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Immunity to emerging pathogens

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Introduction

Emerging infectious diseases constitute one of the most significant health and security challenges facing the world today. Pathogens that are recently adapted to humans, such as human immunodeficiency virus (HIV), have become rampant worldwide, and pathogens that were thought to be under some control are creating new concerns, such as drug-resistant tuberculosis. Furthermore, the threat of 'new' viruses, such as severe acute respiratory syndrome (SARS) virus, and agents of bioterror, such as *Franciscella*, present novel health challenges. Many factors influence the emergence and spread of these pathogens including climate change, man's encroachment into new environments, patterns of travel and migration, and deliberate dissemination. Thus, emerging infectious diseases will pose a major threat to human health well into the future. The challenge for mankind is to develop effective strategies to control these emerging diseases, including establishing surveillance and response networks, improving diagnostics, promoting public health initiatives, establishing vector control strategies, and developing effective vaccines and therapeutics.

The battle against infectious disease has been ongoing since humans developed the capacity for medical intervention. The advent of vaccines and antibiotics was a huge step forward, and, based on early successes, it was expected that in time mankind could eventually conquer infectious diseases. However, in the first article in this volume (1), Prof. Frank Snowdon (Yale University) offers a historical perspective of the fight against infectious diseases that highlights our hubris. Today, we realize that the task is more difficult than was imagined. Despite the many challenges that lie ahead, it is nonetheless essential that humans continue the fight to control major infectious disease killers in this century. Indeed, several national and international organizations are dedicated to this task, including the World Health Organization (WHO), the Centers for Disease Control (CDC), the National Institutes of Health (NIH), the Bill & Melinda Gates Foundation, and others. It is an article of faith for research scientists that new advances will require a deep fundamental understanding of how the pathogen interacts with the host. The articles in this volume highlight recent and important advances in our quest for fundamental knowledge of the immunology of emerging infectious diseases.

Pathogen-specific immunity

Emerging pathogens have been defined as infections that have newly appeared in a population or have existed previously but are expanding in incidence or geographic range. Both the CDC (http://www.cdc.gov/ncidod/diseases/eid/disease_sites.htm) and the NIH (http://www3.niaid.nih.gov/healthscience/healthtopics/emerging/) have classified a number of microbes as emerging pathogens. These lists are overlapping and contain obvious candidates; however, each list also contains pathogens that are unique. Because our focus for this volume of *Immunological Reviews* was immunity, we chose to include reviews of emerging pathogens where studies have led to novel insights into immune processes. We excluded some pathogens that have been highly studied, either because of their medical importance (e.g. HIV) or because they have been utilized in well-developed experimental models (e.g. *Listeria*, *Borrelia*). We also excluded pathogens for which relatively little is understood regarding the immune response (e.g. *Histoplasma*, *Cryptosporidium*, Hanta virus, SARs). The emerging pathogens that we chose come from a wide spectrum of infectious agents from several different phyla (i.e. viruses, bacteria, protozoa). These include pathogens that cause high disease incidence (*Mycobacteria*, *Plasmodium*, influenza), low disease incidence (*Franciscella*, Monkeypox, Ebola), and that differ widely in host niche (i.e. intracellular pathogens such as *Yersinia*, *Franciscella*, and *Salmonella*, versus extracellular pathogens such as Group B Streptococcus). The pathogens we have included also mediate a very wide range of infections, from acute (influenza) to chronic (hepatitis), to latent (tuberculosis). Furthermore, our list includes pathogens that although highly virulent, are not considered to be major killers. For example, despite the fact that 50% of bubonic infections are lethal and only 10 colony-forming units of *Franciscella* are sufficient to kill an adult human, these pathogens cause few deaths worldwide. Finally, several of the emerging pathogens included are important because they are major biothreats (*Franciscella*, *Yersinia*, *Vaccinia*). Our choice of pathogens and authors has therefore resulted in reviews that cover many different types of infectious disease and a breadth of immune responses. An important theme from this compendium is that immunity is pathogen-specific. Each pathogen therefore informs us about a particular feature of the immune response and provides an opportunity to study particular aspects of immunity. Thus, these articles explore the host response to infection, ranging from innate immune responses, to adaptive immunity, as well as the development of vaccines.

Innate immunity

Innate immunity is an important component of anti-microbial immunity and associated pathology. An excellent example of an innate response to a pathogen is the development of an anti-viral state. We now know that infected cells undergo multiple changes in response to a viral infection to block viral replication. We have also learned that viruses, in turn, go to considerable lengths to avoid or block these changes to ensure their survival. For example, type I interferons play a central role in establishing the anti-viral state. The underlying mechanisms of type I interferon function are discussed in detail by Drs Kate Ryman and William Klimstra (Louisiana State University Health Sciences Center) (2) with regard to alphavirus infections. These authors focus on differences between particular viruses, as they relate to viral replication and host responses in dendritic cells and macrophages. These concepts are further illustrated by Dr Paul Rota and colleagues (Centers for Disease Control) (3) with regard to paramyxoviruses and Dr Jacqueline Katz and colleagues (Centers for Disease Control) (4) with respect to influenza. In these cases, the authors focus on viral interference with type I interferon signaling and induction pathways and on the regulation of inflammatory responses. The article by Dr William Golde and colleagues (Plum Island Animal Disease Center) (5) discusses the role of dendritic and natural killer cells in the control of foot and mouth disease virus in cloven-hoofed animals. These innate immune responses are essential to control the infection, and consequently, this highly successful virus has evolved mechanisms that interrupt these immune mediators to ensure rapid replication and spread. Understanding the mechanisms at play will be important for the development of therapeutics against this economically important disease. The relationship between innate immune responses and viral success in the host population is also discussed by Drs Jessica Weaver and Stuart Isaacs (University of Pennsylvania School of Medicine) (6) with respect to monkeypox virus. The key question is what changes need to occur for the virus to establish uncontrolled infection in the human population. As the authors note, it is changes in genes encoding innate immune response proteins that appear to be critical, again highlighting the central role played by innate immunity in the host response to infection.

