S, Weirick ME, Arevalo CP, Bolton MJ, Goodwin EC, Anderson EM, Hensley SE, Jones TK, Mangalmurti NS, Luning Prak ET, Wherry EJ, Meyer NJ, Betts MR. 2020. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol 5:eabd7114. https://doi.org/10.1126/sciimmunol.abd7114.
252. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. 2020. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 27:992–1000.e3. https://doi.org/10.1016/j.chom.2020.04.009.
253. Zhu L, Yang P, Zhao Y, Zhuang Z, Wang Z, Song R, Zhang J, Liu C, Gao Q, Xu Q, Wei X, Sun HX, Ye B, Wu Y, Zhang N, Lei G, Yu L, Yan J, Diao G, Meng F, Bai C, Mao P, Yu Y, Wang M, Yuan Y, Deng Q, Li Z, Huang Y, Hu G, Liu Y, Wang X, Xu Z, Liu P, Bi Y, Shi Y, Zhang S, Chen Z, Wang J, Xu X, Wu G, Wang FS, Gao GF, Liu L, Liu WJ. 2020. Single-cell sequencing of peripheral mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients. Immunity 53:685–696.e3. https://doi.org/10.1016/j.immuni.2020.07.009.
254. Rich HE, McCourt CC, Zheng WQ, McHugh KJ, Robinson KM, Wang J, Alcorn JF. 2019. Interferon lambda inhibits bacterial uptake during influenza superinfection. Infect Immun 87:e00114-19. https://doi.org/10.1128/IAI.00114-19.
255. Planet PJ, Parker D, Cohen TS, Smith H, Leon JD, Ryan C, Hammer TJ, Fierer N, Chen EI, Prince AS. 2016. Lambda interferon restructures the nasal microbiome and increases susceptibility to Staphylococcus aureus superinfection. mBio 7:e01939-15. https://doi.org/10.1128/mBio.01939-15.
256. Major J, Crotta S, Llorian M, McCabe TM, Gad HH, Priestnall SL, Hartmann R, Wack A. 2020. Type I and III interferons disrupt lung epithelial repair during recovery from viral infection. Science 369:712–717. https://doi.org/10.1126/science.abc2061.
257. Broggi A, Ghosh S, Sposito B, Spreafico R, Balzarini F, Lo Cascio A, Clementi N, De Santis M, Mancini N, Granucci F, Zanoni I. 2020. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science 369:706–712. https://doi.org/10.1126/science.abc3545.
258. Califano D, Furuya Y, Roberts S, Avram D, McKenzie ANJ, Metzger DW. 2018. IFN-gamma increases susceptibility to influenza A infection through suppression of group II innate lymphoid cells. Mucosal Immunol 11:209–219. https://doi.org/10.1038/mi.2017.41.
259. Nicol MQ, Campbell GM, Shaw DJ, Dransfield I, Ligertwood Y, Beard PM, Nash AA, Dutia BM. 2019. Lack of IFNgamma signaling attenuates spread of influenza A virus in vivo and leads to reduced pathogenesis. Virology 526:155–164. https://doi.org/10.1016/j.virol.2018.10.017.
260. Verma AK, Bansal S, Bauer C, Muralidharan A, Sun K. 2020. Influenza infection induces alveolar macrophage dysfunction and thereby enables noninvasive Streptococcus pneumoniae to cause deadly pneumonia. J Immunol 205:1601–1607. https://doi.org/10.4049/jimmunol.2000094.
261. Jia L, Zhao J, Yang C, Liang Y, Long P, Liu X, Qiu S, Wang L, Xie J, Li H, Liu H, Guo W, Wang S, Li P, Zhu B, Hao R, Ma H, Jiang Y, Song H. 2018. Severe pneumonia caused by coinfection with influenza virus followed by methicillin-resistant Staphylococcus aureus induces higher mortality in mice. Front Immunol 9:3189. https://doi.org/10.3389/fimmu.2018.03189.
262. Mendy J, Jarju S, Heslop R, Bojang AL, Kampmann B, Sutherland JS. 2018. Changes in Mycobacterium tuberculosis-specific immunity with influenza co-infection at time of TB diagnosis. Front Immunol 9:3093. https://doi.org/10.3389/fimmu.2018.03093.
263. Califano D, Furuya Y, Metzger DW. 2018. Effects of influenza on alveolar macrophage viability are dependent on mouse genetic strain. J Immunol 201:134–144. https://doi.org/10.4049/jimmunol.1701406.
264. Rynda-Apple A, Harmsen A, Erickson AS, Larson K, Morton RV, Richert LE, Harmsen AG. 2014. Regulation of IFN-gamma by IL-13 dictates susceptibility to secondary postinfluenza MRSA pneumonia. Eur J Immunol 44:3263–3272. https://doi.org/10.1002/eji.201444582.
265. Sun K, Metzger DW. 2008. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 14:558–564. https://doi.org/10.1038/nm1765.
266. Li N, Fan X, Xu M, Zhou Y, Wang B. 2020. Flu virus attenuates memory clearance of pneumococcus via IFN-gamma-dependent Th17 and independent antibody mechanisms. iScience 23:101767. https://doi.org/10.1016/j.isci.2020.101767.
267. Sharma-Chawla N, Stegemann-Koniszewski S, Christen H, Boehme JD, Kershaw O, Schreiber J, Guzman CA, Bruder D, Hernandez-Vargas EA. 2019. In vivo neutralization of pro-inflammatory cytokines during secondary Streptococcus pneumoniae infection post influenza A virus infection. Front Immunol 10:1864. https://doi.org/10.3389/fimmu.2019.01864.
268. Roberts S, Salmon SL, Steiner DJ, Williams CM, Metzger DW, Furuya Y. 2019. Allergic airway disease prevents lethal synergy of influenza A

virus-Streptococcus pneumoniae coinfection. mBio 10:e01335-19. https://doi.org/10.1128/mBio.01335-19.
269. Zhang WJ, Sarawar S, Nguyen P, Daly K, Rehg JE, Doherty PC, Woodland DL, Blackman MA. 1996. Lethal synergism between influenza infection and staphylococcal enterotoxin B in mice. J Immunol 157:5049–5060.
270. Cohen NR, Tatituri RV, Rivera A, Watts GF, Kim EY, Chiba A, Fuchs BB, Mylonakis E, Besra GS, Levitz SM, Brigl M, Brenner MB. 2011. Innate recognition of cell wall beta-glucans drives invariant natural killer T cell responses against fungi. Cell Host Microbe 10:437–450. https://doi.org/10.1016/j.chom.2011.09.011.
271. Oikonomou V, Moretti S, Renga G, Galosi C, Borghi M, Pariano M, Puccetti M, Palmerini CA, Amico L, Carotti A, Prezioso L, Spolzino A, Finocchi A, Rossi P, Velardi A, Aversa F, Napolioni V, Romani L. 2016. Noncanonical fungal autophagy inhibits inflammation in response to IFN-gamma via DAPK1. Cell Host Microbe 20:744–757. https://doi.org/10.1016/j.chom.2016.10.012.
272. Oliveira LVN, Costa MC, Magalhaes TFF, Bastos RW, Santos PC, Carneiro HCS, Ribeiro NQ, Ferreira GF, Ribeiro LS, Goncalves APF, Fagundes CT, Pascoal-Xavier MA, Djordjevic JT, Sorrell TC, Souza DG, Machado AMV, Santos DA. 2017. Influenza A virus as a predisposing factor for cryptococcosis. Front Cell Infect Microbiol 7:419. https://doi.org/10.3389/fcimb.2017.00419.
273. Armstrong-James D, Brown GD, Netea MG, Zelante T, Gresnigt MS, van de Veerdonk FL, Levitz SM. 2017. Immunotherapeutic approaches to treatment of fungal diseases. Lancet Infect Dis 17:e393–e402. https://doi.org/10.1016/S1473-3099(17)30442-5.
274. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, Jordan TX, Oishi K, Panis M, Sachs D, Wang TT, Schwartz RE, Lim JK, Albrecht RA, tenOever BR. 2020. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 181:1036–1045.e9. https://doi.org/10.1016/j.cell.2020.04.026.
275. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. 2016. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 19:181–193. https://doi.org/10.1016/j.chom.2016.01.007.
276. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Pere H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pene F, Marin N, Roche N, Szwebel TA, Merkling SH, Treluyer JM, Veyer D, Mouthon L, Blanc C, Tharaux PL, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kerneis S, Terrier B. 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 369:718–724. https://doi.org/10.1126/science.abc6027.
277. Arunachalam PS, Wimmers F, Mok CKP, Perera R, Scott M, Hagan T, Sigal N, Feng Y, Bristow L, Tak-Yin Tsang O, Wagh D, Coller J, Pellegrini KL, Kazmin D, Alaaeddine G, Leung WS, Chan JMC, Chik TSH, Choi CYC, Huerta C, Paine McCullough M, Lv H, Anderson E, Edupuganti S, Upadhyay AA, Bosinger SE, Maecker HT, Khatri P, Rouphael N, Peiris M, Pulendran B. 2020. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. Science 369:1210–1220. https://doi.org/10.1126/science.abc6261.
278. Laing AG, Lorenc A, Del Molino Del Barrio I, Das A, Fish M, Monin L, Munoz-Ruiz M, McKenzie DR, Hayday TS, Francos-Quijorna I, Kamdar S, Joseph M, Davies D, Davis R, Jennings A, Zlatareva I, Vantourout P, Wu Y, Sofra V, Cano F, Greco M, Theodoridis E, Freedman JD, Gee S, Chan JNE, Ryan S, Bugallo-Blanco E, Peterson P, Kisand K, Haljasmagi L, Chadli L, Moingeon P, Martinez L, Merrick B, Bisnauthsing K, Brooks K, Ibrahim MAA, Mason J, Lopez Gomez F, Babalola K, Abdul-Jawad S, Cason J, Mant C, Seow J, Graham C, Doores KJ, Di Rosa F, Edgeworth J, Shankar-Hari M, Hayday AC. 2020. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 26:1623–1635. https://doi.org/10.1038/s41591-020-1038-6.
279. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Munoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S, Consortium UC, Matthay M, Erle DJ, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF, UCSF COMET Consortium. 2021. Global absence and targeting of protective immune states in severe COVID-19. Nature 591:124–130. https://doi.org/10.1038/s41586-021-03234-7.
280. Galani IE, Rovina N, Lampropoulou V, Triantafyllia V, Manioudaki M, Pavlos E, Koukaki E, Fragkou PC, Panou V, Rapti V, Koltsida O, Mentis A, Koulouris N, Tsiodras S, Koutsoukou A, Andreakos E. 2021. Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison. Nat Immunol 22:32–40. https://doi.org/10.1038/s41590-020-00840-x.
281. Lopez J, Mommert M, Mouton W, Pizzorno A, Brengel-Pesce K, Mezidi M, Villard M, Lina B, Richard JC, Fassier JB, Cheynet V, Padey B, Duliere V, Julien T, Paul S, Bastard P, Belot A, Bal A, Casanova JL, Rosa-Calatrava M, Morfin F, Walzer T, Trouillet-Assant S. 2021. Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. J Exp Med 218:e20211211. https://doi.org/10.1084/jem.2021211108132021c.
282. Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, Manry J, Michailidis E, Hoffmann HH, Eto S, Garcia-Prat M, Bizien L, Parra-Martinez A, Yang R, Haljasmagi L, Migaud M, Sarekannu K, Maslovskaja J, de Prost N, Tandjaoui-Lambiotte Y, Luyt CE, Amador-Borrero B, Gaudet A, Poissy J, Morel P, Richard P, Cognasse F, Troya J, Trouillet-Assant S, Belot A, Saker K, Garcon P, Riviere JG, Lagier JC, Gentile S, Rosen LB, Shaw E, Morio T, Tanaka J, Dalmau D, Tharaux PL, Sene D, Stepanian A, Megarbane B, Triantafyllia V, Fekkar A, Heath JR, Franco JL, Anaya JM, Sole-Violan J, Imberti L. 2021. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol 6:eabl4340. https://doi.org/10.1126/sciimmunol.abl4340.
283. Bastard P, Orlova E, Sozaeva L, Levy R, James A, Schmitt MM, Ochoa S, Kareva M, Rodina Y, Gervais A, Le Voyer T, Rosain J, Philippot Q, Neehus AL, Shaw E, Migaud M, Bizien L, Ekwall O, Berg S, Beccuti G, Ghizzoni L, Thiriez G, Pavot A, Goujard C, Fremond ML, Carter E, Rothenbuhler A, Linglart A, Mignot B, Comte A, Cheikh N, Hermine O, Breivik L, Husebye ES, Humbert S, Rohrlich P, Coaquette A, Vuoto F, Faure K, Mahlaoui N, Kotnik P, Battelino T, Trebusak Podkrajsek K, Kisand K, Ferre EMN, DiMaggio T, Rosen LB, Burbelo PD, McIntyre M, Kann NY, et al. 2021. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. J Exp Med 218:e20210554. https://doi.org/10.1084/jem.20210554.
284. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Beziat V, Manry J, Shaw E, Haljasmagi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, et al. 2020. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 370:eabd4585. https://doi.org/10.1126/science.abd4585.
285. Wang EY, Mao T, Klein J, Dai Y, Huck JD, Jaycox JR, Liu F, Zhou T, Israelow B, Wong P, Coppi A, Lucas C, Silva J, Oh JE, Song E, Perotti ES, Zheng NS, Fischer S, Campbell M, Fournier JB, Wyllie AL, Vogels CBF, Ott IM, Kalinich CC, Petrone ME, Watkins AE, Yale IT, Dela Cruz C, Farhadian SF, Schulz WL, Ma S, Grubaugh ND, Ko AI, Iwasaki A, Ring AM. 2021. Diverse functional autoantibodies in patients with COVID-19. Nature 595:283–288. https://doi.org/10.1038/s41586-021-03631-y.
286. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, Ogishi M, Sabli IKD, Hodeib S, Korol C, Rosain J, Bilguvar K, Ye J, Bolze A, Bigio B, Yang R, Arias AA, Zhou Q, Zhang Y, Onodi F, Korniotis S, Karpf L, Philippot Q, Chbihi M, Bonnet-Madin L, Dorgham K, Smith N, Schneider WM, Razooky BS, Hoffmann HH, Michailidis E, Moens L, Han JE, Lorenzo L, Bizien L, Meade P, Neehus AL, Ugurbil AC, Corneau A, Kerner G, Zhang P, Rapaport F, Seeleuthner Y, Manry J, Masson C, Schmitt Y, Schluter A, Le Voyer T, Khan T, Li J, et al. 2020. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 370:eabd4570. https://doi.org/10.1126/science.abd4570.
287. Wilk AJ, Rustagi A, Zhao NQ, Roque J, Martinez-Colon GJ, McKechnie JL, Ivison GT, Ranganath T, Vergara R, Hollis T, Simpson LJ, Grant P, Subramanian A, Rogers AJ, Blish CA. 2020. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. Nat Med 26:1070–1076. https://doi.org/10.1038/s41591-020-0944-y.
288. Bost P, Giladi A, Liu Y, Bendjelal Y, Xu G, David E, Blecher-Gonen R, Cohen M, Medaglia C, Li H, Deczkowska A, Zhang S, Schwikowski B, Zhang Z, Amit I. 2020. Host-viral infection maps reveal signatures of severe COVID-19 patients. Cell 181:1475–1488.e12. https://doi.org/10.1016/j.cell.2020.05.006.
289. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu

B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. 2020. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe 27:883–890.e2. https://doi.org/10.1016/j.chom.2020.04.017.
290. Desai N, Neyaz A, Szabolcs A, Shih AR, Chen JH, Thapar V, Nieman LT, Solovyov A, Mehta A, Lieb DJ, Kulkarni AS, Jaicks C, Xu KH, Raabe MJ, Pinto CJ, Juric D, Chebib I, Colvin RB, Kim AY, Monroe R, Warren SE, Danaher P, Reeves JW, Gong J, Rueckert EH, Greenbaum BD, Hacohen N, Lagana SM, Rivera MN, Sholl LM, Stone JR, Ting DT, Deshpande V. 2020. Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection. Nat Commun 11:6319. https://doi.org/10.1038/s41467-020-20139-7.
291. King C, Sprent J. 2021. Dual nature of type I interferons in SARS-CoV-2-induced inflammation. Trends Immunol 42:312–322. https://doi.org/10.1016/j.it.2021.02.003.
292. Channappanavar R, Perlman S. 2017. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 39:529–539. https://doi.org/10.1007/s00281-017-0629-x.
293. Park A, Iwasaki A. 2020. Type I and type III interferons—induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe 27:870–878. https://doi.org/10.1016/j.chom.2020.05.008.
294. Molony RD, Nguyen JT, Kong Y, Montgomery RR, Shaw AC, Iwasaki A. 2017. Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes. Sci Signal 10:eaan2392. https://doi.org/10.1126/scisignal.aan2392.
295. Israelow B, Song E, Mao T, Lu P, Meir A, Liu F, Alfajaro MM, Wei J, Dong H, Homer RJ, Ring A, Wilen CB, Iwasaki A. 2020. Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling. J Exp Med 217:e20201241. https://doi.org/10.1084/jem.20201241.
296. Cheemarla NR, Watkins TA, Mihaylova VT, Wang B, Zhao D, Wang G, Landry ML, Foxman EF. 2021. Dynamic innate immune response determines susceptibility to SARS-CoV-2 infection and early replication kinetics. J Exp Med 218:e20210583. https://doi.org/10.1084/jem.20210583.
297. Ziegler CGK, Miao VN, Owings AH, Navia AW, Tang Y, Bromley JD, Lotfy P, Sloan M, Laird H, Williams HB, George M, Drake RS, Christian T, Parker A, Sindel CB, Burger MW, Pride Y, Hasan M, Abraham GE, III, Senitko M, Robinson TO, Shalek AK, Glover SC, Horwitz BH, Ordovas-Montanes J. 2021. Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. Cell 184:4713–4733.e22. https://doi.org/10.1016/j.cell.2021.07.023.
298. Davidson S, Maini MK, Wack A. 2015. Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. J Interferon Cytokine Res 35:252–264. https://doi.org/10.1089/jir.2014.0227.
299. Sposito B, Broggi A, Pandolfi L, Crotta S, Clementi N, Ferrarese R, Sisti S, Criscuolo E, Spreafico R, Long JM, Ambrosi A, Liu E, Frangipane V, Saracino L, Bozzini S, Marongiu L, Facchini FA, Bottazzi A, Fossali T, Colombo R, Clementi M, Tagliabue E, Chou J, Pontiroli AE, Meloni F, Wack A, Mancini N, Zanoni I. 2021. The interferon landscape along the respiratory tract impacts the severity of COVID-19. Cell 184:4953–4968.e16. https://doi.org/10.1016/j.cell.2021.08.016.
300. Loske J, Rohmel J, Lukassen S, Stricker S, Magalhaes VG, Liebig J, Chua RL, Thurmann L, Messingschlager M, Seegebarth A, Timmermann B, Klages S, Ralser M, Sawitzki B, Sander LE, Corman VM, Conrad C, Laudi S, Binder M, Trump S, Eils R, Mall MA, Lehmann I. 18 August 2021. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. Nat Biotechnol https://doi.org/10.1038/s41587-021-01037-9.
301. Tobin JM, Nickolich KL, Ramanan K, Pilewski MJ, Lamens KD, Alcorn JF, Robinson KM. 2020. Influenza suppresses neutrophil recruitment to the lung and exacerbates secondary invasive pulmonary aspergillosis. J Immunol 205:480–488. https://doi.org/10.4049/jimmunol.2000067.
302. King J, Henriet SSV, Warris A. 2016. Aspergillosis in chronic granulomatous disease. J Fungi (Basel) 2:15. https://doi.org/10.3390/jof2020015.
303. Rynda-Apple A, Robinson KM, Alcorn JF. 2015. Influenza and bacterial superinfection: illuminating the immunologic mechanisms of disease. Infect Immun 83:3764–3770. https://doi.org/10.1128/IAI.00298-15.
304. Sun K, Metzger DW. 2014. Influenza infection suppresses NADPH oxidase-dependent phagocytic bacterial clearance and enhances susceptibility to secondary methicillin-resistant Staphylococcus aureus infection. J Immunol 192:3301–3307. https://doi.org/10.4049/jimmunol.1303049.
305. McNamee LA, Harmsen AG. 2006. Both influenza-induced neutrophil dysfunction and neutrophil-independent mechanisms contribute to increased susceptibility to a secondary Streptococcus pneumoniae infection. Infect Immun 74:6707–6721. https://doi.org/10.1128/IAI.00789-06.
306. Morgan DJ, Casulli J, Chew C, Connolly E, Lui S, Brand OJ, Rahman R, Jagger C, Hussell T. 2018. Innate immune cell suppression and the link with secondary lung bacterial pneumonia. Front Immunol 9:2943. https://doi.org/10.3389/fimmu.2018.02943.
307. Schliehe C, Flynn EK, Vilagos B, Richson U, Swaminanthan S, Bosnjak B, Bauer L, Kandasamy RK, Griesshammer IM, Kosack L, Schmitz F, Litvak V, Sissons J, Lercher A, Bhattacharya A, Khamina K, Trivett AL, Tessarollo L, Mesteri I, Hladik A, Merkler D, Kubicek S, Knapp S, Epstein MM, Symer DE, Aderem A, Bergthaler A. 2015. The methyltransferase Setdb2 mediates virus-induced susceptibility to bacterial superinfection. Nat Immunol 16:67–74. https://doi.org/10.1038/ni.3046.
308. Ishikawa H, Fukui T, Ino S, Sasaki H, Awano N, Kohda C, Tanaka K. 2016. Influenza virus infection causes neutrophil dysfunction through reduced G-CSF production and an increased risk of secondary bacteria infection in the lung. Virology 499:23–29. https://doi.org/10.1016/j.virol.2016.08.025.
309. Halstead ES, Chroneos ZC. 2015. Lethal influenza infection: is a macrophage to blame? Expert Rev Anti Infect Ther 13:1425–1428. https://doi.org/10.1586/14787210.2015.1094375.
310. Ghoneim HE, Thomas PG, McCullers JA. 2013. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol 191:1250–1259. https://doi.org/10.4049/jimmunol.1300014.
311. Peiro T, Patel DF, Akthar S, Gregory LG, Pyle CJ, Harker JA, Birrell MA, Lloyd CM, Snelgrove RJ. 2018. Neutrophils drive alveolar macrophage IL-1beta release during respiratory viral infection. Thorax 73:546–556. https://doi.org/10.1136/thoraxjnl-2017-210010.
312. Ichinohe T, Pang IK, Iwasaki A. 2010. Influenza virus activates inflammasomes via its intracellular M2 ion channel. Nat Immunol 11:404–410. https://doi.org/10.1038/ni.1861.
313. Allen IC, Scull MA, Moore CB, Holl EK, McElvania-TeKippe E, Taxman DJ, Guthrie EH, Pickles RJ, Ting JP. 2009. The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. Immunity 30:556–565. https://doi.org/10.1016/j.immuni.2009.02.005.
314. Bansal S, Yajjala VK, Bauer C, Sun K. 2018. IL-1 signaling prevents alveolar macrophage depletion during influenza and Streptococcus pneumoniae coinfection. J Immunol 200:1425–1433. https://doi.org/10.4049/jimmunol.1700210.
315. De Filippo K, Henderson RB, Laschinger M, Hogg N. 2008. Neutrophil chemokines KC and macrophage-inflammatory protein-2 are newly synthesized by tissue macrophages using distinct TLR signaling pathways. J Immunol 180:4308–4315. https://doi.org/10.4049/jimmunol.180.6.4308.
316. Guo Y, Kasahara S, Jhingran A, Tosini NL, Zhai B, Aufiero MA, Mills KAM, Gjonbalaj M, Espinosa V, Rivera A, Luster AD, Hohl TM. 2020. During Aspergillus infection, monocyte-derived DCs, neutrophils, and plasmacytoid DCs enhance innate immune defense through CXCR3-dependent crosstalk. Cell Host Microbe 28:104–116.e4. https://doi.org/10.1016/j.chom.2020.05.002.
317. Park SJ, Burdick MD, Brix WK, Stoler MH, Askew DS, Strieter RM, Mehrad B. 2010. Neutropenia enhances lung dendritic cell recruitment in response to Aspergillus via a cytokine-to-chemokine amplification loop. J Immunol 185:6190–6197. https://doi.org/10.4049/jimmunol.1002064.
318. Park SJ, Burdick MD, Mehrad B. 2012. Neutrophils mediate maturation and efflux of lung dendritic cells in response to Aspergillus fumigatus germ tubes. Infect Immun 80:1759–1765. https://doi.org/10.1128/IAI.00097-12.
319. Schulte-Schrepping J, Reusch N, Paclik D, Bassler K, Schlickeiser S, Zhang B, Kramer B, Krammer T, Brumhard S, Bonaguro L, De Domenico E, Wendisch D, Grasshoff M, Kapellos TS, Beckstette M, Pecht T, Saglam A, Dietrich O, Mei HE, Schulz AR, Conrad C, Kunkel D, Vafadarnejad E, Xu CJ, Horne A, Herbert M, Drews A, Thibeault C, Pfeiffer M, Hippenstiel S, Hocke A, Muller-Redetzky H, Heim KM, Machleidt F, Uhrig A, Bosquillon de Jarcy L, Jurgens L, Stegemann M, Glosenkamp CR, Volk HD, Goffinet C, Landthaler M, Wyler E, Georg P, Schneider M, Dang-Heine C, Neuwinger N, Kappert K, Tauber R, Corman V, et al. 2020. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. Cell 182:1419–1440.e23. https://doi.org/10.1016/j.cell.2020.08.001.
320. Silvin A, Chapuis N, Dunsmore G, Goubet AG, Dubuisson A, Derosa L, Almire C, Henon C, Kosmider O, Droin N, Rameau P, Catelain C, Alfaro A, Dussiau C, Friedrich C, Sourdeau E, Marin N, Szwebel TA, Cantin D, Mouthon L, Borderie D, Deloger M, Bredel D, Mouraud S, Drubay D, Andrieu M, Lhonneur AS, Saada V, Stoclin A, Willekens C, Pommeret F, Griscelli F, Ng LG, Zhang Z, Bost P, Amit I, Barlesi F, Marabelle A, Pene F, Gachot B, Andre F, Zitvogel L, Ginhoux F, Fontenay M, Solary E. 2020. Elevated calprotectin and abnormal myeloid cell subsets discriminate

