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Influenza Pathogenesis: The role of host factors on severity of disease

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Abstract

Influenza viruses continue to be a major global health threat. Severity and clinical outcome of influenza disease is determined by both viral and host factors. Viral factors have long been the subject of intense research and many molecular determinants have been identified. However, research into the host factors that protect or predispose to severe and fatal influenza A virus infections is lagging. The goal of this review is to highlight the recent insights into host determinants of influenza pathogenesis.

Influenza viruses are segmented negative-sense RNA viruses that belong to the *Orthomyxoviridae* family. Four types (A, B, C and D) of influenza virus are known, but only types A and B can cause annual epidemics in humans. Influenza A virus (IAV) is divided into different subtypes based on the surface expression of the two surface glycoproteins; hemagglutinin (HA) and neuraminidase (NA). Each year approximately 3–5 million people suffer from severe influenza infection and of those, approximately 250,000 – 500,000 succumb to the disease. The pathogenesis following IAV infection occurs in two phases. The first phase lasts between 1–3 days and determines the peak virus titer as well as the amount of inflammation associated with that. Depending on these two parameters, the second phase may lead to control of the virus or result in severe disease associated with acute respiratory distress syndrome and death. The clinical course and outcome of influenza pathogenesis is determined by both viral and host factors. T- and B-cell immunity against IAV is a key factor in protection from infection and disease. However, other host factors, such as age, sex, microbiome and genetic variation, also modulate the clinical course and outcome of the disease. In this review, we will summarize the current literature for each of these host factors and discuss future studies for the field.

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Adaptive immunity against influenza virus

Adaptive immune responses play a key role in protection against IAV infection and disease (previously reviewed in (1–6)). The humoral immune response can be broadly divided into virus neutralizing and non-neutralizing antibodies. Neutralizing antibodies target the hemagglutinin (HA) protein of IAV that is required for attachment to and entry into cells. The mechanism of neutralizing activity falls into four major categories: blocking binding to sialic acids, inhibiting viral fusion, preventing release of progeny virus, and blocking proteolytic cleavage of the HA protein (7). For reasons that are not entirely clear, the majority of HA-specific antibodies target the head domain of HA and block binding to sialic acids (5). Unfortunately, this region is also the most variable part of the protein and amenable to extensive amino-acid substitution. Changes in the antigenic sites of the HA protein allows the virus to escape pre-existing antibodies and re-infect individuals previously exposed to IAV. This phenomenon of immune escape is called antigenic drift. The stalk region of the HA protein is significantly more conserved and antibodies targeting this region often cross-react with other HA proteins, providing potential protection against antigenically divergent strains of IAV. B-cells also produce non-neutralizing antibodies that target the neuraminidase (NA) or matrix 2 (M2) protein. These antibodies promote uptake of virus particles or virus-infected cells by macrophages and neutrophils and induce antibody-dependent cellular toxicity. Intriguingly, the baseline NA inhibitory antibody titer (NAI) correlated more significantly with all disease severity metrics and had a stronger independent effect on outcome compared to the HA inhibitory antibody titer (HAI) (8), suggesting that future universal vaccines should target both HA and NA protein on the surface of the virion. In addition to B-cells, T-cells also protect against severe IAV disease. CD4+ T-cells provide the necessary T-helper activity to generate high-affinity antibodies, whereas CD8+ T-cells, or cytotoxic T-cells, can kill IAV-infected cells. After IAV infection, a fraction of the T-cells remains at the site of infection and become tissue resident memory T-cells or T_{RM} (9, 10). Like most T-cells, T_{RM} confer protection against infection with a heterologous strain of IAV (11, 12), such as during a IAV pandemic. In mice, T_{RM} cells also prevent dissemination of IAV from the upper respiratory tract to the lungs (13). Thus, future IAV vaccines, including the universal influenza vaccine, should stimulate cross-reactive antibodies as well as CD4+ and CD8+ T-cells to protect against current and emerging strains of IAV.

The effects of age on outcome after influenza infection.

