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Research paper

The well-tempered SIV infection: Pathogenesis of SIV infection in natural hosts in the wild, with emphasis on virus transmission and early events post-infection that may contribute to protection from disease progression

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ABSTRACT

African NHPs are infected by over 40 different simian immunodeficiency viruses. These viruses have coevolved with their hosts for long periods of time and, unlike HIV in humans, infection does not generally lead to disease progression. Chronic viral replication is maintained for the natural lifespan of the host, without loss of overall immune function. Lack of disease progression is not correlated with transmission, as SIV infection is highly prevalent in many African NHP species in the wild. The exact mechanisms by which these natural hosts of SIV avoid disease progression are still unclear, but a number of factors might play a role, including: (i) avoidance of microbial translocation from the gut lumen by preventing or repairing damage to the gut epithelium; (ii) control of immune activation and apoptosis following infection; (iii) establishment of an anti-inflammatory response that resolves chronic inflammation; (iv) maintenance of homeostasis of various immune cell populations, including NK cells, monocytes/macrophages, dendritic cells, Tregs, Th17 T-cells, and γδ T-cells; (v) restriction of CCR5 availability at mucosal sites; (vi) preservation of T-cell function associated with down-regulation of CD4 receptor. Some of these mechanisms might also be involved in protection of natural hosts from mother-to-infant SIV transmission during breastfeeding. The difficulty of performing invasive studies in the wild has prohibited investigation of the exact events surrounding transmission in natural hosts. Increased understanding of the mechanisms of SIV transmission in natural hosts, and of the early events post-transmission which may contribute to avoidance of disease progression, along with better comprehension of the factors involved in protection from SIV breastfeeding transmission in the natural hosts, could prove invaluable for the development of new prevention strategies for HIV.

1. Introduction

A family of retroviruses, collectively referred to as simian immunodeficiency viruses (SIVs), naturally infects a large number of African NHP species. Currently, over 40 different SIVs are known to be circulating in wild African NHPs. As natural hosts of SIVs, these NHPs generally do not progress to AIDS, despite chronic, highly active viral replication that is in same range as or even greater than what is typically reported in HIV patients (Ansari and Silvestri, 2014; Chahroudi et al., 2012; Locatelli et al., 2014; Pandrea and Apetrei, 2010; Pandrea et al., 2008a; VandeWoude and Apetrei, 2006). However, there have been some rare cases where AIDS or AIDS-like symptoms have been reported in natural hosts. These cases occurred primarily in NHPs in captivity that had outlived the normal lifespan of their species in the wild and had been infected and followed for decades (Apetrei et al., 2004; Ling et al., 2004; Pandrea et al., 2001, 2009). This clearly indicates that the lack of disease progression in the natural hosts of SIVs is not the result of infection by benign viruses, but rather that these species have adapted to avoid progression to AIDS. Although relatively sparse compared to the body of data on HIV, the research done on the pathogenesis of SIV-infection in natural hosts indicates that the lack of disease

Abbreviations: AGMs, African green monkeys; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; GALT, gut associated lymphatic tissue; HIV, human immunodeficiency virus; LPS, lipopolysaccharide; MT, microbial translocation; MTIT, mother-to-infant transmission; NHPs, nonhuman primates; PTMs, pig-tailed macaques; RCM, red-capped mangabeys; RMs, rhesus macaques; SIV, simian immunodeficiency virus; SMs, sooty mangabeys; TCM, central memory T cells; Tregs, regulatory T cells; TSCM, memory T-cells with stem cell-like properties; TLRs, Toll-like receptors; VL, viral loads.

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progression does not appear to be mediated by a more effective immune response by the host, but rather better management of the deleterious consequences of infection (Pandrea et al., 2008a).

The exact mechanisms by which natural hosts are able to avoid progression to AIDS in the face of a highly active infection are a subject of intensive research. Whatever they may be, the adaptations leading to control of the deleterious consequences of SIV infection in natural hosts are almost certainly the result of long-term coevolution between African hosts and their species-specific SIVs (Chahroudi et al., 2012; Fischer et al., 2012; Kobayashi et al., 2014; Ma et al., 2013; Pandrea and Apetrei, 2010). Here, we will review the current knowledge regarding SIV-infection in natural hosts, with an extra focus on the events surrounding transmission. The current research indicates that the key events involved in controlling and preventing disease progression appear to occur very early in infection, during the initial period following viral entry, and may be localized to the mucosal sites of infection. Understanding these mechanisms and comparing them to the mechanisms underlying progressive infections has the potential to unlock novel prevention strategies for HIV patients and potentially new paths to reaching a 'functional cure' for HIV.

2. Evolutionary history of SIVs in African NHPs

2.1. SIVs naturally infect only wild African NHPs

Before considering the exact features of SIV infection in African NHPs, it is important to understand the long evolutionary relationship that exists between these viruses and their hosts. SIVs have so far been found to infect over 45 species of African NHPs. This means that >40 genetically distinct SIVs are known to be circulating in the wild. While most natural hosts are infected by a single species-specific SIV, there are several examples of African NHP species, including mandrills, mustached monkeys, and mantled guerezas, which have multiple SIVs cocirculating in the wild (Ansari and Silvestri, 2014). No SIVs have been found yet that infect any wild Asian or New World NHPs. Therefore, Asian macaques are nonnatural hosts of SIV (Ansari and Silvestri, 2014; Lowenstine et al., 1986; Ohta et al., 1988). The various SIVmac variants that are used to experimentally infect rhesus macaques (RMs), pig-tailed macaques, crab-eating macaques and stump-tailed macaques in captivity actually represent cross-species transmissions of SIVs from sooty mangabeys (SM), an African NHP species (Apetrei et al., 2005). In macaques and other Asian NHPs, SIV infections are pathogenic and lead to the development of AIDS, which is why the RM has become the primary model for HIV in humans.

