FEMS Microbiology Reviews, 2025, **49**, fuae032
DOI: 10.1093/femsre/fuae032
Advance access publication date: 28 December 2024
Review Article

Microbial adaptive pathogenicity strategies to the host inflammatory environment

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Editor: [Christian Münz]

Abstract

Pathogenic microorganisms can infect a variety of niches in the human body. During infection, these microbes can only persist if they adapt adequately to the dynamic host environment and the stresses imposed by the immune system. While viruses entirely rely on host cells to replicate, bacteria and fungi use their pathogenicity mechanisms for the acquisition of essential nutrients that lie under host restriction. An inappropriate deployment of pathogenicity mechanisms will alert host defence mechanisms that aim to eradicate the pathogen. Thus, these adaptations require tight regulation to guarantee nutritional access without eliciting strong immune activation. To work efficiently, the immune system relies on a complex signalling network, involving a myriad of immune mediators, some of which are quite directly associated with imminent danger for the pathogen. To manipulate the host immune system, viruses have evolved cytokine receptors and viral cytokines. However, among bacteria and fungi, selected pathogens have evolved the capacity to use these inflammatory response-specific signals to regulate their pathogenicity. In this review, we explore how bacterial and fungal pathogens can sense the immune system and use adaptive pathogenicity strategies to evade and escape host defence to ensure their persistence in the host.

Keywords: adaptation; adaptive prediction; immune sensing; immune evasion; immune escape

Introduction

Despite improvements in sanitation, access to health care, and development of vaccines and antimicrobial therapies, infectious diseases remain a major cause of mortality and morbidity globally (Baker et al. 2022, Shinu et al. 2022). Especially in developing countries, these diseases remain an important cause of death (Baker et al. 2022). Yet, modern healthcare practice involves invasive procedures, indwelling medical devices, prosthetics, and immune-compromising treatments, which clear the path for opportunistic pathogens (Clark and Drummond 2019, Lopes and Lionakis 2022, Kreitmann et al. 2024). Further, demographic and climate changes contribute to the rise and spread of new infectious disease outbreaks (Baker et al. 2022). The increasing incidence of antimicrobial resistance and poorly filled drug-development pipelines make infectious diseases pose again an important threat to global health (Shinu et al. 2022). Understanding the adaptive mechanisms that allow microbial pathogens to thrive and cause disease, and the consequences of these strategies on the host–pathogen interplay during infection, can help to identify new therapeutic targets, as well as biomarkers that could aid in the detection and early diagnosis of infection.

While viruses rely on the infection of host cells and spread from host to host, bacteria and fungi can co-exist in the human body as commensals. Under certain circumstances, some microbes can undergo a commensal-to-pathogen shift and act as opportunistic pathogens. Alternatively, bacteria and fungi can also originate from the environment before infecting susceptible individuals. Several stressors in the environment such as extreme pH, temperature, osmolarity, UV light, and nutrient competition selected traits that help microbes to also overcome challenging conditions within the host (Lange et al. 2023, Huang et al. 2024). This process, known as the environmental virulence school, may explain the evolution of immune evasion mechanisms through competition with other environmental microbes and the development of defence mechanisms against predatory amoebae or nematodes in the environment (Steenbergen et al. 2001, Mylonakis 2002, Casadevall 2008, Bliska and Casadevall 2009). Mechanisms that fulfil important functions in the environmental niche can confer fitness benefits when infecting humans. This functional duality is referred to as 'ready-made' virulence (Casadevall 2003). Despite the imminent danger of predation and the need to evade it, by far not all microorganisms that developed effective countermeasures are human pathogens. A decisive criterion for pathogenicity in humans is the ability to grow at human body temperature. Acclimatization to elevated temperatures in some microbes might have arisen through thermophilic adaptation to the heat resulting from the fermentation of decaying biomass (Tekaia 2005). Moreover, the increased selective pressure to tolerate higher temperatures posed by global warming is believed to drive the emergence of certain environmental microbes as pathogens, such as the fungi *Candida auris* and *Rhodosporidiobolus fluvialis* (Casadevall 2020, 2021, Huang et al. 2024).

Received 11 September 2024; **revised** 19 December 2024; **accepted** 27 December 2024

In contrast to the environmental virulence school, immune evasion strategies acquired during commensalism define the commensal virulence school (Hube 2009, Lange et al. 2023). Symbiotic host–microbe dynamics promoted their coevolution and regulatory mechanisms leading to a host immune balance (Nenciarini et al. 2024). However, disruption of this fine equilibrium could induce the transition from the commensal to a pathogenic status. To traverse through the commensal virulence school (Hube 2009) or exist as an obligate pathogen, adaptation to body temperature is a fundamental prerequisite. Additionally, the establishment of pathogenicity in the host niche requires the ability to compete with other (commensal) microbes, stressing the protective role of a healthy microbiome (Kamada et al. 2012). However, in parallel to fiercely competing with each other, host-associated microbes are under constant surveillance by the immune system (Neutra et al. 1996, Vallon-Eberhard et al. 2006). The continuous interplay with the host and the selective pressure imposed by the immune system foster the co-evolution of commensals and obligate pathogens with the host. In contrast to environmental pathogens, host-associated microbial pathogens rely on their host niches for successful replication and survival (Hube 2009).

Nutritional immunity is one of the first host defence lines that controls the microbial community, and is an illustrative example of the arms race between host and pathogen (Hood 2012, Núñez et al. 2018). This comprises an active restriction of access to essential nutrients like metal ions such as iron, zinc, or manganese by the host (Hood 2012, Núñez et al. 2018). A common microbial strategy to overcome nutritional immunity is the use of chelators to scavenge host-bound metal ions, such as siderophores, which can acquire iron bound to host proteins such as lactoferrin or transferrin (Hood 2012). Another strategy to acquire essential nutrients is by releasing them through damaging host cells (Almeida 2008, 2009, Citiulo 2012, Spaan et al. 2015, Martins et al. 2016, Ristow and Welch 2016, Núñez et al. 2018). This process has to be tightly regulated by the pathogen, as attacking the host inevitably causes the release of damage-associated molecular patterns (DAMPs) and alarmins that activate the immune response (Caffrey 2016). Employing this nutrient-acquisition strategy is a risky gamble for the pathogen, as it marks a turning point in the host–microbe relationship. The adaptations required for a microbe to persist in the host will drastically change after immune activation is elicited. The alarmins and DAMPs released by damaged host cells as well as recognition of the invading pathogen by tissue-resident immune cells will induce further leukocyte recruitment to the site of infection, and will activate adaptive immune responses at later stages (Pittman 2013, Bertheloot 2017). At this point, microbes face a rapidly developing hostile environment with an arsenal of dangerous host defence mechanisms, including reactive oxygen/nitrogen species, proteases, acidic intracellular environments, antimicrobial peptides, and neutralizing antibodies (Bevins and Salzman 2011, Frick 2011, Pauwels 2017, Lu 2018).

To persist after immune activation, a pathogen will need to apply different strategies: (i) hide from incoming immune cells, (ii) withstand the immune response by increasing its resistance to the hostile environment, or (iii) interfere with immune activation.

Due to the essential relationship of viruses with their human hosts, co-evolution has made them masters of immunomodulation and immune evasion (Alcami and Koszinowski 2000). During infection, viruses directly modulate inflammatory cell death pathways, cytokine synthesis, activation, and signal transduction (Xiang and Moss 1999, Alcami and Koszinowski 2000, Born et al. 2000, Kotwal 2000, Smith et al. 2000, Reading and Smith 2003, Parnian et al. 2024, Wu et al. 2024). Strikingly, viral evolution has numerous times achieved this by molecular mimicry of host cytokine receptors and cytokines, allowing them to efficiently interfere with cytokine signalling as well as control immune responses (Alcami and Koszinowski 2000, Kotwal 2000, Alvarez-de Miranda et al. 2021).

