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Jigsaw falling into place: A review and perspective of lymphoid tissue CD8+ T cells and control of HIV

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ABSTRACT

CD8+ T cells are crucial for immunity against viral infections, including HIV. Several characteristics of CD8+ T cells, such as polyfunctionality and cytotoxicity, have been correlated with effective control of HIV. However, most of these correlates have been established in the peripheral blood. Meanwhile, HIV primarily replicates in lymphoid tissues. Therefore, it is unclear which aspects of CD8+ T cell biology are shared and which are different between blood and lymphoid tissues in the context of HIV infection. In this review, we will recapitulate the latest advancements of our knowledge on lymphoid tissue CD8+ T cells during HIV infection and discuss the insights these advancements might provide for the development of a HIV cure.

1. Introduction

Conventional wisdom dictates that cytotoxic T cell (CTL)-mediated immune surveillance of pathogen infected or otherwise aberrant cells is mediated by the selective elimination of the offending targets through cytotoxic activity. In the setting of HIV infection, CTL activity is largely attributed to control of disease progression (Hersperger et al., 2010; Jin et al., 1999; Koup et al., 1994; Matano et al., 1998; Migueles et al., 2002, 2008; Schmitz et al., 1999), but in the case of autoimmunity, it can lead to pathogenic effects within target tissues (Molodtsov and Turk, 2018). CD8+ T cells are the major T cell type that mediates cytotoxicity, leading to the general inter-usage of the terminology "CTL" with CD8+ T cells. However, cytotoxic activity is primarily mediated by a specific subset of CD8+ T cells, which we define as those CD8+ T cells that express perforin, granzyme B, and high levels of the transcription factor T-bet known to regulate the cytotoxic effector gene cassette (Hersperger et al., 2011; Sullivan et al., 2003). While much of our knowledge of CTL activity derives from studies of vascular-derived human lymphocytes or mouse spleens (an organ contiguous with the vasculature), it is becoming increasingly clear, through studies in other organs, that CD8+ T cells have a wide array of functions beyond cytotoxicity, including immune modulation via cytokine production, chemoattraction, and non-cytotoxic suppression of pathogen gene expression (Beura et al., 2018; Guidotti and Chisari, 2001; Nigam et al., 2010; Y. Yu et al., 2018). Moreover, the different CD8+ T cell populations mediating these functions likely have specialized functional roles relating to their specific environment, whether in the vasculature, at barrier sites, lymphoid tissues, or within non-lymphoid organs. Defining how different CD8+ T cell populations function within relevant target sites is paramount to advancing our knowledge in order to therapeutically modulate these cells for specific infection and autoimmune settings.

In this review, we will re-evaluate current models of CD8+ T cell-mediated immune responses in control of HIV by discussing their functions within the tissue environment, specifically lymphoid tissues where the majority of HIV replication occurs (Estes, 2013; Pantaleo et al., 1991; Vago et al., 1989). We will advance the concept that the CD8+ T cells in blood and tissues utilize different mechanisms to control viral replication. This concept is supported by observations that unlike in the blood, CD8+ T cells in HIV-infected lymphoid and mucosal tissues are poorly cytotoxic and therefore inefficient at eliminating infected cells (Kiniry et al., 2017, 2018a; Reuter et al., 2017). Instead, at these sites, tissue resident memory CD8+ T cell populations dominate the response and are likely critical in maintaining control of HIV replication, despite the absence of potent cytotoxic functions (Buggert et al., 2018; Kiniry et al., 2018b). Additionally, in spite of expressing several inhibitory receptors, it is unclear if these resident memory CD8+ T cells are functionally exhausted. We will also review the importance of follicular CD8+ T cells in combating HIV infection, especially since B cell follicles have been shown to be a major sanctuary

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for the viral reservoir (Banga et al., 2016; Connick et al., 2007; Folkvord et al., 2005; Fukazawa et al., 2015; Perreau et al., 2013). Together, the concepts of tissue-specific viral control mechanisms, tissue residency, exhaustion, and follicle-trafficking add complexity to the search for a cure strategy. Current cure strategies, such as "shock and kill"(Deeks, 2012), favor the elimination of the HIV reservoir, which requires the presence of cytotoxic CD8+ T cells in tissues. However, the elevation of cytotoxic CD8+ T cells in tissues has been correlated with pathology in autoimmune diseases. Therefore, is it a good idea to induce these cells in HIV-infected tissues? Should mechanisms of viral suppression rather than elimination be pursued? Additionally, is it important to invoke a large frequency of tissue-resident and follicle-homing CD8+ T cells as a part of a cure strategy? Does the expression of inhibitory receptors of tissue CD8+ T cells render them dysfunctional? We will touch upon issues related to these topics and draw parallels to CD8+ T cell responses against other infections and in autoimmune conditions, with the hope of providing new insights for the development of a HIV cure strategy.

