Brain-Resident T Cells Following Viral Infection

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Abstract

Activated CD8⁺ lymphocytes infiltrate the brain in response to many viral infections; where some remain stationed long term as memory T cells. Brain-resident memory T cells (bT_{RM}) are positioned to impart immediate defense against recurrent or reactivated infection. The cytokine and chemokine milieu present within a tissue is critical for T_{RM} generation and retention; and reciprocal interactions exist between brain-resident glia and bT_{RM}. High concentrations of TGF- β are found within brain and this cytokine has been shown to induce CD103 (integrin $\alpha\beta 7$) expression. The majority of T cells persisting within brain express CD103, which aids in retention through interaction with E-cadherin. Likewise, cytokines produced by T cells also modulate microglia. The anti-inflammatory cytokine IL-4 has been shown to preferentially polarize microglial cells toward an M2 phenotype, with a corresponding increase in E-cadherin expression. These findings demonstrate that the brain microenvironment, both during and following inflammation, prominently contributes to the role of CD103 in T cell persistence. Further evidence shows that microglia, and astrocytes, upregulate programmed death (PD) ligand 1 during neuroinflammation, likely to limit neuropathology, and the PD-1: PD-L1 pathway also aids in bT_{RM} generation and retention. Upon reactivation of quiescent neurotropic viruses, bT_{RM} may respond to small amounts of *de novo*-produced viral antigen by rapidly releasing IFN- γ , resulting in interferon-stimulated gene expression in surrounding glia, thereby amplifying activation of a small number of adaptive immune cells into an organ-wide innate antiviral response. While advantageous from an antiviral perspective; over time, recall response-driven, organ-wide innate immune activation likely has cumulative neurotoxic and neurocognitive consequences.

Keywords: brain, resident memory T cells, viral infection

Introduction

A UNIQUE MICROENVIRONMENT awaits brain-infiltrating lymphocytes. Before antigen (Ag) encounter, naïve T cells recirculate through blood and secondary lymphoid organs (SLO) (9,32). Once activated, these lymphocytes undergo rapid proliferation and migrate to sites of infection. Activated and expanded lymphocytes subsequently differentiate into effector cells, which control acute infection; and long-lived memory cells distributed in various tissues throughout the body (9,75). Tissue resident-memory T cells (T_{RM}) constitute a distinct population that is self-renewing, highly protective against subsequent Ag exposure, and localized long-term at sites of infection. These long-lived tissue-residents do not routinely recirculate with memory T cells in other tissues (49). Instead, their infiltration into tissues occurs in response to acute infection and inflammation (29,33,49,70,88). As in other organs, brain-infiltrating activated T cells orchestrate well-regulated protective effector responses to control acute infection. However, some of these lymphocytes also remain stationed long term within the brain as memory

cells. Following clearance of viral Ag, these brain-resident memory T cells (bT_{RM}) are distributed in a way that imparts immediate and effective defense against recurrent or reactivated brain infection. In this brief review, we first discuss generation of T_{RM} within brain following viral infection, while comparing them to T_{RM} in other tissues like skin, gut, and lung. We next focus on how this unique microenvironment shapes infiltrating CD8⁺ T cells, and discuss the involvement of glial cell: lymphocyte interactions in modulation of adaptive neuroimmune responses. We then summarize the properties and functions of CD8⁺ T cells persisting within brain following acute infection. Further understanding of the unique protective, and pathogenic, roles played by bT_{RM} will aid in development of innovative approaches to defend the brain against viral pathogens, while simultaneously avoiding immune-mediated neurotoxicity.

Resident-Memory T Cells

Lymphocytes patrol blood and SLO and are critical in control of many viral infections. Primary infection initiates activation and proliferation of naïve CD8⁺ T cells in lymph

nodes (clonal expansion); and drives a large amount of activated lymphocyte infiltration into sites of acute inflammation. These activated and expanded CD8⁺ T cells, carrying appropriate Ag receptors, effectively eliminate infected cells via delivery of cytotoxic effector molecules. The majority of these activated T cells are termed short-lived effector cells (SLEC), because they die shortly after performing their effector functions (contraction). SLEC are characterized by expression of killer-like receptor G-1 (KLRG1), and an absence of CD127, the α chain of the IL-7 receptor (34). As infection resolves and local inflammation subsides, a small subpopulation of greatly expanded pathogen-specific CD8⁺ T cells persists as memory precursor effector cells (MPEC), which are identified by increased expression of CD127, and an absence of KLRG1. These are the cells that are capable of giving rise to long-lived memory CD8⁺ T cells. Resident memory T cell populations do not recirculate between organs such as skin, lung, gut, or brain. Instead, the effector cells that give rise to these T_{RM} are able to migrate to nonlymphoid organs for a brief period after being primed. A subset of this effector subpopulation then differentiates into long-lived memory cells (79).

