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Review article

Cytokines and persistent viral infections

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ABSTRACT

Intracellular pathogens such as the human immunodeficiency virus, hepatitis C and B or Epstein–Barr virus often cause chronic viral infections in humans. Persistence of these viruses in the host is associated with a dramatic loss of T-cell immune response due to functional T-cell exhaustion. Developing efficient immunotherapeutic approaches to prevent viral persistence and/or to restore a highly functional T-cell mediated immunity remains a major challenge. During the last two decades, numerous studies aimed to identify relevant host-derived factors that could be modulated to achieve this goal. In this review, we focus on recent advances in our understanding of the role of cytokines in preventing or facilitating viral persistence. We concentrate on the impact of multiple relevant cytokines in T-cell dependent immune response to chronic viral infection and the potential for using cytokines as therapeutic agents in mice and humans.

Contents

Abbreviations: Ag, antigen; AIDS, acquired immune deficiency syndrome; APC, antigen presenting cell; Arm, armstrong; Cl-13, clone-13; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; EBV, Epstein–Barr virus; FDC, follicular dendritic cell; γ_c-chain, common gamma chain; GCB, germinal center B; Gp130, glycoprotein 130; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IFN, interferon; IFNAR1, interferon alpha receptor 1; IgG, immunoglobulin G; IL-2/IL2R, interleukin-2/interleukin 2 receptor; IL-6/IL-6R, interleukin-6/interleukin 6 receptor; IL-7/IL7R, interleukin-7/interleukin 7 receptor; IL-10/IL10R, interleukin-10/interleukin 10 receptor; IL-21/IL21R, interleukin-21/interleukin 21 receptor; IL-27/IL27Rα, interleukin-27/interleukin 27 receptor alpha; ISG, interferon-stimulated genes; JAK, janus tyrosine kinase; LAG-3, lymphocyte activation gene 3; LAP, latency-associated protein; LCMV, lymphocytic choriomeningitis virus; LIF, leukemia inhibitory factor; LLC, large latent complex; LTBP, latent TGFβ binding protein; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; NK, natural killer; OSM, oncostatin M; PD1, programmed cell death 1; PDL1, programmed death ligand 1; p.i., post infection; PI3K, phosphatidylinositide-3 kinase; SIV, simian immunodeficiency virus; SLC, small latent complex; SOCS3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription; Tfh, T follicular helper; Tg, transgenic; TGFβ/TGFBR, transforming growth factor beta/transforming growth factor beta receptor; Th, T helper; Tim3, T cell Ig- and mucin-domain-containing molecule-3; TNFα, tumor necrosis factor alpha; Tyk2, tyrosine kinase 2.

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1. Introduction

Anti-viral T-cell response to acute viral infections is a tightly regulated process. After activation, antigen (Ag)-specific T cells undergo massive clonal expansion and acquire cardinal effector functions essential for the eradication of virally-infected cells. Following resolution of infection, the majority of expanded T cells are rapidly eliminated during the contraction phase to prevent excessive immune activation. A small fraction of these effectors survive to form a long-lasting protective memory pool [1]. However, chronic viruses such as the human immunodeficiency virus (HIV), hepatitis C and B viruses (HCV and HBV) and Epstein–Barr virus (EBV) often manage to avoid immune surveillance and establish a persistent infection in the host. In these particular conditions, the immune system elaborates inherent suppressive strategies to prevent uncontrolled T-cell expansion that might cause severe pathology to the host. However, these immune-derived suppressive functions, while being host protective, further facilitate viral persistence and lead to the gradual loss of T-cell immunity by a process called T-cell exhaustion [2,3]. During that exhaustion process, CD8 T cells are progressively deprived of their cardinal effector functions (i.e. cytokine production, proliferation potential, killing ability) because of increased expression of multiple inhibitory receptors including PD1, LAG-3, 2B4, Tim3 and CD160 [4–6]. In addition, commitment to exhaustion suppresses the development of memory cells precluding the establishment of long-term protective immunity [7,8]. Similarly, CD4 T cells also become exhausted as evidenced by a rapid loss of effector cytokine production (i.e. IL-2, TNFα and IFNγ), sustained expression of PD1, CTLA4 and increased production of IL-10 and/or IL-21 [9–11]. While exhausted T cells continue to display some level of antiviral functions, the effector T-cell pool progressively erodes as the infection persists, which ultimately leads to the complete loss of T-cell immunity [12]. Consequently, identifying the immune-derived factors that favor viral persistence and T-cell dysfunction with the goal of developing new therapeutic strategies to prevent or reverse exhaustion has been the subject of intense research during the last decades. Among the immune-derived factors, there has been a particular focus on cytokines because of their capacity to drive essential stimulatory and suppressive functions on both innate and adaptive immune cells. Based on observations in humans and mice, we discuss recent advances in the understanding of the role of cytokines in preventing or facilitating viral persistence. Our review focuses on the impact of several relevant cytokines on T-cell responses and their potential use as therapeutic agents for humans and mice.