Influenza infections cause high morbidity and mortality rates in the elderly and very young populations. Individuals greater than 65 years of age are the most vulnerable to severe illness from influenza infection and account for about 90% of all influenza and influenza-related deaths (14). During influenza epidemics, individuals >65 years are 4.5 times more likely to suffer from severe disease and nearly 3 times more likely to die as a result of the infection (15). Despite this, age-related changes in immune responses to influenza infection have not been fully explored (16). Immunosenescence is the gradual deterioration of the immune system that is caused by aging and results in increased susceptibility to viral and bacterial infections as well as attenuated vaccination responses (17, 18). Immunosenescence affects both the innate and adaptive immune response to infection. Monocytes from older human

donors show reduced RIG-I like receptor (RLR) signaling and significantly impaired type I interferon (IFN) responses to IAV infection despite preserved inflammatory cytokine production. This defect is associated with dampened upregulation of antiviral ISGs and a corresponding increase in IAV gene expression (19). In concordance, *ex vivo* studies of plasmacytoid dendritic cells and monocyte-derived dendritic cells from older human donors show impaired IFN-α production in response to IAV (20–22). Besides alterations in antiviral immune signaling, immunosenescence in innate immune cells is associated with reduced superoxide generation and phagocytosis in neutrophils and macrophages, reduced TLR expression and function in dendritic cells and macrophages, and increased prostaglandin E2 (PGE2) production in macrophages (reviewed in (23)). Intriguingly, PGE2 is reported to inhibit type I IFN induction as well as antigen presentation and apoptosis, suggesting a possible mechanistic link between aging, PGE2 production and attenuated innate immune cell function (24). The effects of aging on antigen presentation by dendritic cells (DC) are unclear (25). Some studies indicated that T-cell priming by DC is maintained in the aging population (26–28), while others show that it is impaired (29–32). Despite the general decrease in innate immune cell function, aging is associated with an increase in inflammatory cytokine production; a condition described as senescence-associated secretory phenotype (SASP) (19, 33). SASP in turn may contribute to inflamm-aging, which is chronic, sterile, low-grade inflammation that contributes to the pathogenesis of age-related diseases (34). The basal pro-inflammatory environment associated with aging, combined with delayed innate immune responses following IAV infection of elderly individuals, leads to excess immunopathology, tissue damage, more persistent symptoms, and a higher likelihood of progression to acute respiratory distress syndrome (23, 35–38).

The waning of the adaptive immune response has been extensively studied in aging research. At puberty, thymic involution leads to a reduction in the output of naïve T-cells, which becomes more profound as an individual gets older. This results in decreased numbers of naïve T-cells in the periphery of elderly individuals, restricts the ability of the adaptive immune system to mount a defense against new pathogens, and importantly, decreases responses to vaccination (39, 40). Aging is also associated with a clonal expansion of T-cells because of repeated antigenic stimulation by cytomegalovirus (CMV) (41). Clonal expansion further diminishes the response to novel antigens. Additionally, helper T-cell function, overall B-cell numbers, and antibody efficacy against specific pathogens also decline with age (40, 42, 43).

Murine studies also support age-related increases in IAV susceptibility that have been associated with elevated virus titers, prolonged weight loss, and altered cytokine dynamics. A reduction in the numbers and activity of virus-specific CD8+ T-cells in aged mice is one of the factors that contribute to a higher virus load and severe disease. The rationale for this age-dependent decrease in T-cell immunity is not well understood. Aging is also associated with a decline in T-cell repertoire diversity, leading to impaired immunity to IAV in mice (44). Combined these factors lead to prolonged virus replication and disease in aged animals (38). Similar to humans, aged mice also have lower antibody responses to vaccination than young adult mice (45). Overall, these studies indicate that an aged mouse model is a suitable model to study the role of aging on IAV pathogenesis. Specifically, separating the effects of aging from other host factors, such as changes in sex hormone levels or microbiome (see

below) is key to understanding mechanistically how aging and inflamm-aging increases susceptibility to IAV disease. These new insights may help to identify at-risk populations as well as develop future therapies aimed at reducing the impact of immunosenescence.

Sex dependent differences in influenza associated disease

The impact of sex differences on morbidity and mortality after IAV infection is influenced by multiple behavioral, environmental, and social factors. Studies comparing the male and female susceptibilities and disease outcomes after IAV infection have reported widely varied results with some suggesting that young males are more susceptible or others where females are at an increased risk for severe and fatal disease. Outcomes of IAV infection are also complicated by age, immunological and vaccine responses, the specific strain of IAV, and seasonal versus pandemic influenza infection (reviewed in (46–50)).

Females of reproductive age displayed a higher incidence of severe disease following avian H5N1 and H7N9 IAV infection and pandemic IAV infections yet young (pre-pubescent) and elderly males experience more severe disease following seasonal IAV infection. In addition, female mice consistently show greater reductions in body mass, temperature, and survival as compared to males when infected with IAV. The increase in IAV disease in female mice strongly correlates with increased cytokine and chemokine production (51–54). These data underscore the intertwined environment that may be further exacerbated in females of reproductive age (pre-menopause) by increased sex hormones. In contrast, IAV disease in pre-pubescent and elderly males, who display poor vaccination and adaptive immune responses, may be exacerbated by decreased testosterone levels.