severe from mild COVID-19. Cell 182:1401–1418.e18. https://doi.org/10.1016/j.cell.2020.08.002.
321. Su Y, Chen D, Yuan D, Lausted C, Choi J, Dai CL, Voillet V, Duvvuri VR, Scherler K, Troisch P, Baloni P, Qin G, Smith B, Kornilov SA, Rostomily C, Xu A, Li J, Dong S, Rothchild A, Zhou J, Murray K, Edmark R, Hong S, Heath JE, Earls J, Zhang R, Xie J, Li S, Roper R, Jones L, Zhou Y, Rowen L, Liu R, Mackay S, O'Mahony DS, Dale CR, Wallick JA, Algren HA, Zager MA, Wei W, Price ND, Huang S, Subramanian N, Wang K, Magis AT, Hadlock JJ, Hood L, Aderem A, Bluestone JA, Lanier LL, ISB-Swedish COVID19 Biobanking Unit, et al. 2020. Multi-omics resolves a sharp disease-state shift between mild and moderate COVID-19. Cell 183:1479–1495.e20. https://doi.org/10.1016/j.cell.2020.10.037.
322. Kreutmair S, Unger S, Nunez NG, Ingelfinger F, Alberti C, De Feo D, Krishnarajah S, Kauffmann M, Friebel E, Babaei S, Gaborit B, Lutz M, Jurado NP, Malek NP, Goepel S, Rosenberger P, Haberle HA, Ayoub I, Al-Hajj S, Nilsson J, Claassen M, Liblau R, Martin-Blondel G, Bitzer M, Roquilly A, Becher B. 2021. Distinct immunological signatures discriminate severe COVID-19 from non-SARS-CoV-2-driven critical pneumonia. Immunity 54:1578–1593.e5. https://doi.org/10.1016/j.immuni.2021.05.002.
323. Wilk AJ, Lee MJ, Wei B, Parks B, Pi R, Martinez-Colon GJ, Ranganath T, Zhao NQ, Taylor S, Becker W, Stanford C-B, Jimenez-Morales D, Blomkalns AL, O'Hara R, Ashley EA, Nadeau KC, Yang S, Holmes S, Rabinovitch M, Rogers AJ, Greenleaf WJ, Blish CA. 2021. Multi-omic profiling reveals widespread dysregulation of innate immunity and hematopoiesis in COVID-19. J Exp Med 218:e2021082. https://doi.org/10.1084/jem.20210582.
324. Kvedaraite E, Hertwig L, Sinha I, Ponzetta A, Hed Myrberg I, Lourda M, Dzidic M, Akber M, Klingstrom J, Folkesson E, Muvva JR, Chen P, Gredmark-Russ S, Brighenti S, Norrby-Teglund A, Eriksson LI, Rooyackers O, Aleman S, Stralin K, Ljunggren HG, Ginhoux F, Bjorkstrom NK, Henter JI, Svensson M, Karolinska K-SG. 2021. Major alterations in the mononuclear phagocyte landscape associated with COVID-19 severity. Proc Natl Acad Sci U S A 118:e2018587118. https://doi.org/10.1073/pnas.2018587118.
325. Szabo PA, Dogra P, Gray JI, Wells SB, Connors TJ, Weisberg SP, Krupska I, Matsumoto R, Poon MML, Idzikowski E, Morris SE, Pasin C, Yates AJ, Ku A, Chait M, Davis-Porada J, Guo XV, Zhou J, Steinle M, Mackay S, Saqi A, Baldwin MR, Sims PA, Farber DL. 2021. Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19. Immunity 54:797–814.e6. https://doi.org/10.1016/j.immuni.2021.03.005.
326. Thompson EA, Cascino K, Ordonez AA, Zhou W, Vaghasia A, Hamacher-Brady A, Brady NR, Sun IH, Wang R, Rosenberg AZ, Delannoy M, Rothman R, Fenstermacher K, Sauer L, Shaw-Saliba K, Bloch EM, Redd AD, Tobian AAR, Horton M, Smith K, Pekosz A, D'Alessio FR, Yegnasubramanian S, Ji H, Cox AL, Powell JD. 2021. Metabolic programs define dysfunctional immune responses in severe COVID-19 patients. Cell Rep 34:108863. https://doi.org/10.1016/j.celrep.2021.108863.
327. Zhu B, Zhang R, Li C, Jiang L, Xiang M, Ye Z, Kita H, Melnick AM, Dent AL, Sun J. 2019. BCL6 modulates tissue neutrophil survival and exacerbates pulmonary inflammation following influenza virus infection. Proc Natl Acad Sci U S A 116:11888–11893. https://doi.org/10.1073/pnas.1902310116.
328. Vidy A, Maisonnasse P, Da Costa B, Delmas B, Chevalier C, Le Goffic R. 2016. The influenza virus protein PB1-F2 increases viral pathogenesis through neutrophil recruitment and NK cells inhibition. PLoS One 11:e0165361. https://doi.org/10.1371/journal.pone.0165361.
329. Wheeler JL, Martin KC, Lawrence BP. 2013. Novel cellular targets of AhR underlie alterations in neutrophilic inflammation and inducible nitric oxide synthase expression during influenza virus infection. J Immunol 190:659–668. https://doi.org/10.4049/jimmunol.1201341.
330. Teske S, Bohn AA, Regal JF, Neumiller JJ, Lawrence BP. 2005. Activation of the aryl hydrocarbon receptor increases pulmonary neutrophilia and diminishes host resistance to influenza A virus. Am J Physiol Lung Cell Mol Physiol 289:L111–L124. https://doi.org/10.1152/ajplung.00318.2004.
331. White MR, Tecle T, Crouch EC, Hartshorn KL. 2007. Impact of neutrophils on antiviral activity of human bronchoalveolar lavage fluid. Am J Physiol Lung Cell Mol Physiol 293:L1293–L1299. https://doi.org/10.1152/ajplung.00266.2007.
332. Bradley LM, Douglass MF, Chatterjee D, Akira S, Baaten BJ. 2012. Matrix metalloprotease 9 mediates neutrophil migration into the airways in response to influenza virus-induced toll-like receptor signaling. PLoS Pathog 8:e1002641. https://doi.org/10.1371/journal.ppat.1002641.
333. Zhang J, Liu J, Yuan Y, Huang F, Ma R, Luo B, Xi Z, Pan T, Liu B, Zhang Y, Zhang X, Luo Y, Wang J, Zhao M, Lu G, Deng K, Zhang H. 2020. Two waves of pro-inflammatory factors are released during the influenza A virus (IAV)-driven pulmonary immunopathogenesis. PLoS Pathog 16:e1008334. https://doi.org/10.1371/journal.ppat.1008334.
334. Ellis GT, Davidson S, Crotta S, Branzk N, Papayannopoulos V, Wack A. 2015. TRAIL+ monocytes and monocyte-related cells cause lung damage and thereby increase susceptibility to influenza-Streptococcus pneumoniae coinfection. EMBO Rep 16:1203–1218. https://doi.org/10.15252/embr.201540473.
335. Thwaites RS, Sanchez Sevilla Uruchurtu A, Siggins MK, Liew F, Russell CD, Moore SC, Fairfield C, Carter E, Abrams S, Short CE, Thaventhiran T, Bergstrom E, Gardener Z, Ascough S, Chiu C, Docherty AB, Hunt D, Crow YJ, Solomon T, Taylor GP, Turtle L, Harrison EM, Dunning J, Semple MG, Baillie JK, Openshaw PJ, ISARIC4C Investigators. 2021. Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19. Sci Immunol 6:eabg9873. https://doi.org/10.1126/sciimmunol.abg9873.
336. Merad M, Martin JC. 2020. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 20:355–362. https://doi.org/10.1038/s41577-020-0331-4.
337. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, Cheng L, Li J, Wang X, Wang F, Liu L, Amit I, Zhang S, Zhang Z. 2020. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med 26:842–844. https://doi.org/10.1038/s41591-020-0901-9.
338. Laforge M, Elbim C, Frere C, Hemadi M, Massaad C, Nuss P, Benoliel JJ, Becker C. 2020. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Rev Immunol 20:515–516. https://doi.org/10.1038/s41577-020-0407-1.
339. Rendeiro AF, Ravichandran H, Bram Y, Chandar V, Kim J, Meydan C, Park J, Foox J, Hether T, Warren S, Kim Y, Reeves J, Salvatore S, Mason CE, Swanson EC, Borczuk AC, Elemento O, Schwartz RE. 2021. The spatial landscape of lung pathology during COVID-19 progression. Nature 593:564–569. https://doi.org/10.1038/s41586-021-03475-6.
340. Seoane PI, Taylor-Smith LM, Stirling D, Bell LCK, Noursadeghi M, Bailey D, May RC. 2020. Viral infection triggers interferon-induced expulsion of live Cryptococcus neoformans by macrophages. PLoS Pathog 16:e1008240. https://doi.org/10.1371/journal.ppat.1008240.
341. Lionakis MS, Swamydas M, Fischer BG, Plantinga TS, Johnson MD, Jaeger M, Green NM, Masedunskas A, Weigert R, Mikelis C, Wan W, Lee CC, Lim JK, Rivollier A, Yang JC, Laird GM, Wheeler RT, Alexander BD, Perfect JR, Gao JL, Kullberg BJ, Netea MG, Murphy PM. 2013. CX3CR1-dependent renal macrophage survival promotes Candida control and host survival. J Clin Invest 123:5035–5051. https://doi.org/10.1172/JCI71307.
342. Leonardi I, Li X, Semon A, Li D, Doron I, Putzel G, Bar A, Prieto D, Rescigno M, McGovern DPB, Pla J, Iliev ID. 2018. CX3CR1(+) mononuclear phagocytes control immunity to intestinal fungi. Science 359:232–236. https://doi.org/10.1126/science.aao1503.
343. Lin KL, Suzuki Y, Nakano H, Ramsburg E, Gunn MD. 2008. CCR2+ monocyte-derived dendritic cells and exudate macrophages produce influenza-induced pulmonary immune pathology and mortality. J Immunol 180:2562–2572. https://doi.org/10.4049/jimmunol.180.4.2562.
344. Burgess M, Wicks K, Gardasevic M, Mace KA. 2019. Cx3CR1 expression identifies distinct macrophage populations that contribute differentially to inflammation and repair. Immunohorizons 3:262–273. https://doi.org/10.4049/immunohorizons.1900038.
345. Wang J, Li F, Sun R, Gao X, Wei H, Li LJ, Tian Z. 2013. Bacterial colonization dampens influenza-mediated acute lung injury via induction of M2 alveolar macrophages. Nat Commun 4:2106. https://doi.org/10.1038/ncomms3106.
346. Wheeler ML, Limon JJ, Bar AS, Leal CA, Gargus M, Tang J, Brown J, Funari VA, Wang HL, Crother TR, Arditi M, Underhill DM, Iliev ID. 2016. Immunological consequences of intestinal fungal dysbiosis. Cell Host Microbe 19:865–873. https://doi.org/10.1016/j.chom.2016.05.003.
347. Li X, Leonardi I, Semon A, Doron I, Gao IH, Putzel GG, Kim Y, Kabata H, Artis D, Fiers WD, Ramer-Tait AE, Iliev ID. 2018. Response to fungal dysbiosis by gut-resident CX3CR1(+) mononuclear phagocytes aggravates allergic airway disease. Cell Host Microbe 24:847–856.e4. https://doi.org/10.1016/j.chom.2018.11.003.
348. Godwin MS, Jones M, Blackburn JP, Yu Z, Matalon S, Hastie AT, Meyers DA, Steele C. 2020. The chemokine CX3CL1/fractalkine regulates immunopathogenesis during fungal-associated allergic airway inflammation. Am J Physiol Lung Cell Mol Physiol 320:L393–L404. https://doi.org/10.1152/ajplung.00376.2020.
349. Noverr MC, Noggle RM, Toews GB, Huffnagle GB. 2004. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. Infect Immun 72:4996–5003. https://doi.org/10.1128/IAI.72.9.4996-5003.2004.

350. Kim YG, Udayanga KG, Totsuka N, Weinberg JB, Nunez G, Shibuya A. 2014. Gut dysbiosis promotes M2 macrophage polarization and allergic airway inflammation via fungi-induced PGE(2). Cell Host Microbe 15:95–102. https://doi.org/10.1016/j.chom.2013.12.010.
351. Noverr MC, Falkowski NR, McDonald RA, McKenzie AN, Huffnagle GB. 2005. Development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. Infect Immun 73:30–38. https://doi.org/10.1128/IAI.73.1.30-38.2005.
352. Skalski JH, Limon JJ, Sharma P, Gargus MD, Nguyen C, Tang J, Coelho AL, Hogaboam CM, Crother TR, Underhill DM. 2018. Expansion of commensal fungus Wallemia mellicola in the gastrointestinal mycobiota enhances the severity of allergic airway disease in mice. PLoS Pathog 14:e1007260. https://doi.org/10.1371/journal.ppat.1007260.
353. van Tilburg Bernardes E, Pettersen VK, Gutierrez MW, Laforest-Lapointe I, Jendzjowsky NG, Cavin JB, Vicentini FA, Keenan CM, Ramay HR, Samara J, MacNaughton WK, Wilson RJA, Kelly MM, McCoy KD, Sharkey KA, Arrieta MC. 2020. Intestinal fungi are causally implicated in microbiome assembly and immune development in mice. Nat Commun 11:2577. https://doi.org/10.1038/s41467-020-16431-1.
354. Li XV, Leonardi I, Iliev ID. 2019. Gut mycobiota in immunity and inflammatory disease. Immunity 50:1365–1379. https://doi.org/10.1016/j.immuni.2019.05.023.
355. Bacher P, Hohnstein T, Beerbaum E, Rocker M, Blango MG, Kaufmann S, Rohmel J, Eschenhagen P, Grehn C, Seidel K, Rickerts V, Lozza L, Stervbo U, Nienen M, Babel N, Milleck J, Assenmacher M, Cornely OA, Ziegler M, Wisplinghoff H, Heine G, Worm M, Siegmund B, Maul J, Creutz P, Tabeling C, Ruwwe-Glosenkamp C, Sander LE, Knosalla C, Brunke S, Hube B, Kniemeyer O, Brakhage AA, Schwarz C, Scheffold A. 2019. Human anti-fungal Th17 immunity and pathology rely on cross-reactivity against Candida albicans. Cell 176:1340–1355.e15. https://doi.org/10.1016/j.cell.2019.01.041.
356. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, Iwasaki A. 2011. Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci U S A 108:5354–5359. https://doi.org/10.1073/pnas.1019378108.
357. Sencio V, Barthelemy A, Tavares LP, Machado MG, Soulard D, Cuinat C, Queiroz-Junior CM, Noordine ML, Salome-Desnoulez S, Deryuter L, Foligne B, Wahl C, Frisch B, Vieira AT, Paget C, Milligan G, Ulven T, Wolowczuk I, Faveeuw C, Le Goffic R, Thomas M, Ferreira S, Teixeira MM, Trottein F. 2020. Gut dysbiosis during influenza contributes to pulmonary pneumococcal superinfection through altered short-chain fatty acid production. Cell Rep 30:2934–2947.e6. https://doi.org/10.1016/j.celrep.2020.02.013.
358. Deriu E, Boxx GM, He X, Pan C, Benavidez SD, Cen L, Rozengurt N, Shi W, Cheng G. 2016. Influenza virus affects intestinal microbiota and secondary salmonella infection in the gut through type I interferons. PLoS Pathog 12:e1005572. https://doi.org/10.1371/journal.ppat.1005572.
359. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, Lui GCY, Chen N, Li A, Lu W, Chan FKL, Chan PKS, Ng SC. 2020. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology 159:1302–1310.e5. https://doi.org/10.1053/j.gastro.2020.06.048.
360. Ichinohe T, Lee HK, Ogura Y, Flavell R, Iwasaki A. 2009. Inflammasome recognition of influenza virus is essential for adaptive immune responses. J Exp Med 206:79–87. https://doi.org/10.1084/jem.20081667.
361. Thomas PG, Dash P, Aldridge JR, Jr, Ellebedy AH, Reynolds C, Funk AJ, Martin WJ, Lamkanfi M, Webby RJ, Boyd KL, Doherty PC, Kanneganti TD. 2009. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus via the regulation of caspase-1. Immunity 30:566–575. https://doi.org/10.1016/j.immuni.2009.02.006.
362. Lee PH, Bird N, MacKenzie-Kludas C, Mansell A, Kedzierska K, Brown L, McAuley J. 2016. Induction of memory cytotoxic T cells to influenza A virus and subsequent viral clearance is not modulated by PB1-F2-dependent inflammasome activation. Immunol Cell Biol 94:439–446. https://doi.org/10.1038/icb.2015.115.
363. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, Ma L, Watowich SS, Jetten AM, Tian Q, Dong C. 2009. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity 30:576–587. https://doi.org/10.1016/j.immuni.2009.02.007.
364. Sarvestani ST, McAuley JL. 2017. The role of the NLRP3 inflammasome in regulation of antiviral responses to influenza A virus infection. Antiviral Res 148:32–42. https://doi.org/10.1016/j.antiviral.2017.10.020.
365. McAuley JL, Tate MD, MacKenzie-Kludas CJ, Pinar A, Zeng W, Stutz A, Latz E, Brown LE, Mansell A. 2013. Activation of the NLRP3 inflammasome by IAV virulence protein PB1-F2 contributes to severe pathophysiology and disease. PLoS Pathog 9:e1003392. https://doi.org/10.1371/journal.ppat.1003392.
366. Chung WC, Kang HR, Yoon H, Kang SJ, Ting JP, Song MJ. 2015. Influenza A virus NS1 protein inhibits the NLRP3 inflammasome. PLoS One 10:e0126456. https://doi.org/10.1371/journal.pone.0126456.
367. Pinar A, Dowling JK, Bitto NJ, Robertson AA, Latz E, Stewart CR, Drummond GR, Cooper MA, McAuley JL, Tate MD, Mansell A. 2017. PB1-F2 peptide derived from avian influenza A virus H7N9 induces inflammation via activation of the NLRP3 inflammasome. J Biol Chem 292:826–836. https://doi.org/10.1074/jbc.M116.756379.
368. Chen IY, Moriyama M, Chang MF, Ichinohe T. 2019. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. Front Microbiol 10:50. https://doi.org/10.3389/fmicb.2019.00050.
369. Triantafilou K, Triantafilou M. 2014. Ion flux in the lung: virus-induced inflammasome activation. Trends Microbiol 22:580–588. https://doi.org/10.1016/j.tim.2014.06.002.
370. Rodrigues TS, de Sa KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, Goncalves AV, Perucello DB, Andrade WA, Castro R, Veras FP, Toller-Kawahisa JE, Nascimento DC, de Lima MHF, Silva CMS, Caetite DB, Martins RB, Castro IA, Pontelli MC, de Barros FC, do Amaral NB, Giannini MC, Bonjorno LP, Lopes MIF, Santana RC, Vilar FC, Auxiliadora-Martins M, Luppino-Assad R, de Almeida SCL, de Oliveira FR, Batah SS, Siyuan L, Benatti MN, Cunha TM, Alves-Filho JC, Cunha FQ, Cunha LD, Frantz FG, Kohlsdorf T, Fabro AT, Arruda E, de Oliveira RDR, Louzada-Junior P, Zamboni DS. 2021. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med 218:e20201707. https://doi.org/10.1084/jem.20201707.
371. Moriyama M, Chen IY, Kawaguchi A, Koshiba T, Nagata K, Takeyama H, Hasegawa H, Ichinohe T. 2016. The RNA- and TRIM25-binding domains of influenza virus NS1 protein are essential for suppression of NLRP3 inflammasome-mediated interleukin-1beta secretion. J Virol 90:4105–4114. https://doi.org/10.1128/JVI.00120-16.
372. Cheung PH, Ye ZW, Lee TT, Chen H, Chan CP, Jin DY. 2020. PB1-F2 protein of highly pathogenic influenza A (H7N9) virus selectively suppresses RNA-induced NLRP3 inflammasome activation through inhibition of MAVS-NLRP3 interaction. J Leukoc Biol 108:1655–1663. https://doi.org/10.1002/JLB.4AB0420-694R.
373. Yoshizumi T, Ichinohe T, Sasaki O, Otera H, Kawabata S, Mihara K, Koshiba T. 2014. Influenza A virus protein PB1-F2 translocates into mitochondria via Tom40 channels and impairs innate immunity. Nat Commun 5:4713. https://doi.org/10.1038/ncomms5713.
374. Alymova IV, Samarasinghe A, Vogel P, Green AM, Weinlich R, McCullers JA. 2014. A novel cytotoxic sequence contributes to influenza A viral protein PB1-F2 pathogenicity and predisposition to secondary bacterial infection. J Virol 88:503–515. https://doi.org/10.1128/JVI.01373-13.
375. Alymova IV, Green AM, van de Velde N, McAuley JL, Boyd KL, Ghoneim HE, McCullers JA. 2011. Immunopathogenic and antibacterial effects of H3N2 influenza A virus PB1-F2 map to amino acid residues 62, 75, 79, and 82. J Virol 85:12324–12333. https://doi.org/10.1128/JVI.05872-11.
376. McAuley JL, Chipuk JE, Boyd KL, Van De Velde N, Green DR, McCullers JA. 2010. PB1-F2 proteins from H5N1 and 20 century pandemic influenza viruses cause immunopathology. PLoS Pathog 6:e1001014. https://doi.org/10.1371/journal.ppat.1001014.
377. McAuley JL, Hornung F, Boyd KL, Smith AM, McKeon R, Bennink J, Yewdell JW, McCullers JA. 2007. Expression of the 1918 influenza A virus PB1-F2 enhances the pathogenesis of viral and secondary bacterial pneumonia. Cell Host Microbe 2:240–249. https://doi.org/10.1016/j.chom.2007.09.001.
378. Robinson KM, Choi SM, McHugh KJ, Mandalapu S, Enelow RI, Kolls JK, Alcorn JF. 2013. Influenza A exacerbates Staphylococcus aureus pneumonia by attenuating IL-1beta production in mice. J Immunol 191:5153–5159. https://doi.org/10.4049/jimmunol.1301237.
379. Guarda G, Braun M, Staehli F, Tardivel A, Mattmann C, Forster I, Farlik M, Decker T, Du Pasquier RA, Romero P, Tschopp J. 2011. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 34:213–223. https://doi.org/10.1016/j.immuni.2011.02.006.
380. Searles S, Gauss K, Wilkison M, Hoyt TR, Dobrinen E, Meissner N. 2013. Modulation of inflammasome-mediated pulmonary immune activation by type I IFNs protects bone marrow homeostasis during systemic responses to Pneumocystis lung infection. J Immunol 191:3884–3895. https://doi.org/10.4049/jimmunol.1301344.
381. Tavares AH, Burgel PH, Bocca AL. 2015. Turning up the heat: inflammasome activation by fungal pathogens. PLoS Pathog 11:e1004948. https://doi.org/10.1371/journal.ppat.1004948.

