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Immunity
Commentary

The Challenge of Viral Immunity

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Bringing together discussion of innate immunity, B cell and T cell responses, vaccine design and efficacy, and the genetics of HIV and AIDS resistance allows us to access the extraordinary complexity of viral immunity and host responsiveness.

The word immunity is derived from the Latin immunis, meaning without tax. The term refers to the tax-exempt status given for a time to returned soldiers in the Roman state. The tax that our immune systems have evolved to deal with is the tax of infection, of parasitism by simpler life forms. With slow-growing, complex organisms like the vertebrates, our particular concern is the excessive tax levied by pathogens that replicate and (in some cases) mutate with extraordinary rapidity.

As obligate intracellular pathogens, the viruses (Knipe et al., 2006) are the simplest and most intimate of the various life forms (bacteria, fungi, worms, etc.) that are programmed to live in, or on, us. Some viruses can survive for time in the external environment if, say, they are located in sloughed cells protected by mucus (foot-and-mouth disease virus is a case in point), though all ultimately rely on strategies requiring further infection and replication in naive hosts that allow high levels of virus production to facilitate transmission. In the case of measles virus or poliovirus that means other humans, but we are only incidental hosts for the hantaviruses (Hantan and Korean hemorrhagic fever viruses) that are maintained in *Apodemus* species. Other viruses (like dengue) replicate in both mosquitoes and humans, whereas the broadly related Japanese encephalitis virus will multiply in pigs, mosquitoes, and man.

Viruses that live only in a single species can compromise their pathogenicity so that their hosts remain available in sufficient numbers to ensure transmission. The herpesviruses, for example, establish initially as lytic infections that are soon controlled by the innate then adaptive host responses, then transit to a persistent or latent form that allows the maintenance of viral DNA throughout a normal human life span. Such viruses transmit via sporadic reactivation to lytic phase as, for example, in the cold sores caused by *Herpes simplex* virus, or the oropharyngeal production of Epstein-Barr virus (EBV). The immune response then cuts in again to limit the extent of damage.

Continuing analysis of these large, complex, viruses shows how they have evolved various molecular strategies to subvert immune elimination (Lilley and Ploegh, 2005), but not to the extent that they compromise the survival of immunocompetent hosts. Given the long phylogenetic history of such pathogens, it is also likely that our immune systems have coevolved with them. On the other hand, pathogens that infect us as incidental hosts, like West Nile virus, which replicates in birds and mosquitoes, are under no selective pressure to keep even some of us alive.

Four of the five reviews that follow deal with the aspects of adaptive immunity, the extraordinarily specific response mechanism that is thought to have first emerged in the bony fishes about 350 million years ago (Cooper and Alder, 2006) and must presumably have been further enhanced by the transition to land and an air-breathing lifestyle. Thomas Dörner and Andreas Radbruch look at the secreted, circulating, and locally produced immunoglobulins (Igs) that have at least the potential to neutralize virus at the point of mucosal entry, the holy grail for vaccinologists. Their discussion of the balance between established memory, circulating Ig, and recall responses has particular relevance for immunization strategies. Antibody-mediated immunity can be extraordinarily long lived, reflecting the persistence of both B cell memory and plasma cells located in the bone marrow (Crotty et al., 2003).

Susan Kaech and John Wherry deal mainly with the $CD8^+$ T cells that constitute the major mechanism for virus clearance after primary challenge with, particularly, the smaller viruses. Large, complex viruses like the herpesviruses are also controlled by effector $CD4^+$ T cells, operating mainly via interferon-γ (IFN-γ)-mediated mechanisms (Doherty et al., 2001). The analysis of $CD8^+$ T cell responses has, of course, surged ahead since the introduction of the MHCI+peptide tetramer technology by John Altman, Mark Davis, and colleagues some ten years back (Altman et al., 1996).

For the first time, the tetramers allowed the quantitative analysis of virus-specific $CD8^+$ T cell responses while also providing a mechanism for recovering single T lymphocytes directly ex vivo for immediate molecular analysis with, for example, single-cell polymerase chain reaction (PCR) approaches. As a consequence, starting from the partially differentiated naive, postthymic precursor, the virus-specific $CD8^+$ T cell response provides an extraordinarily accessible target for the analysis of immune repertoire selection (Turner et al., 2006) and the progressive acquisition of diverse molecular expression profiles that characterize fully functional effector cells (Johnson et al., 2003; Peixoto et al., 2007), T_{CM} and T_{EM} memory cells, and so forth. Kaech and Wherry focus

particularly on the nature of these lymphocyte subsets and the factors influencing the underlying cell-fate decisions, introducing a burgeoning area of molecular and cellular analysis. As this research proceeds, it's important to bear in mind, of course, that even for T cell clones expanded from a single precursor, we are working with populations rather than direct mother-to-daughter lineages.