Disease outcomes in males and females are greatly influenced by the expression of respective sex hormones. Reducing testosterone levels in young mice by gonadectomy leads to increased morbidity, clinical illness, and pulmonary pathology, despite having no effect on viral replication (55, 56). Treatment of aged males with testosterone improved survival following infection but once again, did not affect viral replication, suggesting that increased levels of testosterone protect against detrimental outcomes following IAV infection. In humans, reduced endogenous testosterone levels correlated with lower responses to influenza vaccination (57). In female mice, exogenous estrogen protected against infection-induced morbidity and mortality (53, 58, 59). Protection was associated with dampening of the pro-inflammatory immune response and tissue damage. However, other studies have shown that the anti-inflammatory effects of elevated estrogen levels led to increased morbidity after IAV infection (60). These conflicting findings may be attributable to differences in viruses used or the amounts of exogenous estrogen used in treatment. It is known that low levels of estrogen stimulate inflammation, whereas high levels of estrogen are anti-inflammatory (61, 62). Like estrogen, the effects of progesterone on IAV disease outcome are also inconclusive. Progesterone treatment prior to infection reduced excessive pulmonary inflammation, improved lung function, and promoted lung epithelium repair and faster recovery in female mice following IAV infection (63), while in a second study, onset of and duration of morbidity was earlier and greater following progesterone treatment (64). Collectively, these data illustrate that sex hormones modulate the immune response and therefore, the outcome after IAV infection. Future studies will determine if the disparity in

susceptibility to IAV disease between male and females is caused by sex hormones or other sex dependent host factors. Interestingly, sex hormones decline with age after puberty, suggesting that some of the age-related effects on IAV disease maybe be due to lower levels of estrogen and testosterone resulting in more inflammation in aging individuals. The underlying mechanism of immune modulation by sex hormones and the role of specific host genes is not well understood. Future studies should identify specific transcriptional networks, regulators, and effectors that regulate these sex-dependent differences in immunity and influenza pathogenesis.

Pregnant women are recognized to be at higher risk for IAV disease and this became more apparent during the 2009 H1N1 pandemic. Pregnant women were about seven times more likely to suffer from severe IAV disease and two times more likely to die from IAV than non-pregnant women were. In the United States, pregnant women account for 5% of all IAV related deaths. However, underlying pathways that cause susceptibility of pregnant women and predispose them to severe disease remain unidentified. In infected pregnant mice, the production of anti-viral molecules and inflammatory cytokines such as type I IFNs was reduced and accompanied by a lack of innate immune response activation following infection with pandemic H1N1 IAV (65). This corroborates studies wherein infection of pregnant Balb/c mice with pandemic H1N1 IAV resulted in higher mortality and more severe histological lesions associated with dampened tissue repair compared to non-pregnant mice (66–68). Aside from developing better virus vaccines, more effort should go into understanding the underlying cause (i.e. increased virus replication, altered inflammatory response or delayed virus control and tissue repair) that predispose pregnant women to more severe disease after IAV infection.

Does the microbiome play a role during influenza pathogenesis?

The role of the human microbiome on influenza infection and associated disease is currently not known but is an up-and-coming area of investigation. Does IAV infection alter the microbiome of the respiratory tract or other organs, and is there an effect of this perturbation? Similarly, does an altered respiratory or gut microbiome pre-dispose to virus infection and severe disease? For example, colonization with certain pathogenic bacteria such as *Staphylococcus* or *Streptococcus* may affect the risk of secondary bacterial infections following primary IAV disease (69).

Most studies on the microbiome have been done in mice. The earliest studies showed that antibiotic treatment predisposes to severe IAV disease, likely through changes in IFN and Toll-like receptor (TLR) signaling (70–72). The gut microbiome also supported a robust vaccine response in mice (73). More recently, it was shown that the bacterial metabolite desaminotyrosine protects from severe IAV through production of type I IFN (74). Gut microbiota from wild mice transferred into laboratory mice also increased survival after IAV infection (75). The mice that received wild-derived microbiota were significantly more resistant to lethal IAV infection compared to control mice or mice that received microbiota from laboratory mice. Resistance to severe disease was associated with reduced early weight loss, lower viral titers and less inflammation. In future studies, it will be important to identify the component of the wild mouse microbiome, i.e. bacteria, virus or other

organisms, that increases resistance to severe IAV infection, and to determine whether similar factors that confer protection against severe IAV disease exist in the human microbiome. There are many important and unanswered questions in the field regarding the relationship between microbiome and IAV. How does the microbiome, and its perturbations, impact human IAV disease? How does the microbiome protect against IAV, and what is the impact of viral and other host factors on microbiome-mediated protection against severe IAV disease?