2. CD8+ T cell function and control of HIV: how do peripheral blood CTL control HIV infection?

The primary CD8+ T cell effector mechanism attributed to control of HIV involves cytotoxic elimination of infected CD4+ T cells (Migueles et al., 2002, 2008). The exact mechanisms of how CD8+ T cells execute their cytotoxic functions have been well defined. After recognition of their cognate antigens presented on MHC-class I molecules, CD8+ T cells undergo major cytoskeletal reorganization in order to form an immunological synapse with their targets (Griffiths et al., 2010) and subsequently release lytic granules that trigger apoptosis in the target cells (Peters et al., 1991). Perforin, a pore-forming protein isolated from lytic granules of peripheral blood-derived CD8+ T cell clones in the mid 1980s (Henkart et al., 1984; Podack et al., 1985), and granzyme B, a serine protease that induces apoptosis by direct cleavage of caspase-3, caspase-8, PARP-1, BID, lamin B, ICAD, DNA-PK, and Nu-Ma (Chowdhury and Lieberman, 2008; Darmon et al., 1995), act in concert to induce the death of cells targeted by CD8+ T cell, with perforin mediating the delivery of granzyme B. Human CD8+ T cells can also express other granzyme proteins, including A, H, K, and M, each of which can induce apoptosis through a variety of mechanisms that may or may not require perforin-mediated delivery (Lieberman, 2003; Voskoboinik et al., 2015).

There is a clear association between the expression of perforin and granzyme family members and T cell memory differentiation. In particular, perforin and granzyme B are rarely expressed by central memory CD8+ T cells, those cells with the ability to directly traffic into lymph nodes (LNs) via CD62 L and CCR7 (Butcher and Picker, 1996; Chattopadhyay et al., 2009; Sallusto et al., 1999). The highest expression of perforin and granzyme B is found within the terminally differentiated CD8+ T cell subset defined by the absence of CCR7 and CD62 L and re-expression of CD45RA (Chattopadhyay et al., 2009), also called the CD8+ T_{EMRA} cell. These cells, as well as specific subsets of the CCR7-CD62L-CD45RO+ (T_{EM}) CD8+ T cell population, are largely believed to mediate viral control in HIV infection. Polyfunctional CD8+ T cells (defined by coordinate expression of IL-2, TNF, IFNg, MIP1b, and CD107a) have also been shown to correlate with control of viremia (Fig. 1) (Betts et al., 2006; Ferre et al., 2009). However, these polyfunctional CD8+ T cells typically are not cytotoxic, as they do not express perforin prior to or after stimulation (Makedonas et al., 2010).

There are clear correlative studies showing that peripheral blood CD8+ T cell cytotoxicity is associated with control of HIV replication; but is this a direct or indirect correlation? How, and where, would a peripheral blood cytotoxic CD8+ T cell encounter, recognize, and eliminate an infected CD4+ T cell? Given the rarity of HIV-RNA+ CD4+ T cells in the blood, as well as the volume and physical forces active within the vasculature, it would seem unlikely that an HIV-specific CD8+ T cell would encounter and eliminate an HIV-infected CD4+ T cell in the blood itself. One potential site where vascular HIV-specific CD8+ T cells could encounter HIV-infected CD4+ T cells is the spleen, which filters blood and therefore contains a similar complement of cytotoxic CD8+ T cells to the peripheral blood. Interestingly, total body quantification of viral RNA-producing CD4+ T cells in viremic SIV-infected rhesus macaques yields an extraordinarily low proportion (~0.2%) of total body infected CD4+ T cells in the spleen compared to other lymphoid organs that are not contiguous with the vasculature (Estes et al., 2017). Thus, one could hypothesize that the correlates of control of HIV infection obtained from peripheral blood CD8+ T cells involving cytotoxicity actually reflect the efficient elimination of HIV-infected CD4+ T cells within the splenic environment. Whether parameters of peripheral blood CD8+ T cells relate to control of HIV-infected CD4+ T cells in lymphoid tissues, however, is less clear.

