NATURAL HOSTS OF SIV

IMPLICATION IN AIDS

Edited by

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Epigraphy

"An accomplished scientist does not always come up with the correct answers to complex biological problems BUT does put together knowledge in a logical order that serves the scientific community a foundation to formulate the right questions."

Ansari, 2014

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Introduction

Natural non-human primate hosts of the simian immunodeficiency virus (SIV) do not develop AIDS despite carrying viral loads that normally lead to pathology and death in non-natural hosts. A large body of data that documents a variety of immunological and virological differences between SIV-infected natural versus non-natural hosts indicate that the clues to disease resistance are mostly host related and have evolved over 100 if not thousands of years. We now face the daunting task of identifying which of these differences (and by what mechanisms) contribute to disease resistance in the natural hosts and ultimately exploit these findings for the design of novel interventions to treat or prevent HIV infection of humans.

CHAPTER

1

Comparative Studies of Natural and Non-natural Hosts of SIV—An Overview

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OVERVIEW

The overall objective of this book is to provide readers with a single reference resource that contains a series of chapters comprising results, views, and concepts formulated by various investigators involved in the comparative studies of the natural and non-natural hosts of primate lentiviruses such as human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV). It is reasoned that such a summary will provide a valuable foundation upon which future studies can be planned, discussions initiated, and critical experiments performed that will move this field forward.

As the titles indicate, the initial chapters include a fascinating story of how SIV was accidentally transmitted in the 1970s from the disease-resistant natural hosts to the disease-susceptible non-natural hosts as an unintended consequence of scientific experimentation by the Nobel laureate Dr Carlton Gajdusek and his colleagues working on "kuru," a rare disease transmitted by brain tissue in a population in New Guinea who practiced cannibalism. Another example of unintended consequences were studies being performed by scientists that were attempting to find a model other than the armadillo for human leprosy and thought that they had developed such a non-human primate model in the early 1980s, i.e., before HIV/SIV were isolated and identified. Concealed within these

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historical descriptions is the finding of the unusual natural transmission of *Mycobacterium leprae* and *Coccidiodes immitis* infections in one of the natural hosts of SIV (sooty mangabey, a species from West Africa) [1–4]. Thus, a sooty mangabey was found to spontaneously acquire *M. leprae* infection and when tissues from this animal were injected into other mangabeys, the recipients developed a lepromatous form of *M. leprae*, which was at the time touted as the first description of a non-human primate (NHP) model to study human leprosy and a major advance in the field of leprosy research. The finding of *C. immitis* infection coupled with the *M. leprae* infections unique to this species prompts the obvious question as to whether the presence of the SIV infection of this natural host makes this species uniquely susceptible or whether the immune system of this species has evolved to confer this unique susceptibility to such microorganisms. This issue still remains to be addressed.

This interesting historical perspective is followed by a chapter on the prevalence and molecular epidemiology of SIVs in the wild, with the use of innovative sequencing techniques that facilitate the understanding of the evolution of these viruses. In addition, it is clear from this chapter that it is likely that >90% of the approximately 70 Old World NHP species in Africa are likely to be infected with species-specific SIVs, but we have knowledge of only 45 such species. It is also clear from this and other chapters that both SIV and the NHP species that harbor such viruses have co-evolved, and adaptation is one of the key elements that need to be recognized. A cautionary note was also expressed by the authors with regard to the pathogenicity of SIVs in natural hosts, citing the more recent studies of the evidence for pathogenicity of SIVcpz in chimpanzees in the wild. Thus, the blanket statement of disease resistance of natural hosts of SIV that are being raised in captivity at the various primate centers needs to be punctuated with the realization that detailed studies of its potential to cause disease in the wild in the same natural hosts are lacking at present. The idea being conveyed here is that there is likely to be continued evolution of both SIVs and the natural hosts that results in survival of only those within the species that co-evolve mechanisms that protect them from developing disease.