During the 2009 H1N1 pandemic, obesity was recognized as a risk factor (odd ratio between 2 and 4) for complications from IAV infection (76–80). Since then, the impact of obesity on severe IAV disease is diminished (81, 82) or not present (83, 84). Perhaps the emergence of pre-existing immunity to the 2009 H1N1 IAV in obese and lean individuals masks the detrimental effects of obesity on IAV disease. Obesity is also an important risk factor for severe IAV disease after H7N9 IAV infection (15, 85, 86). There is growing evidence that obesity affects the effectiveness of the adaptive immune system following IAV infection or vaccination. T-cells from influenza-vaccinated obese adults are less activated when stimulated with vaccine strains of influenza (87, 88). *Ex vivo*, CD4+ and CD8+ T-cells from overweight and obese individuals expressed lower levels of CD69, CD28, and CD40 ligand, as well as the effector molecules IFN-γ and granzyme B, suggesting deficiencies in activation following stimulation with IAV (87). Also, vaccinated obese adults were twice more likely to report influenza infection and influenza-like illness than their healthy weight counterparts, despite similarly robust serological responses (89). A higher body mass index also correlated with the prolonged shedding of infectious virus from IAV infected individuals (90, 91).

In animal models, diet-induced obese mice infected with IAV have increased mortality, greater lung inflammation and damage, higher numbers of cytotoxic CD8+ T cells in the lungs, and fewer suppressive T-regulatory cells when compared with lean mice (92, 93). In secondary challenge studies, obese mice had impaired adaptive responses as indicated by decreased memory CD8+ T cells and production of IFN-γ. Additionally, obese mice had higher mortality following vaccination and challenge despite increased production of neutralizing and non-neutralizing IAV-specific antibodies, similar to observations in humans (94). These animal models capture the influence of diet-induced obesity on IAV morbidity, and models of genetic predisposition to obesity also show similar outcomes. Compared with lean mice, global leptin receptor-deficient mice (ob/ob) and hypothalamic leptin receptor-knockout ($LepR^{H-/-}$) mice display increased mortality, higher lung inflammation, and decreased viral clearance when infected with pandemic H1N1 IAV (92, 95). In contrast, mice depleted of leptin receptor specifically in macrophages and lung epithelial cells had similar outcomes compared to wild-type mice following IAV infection. This may be due to a critical role of leptin in other cell types, such as T-cell metabolic or glycolytic activity and adaptive immunity (95). Interestingly, obesity is associated with a change in the gut microbiome composition in both mice and humans (96–98). Future studies should determine how each of these two host factors independently and in combination affect IAV disease.

Host genetic factors that modulate influenza disease.

Considerable progress has been made with the identification of human genetic polymorphisms associated with severe or fatal IAV disease. After the first human genetic association study, performed shortly after the 1957 (H2N2) IAV pandemic (99, 100), it took nearly 40 years before the impact of host genetic variation on IAV disease was considered again (101–103). The identification of host genetic factors associated with clinical outcome of IAV infection in humans is often complicated by the presence of pre-existing immunity in the population. Therefore, many of the host genetic factors identified to-date were discovered during the 2009 H1N1 IAV pandemic or in infants and young children, who are immunologically naïve for IAV. Currently, there are approximately twenty-five different host genes, whose genetic variation has been associated with the outcome after IAV infection in humans (Table 1) (104). Some of these genes have been independently validated, providing strong evidence that the severity of IAV disease is genetically predisposed. This important observation allows for the identification of at-risk individuals who should be prioritized to receive one or more IAV vaccines annually and supports the discovery of additional host factors that modulate IAV outcome.

The effects of genetic variation in the *IFITM3* gene on IAV disease was first identified during the 2009 H1N1 pandemic. IFITM3 or interferon-induced transmembrane protein 3 is a potent antiviral protein that blocks release of the viral genome into the cells cytoplasm by preventing viral fusion with the endosomal membrane (105–107). Two groups reported on a polymorphism (rs12252_C) that predisposed to severe and fatal H1N1 IAV (101, 102). Similar findings were reported for Chinese patients infected with the emergent avian H7N9 IAV (108). The rs12252_C polymorphism was predicted to effect RNA splicing and truncate the *IFITM3* protein. However, next-generation sequencing on cells derived from individuals with all three genotypes showed that full-length *IFITM3* messenger RNA (mRNA) was present in all genotypes (109). Thus, the mechanism by which rs12252_C affects susceptibility to IAV disease remains unknown. Recently, a second polymorphism in the *IFITM3* gene, rs34481144, was associated with severe IAV disease in predominantly non-Chinese populations (110). This polymorphism is located in the promotor region of the *IFITM3* gene and affects *IFITM3* expression level in CD8+ T-cells, which is consistent with an earlier study in mice showing that *IFITM3* expression protect tissue resident memory T-cells from IAV infection (111).