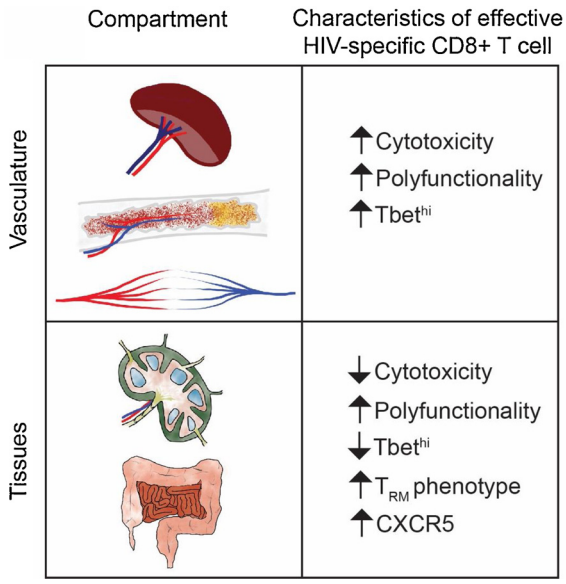

Fig. 1. Summary of HIV-specific CD8+ T cell functional properties in tissues and vasculature. In vasculature, HIV-specific CD8+ T cells associated with HIV control are highly cytolytic, which is associated with a high level of Tbet expression. Subsets of these cells are also highly polyfunctional. In tissues, CD8+ T cells linked with HIV control are largely non-cytolytic. However, they display a profile of TRM and polyfunctionality. Subsets of these cells also have potential to traffic to B cell follicles by virtue of CXCR5 expression.

3. CD8+ T cell function and control of HIV: how do lymph node CD8+ T cells control HIV infection?

Based upon studies in SIV-infected rhesus macaque (RM) controller models, it is clear that CD8+ T cells play a significant role in controlling viral replication within lymphoid tissues (Fukazawa et al., 2015). In these studies, depletion of CD8+ T cells in Mamu-B*08/B*17 controller animals resulted in recrudescence of viral replication in the T cell zone of lymph nodes, whereas in the presence of CD8+ T cells viral replication was restricted to lymphoid follicles. However, it is not clear whether this viral control is mediated by CD8+ T cell cytotoxicity or other CD8+ T cell functional mechanisms.

The differential expression pattern of perforin and granzyme B within CD8+ T cell subsets is especially relevant when considering the potential role of peripheral blood CD8+ T cell cytotoxicity and control of HIV within the vascular (blood, spleen, bone marrow) versus the lymphoid tissue space. As discussed above, vascular T cell access to LNs is provided by L-selectin (CD62 L) and CCR7, allowing transmigration through high endothelial venules towards a CCL19/21 gradient (Butcher and Picker, 1996; Sallusto et al., 1999). T_{EM} have access to non-lymphoid tissues (NLT) and can return to blood via the lymphatics

(with possible stops along draining LNs). Transit to NLT is controlled by homing receptors (e.g. CLA, CCR4, CCR6, CCR9, CXCR3, CXCR6, a4b7) (for a detailed review see Griffith et al., 2014)). T_{EMRA} are found in the blood and spleen at steady-state, but may express CXCR3 and enter NLTs under inflammatory conditions (Pirozyan et al., 2019; Uno et al., 2010). Given the absence of CD62 L expression on cytotoxic CD8+ T cell subsets in the peripheral blood, it is unlikely that CD8+ CTL (T_{EM} and T_{EMRA}) traffic directly into the LN across high endothelial venules (Butcher and Picker, 1996). However, as mentioned above, inflammatory signals can drive vascular CTL into tissues (Sallusto et al., 1999) and HIV is known to drive inflammation in lymphoid tissue (Biancotto et al., 2007). Until recently however, it has been unclear whether peripheral blood CD8+ CTL are recruited into lymphoid tissues or lymphoid tissue CD8+ T cells acquire CTL activity during chronic HIV infection in an effort to control viral replication.

Many studies have demonstrated the presence of CD8+ T cells, including HIV- and SIV-specific CD8+ T cells, in the lymph nodes of HIV-infected humans and SIV-infected RM (Andersson et al., 1999; Connick et al., 2014, 2007; Folkvord et al., 2003; Li et al., 2016). However, variations in the parameters measured, mis- or over-interpretation of results, and the overall interchangeable usage of the term "CTL" with CD8+ T cells have led to misconceptions regarding whether peripheral blood CD8+ CTL are found in lymphoid tissue. It is clear that both perforin and granzyme A and B expression can be found in lymphoid tissue CD8+ T cells, and that the frequency of cells expressing these proteins increases in HIV- and SIV- infection compared to uninfected controls (Andersson et al., 1999; Connick et al., 2014; Petrovas et al., 2017; Reuter et al., 2017). However, the coordinate expression of perforin and granzyme B is lower in HIV-infected lymphoid tissue CD8+ T cells compared to peripheral blood, in terms of both the frequency of co-expressing cells and the expression level of each protein on a per-cell basis (Fig. 2B-E) (Reuter et al., 2017). Moreover, expression of perforin and granzyme in lymphoid tissue CD8+ T cells is dissociated from T-bet expression compared to peripheral blood in HIV uninfected as well as HIV/SIV-infected lymph nodes (Reuter et al., 2017; Roberts et al., 2016). As a result of these shortcomings, it is not entirely surprising that lymphoid tissue CD8+ T cells (whether from HIV + or HIV- LNs) generally have poor *in vitro* target killing ability compared to peripheral blood CD8+ T cells (Nguyen et al., 2019; Reuter et al., 2017).