Along similar lines, the book includes a chapter devoted to SIVcpz in chimpanzees, with a more detailed description of the various chimpanzee species and the characterization of viruses from such species. The authors describe the differences and similarities between other natural hosts of SIV and the SIVcpz that infects chimpanzees. As cautioned above, while the previous paradigm predicated that the chimpanzees have been infected for thousands of years and are to a large extent disease resistant, emerging data have questioned this view. Thus, based on the fact that there is evidence for pathogenicity of SIVcpz infection of chimpanzees, the argument that transmission of SIV in this species is a more recent occurrence has

strengthened, also explaining the presence of pathology as a result of the lack of sufficient time to reach a peaceful co-adaptation between host and virus. Further studies are clearly in order to address this issue.

These findings are logically followed by a detailed review of our current knowledge on the role of the various viral proteins, including the "accessory" proteins, that have been identified and sequenced and their functional consequences described. Thus, the repertoire of these virally encoded accessory proteins, including Nef, Vpu, and Vpx, that have evolved and the pathogenic consequences of such evolution are elegantly outlined. What is most striking is the list of unanswered questions that still remain with regard to these accessory proteins. In addition, a discussion of the role of the corresponding host antiviral restriction factors, which include TRIM-5α, tetherin, APOBEC3G, and SAMHD1, are presented with an emphasis that the role of such host proteins is still in its infancy and there are likely to be additional host factors that have yet to be identified. Understanding how such viral and host proteins have co-evolved will provide not only some important insights on the molecular mechanisms of host/parasite relationships but also crucial information that could be potentially harnessed for the design of candidate vaccines against HIV-1.

One of the issues that has garnered serious attention during the past several years is the phenomenon termed "microbial translocation," a term that has entered our lexicon in HIV/AIDS research. Indeed, a key biological event identified to date that differentiates pathogenic from non-pathogenic HIV/SIV infection, natural versus non-natural hosts of SIV, and the kinetics of disease progression is the occurrence of chronic immune activation (CIMA). Thus CIMA has been heralded as one of the most important correlates of pathogenic infection and the best marker for disease progression. It has been shown that CIMA is at least in part the result of microbial translocation that results from the loss of integrity of the gastrointestinal tissue barrier that separates the microbial flora from the lumen of the intestine to the systemic circulation. The chronic flow of microbiota and its products from the gut to the circulation induce both innate and adaptive immune cell activation with resulting toxic levels of cytokines, which dysregulate multiple biological systems, including, eventually, the coagulation cascade, leading to multiple organ system failure and death. Thus, there are two chapters within this book that concern CIMA. One of the chapters is focused on outlining the physiological and immunological mechanisms that maintain mucosal integrity and how its breach leads to microbial translocation resulting in CIMA in the disease-susceptible hosts—while, interestingly, such a breach occurs only mildly and transiently in the natural hosts. An important side note of this chapter is an emphasis on the fact that the mechanisms that lead to reversal and subsequent maintenance of mucosal integrity in one natural host may not in fact be similar to those in another host. The second chapter

expands on the overall concepts laid out in the previous chapter by outlining all the cellular characters that are involved in the dialogue between the pro- and anti-inflammatory effects of the host immune system, with a focus on those that are functional at the mucosal interface. Thus, the basic tenets of this chapter are that natural hosts have developed a remarkable array of regulatory mechanisms that can dampen/mute proinflammatory responses and maintain homeostasis. It is clear from the gist of this chapter that these unique regulatory mechanisms that have been acquired by the natural hosts of SIV are the ones we need to exploit and target as part of novel therapeutic strategies aimed to minimize the damage that SIV (and, by implication, HIV) mediates against the gut mucosa. A related chapter with regard to the mechanisms by which the natural hosts protect themselves from the development of disease is the important finding of differences in the phenotypically defined subset of cells that SIV targets in the natural hosts. Thus, the findings outlined in this chapter suggest that the natural hosts best studied so far, which include the sooty mangabeys and the African green monkeys (AGMs), each have naturally evolved a set of mechanisms that modulate the major receptors for SIV and promote the infection of a subset of cells that are more dispensable for the host. This deviation allows for the survival and function of the subset that is critical for the host to maintain antigen-specific recall responses, immune homeostasis, mucosal barrier integrity, and, importantly, lymphoid tissue architecture [5]. Obviously, more detailed studies are required in efforts to exploit this finding for therapeutic purposes because it is not clear how this deviation evolved in the natural hosts over the millennia and is in fact mediated at the molecular level. Once again, it does appear that the mechanisms are species specific; and thus, while there is a common endpoint (disease resistance), the pathways are quite distinct, which can be viewed as hurdles or can be viewed as multiple targets available for identifying therapeutic strategies.

