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Short Communication Open Access

Human Immunodeficiency Virus Arrests Plasmacytoid Dendritic Cells in a Granzyme B^{high} Tolerogenic State

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The serine protease granzyme B (GzmB) is classically known to be an apoptogenic effector molecule produced by cytotoxic cells including NK cells and CD8+ T lymphocytes [1]. However, a series of further cell types are able to express GzmB, most of them in the absence of perforin. Below them are different antigen-presenting cells (APC) including B cells, monocyte-derived dendritic cells and plasmacytoid dendritic cells (pDC) [2-7]. Here, we report that GzmB contributes to a variety of dendritic cell-related functions including antigen uptake and T cell regulation, and that HIV can impact on these functions.

Recent years have uncovered a variety of non-cytotoxic roles of GzmB [8,9]. Of note, the cytotoxic function of T cells and NK cells results from GzmB being secreted in the presence of the pore-forming protein perforin (Pfn). This allows GzmB to reach the cytosol of target cells after exocytosis, where it may then activate apoptosis-inducing enzymes including caspases, DNAses and BID [1]. In contrast, certain immune cells including plasmacytoid dendritic cells (pDC) and B cells can produce GzmB only, but not Pfn [6,10-12]. GzmB secreted by these APC types therefore primarily encounters substrates with an extracellular or membrane-close localisation such as extracellular proteins or membrane-bound receptors [8]. As a result, these cells develop a strong immunoregulatory potential based on GzmB-dependent cleavage of the T cell receptor (TCR)-ζ-chain [6,9-13]. Degradation of the TCR-ζ-chain by GzmB directly limits the proliferative capacity and survival of effector T cells.

GzmB produced by APC however may not only play an important role for their interaction with T cells, but also for antigen processing. Recently, GzmB was shown to enhance both the uptake of antigens by release of "eat-me" signals on dying cells as well as their cross-presentation [14,15]. Importantly, the cleavage of peptides by GzmB can result in fragments that represent neo-antigens, allowing the establishment of increased immune responses towards such antigens [16,17]. This suggests that antigens generated by GzmB are principally more immunogenic than antigens generated by other proteases. If GzmB-borne antigens arise, for example in the course of a T cell-mediated attack of virus-infected cells, they may pose a substantial risk of triggering autoimmune responses. Therefore, GzmB produced by pDC and other APC is partly secreted into the extracellular space, where it can prevent early activation of unspecific T cells as described above (Figure 1, middle panel).

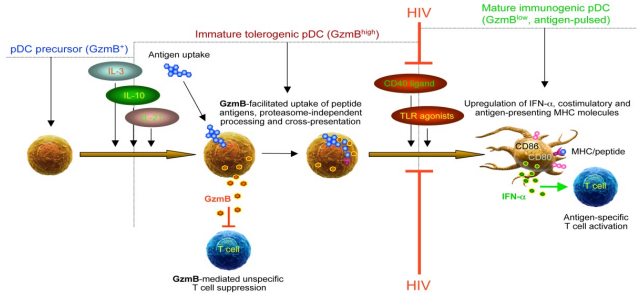

Figure 1: Current hypothesis for the maturation of plasmacytoid dendritic cells. Maturation of pDC precursors occurs in a biphasic process. During the first phase, pDC develop a tolerogenic phenotype in response to different cytokines including IL-3, IL-10 and IL-21. This phenotype involves the production of large amounts of the serine protease GzmB, which is involved not only in the suppression of effector T cell responses, but also in antigen uptake and proteasome-independent antigen processing. In the second phase, pDCs are rapidly (within 24 hours) matured in response to TLR ligands and CD40 ligand. GzmB is downmodulated, while co-stimulatory molecules and MHC/peptide complexes are simultaneously upregulated, resulting in a highly immunogenic and mature pDC phenotype. Our data suggest that the transition of pDC into this second phase is blocked during acute HIV infection, possibly by virus-associated factors antagonizing CD40- and TLR-mediated signals.

Simultaneously, GzmB facilitates antigen uptake and processing into immunogenic fragments for cross-presentation. The GzmB^{high} phase of pDC maturation is subsequently followed by a second phase, initiated by toll-like-receptor (TLR) ligand- and CD40 ligand-induced signals. These signals downregulate GzmB and induce co-stimulatory as well as antigen-presenting molecules on the pDC surface (Figure 1, right panel). Current data from our laboratory demonstrate that HIV enhances and maintains an immature and GzmB^{high} phenotype in peripheral blood-derived pDC (Figure 2). This suggests that the transition of pDC into the second maturation phase is blocked by HIV, resulting in the persistence of a GzmB^{high} tolerogenic state during HIV infection (Figure 1). Of note, while expression of GzmB is part of the maturity state of pDC, it is not believed to be causally involved in the transition of pDC from an immature into a mature state. Instead, virus-associated factors antagonizing CD40- or TLR-mediated signals

may be responsible for the observed transition arrest [6,10]. Support for our hypothesis comes from an independent group, which demonstrated that gut-associated pDC from patients with HIV infection are also characterized by an immature phenotype and enhanced GzmB expression [18].

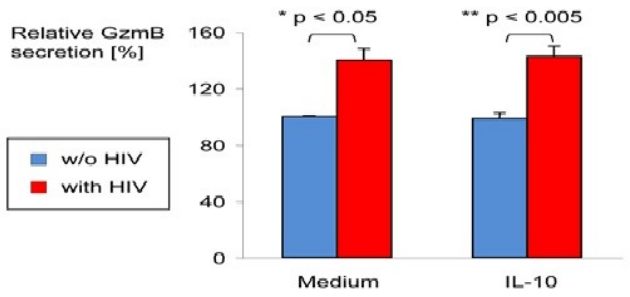

Figure 2: Human HIV increases GzmB secretion by pDC. PDC from five healthy donors were incubated for 16 hours in IL-3-supplemented (10 ng/ml) medium, in the presence or absence of IL-10 (25 mg/ml) and with or without (w/o) HIV 1 (5 ng/ml) as indicated. GzmB secretion was measured in supernatants by ELISA. Bar graphs represent average concentration values relative to medium control from five independent experiments. Error bars indicate standard error of means (SEM), p-values indicate statistically significant differences. Abbreviations: IL=Interleukin, HIV=human immunodeficiency virus, GzmB=granzyme.

Overall, our data suggest the maturation of pDC involves a dynamic process of GzmB expression and secretion, which is connected to different pDC functions and which is influenced by HIV. Further studies are necessary to elucidate, whether GzmB produced by pDC may serve as a target for therapeutic manipulation of immune responses after viral infections such as with HIV and during pDC-based vaccinations. For example, the suppression of pDC by pharmacological means, or direct neutralization of GzmB secreted by pDC may allow a better establishment of cellular antiviral immune responses during infection, resulting in faster clearance of virus-infected cells.

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