Via convergent evolutionary processes, bacterial and fungal pathogens have developed various strategies to cope with immune-imposed stresses, and even adapted to a lifestyle within professional immune cells (Hmama et al. 2015, Ray and Rappleye 2019, Montano et al. 2022). Thus, a timely induction of the necessary stress and evasion responses requires precise sensing of the current environment and its potential threats. In line with the widespread capacity of viruses to interfere with immune activation, there is evidence that some bacterial and fungal pathogens have similarly evolved efficient strategies to interact with immune mediators. In this review, we discuss how bacterial and fungal pathogens can sense different states of immune activation within the mammalian host and, in consequence, integrate these signals to adaptively engage pathogenicity under adequate circumstances to ensure their persistence during infection.

Adaptation *versus* adaptive prediction

When microbes exist in a commensal relationship with their host, the environment is relatively stable or follows patterns of systematic fluctuation ('microbe-host homeostasis'). However, this changes drastically when microbes apply their pathogenicity mechanisms and the host's immune defences are triggered. Disruption of the commensal status can also be associated with the exchange of one host niche for another, which is accompanied by drastic changes in the environmental conditions that the microbe encounters. Exemplary, the opportunistic pathogenic yeast *Candida albicans* lyses host cells using its toxin candidalysin (Moyes et al. 2016) and thereby can translocate through the intestinal epithelium (Allert et al. 2018) from the intestine (its commensal niche) to the bloodstream (Kullberg and Arendrup 2015, Kumamoto et al. 2020). Such stressful scenarios within the host demand rapid sensing of environmental changes by pathogens in order to survive and become better suited to their new niche, also known as adaptation (Peck and Waxman 2018). These environmental changes often follow regular sequential or cyclic patterns. By sensing specific markers of these sequential or cyclic patterns, pathogens can 'predict' upcoming environmental changes and challenges (Cao and Goodrich-Blair 2017). Microbes capable of such adaptive prediction have a fitness benefit even before encountering the actual threat (Mitchell et al. 2009, Brunke and Hube 2014, Pradhan et al. 2019). These molecular mechanisms of adaptive prediction are driven by evolutionary coupling and reconnecting of stress-response pathways (Brown et al. 2019). Responses to two unrelated stimuli or stresses can be rearranged and connected on a microbial evolutionary timescale, which can be exemplified for specific microbes. *Escherichia coli*, a commensal bacterium in the human intestine, induces the expression of genes required for maltose metabolism upon exposure to the unrelated metabolite lactose (Savageau 1998). This response is in line with lactose being the first carbon source that *E. coli* encounters in the upper digestive tract, followed by maltose in the lower digestive tract (Savageau 1998). The predictable pattern in nutrient availability has evolutionarily favoured *E. coli* variants that express genes for maltose metabolism upon exposure to lactose. This adaptive prediction could be uncoupled by continuously growing *E. coli* on lactose, without subsequent exposure to

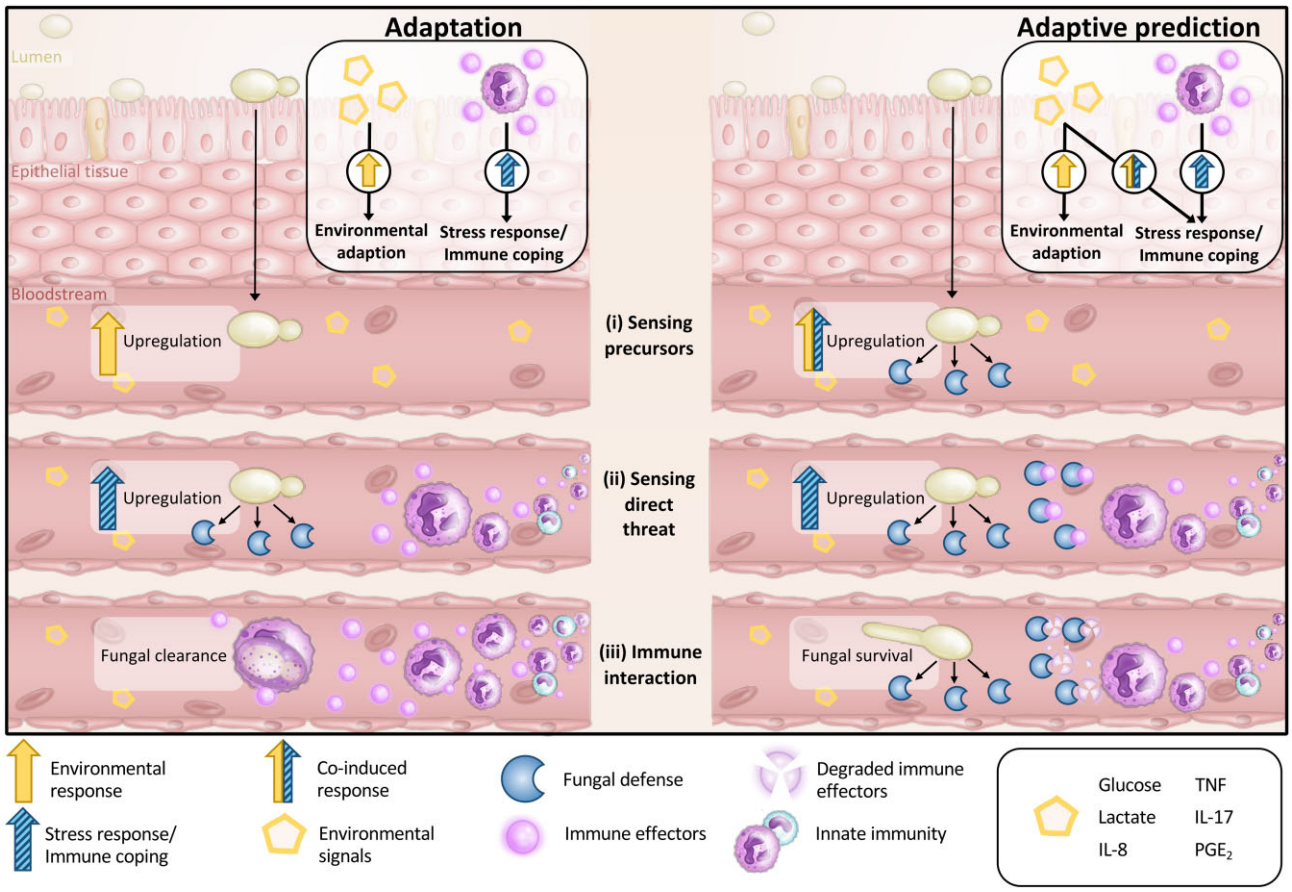

Figure 1. Comparison of adaptation and adaptive prediction on the example of *C. albicans* and glucose (Rodaki et al. 2009). To cause systemic infection, *C. albicans* needs to translocate from the intestine, a commensal niche, into the bloodstream. There *C. albicans* encounters a new environment with stressors imposed by the host. The survival of the fungus depends on its acquired adaptation strategies. Adaptation (left panel): (i) Upon entering the bloodstream, *C. albicans* senses a higher glucose concentration compared to its previous niche. This leads to the expression of genes involved in metabolic remodelling (yellow arrow) to utilize the carbon source efficiently. (ii) *Candida albicans* will further encounter immune cells, which are perceived as a direct threat, resulting in the expression of genes involved in its defence mechanisms (blue/diagonal-patterned arrow). (iii) The pathogenic yeast was unsuccessful in rapidly adapting to the threat, giving the immune cells the advantage to overcome and eliminate the fungus. In this scenario, adaptation to environmental signals and adaptation to imposed stress are not linked to each other, potentially leading to delayed reactions. Adaptive prediction (right panel): (i) Upon entering the bloodstream, *C. albicans* senses the elevated glucose concentration and recognizes it not only as a nutrient source but as a potential precursor. Consequently, genes related to glucose metabolism are upregulated along with those involved in oxidative and cationic stress resistance (yellow - blue/diagonal-patterned arrow). (ii) This co-induced response prepares for the upcoming threat imposed by the immune system, thereby providing a proactive advantage. (iii) The mechanism of adaptive prediction provides a fitness benefit and enhances fungal survival. In this scenario, the response to glucose is linked to the 'microbial memory' as a prediction for the danger posed by the immune system. Additionally to glucose, other host-derived signals such as lactate (Childers et al. 2020), interleukin (IL)-8 (Ali et al. 2006), IL-17 (Zelante et al. 2012), tumour necrosis factor (TNF; Rocha et al. 2017), and prostaglandin E2 (PGE_2) (Kundu and Noverr 2011) are also associated with adaptive prediction in *C. albicans*.

maltose (Mitchell et al. 2009). This suggests that *E. coli* acquired its predictive adaptive trait due to the 'predictable' consecutive environmental conditions and the fitness benefits of faster adaption. Nevertheless, when no fitness benefit is achieved, predictive adaptive traits can be lost, likely due to the high costs of sustaining the response (Mitchell et al. 2009).

