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Host–pathogen interactions in the 21st century

Editorial overview

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Bali Pulendran's research focuses on the systems biology of dendritic cells (DCs) and pathogen recognition receptors (PRRs), including Toll-like receptors (TLRs); immune regulation and evasion by pathogens, including biothreat agents (anthrax, Ebola and Lassa viruses); signaling networks within DCs that regulate immune responses; basic mechanisms by which DCs control innate and adaptive immunity, and exploitation of these mechanisms in vaccinology, immune therapy, and in the design of novel adjuvants and vaccines.

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Robert Seder's research focuses on rational vaccine design for infectious diseases requiring cellular immune responses. Specific areas of interest are understanding the factors that regulate the differentiation and maintenance of memory/effector Th1 cells and CD8⁺ T cells *in vivo*; developing vaccines that can directly target DC subsets using specific TLR ligands to induce protective memory cellular immune responses and to define immune correlates of protection for diseases such as HIV, *Mycobacterium tuberculosis* and *Leishmania major* by analyzing the qualitative aspects of the memory T-cell response.

Host–pathogen wars in the 21st century

One of the greatest challenges facing humanity in the coming decades is learning how to harness our immune systems in the fight against a multitude of existing and emerging infectious diseases. Vaccination has been called the most cost-effective public health tool in human history [1]. Although vaccinology and immunology have a common origin in the pioneering work of Pasteur and Jenner, the two disciplines have evolved such different trajectories that immunologists are largely ignorant of how the best vaccines (empirical) work, and vaccinologists have little patience for the intricacies of immune regulation. Understanding the immunology of vaccines and infections, however, is of paramount importance in the rational design of future vaccines against pandemics such as HIV, malaria, tuberculosis (TB) and cholera, and against emerging infections such as severe acute respiratory syndrome (SARS), dengue and anthrax, and viral hemorrhagic fevers. Spectacular recent advances in the field of innate immunity have sparked a new flurry of research into the immunology of infectious diseases and vaccines to such an extent that there is much hope that we are on the threshold of a conceptual paradigm shift, with several therapeutic spin-offs.

Fittingly, this section of *Current Opinion in Immunology*, entitled 'Host–pathogen interactions in the 21st century' is a collection of reviews, aimed at providing the reader with a panoramic view of host–pathogen research today. Thus, the reviews span the entire spectrum of host–pathogen research, from recent novel insights into innate immunity to the pathogenesis of major global pandemics, such as HIV, TB, malaria and diarrheal diseases, the pathogenesis of emerging infections such as SARS and hemorrhagic fevers, and to an overview of vaccinology at the beginning of the 21st century.

The first four reviews focus on aspects of innate immunity, specifically on how the innate immune system 'senses' pathogens and modulates the adaptive immunity against them. Recent spectacular advances in innate immunity and pathogen recognition has indicated a critical role for dendritic cells (DCs) and pathogen recognition receptors (PRRs), in sensing pathogens (or vaccines) and launching the appropriate type of immune response against the pathogen (or vaccine). Kawai and Akira kick-off the section with a review on pathogen recognition by Toll-like receptors [TLRs]. In the seven years since their demonstration in mammalian immunity, it is now clear that each TLR senses a different set of microbial stimuli. Remarkably, individual TLRs activate distinct signaling pathways and transcription

factors that drive specific biological responses against the pathogens [2]. Thus, pathogen sensing by TLRs is a novel conceptual paradigm in immunology.