The significance of innate immunity and antiviral host defense for protection against severe IAV disease is further highlighted by the discovery of a 2.5-year old patient who suffered from severe IAV disease (112). Next generation sequencing of her genome, as well as her parents, identified two missense mutations in the host gene *IRF7*. These two rare mutations impaired the function of IRF7 protein and diminished the amplification of type I and III IFN after infection. Interestingly, the impaired IRF7 function did not lead to severe disease after RSV, VZV and CMV infection suggesting redundant pathways or mechanisms of protection against these pathogens. This same group also identified rare mutations in the gene *DBR1* that result in severe disease after IBV, HSV and norovirus infection (113). *DBR1* (debranching RNA lariats 1) is an enzyme that is involved in the degradation of RNA lariats (leftover molecules from RNA splicing) (114). Abrogation of DBR1 activity leads to

elevated levels of RNA lariats, attenuation of IFN signaling and increased severity of disease. Besides host genes that are important for innate and antiviral immunity, genetic variation in genes associated with cellular homeostasis can also predispose to severe clinical outcomes after IAV infection. CPTII (carnitine palmitoyltransferase II) is a mitochondrial membrane protein required for fatty acid oxidation. Missense mutations in *CPTII* produce a temperature sensitive form of the CPTII protein, which upon high fever, induced by severe IAV disease, becomes inactive. This results in a buildup of long-chain fatty acids, leading to influenza-associated encephalopathy (115–117).

Animal models, such as mice, offer an alternative to identify and study host factors associated with severe and fatal IAV disease. The first antiviral host gene *Mx1* was identified in 1962 after comparing IAV resistant and susceptible mouse strains (118, 119). Our work and that of others have since identified many genetic loci associated with severe disease after pathogenic IAV infection in mice (120–130) and chickens (131). In some cases, the host gene within the loci (*Hc*, *Ifi35*, *Lst1*, and *Mx1*) has been identified (120, 126, 132, 133). Ifi35 was recently shown to exacerbate weight loss and disease in mice after IAV infection (133). The expression of Ifi35 increases the production of the pro-inflammatory cytokine IL-12p80 (a homodimer of IL-12p40). Neutralization of IL-12p80 ameliorated weight loss after infection. The significance of these host genes and associated mechanisms in human IAV needs to be investigated. Ongoing developments in next generation sequencing and genome editing will accelerate the identification of host genes and associated polymorphisms that contribute to differences in clinical outcome after IAV infection.

A significant advantage of the mouse model is the ability to study gene function in the context of primary IAV infection and identify the mechanism of severe disease. Analysis of the literature identified several hundred citations containing a Kaplan-Meier survival analysis comparing IAV induced mortality between wild type and gene-deficient mouse strains. One hundred seventy different host genes have been studied to-date for susceptibility or resistance against different strains of IAV (Fig. 1). Many host genes in this analysis (*Ifnar1*, *Ifnl1*, *Stat1*, *Ifitm3*, *Sfpta1*, and *Irf7)* are involved in innate and antiviral immune pathways and are required for survival after IAV infection. These findings recapitulate what is observed in humans that are deficient in key components of the interferon and antiviral immune system. Deletion of host genes involved in the complement pathway, C3, C4 and C5, also increase the susceptibility to infection. A second set of host genes (Fig. 1, green box) exacerbate IAV disease and deletion of these genes protect the mice from severe and fatal IAV infection. These genes are essential for IAV replication (*Tmprss2, Ipo7*), involved in inflammation (*Par1*, *Tnfaip3, Nos2, Ptges2, and Ifi35*), or tissue homeostasis (*Epg5, Atg14 and Atg7*). The negative impact of inflammatory gene expression on IAV disease is consistent with the idea of immunopathology contributing to the severity of IAV disease. The third group (Fig. 1, blue box) includes *Ccr2*, *Tlr3*, *Tlr4* and *Myd88*, and their role during IAV pathogenesis is conflicting. Variation in virus strain, microbiome or laboratory environment may contribute to the differences in disease outcome of these gene-deficient mice. The fourth and final group of host genes (Fig. 1, grey box) do not affect survival after IAV infection. Despite the challenges in reporting negative results, it is important for the field that these results are published or deposited in a publicly available database. This avoids duplication and allows for a systems-wide analysis to study and infer gene function