382. Said-Sadier N, Padilla E, Langsley G, Ojcius DM. 2010. Aspergillus fumigatus stimulates the NLRP3 inflammasome through a pathway requiring ROS production and the Syk tyrosine kinase. PLoS One 5:e10008. https://doi.org/10.1371/journal.pone.0010008.
383. Moretti S, Bozza S, Oikonomou V, Renga G, Casagrande A, Iannitti RG, Puccetti M, Garlanda C, Kim S, Li S, van de Veerdonk FL, Dinarello CA, Romani L. 2014. IL-37 inhibits inflammasome activation and disease severity in murine aspergillosis. PLoS Pathog 10:e1004462. https://doi.org/10.1371/journal.ppat.1004462.
384. Iannitti RG, Napolioni V, Oikonomou V, De Luca A, Galosi C, Pariano M, Massi-Benedetti C, Borghi M, Puccetti M, Lucidi V, Colombo C, Fiscarelli E, Lass-Florl C, Majo F, Cariani L, Russo M, Porcaro L, Ricciotti G, Ellemunter H, Ratclif L, De Benedictis FM, Talesa VN, Dinarello CA, van de Veerdonk FL, Romani L. 2016. IL-1 receptor antagonist ameliorates inflammasome-dependent inflammation in murine and human cystic fibrosis. Nat Commun 7:10791. https://doi.org/10.1038/ncomms10791.
385. Karki R, Man SM, Malireddi RKS, Gurung P, Vogel P, Lamkanfi M, Kanneganti TD. 2015. Concerted activation of the AIM2 and NLRP3 inflammasomes orchestrates host protection against Aspergillus infection. Cell Host Microbe 17:357–368. https://doi.org/10.1016/j.chom.2015.01.006.
386. Briard B, Fontaine T, Samir P, Place DE, Muszkieta L, Malireddi RKS, Karki R, Christgen S, Bomme P, Vogel P, Beau R, Mellado E, Ibrahim-Granet O, Henrissat B, Kalathur RC, Robinson C, Latge JP, Kanneganti TD. 2020. Galactosaminogalactan activates the inflammasome to provide host protection. Nature 588:688–692. https://doi.org/10.1038/s41586-020-2996-z.
387. Kuriakose T, Man SM, Malireddi RK, Karki R, Kesavardhana S, Place DE, Neale G, Vogel P, Kanneganti TD. 2016. ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. Sci Immunol 1:aag2045. https://doi.org/10.1126/sciimmunol.aag2045.
388. Thomas PG, Shubina M, Balachandran S. 23 January 2020. ZBP1/DAI-dependent cell death pathways in influenza A virus immunity and pathogenesis. Curr Top Microbiol Immunol https://doi.org/10.1007/82_2019_190.
389. Robinson KM, Ramanan K, Clay ME, McHugh KJ, Pilewski MJ, Nickolich KL, Corey C, Shiva S, Wang J, Muzumdar R, Alcorn JF. 2018. The inflammasome potentiates influenza/Staphylococcus aureus superinfection in mice. JCI Insight 3:e97470. https://doi.org/10.1172/jci.insight.97470.
390. Rodriguez AE, Bogart C, Gilbert CM, McCullers JA, Smith AM, Kanneganti TD, Lupfer CR. 2019. Enhanced IL-1beta production is mediated by a TLR2-MYD88-NLRP3 signaling axis during coinfection with influenza A virus and Streptococcus pneumoniae. PLoS One 14:e0212236. https://doi.org/10.1371/journal.pone.0212236.
391. de Luca A, Smeekens SP, Casagrande A, Iannitti R, Conway KL, Gresnigt MS, Begun J, Plantinga TS, Joosten LA, van der Meer JW, Chamilos G, Netea MG, Xavier RJ, Dinarello CA, Romani L, van de Veerdonk FL. 2014. IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans. Proc Natl Acad Sci U S A 111:3526–3531. https://doi.org/10.1073/pnas.1322831111.
392. Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. 2008. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 133:235–249. https://doi.org/10.1016/j.cell.2008.02.043.
393. Snelgrove RJ, Edwards L, Rae AJ, Hussell T. 2006. An absence of reactive oxygen species improves the resolution of lung influenza infection. Eur J Immunol 36:1364–1373. https://doi.org/10.1002/eji.200635977.
394. To EE, Broughton BR, Hendricks KS, Vlahos R, Selemidis S. 2014. Influenza A virus and TLR7 activation potentiate NOX2 oxidase-dependent ROS production in macrophages. Free Radic Res 48:940–947. https://doi.org/10.3109/10715762.2014.927579.
395. Vlahos R, Stambas J, Bozinovski S, Broughton BR, Drummond GR, Selemidis S. 2011. Inhibition of Nox2 oxidase activity ameliorates influenza A virus-induced lung inflammation. PLoS Pathog 7:e1001271. https://doi.org/10.1371/journal.ppat.1001271.
396. Vlahos R, Stambas J, Selemidis S. 2012. Suppressing production of reactive oxygen species (ROS) for influenza A virus therapy. Trends Pharmacol Sci 33:3–8. https://doi.org/10.1016/j.tips.2011.09.001.
397. Vlahos R, Selemidis S. 2014. NADPH oxidases as novel pharmacologic targets against influenza A virus infection. Mol Pharmacol 86:747–759. https://doi.org/10.1124/mol.114.095216.
398. To EE, Vlahos R, Luong R, Halls ML, Reading PC, King PT, Chan C, Drummond GR, Sobey CG, Broughton BRS, Starkey MR, van der Sluis R, Lewin SR, Bozinovski S, O'Neill LAJ, Quach T, Porter CJH, Brooks DA, O'Leary JJ, Selemidis S. 2017. Endosomal NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. Nat Commun 8:69. https://doi.org/10.1038/s41467-017-00057-x.
399. Kelkka T, Kienhofer D, Hoffmann M, Linja M, Wing K, Sareila O, Hultqvist M, Laajala E, Chen Z, Vasconcelos J, Neves E, Guedes M, Marques L, Kronke G, Helminen M, Kainulainen L, Olofsson P, Jalkanen S, Lahesmaa R, Souto-Carneiro MM, Holmdahl R. 2014. Reactive oxygen species deficiency induces autoimmunity with type 1 interferon signature. Antioxid Redox Signal 21:2231–2245. https://doi.org/10.1089/ars.2013.5828.
400. Campbell AM, Kashgarian M, Shlomchik MJ. 2012. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. Sci Transl Med 4:157ra141. https://doi.org/10.1126/scitranslmed.3004801.
401. Sun K, Yajjala VK, Bauer C, Talmon GA, Fischer KJ, Kielian T, Metzger DW. 2016. Nox2-derived oxidative stress results in inefficacy of antibiotics against post-influenza S. aureus pneumonia. J Exp Med 213:1851–1864. https://doi.org/10.1084/jem.20150514.
402. Schultz-Cherry S. 2015. Role of NK cells in influenza infection. Curr Top Microbiol Immunol 386:109–120. https://doi.org/10.1007/82_2014_403.
403. Mahmoud AB, Tu MM, Wight A, Zein HS, Rahim MM, Lee SH, Sekhon HS, Brown EG, Makrigiannis AP. 2016. Influenza virus targets class I MHC-educated NK cells for immunoevasion. PLoS Pathog 12:e1005446. https://doi.org/10.1371/journal.ppat.1006021.
404. Zhao X, You Y, Wang G, Gao H, Cui X, Duan L, Zhang S, Wang Y, Lin-Yao Li L, Lu J, Wang H, Fan J, Zheng H, Dai E, Tian L, Ma M. 2020. Longitudinal single-cell immune profiling revealed distinct innate immune response in asymptomatic COVID-19 patients. BioRxiv https://doi.org/10.1101/2020.09.02.276865.
405. Liu C, Martins AJ, Lau WW, Rachmaninoff N, Chen J, Imberti L, Mostaghimi D, Fink DL, Burbelo PD, Dobbs K, Delmonte OM, Bansal N, Failla L, Sottini A, Quiros-Roldan E, Han KL, Sellers BA, Cheung F, Sparks R, Chun TW, Moir S, Lionakis MS, NIAID COVID Consortium, COVID Clinicians, Rossi C, Su HC, Kuhns DB, Cohen JI, Notarangelo LD, Tsang JS. 2021. Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19. Cell 184:1836–1857.e22. https://doi.org/10.1016/j.cell.2021.02.018.
406. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. 2020. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 17:533–535. https://doi.org/10.1038/s41423-020-0402-2.
407. Small CL, Shaler CR, McCormick S, Jeyanathan M, Damjanovic D, Brown EG, Arck P, Jordana M, Kaushic C, Ashkar AA, Xing Z. 2010. Influenza infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. J Immunol 184:2048–2056. https://doi.org/10.4049/jimmunol.0902772.
408. Rodriguez L, Pekkarinen PT, Lakshmikanth T, Tan Z, Consiglio CR, Pou C, Chen Y, Mugabo CH, Nguyen NA, Nowlan K, Strandin T, Levanov L, Mikes J, Wang J, Kantele A, Hepojoki J, Vapalahti O, Heinonen S, Kekalainen E, Brodin P. 2020. Systems-level immunomonitoring from acute to recovery phase of severe COVID-19. Cell Rep Med 1:100078. https://doi.org/10.1016/j.xcrm.2020.100078.
409. Ni L, Ye F, Cheng ML, Feng Y, Deng YQ, Zhao H, Wei P, Ge J, Gou M, Li X, Sun L, Cao T, Wang P, Zhou C, Zhang R, Liang P, Guo H, Wang X, Qin CF, Chen F, Dong C. 2020. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity 52:971–977.e3. https://doi.org/10.1016/j.immuni.2020.04.023.
410. Nouer SA, Nucci M, Kumar NS, Grazziutti M, Restrepo A, Anaissie E. 2012. Baseline platelet count and creatinine clearance rate predict the outcome of neutropenia-related invasive aspergillosis. Clin Infect Dis 54:e173-83. https://doi.org/10.1093/cid/cis298.
411. Cilloniz C, Ewig S, Menendez R, Ferrer M, Polverino E, Reyes S, Gabarrus A, Marcos MA, Cordoba J, Mensa J, Torres A. 2012. Bacterial co-infection with H1N1 infection in patients admitted with community acquired pneumonia. J Infect 65:223–230. https://doi.org/10.1016/j.jinf.2012.04.009.
412. Bernardes JP, Mishra N, Tran F, Bahmer T, Best L, Blase JI, Bordoni D, Franzenburg J, Geisen U, Josephs-Spaulding J, Köhler P, Künstner A, Rosati E, Aschenbrenner AC, Bacher P, Baran N, Boysen T, Brandt B, Bruse N, Dörr J, Dräger A, Elke G, Ellinghaus D, Fischer J, Forster M, Franke A, Franzenburg S, Frey N, Friedrichs A, Fuß J, Glück A, Hamm J, Hinrichsen F, Hoeppner MP, Imm S, Junker R, Kaiser S, Kan YH, Knoll R, Lange C, Laue G, Lier C, Lindner M, Marinos G, Markewitz R, Nattermann J, Noth R, Pickkers P, Rabe KF, Renz A, HCA Lung Biological Network, Deutsche COVID-19 Omics Initiative (DeCOI), et al. 2020. Longitudinal

