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Strengthening the Role of Dendritic Cells in AIDS Vaccine Development

Zhiwei Chen* and Jingying Zhou

AIDS Institute and Department of Microbiology, Research Center for Infection and Immunity, Li KaShing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong Special Administrative Region, China

2013 marks the thirtieth anniversary of the discovery of human immunodeficiency virus type 1 (HIV-1), the causative infectious agent of acquired immunodeficiency syndrome (AIDS) [1]. In the past 30 years, significant progresses have been made in the understanding of the origin of HIV-1, its transmission, pathogenesis, immune responses and clinical treatment [2]. Clinical use of existing and new antiretroviral therapy (ART) improves the life quality and life span of the infected individuals but cannot eradicate HIV virus. Issues of emerging drug resistance and long-term toxicity, often lead to treatment failure and death especially in developing countries. In addition life-long antiviral treatment is not affordable for heavily affected populations in developing countries and has become an accumulating economical burden in developed countries [3]. Effective vaccines and therapeutic cures remain to be the ultimate solutions to end the AIDS pandemic. Understanding the role of professional antigen presentation cells (APCs), especially dendritic cells (DCs) in vaccine and immunotherapy, is one of the important areas of study on how an effective immune response against HIV can be raised to achieve protection and therapeutic cure.

DC was first identified by Ralph Steinman in 1973 with microscopic morphology of dendrites protruding out from the cells [4]. DC is defined by its surface markers including lin$^-$, CD11c$^+$, MHC class II$^+$ as well as co-stimulatory factors CD80, CD86 and CD40, or CD83. DC has the capacity to capture, process and present antigens, which is 10 to 100 times more efficient than B cell and macrophage, and is the key bridge between innate and adaptive immunities [5]. DC responds directly to antigens (or pathogen-associated molecular patterns; PAMPs) using pattern recognition receptors (PRRs) to trigger the release of pro-inflammatory cytokines or type I/II interferons [6]. Meantime, steady state immature DC can capture antigen directly or via receptor-mediated (e.g. DEC-205 and Clec9A) endocytosis [7,8]. In response to proper level of cytokines or chemokines (e.g. TNF-α, IL-1, MIP-1α/β), immature DC develops into mature DC, gaining the ability to produce cytokines (e.g. IL-12) and to upregulate MHC class I/II and co-stimulatory molecules, and then migrates to lymphoid tissues to prime naïve T cells through antigen presentation [5,9]. Besides indirect effects *via* T helper cells (or follicular T helper), DC (e.g. follicular DC, FDC) has direct effects on B cells for antibody production and immunoglobulin class-switching [10].

For HIV vaccine design, significant progress has been made on strategies to target foreign antigens to DCs in order to enhance both the antigen uptake efficiency and the processing of antigens to activate and direct naïve T and B cell responses [5]. For example, antibody response was about 100-fold enhanced after antigen was targeted to DCs via its surface negative immunoregulatory molecule CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4 or CD152) [11]. A DNA vaccine of fused soluble CTLA-4 (sCTLA-4) and HIVgp120 resulted in 16-fold higher gp120-specific immune responses [12]. Moreover, C-type lectins (e.g. DEC205) are another group of DC surface receptors for DC-targeting vaccine strategies with one product in clinical trials [13,14]. Using anti-DEC205 antibody fused with HIV-1 Gag p24/p41 antigens, Steinman et al. [15] showed the induction of stronger HIV-1 antigen-specific CD4$^+$ T cell responses and protection in mice. Subsequently, a DNA vaccine that encodes scFv DEC205 fused with HIV Gag p41 generated similar findings [16]. Recently, anti-DEC205 fused to MAGE-A3 (an HLA-DP4-restricted epitope of tumor antigen) was demonstrated to significantly enhance IL-2 release from T cells in malignant melanoma patients [17]. Similarly, antigen DC-targeting via other C-type lectins (e.g. DC-SIGN, Langerin, Clec12A, DC-SIGN) has also improved vaccine-elicited immunity with varying degrees [18,19].

Our group recently reported the development of a novel antigen-targeting vaccine strategy that exploits the binding of programmed death-1 (PD1) to its ligands expressed on DCs by fusing soluble PD1 with HIV-1 Gagp24 antigen [20]. Compared with non-DC-targeting vaccines, we found that intramuscular immunization via electroporation (EP) of the fusion DNA vaccine elicited consistently high frequencies of Gag-specific, broadly reactive, polyfunctional, long-lived, and cytotoxic CD8$^+$ T cells and robust anti-Gag antibody titres in mice, which conferred remarkable protection against mucosal challenge with vaccinia-Gag viruses [20]. Interestingly, in another fusion DNA vaccine, when we used a new isoform of PD1 namely Δ42PD1 in the same construction, similarly long-lived and potent cytotoxic CD8$^+$ T cells were elicited although the native ligand of this isoform on DC remains unknown [21]. Since Gag-specific cytotoxic CD8$^+$ T cells are essential for the elimination of HIV-infected and latent reservoir [22,23], our findings may provide a new tool for vaccine-based prevention and therapeutic cure, which may overcome the issues of pre-existing immunity and safety related to live viral vector-based vaccines.

Many unanswered questions remain in strengthening the role of dendritic cells in AIDS vaccine development. We have provided evidence that PD1-based vaccination potentiated CD8$^+$ T cell responses by increasing IL-12 secretion in DCs and engaging antigen cross-presentation pathway when compared with anti-DEC205 antibody-mediated DC targeting [20]. This finding suggested that targeting antigen to DCs through different DC surface molecules may attribute different antigen-specific immune responses. Meanwhile, varying expression level of surface molecules in DC subtypes and the complicated characteristics of DC subtypes could affect antigen presentation efficiency as well. Other questions, such as anatomic distribution of DC subsets and intracellular pathways involved in antigen

***Corresponding author:** Dr. Zhiwei Chen, AIDS Institute and Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, L5-42, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China; Tel: +852 2819 9831; Fax: +852 2817 7805; E-mail: zchenai@hku.hk

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presentation are currently under investigation. Most importantly, it remains unclear if data generated in animals can be readily reproduced in humans. To this end, studies of human CD141⁺ or Blood DC antigen (BDCA)3⁺ DCs were reported to be the homologue of mouse CD8α⁺ DCs as a subtype with the ability to cross-present antigen to CD8⁺ T cells upon stimulation by polyinosinic-polycytidylic acid (poly I:C; Toll-like receptor 3 (TLR3) ligand) [24]. Human CD1a⁺ or BDCA1⁺ DCs can also cross-present soluble proteins [25]. In contrast to mouse plasmacytoid (p)DCs, human CD123⁺ or BDCA2⁺ (CD303⁺) pDCs has the ability of cross-presentation [26,27]. As cross-presentation by DCs is advantageous for inducing a prominent CD8⁺ T cell response, trials to improve cross-presentation-based vaccination has shown some advantages. One approach is to modulate antigen process *in vivo* by a drug chloroquine resulting in inducing T cell-based protection against malaria infection in both mice and human [28,29]. Our PD1-based DNA vaccine also demonstrated the ability to induce targeted DCs to engage in cross-presentation [20], but future work is required to determine if this strategy is effective in humans. Clearly, developing DC-targeted vaccines for improving adaptive immunity in humans remains a complex and time-consuming process. Nevertheless, recent achievements in strengthening the role of dendritic cells in immunogen discovery may shed light to the development of an effective AIDS vaccine in the future.

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