2. Immuno-regulatory cytokines

2.1. IL-10

Several hematopoietic cell types produce IL-10 including dendritic cells (DCs), B cells, monocytes, macrophages, CD4 T cells, CD8 T cells and regulatory T cells [13]. IL-10 signals via a heterodimeric class II cytokine receptor composed of an inducible IL10R1-chain and an IL10R2-chain constitutively expressed on both hematopoietic and non-hematopoietic cell types that are also shared by the class II cytokines IL-22, IL-26, IL-28 and IL-29 [14,15]. Engagement of IL-10 to its cognate receptor triggers activation of the janus tyrosine kinases Jak1 and Tyk2 and phosphorylation of the signal transducers and activators of transcription STAT3, STAT1 and also STAT5 [16–20]. Subsequent signals allow IL-10 to mediate its immuno-suppressive functions that affect multiple hematopoietic cell types.

In several persistent infections, notably in patients with HIV, HBV, HCV or EBV infections, IL-10 levels were reported to be elevated [13,21–25]. Concomitantly, polymorphisms within the IL-10 promoter region that reduce the secretion of the cytokine were correlated with enhanced control of these viruses [26–32]. Moreover, numerous viruses including EBV, human cytomegalovirus (HCMV) and some poxviruses produce their own IL-10 homologs to dampen antiviral immunity and favor their persistence in the hosts [33]. Interestingly, IL-10 blockade potently increases the proliferation and cytokine secretion of T cells isolated from chronically infected HIV or HCV patients [34–38]. On the contrary, engagement of PD1 with its ligand PDL1 can trigger IL-10 expression, thus contributing to functional T-cell exhaustion [37,39]. Together, these cumulative evidence suggest a potential immunosuppressive role of IL-10 during chronic viral infections in humans.

Two concomitant studies of Brooks and Ejrnaes modeled chronic viral infection in mice and unravelled an essential role of IL-10 in promoting viral persistence [40,41]. Similar to what was observed in persistent human infections, both teams reported superior IL-10 levels after infection with the variant lymphocytic choriomeningitis virus (LCMV) strain clone 13 (Cl-13), which induces a 2–3 month viremia in the host, compared to the LCMV Armstrong (Arm) strain, which is rapidly cleared [42,43]. Remarkably, infection of IL-10-deficient mice by LCMV Cl-13 led to rapid viral control by day 9 post infection (p.i.). Early blockade of IL-10 signals with anti-IL10R specific antibodies similarly resulted in accelerated clearance of Cl-13 infection [40,41]. Rapid elimination of the Cl-13 virus was associated with enhanced magnitude and functionality of CD4 and CD8 T cells. Importantly, IL-10 blockade at later time points also led to enhanced viral control and T-cell responses. However, in both studies, these effects were less impressive than what was observed in IL-10$^{-/-}$ mice or mice treated early with anti-IL10R specific antibodies. Hence, IL-10 acts essentially as an early determinant of viral persistence, while it continuously dampens immune functions throughout chronicity. This latter point was emphasized in a study that demonstrated that IL10R-antibody treatment of mice with a well-established persistent Cl-13 infection still improved T-cell immunity and substantially decreased viral loads [44]. More importantly, this study revealed that IL-10 blockade was even more effective when combined with anti-PDL1 treatment, suggesting that this dual regimen might be effective in combating established persistent infections.

Remaining is the question of how IL-10 favors viral persistence (Fig. 1). IL-10 was previously shown to alter DC maturation by reducing the expression of MHC class I and II as well as the co-stimulatory molecules CD80 (B7.1) and CD86 (B7.2) [13,16,45,46]. Hence, IL-10-primed DCs or DCs isolated from HIV patients are poor inducers of CD4 T-cell proliferation [45–47]. Further, DCs from chronically-infected mice diverge naïve CD4 T cells from a Th1 IFNγ^+ profile to an IL-10 secretion profile (Fig. 1) [41]. That effect was not observed when DCs were isolated from anti-IL10R treated mice [41]. This is in support of a direct impact of IL-10 on DCs' priming abilities that favor the accumulation of suppressive IL-10$^+$ CD4 T cells (Fig. 1). Thus, IL-10 indirectly promotes CD4 T-cell exhaustion by altering DC maturation leading to dampened priming of the cells and divergence to a suppressive IL-10 producing profile. Conversely, IL-10 can behave as a proliferative factor for CD8 T cells *in vitro* and as a growth factor *in vivo* during primary response to *Listeria monocytogenes* [48–50]. However, IL-10 restrains HIV-specific CD8 T-cell proliferation *in vitro* [34]. Hence, the impact of IL-10 on CD8 T-cell response is likely context-dependent and preferentially inhibiting during chronic viral infections (Fig. 1). Those assertions define IL-10 as an overall suppressor of T-cell response during persistent viral infections. However, whether IL-10 favors viral persistence by directly promoting T-cell exhaustion remains to be determined.