CD8⁺ T cells that persist long term within infected tissues provide sustained and rapid protective immunity against Ag rechallenge. Over the past two decades, several subsets of memory cells have been defined based on their migration, function, and location (12,77). Subpopulations of memory T cells are based on expression of the tissue homing receptors CD62L (L-selectin) and CCR7. Two main populations are termed central memory T cells (T_{CM}) and effector memory cells (T_{EM}). The subset of T_{CM} express CD62L and CCR7, and predominantly reside within lymphoid tissue. In contrast, T_{EM} lack CD62L and CCR7 and are thus found in peripheral circulation; lymphoid tissue homing markers are largely absent. However, both T_{CM} and T_{EM} display high expression of CD127 (4,76,77,92). More recent advances in understanding T cell memory have revealed a third cellular subset that does not recirculate, but remains stationed within tissues (i.e., T_{RM}). These T_{RM} have been identified in various nonlymphoid organs like skin, gut, salivary gland, female reproductive tract, mucosa, liver, and brain following viral infection (7,18,45,46,59,64,80,86).

A number of phenotypic markers are used to identify bona fide T_{RM} within various tissues. These cells have most often been reported to express CD103 (i.e., integrin $\alpha\epsilon\beta 7$) and CD69, which interferes with sphingosine 1-phosphate receptor1 (S1P1) to prevent tissue egress. In addition to these markers, T_{RM} may also express CD49a, which constitutes the α subunit of $\alpha 1\beta 1$ integrin receptor, also known as very late Ag 1 (VLA-1), (18,24,87,94). While imperfect, phenotypic markers are used to identify T_{RM} populations when stringent migration studies, such as parabiosis, are not feasible (80). Although phenotypic markers are useful in identification of T_{RM}, it is clear that cells residing in diverse tissues have different requirements for their migration and persistence; and how memory precursor cells receive precise signals from within a particular microenvironment to attain properties of T_{RM} is currently under investigation. Several anatomical locations within the brain namely, choroid plexus, meninges, and parenchyma have been identified as potential sites of T cell residence (5,39,67,72,85). However, little is known about the generation, maintenance, and fate

of bT_{RM}. In several viral infection models, CD8⁺ T cells were found to persist within brain (55,89,90) and these cells present unique phenotypic properties. A dramatic upregulation of the integrin subunit CD103 has been identified as a cardinal feature of CD8⁺ T cells persisting within brain following acute viral infection (67,68,90). CD103 is a known ligand of E-cadherin. It has been shown that $\alpha\epsilon\beta 7$ (CD103)-deficient CD8⁺ T cells are able to migrate to skin, brain, and small intestine but are not retained (13,46,89). The majority of CD8⁺ T cells that persist following acute murine cytomegalovirus (MCMV) brain infection preferentially express CD103 (10,67), similar to findings reported in other experimental models (8,54). However, expression of CD103 may not be a universal requirement for persistence within brain. In a vesicular stomatitis virus (VSV) model, persistence of both CD103⁺ and CD103⁻ populations was reported; however, the two subsets differed in their effector function (89). Likewise, using a brain infection model with lymphocytic choriomeningitis virus (LCMV), CD103 was expressed only on a portion of bT_{RM}, however, both CD103⁺ and CD103⁻ populations persisted in stable proportions over time and showed equal proliferation following reactivation (85). Studies using herpes simplex virus (HSV)-1 skin infection also indicate persistence of Ag-specific CD8⁺ T cells that lack expression of CD103. However, it can be up-regulated in response to TGF- β (46). Other studies report that binding to E-cadherin is not absolutely required for T_{RM} persistence, as these cells have been detected in dermis lacking its expression (57,60). Despite the variability of these reports, in the majority of studies performed in both mice and humans, high expression of CD103 and CD69 (the S1P1 antagonist) is a common feature of T_{RM} (87). Additional markers are also being used to identify residency, such as CD49a (which is an integrin $\alpha 1$ paired with $\beta 1$), and hyaluronic acid binding to CD44 (87).

