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Innate immune cell responses in non pathogenic *versus* pathogenic SIV infections

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HIV-1/SIVmac infections deeply disturb innate host responses. Most studies have focused on the impact on dendritic cells and NK cells. A few but insufficient data are available on other innate immune cell types, such as neutrophils. It has been shown that innate lymphoid cells are depleted early and irreversibly during SIVmac/HIV-1 infections. Studies in natural hosts of SIV have contributed to pinpoint that early control of inflammation is crucial. In natural hosts, plasmacytoid dendritic cells, myeloid dendritic cells and NK cells are depleted during acute infection but return to normal levels by the end of acute infection. We summarize here the similarities and differences of various types of innate immune responses in natural hosts compared to pathogenic HIV/SIV mac infections.

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Introduction

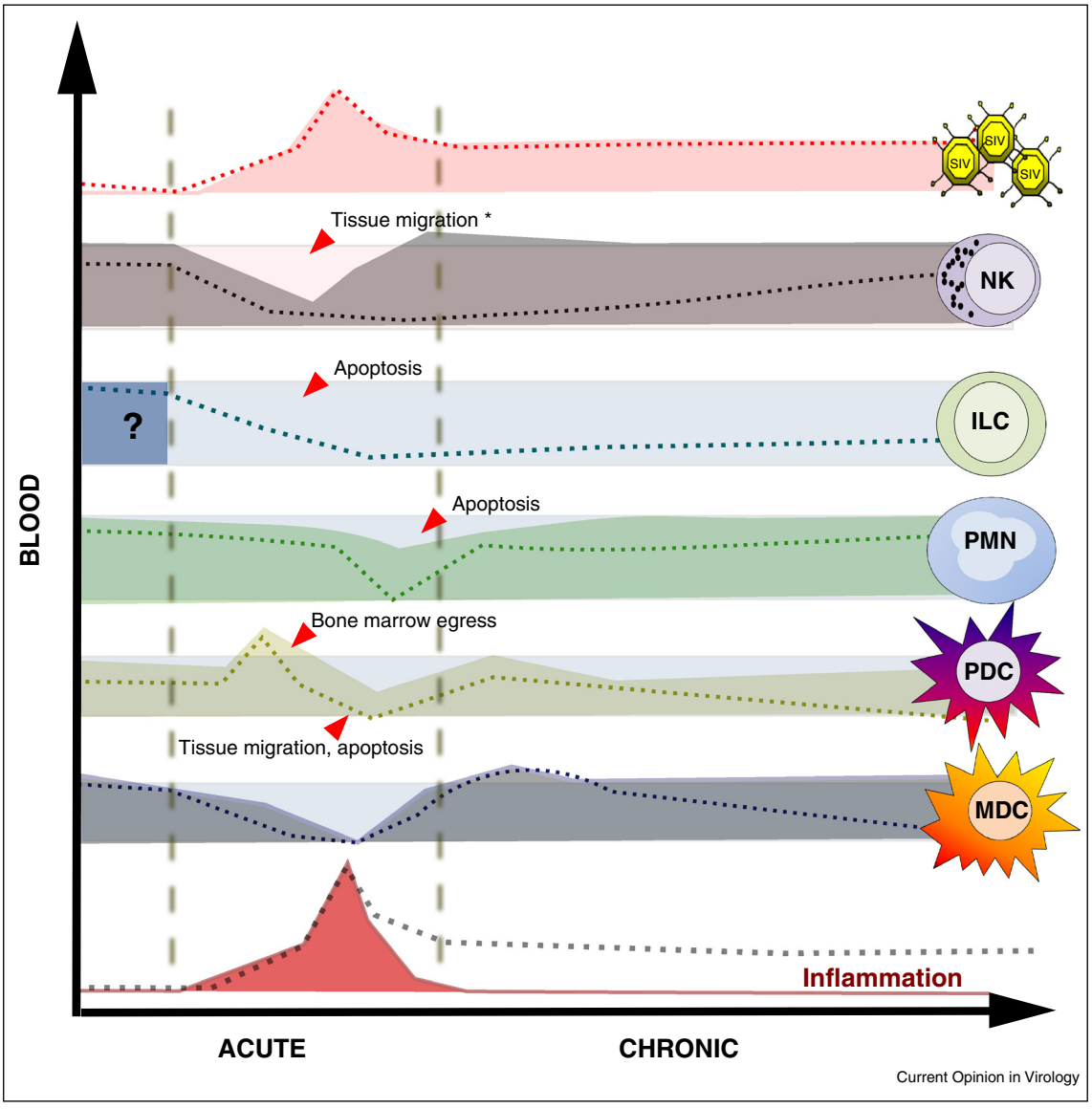
The infection of a host by a virus leads to one of the following three distinct outcomes: clearance of the virus, establishment of a chronic infection and the worst possibility, the death of the host. The quality and the duration of the host response, which may be influenced intrinsically (i.e. genetic background) or extrinsically (i.e. medication) engages the resolution of the infection toward one of those possibilities.