During the acute induction phase of CD8+ T cell responses in LCMV infected mice, CD8+ T cells initially have high killing capacity in lymphoid tissues (Wolint et al., 2004). Subsequent to viral clearance, lymphoid tissue LCMV-specific CD8+ T cells transition to a memory state lacking cytotoxic ability. The same transition occurs during acute SIV infection: acute SIV-specific CD8+ T cells display high levels of perforin and granzyme B until approximately day 28 post infection, after which expression of both molecules decreases, reaching baseline levels by day 90 even though viremia is not cleared (Quigley et al., 2006; Roberts et al., 2016). In the same animals, peripheral blood SIV-specific CD8+ T cells partially retain perforin and granzyme B expression through day 90. During acute HIV infection, very high levels of perforin and granzyme B+ CD8+ T cells are found in both peripheral blood (Demers et al., 2016) and LN (Nguyen et al., 2019), but with a notable absence of T-bet expression in the LN CD8+ T cells. After establishment of chronic HIV infection, coordinate perforin and granzyme expression by LN CD8+ T cells is mostly lost, and only partially retained in peripheral blood CD8+ T cells (Demers et al., 2016; Nguyen et al., 2019; Reuter et al., 2017).

HIV elite controllers have peripheral blood HIV-specific CD8+ T cells with higher cytotoxic capacity compared to HIV viremic individuals (Fig. 1) (Hersperger et al., 2010; Migueles et al., 2008), raising the question as to whether these individuals also have superior lymphoid tissue cytolytic HIV-specific CD8+ T cells. Surprisingly, we found the opposite: HIV elite controller lymphoid tissue HIV-specific CD8+ T cells are resoundingly non-cytolytic, being nearly indistinguishable from an HIV-uninfected individual (Fig. 1) (Nguyen et al., 2019). Importantly, these cells are capable of suppressing virus replication through alternative mechanisms. As mentioned previously, CD8+ T cells produce many different types of immunomodulatory cytokines and potentially antiviral products. Non-cytolytic mechanisms of HIV inhibition were first documented in 1986, where CD8+ T cells were found to suppress HIV replication without killing infected cells *in vitro* (Walker et al., 1986). In addition, CD8+ T cell depletion in rhesus macaques did not increase the life-span of SIV-infected cells, indicating that direct killing was unlikely the main mechanism antagonizing viral replication (Klatt et al., 2010; Wong et al., 2010). The suppressive effect is attributed, at least in part, to a still unidentified soluble molecule known as cellular antiviral factor or CAF (Levy, 2003; Walker et al., 1986). In addition to CAF, beta-chemokines produced by $CD8^+$ T cells such as CCL3 (MIP1-α), CCL4 (MIP1-β), and CCL5 (RANTES) have been shown to exert anti-HIV activities as these molecules interfere with viral entry by binding to CCR5, a key co-receptor of HIV (Cocchi et al., 1995). We found evidence of HIV-specific CD8+ T cells in the LNs of HIV elite controllers producing enhanced levels of non-cytolytic molecules (Nguyen et al., 2019), some of which have been shown to display antiviral activities including CCL5, TNF, RNase-1, and IL-32 (Bedoya et al., 2006; Cocchi et al., 1995; Lane et al., 1999; Rasool et al., 2008; Ribeiro-Dias et al., 2017). Importantly, these cells did not upregulate cytotoxic properties upon short (6–8 hours) or long (2–3 days) stimulation, suggesting that the absence of cytotoxic properties *ex vivo* was not simply due to the absence of *in vivo* stimulation but rather represents a stable differentiation state to a non-cytolytic subset that can control viral replication without eliminating infected CD4+ T cells (Nguyen et al., 2019).

4. CD8+ T cell function and control of HIV: the role of lymphoid tissue resident memory CD8+ T cells

Recent studies have found that the numerically most abundant memory CD8+ T cells in human tissues are considered to be "tissue resident" (TRM) (Thome et al., 2014). These cells can be identified by the expression of CD69, an inhibitor of S1PR1-mediated trafficking, and other cell adhesion molecules (Bankovich et al., 2010; Masopust et al., 2001; Shiow et al., 2006). TRM do not express tissue exit and lymphoid tissue homing cues such as S1PR1, CD62 L and CCR7. These cells have

