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Host–pathogen interactions

Editorial overview

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Infectious diseases continue to rampage globally. True, in the past decade mortality caused by infectious diseases has decreased from one-third to one-quarter of all premature deaths. Yet, it is still worrying that 15 million people will die this year of infectious diseases. Moreover, newly emerging infectious diseases have entered the stage, with the most recent examples being severe acute respiratory syndrome caused by a coronavirus and bird influenza caused by the H5N1 influenza virus. Human immunodeficiency virus (HIV) was unknown to us before the 1980s. Nowadays, it infects 15 000 and kills 7000 individuals daily, having already left 20 million deaths in its wake. This illustrates the success of newly emerging pathogens if they are able to find an adequate niche as a habitat for propagation. Other diseases such as tuberculosis, which currently is estimated to infect a third of the world's population, remain a threat of comparable dimension. Tuberculosis infects 150 000 individuals daily, most of whom will not develop disease thanks to an effective immune response, yet causes the death of 6000 individuals every day.

The overall reduction in mortality caused by infectious diseases is owing to the success of biomedical measures, notably chemotherapy and vaccination, and non-biomedical measures, including an increase in hygiene and living standards. So what makes the analysis of host-pathogen interactions so attractive for immunologists? The immune system has evolved as a measure to control microbes that have exploited the macroorganism for living, with disease being a possible, but not essential, outcome. Thus, the host-pathogen relationship is characterized by a dynamic interplay, with both sides exploiting their survival stratagems to their own benefit. Indeed, pathogens have developed a broad arsenal of different survival strategies in the macroorganisms, which for convenience and with the risk of oversimplification can be categorized in terms of warfare. Toxin producers such as anthrax bacilli have chosen biowarfare, whereby the toxin rather than the pathogen itself attacks the human host. Other microorganisms such as influenza virus have chosen a 'blitzkrieg' strategy to overwhelm the host rapidly. At the other end of the spectrum, several pathogens such as *Mycobacterium tuberculosis* or herpes viruses have chosen trench warfare; this allows for an apparently peaceful coexistence over long periods of time, with the risk of disease activation at a later time point once the host defense line has been weakened. Others are even more malicious. HIV, for example, has chosen guerrilla warfare, undermining host defense by attacking the central regulator of the immune response — the helper T cells. Equally malignant are pathogens such as *Trypanosoma cruzi* that initiate a civil war in which the immune response attacks our own host cells under the false impression that it is attacking the invaders.

To combat such an enormous variety of offensive strategies is not an easy task for our immune system. It has had to devise a plethora of defensive

strategies in order to provide the best countermeasure for a given type of invader. By sensing different types of pathogens and building up a rapid first line of defense, the innate immune system takes the first burden. By building a highly specific and specialized response that develops a long-lasting memory, the acquired immune response serves as the second and highly powerful defense line. Of course, these two systems do not act independently from each other but are highly intertwined, with the innate immune system instructing the acquired immune response about the type of infectious agent and the acquired immune response taking advantage of the potent effector mechanisms of the innate immune system, to name the two most important activities. Moreover, the outcome of infection with the same pathogen can vary dramatically owing to host genetic factors that modulate both innate and adaptive immune responses.

Phagocytes play a central role in defense, particularly against bacteria and protozoa. Accordingly, a large proportion of survival strategies of these pathogens are focused on phagocytes. Some pathogens resist phagocytosis whereas others resist intracellular killing by phagocytes, to name just the two most extreme forms. In between are strategies that allow phagocytosis but then induce host cell death. The role of pathogen-induced host cell apoptosis in determining the outcome of infection is well appreciated. More recently, autophagy has been identified as a general defense mechanism against various intracellular pathogens. Also, it is still unknown whether autophagy in infected macrophages is always to the benefit of the host or not. As described by Deretic in this issue of *Current Opinion in Immunology*, current evidence suggests it plays a protective role in tuberculosis.

So what are the factors that influence disease, and how might these be manipulated to tip the balance in favor of the host? As reviewed by Abel and co-workers, defects in several genes have been identified to specifically predispose to infection with certain invading pathogens in otherwise healthy individuals, whereas other host genetic mutations appear to provide inherent resistance to infection and/or disease. A number of inborn errors in immunity that affect single genes have been identified, and more Mendelian mutations of this type will undoubtedly be identified in the future.

In addition to the modulating role of host genetics, there are increasing data indicating that, for certain pathogens, the ultimate outcome of the war between pathogen and host is determined in the earliest stages of infection. Modulating the earliest events in acute infections falls to the innate immune response, and a key effector cell in this response is the natural killer (NK) cell. Lodoen and Lanier provide evidence regarding how NK cells recognize and respond to viruses, parasites and bacteria, and offer data that support the crucial role of these cells in the acute phase of infection and in the evolution of the adaptive immune response. Understanding this interaction between innate and adaptive immune responses also has important implications for vaccine approaches aimed at sustaining effective adaptive immunity.