The immune system, however, does not appear to live by TLRs alone! As discussed by [Cambi and Figdor](#), C-type lectins are a family of receptors that bind carbohydrate structures in a Ca^{2+} -dependent manner, and act both as adhesion and as pathogen recognition receptors. Notably, a growing list of pathogens, including HIV, hepatitis C virus (HCV), *Helicobacter pylori* and SARS appear to target DC-SIGN, perhaps facilitating their dissemination and modulating host immunity. Continuing with this theme of pathogen recognition, [Murray](#) discusses the role of NOD proteins as potential sensors of intracellular bacteria. NOD1 and NOD2 are members of a diverse family of cytoplasmic proteins that contain carboxy-terminal leucine rich repeats. Because of their similarity to a family of plant proteins involved in pathogen resistance, and because mutations in *Card15* encoding NOD2 are frequently found in familial cases of Crohn's disease, NOD proteins are thought to be involved in intracellular sensing of bacteria. However, the question of whether NOD proteins directly recognize pathogens, or serve instead to modify the response to pathogens is controversial. Interestingly, this issue of direct recognition, or microbial components versus some indirect 'sensing' or modification of the response, is one that awaits resolution, even for TLRs.

Upon pathogen sensing, another critical role played by the innate immune system is to emit 'alarm signals' that warn of pathogens in the vicinity. These signals result in the rapid recruitment and activation of antigen presenting cells, which are critical early events in launching an immune response. In addition to the roles played by chemokines in this process, [Oppenheim and Yang](#) review the importance of a group of structurally diverse multifunctional host proteins that are rapidly released upon pathogen encounter and/or cell death and exhibit chemotactic activity for DCs. These proteins include defensins, cathelicidin, eosinophil-derived neurotoxin and high-mobility group box 1, a group that the authors have appropriately termed 'alarmins'.

Despite these impressive strides in our understanding of how the innate immune system senses pathogens and shapes the adaptive immune response, progress in understanding what roles such mechanisms play in the pathogenesis of global pandemics and emerging infections has thus far been slow. As discussed in the next four reviews, however, this situation appears to be changing. Thus, these reviews focus on our current understanding of the pathogenesis of AIDS, TB, malaria, diarrheal diseases and emerging infections, such as viral hemorrhagic infection fevers and SARS. As discussed by [Derden and Silvestri](#), the AIDS pandemic, with some 40 million HIV-infected

people, is undoubtedly one of the most tragic experiments of nature in recent human history. Despite much progress, the precise immunological mechanisms that determine disease progression and the establishment of chronicity are poorly understood. As the authors point out, a key advance in recent years is the identification of two distinct phases of infection — an acute, early phase, characterized by massive infection of $\text{CD4}^+ \text{CCR5}^+$ memory T cells in mucosal tissues, and a chronic phase of generalized immune activation and slow attrition of CD4^+ T cells. Intriguingly, natural SIV infection of sooty mangabeys results in high levels of viral replication and lack of pathogenicity. Taken together, these observations suggest that our conceptual understanding of the relationships between specific aspects of innate immune function, immune activation in general, viral loads and disease progression are poorly understood. Thus, the answers to fundamental questions concerning the early innate events that occur after HIV infection, how these modulate the quality of the ensuing adaptive immune response, the role of regulatory T cells, and how such responses result in immune deficiency and chronicity are urgently needed.

One of the catastrophic influences of AIDS was to greatly increase the risk of latent *Mycobacterium tuberculosis* infection progressing to active disease and being transmitted to others. As discussed by [Salgame](#), although it is clear that Th1 responses can confer resistance to acute TB, precisely what type of host immunity is capable of effectively controlling latent, chronic TB is poorly understood. Recent research has revealed that *M. tuberculosis* signals via several innate immune receptors, including TLR2 and DC-SIGN, but the precise roles that these receptors play in TB pathogenesis remain to be fully understood.

As discussed by [Engwerda and Good](#), recent research in malaria identified the first malaria-specific antigen to be recognized by TLR9 — hemozoin. They also discuss recent progress in understanding the roles of DC subsets and how they modulate the immune response. These initial observations for a potential link between how a specific malaria protein can alter innate and adaptive immunity will be important in further elucidating mechanisms of resistance against malaria and providing insights for improving vaccines. In this regard, the authors describe all the current vaccine strategies aimed at specific stages of malaria infection and the likely requirement for broad-based adaptive immune responses for protection.