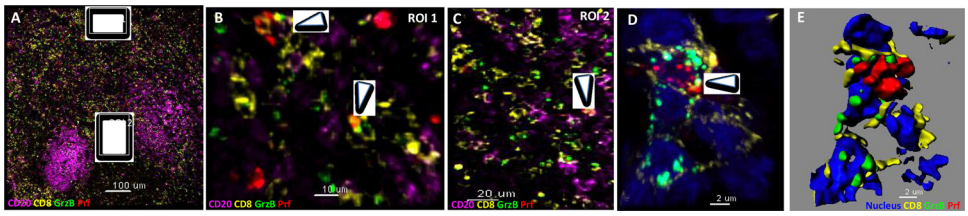

Fig. 2. Low level of perforin and granzyme B co-expression by lymph node CD8+ T cells. (**A**) Multiplexed confocal image (20x) showing the expression of CD20 (magenta), CD8 (yellow), granzyme B (GrzB, green) and perforin (Prf, red) in a chronically HIV infected lymph node. The follicular areas, characterized by abundant CD20 staining, and two zoomed areas (white boxes), one in distance from the follicle (ROI 1) and one at the T – B cell border area (ROI 2), are also shown. (**B, C**) The presence of GrzB+ Prf+ CD8 T cells in the zoomed ROI 1 and 2 areas is show (white arrows). (**D**) A 63X confocal image showing the presence of a GrzB+ Prf+ CD8+ T cell (nuclear staining in blue) as well as the computationally derived surfaces showing the spatial organization of GrzB and Prf (*E*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

distinct transcriptional and functional signatures, and play a crucial role as sentinels within their local milieu upon antigenic re-exposure, reinfection, or reactivation in the case of chronic/episodic pathogens; for thorough reviews of TRM biology see (Gebhardt et al., 2018; Masopust and Soerens, 2019; Schenkel and Masopust, 2014). While reports of TRM cytotoxic effector function vary, TRM can secrete cytokines with potential direct effects on pathogens and chemokines to promote influx of other innate and adaptive immune cells to the site of infection (Park et al., 2018; Schenkel et al., 2014, 2013).

We and others have recently examined CD8+ TRM in HIV-infected lymphoid and gut tissues, finding that the majority of HIV-specific CD8+ T cells in these tissues bear a resident memory phenotype (Buggert et al., 2019, 2018; Kiniry et al., 2018b; Shacklett et al., 2019). In lymphoid tissues, CD8+ TRM represent the majority of cells that bear an effector memory phenotype (Farber et al., 2014; Thome et al., 2014), and in HIV infection, the proportion of lymphoid tissue HIV-specific CD8+ T cells with a TRM phenotype tends to be higher in HIV elite controllers, potentially implying a role in the control of viremia (Fig. 1) (Buggert et al., 2018). In both HIV-infected lymphoid tissues and gut mucosa, HIV-specific TRM appear to have limited immediate cytotoxic potential based on low or absent expression of perforin and or granzyme B and poor target cell killing *ex vivo*. Whether TRM in HIV-infected tissues can acquire cytolytic activity upon encountering an HIV infected CD4+ T cell remains unclear, though *in vitro* these cells do not appear to acquire cytolytic function in short term cultures. Thus, as discussed above, non-cytolytic functions by TRM may be the primary HIV-specific response invoked in lymphoid tissues and non-lymphoid tissues. Because they are primarily non-cytolytic, might their function actually suppress virus replication and therefore support establishment of latency and the latent reservoir in lymphoid tissues? Do they drive viral escape? Do they become exhausted in a similar fashion to peripheral blood CD8+ T cells? Given the potential importance of TRM as mediators of tissue-based immunity in the control of HIV, focused efforts should be made towards understanding these and other questions in future studies in both lymphoid and non-lymphoid tissues.

5. CD8+ T cell function and control of HIV: follicular CD8+ T cells

Lymph nodes, are typically organized into two regions: the medulla and cortex. The cortex is further subdivided into B cell follicles and the T cell zone (or paracortex) (von Andrian and Mempel, 2003). While most T cells are found in the T cell zone, CD4+ T cells, and to lesser extent CD8+, are capable of entering B cell follicles. Follicular-homing CD4+ T cells, or TFH, play a major role in regulating the germinal center reaction and the eventual antibody response (Vinuesa et al., 2016). Given the importance of CD4+ TFH for the formation and maintenance of the HIV/SIV reservoir (Aid et al., 2018; Banga et al., 2016; Boritz et al., 2016; Kohler et al., 2016; Lindqvist et al., 2012; Miller et al., 2017; Perreau et al., 2013; Xu et al., 2017a) the dynamics of CD8+ T cells within the follicular areas have been the focus of recent studies (Buggert et al., 2018; Ferrando-Martinez et al., 2018; Fukazawa et al., 2015; He et al., 2016; J. J. Hong et al., 2012; Li et al., 2019; Miles et al., 2016; Mylvaganam et al., 2017; Petrovas et al., 2017; Rahman et al., 2018; Reuter et al., 2017). Chronic HIV/SIV infection is characterized by an increased presence of CD8+ T cells in the lymph nodes, particularly in the follicular areas (Ferrando-Martinez et al., 2018; Leong et al., 2016; Petrovas et al., 2017; Reuter et al., 2017). Follicular CD8+ T cells upregulate the expression of CXCR5, although at significantly lower levels compared to CD4+ TFH (Ferrando-Martinez et al., 2018), and express a unique gene signature (Mylvaganam et al., 2017; Petrovas et al., 2017; Quigley et al., 2007). Advanced imaging assays have allowed the comprehensive investigation of these cells with regards to their topology and surrounding microenvironment (Estes et al., 2018). Despite the recent efforts, many questions related to follicular CD8+ T cell biology and dynamics remain to be addressed.

