

INTERVIEW about Plasmacytoid dendritic cells and anti-HIV immunity with

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What is the role of plasmacytoid dendritic cells?

Stéphanie Louis and Anne Hosmalin: Dendritic cells (DCs) are considered as “professional” antigen-presenting cells. In humans, two distinct subsets are identified in the peripheral blood: myeloid (mDC) and plasmacytoid dendritic cells (pDC). Plasmacytoid DC, also called “Natural Interferon Producing Cells” (NIPC), represent 0.2-0.8% of peripheral blood cells and have also been found in the spleen, bone marrow, tonsil and lymph nodes (1-3). They are specialized in the production of type I interferons (IFN α , β and others, (4). Partially due to a constitutive expression of the transcription factor IRF7, pDC rapidly produce large amounts of IFN α (100 fold more than other cell types) in response to a broad range of enveloped viruses like HIV (5). This

production responds to stimulation of the Toll-like receptors TLR 7,-8 and TLR-9. In addition to a strong antiviral activity, type I IFNs can act indirectly on innate immunity. By a positive loop, they increase pDC survival. They enhance cytotoxicity of NK cells and CD8⁺ T cells (6). Plasmacytoid DC also participate in adaptive immunity by promoting IFN γ production by CD8⁺ and CD4⁺ T cells. When matured by viruses such as influenza, they strongly stimulate allogeneic mixed reactions and specific CD4⁺ and CD8⁺ T cell responses (3,7,8). They are good adjuvants for vaccination (9). They can stimulate either immunity or tolerance (2,10). Thus pDC represent an important link between innate and adaptive immune responses.

During anti-HIV immunity, how are pDC and their functions affected?

Stéphanie Louis and Anne Hosmalin: Dendritic cells play an important role in HIV infection (10-16). In primary and chronically HIV-1 infected patients, a decrease in blood pDC number and in IFN α production after stimulation of peripheral blood mononuclear cells *in vitro* are observed (17-22) (reviewed in (16)). Globally, these

reductions are inversely correlated with plasma viral loads and positively with CD4⁺ T cell counts. Several hypotheses may be advanced for the decline in circulating pDC in HIV infection: primary bone marrow precursor defect, HIV cytopathicity, lack of survival factors such as IFN α or homing to secondary lymphoid organs.

Is type I IFN a good marker for the immune control of HIV-1 replication?

Stéphanie Louis and Anne Hosmalin: Highly active anti-retroviral therapy (HAART)

induces a partial recovery of pDC during chronic and primary HIV infection and an

increase in IFN α production (22-24). This restoration occurs before the recovery of CD4⁺ T cells and is associated with protection from recurrent or opportunistic infection (23). Despite the antiviral efficacy of HAART, side effects drive many patients to ask for treatment interruptions. However, in most cases, HAART interruption leads to HIV replication rebound to a level depending on each patient's ability to control replication by immune responses. The identification of reliable predictors of replication control by the immune systems is needed. We found in a

small cohort of primary HIV-infected patients that the recovery of pDC by HAART was correlated with the ability to control spontaneously replication after treatment interruption (21). So pDC counts might be a good marker for the immune control of HIV-1 replication. As pDC are the main producers of type I IFNs, it seems likely that IFN α is related to low HIV replication rebounds. Nevertheless, other investigations are needed to consider IFN α production as a predictive factor for immune control of HIV replication.

How can we benefit from your findings?

Stéphanie Louis and Anne Hosmalin: Plasmacytoid DC counts or perhaps IFN α production might be used, in conjunction with other parameters currently measured (CD4⁺ T cell count, plasma HIV RNA, proviral DNA load in peripheral blood mononuclear cells...), as predictive factors for viral replication control by the immune system when HAART interruption is needed. Therapeutic perspectives emerge from correlations between HIV replication control and pDC

and type I IFN production levels accumulated by different laboratories (11). Early treatment of primary infected patient by PEG-IFN seems to hold promise (25), perhaps to compensate the decreased IFN α production observed at this stage (22). Moreover, CpG oligodeoxynucleotides or imiquimod analogs, which stimulate type I IFN production by pDC through TLR9 or TLR7/8, respectively, might be used as adjuvants for vaccination (26).

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