multi-omics analyses identify responses of megakaryocytes, erythroid cells, and plasmablasts as hallmarks of severe COVID-19. Immunity 53:1296–1314.e9. https://doi.org/10.1016/j.immuni.2020.11.017.
413. Ren X, Wen W, Fan X, Hou W, Su B, Cai P, Li J, Liu Y, Tang F, Zhang F, Yang Y, He J, Ma W, He J, Wang P, Cao Q, Chen F, Chen Y, Cheng X, Deng G, Deng X, Ding W, Feng Y, Gan R, Guo C, Guo W, He S, Jiang C, Liang J, Li YM, Lin J, Ling Y, Liu H, Liu J, Liu N, Liu SQ, Luo M, Ma Q, Song Q, Sun W, Wang G, Wang F, Wang Y, Wen X, Wu Q, Xu G, Xie X, Xiong X, Xing X, Xu H, et al. 2021. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. Cell 184:1895–1913.e19. https://doi.org/10.1016/j.cell.2021.01.053.
414. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, Liu M, Zhao X, Xie Y, Yang Y, Zhang S, Fan Z, Dong J, Yuan Z, Ding Z, Zhang Y, Hu L. 2020. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol 13:120. https://doi.org/10.1186/s13045-020-00954-7.
415. Cella M, Facchetti F, Lanzavecchia A, Colonna M. 2000. Plasmacytoid dendritic cells activated by influenza virus and CD40L drive a potent TH1 polarization. Nat Immunol 1:305–310. https://doi.org/10.1038/79747.
416. Fonteneau JF, Gilliet M, Larsson M, Dasilva I, Munz C, Liu YJ, Bhardwaj N. 2003. Activation of influenza virus-specific CD4+ and CD8+ T cells: a new role for plasmacytoid dendritic cells in adaptive immunity. Blood 101:3520–3526. https://doi.org/10.1182/blood-2002-10-3063.
417. Lui G, Manches O, Angel J, Molens JP, Chaperot L, Plumas J. 2009. Plasmacytoid dendritic cells capture and cross-present viral antigens from influenza-virus exposed cells. PLoS One 4:e7111. https://doi.org/10.1371/journal.pone.0007111.
418. Hemann EA, Sjaastad LE, Langlois RA, Legge KL. 2015. Plasmacytoid dendritic cells require direct infection to sustain the pulmonary influenza A virus-specific CD8 T cell response. J Virol 90:2830–2837. https://doi.org/10.1128/JVI.02546-15.
419. Severa M, Diotti RA, Etna MP, Rizzo F, Fiore S, Ricci D, Iannetta M, Sinigaglia A, Lodi A, Mancini N, Criscuolo E, Clementi M, Andreoni M, Balducci S, Barzon L, Stefanelli P, Clementi N, Coccia EM. 2021. Differential plasmacytoid dendritic cell phenotype and type I Interferon response in asymptomatic and severe COVID-19 infection. PLoS Pathog 17:e1009878. https://doi.org/10.1371/journal.ppat.1009878.
420. Onodi F, Bonnet-Madin L, Meertens L, Karpf L, Poirot J, Zhang SY, Picard C, Puel A, Jouanguy E, Zhang Q, Le Goff J, Molina JM, Delaugerre C, Casanova JL, Amara A, Soumelis V. 2021. SARS-CoV-2 induces human plasmacytoid predendritic cell diversification via UNC93B and IRAK4. J Exp Med 218:e20201387. https://doi.org/10.1084/jem.20201387.
421. Cervantes-Barragan L, Vanderheiden A, Royer CJ, Davis-Gardner ME, Ralfs P, Chirkova T, Anderson LJ, Grakoui A, Suthar MS. 2021. Plasmacytoid dendritic cells produce type I interferon and reduce viral replication in airway epithelial cells after SARS-CoV-2 infection. bioRxiv https://doi.org/10.1101/2021.05.12.443948.
422. Ramirez-Ortiz ZG, Lee CK, Wang JP, Boon L, Specht CA, Levitz SM. 2011. A nonredundant role for plasmacytoid dendritic cells in host defense against the human fungal pathogen Aspergillus fumigatus. Cell Host Microbe 9:415–424. https://doi.org/10.1016/j.chom.2011.04.007.
423. Ramirez-Ortiz ZG, Specht CA, Wang JP, Lee CK, Bartholomeu DC, Gazzinelli RT, Levitz SM. 2008. Toll-like receptor 9-dependent immune activation by unmethylated CpG motifs in Aspergillus fumigatus DNA. Infect Immun 76:2123–2129. https://doi.org/10.1128/IAI.00047-08.
424. Loures FV, Rohm M, Lee CK, Santos E, Wang JP, Specht CA, Calich VL, Urban CF, Levitz SM. 2015. Recognition of Aspergillus fumigatus hyphae by human plasmacytoid dendritic cells is mediated by dectin-2 and results in formation of extracellular traps. PLoS Pathog 11:e1004643. https://doi.org/10.1371/journal.ppat.1004643.
425. Guermonprez P, Valladeau J, Zitvogel L, Thery C, Amigorena S. 2002. Antigen presentation and T cell stimulation by dendritic cells. Annu Rev Immunol 20:621–667. https://doi.org/10.1146/annurev.immunol.20.100301.064828.
426. Horst D, Verweij MC, Davison AJ, Ressing ME, Wiertz EJ. 2011. Viral evasion of T cell immunity: ancient mechanisms offering new applications. Curr Opin Immunol 23:96–103. https://doi.org/10.1016/j.coi.2010.11.005.
427. Forsyth KS, Eisenlohr LC. 2016. Giving CD4+ T cells the slip: viral interference with MHC class II-restricted antigen processing and presentation. Curr Opin Immunol 40:123–129. https://doi.org/10.1016/j.coi.2016.03.003.
428. Lin J, Xia J, Tu CZ, Zhang KY, Zeng Y, Yang Q. 2017. H9N2 avian influenza virus protein PB1 enhances the immune responses of bone marrow-derived dendritic cells by down-regulating miR375. Front Microbiol 8:287. https://doi.org/10.3389/fmicb.2017.00287.
429. Sadaka C, Marloie-Provost MA, Soumelis V, Benaroch P. 2009. Developmental regulation of MHC II expression and transport in human plasmacytoid-derived dendritic cells. Blood 113:2127–2135. https://doi.org/10.1182/blood-2008-10-178152.
430. Smed-Sorensen A, Chalouni C, Chatterjee B, Cohn L, Blattmann P, Nakamura N, Delamarre L, Mellman I. 2012. Influenza A virus infection of human primary dendritic cells impairs their ability to cross-present antigen to CD8 T cells. PLoS Pathog 8:e1002572. https://doi.org/10.1371/journal.ppat.1002572.
431. Frleta D, Yu CI, Klechevsky E, Flamar AL, Zurawski G, Banchereau J, Palucka AK. 2009. Influenza virus and poly(I:C) inhibit MHC class I-restricted presentation of cell-associated antigens derived from infected dead cells captured by human dendritic cells. J Immunol 182:2766–2776. https://doi.org/10.4049/jimmunol.0801720.
432. Burster T, Giffon T, Dahl ME, Bjorck P, Bogyo M, Weber E, Mahmood K, Lewis DB, Mellins ED. 2007. Influenza A virus elevates active cathepsin B in primary murine DC. Int Immunol 19:645–655. https://doi.org/10.1093/intimm/dxm030.
433. Yang D, Chu H, Hou Y, Chai Y, Shuai H, Lee AC, Zhang X, Wang Y, Hu B, Huang X, Yuen TT, Cai JP, Zhou J, Yuan S, Zhang AJ, Chan JF, Yuen KY. 2020. Attenuated interferon and proinflammatory response in SARS-CoV-2-infected human dendritic cells is associated with viral antagonism of STAT1 phosphorylation. J Infect Dis 222:734–745. https://doi.org/10.1093/infdis/jiaa356.
434. Roquilly A, McWilliam HEG, Jacqueline C, Tian Z, Cinotti R, Rimbert M, Wakim L, Caminschi I, Lahoud MH, Belz GT, Kallies A, Mintern JD, Asehnoune K, Villadangos JA. 2017. Local modulation of antigen-presenting cell development after resolution of pneumonia induces long-term susceptibility to secondary infections. Immunity 47:135–147.e5. https://doi.org/10.1016/j.immuni.2017.06.021.
435. Didierlaurent A, Goulding J, Patel S, Snelgrove R, Low L, Bebien M, Lawrence T, van Rijt LS, Lambrecht BN, Sirard JC, Hussell T. 2008. Sustained desensitization to bacterial Toll-like receptor ligands after resolution of respiratory influenza infection. J Exp Med 205:323–329. https://doi.org/10.1084/jem.20070891.
436. Kuri T, Sorensen AS, Thomas S, Karlsson Hedestam GB, Normark S, Henriques-Normark B, McInerney GM, Plant L. 2013. Influenza A virus-mediated priming enhances cytokine secretion by human dendritic cells infected with Streptococcus pneumoniae. Cell Microbiol 15:1385–1400. https://doi.org/10.1111/cmi.12122.
437. Spelmink L, Sender V, Hentrich K, Kuri T, Plant L, Henriques-Normark B. 2016. Toll-like receptor 3/TRIF-dependent IL-12p70 secretion mediated by Streptococcus pneumoniae RNA and its priming by influenza A virus coinfection in human dendritic cells. mBio 7:e00168-16. https://doi.org/10.1128/mBio.00168-16.
438. Law HK, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, Nicholls JM, Peiris JS, Lau YL. 2005. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood 106:2366–2374. https://doi.org/10.1182/blood-2004-10-4166.
439. Zhou R, To KK, Wong YC, Liu L, Zhou B, Li X, Huang H, Mo Y, Luk TY, Lau TT, Yeung P, Chan WM, Wu AK, Lung KC, Tsang OT, Leung WS, Hung IF, Yuen KY, Chen Z. 2020. Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses. Immunity https://doi.org/10.1016/j.immuni.2020.07.026.
440. Sanchez-Cerrillo I, Landete P, Aldave B, Sanchez-Alonso S, Sanchez-Azofra A, Marcos-Jimenez A, Avalos E, Alcaraz-Serna A, de Los Santos I, Mateu-Albero T, Esparcia L, Lopez-Sanz C, Martinez-Fleta P, Gabrie L, Del Campo Guerola L, Calzada MJ, Gonzalez-Alvaro I, Alfranca A, Sanchez-Madrid F, Munoz-Calleja C, Soriano JB, Ancochea J, Martin-Gayo E. 2020. Differential redistribution of activated monocyte and dendritic cell subsets to the lung associates with severity of COVID-19. medRxiv https://doi.org/10.1101/2020.05.13.20100925.
441. Marongiu L, Protti G, Facchini FA, Valache M, Mingozzi F, Ranzani V, Putignano AR, Salviati L, Bevilacqua V, Curti S, Crosti M, Sarnicola ML, D'Angio M, Bettini LR, Biondi A, Nespoli L, Tamini N, Clementi N, Mancini N, Abrignani S, Spreafico R, Granucci F. 1 August 2021. Maturation signatures of conventional dendritic cell subtypes in COVID-19 suggest direct viral sensing. Eur J Immunol https://doi.org/10.1002/eji.202149298.
442. Richert LE, Rynda-Apple A, Harmsen AL, Han S, Wiley JA, Douglas T, Larson K, Morton RV, Harmsen AG. 2014. CD11c(+) cells primed with unrelated antigens facilitate an accelerated immune response to influenza virus in mice. Eur J Immunol 44:397–408. https://doi.org/10.1002/eji.201343587.
443. Lu Q, Liu J, Zhao S, Gomez Castro MF, Laurent-Rolle M, Dong J, Ran X, Damani-Yokota P, Tang H, Karakousi T, Son J, Kaczmarek ME, Zhang Z, Yeung ST, McCune BT, Chen RE, Tang F, Ren X, Chen X, Hsu JCC, Teplova M, Huang B, Deng H, Long Z, Mudianto T, Jin S, Lin P, Du J, Zang R, Su