Establishment of T_{RM} Within Brain

The brain is well known as a reservoir for latent and persistent virus following acute infection and, therefore, presents unique challenges to effective pathogen clearance. Immune responses within the brain are mostly dormant under normal conditions, but they are vigorously awakened following infection or injury. Infection and inflammation drive T cell infiltration, and establishment of bT_{RM} (83). Activated CD8⁺ T cells infiltrate peripheral tissues through downregulation of molecules that promote SLO homing (e.g., L-selectin) and, conversely, upregulation of adhesion molecules that facilitate entry to sites of inflammation. Migration studies indicate that only effector CD8⁺ T cells enter infected tissues (29,49,89). So, subsequent derivation of a CD103⁺CD69⁺ population demonstrates that they originate from MPEC, which are identified by expression of the α chain of IL-7R and minimal KLRG1 (36,93). To provide immediate recall responses to Ag rechallenge, T_{RM} preferentially remain positioned at sites of pathogen exposure through displaying the appropriate integrins and receptors that facilitate persistence (71). In brain, the majority of persisting CD8⁺ T cells co-express CD103 and CD69 (10,67). Local conversion of brain-infiltrating CD8⁺ T cells to a CD69⁺CD103⁺ population has been reported in various disease settings (10,12,66,89,90). CD103 functions through aiding in tissue retention through interaction with

E-cadherin, which has been well established in epithelial cells (14,15). In some tissues like salivary gland, E-cadherin is detected on Ag-specific CD8⁺ T cells themselves; however, how these cells acquire expression is still unclear (29).

Within brain, pro- and anti-inflammatory cytokines produced by T cells at sites of inflammation are well known to modulate resident microglia, the major innate immune cell type within the CNS. The anti-inflammatory cytokine IL-4 has been shown to preferentially polarize microglial cells toward an M2 phenotype, with a corresponding increase in E-cadherin expression (16). These findings further demonstrate that the precise brain microenvironment, both during and following inflammation, largely contributes to the role of CD103 in T cell persistence. In addition, it helps to explain the interaction of CD103 with E-cadherin in tissues, like brain, which lack epithelium. Other molecules, such as S1P1, have also been implicated in accumulation and retention of T_{RM}. Expression of S1P1 is regulated by the transcription factor Kruppel-like factor 2 (KLF2). CD69 interacts and interferes with S1P1, and KLF2, thus preventing tissue egress (45). However, the question of whether CD69 contributes to bT_{RM} development in a similar fashion remains to be answered.

Local cues (i.e., the cytokine and chemokine milieu) within a tissue are critical for T_{RM} generation and retention. Microglial cells respond to infection and inflammatory stimuli by upregulating various mediators (1,26), such as proinflammatory (e.g., IL-1, IL-6, IL-12, and TNF- α), and anti-inflammatory (e.g., IL-10 and TGF- β) cytokines (22,43,52,56,69,74). These cells are also a major source of chemokines that drive leukocyte infiltration. During the course of viral infection, microglia become activated, upregulate MHC expression, acquire functions of Ag presenting cells (APC), and interact with brain-infiltrating lymphocytes (20,26,40,81). Depending upon the kinetic time course of infection, anti-inflammatory cytokines like IL-10, IL-4, and TGF- β are produced within brain following viral infection. These cytokines are made to inhibit production of proinflammatory cytokines, thereby turning off neuroinflammatory responses to limit deleterious, neurotoxic consequences. Furthermore, accumulating evidence indicates that TGF- β , IL-15, and IL33 can induce CD103 expression. TGF- β has been demonstrated to induce expression of $\alpha\beta$ 7 (CD103) on effector CD8⁺ T cells from spleen (13,46,94). Another study revealed that TGF- β production by CD4⁺ regulatory T cells (Treg) leads to increased expression of CD103 on CD8⁺ T cells, thus allowing a large population of T_{RM} to be retained within infected brain (27). Furthermore, results from our studies using MCMV show reduced numbers of brain-resident CD103⁺CD8⁺ T cells in Treg-ablated mice, possibly through decreased TGF- β (68). Additional studies using primary astrocyte: microglial cell coculture systems have demonstrated that the anti-inflammatory effects of IL-10 on microglia were mediated through the production of TGF- β . Finally, IL-10 reduces IL-1 β and increases expression of the fractalkine receptor CX3CR1, a mediator of anti-inflammation (58). Taken together, the TGF- β -rich brain microenvironment could be ideal for retention of T_{RM}.