Besides bacteria, adaptive prediction has also been reported throughout the fungal kingdom from environmental to commensal and human pathogenic fungi. Exemplary, the fungal genetics model organism *Neurospora crassa* responds to the monosaccharide L-rhamnose not only with upregulation of a broad pectin degradation machinery, but the corresponding master regulator PDR1 also promotes gene expression for the utilization of the hemicellulose arabinan (Thieme et al. 2017). Thereby, the fungus not only expects other sugars present in the polysaccharide pectin, where L-rhamnose is most likely to be encountered but also readies itself to degrade other components of a plant cell wall, where it would naturally find pectin. A later study corroborated and extended this observation of cross-induction of small saccharides for utilization of polysaccharides beyond their common parent structure to a general concept in fungal plant cell wall degradation (Wu et al. 2020). As mentioned above, the opportunistic pathogenic yeast *C. albicans* can cause systemic infections when it translocates from its commensal niche (Kumamoto et al. 2020). During this process, *C. albicans* transits from the gut where glucose levels are low, into the bloodstream where higher glucose levels are encountered (Fig. 1). The exposure of *C. albicans* to blood glucose concentrations increases oxidative and cationic stress resistance via the upregulation of the genes *hog1* and *cap1*, a response that is not required for glucose metabolism (Rodaki et al. 2009). Nevertheless, this response is beneficial for confrontation with immune cells, which can take place when the fungus enters the bloodstream and disseminates to vital organs (Lionakis et al. 2011, Kammer et al. 2020), as both Hog1 and Cap1 proteins are known to

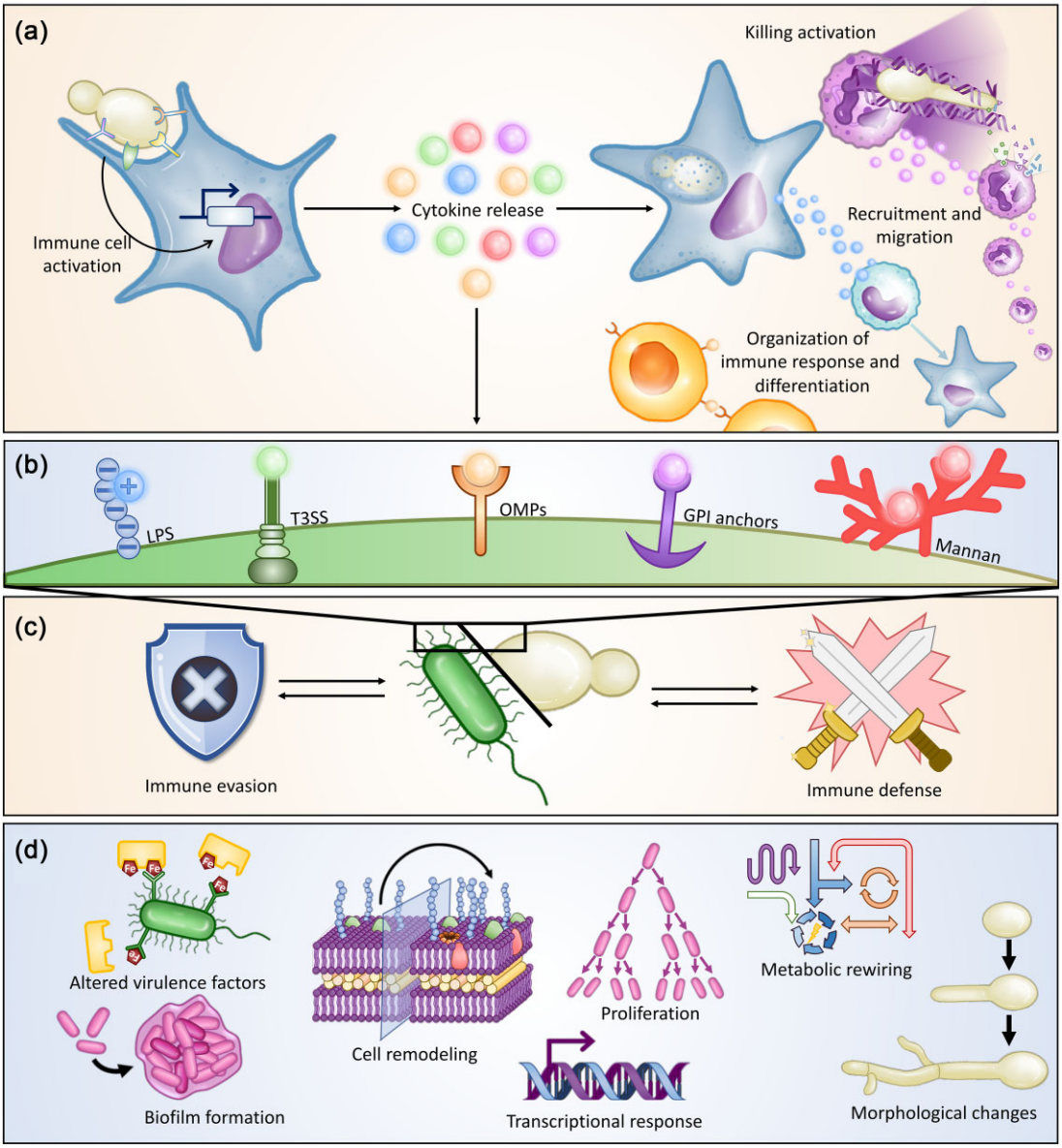

Figure 2. Microbial sensing of immunological communication signals. (A) Cytokines facilitate communication between immune cells. Upon recognition of pathogenic microbes, immune cells undergo activation and subsequently release an array of cytokines. Other immune cells respond to these signal molecules by killing the pathogen, recruiting more immune cells, or priming downstream signalling pathways to activate several cellular processes. (B) Cytokines can bind to microbial structures on the surface of microbes. Negatively charged lipopolysaccharides (LPS), type III secretion systems (T3SS), receptors such as outer membrane proteins (OMPs), glycosylphosphatidylinositol (GPI) anchor proteins, or cell wall polysaccharides have the capacity of binding cytokines. (C) The interaction between cytokines and pathogens can lead to two distinct outcomes: either the pathogen evades the immune response, or it activates defensive responses to counteract immune cells. (D) Cytokine sensing can induce various adaptive behaviours in pathogens, altering virulence factors and inducing biofilm formation. Cell membrane remodelling and morphological changes may also occur in response to cytokine binding, along with transcriptional and metabolic rewiring.

regulate the protection against oxidative stresses (Alonso-Monge et al. 2003). Immune cells such as neutrophils eliminate the fungus via oxidative burst, neutrophil extracellular traps formation, or the influx of cations into phagocytic vacuoles (Lee et al. 2003b, Naglik et al. 2017, Hopke et al. 2020). Moreover, bloodstream glucose concentration also induces filamentous growth of *C. albicans*, which is a crucial feature of its virulence (Alves et al. 2020) and further complicates clearance by the immune system (Austermeier et al. 2020). Such predictive adaptations and pathogenicity programs allow *C. albicans* to anticipate potential threats, thereby increasing its survival chances and fitness. Besides glucose, other carbohydrates can drive adaptation, mostly leading to immune evasion through cell wall remodelling (reviewed in Hopke et al. 2018, Childers et al. 2020).