In the case of cholera and enterotoxigenic *Escherichia coli* [ETEC], discussed by [Sanchez and Holmgren](#), the enterotoxins produced by *Vibrio cholerae* and ETEC appear to be important virulence factors, thus facilitating the development of vaccines. Previously used parenteral cholera vaccines did not induce significant gut mucosal immune

response, were poorly protective, and thus abandoned. However, as the authors write: ‘... recent studies have provided much support for the usefulness of new, oral cholera vaccines as an important public health tool in the control of cholera’.

This theme of innate immunity as a critical regulator of host–pathogen interactions, is again discussed in the context of two emerging infections of viral hemorrhagic fevers and SARS. As discussed by Bray, viral hemorrhagic fevers are caused by single-stranded RNA from four different families. Despite the importance of cytopathic effects on disease severity, it is now known that innate immune factors, including pro-inflammatory cytokines and mediators, modify vascular function and contribute to disease progression. Thus, such viruses appear to have learned to force the hand of innate immunity for their own gains. As discussed by the author: ‘It is tempting to speculate that natural selection has ‘chosen’ a set of innate immune responses that are beneficial when localized, but harmful when systemic, as a way of favoring the survival of the community over the individual, as those with minor injuries and infections are salvaged, whereas those infected by virulent agents become quickly incapacitated and incapable of transmitting disease’.

As discussed by Lau and Peiris, since the two short years that SARS appeared in Guangdong Province, China in November 2002, it has been identified as a coronavirus, its genome sequenced and a functional receptor (angiotensin-converting enzyme 2 [ACE2]) identified. In addition, two C-type lectins, L-SIGN and DC-SIGN, have been shown to bind the virus. Interestingly, despite a robust innate immune response to SARS, induction of type 1 IFNs might be impaired. Moreover, lymphopenia (decreased CD4⁺ and CD8⁺ T cells) is common in the acute phase of the disease. Despite these impressive advances, discussed earlier with respect to HIV, malaria and TB, the answers to fundamental questions concerning the early innate events that occur after SARS infection, how these modulate the quality of the ensuing adaptive immune response, and how such a response results in immune deficiency are urgently needed.

As will be evident from the reviews discussed above, the renaissance in innate immunity, including the discovery of receptors that recognize microbial patterns and result in DC activation, appears clearly to be on the verge of

providing fresh insights into the pathogenesis of major killers. However, it also appears to be on the verge of revolutionizing vaccinology. Indeed, the recent demonstration that the Yellow Fever Vaccine 17D (one of the most effective vaccines known, which consists of a live attenuated viral vector that effectively induces cytotoxic T lymphocytes (CTLs) and neutralizing antibodies for up to 30 years after a single shot), achieves its effects by activating multiple subsets of DCs via at least four different TLRs provides new hope that the spectacular successes of our best empirical vaccines will soon be recapitulated by a judicious choice of adjuvants, including combinations of TLR ligands, designed to elicit a broad spectrum of immune responses, including Th1, Th2, CTL and antibody (T Querec and B Pulendran, unpublished; [3]). As discussed by Wack and Rappuoli in the final review of this section, this grand challenge will be driven by advances in genomics that that permit us to mine whole genomes in the search of promising antigens. As the authors write: ‘Although work on the ‘easy’ vaccines has already been completed, it is hoped that a combination of conceptual and technical innovation will enable the development of more complex and sophisticated vaccines in the future’.

In recent years, it has been argued that immunology, unlike neuroscience, is a science in which the ‘fundamental laws’ have already been discovered, and what remains is largely a question of filling in the details of what molecules and cytokines mediate what responses. Although there is some truth in this view, immunologists are guided by the belief that an integrated, deeper understanding of the molecular and cellular mechanisms of host–pathogen interactions will offer insights into the correlates of protective immunities, early genomic signatures of the efficacy of vaccines, and the rational design of novel vaccines that induce optimally effective immune responses. Perhaps then, the divergent legacies of the Pasteur/Jenner era may once more be reunited!

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