and activity in the context of different microbial infections. Overall, this comprehensive analysis of the different host factors modulating the outcome after IAV infection reveals three things. First, genes involved in the innate and antiviral immune response are important for protection against IAV. However, genes involved in inflammation often exacerbate disease, although these effects may depend on other host and viral factors that contribute to the immune status of the animal. Secondly, future studies should include more genetically modified mouse strains to identify additional host genes that modulate IAV disease, but perhaps more importantly to identify the cell type (using conditional knockouts) and molecular mechanism that is driving this difference in disease outcome. Finally, it is important to evaluate gene activity in different contexts including aging, obesity, and hosts (i.e. different animal models or mouse strains). An elegant example of the significance of host genetic variation on gene activity is a study of the antiviral host gene Mx1, which protects against IAV in a C57BL/6 mouse strain, but not in a DBA/2J mouse strain (134). The analyses of gene activity and function in different contexts associated with severe IAV disease will further enhance our understanding of IAV disease and facilitate the transition of basic science in animal models to clinical practice and development of host-targeted therapies against IAV.

Conclusions

Influenza pathogenesis occurs in two phases (Fig. 2). The first phase starts immediately after infection and lasts for anywhere between 1–3 days. It is during this phase that much of the clinical course and outcome of the disease is determined. Reduced or no pre-existing immunity will result in high peak viral titer and thus more inflammation. This scenario occurs often during IAV pandemics, or in the very young and elderly population. In contrast, pre-existing immunity or effective antiviral immunity will limit early virus replication and thus produce fewer clinical symptoms and disease. Depending on the amount of virus and inflammation after this phase, the second phase may lead to control of the virus or result in severe disease associated with acute respiratory stress syndrome and death. Control of IAV replication often occurs in healthy adults who are able to limit peak viral titer in phase 1 or mount a strong adaptive immune response in phase 2. Occasionally, the immune response becomes dysregulated causing severe and sometimes fatal disease in young adults. In contrast, older individuals who are obese or have underlying co-morbidities are less likely to control virus replication at early and late time points during infection, resulting in more inflammation and severe IAV disease. Excessive inflammation hampers tissue repair and has a negative effect on T- and B-cell immune responses. Virus and host factors including age, microbiome, obesity and sex (sex hormones) can modulate each of these processes to produce the spectrum of IAV disease that we see to date. Development of effective and broadly protective IAV vaccines and antiviral therapies, including host-directed therapies, are key areas for future investigations to prevent severe IAV disease.

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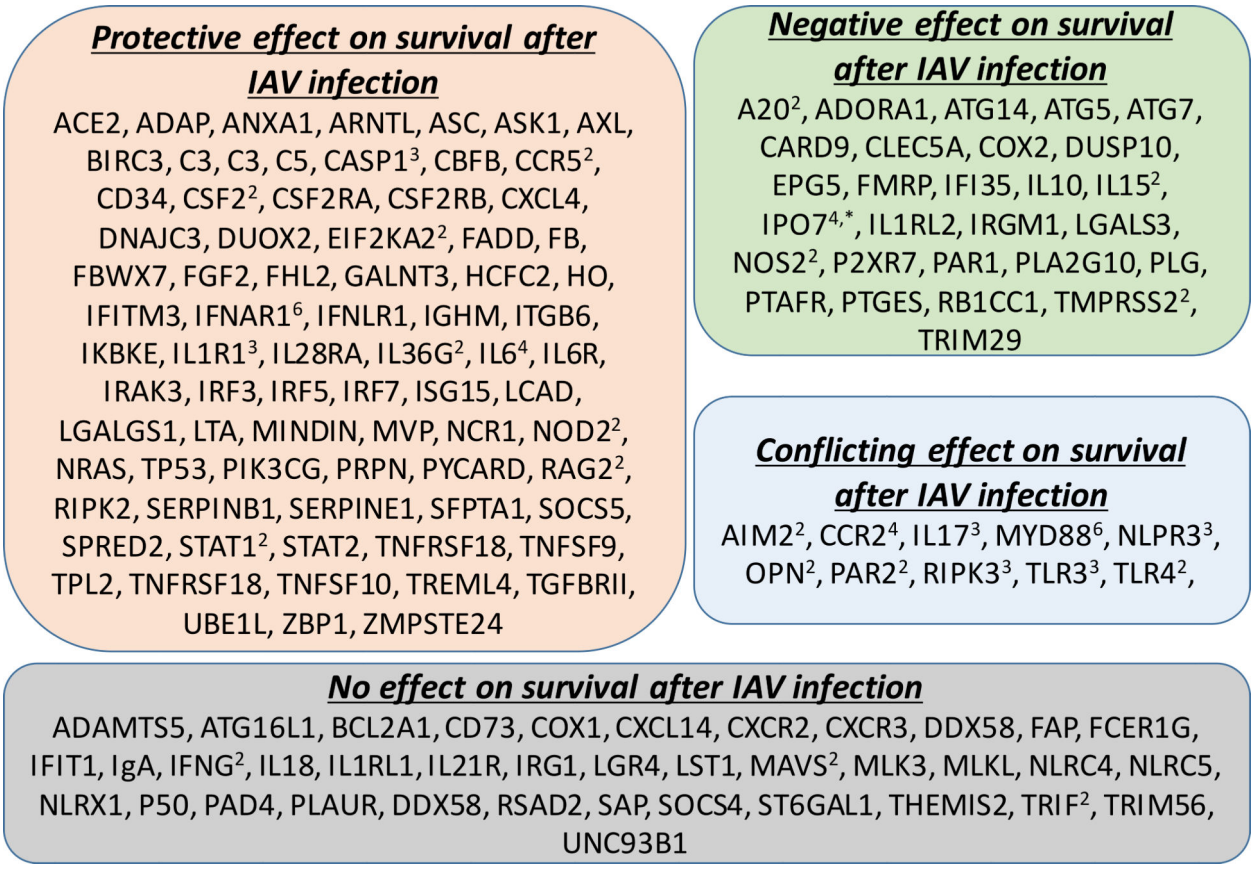