What is the lineage origin of follicular CD8+ T cells? Similar to CD4+ TFH, follicular CD8+ T cells express a unique phenotype and molecular profile (Mylvaganam et al., 2017; Petrovas et al., 2017; D. Yu and Ye, 2018). Furthermore, cytokines/chemokines (like TGF-b1, IL-23, IL-12) and transcription factors (including Bcl-6, Blimp1, TCF1, E2A), involved in the development of CD4+ TFH cells, also regulate follicular CD8+ T cells (Perdomo-Celis et al., 2019; Schmitt et al., 2014; D. Yu and Ye, 2018). Whether follicular CD8+ T cells represent an advanced differentiation stage of a particular CD8+ population or trafficking of bulk CD8+ T cells present in the T cell zone into the follicular areas is not known. It is also possible that non-follicular CXCR5^{lo} CD8+ T cells give rise to the follicular CXCR5^{hi} CD8+ T cells driven primarily by TGFb present in chronic HIV/SIV infection (Estes et al., 2007; Mylvaganam et al., 2017; Zeng et al., 2011). In support of this concept, an increased frequency of lymph node CCR7^{lo}CXCR5^{lo} CD8+ T cells was found in early chronic SIV infection, preceding the accumulation of follicular CCR7^{lo}CXCR5^{hi} CD8+ T cells observed in chronic SIV infection (Ferrando-Martinez et al., 2018).

What makes B cell follicles an immunologically privileged area? Historically, immune privileged areas are tissue sites that have been adapted to avoid tissue damage from local inflammation and recruitment of effector immune cells (Dai et al., 2005; S. Hong and Van Kaer, 1999). The presence of CD8+ T cells within follicles, particularly germinal centers, and the expression of cytolytic proteins are limited during homeostasis. The majority of follicular CD4+ and B cells express increased amounts of CD95/Fas (Koncz and Hueber, 2012; Marinova et al., 2006) making them highly sensitive to Fas-induced cell death. Therefore, one could hypothesize that limiting the access of CD8+ CTL into follicles protects the follicular populations from such deleterious signals. However, the molecular and cellular nature of mechanisms restricting the trafficking of CD8+ T cells into follicles are not known. The relative low expression of CXCR5 in lymph node CD8+ T cells could be a part of these mechanisms. In chronic SIV infection, a significantly higher frequency of follicular CD8+ T cells were found in both enlarged/lysed and intact mature follicles (Ferrando-Martinez et al., 2018), suggesting that trafficking of potential CTLs into follicles/germinal centers is not just a passive process. Comparing the local follicular environment in diseases characterized by irregular sequestration of CD8+ T cells in follicles could provide useful information regarding cellular and molecular pathways mediating this process.

Cognate vs non-cognate immune reactions; impact on follicular CD8+ T cell accumulation during chronic infection. HIV/SIV-specific follicular CD8+ T cells, defined by tetramer or intracellular cytokine staining, represent a small fraction of the follicular CD8+ T cell pool found in chronic HIV/SIV (Connick et al., 2007; Ferrando-Martinez et al., 2018; Li et al., 2019; Petrovas et al., 2017; Reuter et al., 2017). Although the presence of CD8+ T cell responses against other antigens cannot be excluded, it is possible that many of the follicular CD8+ T cells found in chronic infection are the result of a non-cognate differentiation process that is mediated by stimuli from the local microenvironment. No accumulation of follicular CD8+ T cells was observed in acute and early chronic SIV infection (Ferrando-Martinez et al., 2018; Li et al., 2019), while in chronic HIV/SIV infection accumulation of LN and follicular CD8+ T cells is associated with increased frequencies of circulating effector memory CD8+ T cells. Therefore, one could hypothesize that circulating CD8+ T cells can traffic back to LN possibly by a CXCR3-mediated mechanism (Alanio et al., 2018; Ferrando-Martinez et al., 2018; Khan et al., 2000; Reinhart et al., 2002), contributing to their accumulation in the T and B cell areas. The absence of CD8+ T cell accumulation in the LN areas (Ferrando-Martinez et al., 2018) in chronically SIV infected African Green Monkeys (AGMs, SIV natural host species), an infection characterized by low levels of immune activation (Silvestri et al., 2003), further supports the role of tissue inflammation and immune activation for this process.

