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Editorial: Reviews in microbial pathogenesis

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Editorial on the Research Topic Reviews in microbial pathogenesis

Microbiology is a fast-growing research field. The rapid expansion of this field is driven by ongoing discoveries of emerging pathogens, microbial adaptation, resistance mechanisms and technological advancements. While these trends will likely continue to drive new discoveries and novel solutions for infectious diseases, the overwhelming volume of research publications makes it difficult for scientists to keep pace with the latest findings. Additionally, access to cutting-edge research can be limited by paywalls, creating barriers for both early-career researchers and those in resource-limited settings.

The present Research Topic, focusing on reviews in microbial pathogenesis, includes 16 publications (15 peer-reviewed articles and 1 erratum), including 72 authors, to address these challenges. By providing open-access, comprehensive reviews and accessible summaries of recent findings, this Research Topic offers a valuable platform for the researchers to navigate key advancements in the field of microbiology, emphasizing important directions for future research and offer insights into emerging trends and methodologies.

The review by [Mohammad et al.](#) addressed the role of lipoproteins (Lpps) in the pathogenesis of *Staphylococcus aureus*. *S. aureus* produces Lpps that contribute to metabolism, are essential for the survival of bacteria and are important for tissue invasion. Additionally, they are capable of affecting disease pathogenesis by modulating the immune response ([Mohammad et al., 2020](#); [Nguyen and Götz, 2016](#)) via binding to Toll-Like Receptors 2 (TLR2), leading to activation of innate immune responses ([Hashimoto et al., 2006](#)). Binding of these molecules to TLR2 causes rapid migration of innate immune cells, including monocytes/macrophages and neutrophils ([Mohammad et al., 2019, 2021](#)). Also, Lpps can stimulate interferon γ producing T cells ([Saito and Quadery, 2018](#)), although there is limited effect on B cell activation ([Mohammad et al., 2019](#)). The *in vitro* and *in vivo* effects of Lpps are believed to be mediated by interaction with TLR2-dependent neutrophil recruitment ([Mohammad et al., 2019](#)). It was demonstrated that neutrophils and macrophage recruitment is facilitated by the release of chemokines such as MIP-2, KC, MCP-1 and MPO ([Mohammad et al., 2021](#)). The role of TLR2 in the pathogenesis of Lpps-induced pathology is also supported by the TLR2-knockout mouse model ([Schmaler et al., 2009](#)).

In another review, [Schwermann and Winstel](#) summarize the functional diversity of *Staphylococcus* surface proteins, which play a crucial role in host interaction and pathogenesis. *Staphylococcus* expresses several surface proteins, including clumping

factor B (ClfB), fibronectin-binding protein B (FnBPB), and iron-regulated surface determinant protein A (IsdA), which bind to human loricrin receptor on epithelial cells. This binding facilitates initial adhesion and invasion of host cells (Clarke et al., 2009; da Costa et al., 2022; Mulcahy et al., 2012), particularly on skin and nasal surfaces. Bacterial surface proteins also contribute to immune evasion and persistence (Kim et al., 2010). For example, Clumping factor A (ClfA), collagen adhesin and protein A (SpA) are key factors in the pathogenesis of septic arthritis (Josefsson et al., 2001; Palmqvist et al., 2002; Xu et al., 2004). ClfA is also involved in biofilm formation, which protects *S. aureus* from phagocytosis (Dastgheyb et al., 2015). The essential role of *S. aureus* surface proteins in infections make them attractive targets for the development of novel therapeutics. Immunization with IsdA or IsdB has been shown to reduce the virulence of *S. aureus* (Kim et al., 2010). Additionally, anti-SpA monoclonal antibodies demonstrated therapeutic potential in mouse abscess models (Cheng et al., 2011). Overall, this strongly indicates that targeting specific surface proteins could be a viable strategy for controlling *S. aureus* infections.