Figure 1: The different host genes that have been tested in gene-knockout mice in IAV pathogenesis models:

[2–6] Number of publications reporting on the role of the host gene on survival after intranasal IAV challenge. * The significance of Ipo7 depends on the strain of IAV used. A table containing the names of the host genes, the associated IAV phenotypes and a web-link to the paper in NCBI is available upon request.

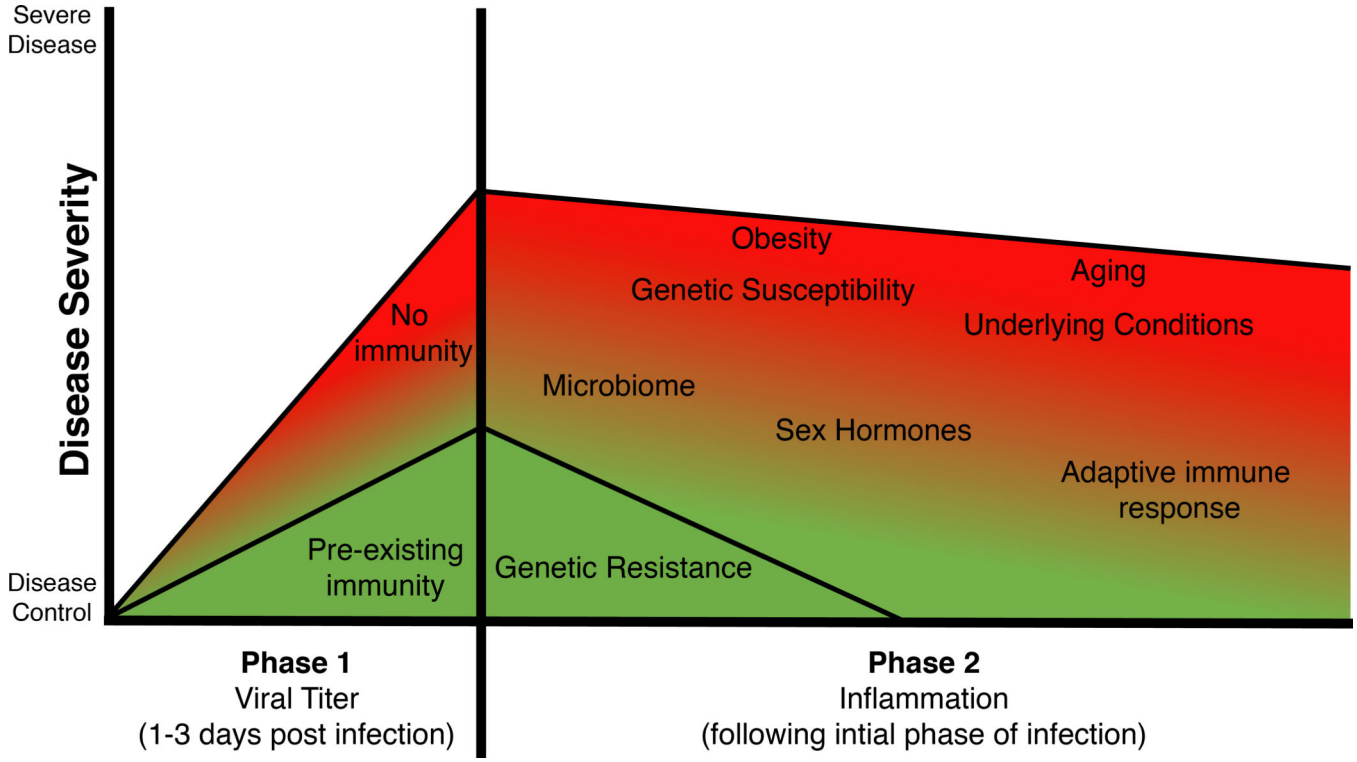

Figure 2:
Host factors that modulate influenza virus pathogenesis.

