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Considering the host in host–pathogen interactions

Studying the host response to infection advances our biological and evolutionary understanding, while broadening our capacity to prevent and mitigate infectious diseases.

Infectious diseases were historically the leading cause of death in humans[1]. Despite improvements in prevention, treatment and control contributing to substantial reductions in the burden of infectious diseases over the twentieth century, some of these diseases remain among the top ten leading causes of morbidity and mortality worldwide[2]. Therefore, continued efforts are needed to develop effective, globally applicable and deliverable strategies to cure and prevent infectious diseases. This is complicated by the ever-increasing issue of antimicrobial resistance and the emergence of new pathogens, such as the fungus *Candida auris*. Climate change also has wide-reaching impacts on pathogen-carrying vectors such as mosquitoes or ticks, on human incursion into the natural environment resulting in increased exposure to certain pathogens, as well as on increased travel and human migration; these all further impact the burden and distribution of existing, emerging and new pathogens.

A fundamental understanding of microbial physiology and pathogenesis underpins the development of new intervention strategies. Many existing antibiotics target crucial cell biology pathways, as evidenced by two recent studies demonstrating the antimicrobial potential of inhibitors targeting lipopolysaccharide transport in *Acinetobacter baumannii*[3,4]. Such advances are only made possible with knowledge of the machinery and mechanisms essential for microbial life. Identifying underlying pathogenesis mechanisms can lead to the development of anti-virulence approaches, such as therapeutic antibodies targeting clostridial toxins to limit pathology during *Clostridioides difficile* infection[5]. However, both virulence factors and the very biology of the pathogen itself are shaped in the context of co-evolution with the host. Studying infection through the lens of the host response can inform us about the dynamics of pathogen physiology, its environmental context and the selective pressures against which the pathogen must adapt. All these insights can yield potential therapeutic targets: they equip us with an understanding of immune correlates of protection, effector mechanisms, and transcriptional or metabolic signatures associated with susceptibility or resistance. This understanding can focus the design of vaccination and therapeutic or diagnostic approaches, ultimately reducing our dependency on antimicrobials and helping to circumvent the issue of resistance.

As an example, analysing the human B cell or antibody repertoire has identified effective antibodies, and the antigens and epitopes responsible for eliciting them, for *Plasmodium*[6] and other infections. We know that T cells are important in combating viral infections, and understanding their biology and how they interact with other immune and non-immune cells can help develop more effective vaccines[7]. However, the immune system is complex and involves many different players — innate and adaptive immune cell populations, humoral factors, sensors, cytokines, chemokines and other secreted mediators. Even mimicry is used as an innate defence, as exemplified by host-derived extracellular vesicles that can compete with viruses for entry receptors on host cells and prevent viral infections[8]. Further complexity is added by neuroimmune crosstalk[9] and the influence of nutritional and metabolic status on susceptibility to infection and disease outcome[10]. At times, the host response to infection can be detrimental and the impact can be long-lasting with or without pathogen persistence, as we have recently seen in the aftermath of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the emergence of post-acute sequelae. To manipulate these processes towards better infection control, we need a deeper understanding of the basic processes and regulatory mechanisms involved in neuroimmune crosstalk, metabolic adaptation and tissue repair. We also need to understand how non-immune and immune cell biology intertwine to fine-tune immune effector responses, influence pathogen behaviour, elicit effective memory and limit the detrimental consequences of infection and immunopathology.

Host-directed therapies have therapeutic potential. Through continued research, cross-disciplinary efforts involving fundamental and clinical research, and effective dissemination and discussion of results, we can address the remaining knowledge gaps to find alternative strategies to treat infections. We need to understand heterogeneity and the response to different pathogen lineages, as well as responses across different human populations. We also need insight into immune function during co-infections. We lack understanding of why some individuals clear infection and why others do not, and how pathogen, environmental or other factors influence this balance. We need to know how to push the balance in favour of the former and we need tools to predict who falls into which category, as well as how best to personalize treatment strategies.

Pathogenesis is an interactive process. The host responds to the pathogen, and in this co-evolutionary framework, the pathogen responds to the host. We cannot fully understand pathogen biology without studying it in the context of the host response, making this aspect of host–microbe interactions a key part of our journal scope. We seek to publish fundamental, preclinical and clinical work that addresses the outstanding questions in the field and draws us closer to solutions that reduce the global burden of infectious diseases.

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