Localization of T_{RM} within tissues is also associated with chemokine receptors. The chemokines CXCL9 and CXCL10 have been shown to facilitate entry of T lymphocytes during HSV infection (82). Similarly, CXCR3, the receptor for CXCL9 and CXCL10, is required for appropriate localiza-

tion of T cells (84). In addition, expression of CXCR3 and CCR7 define T cell migration in various tissues like skin, gut, and lung (41,53,84). Within brain, activated microglial cells are a known source of CXCL9 and CXCL10 in response to MCMV infection (44). In addition, an elevated level of CXCR3 has been reported on CD103⁺CD8⁺ T cells persisting within MCMV-infected brains (67). Additional reports using a skin model suggest that CCR7 expression is required by T cells to exit out of the tissue, whereas decreased expression of CCR7 enabled persistence (60,91). Likewise, following MCMV infection, bT_{RM} show negligible expression of CCR7 (67).

Evidence shows that resting microglia, and astrocytes, upregulate programmed death (PD) ligand 1 (B7-H1; CD274) during neuroinflammation (78), likely to limit CNS pathology through suppression of T cell responses (17,55,78). Additional studies have investigated the involvement of PD-1 (CD279): PD-L1 signaling in the retention of bT_{RM} (61,67). Using our MCMV model, we have shown that a reduced number of T_{RM} reside within chronically infected brains of PD-1 knockout (KO), and PD-L1 KO animals (67). Another study using Theiler's murine encephalomyelitis virus (TMEV) also demonstrates that PD-1: PD-L1 signaling is critical for maintenance of the bT_{RM} population (61). In addition, an increased population of CD103⁺CD8⁺ T cells, was also reported in PD-L1 KO animals (61). It is likely that elevated levels of proinflammatory cytokines suppress bT_{RM} accumulation within brains of PD-L1 KO animals, as reported in lung following influenza infection (65). It has been reported that IFN- γ induces T-bet (T-box expressed in T cell) expression and subsequently inhibits expression of the IL-7 receptor, further contributing to death of SLEC (31,73). Interestingly, *in vitro* studies using blockade of the PD-1: PD-L1 pathway in both primary microglial cell and astrocyte: CD8⁺ T cell cocultures resulted in increased production of IFN- γ (78). Recent *in vitro* studies have identified a role for activated microglia in promoting generation and retention of bT_{RM}. In these studies, upregulation of CD69, CD103, and CD127 on CD8⁺ T cells was noted in the presence of glial cells (66). Additionally, blocking of PD-L1 on glia led to decreased expression of CD103, and CD127, on CD69⁺CD8⁺ T cells. PD-L1 blocking also led to increased T-bet expression on CD69⁺CD103⁺CD8⁺ T cells, along with reduced CD127. Taken together, these data provide further evidence that the PD-1: PD-L1 pathway aids in bT_{RM} retention. Additionally, expression of $\alpha\beta$ 7 on CD8⁺ T cells promotes their survival through expression of B cell lymphoma (Bcl)-2 (46,89). So, reduced expression of Bcl-2 in CD103⁺ T_{RM} from PD-L1 KO animals may be yet another factor that affects bT_{RM} survival (67).

Role of T_{RM} in Defense of the Brain

Upon Ag restimulation, T_{RM} exhibit rapid production of cytokines like IFN- γ , TNF- α , IL-2, and IL-17 (21,29,30,50,66). As in other tissues, bT_{RM} also produce high levels of IFN- γ following pathogen restimulation (10,42,85). In addition to cytokine production, T_{RM} perform direct cytotoxic activity using granzyme B and perforin to kill infected targets. CD103⁺ bT_{RM} have been reported to produce elevated levels of

granzyme B relative to CD103⁺ cells in a brain infection model, similar to findings in tissues like gut and intestine (89). Additionally, Treg-deficient animals, which produce fewer bT_{RM}, showed reduced amounts of granzyme B in response to peptide restimulation (68). Additional studies using depletion of circulating CD8⁺ T cells, and perforin-deficient mice, demonstrate the contribution of cytolytic effector functions to bT_{RM}-mediated viral clearance in CNS (85). However, low granzyme B production by Ag-specific T_{RM} in the lung suggest both cytolytic and noncytolytic effector functions are employed (23,35,62). Another interesting study demonstrated a noncytolytic function of granzyme B in defense against HSV-1, where it mediates degradation of viral immediate early proteins (38). Taken together, the type of protective effector response displayed by T_{RM} varies between tissues and depends upon the nature of infectious agent.