Acosta-Espana and Voigt shed light into the differences between entomophthoromycosis and mucormycosis. Fungi, causing entomophthoromycosis and mucormycosis, were initially placed into the class *Zygomycetes* (Voigt et al., 1999), including *Entomophthorales* and *Mucorales*. In 2007, the phylum *Zygomycetes* was replaced by *Mucoromycota* and *Zoopagomycota* (Spatafora et al., 2016). However, the old terms are still used in many publications, creating confusion about fungal species identification. The authors summarize information on *Basidiobolales*, *Entomophthorales*, and *Mucorales* to address this confusing issue and make it clear and easy for clinical researchers to use the updated fungal taxonomy. The authors state that current taxonomy identifies the classes *Mucoromycota* (order *Mucorales*), *Zoopagomycota* (order *Entomophthorales* [*Conidiobolus* spp.]) and *Basidiobolales* (*Basidiobolus* spp.). Instead of the term “zygomycosis”, more defined terms should be used, such as: 1. Infection with *Mucorales* should be referred to as mucormycosis; 2. Infection with *Basidiobolus* spp. as basidiobolomycosis; 3. *Conidiobolus* spp. as conidiobolomycosis. These fungal infections have differences in pathogenesis as mucormycosis is diagnosed primarily in patients with impaired cellular immunity [Center for Disease and Prevention (CDC), n.d.], while basidiobolomycosis and conidiobolomycosis occur in immunocompetent patients (Geramizadeh et al., 2015; Kundu and Chakraborty, 2023; Spatafora et al., 2016). Clinical presentations of these infections differ as well. Patients infected with *Mucorales* species have rapid spread with angioinvasion and necrosis [Center for Disease and Prevention (CDC), n.d.]. In contrast, the slow progression of clinical symptoms is characteristic of *Basidiobolus* spp. and *Conidiobolus* spp. (Raghavan et al., 2020). The diagnosis is based on epidemiologic, clinical, imaging, histopathologic, microbiologic, and molecular data, followed by the confirmatory report of a fungal culture.

A review by Mlynek and Bozue addressed the impact of phase variation and biofilm formation in *Francisella tularensis*. *F. tularensis* causes tularemia, a zoonotic disease often transmitted

through contact with rabbits (Ellis et al., 2002). There are two primary subspecies: *F. tularensis subsp. tularensis* (Type A) and *F. tularensis subsp. holarctica* (Type B), both can be transmitted to humans (Larson et al., 2020). Different species within the *Francisella* genus exhibit varying capabilities to form biofilms. Subspecies of *F. tularensis* tend to form less defined structures compared to *Francisella novicida* (Mahajan et al., 2011; Margolis et al., 2010). These differences are partly due to genetic variations. For example, *F. novicida* retains a functional cyclic-di-GMP system (c-di-GMP), which is absent in *F. tularensis* (Kingry and Petersen, 2014). The *wbt* locus in *F. tularensis*, which contributes to O antigen synthesis, contains genes that are not present in *F. novicida* (Kingry and Petersen, 2014). GMP stimulates biofilm formation by upregulating genes encoding extracellular polysaccharides (Hickman et al., 2005). Additionally, the O antigen contributes to biofilm formation in *F. tularensis* isolates (Champion et al., 2019). Biofilms enhance bacterial persistence by protecting against host defenses and antibiotic treatment. Notably, biofilm formation has been shown to reduce susceptibility of *F. tularensis* to ciprofloxacin (Siebert et al., 2020), further complicating treatment efforts.

The role of *Francisella* peptidoglycan biosynthesis enzymes in morphology, pathogenesis and treatment of infection is discussed in the review by Bachert and Bozue. The bacterial cell wall is constantly remodeling in response to environmental changes and cell division. Peptidoglycan (PG) remodeling is a coordinated process involving several enzymes. PG biosynthesis begins with the formation of a lipid II precursor (Egan et al., 2020). The precursor is subsequently polymerized with penicillin-binding proteins (PBPs). Many organisms encode multiple PG enzymes with redundant function (Lee et al., 2017; van Heijenoort, 2011). Interestingly, this is not a characteristic of *F. tularensis* (Kijek et al., 2019). There are currently five carboxypeptidases and two lytic transglycosylases known in *Francisella* (Sauvage et al., 2008). They all have distinct roles in cell morphology (Spidlova et al., 2018; Zellner et al., 2021) and contribute to the immunomodulating activity of this bacterium (Nakamura et al., 2021). This suggests that PG enzymes could be used as a therapeutic target specifically against this organism.