Microbial sensing of immunological communication

Factors that induce adaptive prediction in bacteria and fungi do not necessarily need to be of metabolic nature. Cytokines are signalling molecules that orchestrate intercellular communication between both immune and non-immune cells (Fig. 2A) (Ramesh et al. 2013, Akdis et al. 2016, Taherkhani et al. 2020). Early during infection, cytokines as well as DAMPs are released by

tissue-resident immune cells and non-professional immune cells, such as epithelial cells (Stadnyk 2002, Naglik and Moyes 2011), inducing the recruitment of professional phagocytes to the site of infection. Some of the immunological signalling cytokines dictate very specific immune responses, e.g. IL-17 and IL-8 regulate neutrophil recruitment and activation (Azevedo et al. 2021, Matsushima et al. 2022), whereas chemokines such as MCP-1/CCL2 will specifically recruit monocytes to the site of infection (Zhang et al. 1994, Gunn et al. 1997), and IL-1 is a general inducer of potent innate immune activation (Mantovani et al. 2019). Bacterial and fungal pathogens that can sense cytokine production and 'predict' the host immune response would have a major fitness advantage to regulate pathogenicity, immune evasion, and escape mechanisms. On multiple occasions, bacterial and fungal pathogens have been described to interact with specific cytokines and chemokines (Table 1) that execute crucial roles in the host immune system (Table 2). The extent of these interactions varies dramatically between studies. Most commonly shown is the ability of bacteria and fungi to bind host cytokines and chemokines (Fig. 2B).

Binding of mammalian cytokines by microbial pathogens

Many microbe–cytokine binding interactions have been associated with the lectin-like properties of cytokines. Lectin-like domains are present in cytokines such as IL-1α (Cebo et al. 2002), IL-1β (Fukushima et al. 1997, Cebo et al. 2002), IL-2 (Sherblom et al. 1989, Cebo et al. 2002), IL-3, IL-4, IL-6, IL-7 (Cebo et al. 2002), and TNF (Cebo et al. 2002, Rocha et al. 2017). These lectin-like domains in cytokines were suggested to play a role in receptor and cell specificity of cytokines depending on carbohydrate recognition (Cebo et al. 2002) and can bind to glycans and glycosylated proteins constituting microbial cell walls.

The yeast *C. albicans* was found to bind a variety of cytokines with lectin-like domains. Abundantly exposed mannose residues on the fungal cell wall enable IL-2 binding, which can be inhibited by the addition of exogenous mannan (Treseler et al. 1992, Zanetta et al. 1998). Similarly, TNF binds *C. albicans* via its lectin-like properties (Rocha et al. 2017). Lectin-mediated effects were also proposed as the mechanism of IL-8 and TNF binding by the type four pili (Tpf) subunit PilE of *Neisseria meningitidis*. Cytokine binding and internalization were associated with pili glycosylation, as the binding of these cytokines could be competed away using lectins (Mahdavi et al. 2013).

The interaction of oppositely charged molecules may also facilitate cytokine binding by microbes. *Aggregatibacter actinomycetemcomitans* negatively charged lipopolysaccharide (LPS) on the outer membrane was found to bind host positively charged IL-8. This cytokine also binds to *A. actinomycetemcomitans* outer membrane vesicles (OMVs), of which LPS is one of the major components, supporting the existence of opposite-charge-based interactions that could also be involved in cytokine binding by other Gram-negative bacteria (Ahlstrand et al. 2019).

Collectively, this suggests that the binding of human cytokines to many microbes relies on natural lectin-like properties and molecular charges of cytokines. Although the function of these interactions remains elusive, this may have evolved by the immune system to serve as an opsonizing mechanism. This was observed for *Mycobacterium tuberculosis* binding of IL-8, which promotes phagocytic uptake and killing by neutrophils (Krupa et al. 2015). Similarly, *C. albicans* with bound IL-2 was shown to elicit increased proliferation rates of PBMCs compared to *C. albicans* without bound cytokine (Treseler et al. 1992).

Even though cytokine binding by microbes can be mediated by non-specific interactions, several studies elucidated specific bacterial and fungal receptors involved in host cytokine binding (Zav'yalov et al. 1995, Wu et al. 2005, Gendrin et al. 2010, Yung et al. 2011, Zelante et al. 2012, Mahdavi et al. 2013, Paino et al. 2013, Moriel et al. 2016, Ahlstrand et al. 2017, Hogbom and Ihalin 2017, Dyakov et al. 2020, Ahmed et al. 2022), a feature that is also widespread among viruses (Hernaez and Alcamí 2020). Besides minor structural similarities, no remarkable commonly shared structures can be observed, neither between the different bacterial cytokine-binding receptors nor between bacterial and human cytokine receptors. This could indicate that bacterial cytokine-binding proteins did not arise from a single origin, suggesting that cytokine-binding proteins evolved convergently (Hogbom and Ihalin 2017).

Specific receptors for host cytokines have been found in the outer membrane of Gram-negative bacteria and classified within the family of outer membrane proteins (OMPs), which serve essential roles in cell functions and as virulence factors in immune evasion (Rollauer et al. 2015). *Yersinia pestis* capsule antigen F1 assembly protein (Caf1A) was the first pore-forming OMP identified to bind host cytokines. Caf1A binds host IL-1β through its PapC domain, overlapping with Caf1 capsular protein binding site (Zav'yalov et al. 1995). Other pore-forming OMPs of *Pseudomonas aeruginosa* (OprF) and *N. meningitidis* (PilQ) were found to bind host interferon-γ (IFN-γ) (Wu et al. 2005) or bind and internalize IL-8 and TNF, respectively (Mahdavi et al. 2013). PilQ is involved in type IV pili (Tfp) assembly, interacting with Tfp PilE subunit, which has also shown the ability to bind these cytokines in a glycosylation-dependent manner (Mahdavi et al. 2013). In *A. actinomycetemcomitans*, an intrinsically disordered outer membrane lipoprotein, bacterial interleukin receptor I (BilRI), located both on the bacterial outer membrane and OMVs, was demonstrated to interact with IL-1β, IL-8, IL-10, TNF, TGF-β, and IFN-γ, and also mediates internalization of IL-1β (Paino et al. 2013, Ahlstrand et al. 2017). Not attached to the membrane but in the extracellular space, a secreted soluble protein termed IrmA (interleukin receptor mimic protein A) of *E. coli* was found to bind IL-2, IL-4, and, to a lesser extent, IL-10, due to its structural similarity with those cytokines' corresponding receptors (Moriel et al. 2016).

Apart from IL-1β binding through Caf1A protein, *Y. pestis* interacts with IFN-γ and TNF via its type 3 secretion system (T3SS) protein LcrV (V-antigen) (Nakajima and Brubaker 1993, Nakajima et al. 1995, Gendrin et al. 2010), which constitutes a major virulence factor. This interaction occurs in a concentration-dependent fashion, and was suggested not to disturb the association of IFN-γ with its receptor (Gendrin et al. 2010). However, it was suggested to suppress IFN-γ and TNF levels in mice (Nakajima and Brubaker 1993, Nakajima et al. 1995). *Mycobacterium tuberculosis* can also associate with IFN-γ through the membrane protein large 10 (Mmp10), modulating host–pathogen interplay (Ahmed et al. 2022). *Mycobacterium tuberculosis* interaction with IL-8 was also reported, even though the bacterial receptor implicated has not been clarified (Krupa et al. 2015).

The Gram-positive bacterium, *Staphylococcus aureus*, was observed to interact with a striking myriad of 31 human chemokines out of a screening of 42 chemokines. Further characterization of the chemokines CXCL9 and CXCL10 revealed direct binding of the chemokines to both, the cell wall and the membrane (Yung et al. 2011). Regarding bifidobacteria, most species carry the PFNA gene cluster, which is thought to be involved in microbe–host communication. A purified fragment of FN3 protein (encoded in the PFNA gene cluster) of *Bifidobacterium longum* was shown to bind human

Table 1. Cytokines that are bound by bacteria and fungi.