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Toll-like receptors (TLRs) are well known to play major roles in the recognition of bacterial pathogens. Although typically viewed as important components in protective immunity, innate TLR signals may be detrimental to the host. This is illustrated by Dr Philipp Henneke and colleagues (University Medical Centre, Freiburg) (7), who discuss how excessive inflammatory signaling mediated by TLR2 during Group B Streptococcus infection causes excessive inflammatory signaling, which may have neurological sequelae in newborns. Another example of a deleterious innate immune response is described in the review by Dr Henry Tabel and colleagues (University of Saskatchewan) (8), who discuss dysregulation of macrophage function by CD4$^+$ T cells and regulatory T cells during Trypanosome infections. Dendritic cell and macrophage maturation via TLR-dependent and -independent mechanism in intestinal lymphoid-associated *Salmonella* infections are discussed in the review by Dr Mary Jo Wick and colleagues (Goteborg University) (9).

Adaptive immunity

Adaptive immune responses are characterized by their ability to enhance the specificity, magnitude, and quality of the response as the infection progresses. Such responses include the development of pathogen-specific antibodies and T cells. The interdependence of T cell and antibody-mediated immunity and the underlying relationship to innate immunity is outlined in the article on Hantaviruses by Dr Rainer Ulrich and colleagues (Friedrich-Loeffler Institute) (10). These authors consider all aspects of the immune response, including immune evasion by the pathogen, immunopathology, and the role of the immune response in pathogen dissemination. The article by Dr Ralph Baric and colleagues (University of North Carolina) (11) builds on some of these concepts to illustrate the interplay between the antibody response and the evolution of norovirus infections. In this case, the persistence of this virus is linked to its ability to evade antibody responses, while retaining the ability to bind to viral receptors in the host. The blockade of pathogen binding to the host receptor is another important component of antibody-mediated pathogen neutralization. This is illustrated for West Nile virus in an article by Dr Michael Diamond and colleagues (Washington University School of Medicine) (12). Here, beautiful structural and molecular studies identify the immunologic basis of antibody protection against West Nile virus. In a related study, Drs John Fraser and Thomas Proft (University of Auckland) (13) describe the structural characteristics of a large family of staphylococcal and related bacterial superantigens and superantigen-like proteins that play important roles in human diseases.

Until relatively recently, antibodies have not been considered to play important roles in intracellular bacterial infections, but recent work suggest that antibodies are important components of host defense against such emerging pathogens. This is highlighted by Dr Dennis Metzger and colleagues (Albany Medical College) (14) and Dr Stephen Smiley (Trudeau Institute) (15) in their reviews that document roles for antibodies in studies of *Franciscella* and *Yersinia* infections, respectively. Several of the reviews in this volume discuss the important role of T cells in viral, bacterial, and parasite emerging infections. For example, CD8$^+$ T cells play a major role in protective immunity during *Plasmodium* liver stage infection, as described by Dr Fidel Zavala and colleagues (Johns Hopkins University) (16) in their review of malaria immunity. Dr Gary Winslow and colleagues (Wadsworth Center) (17) describe the genesis of the protective CD4$^+$ T-cell response following *Mycobacterium tuberculosis* infection; CD4$^+$ T-cell responses are delayed after *M. tuberculosis* infection, relative to many other respiratory pathogens, and this likely allows the pathogen time to gain a foothold before the development of adaptive immunity.

While T cells can play a key role in protective immunity, they can also mediate considerable pathogenic effects. Dr Alan Rothman and colleagues (University of Massachusetts Medical School) (18) discuss the impact of T-cell responses on dengue virus infections. In this case, immune responses to secondary virus infection can result in enhanced disease and dengue hemorrhagic fever. This effect appears to be mediated by a skewed T-cell cytokine response that was primed by the initial, and largely asymptomatic, primary infection.

Vaccines

An important goal of immunological studies is the development of effective and durable vaccines. While vaccines have considerable benefits over drug treatments, the major limitation in developing novel vaccination approaches is our lack of understanding of immunity to many emerging pathogens. Furthermore, many emerging infections are prevalent in Third-world countries, where it can be problematic to test new vaccines. One area where vaccines are being developed, without the constraints associated with clinical studies, is animal vaccines. For example, highly pathogenic influenza is a major economic concern for poultry production throughout the world. It is also classified as an emerging disease in poultry that has the potential to infect the human population. Protection against disease in chickens is dependent on the development of neutralizing antibody. While homotypic vaccines are generally very effective, it is difficult to develop vaccines with broad heterosubtypic protection against drift variants. Drs David Swayne and Darrel Kapczynski (US Department of Agriculture) (19) discuss the challenges in developing and delivering avian vaccines against avian influenza. The lessons learned from these studies have considerable implications for vaccines against human influenza, especially pandemic influenza. Vaccination is a major goal of much of the research described in this volume, including the work described by Drs Golde, Diamond, Metzger, Smiley, Rothman, and Swayne (5, 12, 14, 15, 18, 19).

Together these articles on various aspects of the immune response highlight what we feel are important areas of research in immunity to emerging infections. One 'emerging' theme that these reviews illustrate is not only the wide variety of lifestyles encompassed by emerging pathogens, but the wide variety of immunological defenses and pathological responses employed by the host to combat such a range of pathogens. Research into this panoply of pathogens will continue to inform us of the plasticity of the immune response and the variety of different mechanisms that are utilized for host defense.

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