Can follicular CD8+ T cells eliminate or control the virus? Virus elimination is a multistep process requiring either local CD8+ T cells to

differentiate into CTLs, or CTLs to traffic from blood into the inflamed tissue (lymph node), navigate to follicular areas, scan/recognize infected cells, and finally secrete their killing mediators in a target-specific way through the immunological synapse. Therefore, this process is a matter of functionality and trafficking. Several reports have shown the limited presence of HIV/SIV-specific cytolytic CD8+ T cells in the follicles (Connick et al., 2014, 2007; Fukazawa et al., 2015; Kohler et al., 2016; Li et al., 2016). Even when present, these cells are usually found at the T-B border area (Fig. 2C). Furthermore, the perforin/granzyme B-mediated killing ability of LN antigen-specific CD8+ T cells, which express several inhibitory receptors (Petrovas et al., 2017), is probably compromised at least compared to their blood counterparts (Reuter et al., 2017). However, the frequency of CXCR5+ CD8+ T cells has been shown to be negatively correlated with viral load, implying that these cells can potentially control viral replication through cytolytic-independent mechanisms (Fig. 1) (Nguyen et al., 2019; Reuter et al., 2017). Therefore, the identification of these mechanisms and potential induction of them in follicular CD8+ T cells should be pursued. An alternative approach that takes advantage of the increased presence of follicular CD8+ T cells in chronic infection is the use of immunotherapies like bispecific/tri-specific (Petrovas et al., 2017; Xu et al., 2017b) antibodies that can direct bulk follicular CD8+ T cells to the infected cells in a manner that is not affected by the limited TCR repertoire, inhibitory receptors expression, and specificity of the very few antigen-specific CD8+ T cells in follicles.

6. Are lymphoid tissue CD8+ T cells dysfunctional in HIV infection?

Based upon the low frequency of cytolytic CD8+ T cells within lymphoid tissues of HIV-infected individuals, one could propose that these cells are generally dysfunctional in chronic HIV infection. However, numerous reports have demonstrated that fully differentiated cytolytic CD8+ T cells are rarely, if ever, found in lymphoid tissue or non-lymphoid tissues at steady-state in HIV negative individuals (Buggert et al., 2018; Reuter et al., 2017; Thome et al., 2014; Woon et al., 2016). Considering these observations, are CD8+ T cells in HIV-infected lymphoid tissues actually dysfunctional, or do their properties simply reflect the normal biology of lymphoid tissues?

In the context of acute viral infections, viral-specific CD8+ T cells have been shown to be important for protection against primary challenge or re-infection. In several acute respiratory infections, including severe acute respiratory syndrome coronavirus (SARS-CoV), influenza, and respiratory syncytial virus (RSV) infection, CD8+ T cells, presumably within the respiratory tract, can mediate protection upon challenge or in vaccine-challenge models (Channappanavar et al., 2014; Graham et al., 1991; Schmidt et al., 2018; Slutter et al., 2013). However, in these infections, protection is not likely mediated directly in lymphoid tissues, but rather at the respiratory epithelial barrier. In chronic human viral infections, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), CD8+ T cells are important for long-term control and preventing disease progression, in spite of their inability to clear these viruses. Primary EBV infection causes a massive expansion of CD8+ T cells that ultimately contracts as antigen load decreases, indicating a role for CD8+ T cells in clearing virally infected cells (Bharadwaj et al., 2001; Hoshino et al., 1999; Tomkinson et al., 1987). Because EBV infects B cells, lymphoid tissue EBV-specific CD8+ T cell responses may be of particular importance for control, especially follicular CD8+ T cells. EBV-specific CD8+ T cells have been shown to establish residency within and outside of follicular areas of the human nasopharyngeal lymphoid tissues (Hislop et al., 2005; Leong et al., 2016). While these cells are attributed to the control of EBV at these sites, the mechanism by which they do so remains unclear. CMV-specific CD8+ T cells in these same tissues are present, but do not appear to establish residency (Woon et al., 2016). Whether CMV-specific CD8+ T cells in lymphoid tissues have cytolytic properties remains undefined. Of note, EBV-specific CD8+ T cells, both in the periphery and in lymphoid tissues, express a combination of inhibitory receptors, including PD-1, TIGIT, TIM-3, and KLRG1 (Chatterjee et al., 2019; Duraiswamy et al., 2011), yet are able to potently produce cytokines and undergo cell division upon stimulation (Chatterjee et al., 2019). CD8+ T cells, including HIV-specific CD8+ T cells, in LN of HIV- and HIV+ individuals typically express high levels of PD-1, TIGIT, CD160, and 2B4, yet respond upon stimulation by producing cytokines and proliferating, but not necessarily acquiring cytolytic ability (Petrovas et al., 2017; Reuter et al., 2017). These observations indicate a key disconnect between the simple presence of inhibitory receptors and dysfunction/exhaustion, and instead implies an undescribed functional regulation that may specifically be characteristic of CD8+ T cells that are present in lymphoid tissues.