Approaches for identifying bacterial effector kinases are summarized in the review by Louis et al. Many pathogens encode proteins with sequence homology to eukaryotic kinase domains (Anderson et al., 2015; Moss et al., 2019; Navarro et al., 2007). Some of these bacterial kinases can phosphorylate host cell proteins to manipulate signaling pathways, thereby promoting bacterial replication and survival within the host (Park et al., 2019; Tegtmeyer et al., 2017). However, understanding the role of these kinases in the pathogenesis of bacterial disease is limited, primarily due to insufficient knowledge of their target host proteins. Improved identification of host targets for bacterial kinases could pave the way for the development of novel antimicrobial therapeutics that disrupt these critical interactions.

Manipulation of host signaling pathways by *Neisseria gonorrhoeae* is discussed by Walker et al. The mucosal epithelium serves as the primary portal of entry for *N. gonorrhoeae* (Quillin and Seifert, 2018). During colonization, bacterial pili facilitate

cell-to-cell contact with the epithelium, while Opa proteins further promote adherence. Gonococci pili bind to several host receptors, including $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins in the male urethral epithelium (Edwards and Apicella, 2005). In contrast, gonococcal pili can also bind to the complement receptors, CD46 and CR3, as well as the I-domain containing integrin receptors (Edwards et al., 2001). The interaction between microbial Opa protein and the CEACAM family of receptors on neutrophils contributes to the clinical manifestation of gonococcal infection (Sarantis and Gray-Owen, 2012). The CEACAM-Opa interaction promotes the colonization of cervical epithelial cells by suppressing exfoliation (Yu et al., 2019). Furthermore, CEACAM-Opa inhibits Th1/Th2 lymphocyte responses while promoting a pro-inflammatory Th17 lymphocyte phenotype (Feinen et al., 2010; Liu et al., 2012). Another key gonococcal protein, PorB, increases calcium influx, which is required to reduce lysosome counts in infected cells (Hopper et al., 2000). PorB also reprograms macrophages (Mosleh et al., 1998) to create a more favorable environment for survival. Additionally, PorB can bind to soluble C4b-binding protein (C4BP) and factor H of complement (Ram et al., 1998, 2001), aiding immune evasion. Understanding the mechanisms employed by *N. gonorrhoeae* to evade immune clearance and promote intracellular replication is essential for the development of vaccines and therapeutics.

The importance of interaction between host and microbial neuraminidases (NA) in the pathogenesis of viral and bacterial co-infection of respiratory epithelium is discussed by Escuret and Terrier. Pathogens infecting epithelial cells of the respiratory tract such as influenza viruses use NA and hemagglutinin (HA) to enter the cell. Bacteria can also express NA for adherence and invasion of epithelial cells (Vimr and Lichtensteiger, 2002). Intriguingly, during viral-bacterial co-infections, viral NA can remove sialic acids that typically mask bacterial adhesion receptors, thereby facilitating bacterial colonization (Peltola and McCullers, 2004). This synergistic effect enhances the severity of respiratory infections (Wren et al., 2017). Given the pivotal role of NA in viral and bacterial interactions, they present attractive targets for developing preventive and therapeutic strategies aimed at mitigating co-infection severity.

Jin et al. discussed the advancements in the understanding of mechanisms of *Bartonella* pathogenesis. Endothelial cells are the primary target for *Bartonella* species (Deng et al., 2012). The bacterium uses α -enolase or phosphopyruvate hydratase to activate plasmin and promote extracellular matrix degradation (Díaz-Ramos et al., 2012). The *Bartonella* BadA protein can activate hypoxia-inducible factor-1 and secrete pro-angiogenic cytokines (Kempf et al., 2001, 2005). It can also provide resistance to complement killing (Deng et al., 2012). BadA and Vomp proteins also facilitate immune evasion by antigen variations (Linke et al., 2006). To evade the immune response, *Bartonella* produces LPS, an antagonist of the TLR4 receptor (Malgorzata-Miller et al., 2016). Still, many aspects of *Bartonella*'s pathogenesis remain unknown, requiring the development of novel *in vivo* and *in vitro* methods.

Recent data on pathogens causing sepsis are summarized in the review by Gatica et al. A diverse group of pathogens that belong to the normal microflora (*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*,

and *Streptococcus pyogenes*) can cause sepsis (Gouel-Cheron et al., 2022). Sepsis risk increases with age, compromised immunocompetence and comorbidities. Also, each microbe has a unique set of virulence factors facilitating adhesion, penetration and replication. Therefore, approaches for diagnosis and treatment will differ for each type of sepsis. The traditional use of antibiotics led to the development of drug-resistant strains, making therapeutic options limited. Therefore, searching for new approaches for diagnosing and treating sepsis remains a pressing medical issue.

