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Autologous dendritic cell vaccination against HIV-1 induces changes in natural killer cell phenotype and functionality

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BEST PAPER

Basic Science

Although natural killer (NK) cells have been studied in connection with dendritic cell (DC)-based vaccination in the field of cancer immunology, their role has barely been addressed in the context of therapeutic HIV-1 vaccination. In this study, we evaluated whether a therapeutic vaccine consisting of monocyte-derived DCs electroporated with Tat, Rev and Nef encoding mRNA affects NK cell frequency, phenotype and functionality in HIV-1-infected individuals. Although the frequency of total NK cells did not change, we observed a significant increase in cytotoxic cells following vaccination. In addition, significant changes in the NK cell phenotype associated with migration and exhaustion were observed together with increased NK cell-mediated killing and (poly)functionality. Our results show that DC-based vaccination has profound effects on NK cells, which highlights the importance of evaluating NK cells in future clinical trials looking at DC-based immunotherapy in the context of HIV-1 infection.

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INTRODUCTION

To date, antiretroviral therapy (ART) is the only effective treatment available to reliably suppress replication of human immunodeficiency virus (HIV-1) and avoid progression to acquired immunodeficiency syndrome (AIDS). However, ART cannot eliminate latently integrated virus meaning that life-long treatment is required and immune-based strategies to control HIV-1 infection are still needed. Discoveries in the field of HIV-1 pathogenesis and the role of the immune system in the majority of people living with HIV-1 (PLWH)¹. Therefore, immune-based strategies to control HIV-1 infection are still needed. Being explored are strategies that aim to suppress HIV-1 replication without the need of ART. Dendritic cells (DCs) are important players in this strategy as they are critical mediators of both innate and adaptive immune responses. Therefore, therapeutic vaccination with autologous monocyte-derived DCs expressing HIV-1 antigens is being evaluated in clinical trials^{2–4}.

Most DC-based vaccination studies focus on the impact on T cell responses whereas natural killer (NK) cells are only superficially studied^{2,4–6}. However, NK cells play an essential role in the defence against viruses, including HIV-1, by eliminating infected cells without the need for prior sensitisation. Human NK cells are classically dichotomized into two subgroups: CD56^{bright}CD16^{low} regulatory NK cells and CD56^{dim}CD16^{high} cytotoxic NK cells⁷. NK cells also express activating (e.g. NKG2D, NKG2C and NKp46) and inhibitory (e.g. killer immunoglobulin-like receptors [KIRs] and NKG2A) receptors, allowing them to survey the environment for expression of stress-induced ligands and self-antigens (MHC-I). NK cell functionality strongly depends on the engagement of inhibitory KIRs with MHC-I molecules in a process called NK cell education. Educated NK cells mediate enhanced cytotoxic functions upon later stimulation, whereas non-educated NK cells remain hypofunctional⁸. Interestingly, educated NK cells play a beneficial role in DC maturation

and the subsequent adaptive immune response⁹. In addition, NK cells can lyse target cells through an indirect pathway using FcγR11a/CD16a and immunoglobulin G (mainly IgG1 and IgG3) antibodies specific for viral surface proteins via antibody-dependent cellular cytotoxicity (ADCC) resulting in the release of IFN-γ, granzymes and perforins¹⁰. The importance of this indirect pathway is highlighted by the fact that impaired ADCC and delayed disease progression¹¹. Furthermore, in the prophylactic setting, NK cells can shape the immune response via bi-directional interactions with DCs. Thus, NK cells play an important role in the maturation of DCs by either killing immature DCs or by stimulation of DC maturation^{12,13}. Whereas mature DCs stimulate NK cells and produce interferon (IFN)γ, NK cells produce IFNγ and granzymes¹⁴. Therefore, modulation of the NK-DC crosstalk by immunotherapy is an interesting issue to explore. Existing evidence reveals the importance of the NK-DC interplay in anti-HIV-1 immunity, only few DC-based vaccination studies have attempted to evaluate NK cell responses after therapeutic vaccination^{17,18}. Most studies assessing NK cell responses following vaccination, focussed only on NK cell frequency and phenotype, with a limited analysis of NK cell functionality and cytotoxic capacity. A minority of studies also investigated the cytotoxic capacity of NK cells using MHC-devoid K562 cells as targets. However, a comprehensive functional analysis is lacking in these studies.

In a non-randomized phase I/IIa trial, we vaccinated PLWH with autologous DCs electroporated with mRNA encoding for Tat, Rev and Nef. Next, participants were submitted to an analytical treatment interruption (ATI) (Fig. 1). Although this vaccine was shown to be safe, well-tolerated and to enhance CD4⁺ and CD8⁺ T cell responses, no significant correlation with time off treatment

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