TT, Herrera A, Zhou M, Yan R, Cui J, Zhu J, Zhou Q, Wang T, Ma J, Koralov SB, Zhang Z, Aifantis I, Segal LN, Diamond MS, Khanna KM, Stapleford KA, Cresswell P, Liu Y, Ding S, Xie Q, Wang J. 2021. SARS-CoV-2 exacerbates proinflammatory responses in myeloid cells through C-type lectin receptors and Tweety family member 2. Immunity 54:1304–1319.e9. https://doi.org/10.1016/j.immuni.2021.05.006.
444. Amraei R, Yin W, Napoleon MA, Suder EL, Berrigan J, Zhao Q, Olejnik J, Chandler KB, Xia C, Feldman J, Hauser BM, Caradonna TM, Schmidt AG, Gummuluru S, Muhlberger E, Chitalia V, Costello CE, Rahimi N. 2021. CD209L/L-SIGN and CD209/DC-SIGN act as receptors for SARS-CoV-2. ACS Cent Sci 7:1156–1165. https://doi.org/10.1021/acscentsci.0c01537.
445. Serrano-Gomez D, Leal JA, Corbi AL. 2005. DC-SIGN mediates the binding of Aspergillus fumigatus and keratinophylic fungi by human dendritic cells. Immunobiology 210:175–183. https://doi.org/10.1016/j.imbio.2005.05.011.
446. Serrano-Gomez D, Dominguez-Soto A, Ancochea J, Jimenez-Heffernan JA, Leal JA, Corbi AL. 2004. Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin mediates binding and internalization of Aspergillus fumigatus conidia by dendritic cells and macrophages. J Immunol 173:5635–5643. https://doi.org/10.4049/jimmunol.173.9.5635.
447. Sainz J, Lupianez CB, Segura-Catena J, Vazquez L, Rios R, Oyonarte S, Hemminki K, Forsti A, Jurado M. 2012. Dectin-1 and DC-SIGN polymorphisms associated with invasive pulmonary Aspergillosis infection. PLoS One 7:e32273. https://doi.org/10.1371/journal.pone.0032273.
448. Netea MG, Dominguez-Andres J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, Joosten LAB, van der Meer JWM, Mhlanga MM, Mulder WJM, Riksen NP, Schlitzer A, Schultze JL, Stabell Benn C, Sun JC, Xavier RJ, Latz E. 2020. Defining trained immunity and its role in health and disease. Nat Rev Immunol 20:375–388. https://doi.org/10.1038/s41577-020-0285-6.
449. Mitroulis I, Ruppova K, Wang B, Chen LS, Grzybek M, Grinenko T, Eugster A, Troullinaki M, Palladini A, Kourtzelis I, Chatzigeorgiou A, Schlitzer A, Beyer M, Joosten LAB, Isermann B, Lesche M, Petzold A, Simons K, Henry I, Dahl A, Schultze JL, Wielockx B, Zamboni N, Mirtschink P, Coskun U, Hajishengallis G, Netea MG, Chavakis T. 2018. Modulation of myelopoiesis progenitors is an integral component of trained immunity. Cell 172:147–161.e12. https://doi.org/10.1016/j.cell.2017.11.034.
450. Kaufmann E, Sanz J, Dunn JL, Khan N, Mendonca LE, Pacis A, Tzelepis F, Pernet E, Dumaine A, Grenier JC, Mailhot-Leonard F, Ahmed E, Belle J, Besla R, Mazer B, King IL, Nijnik A, Robbins CS, Barreiro LB, Divangahi M. 2018. BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 172:176–190.e19. https://doi.org/10.1016/j.cell.2017.12.031.
451. Chavakis T, Mitroulis I, Hajishengallis G. 2019. Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation. Nat Immunol 20:802–811. https://doi.org/10.1038/s41590-019-0402-5.
452. Novakovic B, Habibi E, Wang SY, Arts RJW, Davar R, Megchelenbrink W, Kim B, Kuznetsova T, Kox M, Zwaag J, Matarese F, van Heeringen SJ, Janssen-Megens EM, Sharifi N, Wang C, Keramati F, Schoonenberg V, Flicek P, Clarke L, Pickkers P, Heath S, Gut I, Netea MG, Martens JHA, Logie C, Stunnenberg HG. 2016. beta-Glucan reverses the epigenetic state of LPS-induced immunological tolerance. Cell 167:1354–1368.e14. https://doi.org/10.1016/j.cell.2016.09.034.
453. Yao Y, Jeyanathan M, Haddadi S, Barra NG, Vaseghi-Shanjani M, Damjanovic D, Lai R, Afkhami S, Chen Y, Dvorkin-Gheva A, Robbins CS, Schertzer JD, Xing Z. 2018. Induction of autonomous memory alveolar macrophages requires T cell help and is critical to trained immunity. Cell 175:1634–1650.e17. https://doi.org/10.1016/j.cell.2018.09.042.
454. Eastman AJ, Xu J, Bermik J, Potchen N, den Dekker A, Neal LM, Zhao G, Malachowski A, Schaller M, Kunkel S, Osterholzer JJ, Kryczek I, Olszewski MA. 2019. Epigenetic stabilization of DC and DC precursor classical activation by TNFalpha contributes to protective T cell polarization. Sci Adv 5:eaaw9051. https://doi.org/10.1126/sciadv.aaw9051.
455. Downes JE, Marshall-Clarke S. 2010. Innate immune stimuli modulate bone marrow-derived dendritic cell production in vitro by toll-like receptor-dependent and -independent mechanisms. Immunology 131:513–524. https://doi.org/10.1111/j.1365-2567.2010.03324.x.
456. Beshara R, Sencio V, Soulard D, Barthelemy A, Fontaine J, Pinteau T, Deruyter L, Ismail MB, Paget C, Sirard JC, Trottein F, Faveeuw C. 2018. Alteration of Flt3-ligand-dependent de novo generation of conventional dendritic cells during influenza infection contributes to respiratory bacterial superinfection. PLoS Pathog 14:e1007360. https://doi.org/10.1371/journal.ppat.1007360.
457. Rezinciuc S, Bezavada L, Bahadoran A, Duan S, Wang R, Lopez-Ferrer D, Zink EE, Finklestein D, Green DR, Pasa-Tolic L, Thomas PG, Smallwood HS. 2020. Dynamic metabolic reprogramming in dendritic cells: an early response to influenza infection that is essential for effector function. BioRxiv https://doi.org/10.1101/2020.01.14.906826.
458. GeurtsvanKessel CH, Willart MA, van Rijt LS, Muskens F, Kool M, Baas C, Thielemans K, Bennett C, Clausen BE, Hoogsteden HC, Osterhaus AD, Rimmelzwaan GF, Lambrecht BN. 2008. Clearance of influenza virus from the lung depends on migratory langerin^{+}CD11b^{-} but not plasmacytoid dendritic cells. J Exp Med 205:1621–1634. https://doi.org/10.1084/jem.20071365.
459. Waithman J, Zanker D, Xiao K, Oveissi S, Wylie B, Ng R, Togel L, Chen W. 2013. Resident CD8(+) and migratory CD103(+) dendritic cells control CD8 T cell immunity during acute influenza infection. PLoS One 8:e66136. https://doi.org/10.1371/journal.pone.0066136.
460. Ho AW, Prabhu N, Betts RJ, Ge MQ, Dai X, Hutchinson PE, Lew FC, Wong KL, Hanson BJ, Macary PA, Kemeny DM. 2011. Lung CD103+ dendritic cells efficiently transport influenza virus to the lymph node and load viral antigen onto MHC class I for presentation to CD8 T cells. J Immunol 187:6011–6021. https://doi.org/10.4049/jimmunol.1100987.
461. Kim TS, Braciale TJ. 2009. Respiratory dendritic cell subsets differ in their capacity to support the induction of virus-specific cytotoxic CD8+ T cell responses. PLoS One 4:e4204. https://doi.org/10.1371/journal.pone.0004204.
462. Ng SL, Teo YJ, Setiagani YA, Karjalainen K, Ruedl C. 2018. Type 1 conventional CD103(+) dendritic cells control effector CD8(+) T cell migration, survival, and memory responses during influenza infection. Front Immunol 9:3043. https://doi.org/10.3389/fimmu.2018.03043.
463. Cook PC, MacDonald AS. 2016. Dendritic cells in lung immunopathology. Semin Immunopathol 38:449–460. https://doi.org/10.1007/s00281-016-0571-3.
464. Kudva A, Scheller EV, Robinson KM, Crowe CR, Choi SM, Slight SR, Khader SA, Dubin PJ, Enelow RI, Kolls JK, Alcorn JF. 2011. Influenza A inhibits Th17-mediated host defense against bacterial pneumonia in mice. J Immunol 186:1666–1674. https://doi.org/10.4049/jimmunol.1002194.
465. Robinson KM, McHugh KJ, Mandalapu S, Clay ME, Lee B, Scheller EV, Enelow RI, Chan YR, Kolls JK, Alcorn JF. 2014. Influenza A virus exacerbates Staphylococcus aureus pneumonia in mice by attenuating antimicrobial peptide production. J Infect Dis 209:865–875. https://doi.org/10.1093/infdis/jit527.
466. Robinson KM, Lee B, Scheller EV, Mandalapu S, Enelow RI, Kolls JK, Alcorn JF. 2015. The role of IL-27 in susceptibility to post-influenza Staphylococcus aureus pneumonia. Respir Res 16:10. https://doi.org/10.1186/s12931-015-0168-8.
467. Lee B, Gopal R, Manni ML, McHugh KJ, Mandalapu S, Robinson KM, Alcorn JF. 2017. STAT1 is required for suppression of type 17 immunity during influenza and bacterial superinfection. Immunohorizons 1:81–91. https://doi.org/10.4049/immunohorizons.1700030.
468. Piersma SJ, van der Hulst JM, Kwappenberg KM, Goedemans R, van der Minne CE, van der Burg SH. 2010. Influenza matrix 1-specific human CD4+ FOXP3+ and FOXP3(-) regulatory T cells can be detected long after viral clearance. Eur J Immunol 40:3064–3074. https://doi.org/10.1002/eji.200940177.
469. Ballesteros-Tato A, Leon B, Lund FE, Randall TD. 2013. CD4+ T helper cells use CD154-CD40 interactions to counteract T reg cell-mediated suppression of CD8+ T cell responses to influenza. J Exp Med 210:1591–1601. https://doi.org/10.1084/jem.20130097.
470. Betts RJ, Prabhu N, Ho AW, Lew FC, Hutchinson PE, Rotzschke O, Macary PA, Kemeny DM. 2012. Influenza A virus infection results in a robust, antigen-responsive, and widely disseminated Foxp3+ regulatory T cell response. J Virol 86:2817–2825. https://doi.org/10.1128/JVI.05685-11.
471. Bedoya F, Cheng GS, Leibow A, Zakhary N, Weissler K, Garcia V, Aitken M, Kropf E, Garlick DS, Wherry EJ, Erikson J, Caton AJ. 2013. Viral antigen induces differentiation of Foxp3+ natural regulatory T cells in influenza virus-infected mice. J Immunol 190:6115–6125. https://doi.org/10.4049/jimmunol.1203302.
472. Moser EK, Hufford MM, Braciale TJ. 2014. Late engagement of CD86 after influenza virus clearance promotes recovery in a FoxP3+ regulatory T cell dependent manner. PLoS Pathog 10:e1004315. https://doi.org/10.1371/journal.ppat.1004315.
473. Bacher P, Heinrich F, Stervbo U, Nienen M, Vahldieck M, Iwert C, Vogt K, Kollet J, Babel N, Sawitzki B, Schwarz C, Bereswill S, Heimesaat MM, Heine G, Gadermaier G, Asam C, Assenmacher M, Kniemeyer O, Brakhage AA, Ferreira F, Wallner M, Worm M, Scheffold A. 2016. Regulatory T cell specificity directs tolerance versus allergy against aeroantigens in humans. Cell 167:1067–1078.e16. https://doi.org/10.1016/j.cell.2016.09.050.