The next wave of the pathogen offensive is dealt with by the adaptive immune response, and again data suggest that the early events might influence the ultimate outcome. This is addressed for HIV by Picker, who focuses on the early destruction of gut-associated CD4 T cells in acute HIV infection, followed by a state of immune hyperactivation and further loss of these cells in tissues to below a crucial level needed to protect from opportunistic infections.

One of the potential problems of a vigorous adaptive immune response to an invading pathogen is that the immune response must be regulated. Belkaid *et al.* address this in the setting of persistent parasitic infections, discussing recent insights regarding the role of Treg and their major mediators IL-10 and TGF-β in modulating the steady-state interactions between pathogen and host, and the implications for new approaches to achieve therapeutic benefit from manipulating these immunoregulatory networks.

Treg play a beneficial role, notably in acute infections by avoiding collateral damage by the immune responses sustained after pathogen eradication. However, in chronic infections, in which pathogen eradication is not achieved, protective immune responses need to continue to avoid disease outbreak. In these situations, Treg can be harmful to the host.

Both the innate and adaptive immune responses, which act to control pathogens, are influenced by host genetic factors. An increasing number of these have been identified, as outlined in the setting of HIV infection by Mallal and co-workers. These include MHC alleles, killer-cell inhibitory receptors and chemokine receptor polymorphisms, all of which influence the outcome of disease and are highly relevant to vaccine design. Population studies incorporating high-resolution HLA typing and detailed virus sequencing are revealing a crucial role of the host–virus interaction in shaping both host and virus diversity; the extent of predictability in evolution of mutations within targeted viral epitopes is something that might eventually benefit vaccine immunogen design.

Recent advances in biotechnology have also contributed to large-scale analyses of host–pathogen interactions, now on a global level. Thus, it is now possible to define differential gene expression profiles both in the pathogen and in the host. These findings have often been discounted as data-driven rather than hypothesis-driven research. However, it is becoming increasingly clear that

such studies frequently lead to the discovery of previously unknown genes in the infection process, which can then be characterized by conventional experimental approaches. In addition, transcriptome analyses allow identification of unique biosignatures, for example downstream events induced by virulence factors or by distinct host defense molecules. As discussed by Hossain *et al.*, researchers interested in host–pathogen interactions will benefit from global analyses of the dialogue between pathogen and host given that appropriate bioinformatics and conventional experiments are merged.

The list of the major killer pathogens is still headed by HIV, *M. tuberculosis* and malaria plasmodia, and general agreement exists that vaccines are needed to efficiently control these threats. Accordingly, three articles in this section of *Current Opinion in Immunology* highlight new strategies aimed at the development of novel vaccines against acquired immunodeficiency syndrome (AIDS), tuberculosis and malaria. It is obvious that vaccines against these three diseases cannot rely on trial-and-error strategies, but need to harness our most recent findings about the immune response against the pathogen for the rational design of novel candidates.

In HIV, although numerous vaccine candidates are now in various stages of development, none of the available candidates are likely to be able to overcome the viral genetic diversity that remains a key challenge in vaccine design. Among circulating strains of HIV globally, particular protein sequences can vary up to 35%, and thus it is of little surprise that development of a broadly cross-reactive immunogen has been elusive. As described by Brander *et al.*, computationally intensive design of sequence combinations that optimize coverage of sequence diversity might be a way to overcome this challenge, and can take advantage of large population data sets now being developed.

In tuberculosis, several vaccine candidates have passed preclinical testing and are ready for clinical trials. Yet, as discussed by Baumann *et al.*, this is not the end for immunology research in tuberculosis. Rather, iterative strategies need to be developed to further improve vaccine efficacy of novel candidates on the basis of our increasing knowledge about the mechanisms that control protective immunity against tuberculosis. This includes improving migratory patterns of T cells, strengthening memory T cells (Tm), and weakening regulatory T cells. Time will tell whether a single vaccine can reach this goal or whether combinations of different vaccines will be required.

As discussed by Matuschewski, a subunit vaccine against malaria has already passed a Phase IIb clinical trial, which gives hope for a vaccine that can protect young children from malaria transmission. Yet, the end has not been reached to date and novel vaccine candidates, including attenuated live vaccines and transgenic viral vectors that express malaria antigens, might be needed to solve this problem.

Memory T cells are essential mediators of many vaccines including those against malaria, tuberculosis and AIDS. New insights into the different memory subpopulations of memory T cells and the rules that govern their development will therefore provide important guidelines for future vaccine development. Huster *et al.* describe these features and provide the first information on how to stimulate the balanced ratio of different memory T cells required for optimum vaccine-induced protection.

Pathogenic fungi have long been neglected by immunologists interested in host–pathogen interactions. However, the realisation that human pathogenic fungi play an increasing role in immunocompromised patients has stimulated research into the immunity to fungi more recently. The review of Hohl *et al.* provides an update of the most recent findings that underlie antifungal defense, which provides a starting point for new immune intervention strategies.

Together, the contributions to this section of *Current Opinion in Immunology* provide an increasing understanding of the dance between host and pathogen. These advances offer new avenues to explore for interventions both in terms of prevention and treatment that are desperately needed — both for the pathogens we already know of and the new ones that are certain to arise in the future.