Cytokine *Cytokine has a lectin-like domain	Receptor	Microbe	Microbial response # No microbial response has been described	Reference
INF-γ	Mmp10	*M. tuberculosis*	Increased oxygen consumption rate and upregulation of virulence factors	Ahmed et al. (2022)
	T3SS	*Y. pestis*	#	Zav'yalov et al. (1995)
	OprF	*P. aeruginosa*	Upregulation of PA-I expression	Wu et al. (2005)
	BilRI	*A. actinomycetemcomitans*	#	Ahlstrand et al. (2017)
IL-8*	Unknown	*M. tuberculosis*	#	Krupa et al. (2015)
	PilQ	*N. meningitidis*	Cell wall remodelling, modified transcriptional profiling, and enhanced complement resistance	Mahdavi et al. (2013)
	BilRI	*A. actinomycetemcomitans*	Reduced biofilm eDNA content	Ahlstrand et al. (2017)
	LPS		#	Ahlstrand et al. (2019)
	Unknown	*C. albicans*	Modified hyphal tip growth pattern	Ali et al. (2006)
TNF*	FN3 protein	*B. longum*	#	Dyakov et al. (2020)
	Glycosilated PilE	*N. meningitidis*	Cell wall remodelling, modified transcriptional profiling, and enhanced complement resistance	Mahdavi et al. 2013)
	Unknown	*S. flexneri*	Increased invasion of non-professional phagocytic cells	Luo et al. (1993)
		S. typhimurium	#	
		E. coli	Increased planktonic growth of virulent, but not avirulent, strains	Luo et al. (1993)
	BilRI	*A. actinomycetemcomitans*	#	Lee et al. (2003a)
	N,N′-diacetylchitobiose	*C. albicans*	Reduced biofilm metabolism and yeast-to-hyphae transition	Ahlstrand et al. (2017)
IL-1β*	Caf1A	*Y. pestis*	#	Rocha et al. (2017)
	Unknown	*E. coli*	Increased planktonic growth of virulent, but not avirulent, strains	Zav'yalov et al. (1995)
	BilRI	*A. actinomycetemcomitans*	Reduced biofilm eDNA content	Porat et al. (1991)
IL-2*	IrmA protein	*E. coli*	Increased planktonic growth of virulent, but not avirulent, strains	Paino et al. (2013)
IL-4*	IrmA protein	*E. coli*	#	Ahlstrand et al. (2017)
IL-10	IrmA protein	*E. coli*	#	Denis et al. (1991)
	BilRI	*A. actinomycetemcomitans*	#	Moriel et al. (2016)
IL-17A	Crh11p	*C. albicans*	Augmented filamentous growth, adhesion, and autophagy	Moriel et al. (2016)
	Crf1	*A. fumigatus*	Increased biofilm formation and autophagy	
CXCL9, CXCL10	Unknown	*S. aureus*	Protein A (SPA) release	Ahlstrand et al. (2017)

Table 2. Immune mediators and their function that microbes could benefit from interfering with.

Immune mediator	Function
IL-1α	General alarmin released upon tissue damage that potently activates immune responses
IL-1β	Potent broad-spectrum mediator of inflammation released upon innate immune activation
IL-1Ra	Endogenous antagonist of the interleukin-1 receptor
IL-2	Activator of T-cell proliferation
IL-3	Hematopoietic growth factor of myeloid cells and their progenitors
IL-4	Potent driver of T-helper 2 and B-cell responses
IL-6	Mediator of systemic inflammatory responses
IL-7	Stimulation of T and B-cell proliferation
IL-8 (CXCL8)	Neutrophil chemoattractant and activator
IL-10	Potent anti-inflammatory cytokine
IL-17A	Potent driver of neutrophil-mediated inflammation and activator of mucosal host defence
IL-18	Activation of T-helper 1 immunity and driving IFN-γ responses
α1-antitrypsin	Acute-phase protein with potent protease inhibitory function
CXCL9 (MIG)	IFNγ-induced broad-spectrum chemokine
CXCL10 (IP10)	IFNγ-induced broad-spectrum chemokine
GM-CSF	Activation, survival, and proliferation factor for myeloid cells
MCP3 (CCL7)	Broad-spectrum chemokine
MIP1α (CCL3)	Recruitment and activation of granulocytes
PGE_2	Immunoregulatory lipid mediator
TGF-β	Broad spectrum immunoregulatory cytokine with antiproliferative effects
IFN-γ	Activator of myeloid phagocytes, promotes killing of intracellular and phagocytosed pathogens
TNF	Potent broad-spectrum mediator of inflammation released upon innate immune activation

TNF, presumably due to the presence of two fibronectin domains similar to cytokine-binding sites of human receptors (Dyakov et al. 2020). Further interactions of *E. coli* with IL-1β (Porat et al. 1991) and TNF (Luo et al. 1993), as well as *Shigella flexneri* and *Salmonella typhimurium* with TNF (Luo et al. 1993), were reported, although the bacterial receptors involved in these interactions have not been identified yet.

In fungi, the *C. albicans* Crh11p protein, a GPI-anchored fungal protein involved in cell wall assembly and regeneration (Pardini et al. 2006), was identified to bind human IL-17A, leading to changes in fungal virulence. Similarly, IL-17A binding was observed in the environmental fungus *Aspergillus fumigatus* depending on Crf1, an orthologue of *C. albicans* CRH GPI proteins (Zelante et al. 2012). *Candida albicans* also binds the neutrophil chemoattractant IL-8 during germination (Ali et al. 2006). Interestingly, antibody staining for IL-8 receptor A (IL-8RA) also stained the tips of the hyphae (Ali et al. 2006). This could suggest the presence of proteins in the fungal cell wall similar to IL-8RA that exhibit cross-reactivity with anti-IL-8RA antibodies.

Microorganisms can also indirectly bind various host glycoproteins, including cytokines such as the monocyte chemotactic protein 3 (MCP3), the macrophage inflammatory protein 1α (MIP-1α/CCL3) or IFN-γ, via heparin, leading to reduced chemokine-induced chemotaxis (Duensing et al. 1999). *Staphylococcus aureus* protein A (SpA), known for its ability to bind the Fc region of immunoglobulins (Foster 2005), was also found to bind heparin (Shi et al. 2021), and thereby potentially several cytokines with it.

Some microbial cytokine-binding molecules seem to have broad binding capacity, such as BilRI. This interestingly can be explained based on its properties as an intrinsically disordered protein, which lacks a properly defined 3D structure, allowing the interaction with several different molecules (Ahlstrand et al. 2017), while for cytokines with lectin-like domains, it appears plausible that specific carbohydrate structures are preferred binding partners.

For many of the interactions of microorganisms with immune mediators through binding, downstream microbial responses, physiological adaptations, or consequences have not been described or studied in depth (Table 1). However, even without inducing microbial responses, cytokine binding can already impact host–pathogen interactions drastically. Based on literature on other consequences of protein binding, we can extrapolate some potential effects resulting from binding of cytokines to microbial pathogens. Although it has not been described for cytokines, binding of host proteins (e.g. extracellular matrix components) can mask pathogen-associated molecular patterns (PAMPs) that are recognized by innate immune cells (Bhattacharya and Horswill 2024) or avoid complement activation, promoting immune evasion (Tomlin and Piccinini 2018). This is similar to how immunologically inert proteins mask PAMPs of spores of fungi such as *A. fumigatus* or how a capsule masks *Cryptococcus neoformans* PAMPs (Erwig and Gow 2016, van de Veerdonk et al. 2017). The binding of complement regulatory proteins by pathogens is a strategy to decrease complement activation, which increases survival (Kotwal 2000, Reuter et al. 2010, Meri et al. 2013, Hovingh et al. 2016, Moore et al. 2021).