In the review by Ayesha et al. the role of *Legionella pneumophila* outer membrane vesicles (OMVs) in interaction with the host is discussed. *L. pneumophila* secretes OMVs containing proteins, toxins, nucleic acids and antibiotic-resistance enzymes (Fletcher et al., 1979). OMV cargo delivered to eukaryotic cells can inhibit innate protection against bacteria. For example, it was shown that proteins delivered by OMVs can inhibit the fusion of legionella-containing phagosomes and lysosomes (Fernandez-Moreira et al., 2006). Also, OMVs can inhibit the production of pro-inflammatory cytokines by macrophages (Jung et al., 2016). The ability of OMVs to deliver the cargo could be used to develop vaccines and deliver drugs.

The role of infection in Kawasaki vasculitis is discussed in the review by Wang et al. Environmental factors were suggested to play a role in the disease pathogenesis (Chang et al., 2020). However, the seasonal nature of outbreaks suggests an infectious etiology of Kawasaki vasculitis (Valtuille et al., 2023). Multiple DNA and RNA viruses and bacterial pathogens were suggested as causing Kawasaki vasculitis (Guo et al., 2022; Huang et al., 2020; Kafetzis et al., 2001; Xiao et al., 2020). Having many microbes linked to Kawasaki vasculitis could indicate that the disease is multifactorial, where multiple factors contribute to the disease pathogenesis.

The role of lipolytic enzymes in the pathogenesis of *Mycobacterium tuberculosis* is discussed in the review by Lin et al. There are four types of lipolytic enzymes in *M. tuberculosis* (Mtb) based on specificity to a substrate (Dedieu et al., 2013; Delorme et al., 2012). The first class contains lipases hydrolyzing water-insoluble long-chain carboxylesters like long-chain triglycerides (TAG). Esterases are in the second group, which hydrolyze small water-soluble carboxylesters. The third group includes phospholipases. The last four groups contain cutinases, which digest carboxylesters. Lipases digest lipids in the extracellular matrix, promoting Mtb tissue penetration (Nazarova et al., 2017). Also, Mtb lipases digest lipids to release energy and survive inside the cells (Kumari et al., 2020). Mtb lipases could be used as a disease biomarker (Low et al., 2009) or could be a target for novel therapeutics (West et al., 2011).

The interaction between microflora and cervical cancer progression is discussed by Amaris et al. Cervical cancer is ranked as the most common cancer in women (Arbyn et al., 2020). *Fusobacterium* spp., *Peptostreptococcus* spp., *Campylobacter* spp., and *Haemophilus* spp., as potential biomarkers for cervical cancer progression (He et al., 2022; Wu et al., 2021; Zhou et al., 2022). Additionally, *Alloscardovia* spp., *Eubacterium* spp., and *Mycoplasma* spp. were identified in HPV-positive cervical cancer (Gao et al., 2013), while *Methylobacterium* spp. were more often detected in HPV-negative carcinomas.

Animal models of *Klebsiella pneumoniae* infection of the mucosa are summarized by Assoni et al. Multiple factors should be considered when selecting an animal model: site of infection, type of immune response and susceptibility of an animal. Mice and rats were the most used to study *K. pneumoniae* respiratory tract infection (Ferreira et al., 2019; van der Weide et al., 2020). A rabbit model was used to study empyema caused by *K. pneumoniae* (Shohet et al., 1987). More recently, cynomolgus macaques were used to study the pathogenesis and immune response to *K. pneumoniae* (Liu et al., 2022). This model provides an inside look at the immune response to this microbe. The Zebrafish model was used to study neutrophil and macrophage reaction to *K. pneumoniae* (Zhang et al., 2019). *K. pneumoniae* can colonize different niches, which makes it challenging to select an appropriate animal model. Careful considerations should be taken before selecting a model to study *K. pneumoniae* infection.

In conclusion, this Research Topic provides a collection of reviews covering pathogenic mechanisms of some important microbial pathogens of the section Infectious Agents and Disease. This Research Topic will be of interest for researchers, healthcare providers and infection control officials.

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Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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