The host response can be divided into two main arms: the innate immune system and its orchestration of cells belonging to the adaptive immune system and the adaptive immune system itself. These different arms are interdependent and their actions are spatially and temporally organized in order to give an optimal response against the pathogen.

HIV infection is disturbing both the innate and adaptive arms of the host response. The introduction of the combined anti-retroviral treatment (cART) allows immune restoration, however to variable degrees. The capacity of the treatment to restore the functionality of the immune system varies depending on several factors, in particular the stage of infection at which the treatment is initiated.

Little is known on the impact of cART on the innate immune system. This lack of knowledge is partly due to the fact that patients were rarely detected for HIV during the acute phase of infection, at the moment where the inflammation and the innate response is the most active. In this context, the study of SIV infection in non human primates (NHP) remains a major model of choice to study the first steps of infection. Indeed, Asian species of NHP, such as rhesus and cynomolgus macaques, experimentally infected by SIV, experience a spectrum of disorders identical to HIV-1 infected humans. NHP models contributed to increase significantly our knowledge on HIV infection, for instance helped to apprehend the early establishment of the viral reservoirs and the immense immunological insult to the gut, as well as other tissues, given by the viral infection [1,2,3•,4]. NHP from Africa, such as African green monkeys (AGM), sooty mangabeys (SM) and mandrills, are natural hosts of SIV. SIV infection in these natural hosts generally does not lead to any signs of disease, even though they carry high plasma and intestinal viral load [5]. One major difference between AIDS progressors and non-progressors is the duration of the inflammation, which is totally resolved in natural hosts by the end of the acute infection, while chronic inflammation persists in AIDS progressors (Figure 1). Inflammation is initially induced by cells that sense the virus. Subsequently, cells of the adaptive immune system, as well as other mechanisms, might contribute to chronic inflammation, for instance microbial translocation which is absent in natural hosts [6–8]. Indeed, natural hosts maintain the integrity of the intestinal barrier and do not loose their Th17 cells [5,8,9]. Another remarkable difference in the natural host is the preservation of the architecture of the secondary lymphoid tissues, the latter being progressively disrupted in HIV and SIVmac infections [10,11]. The preservation of such a structure could

Figure 1



Dynamics of the innate immune cells during pathogenic and non pathogenic SIV infections. The dynamics are indicated for the natural hosts (full) and for the pathogenic models (dotted). The schemes illustrate what is known about innate immune cell population changes during the time of infection. The evolution of the different innate immune cells is compared to the dynamics of viremia (top) and the evolution of inflammation (bottom). The main reason(s) suggested to explain a change in cell subset frequencies are indicated by a red arrow. The asterisk means that the mechanism has only been observed in pathogenic infection. The question mark indicates a population for which the evolution has not been characterized in the natural host.

participate to the better orchestration of immune responses in natural hosts. This review will discuss in particular the hallmarks of innate immune responses in natural hosts. Innate immunity is generally less well explored than T and B cell responses, except for dendritic cells and NK cells. We will here summarize the information that is available on innate immune responses in natural hosts and explain the major differences with respect to pathogenic HIV and SIVmac infections.

Monocyte/macrophages

Monocytes and macrophages possess receptors for entry of HIV/SIV viruses, like dendritic cells and CD4 T cells. While primary monocytes are not susceptible to HIV infection, HIV infection of macrophages in tissues, such as the brain, lung and decidua, has been reported in many studies [12,13]. It has been suggested that this cell population figures among the first target cells to be infected by SIV/HIV in vaginal mucosa [13,14]. PCR