

## Macrophage infection by HIV-1: focus on viral reservoirs and pathogenesis

Topics from this 4<sup>th</sup> International Workshop on HIV and Cells of Macrophage Lineage and other Reservoirs and those reviewed in this issue center on the host and immune factors affecting macrophage infection by HIV-1, the role of monocytes and tissue macrophages as a reservoir for HIV, and the potential role that infected macrophages have in mediating virus-induced neuropathology.

Immune activation continues to be recognized as a major factor driving HIV-1 expression in infected macrophages. Additional data supporting this concept were presented by Wahl et al. [1], who described the molecular factors associated with increased permissiveness to viral infection and replication in *Mycobacterium avium* complex infected macrophages. In addition to immune activation or co-infection, Cunningham et al. [2] described host-determined factors affecting the initial steps of viral binding and initiation of reverse transcription, which were important variables acting to determine the efficiency of macrophage infection between different donors.

Studies on the interaction between HIV gp41/gp120 and cell surface receptors on macrophages have now shown clearly that CXCR4, as well as CCR5, can mediate productive infection. The identification of strains of macrophage-tropic HIV-1 isolates that require and signal through CXCR4, as well as the advantage of qualifying viral isolates by co-receptor usage rather than their cytolytic potential on immortalized T-cell lines, (the “syncytium inducing” or SI versus “non-syncytium-inducing or NSI dichotomy), was presented by Collman et al. [3] and Lathey et al. [4], respectively. These studies, together with DeJucq’s [5] showing evolution of HIV-1 in the usage of CCR5 and CXCR4, clearly indicate that HIV-1 can evolve *in vitro* to using both CCR5 and CXCR4 even in the absence of an immune response and that isolates using either co-receptor can infect macrophages.

Previous studies had shown a potential role for macrophages in the early steps of HIV-1 infection and for virus replication in non-lymphoid tissues such as the lung or brain. Brodie et al. [6] expand on this area by presenting observations within lung and gut tissues from infected subjects at end-stage disease. The latter support a role for infected macrophage cell subsets as a major source of viral particles in patients with high viral loads and severely reduced CD4 T-cell subsets. In contrast to the role of gut macrophages at end-stage disease, work by Smith et al. [7] shows that resident macrophages from the lamina propria in gut tissue are less permissive to HIV-1 infection than T-cells. Taken together, these studies suggest macrophage permissiveness to HIV-1 infection may fluctuate between early and late disease and within different anatomical compartments. Further characterization of the interplay between HIV-1 infection of resident versus recruited macrophages within intact or depleted T-cell micro-environments

will be needed to further elucidate permissiveness of cells to HIV-1 infection *in vivo*.

The recent widespread use of effective antiretroviral regimens has highlighted the need to understand the cells thought to be HIV reservoirs *in vivo*. Zhu [8] and Crowe et al. [9] present data to support the hypothesis that blood monocytes harbor infectious HIV in patients with undetectable viral load (50 copies of HIV RNA/ml plasma) on highly active antiretroviral therapy (HAART). Monocyte reservoirs are established shortly after infection, and maintain a cell-specific viral evolution history, which is sustained during suppressive antiretroviral therapy. It seems evident that the interactions of HIV-1 with cells of the monocyte-macrophage lineage are important to understand viral turnover in macrophage reservoirs *in vivo*, in addition to providing an accessible population to monitor in any eradication strategy.

Many viruses have been shown to modulate emerging immune responses by infecting monocyte-macrophages. Muthumani et al. [10] present data supporting a direct role of HIV-1 Vpr in impairment of beta chemokine secretion by infected cell targets while Kornbluth [11] and Ma et al. [12] review how HIV-1 infection alters CD40/CD40 ligand interactions and IL-12 expression, respectively. These reviews clearly illustrate how the immune cascades associated with macrophage/T-cell recruitment and activation are affected following HIV-1 infection, both *in vitro* and *in vivo*. Conversely, Fantuzzi et al. [13], Vicenzi et al. [14], and Mantovanni [15] have shown that the innate immune functions of monocyte-macrophages, such as recruitment, differentiation and chemokine secretion or activation of adaptive responses through cytokine secretion, may alter the capacity of HIV-1 to infect and replicate in macrophages.

In addition to the central role of macrophages in contributing to the immunopathology leading to AIDS, macrophage infection in the CNS is directly associated with viral-induced neuropathology. Persidsky et al. [16] present an interesting model for analysis of cell recruitment through the blood brain barrier, and shown that recruitment is impaired following HIV-1 infection of macrophages. The casual relationship between macrophage infection and impairments of neuronal function was enlarged by Pereira et al. [17] and Aquaro et al. [18] using *in vitro* model systems of HIV-1 infection. HIV-infected macrophages induce a pro-inflammatory response when interacting with endothelial cells [17] and induce apoptosis in bystander astrocytes [18]. Together, these observations underscore the role of macrophages in HIV-induced CNS disease.

In this issue, the groups participating in the workshop have summarized recent progress in our understanding of HIV-1 infection of macrophages, and have reinforced the central role of these cells play in HIV-1-induced effects on immune func-

tion, viral persistence in lymphoid and non-lymphoid organs, and processes leading to neural pathology.

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