In line with this, cytokine binding by pathogenic fungi and bacteria could, under specific circumstances, serve as a mechanism to sequester cytokines from reaching the cognate receptor on immune cells, thus hindering their subsequent initiation or chemoattraction. This strategy was shown for several poxviruses, which express a viral IL-18 bp to sequester host IL-18 and impair the subsequent IL-18-induced IFN-γ production and natural killer cell responses (Xiang and Moss 1999, Born et al. 2000, Smith et al. 2000). Yet, bacterial cytokine sequestration also has been shown to impact cells expressing the appropriate receptors (Duensing et al. 1999). Moreover, internalization of cytokines by bacteria (Mahdavi et al. 2013, Paino et al. 2013, Ahlstrand et al. 2017) will limit their availability for the corresponding recipient immune cells.

In conclusion, cytokine binding has been identified in numerous bacterial and fungal pathogens mediated by several diverse microbial binding components. These range from oppositely charged proteins to cell wall structures, secretory proteins, and microbial cytokine receptors (Table 1). Cytokine–microbe

interaction can occur through biophysical mechanisms, often involving the lectin-like properties of cytokines. Cytokine binding may serve as a strategy for immune evasion or escape (Fig. 2C), suggesting an adaption by microbes to exploit host immune signals. While the precise functions of these interactions remain to be fully elucidated, in a variety of cases microbes have been observed to activate anticipatory responses to the cytokines they interact with.

Microbial responses to mammalian cytokines and immune mediators

While viruses can efficiently modulate immune responses, several bacterial and fungal pathogens have been shown to actively respond when interacting with host immune mediators. A microbial response to host cytokines requires a reciprocal interaction between both, the host and the pathogen. Exemplary, incubation of peripheral blood mononuclear cells (PBMCs) with *P. aeruginosa* biofilms activates an inflammatory response reflected in the corresponding cytokine secretion. Interestingly, the PBMC:Biofilm co-culture is beneficial for the pathogen, as it increases the number of biofilm-associated bacteria (Kaya et al. 2020). *Pseudomonas aeruginosa* biofilms cultured with challenged PBMC supernatants, which contain pro-inflammatory and anti-inflammatory cytokines, also increased the number of viable colony-forming units, suggesting bacterial feedback to the host inflammatory environment (Kaya et al. 2020). In addition to physical interaction, specific mammalian immune mediators have been observed to trigger microbial responses in terms of metabolism, growth, morphology, and/or biofilm formation. These responses could suggest that adaptations favouring pathogenicity are induced by prior recognition of host cytokines before immune cells are encountered.

Similar to the example above, a variety of bacterial pathogens induce adaptations in response to cytokines. Growth of virulent, but not avirulent, *E. coli* strains increases when cultured in the presence of IL-1β (Porat et al. 1991), IL-2, GM-CSF (Denis et al. 1991), and TNF (Lee et al. 2003a), suggesting that cytokine sensing is a virulence-associated trait. The effects of IL-1β on *E. coli* growth could be neutralized by the host endogenous IL-1 receptor antagonist (IL-1Ra) (Porat et al. 1991). This could suggest that IL-1β sensing by the bacteria is mediated by an IL-1-receptor-like structure (Porat et al. 1991). Despite enhancing planktonic bacterial growth, IL-1β seems to reduce biofilm formation and haemolytic activity of uropathogenic *E. coli* (UPEC; Engelsoy et al. 2019). Effects of TNF on *E. coli* growth were also validated in a mouse model. While TNF-deficient mice show a drastically increased susceptibility to *E. coli* infections due to a compromised host response, in the background of neutropenia, the bacterial burden was reduced in TNF-deficient mice (Lee et al. 2003a).

Clinical isolates of *S. aureus* and *Acinetobacter* sp. also show enhanced growth when incubated in the presence of IL-1β, while *P. aeruginosa* growth can be increased by the presence of IL-6 (Meduri et al. 1999). Interestingly, continuous passages of the clinical isolates *in vitro* were associated with a loss of the phenotype (Meduri et al. 1999), which could indicate that the ability to adapt in response to mammalian cytokines is transient and only coupled to adaptation when bacteria have recently encountered the immune system in the host. IL-6 also promoted the growth of *M. avium*, a bacterium that survives within macrophages, demonstrated by increased intracellular growth rates when IL-6 was present (Denis and Gregg 1991). Strikingly, growth was also augmented by IL-6 in the absence of macrophages, suggesting a direct effect of IL-6 on bacterial growth. *Staphylococcus aureus* biofilms showed an increased biomass when exposed to proinflammatory IL-1β (McLaughlin and Hoogewerf 2006, Gutierrez Jauregui et al. 2019). Interestingly, nasal carrier strains of *S. aureus* induce lower IL-1α and IL-1β responses in naïve nasal epithelial cells compared to non-carrier strains. This modulation of the immune response favours the bacterium, since IL-1α can drive inflammatory responses as well as negatively affect bacterial planktonic growth directly (Quinn et al. 2009). *Aggregatibacter actinomycetemcomitans* biofilm composition changes in response to IL-1β and IL-8, which seems mediated by its BilRI (Ahlstrand et al. 2017). Strikingly, BilRI-deficient mutants (*bilRI*$^-$) and thus unable to bind these cytokines, exhibited a different biofilm composition compared to wild-type (Ahlstrand et al. 2017).

In *M. tuberculosis*, exposure to IFN-γ increases oxygen consumption rate and improves microbial persistence *in vitro* in a 3D granuloma model (Ahmed et al. 2022). Of note, IFN-γ did not increase *M. tuberculosis* growth in the absence of immune cells, suggesting that the augmented bacterial burden is due to increased fitness and resistance to the immune attack, rather than increased bacterial growth itself (Ahmed et al. 2022). Despite the effects of IFN-γ on potentiating *M. tuberculosis* growth, the enhanced metabolic activity translates to increased sensitivity to isoniazid (Ahmed et al. 2022), for which normally extremely long treatment regimens are required due to slow mycobacterial growth.

Further studies characterized specific bacterial and fungal responses to mammalian cytokines such as altered virulence factor expression and/or increased virulence in infection models. *Pseudomonas aeruginosa* senses IFN-γ through OprF, and upregulates expression of *P. aeruginosa* type I lectin (PA-I), one of its key adhesins and virulence factors, which is involved in epithelial barrier disruption (Wu et al. 2005). *Pseudomonas* response to IFN-γ was proved to be mediated by activation of a quorum sensing (QS) signalling system, as the increase of PA-I after IFN-γ exposure was abrogated in mutant strains lacking the required genes for QS system activation (*rhlI* and *rhlR*). Similarly, sensing of IFN-γ by *M. tuberculosis* results in upregulation of virulence factor genes, including the RNase toxin *vapC14* and ESAT-6-like protein *esxP* (Ahmed et al. 2022). Sensing of TNF by *S. typhimurium* alters expression of virulence effectors, consequently increasing invasiveness of epithelial cells and altering the host immune responses (Ma et al. 2010). Chronic *Salmonella* infection was associated with an increased risk of inflammatory bowel disease development, where TNF is increased (Ma et al. 2010). This association is due to the altered immune response triggered by the bacterium (Zha et al. 2019). *Neisseria meningitidis* induces bacterial cell membrane remodelling, transcriptional responses, and enhanced virulence following uptake of pro-inflammatory cytokines (Mahdavi et al. 2013). Mutant strains lacking the specific receptors result in reduced animal mortality (Mahdavi et al. 2013). UPEC sensing of cytokines increases the expression of iron acquisition systems and those related to fimbriae production, resulting in enhanced virulence in a *C. elegans* infection model (Engelsoy et al. 2019). *Staphylococcus aureus* sensing of IL-1β increases its growth but is also related to changes in virulence gene expression, including leukotoxins and surface proteins involved in extracellular matrix binding such as the fibronectin-binding protein or the collagen-binding protein (Kanangat et al. 2007). This was suggested to potentially contribute towards improved invasion and persistence within the host inflammatory environment. Further, the binding of CXCL9 and CXCL10 by *S. aureus* was observed to induce protein A (SpA) release (Yung et al. 2011), a wall-anchored protein

