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Editorial overview: Host pathogens: New paradigms and tools to decipher and deconstruct the host–pathogen interaction

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Guido Silvestri received his MD in Ancona, Italy, and completed Residency training in Internal Medicine & Clinical Immunology (Florence 1990) and Pathology (U. Penn 2001). He currently is the Chief of the Division of Microbiology & Immunology at the Yerkes National Primate Research Center. He has been extensively involved in studies of AIDS pathogenesis, prevention and therapy, mostly using nonhuman primate models of SIV and SHIV infection, with particular focus on comparative studies of pathogenic and non-pathogenic primate lentiviral infections.

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Introduction

The discovery that microorganisms such as virus, bacteria, and protozoa are responsible for many human diseases was a key milestone in the history of modern medicine and provided the foundation for the scientific disciplines of microbiology and immunology. For a long time, the interaction between these agents and the host organism was often studied (and interpreted) with the glasses of a military metaphor, in which the microbes represented the offending invaders, and the host immune system serves as the guardian angel of health. A case in point of this rather simplistic approach is the very name 'virus' (from the Latin word for 'poison') that we currently use to define an extremely large category of non-cellular, cell-dependent micro-organisms of which only a very small minority causes diseases. More recently, the general concept has emerged that what causes disease is not, in most cases, an intrinsic virulence/pathogenicity features of the microbe or a clearcut defect in the host immune system, but rather the establishment of an aberrant host–pathogen interaction in which both actors play a fundamental role. In the setting of primate lentiviral infections, for instance, it is now well appreciated that AIDS is essentially the results of an insufficient adaptation of the human immune system to the presence of a virus (i.e., HIV-1) whose ancestors, which are found in African non-human primates (i.e., SIVs), cause a very benign, nonpathogenic chronic infection [1–4]. Along those lines, it is also clear that dysfunctional and/or deregulated host responses may play an essential role in the pathogenesis of many of the so-called 'emerging' infectious diseases, such as SARS, MERS, Ebola, Avian flu, and various others, in which zoonotic cross-species transmission to humans is at the origin of the epidemics [5]. An even more dramatic example of how blurred can be the definition of 'pathogen' comes from the recognition of how complex and far-reaching is the interaction between the human organism and the intestinal microbiota, in which classical definitions such as symbiosis, commensalism, parasitism, and pathogenicity have become more and more difficult to apply [6]. In this volume of 'Current Opinion in Immunology', a series of articles by internationally recognized experts in the field will describe the state-of-the-art of what is known in terms of the host–pathogen interaction occurring in the setting of specific clinical diseases and conditions.

The first article by Dr. Walker and colleagues (pp. 1–7) focuses on the host–pathogen interaction during bacterial vaccination and summarizes both the success stories, such as *Neisseria meningitidis*, *Bordetella pertussis*, *Streptococcus pneumonia*, as well as the current challenges in developing new anti-bacterial

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vaccines, including the selection of new vaccine escape mutants. The article concludes by emphasizing how major efforts in epidemiological surveillance, vaccine research, and understanding of the host–pathogen interaction are required to overcome these challenges.

A report by Drs. Garon and Orenstein (pp. 8–13) continues this series of reviews with a clearly 'translational' tone by reminding our readers how understanding the host–pathogen interaction has a major impact in terms of human health. This review first explores the role played by an improved understanding of the host–pathogen interaction in the current efforts of vaccine development and then discusses a number of operational and policy considerations that may impact vaccine success post-licensure.

The review by Dr. Kalergis (pp. 14–21) focuses on the role played by the host-mediated inflammatory damage at the level of the respiratory tract and the central nervous system during the course of a viral infection. The authors focus on human respiratory syncytial virus infection (huRSV) as the model pathogen and discuss how the immune response to this virus includes both components that promote clearance of the infection as well as factors that exacerbate its clinical symptoms.

The following review by Dr. Klatt and her colleagues (pp. 22–30) discuss in detail the mucosal barrier as the site of a critical transition between the external environment and human internal body and focuses on the role of this tissue in the setting of HIV transmission, early dissemination, and pathogenesis. The proposed paradigm is, once again, that a dysfunction and/or dysregulated interaction between HIV and the host immune system triggers the long-term manifestations of AIDS.

The review by Liuzzi *et al.* (pp. 31–37) describes microbial pattern recognition by unconventional human T cells, a pattern recognition process normally thought to be a function of innate effector cells. There has been increased recognition that T cells bearing semi-invariant or invariant T Cell Receptors recognize microbial-produced molecules through novel mechanisms of antigen presentation. The Authors discus how these cells represent critical links between innate and adaptive immune responses

Drs. Messaoudi and Basler review the pathophysiology of viral hemorrhagic fever (VHF) viruses (pp. 38–46), with emphasis on Ebola Virus (EBOV) and Yellow Fever Virus (YFV). While clinical sequelae are well described, the viral mechanisms of pathogenesis are not. A unifying theme of VHF viruses is suppression of innate immune functions, resulting in uncontrolled cytokine responses, vascular leakage, hemorrhage, and shock. The Authors highlight that nonhuman primate models of EBOV and YFV offer unparalleled opportunities for investigating viral-mediated induction of VHF.

Drs. Nair and Diamond discuss innate antiviral immune mechanisms in the Central Nervous System (CNS) (pp. 47–53), which are especially critical in light of the specialized regulation of the Blood-Brain Barrier. Once the BBB is breached by viruses and other pathogens, cell-intrinsic responses, including activation of TLRs, RIG-I-like receptors, and DNA sensors, lead to activation of several innate immune pathways, including Type I interferons and IFN-stimulated genes. The Authors explore in depth several innate antiviral strategies unique to the CNS.

The article by Christiaansen *et al.* (pp. 54–60) characterizes the elegant and elaborate mechanisms by which viruses coopt, manipulate, and/or attenuate