Table 1:

Host genes associated with severe influenza virus in humans.

Host gene	Reported findings	Animal studies
IFITM3	rs12252 was associated with severe IAV-H1H1 and IAV-H7N9 disease in some, but not all cohorts (135–144). rs34481144 was associated with reduced gene expression in CD8+ T-cells and severe IAV disease (110).	+
IRF7	Compound heterozygous null mutations in a single child who suffered life-threatening IAV infection (112).	+
TMPRSS2	rs2070788 was associated with severe IAV-H1N1 disease in 162 cases and 247 controls (145). rs2070788 and rs383510 were associated with susceptibility to IAV-H7N9 in 102 patients and 106 heavily exposed controls (145).	+
LGALS1	Identified in a single cohort of 102 H7N9 IAV patients and 106 heavily exposed poultry workers (146).	+
SFTPA2	rs1965708 and rs1059046 were associated with severe disease in 93 patients infected with IAV-H1N1 (147). rs1965708 and rs1059046 were not associated with severe IAV-H1N1 disease in 320 infected patients and 115 controls (148).	NA
SFTPB	rs1130866 was associated with severe IAV-H1N1 disease in 380 patients (149). rs1130866 was not associated with severe IAV-H1N1 disease in 320 patients and 115 controls (148).	-
CD55	rs2564978 was associated with severe IAV-H1N1 disease in 425 patients (150) as well as severe IAV-H7N9 and IAV-H1N1 disease in 275 patients (137).	-
C1QBP	rs3786054 was associated with severe IAV-H1N1 disease in 91 patients and 98 household contacts (151).	-
FCGR2A	rs1801274 was associated with severe IAV-H1N1 disease in 91 patients and 98 household contacts (151). rs1801274 was not associated with severe disease in 436 patients (55).	NA
CPT2	Compound heterozygotes mutations were associated with increased risk for IAV-associated encephalopathy (115–117).	-
TNF	rs909253 was associated with severe IAV-H1N1 disease in a cohort of 145 patients and 360 healthy contacts. Infection with IAV-H1N1 was associated with rs361525 and rs1800750 (152).	+
IL1A	rs17561 was associated with IAV-H1N1 infection in 167 patients and 192 controls (153).	-
IL1B	rs1143627 was associated with IAV-H1N1 infection in 167 patients and 192 controls (153). rs16944 and rs3136558 were associated with IAV-H1N1 infection in 145 patients and 360 asymptomatic healthy contacts (154). rs16944 was associated with reduced risk of IAV-H3N2 infection (155).	-
TLR3	rs5743313 was associated with death after IAV infection among 275 adults (137), and increased risk of pneumonia in children infected with IAV-H1N1 (156).	+
KIR	Killer-cell immunoglobulin-like receptors are associated with severe disease after IAV-H1N1 infection (157, 158).	NA
CCR5	CCR5Δ32 was associated with higher mortality after IAV-H1N1 in 171 cases (159). CCR5Δ32 was not associated with the risk of IAV-H1N1 infection or with severe disease in a cohort of 29 patients (160) and 330 patients (161).	+
RPAIN	rs8070740 was associated with severe IAV-H1N1 disease in 91 patients and 98 household contacts (151).	-
DBR1	DBR1 mutations in unrelated patients result in brainstem infection with IAV (113).	-
IL10	rs1800872 was associated with risk of infection with IAV-H3N2 (155). rs1800896 was associated with risk for IAV-related pneumonia (152).	+
IL28	rs8099917 was associated with risk of ILI symptom after IAV-H3N2 (155).	-
IL6	rs1818879 was associated with severe IAV-H1N1 infection in 145 patients and 360 asymptomatic healthy contacts (154).	+
ST3GAL1	rs113350588 and rs1048479 were associated with increased risk of severe IAV-H1N1 disease among 356 subjects (162).	-
IL17	rs2275913 was associated with risk of IAV-H3N2 infection in case-control study (155).	+
NOS3	rs2070744 was associated with risk for IAV-related pneumonia (152).	-
GATA2	Haplo-insufficiency of GATA2 was associated with severe IAV-H1N1 disease (163).	-

NA, not applicable due to orthologue not present in mice.