The next few chapters sequentially deal with the characteristics of the innate and acquired humoral/cellular responses; each chapter covers not only the subtle differences in the phenotype of cell lineages that execute these functions, but also how these functions differ between the natural hosts and the non-natural hosts of SIV. A comprehensive description of the various cell lineages that comprise the innate immune system and their role in either influencing the quality and quantity of virus-specific immune responses or regulating viral loads is described. Among the highlights of this chapter is the description of the role of the plasmacytoid dendritic cells (pDCs), whose trafficking from the periphery to the gut tissues and their subsequent accumulation within the gut was shown to lead to high levels of IFN-α in the non-natural hosts, associated with disease progression. On the contrary, such trafficking of pDCs in the natural hosts was found to be transient following acute infection. These findings suggest a

potentially important difference in the role of pDCs in natural versus non-natural hosts. The coincident depletion of Th17/IL-22 synthesizing cells, also uniquely in the SIV-infected non-natural but not the natural hosts, suggests perhaps a linkage between these two events. Attempts to convert the infection and disease profile of natural hosts to that of non-natural hosts with the administration of IFN-α to promote innate immune signaling, however, while inducing a transient increase in the activation of $CD8^+$ T cells, failed to show $CD4^+$ T-cell depletion and showed no major effects on viral loads. An opposite strategy with the use of TLR7/9 antagonist to block IFN-α signaling in SIV-infected non-natural hosts not only had no effect on the depletion of $CD4^+$ or $CD8^+$ T cells, but—of interest—did not affect the expression of interferon-stimulating genes, suggesting that such manipulations in vivo perhaps are not effective because they do not function individually and/or they represent a downstream event. Similarly, attempts to administer lipopolysaccharides to the SIV-infected natural hosts to mimic the effect of microbial translocation in the non-natural hosts induced a transient increase in plasma viral loads but did not lead to disease, suggesting either that such manipulations do not faithfully replicate the conditions noted in the non-natural hosts or that the disease-inducing events are complex and require multiple system manipulations. Another cell lineage that appears to be important is the innate lymphoid cells (unique lineage only present in gut tissues). Their depletion/absence in the SIV-infected non-natural hosts but continued presence in the natural SIV-infected host, coupled with a role of these cells to maintain Th17/IL-22 in the gut mucosa, prompts the need for further detailed study of this difference. Of interest are the studies on the role of NK cells. Depletion studies during acute infection using either in vivo depleting antibodies or the use of a JAK3 inhibitor while showing varying levels of depletion of this cell lineage failed to show any major difference in viral loads. However, depletion of NK cell lineage using the JAK3 inhibitor during acute infection did appear to influence plasma and cellular viral loads during chronic infection by an as-yet-unidentified mechanism [6]. A role of this cell lineage in mediating ADCC activity and to serve as enhancers of immune responses by adjuvants has also been highlighted in this chapter. In all, it appears that much has yet to be learned on the role of the innate immune network on influencing the course of disease in the natural and non-natural hosts of SIV.