474. Bacher P, Kniemeyer O, Schonbrunn A, Sawitzki B, Assenmacher M, Rietschel E, Steinbach A, Cornely OA, Brakhage AA, Thiel A, Scheffold A. 2014. Antigen-specific expansion of human regulatory T cells as a major tolerance mechanism against mucosal fungi. Mucosal Immunol 7:916–928. https://doi.org/10.1038/mi.2013.107.
475. Montagnoli C, Fallarino F, Gaziano R, Bozza S, Bellocchio S, Zelante T, Kurup WP, Pitzurra L, Puccetti P, Romani L. 2006. Immunity and tolerance to Aspergillus involve functionally distinct regulatory T cells and tryptophan catabolism. J Immunol 176:1712–1723. https://doi.org/10.4049/jimmunol.176.3.1712.
476. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, Moreira A, Park MD, Pia L, Risson E, Saffern M, Salomé B, Esai Selvan M, Spindler MP, Tan J, van der Heide V, Gregory JK, Alexandropoulos K, Bhardwaj N, Brown BD, Greenbaum B, Gümüş ZH, Homann D, Horowitz A, Kamphorst AO, Curotto de Lafaille MA, Mehandru S, Merad M, Samstein RM, Sinai Immunology Review Project. 2020. Immunology of COVID-19: current state of the science. Immunity 52:910–941. https://doi.org/10.1016/j.immuni.2020.05.002.
477. Krammer F. 2019. The human antibody response to influenza A virus infection and vaccination. Nat Rev Immunol 19:383–397. https://doi.org/10.1038/s41577-019-0143-6.
478. Lindell DM, Moore TA, McDonald RA, Toews GB, Huffnagle GB. 2005. Generation of antifungal effector CD8+ T cells in the absence of CD4+ T cells during Cryptococcus neoformans infection. J Immunol 174:7920–7928. https://doi.org/10.4049/jimmunol.174.12.7920.
479. McAllister F, Mc Allister F, Steele C, Zheng M, Young E, Shellito JE, Marrero L, Kolls JK. 2004. T cytotoxic-1 CD8+ T cells are effector cells against pneumocystis in mice. J Immunol 172:1132–1138. https://doi.org/10.4049/jimmunol.172.2.1132.
480. Carvalho A, De Luca A, Bozza S, Cunha C, D'Angelo C, Moretti S, Perruccio K, Iannitti RG, Fallarino F, Pierini A, Latge JP, Velardi A, Aversa F, Romani L. 2012. TLR3 essentially promotes protective class I-restricted memory CD8(+) T-cell responses to Aspergillus fumigatus in hematopoietic transplanted patients. Blood 119:967–977. https://doi.org/10.1182/blood-2011-06-362582.
481. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. 2003. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384. https://doi.org/10.1097/01.md.0000100046.06009.b0.
482. Matheson DS, Green BJ. 1987. Defect in production of B cell differentiation factor-like activity by mononuclear cells from a boy with hypogammaglobulinemia. J Immunol 138:2469–2472.
483. Verma A, Wuthrich M, Deepe G, Klein B. 2014. Adaptive immunity to fungi. Cold Spring Harb Perspect Med 5:a019612. https://doi.org/10.1101/cshperspect.a019612.
484. Fitzpatrick Z, Frazer G, Ferro A, Clare S, Bouladoux N, Ferdinand J, Tuong ZK, Negro-Demontel ML, Kumar N, Suchanek O, Tajsic T, Harcourt K, Scott K, Bashford-Rogers R, Helmy A, Reich DS, Belkaid Y, Lawley TD, McGavern DB, Clatworthy MR. 2020. Gut-educated IgA plasma cells defend the meningeal venous sinuses. Nature 587:472–476. https://doi.org/10.1038/s41586-020-2886-4.
485. Millet N, Solis NV, Swidergall M. 2020. Mucosal IgA prevents commensal Candida albicans dysbiosis in the oral cavity. Front Immunol 11:555363. https://doi.org/10.3389/fimmu.2020.555363.
486. Youssef EG, Zhang L, Alkhazraji S, Gebremariam T, Singh S, Yount NY, Yeaman MR, Uppuluri P, Ibrahim AS. 2020. Monoclonal IgM antibodies targeting Candida albicans Hyr1 provide cross-kingdom protection against gram-negative bacteria. Front Immunol 11:76. https://doi.org/10.3389/fimmu.2020.00076.
487. Wiley JA, Harmsen AG. 2008. Pneumocystis infection enhances antibody-mediated resistance to a subsequent influenza infection. J Immunol 180:5613–5624. https://doi.org/10.4049/jimmunol.180.8.5613.
488. Agrawal B. 2019. Heterologous immunity: role in natural and vaccine-induced resistance to infections. Front Immunol 10:2631. https://doi.org/10.3389/fimmu.2019.02631.
489. Yip MS, Leung NH, Cheung CY, Li PH, Lee HH, Daeron M, Peiris JS, Bruzzone R, Jaume M. 2014. Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus. Virol J 11:82. https://doi.org/10.1186/1743-422X-11-82.
490. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, Tang H, Nishiura K, Peng J, Tan Z, Wu T, Cheung KW, Chan KH, Alvarez X, Qin C, Lackner A, Perlman S, Yuen KY, Chen Z. 2019. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight 4:e123158. https://doi.org/10.1172/jci.insight.123158.
491. Andrews SF, Huang Y, Kaur K, Popova LI, Ho IY, Pauli NT, Henry Dunand CJ, Taylor WM, Lim S, Huang M, Qu X, Lee JH, Salgado-Ferrer M, Krammer F, Palese P, Wrammert J, Ahmed R, Wilson PC. 2015. Immune history profoundly affects broadly protective B cell responses to influenza. Sci Transl Med 7:316ra192. https://doi.org/10.1126/scitranslmed.aad0522.
492. Li Y, Myers JL, Bostick DL, Sullivan CB, Madara J, Linderman SL, Liu Q, Carter DM, Wrammert J, Esposito S, Principi N, Plotkin JB, Ross TM, Ahmed R, Wilson PC, Hensley SE. 2013. Immune history shapes specificity of pandemic H1N1 influenza antibody responses. J Exp Med 210:1493–1500. https://doi.org/10.1084/jem.20130212.
493. Henry C, Palm AE, Krammer F, Wilson PC. 2018. From original antigenic sin to the universal influenza virus vaccine. Trends Immunol 39:70–79. https://doi.org/10.1016/j.it.2017.08.003.
494. Monto AS, Malosh RE, Petrie JG, Martin ET. 2017. The doctrine of original antigenic sin: separating good from evil. J Infect Dis 215:1782–1788. https://doi.org/10.1093/infdis/jix173.
495. Tang J, Templeton TJ, Cao J, Culleton R. 2019. The consequences of mixed-species malaria parasite co-infections in mice and mosquitoes for disease severity, parasite fitness, and transmission success. Front Immunol 10:3072. https://doi.org/10.3389/fimmu.2019.03072.
496. Williams AE, Edwards L, Humphreys IR, Snelgrove R, Rae A, Rappuoli R, Hussell T. 2004. Innate imprinting by the modified heat-labile toxin of Escherichia coli (LTK63) provides generic protection against lung infectious disease. J Immunol 173:7435–7443. https://doi.org/10.4049/jimmunol.173.12.7435.
497. Shao TY, Ang WXG, Jiang TT, Huang FS, Andersen H, Kinder JM, Pham G, Burg AR, Ruff B, Gonzalez T, Khurana Hershey GK, Haslam DB, Way SS. 2019. Commensal Candida albicans positively calibrates systemic Th17 immunological responses. Cell Host Microbe 25:404–417.e6. https://doi.org/10.1016/j.chom.2019.02.004.
498. Kudo E, Song E, Yockey LJ, Rakib T, Wong PW, Homer RJ, Iwasaki A. 2019. Low ambient humidity impairs barrier function and innate resistance against influenza infection. Proc Natl Acad Sci U S A 116:10905–10910. https://doi.org/10.1073/pnas.1902840116.
499. Moriyama M, Hugentobler WJ, Iwasaki A. 2020. Seasonality of respiratory viral infections. Annu Rev Virol 7:83–101. https://doi.org/10.1146/annurev-virology-012420-022445.
500. Sooryanarain H, Elankumaran S. 2015. Environmental role in influenza virus outbreaks. Annu Rev Anim Biosci 3:347–373. https://doi.org/10.1146/annurev-animal-022114-111017.
501. Ma Y, Pei S, Shaman J, Dubrow R, Chen K. 2021. Role of meteorological factors in the transmission of SARS-CoV-2 in the United States. Nat Commun 12:3602. https://doi.org/10.1038/s41467-021-23866-7.
502. Alshareef F, Robson GD. 2014. Prevalence, persistence, and phenotypic variation of Aspergillus fumigatus in the outdoor environment in Manchester, UK, over a 2-year period. Med Mycol 52:367–375. https://doi.org/10.1093/mmy/myu008.
503. Oliveira M, Ribeiro H, Delgado JL, Abreu I. 2009. The effects of meteorological factors on airborne fungal spore concentration in two areas differing in urbanisation level. Int J Biometeorol 53:61–73. https://doi.org/10.1007/s00484-008-0191-2.
504. Li DW, Kendrick B. 1995. A year-round study on functional relationships of airborne fungi with meteorological factors. Int J Biometeorol 39:74–80. https://doi.org/10.1007/BF01212584.
505. Grinn-Gofron A. 2011. Airborne Aspergillus and Penicillium in the atmosphere of Szczecin, (Poland) (2004–2009). Aerobiologia (Bologna) 27:67–76. https://doi.org/10.1007/s10453-010-9177-8.
506. Goncalves FL, Bauer H, Cardoso MR, Pukinskas S, Matos D, Melhem M, Puxbaum H. 2010. Indoor and outdoor atmospheric fungal spores in the Sao Paulo metropolitan area (Brazil): species and numeric concentrations. Int J Biometeorol 54:347–355. https://doi.org/10.1007/s00484-009-0284-6.
507. Beaumont F, Kauffman HF, van der Mark TH, Sluiter HJ, de Vries K. 1985. Volumetric aerobiological survey of conidial fungi in the North-East Netherlands. I. Seasonal patterns and the influence of metereological variables. Allergy 40:173–180. https://doi.org/10.1111/j.1398-9995.1985.tb00213.x.
508. Priyamvada H, Singh RK, Akila M, Ravikrishna R, Verma RS, Gunthe SS. 2017. Seasonal variation of the dominant allergenic fungal aerosols—one year study from southern Indian region. Sci Rep 7:11171. https://doi.org/10.1038/s41598-017-11727-7.
509. Shelton BG, Kirkland KH, Flanders WD, Morris GK. 2002. Profiles of airborne fungi in buildings and outdoor environments in the United States. Appl Environ Microbiol 68:1743–1753. https://doi.org/10.1128/AEM.68.4.1743-1753.2002.

510. Larsen LS. 1981. A three-year-survey of microfungi in the air of Copenhagen 1977–79. Allergy 36:15–22. https://doi.org/10.1111/j.1398-9995.1981.tb01819.x.
511. Gounder AP, Boon ACM. 2019. Influenza pathogenesis: the effect of host factors on severity of disease. J Immunol 202:341–350. https://doi.org/10.4049/jimmunol.1801010.
512. Daniloski Z, Jordan TX, Wessels HH, Hoagland DA, Kasela S, Legut M, Maniatis S, Mimitou EP, Lu L, Geller E, Danziger O, Rosenberg BR, Phatnani H, Smibert P, Lappalainen T, tenOever BR, Sanjana NE. 2021. Identification of required host factors for SARS-CoV-2 infection in human cells. Cell 184:92–105.e16. https://doi.org/10.1016/j.cell.2020.10.030.
513. Schneider WM, Luna JM, Hoffmann HH, Sanchez-Rivera FJ, Leal AA, Ashbrook AW, Le Pen J, Ricardo-Lax I, Michailidis E, Peace A, Stenzel AF, Lowe SW, MacDonald MR, Rice CM, Poirier JT. 2021. Genome-scale identification of SARS-CoV-2 and pan-coronavirus host factor networks. Cell 184:120–132.e14. https://doi.org/10.1016/j.cell.2020.12.006.
514. Wang R, Simoneau CR, Kulsuptrakul J, Bouhaddou M, Travisano KA, Hayashi JM, Carlson-Stevermer J, Zengel JR, Richards CM, Fozouni P, Oki J, Rodriguez L, Joehnk B, Walcott K, Holden K, Sil A, Carette JE, Krogan NJ, Ott M, Puschnik AS. 2021. Genetic screens identify host factors for SARS-CoV-2 and common cold coronaviruses. Cell 184:106–119.e14. https://doi.org/10.1016/j.cell.2020.12.004.
515. Wei J, Alfajaro MM, DeWeirdt PC, Hanna RE, Lu-Culligan WJ, Cai WL, Strine MS, Zhang SM, Graziano VR, Schmitz CO, Chen JS, Mankowski MC, Filler RB, Ravindra NG, Gasque V, de Miguel FJ, Patil A, Chen H, Oguntuyo KY, Abriola L, Surovtseva YV, Orchard RC, Lee B, Lindenbach BD, Politi K, van Dijk D, Kadoch C, Simon MD, Yan Q, Doench JG, Wilen CB. 2021. Genome-wide CRISPR screens reveal host factors critical for SARS-CoV-2 infection. Cell 184:76–91.e13. https://doi.org/10.1016/j.cell.2020.10.028.
516. Asano T, Boisson B, Onodi F, Matuozzo D, Moncada-Velez M, Maglorius Renkilaraj MRL, Zhang P, Meertens L, Bolze A, Materna M, Korniotis S, Gervais A, Talouarn E, Bigio B, Seeleuthner Y, Bilguvar K, Zhang Y, Neehus AL, Ogishi M, Pelham SJ, Le Voyer T, Rosain J, Philippot Q, Soler-Palacin P, Colobran R, Martin-Nalda A, Riviere JG, Tandjaoui-Lambiotte Y, Chaibi K, Shahrooei M, Darazam IA, Olyaei NA, Mansouri D, Hatipoglu N, Palabiyik F, Ozcelik T, Novelli G, Novelli A, Casari G, Aiuti A, Carrera P, Bondesan S, Barzaghi F, Rovere-Querini P, Tresoldi C, Franco JL, Rojas J, Reyes LF, Bustos IG, Arias AA, et al. 2021. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. Sci Immunol 6:eabl4348. https://doi.org/10.1126/sciimmunol.abl4348.
517. Martin-Sancho L, Lewinski MK, Pache L, Stoneham CA, Yin X, Becker ME, Pratt D, Churas C, Rosenthal SB, Liu S, Weston S, De Jesus PD, O'Neill AM, Gounder AP, Nguyen C, Pu Y, Curry HM, Oom AL, Miorin L, Rodriguez-Frandsen A, Zheng F, Wu C, Xiong Y, Urbanowski M, Shaw ML, Chang MW, Benner C, Hope TJ, Frieman MB, Garcia-Sastre A, Ideker T, Hultquist JF, Guatelli J, Chanda SK. 2021. Functional landscape of SARS-CoV-2 cellular restriction. Mol Cell 81:2656–2668.e8. https://doi.org/10.1016/j.molcel.2021.04.008.
518. Merkhofer RM, Klein BS. 2020. Advances in understanding human genetic variations that influence innate immunity to fungi. Front Cell Infect Microbiol 10:69. https://doi.org/10.3389/fcimb.2020.00069.
519. Cunha C, Aversa F, Romani L, Carvalho A. 2013. Human genetic susceptibility to invasive aspergillosis. PLoS Pathog 9:e1003434. https://doi.org/10.1371/journal.ppat.1003434.
520. Maskarinec SA, Johnson MD, Perfect JR. 2016. Genetic susceptibility to fungal infections: what is in the genes? Curr Clin Microbiol Rep 3:81–91. https://doi.org/10.1007/s40588-016-0037-3.
521. Smith AM, Adler FR, Ribeiro RM, Gutenkunst RN, McAuley JL, McCullers JA, Perelson AS. 2013. Kinetics of coinfection with influenza A virus and Streptococcus pneumoniae. PLoS Pathog 9:e1003238. https://doi.org/10.1371/journal.ppat.1003238.
522. Conenello GM, Zamarin D, Perrone LA, Tumpey T, Palese P. 2007. A single mutation in the PB1-F2 of H5N1 (HK/97) and 1918 influenza A viruses contributes to increased virulence. PLoS Pathog 3:1414–1421. https://doi.org/10.1371/journal.ppat.0030141.
523. Conenello GM, Tisoncik JR, Rosenzweig E, Varga ZT, Palese P, Katze MG. 2011. A single N66S mutation in the PB1-F2 protein of influenza A virus increases virulence by inhibiting the early interferon response in vivo. J Virol 85:652–662. https://doi.org/10.1128/JVI.01987-10.
524. Perrone LA, Plowden JK, Garcia-Sastre A, Katz JM, Tumpey TM. 2008. H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice. PLoS Pathog 4:e1000115. https://doi.org/10.1371/journal.ppat.1000115.
525. Abdool Karim SS, de Oliveira T. 2021. New SARS-CoV-2 variants—clinical, public health, and vaccine implications. N Engl J Med 384:1866–1868. https://doi.org/10.1056/NEJMc2100362.
526. Burki T. 2021. Understanding variants of SARS-CoV-2. Lancet 397:462. https://doi.org/10.1016/S0140-6736(21)00298-1.
527. Mallapaty S. 2021. India's massive COVID surge puzzles scientists. Nature https://doi.org/10.1038/d41586-021-01059-y.
528. Stone N, Gupta N, Schwartz I. 2021. Mucormycosis: time to address this deadly fungal infection. Lancet Microbe 2:E343–E344. https://doi.org/10.1016/S2666-5247(21)00148-8.
529. Arakeri G, Rao V, Amaral Mendes R, Oeppen RS, Brennanf PA. 16 September 2021. COVID-associated mucormycosis (CAM): is the Delta variant a cause? Br J Oral Maxillofac Surg https://doi.org/10.1016/j.bjoms.2021.08.009.
530. Dewi IMW, Cunha C, Jaeger M, Gresnigt MS, Gkountzinopoulou ME, Garishah FM, Duarte-Oliveira C, Campos CF, Vanderbeke L, Sharpe AR, Bruggemann RJ, Verweij PE, Lagrou K, Vande Velde G, de Mast Q, Joosten LAB, Netea MG, van der Ven A, Wauters J, Carvalho A, van de Veerdonk FL. 2021. Neuraminidase and SIGLEC15 modulate the host defense against pulmonary aspergillosis. Cell Rep Med 2:100289. https://doi.org/10.1016/j.xcrm.2021.100289.
531. Recovery Collective Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. 2020. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 384:693–704. https://doi.org/10.1056/NEJMoa2021436.
532. Kyrmizi I, Gresnigt MS, Akoumianaki T, Samonis G, Sidiropoulos P, Boumpas D, Netea MG, van de Veerdonk FL, Kontoyiannis DP, Chamilos G. 2013. Corticosteroids block autophagy protein recruitment in Aspergillus fumigatus phagosomes via targeting dectin-1/Syk kinase signaling. J Immunol 191:1287–1299. https://doi.org/10.4049/jimmunol.1300132.
533. Fraczek MG, Chishimba L, Niven RM, Bromley M, Simpson A, Smyth L, Denning DW, Bowyer P. 2018. Corticosteroid treatment is associated with increased filamentous fungal burden in allergic fungal disease. J Allergy Clin Immunol 142:407–414. https://doi.org/10.1016/j.jaci.2017.09.039.
534. Lionakis MS, Kontoyiannis DP. 2003. Glucocorticoids and invasive fungal infections. Lancet 362:1828–1838. https://doi.org/10.1016/S0140-6736(03)14904-5.
535. Delliere S, Dudoignon E, Fodil S, Voicu S, Collet M, Oillic PA, Salmona M, Depret F, Ghelfenstein-Ferreira T, Plaud B, Chousterman B, Bretagne S, Azoulay E, Mebazaa A, Megarbane B, Alanio A. 2020. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect 27:790.e1–790.e5. https://doi.org/10.1016/j.cmi.2020.12.005.
536. Wang J, Yang Q, Zhang P, Sheng J, Zhou J, Qu T. 2020. Clinical characteristics of invasive pulmonary aspergillosis in patients with COVID-19 in Zhejiang, China: a retrospective case series. Crit Care 24:299. https://doi.org/10.1186/s13054-020-03046-7.
537. Chauvet P, Mallat J, Arumadura C, Vangrunderbeek N, Dupre C, Pauquet P, Orfi A, Granier M, Lemyze M. 2020. Risk factors for invasive pulmonary aspergillosis in critically ill patients with coronavirus disease 2019-induced acute respiratory distress syndrome. Crit Care Explor 2:e0244. https://doi.org/10.1097/CCE.0000000000000244.
538. Apostolopoulou A, Esquer Garrigos Z, Vijayvargiya P, Lerner AH, Farmakiotis D. 2020. Invasive pulmonary aspergillosis in patients with SARS-CoV-2 infection: a systematic review of the literature. Diagnostics (Basel) 10:807. https://doi.org/10.3390/diagnostics10100807.
539. Ezeokoli OT, Gcilitshana O, Pohl CH. 2021. Risk factors for fungal co-infections in critically ill COVID-19 patients, with a focus on immunosuppressants. J Fungi (Basel) 7:545. https://doi.org/10.3390/jof7070545.
540. Lewis RE, Kontoyiannis DP. 2009. Invasive aspergillosis in glucocorticoid-treated patients. Med Mycol 47(Suppl 1):S271–S281. https://doi.org/10.1080/13693780802227159.
541. Ho KS, Narasimhan B, Difabrizio L, Rogers L, Bose S, Li L, Chen R, Sheehan J, El-Halabi MA, Sarosky K, Wang Z, Eisenberg E, Powell C, Steiger D. 2021. Impact of corticosteroids in hospitalised COVID-19 patients. BMJ Open Respir Res 8:e000766. https://doi.org/10.1136/bmjresp-2020-000766.
542. Meira F, Moreno-Garcia E, Linares L, Macaya I, Tome A, Hernandez-Meneses M, Albiach L, Morata L, Letona L, Bodro M, Cozar-Llisto A, Cardozo C, Chumbita M, Pitart C, Ambrosioni J, Rico V, Aguero D,