The past 10 to 15 years have also seen enormous advances in our understanding of the evolutionarily ancient innate immune system that we share with nonvertebrate life forms. Andreas Pichlmair and Caetano Reis e Sousa focus particularly on the coupling of viral recognition and the induction of type 1 interferon (IFN-I) genes. Those of us who work with the influenza A viruses have long known about the importance of IFN-I-mediated early control from the work of Otto Haller and colleagues with the Mx genes (Salomon et al., 2007; Tumpey et al., 2007). Most of us are now also very conscious (Kabelitz and Medzhitov, 2007) of the toll-like receptors (TLRs) that were first discovered in *Drosophila* by the fly geneticists (Ip and Levine, 1994) We "adaptive immunologists," if that is a legitimate description, might, though, be much less aware of the role played by atypical nucleic acids in different subcellular compartments, a particular focus of this review.

The two remaining articles that were commissioned for this issue of *Immunity* deal principally with the limits of host responsiveness when it comes to dealing with a persistent pathogen, the human immunodeficiency virus (HIV), which jumped recently from chimpanzees to become established in us (Keele et al., 2006). Through the course of evolutionary time we would, as implied in the discussion by Steven Deeks and Bruce Walker, select a human population that lives happily with HIV. Socially, of course, we could never accept the massive dieback in the human family that this would involve. Even so, some of the most promising avenues for developing novel possibilities for HIV control lie in determining how the inherent genetic resistance mechanisms described by Deeks and Walker work at the molecular and cellular levels. As those of us who are involved in the Centre for HIV and AIDS Vaccine Immunology (CHAVI), the National Institutes of Health (NIH) vaccine grant administered by Barton Haynes at Duke University, realize, we have to go back to analyzing the basics of virus transmission, genetic resistance, and the earliest phases of both innate and adaptive immune responsiveness if we are to develop novel conceptual and technical strategies for defeating this virus.

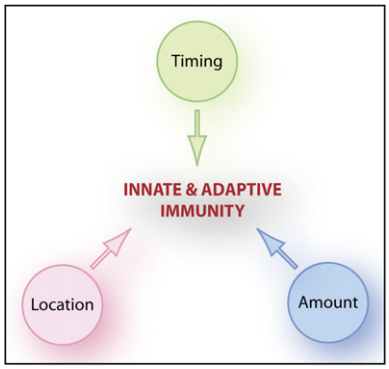

Figure 1. Shaping the Antiviral Response
The themes that location, amount, and timing are important in determining antiviral response magnitude and quality are as true for the part played within the cell by viral nucleic acids that modulate type 1 interferon production and innate immunity as they are for the nonself proteins and MHC+peptide complexes that stimulate B cells and T cells. Understanding and exploiting the complex, interactive processes that operate between and within the innate and adaptive responses is a central challenge for viral immunity and vaccine design.

The extraordinarily difficult and frustrating problem of making an HIV vaccine is discussed by Norman Letvin, who also gives us a short history of vaccination going back to the preimmunology era of Edward Jenner. It is salutary for immunologists to reflect that, with the exception of the very successful human papilloma virus vaccine developed by the immunologist Ian Frazer and colleagues (Liu et al., 1998), the enormous intellectual advances that we have made in understanding the nature of specific host responsiveness have so far had little impact on immunization. Of course, that might be in the process of changing as we incorporate new molecular strategies gained from the analysis of the innate immunity into product design, but we should be modest when we recall that we still have no effective vaccines to protect children in the developing world against infection with malaria species. and *Mycobacterium tuberculosis*.

A particularly fascinating consequence of bringing these varied discussions of innate and adaptive immunity together is the insights that emerge concerning the commonality of response mechanisms and the nature of self versus nonself discrimination, an obsession for our field since the time of Paul Ehrlich (Silverstein, 2005). Amounts, whether they be foreign nucleic acids, proteins, or peptides complexed to MHC glycoproteins, are important when it comes to triggering responses within the infected cell or in a responding lymph node. The same point can be made concerning both location and timing (Figure 1).

Immunity in all its aspects is an evolved not a designer system that has, as we are coming to realize, distinct limitations when it comes to dealing with rapidly mutating viruses and microorganisms that have well-developed mechanisms for hiding in various host ecological niches. Given the assistance provided by vaccines, antibiotics, and antivirals, our immune responses function to protect a good number of us through a normal human lifespan. What would happen, though, if we should suddenly find ourselves exposed to a virus that is as difficult to deal with as HIV but spreads readily via a respiratory route? The recent SARS experience was a wake-up call, though it turned out that the coronavirus in question could be handled well by healthy, young immune systems (Chen and Subbarao, 2007).

We can't afford to let up. The challenge for us as immunologists is to understand how the various elements work and fit together, and then to then develop innovative solutions that do better than nature. Reading the current set of reviews together might trigger some new insights into how to proceed with the challenge of making more-effective vaccines. Immunity ranks with the most complex of complex systems, along with neurobiology and climate change. Bringing together a diversity of understanding allows us to access at least some of that complexity.

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