A summary of the humoral anti-SIV response in the natural host with a focus on the sooty mangabeys and a comparative analysis of the antibody response between sooty mangabeys and rhesus macaques is outlined in the next chapter. To a large extent, it appears that natural SIV hosts do not mount a robust virus-specific neutralizing antibody response and the elimination of B cells in the natural hosts does not lead to increases in plasma viral loads. While the author is clear that these are not likely

contributing to the disease resistance of the natural hosts, it is indeed possible that the blunting of vigorous virus-neutralizing antibody responses contributes to the disease-protective mechanisms in these natural hosts by preventing the development of hyperimmune activation, dysregulation, and perturbation of lymphoid tissue architecture that is characteristic of the non-natural hosts. One is thus left with the idea that the natural hosts have developed a potent regulatory mechanism that prevents the development of vigorous humoral virus-specific immune responses and its corollary: that vigorous virus-specific immune responses are contributing to the development of disease. It is requested that the reader keep this thought in mind as we try to put this in context with all the other findings displayed in the chapters.

The comparative analysis of SIV-specific humoral responses is followed by a chapter on the virus-specific cellular responses, including the responses of cells that form a bridge between humoral and cell-mediated immune responses. The findings of this chapter suggest that while the virus-specific cellular immune responses are noted in both the natural and non-natural hosts of SIV, the response in the natural hosts may in fact be more effective in limiting tissue damage and resulting immunopathology, particularly in secondary lymphoid tissues and in specific $CD4^+$ T-cell subsets. The emphasis is also being placed on the importance of regulatory mechanisms and specific molecules (PD-1, CTLA-4, LAG-2, 2B4, CD160 and GP149) that mediate such regulatory function of adaptive immune responses that have evolved selectively with enhanced function evolved in the natural hosts and, of importance, a constellation of mechanisms that maintain the presence of normal frequencies and function of these so-called cell lineages that fall within the cusp of humoral and cellular immune responses (NK regs, NK-T cells and KIRs) are illustrated in Figure 1.1.

This is followed by two chapters that address additional important roles in the field of natural and non-natural SIV infections, including the mechanisms of viral transmission and the role of genetic factors. With regard to the studies of viral transmission, it does seem ironic that even after three decades of research in the field of HIV/SIV, we still do not fully comprehend the impact of the route of transmission on disease outcome. Thus, while it is clear that the mucosal route is the major route of natural transmission, we do not fully understand how the different routes affect the generation of virus-specific humoral and cellular responses and the impact of the innate immune system in the localized environment that influences the outcome in natural versus non-natural hosts of SIV. This is because this subject encompasses multiple routes and involves not only the transmission between adults but also mother-to-child transmission and how this differs between natural and non-natural hosts. There does seem to be a hierarchy, however, in the dose of virus required for transmission via the different routes in adults. Thus, the dose of virus required to transmit infection increases, in order, via

