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INVARIANT NKT CELLS AND CD1d IN HIV-1 INFECTION

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ABSTRACT

The invariant natural killer T (iNKT) cells are a subset of T lymphocytes that share characteristics of both innate and adaptive immunity. These cells are defined as T cells restricted by the lipid antigen presenting molecule CD1d and express an invariant T cell receptor (TCR) as well as classical NK cell markers. Upon stimulation iNKT cells rapidly produce large amounts of cytokines and chemokines and activate various other cell types including NK cells and DCs. iNKT cells have been implicated in the protection against infectious pathogens, including viruses, bacteria and parasites. In addition they are involved in the immune responses against tumors and in regulating autoimmune and inflammatory diseases.

Several viruses have been shown to evade human iNKT cell responses by down-regulating CD1d expression in infected cells. In this thesis the effect of HIV-1 infection on CD1d expression in DCs and the ability of DCs to activate iNKT cells were investigated. We found that HIV-1 interferes with CD1d expression and that this effect was mediated by the HIV-1 accessory protein Vpu. Down-regulation of CD1d contributed to inhibition of iNKT cell activation, as indicated by lower IFN-γ production and less centrosome polarization in iNKT cells in contact with infected DCs. The mechanism behind CD1d down-regulation was dependent on inhibition of CD1d recycling, and interaction between CD1d and Vpu in early endosomal compartments. Vpu down-regulates different host-proteins involved in innate immunity. Interestingly, down-regulation of CD1d and CD4 was found to occur by distinct mechanisms. In addition to Vpu-mediated interference with CD1d expression and iNKT cell activation, HIV-1 infection leads to depletion and functional impairment of iNKT cells in infected individuals. Collectively, these findings suggest that the Vpu protein of HIV-1 may play a significant role in evasion from CD1d-specific immune responses, and moreover support the notion that iNKT cells play an important role in the host defence against HIV-1.

In addition to recognition of exogenous lipid antigens presented by CD1d, iNKT cells can be activated by cytokine or surface receptor stimulation with or without presentation of endogenous lipids. In this thesis, we demonstrate NKG2D-dependent iNKT cell activation. Specifically, the CD4-negative iNKT cell subset was able to degranulate and kill target cells upon NKG2D triggering in a TCR-independent manner. Moreover, NKG2D-engagement co-stimulated TCR-mediated iNKT cell activation in response to endogenous CD1d ligands. These alternative pathways for iNKT cell activation may be particularly important in settings where target cells express no or low levels of CD1d, such as transformed or virus infected cells. In summary, the work presented in this thesis expands our knowledge about how iNKT cells respond to target cells and how viruses work to counteract such recognition.

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