involved in immune evasion, avoiding opsonization (Foster 2005). SpA can also be secreted to the extracellular compartment, where it acts as a superantigen (Bear et al. 2023). Protein A deletion increases bacterial killing by phagocytes and results in decreased virulence *in vivo* (Foster 2005). The relevance of *S. aureus* responding to CXCL9 is reflected by the fact that this chemokine is present in high amounts in the skin, the natural niche of *S. aureus* (Yung et al. 2011). Additionally, both CXCL9 and CXCL10 are upregulated by the type 1 immunity hallmark cytokine IFN-γ (Kanda et al. 2007, Corbera-Bellalta et al. 2016). This could suggest that *S. aureus* uses the chemokine presence to evaluate the current host immune status. Although CXCL9 and CXCL10 were not addressed specifically, another study showed that IFN-γ-associated CXCL-type chemokine production can support *S. aureus* infection in the skin (McLoughlin et al. 2008). A detrimental involvement of IFN-γ in *S. aureus*-caused disease suggests that the bacterium uses CXCL chemokines to recognize a state of host susceptibility, before engaging a virulence program (Wei et al. 1999, McLoughlin et al. 2008, Satorres et al. 2009, Yung et al. 2011). Similarly, this could be the case for *E. coli* IrmA protein, which mimics IL-4 and IL-2 receptors, thereby sensing a Th2-dominated environment (Moriel et al. 2016). As IL-4/IL-13-driven type 2 immunity generally is considered inadequate for efficient antibacterial defence (Hultgren et al. 1998, Potian 2011, Woytschak 2016), IrmA thus might also act as a host susceptibility sensor and downstream lead to engagement of a virulence program.

Similar to bacteria, fungi also exhibit responses to host cytokines, promoting their persistence during infection. The sensing of the neutrophil chemoattractant IL-8 by *C. albicans* leads to a modification in the hyphal tip growth pattern, away from areas with high IL-8 concentrations (Ali et al. 2006). Since the hyphal tip is likely more sensitive to neutrophil attack and IL-8 promotes their recruitment, such a response could have evolved as a strategy to avoid a neutrophil attack. Sensing of IL-17A by *C. albicans* induces not only changes in fungal growth but also in filamentation dynamics and transcriptional responses, characterized by the upregulation of genes involved in autophagy and hyphal morphogenesis, which was associated with improved fungal fitness against neutrophils (Zelante et al. 2012). Similar observations were made with *A. fumigatus* (Zelante et al. 2012), which is surprising since *A. fumigatus* evolved its pathogenicity in environmental niches (Casadevall 2003, Tekaia 2005, Hube 2009). Thus, *A. fumigatus* unlikely would have co-evolved with a host expressing IL-17. However, proteins with structural similarity to IL-17A have been found in *C. elegans* (Chen et al. 2017). As nematodes and amoebae can represent a major predatory threat to environmental fungi (Mylonakis 2002, Casadevall 2003), this raises the possibility of the development of IL-17A sensing capability in an early common ancestor. In contrast, when interacting with TNF, *C. albicans* exhibits reduced biofilm metabolism and yeast-to-hyphae transition (Rocha et al. 2017) and also IFN-γ limits its filamentous growth (Kalo-Klein and Witkin 1990).

The ability of microbial pathogens to react to host cytokines and other immune mediators reveals a complex field of host–pathogen interactions. Thereby, specific cytokine signalling facilitates microbial adaptation such as enhanced proliferation, altered virulence factor expression, biofilm formation, morphological changes, cell remodelling, as well as metabolic and transcriptional alterations (Fig. 2D). The observed microbial responses suggest that cytokine sensing is a virulence-associated trait, enabling pathogens to modulate their response to the host immune environment.

Adaptation to in-direct signals of altered immune activation

Microbial interaction with immune cells can elicit host cell death. In the case of *C. albicans*, the toxin candidalysin induces macrophage lysis and subsequent release of intracellular content as well as NLRP3 inflammasome activation (Kasper et al. 2018). In this context, the release of macrophage cytosolic content and IL-1β through pyroptosis will promote recruitment and activation of further immune cells to overcome the infection (Gross et al. 2009, Drummond et al. 2019). Interestingly, the macrophage-derived protein prothymosin α, found in macrophage lysates, can augment fungal pathogenicity by inducing filamentation (Case et al. 2021). This example showcases that microbes have evolved strategies to cope with the immune activation upon macrophage lysis through recognition of macrophage cytosolic molecules.

Activation of inflammation causes induction of acute-phase proteins. Intriguingly, the acute phase serum protein α1-antitrypsin can induce transcriptional changes in *C. albicans* characterized by reduced expression of filamentation repressors, also leading to more potent filamentation and thereby impairing fungal clearance by innate immune cells (Jaeger et al. 2024). Inflammation is also associated with epithelial barrier disruption, vascular leakage, and infiltration of serum proteins in infected tissues. In line with this, albumin, the most abundant protein in human serum, was found in the vaginal fluid of vaginal candidiasis patients (Tang et al. 2007). Interestingly, the presence of albumin boosts proliferation and unlocks pathogenic potential, as well as oxidative stress resistance, of the yeast pathogen *C. glabrata* (Pekmezovic et al. 2021). Albumin was also found to protect group G streptococci against antibacterial peptides released upon epithelial activation. As common commensals of the oropharyngeal tract, albumin-binding capability was hypothesized to have a role in nutrient acquisition under non-inflammatory conditions (Egesten et al. 2011).

Cross-kingdom communication via lipid mediators and hormones

In addition to cytokines that are specific to the mammalian host, the immune system also relies on a network of lipid mediators (eicosanoids) that not only mediate pro-inflammatory effects but also play crucial roles in resolving inflammation (Dennis and Norris 2015). The family of eicosanoids includes prostaglandins, thromboxanes, and leukotrienes, metabolites derived from either cyclooxygenases or lipoxygenases acting on the precursor arachidonic acid (AA), which is released from host membranes (Debeuf 2018). Although synthesis of cytokines has not been described in microbes, most human pathogenic fungi, but not bacteria, can synthesize eicosanoids, especially when free AA is available to them (Noverr et al. 2002). In fungi, different enzymes are involved in the process of prostaglandin synthesis. While *Aspergillus* spp. possess genes (*ppoA*, *ppoB*, and *ppoC*) that encode for cyclooxygenase-like enzymes (Tsitsigiannis et al. 2005), *C. albicans* employs a fatty acid desaturase (Ole2) and a multicopper oxidase (Fet3) for PGE_2 production (Erb-Downward and Noverr 2007). Nevertheless, compounds commonly used to inhibit PGE_2 production in humans are also effectively decreasing the production levels of PGE_2 by *C. albicans* and *C. dubliniensis* (Ells et al. 2011). This suggests that fungal enzymes not only exhibit functional similarities but also structural resemblances to their human counterparts. *Candida albicans* and *C. neoformans* do not only possess the machinery to produce prostaglandins, but their secreted prostaglandins

modulate immune responses by increasing the release of the anti-inflammatory cytokine IL-10 (Noverr et al. 2001). *Cryptococcus neoformans*-derived phospholipase can aid its survival within macrophages by facilitating eicosanoid production and impairing macrophage antifungal defences (Noverr et al. 2003). *Candida albicans* mutants deficient in PGE_2 production exhibited reduced fitness in the gastrointestinal tract of mice, and fungal PGE_2 production protected *C. albicans* from intestinal phagocytes (Tan et al. 2019). These findings imply that PGE_2 promotes colonization and survival in the commensal niche (Tan et al. 2019). Fungal eicosanoids also seem to play a key role in pathogenicity mechanisms and fungal survival, as cyclooxygenase inhibitors were observed to reduce the viability of *C. albicans* and *C. neoformans* (Noverr et al. 2001). In *C. albicans*, eicosanoids were observed to regulate the yeast-to-hypha transition (Kalo-Klein and Witkin 1990, Noverr et al. 2001, Noverr and Huffnagle 2004, Ells et al. 2011). Strikingly, the hyphal, but not yeast, morphology of *C. albicans* is also a strong inducer of eicosanoids in neutrophils and macrophages (Fischer et al. 2021, Schimanski et al. 2024), suggesting an adaptive strategy to anticipate the neutrophil-imposed stress that would follow eicosanoid production.