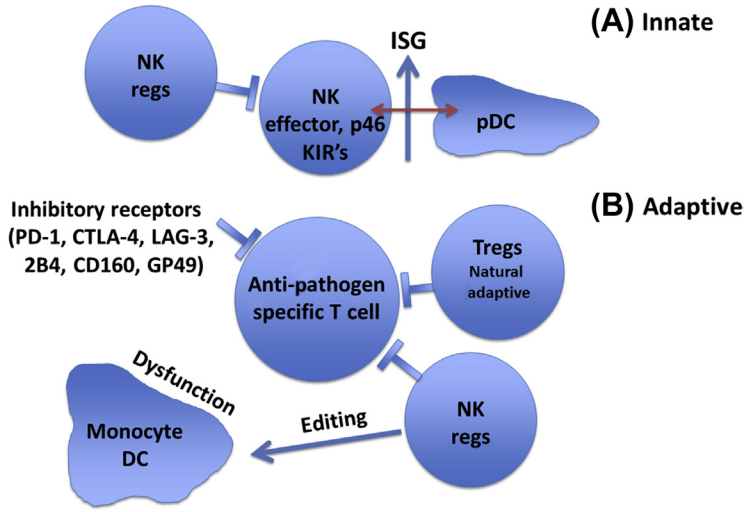

FIGURE 1.1 Mechanisms that contribute to distinct outcomes of SIV infection in natural versus non-natural non-human primate hosts. Nature has built in a series of redundant effector regulatory mechanisms to insure that the immune responses of the host stay in check and do not result in pathology. This regulatory process occurs during both (A) innate and (B) adaptive immune responses. For innate immune responses, regulation of the synthesis of interferon-stimulated genes is one good example. In the case of adaptive immune responses, the regulatory molecules include the gradual expression and upregulation of the inhibitory receptors (PD-1, CTLA-4, LAG-3, 2B4, CD160, and gp49), which generate negative signals upon ligation, and the activation of regulatory T cells (Tregs) and regulatory NK cells (NKregs), which also function to kill immature dendritic cells to promote muting of the immune responses. Some of these regulatory mechanisms function systemically and others function in select tissues and organs, providing a multi-pronged safeguard to fine-tune the host anti-pathogen relationship. The natural hosts of SIV have evolved to optimally utilize such regulatory mechanisms, whereas dysregulation of such regulatory mechanisms characterizes the non-natural hosts of SIV.

blood, rectal tissues, vaginal tissues, and oral tissues, respectively. It is also clear that vaginal transmission is a rare event, which has prompted the use of low-dose repeated intravaginal transmission as a model to better mimic HIV-1 transmission in humans. Germane to the major thrust of this book are studies of the differences between the natural versus the non-natural hosts of SIV. A number of points appear to be clear from the studies performed to date. First of all, the majority of SIV transmitted in the natural hosts is via the sexual route, and there is high concordance between age of the natural hosts and seroconversion and virus positivity. Secondly, one of the most important differences between the natural and non-natural hosts of SIV is the relative resistance from mother-to-child transmission in the natural hosts as compared with the non-natural hosts of SIV. This is true not only for natural epidemiologic studies of animals in the wild but also for experimental studies

in which the mother's milk was experimentally manipulated to contain high viral levels. However, what is lacking in these studies are the precise mechanisms involved in the resistance of the infants of the natural hosts. One of the suggested mechanisms implicates the differences in the cell lineages that are targets for infection in the natural hosts, similar to the argument advanced above as a mechanism of disease protection. However, the molecular mechanisms responsible for these differences in the type of target cells between natural and non-natural hosts remain incompletely understood.

The subject of the role of genetic factors in differences in susceptibility to transmission, infection, and disease progression has been, unfortunately, the most difficult to study. This is because most studies being performed at primate centers involve a limited number of animals of each species and genetic association studies clearly require studies of large cohorts. This problem is further compounded by the lack of detailed knowledge of the sequences of the genes involved and the nature of the polymorphisms of the select genes, particularly in the natural hosts. Thus, basic studies of the detailed characterization of the degree of MHC class I and II polymorphisms in the non-natural hosts are still lacking and there is very limited knowledge of the MHC genes of the natural hosts. Nonetheless, since there is now clear evidence for the role of MHC class I/II and those that involve NK cell function such as NK cell receptors, KIRs, and FcR on the pathogenesis of human HIV-1, it was important to include a chapter on this subject, which is very ably summarized herein.

Finally, a very fascinating topic is covered by the last two chapters of this book. These chapters summarize what we know at present with regard to HIV-1-infected humans that show characteristics similar to natural SIV hosts. While there are clear differences between "elite controllers" of human HIV-1 infection and the natural hosts of SIV, which include low viremia and potent antiviral T-cell immune responses in the former but not the latter, the number of similarities is of great interest. This includes the absence of chronic immune activation, a downregulated IFN-α response, lower viral loads in lymph nodes, and relative sparing of the central memory and potentially the follicular helper $CD4^+$ T cells. A similar theme is projected in the second chapter on this subject but also includes the remarkable description of a rare but interesting subset of HIV-1-infected humans that maintain high viral loads for a substantial time period, but with no loss of $CD4^+$ T cells and no signs of disease progression (i.e., viremic nonprogressors or VNP). The authors also highlight our limited understanding of the biology and pathogenesis of HIV-2 infection in humans and that more detailed studies of these individuals, in concert with studies of elite controllers, VNPs, highly HIV-1-exposed but noninfected humans, and normal and/or fast progressors, provide the entire spectrum of HIV-1-infected humans. A study of the differences in the pathogenic mechanisms of these cohorts is clearly in order and likely to be highly informative.