From an evolutionary perspective, humans could also be considered to be a nonnatural host for HIV, as HIV only appeared in human populations within the last century, when the virus was acquired from chimpanzees/gorillas and sooty mangabeys. The progression to AIDS reflects the poor evolutionary adaption between HIV and humans. A similar situation exists in chimpanzees, which also acquired SIVcpz from various monkey species through cross-species transmissions and recombination events (Bailes et al., 2003), and then became the source of the SIVgor that infects gorillas (D'arc et al., 2015; Faria et al., 2014; Hirsch et al., 1989; Keele et al., 2006; Van Heuverswyn et al., 2006). Like HIV in humans, progression to AIDS has been shown to be a possible outcome of SIVcpz infection in chimpanzees, both in captivity and in the wild, though it is as of yet unclear how prevalent progression to AIDS is among wild chimps (Etienne et al., 2012; Keele et al., 2009a).

2.2. African NPHs and SIVs have coexisted for an extremely long period of time

Various studies incorporating geology, phylogeny and molecular genetics point to very ancient origin of SIV, though the exact estimates vary greatly. Some of the most concrete evidence for the origin of SIV infections comes from a study of NHPs isolated on Bioko Island. Located off the northern coast of Equatorial Guinea, Bioko Island was separated from the mainland around 10,000 years ago. Phylogenetic analysis of the SIVs endemic to the NHPs on the island revealed that each SIV was most genetically similar to SIVs infecting NHPs of the same genus on the mainland. This suggests that SIVs were already circulated in these species at the time of Bioko Island separation from the mainland, i.e., that SIVs are at the very least over 10,000 years old (Worobey et al., 2010). On the other end of the spectrum, an endogenous lentivirus infecting the gray mouse lemur in Madagascar was shown to be genetically related to mainland SIVs. As the NHPs on Madagascar have been separated from African NHPs for at least 14 million years, this study points to an extremely ancient origin of SIVs (Gifford et al., 2008; Perelman et al., 2011). Due to the discrepancy with the molecular clock data, it generally can be surmised that SIVs have been infecting African primates for anywhere between tens of thousands to millions of years (Compton and Emerman, 2013; Gifford et al., 2008; Ma et al., 2013). In fact, it is possible that SIVs have been infecting NHPs since the time of primate speciation, given the complete absence of SIVs in Asian and New World NHPs (VandeWoude and Apetrei, 2006).

While the precise age of SIV infections in their natural hosts may be uncertain, they clearly share a long evolutionary history together. One notable example illustrating this relationship can be found in the phylogeny of the various strains of SIVagm, which infect African green monkeys (AGMs). AGMs are NHPs belonging to the genus *Chlorocebus*. The genus encompasses four species of AGM: sabaeus, grivet, tantalus, and vervet (Ansari and Silvestri, 2014; Pandrea et al., 2008a), which were shown to be infected with a species-specific virus (Allan et al., 1991). The AGM subspecies are known to have diverged from their common ancestor between 1.5 and 3 million years ago and then spread out over sub-Saharan African, each settling into a different region (Xing et al., 2007). Given the geographical and temporal divergence of the subspecies, it is likely that their respective viruses also evolved in tandem with their hosts (Ma et al., 2013). This conclusion is supported by a recent study examining the diversity of SIVagm in AGMs geographically separated by the Drakensberg mountains along the coast of South Africa. Phylogenetic analysis demonstrated that the costal viruses and the inland viruses clustered separately and were genetically distinct from each other. As the Drakensberg mountains are around 280 million years old, the divergence between the two groups could have occurred anywhere between the aforementioned spread of AGMs 3 million years ago to around 100,000 years ago, during the mass migrations that occurred in the Plio-Pleistocene glacial period (Ma et al., 2013).

2.3. SIVs are genetically diverse and readily undergo cross-species transmission and recombination

The extensive evolutionary history of SIVs is also reflected in part by the extreme genetic diversity of SIVs and, subsequently, HIVs. Phylogenetic analysis of SIVs has revealed that there have been numerous cross-species transmissions and recombination events in the past, with many SIVs arising after crossing over between two sympatric species (Pandrea and Apetrei, 2010). There are also multiple examples of cross-species transmission subsequently followed by recombination, including: (i) SIVmnd-2, which is the result of a recombination between SIVmnd-1 and SIVrcm; (ii) SIVsab, which is an ancient recombinant of an ancestral SIVsab and SIVrcm; (iii) SIVmus, SIVmon, and SIVgsn, three viruses from three different NHP species (mustached monkeys, mona monkeys and greater spot-nosed monkeys) which share genetic and phylogenetic features, suggesting recombination (Jin et al., 1994a; Liégeois et al., 2014; Takemura and Hayami, 2004).

Another notable example is SIVcpz, which shares genetic similarity to both SIVrcm and SIVgsn. Chimpanzees regularly hunt other primates for food and the recombination of these two viruses almost certainly occurred in chimps (Bailes et al., 2003). This emergence of SIVcpz is most likely a relatively recent event, as is reflected by the reports of 10- to 16-

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