7. Is inducing cytotoxicity of CD8+ T cells in HIV-infected lymph nodes a good idea?

While it may be thought that having strong cytotoxic responses in lymphoid or other tissues is beneficial by enabling the elimination of HIV-infected CD4+ T cells, simply increasing the frequency or potency of cytotoxic CD8+ T cells may have untoward consequences. CD8+ T cells can cause significant damage to tissues by secreting pro-inflammatory cytokines and/or by direct killing of target cells. Pathogenic effects of CD8+ T cells have been demonstrated in several parasitic and viral infections, including Leishmaniasis, Malaria, Chagas disease, Coxsackie virus, and Zika virus infections (Ferreira et al., 2017; Henke et al., 1995; Jurado et al., 2018; Nitcheu et al., 2003; Novais et al., 2017, 2013). In each of these diseases, the observed pathology has been attributed largely to CD8+ T cells with aberrant pathogen-specific perforin-mediated cytotoxic activity in the target tissues. Cytokine production by these T cells largely does not confer pathogenic effects in model systems of each of these infections (Gebhard et al., 1998; Haque et al., 2011; Novais et al., 2013; Silverio et al., 2012). Whether the presence of pathogenic cytotoxic CD8+ T cells reflects migration from the peripheral blood or differentiation within tissue remains unclear, but either scenario in the case of HIV infection could readily yield undesired tissue pathology in lymphoid or non-lymphoid tissues.

Pathogenic resident-memory CD8+ T cells have also been described in autoimmune settings. However, the mechanisms underlying their pathogenic effects is not restricted to cytotoxic activity. For example, in type 1 diabetes mellitus, CD8+ T cells are known to infiltrate pancreatic islets, where they are believed to mediate the destruction of beta-cells (Coppieters et al., 2012; Skowera et al., 2008; Unger et al., 2012; Willcox et al., 2009). While there is evidence of traditional perforin/granzyme B-mediated cytotoxic activity, cytokine-mediated mechanisms have also been implicated in beta-cell destruction (Coppieters and von Herrath, 2011; Knight et al., 2013; Trivedi et al., 2016). Similarly, differential pathogenic mechanisms have been implicated in aberrant self-reactivity by skin CD8+ TRM in vitiligo (cytotoxicity and cytokine production) and psoriasis (cytokine-mediated inflammation) (Cheuk et al., 2017, 2014; van den Boorn et al., 2009). Finally, multiple sclerosis (MS), a neurodegenerative disease caused by demyelination of nerve fibers in the CNS, is largely believed to be mediated by T cells with aberrant functions in the central nervous system. T cell receptor analyses of T cells isolated from the CSF, brain biopsies and peripheral blood of MS patients showed increased oligoclonality among CD8+, but not CD4+, T cells, indicating clonal expansion (Babbe et al., 2000; Jacobsen et al., 2002; Skulina et al., 2004). The mechanism responsible for neuronal loss is still not fully understood, but there is some evidence that IFNγ and IL-17A play a role (Annibali et al., 2011; Tzartos et al., 2008).

8. Conclusion

Given the potential role of CD8+ T cells in viral control and/or elimination, particularly in lymph node/follicles, several approaches aiming to favor the influx or expansion of CD8+ T cells in these areas are under development. *in vivo* administration of IL-15, a pleiotropic cytokine (Waldmann, 2006), was able to increase the presence of CD8+ T cells in the follicular/germinal centers and suppress the virus locally (Watson et al., 2018; Webb et al., 2018). Inhibition of T cell egress from the LN, using an S1PR1 antagonist, increased the frequency of follicular CD8+ T cells and decreased infection of follicular CD4+ T cells (Pino et al., 2019). In another approach, genetically modified CD8+ T cells overexpressing CXCR5 were able to traffic into the spleen follicular areas (Ayala et al., 2017). Combinatorial immunotherapies (for example co-administration of bispecific/trispecific antibodies and reagents promoting the trafficking of CD8+ T cells into follicles) represent another potential strategy for virus control or elimination.

However, the challenge of all of these strategies is to understand precisely what type of CD8+ T cell response is desired, and whether it will be possible to induce and durably maintain it within the lymphoid tissue environment. Studies by our group and others challenge the notion that cytotoxic CD8+ T cell responses are necessary for control of HIV replication in tissues. Hence, improving non-cytolytic CD8+ T cell mediated suppression of viral replication could be sufficient to maintain durable control of viremia. Given the accumulating data that cytotoxic function exerted by tissue CD8+ T cells is rare and likely heavily regulated through inhibitory pathways, attempting to permanently invoke cytolytic function in lymphoid tissues may be more difficult than anticipated and yield undesirable results through the induction of deleterious pathology. Further studies should aim to determine the exact non-cytolytic mechanisms involved in CD8+ T cell-mediated control of HIV. The elucidation of these mechanisms can provide targets for the development of functional cure strategies.

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