Puerta-Alcalde P, Garcia-Pouton N, Marco F, Garcia-Vidal C, Soriano A, Martinez JA. 2021. Impact of inflammatory response modifiers on the incidence of hospital-acquired infections in patients with COVID-19. Infect Dis Ther 10:1407–1418. https://doi.org/10.1007/s40121-021-00477-9.

543. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettila V, Rademaker E, Santos MS, Saunders CT, Seymour CW, et al. 2021. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 384:1491–1502. https://doi.org/10.1056/NEJMoa2100433.
544. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, Abbott A, Abdallah N, Abdelaziz A, Abdelfattah M, Abdelqader B, Abdul B, Abdul Rasheed A, Abdulakeem A, Abdul-Kadir R, Abdulmumeen A, Abdul-Raheem R, Abdulshukkoor N, Abdusamad K, Abed El Khaleq Y, Abedalla M, Abeer Ul Amna A, Abernethy K, Aboaba A, Abo-Leyah H, Abou-Haggar A, Abouibrahim M, Abraham M, Abraham T, Abraheem A, Abrams J, Abu H-J, Abu-Arafeh A, Abubacker SM, Abung A, Aceampong Y, Achara A, Acharya D, Acheampong S, Acheson J, Acosta A, Acton C, Adabie-Ankrah J, Adam F, Adam M, Adamali H, Adams C, Adams C, Adams K, Adams R, et al. 2021. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 397:1637–1645. https://doi.org/10.1016/S0140-6736(21)00676-0.
545. Deana C, Vetrugno L, Bassi F, De Monte A. 2021. Tocilizumab administration in COVID-19 patients: water on the fire or gasoline? Med Mycol Case Rep 31:32–34. https://doi.org/10.1016/j.mmcr.2021.01.002.
546. Witting C, Quaggin-Smith J, Mylvaganam R, Peigh G, Angarone M, Flaherty JD. 2021. Invasive pulmonary aspergillosis after treatment with tocilizumab in a patient with COVID-19 ARDS: a case report. Diagn Microbiol Infect Dis 99:115272. https://doi.org/10.1016/j.diagmicrobio.2020.115272.
547. Cenci E, Mencacci A, Casagrande A, Mosci P, Bistoni F, Romani L. 2001. Impaired antifungal effector activity but not inflammatory cell recruitment in interleukin-6-deficient mice with invasive pulmonary aspergillosis. J Infect Dis 184:610–617. https://doi.org/10.1086/322793.
548. Pawar A, Desai RJ, Solomon DH, Santiago Ortiz AJ, Gale S, Bao M, Sarsour K, Schneeweiss S, Kim SC. 2019. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. Ann Rheum Dis 78:456–464. https://doi.org/10.1136/annrheumdis-2018-214367.
549. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, Husain AN, Mutlu EA, Mutlu GM. 2020. IL-6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. Front Med (Lausanne) 7:583897. https://doi.org/10.3389/fmed.2020.583897.
550. Weinberger DM, Simonsen L, Jordan R, Steiner C, Miller M, Viboud C. 2012. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis 205:458–465. https://doi.org/10.1093/infdis/jir749.
551. Powers-Fletcher MV, Hanson KE. 2016. Molecular diagnostic testing for Aspergillus. J Clin Microbiol 54:2655–2660. https://doi.org/10.1128/JCM.00818-16.
552. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Munoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. 2008. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813–1821. https://doi.org/10.1086/588660.
553. Beer KD, Jackson BR, Chiller T, Verweij PE, Van de Veerdonk FL, Wauters J. 2020. Does pulmonary aspergillosis complicate coronavirus disease 2019? Crit Care Explor 2:e0211. https://doi.org/10.1097/CCE.0000000000000211.
554. Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, Linton CJ, Gough M, Brown P, Dzietczyk A, Hedley M, McLachlan S, King J, Johnson EM. 2020. COVID-19 associated invasive aspergillosis: data from the UK National Mycology Reference Laboratory. J Clin Microbiol https://doi.org/10.1128/JCM.02136-20.
555. Verweij PE, Gangneux JP, Bassetti M, Bruggemann RJM, Cornely OA, Koehler P, Lass-Florl C, van de Veerdonk FL, Chakrabarti A, Hoenigl M, European Confederation of Medical Mycology, International Society for Human and Animal Mycology, European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, ESCMID Study Group for Infections in Critically Ill Patients. 2020. Diagnosing COVID-19-associated pulmonary aspergillosis. Lancet Microbe 1:e53–e55. https://doi.org/10.1016/S2666-5247(20)30027-6.
556. Meijer EFJ, Dofferhoff ASM, Hoiting O, Buil JB, Meis JF. 2020. Azole-resistant COVID-19-associated pulmonary aspergillosis in an immunocompetent host: a case report. J Fungi (Basel) 6:79. https://doi.org/10.3390/jof6020079.
557. Ghelfenstein-Ferreira T, Saade A, Alanio A, Bretagne S, Araujo de Castro R, Hamane S, Azoulay E, Bredin S, Delliere S. 2020. Recovery of a triazole-resistant Aspergillus fumigatus in respiratory specimen of COVID-19 patient in ICU—a case report. Med Mycol Case Rep 31:15–18. https://doi.org/10.1016/j.mmcr.2020.06.006.
558. Mohamed A, Hassan T, Trzos-Grzybowska M, Thomas J, Quinn A, O'Sullivan M, Griffin A, Rogers TR, Talento AF. 2020. Multi-triazole-resistant Aspergillus fumigatus and SARS-CoV-2 co-infection: a lethal combination. Med Mycol Case Rep 31:11–14. https://doi.org/10.1016/j.mmcr.2020.06.005.
559. Talento AF, Dunne K, Murphy N, O'Connell B, Chan G, Joyce EA, Hagen F, Meis JF, Fahy R, Bacon L, Vandenberge E, Rogers TR. 2018. Post-influenzal triazole-resistant aspergillosis following allogeneic stem cell transplantation. Mycoses 61:570–575. https://doi.org/10.1111/myc.12770.
560. Wiederhold NP, Verweij PE. 2020. Aspergillus fumigatus and pan-azole resistance: who should be concerned? Curr Opin Infect Dis 33:290–297. https://doi.org/10.1097/QCO.0000000000000662.
561. Mathew D, Giles JR, Baxter AE, Greenplate AR, Wu JE, Alanio C, Oldridge DA, Kuri-Cervantes L, Pampena MB, D'Andrea K, Manne S, Chen Z, Huang YJ, Reilly JP, Weisman AR, Ittner CAG, Kuthuru O, Dougherty J, Nzingha K, Han N, Kim J, Pattekar A, Goodwin EC, Anderson EM, Weirick ME, Gouma S, Arevalo CP, Bolton MJ, Chen F, Lacey SF, Hensley SE, Apostolidis S, Huang AC, Vella LA, Unit UPCP, Betts MR, Meyer NJ, Wherry EJ. 2020. Deep immune profiling of COVID-19 patients reveals patient heterogeneity and distinct immunotypes with implications for therapeutic interventions. bioRxiv https://doi.org/10.1101/2020.05.20.106401.
562. Perlman S. 2020. COVID-19 poses a riddle for the immune system. Nature 584:345–346. https://doi.org/10.1038/d41586-020-02379-1.
563. Smallwood HS, Duan S, Morfouace M, Rezinciuc S, Shulkin BL, Shelat A, Zink EE, Milasta S, Bajracharya R, Oluwaseum AJ, Roussel MF, Green DR, Pasa-Tolic L, Thomas PG. 2017. Targeting metabolic reprogramming by influenza infection for therapeutic intervention. Cell Rep 19:1640–1653. https://doi.org/10.1016/j.celrep.2017.04.039.
564. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. 2021. Post-acute COVID-19 syndrome. Nat Med 27:601–615. https://doi.org/10.1038/s41591-021-01283-z.
565. Al-Aly Z, Xie Y, Bowe B. 2021. High-dimensional characterization of post-acute sequalae of COVID-19. Nature 594:259–264. https://doi.org/10.1038/s41586-021-03553-9.
566. Thomas T, Stefanoni D, Reisz JA, Nemkov T, Bertolone L, Francis RO, Hudson KE, Zimring JC, Hansen KC, Hod EA, Spitalnik SL, D'Alessandro A. 2020. COVID-19 infection alters kynurenine and fatty acid metabolism, correlating with IL-6 levels and renal status. JCI Insight 5:e140327. https://doi.org/10.1172/jci.insight.140327.
567. Shen B, Yi X, Sun Y, Bi X, Du J, Zhang C, Quan S, Zhang F, Sun R, Qian L, Ge W, Liu W, Liang S, Chen H, Zhang Y, Li J, Xu J, He Z, Chen B,

Wang J, Yan H, Zheng Y, Wang D, Zhu J, Kong Z, Kang Z, Liang X, Ding X, Ruan G, Xiang N, Cai X, Gao H, Li L, Li S, Xiao Q, Lu T, Zhu Y, Liu H, Chen H, Guo T. 2020. Proteomic and metabolomic characterization of COVID-19 patient sera. Cell 182:59–72.e15. https://doi.org/10.1016/j.cell.2020.05.032.

568. Cai Y, Kim DJ, Takahashi T, Broadhurst DI, Ma S, Rattray NJW, Casanovas-Massana A, Israelow B, Klein J, Lucas C, Mao T, Moore AJ, Muenker CM, Silva J, Wong P, Ko AJ, Khan SA, Iwasaki A, Johnson CH. 2020. Kynurenic acid underlies sex-specific immune responses to COVID-19. medRxiv https://doi.org/10.1101/2020.09.06.20189159.

Fabián Salazar, Ph.D., is a postdoctoral research fellow at the laboratory of Professor Gordon Brown in the MRC Centre for Medical Mycology at the University of Exeter. He is currently working on understanding the underlying mechanisms by which C-type lectin receptors influence innate and adaptive immune responses during fungal infections. A biochemist by training, Fabian received his Ph.D. in 2016 from the School of Life Sciences at the University of Nottingham, investigating the role of C-type lectin receptors in allergen recognition and modulation of human allergic responses. His research interests include the study of the early immunological events that initiate protective immunity or drive susceptibility against fungal infections, with a particular focus on innate immune cells.

Elaine Bignell, Ph.D., is a Professor of Medical Mycology and a Co-Director (Research) for the MRC Centre for Medical Mycology at the University of Exeter. Her work addresses the mechanistic basis of lung diseases caused by the major mould pathogen of humans, *Aspergillus fumigatus*. Major contributions to the field have included work on the role of *Aspergillus* pH sensing in pathogenicity, transcriptional regulation of host adaptation, and the mechanistic basis of tissue invasion during invasive fungal lung disease. A molecular geneticist by training, Elaine began her independent research career as an MRC New Investigator and by securing a fast-track to a Lectureship Award at Imperial College London. Elaine's research seeks a mechanistic understanding of fungal lung disease with a view to developing novel diagnostics and antifungal therapies. Her approach integrates infection models which transcend multiple experimental scales to address disease outcomes at the molecular, cellular, tissue, organ, and whole animal levels.

Gordon D. Brown, Ph.D., completed his Ph.D. at the University of Cape Town, and following Wellcome Trust Fellowships at the University of Oxford and then at the University of Cape Town, he moved in 2009 to the University of Aberdeen as a Professor of Immunology. In 2019, he relocated to the University of Exeter, where he is Director of the MRC Centre for Medical Mycology and Director of the AFGrica Unit, based at the University of Cape Town. His primary research interests are C-type lectin receptors and their role in homeostasis and immunity, with a particular focus on antifungal immunity.

Peter C. Cook, Ph.D., is a Wellcome Trust Sir Henry Dale Fellow at the MRC Centre for Medical Mycology (MRC CMM), University of Exeter. His group focuses on understanding how the ubiquitous environmental mould *Aspergillus fumigatus* triggers our immune response to mediate chronic airway allergic diseases such as asthma. Peter undertook his Ph.D. at the University of York, followed by postdoctoral research at the University of Edinburgh and the University of Manchester. In 2016, he was awarded the University of Manchester Dean's Prize and a Springboard award from the Academy of Medical Sciences. This has resulted in novel discoveries about the induction and regulation of type 2 inflammation at barrier sites. In 2020, he moved to the MRC CMM, where his group is investigating how innate immune cells in the lung orchestrate inflammation against fungal spores. This work will provide insights with the aim to improve therapeutic strategies for asthmatic and fungal diseases.

Adilia Warris, M.D., Ph.D., is a professor of pediatric infectious diseases specialist with a specific interest in medical mycology. She is Co-Director of the MRC Centre for Medical Mycology at the University of Exeter, United Kingdom. She holds an honorary position in pediatric infectious diseases at Great Ormond Street Hospital in London, United Kingdom. Professor Warris' research profile has a strong translational focus, and specific areas of interest include host-fungus interactions in specific patient populations, antifungal resistance and antifungal stewardship, and epidemiology and management of fungal diseases in pediatric patient populations, in particular, those with primary immunodeficiency and cystic fibrosis.