Host, as well as fungal-derived PGE_2, was shown to compromise vaccination efficiency and redirect cytokine responses from a protective Th1- towards a Th2-associated phenotype (Kundu and Noverr 2011). Opportunistic pathogenic fungi may produce lipids to modulate the host immune response, but also exploit host-produced lipids to enhance their pathogenicity. Altogether, recognition and even more so the production of lipid mediators enables pathogenic fungi to directly manipulate signalling processes of the immune network, which might play an important effector role in deploying adaptive pathogenicity. Elucidating how and under which circumstances eicosanoid synthesis is switched on is essential to understand virulence of pathogenic fungi such as *Candida* spp., and *Aspergillus* spp.

A special case of lipid mediator communication between host and pathogen is steroid hormones. Steroid hormones, both glucocorticoids and sex hormones, play a role in immunity, reducing inflammation and shaping immune cell differentiation and cytokine production (Bereshchenko et al. 2018). As a commensal of the vaginal mucosa, *C. albicans* is widely exposed to estrogen and also expresses a high-affinity estrogen-binding protein that partially mediates the inhibitory effect of hyphal formation by 17β-estradiol (Madani et al. 1994, Kurakado et al. 2017, Sherrington et al. 2018). More recently, it was shown that upon exposure to this hormone, *C. albicans* undergoes further adaptions, and expresses a receptor to bind the complement regulatory protein factor H on its surface to sabotage complement-mediated opsonization and phagocytosis (Kumwenda et al. 2022).

Bacteria are also known to sense and adapt to human sex hormones, which is associated with differences in infection rates and disease outcomes between genders (Garcia-Gomez et al. 2013, Vom Steeg and Klein 2017, Vidaillac et al. 2020). *Pseuromonas aeruginosa* exposure to different estrogens proved to increase bacterial motility—a key requisite for initiation of biofilm formation—as well as biofilm formation, adherence, and invasiveness of the bronchial epithelium (Tyrrell and Harvey 2020). In female cystic fibrosis patients, exacerbations have been associated with the follicular phase of the menstrual cycle, where estrogen levels are increased. Estrogens (estriol and estradiol) can drive alginate production in *P. aeruginosa*, a polysaccharide involved in bacterial pathogenicity, parenchymal damage, and the mucoid morphology (Chotirmall et al. 2012). The transition to the mucoid morphology is linked to loss-of-function mutations in the *mucA* gene, the main regulator of alginate production, which occurs upon estrogen exposure (Chotirmall et al. 2012). *Chlamydia trachomatis* exposure to sex hormones influences its transcription, and chlamydial infection outcome has been associated with the hormonal status of the epithelium. Estradiol treatment *in vitro* induces a transcriptional pattern suggestive of a *C. trachomatis* persister strategy, while progesterone induces a pattern rather resembling an active infection (Amirshahi et al. 2011).

Host amine hormones, such as adrenaline or noradrenaline, can also elicit microbial responses. The ability to sense these neurotransmitters facilitates bacterial adaptation to changing host environments, and is mediated via quorum-sensing systems, which induce a synchronized response to efficiently avoid the host defences (Karavolos et al. 2013). Bacteria were shown to directly bind adrenaline and noradrenaline through the QseC sensor kinase, a part of the autoinducer-3 (AI-3) quorum-sensing system, leading to expression of virulence genes in enterohemorrhagic *E. coli* O157:H7. Further, *qseC*-deficient mutants exhibit a reduced virulence, highlighting the importance of this signalling system during host–pathogen interactions. Interestingly, the periplasmic sensing domain of QseC is conserved among several bacterial species, as well as homologue to a fungal protein of unknown function in *Aspergillus nidulans* (Clarke et al. 2006). Another putative adrenaline receptor, the BasSR two-component signal transduction system, was identified in *S. typhimurium*. Adrenaline signalling through this receptor reduces antimicrobial peptide resistance of the bacteria. However, sensing of adrenaline also induces expression of oxidative stress resistance genes (such as *sodA*), suggesting that adrenaline sensing may serve as a cue for upcoming host-imposed stresses (Karavolos et al. 2008). Conversely, sensing of serotonin by the receptor CpxA, commonly found in enteric bacteria, can reduce virulence of enterohemorrhagic *E. coli* and *Citrobacter rodentium* (Kumar et al. 2020), possibly serving as a surrogate for a resistant host status, where engagement of virulence would be detrimental for the microorganism.

Conclusions and future perspectives

The success of pathogenic bacteria and fungi can be linked to their ability to adapt to the host and escape host defence mechanisms. Nevertheless, apart from a handful of primary pathogens that can cause infections at low inocula, human pathogens are highly restricted in causing infection due to protective layers of innate and adaptive immune defences. Among viruses, the manipulation of host responses is widespread, yet as outlined in this review, it has become evident that also bacteria and fungi can adapt to and anticipate immune activation by sensing and responding to immune mediators. Interestingly, microbial ability to bind/sense host cytokines is extensively distributed among regular commensal microorganisms, such as *E. coli* or *S. aureus*, suggesting that these mechanisms could be a consequence of host–microbe co-evolution. This cross-kingdom sensing facilitates metabolic adaptation to overcome nutritional immunity, PAMP masking to evade immune recognition, defensive and offensive pathogenicity strategies that facilitate the escape from innate immune cells, as well as the formation of biofilms that aid persistence in the host. Microbial adaptations in response to inflammatory mediators may offer an additional explanation to why chronic inflammatory diseases, such as inflammatory bowel disease or diabetes, are associated with drastic changes in the microbiome (Standaert-Vitse et al. 2009, Gosiewski et al. 2014, Wheeler et al. 2017).

However, microbial sensing of the immune status should also be considered with the increasing use of immunotherapeutic and immunomodulatory strategies used in the clinics. A potential example of this is the anti-PD-1 therapy. This immune checkpoint inhibitor boosts levels of IFN-γ, leading to *M. tuberculosis* reactivation. It is not clear if the described sensing of IFN-γ by *M. tuberculosis* (Ahmed et al. 2022) plays a direct role, but it is an intriguing possibility. Similarly, PD-1 inhibition also increases Th17 responses (Dulos et al. 2012) and can trigger allergic bronchopulmonary aspergillosis (ABPA) (Pradere et al. 2017, Donato and Krol 2019). Here, it also is unclear whether IL-17 sensing by *A. fumigatus* contributes (Zelante et al. 2012), yet Th17 responses are also associated with acute ABPA (Bacher et al. 2019).

Adaptation in response to immune mediators provides pathogens with the key advantage of tailoring pathogenicity mechanisms to the host immune status. An in-depth understanding of the molecular mechanisms driving adaptive pathogenicity strategies could reveal potential targets for therapeutic strategies against virulence and pathogenicity (Siscar-Lewin et al. 2019). In contrast to conventional antimicrobial therapy, which often affects the growth and survival of large groups of microorganisms, targeting virulence specifically would circumvent eradicating opportunistic pathogens as long as they are still part of a beneficial microbiome (Siscar-Lewin et al. 2019, Alonso-Monge et al. 2021).

Acknowledgements

The authors acknowledge Sophie Austermeier for feedback on early drafts of the manuscript.

Conflict of interest: The authors have no conflict of interest to declare.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) Emmy Noether Program [project no. 434385622/GR 5617/1-1 to M.S.G.]. We further acknowledge funding of this project from the Carl Zeiss Stiftung [to M.S.G.] and by an Exploration Grant of the Boehringer Ingelheim Foundation (BIS) [to M.S.G.].

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Received 11 September 2024; **revised** 19 December 2024; **accepted** 27 December 2024