Effective protection against pathogen rechallenge requires T_{RM} to survey tissue for Ag. CD8⁺ T_{RM} in epidermis acquire dendritic-like morphology, which increases their ability to interact with infected cells (2,25). In another instance, T_{RM} were found to reduce their mobility in female reproductive tract, to help them locate Ag through interaction with dendritic cells (9). It has been shown that lack of a T_{RM} population leads to delay in combating Ag rechallenge (19,47,79). T_{RM} accumulate at sites of pathogen entry in most barrier tissues, where they provide first-line defense against infection. However, it is unlikely for any viral infection to begin within brain, suggesting the primary role of bT_{RM} may be clearance of Ag from reactivated virus.

In addition to defense against pathogens, host immune responses must possess the ability to calm overwhelming inflammation to prevent excessive tissue damage. Well-controlled responses induce the expression of various immune checkpoints inhibitory receptors like PD-1, lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4). These receptors dampen T cell effector function and reduce immunopathology. Inhibitors of these immune checkpoints unleash CTL activity and have revolutionized immunotherapeutic approaches to cancer treatment (28). Ag-experienced CD8⁺ T cells upregulate PD-1 as an activation marker. Paradoxically, despite the fact that T_{RM} exert immediate and effective immune responses upon Ag restimulation (66,89), in a variety of experimental models, the upregulation of immune inhibitors like PD-1, LAG-3, TIM-3, and CTLA-4 has been demonstrated on these cells. Ag-specific bT_{RM} have been shown to express high levels PD-1 and blockade of this pathway, correspondingly, resulted in increased IFN- γ production during chronic infection (83). Additionally, fewer bT_{RM} were detected within PD-1 KO animals (66). The maintenance of PD-1 on T_{RM} has been reported to be independent of Ag or inflammation (83). Taken together, it appears that the brain microenvironment favors maintenance of PD-1, through which it exerts a brake on unwanted immune activation and unnecessary self-attack, thereby limiting immunopathology. However, little is currently known about how PD-1 modulates the function and maintenance of bT_{RM}.

Reactive Glia and bT_{RM}

While Ag-specific CD8⁺ T cell populations residing within brain likely aid in rapid Ag clearance, dysregulated

neuroimmune responses and unwanted reactive gliosis are associated with neurotoxicity and neurocognitive dysfunction (37). Heightened expression of markers indicating cellular activation (e.g., MHC and PD-L1) on glia themselves, which are not seen in uninfected brain, is observed in response to proinflammatory cytokines produced by infiltrating CD8⁺ T cells (55,78). Results obtained in our laboratory have shown that resting microglia, identified as the CD11b⁺ CD45^{int} cell population using flow cytometry, from uninfected brain express very low constitutive levels of MHC class II (44,55). However, following MCMV or HSV-1 brain infection, MHC II expression is strikingly upregulated on approximately 90% of these cells, including in widespread areas distal to viral infection (48,55). However, similar activation was not observed using infected, IFN- γ KO animals (55). These data demonstrate that microglial cells do not acquire reactive phenotypes solely due to innate responses against viral proteins themselves, but rather react to immune mediators produced within the brain. Murine models of neurodegenerative diseases, stroke, multiple sclerosis, and brain infection all demonstrate the prolonged activation of microglia associated with persistence of long-lived memory T cells (6,11,48,63,81).

The precise reciprocal interactions between bT_{RM} and brain-resident glia that modulate each other's functions are currently under investigation. It is likely that upon reactivation of quiescent neurotropic viruses, bT_{RM} respond to minute amounts of *de novo*-produced viral Ag by rapidly releasing IFN- γ , which in turn drives glial activation. This scenario has been well described in skin infection and has been termed "tissue-wide pathogen alert," where Ag-specific adaptive recall responses drive innate responses (3,80). In several infection models, it is clear that recall responses by T_{RM} result in production of IFN- γ (51,85). Furthermore, this IFN- γ production results in interferon-stimulated gene (ISG) expression in surrounding cells, thereby amplifying the activation of a small number of adaptive immune cells into an organ wide antiviral response (3). While this function of T_{RM} is advantageous from an antiviral perspective (i.e., for rapid viral clearance), the disadvantage is that, in tissues such as the brain, over time this recall response-driven, organ-wide innate immune activation likely has neurotoxic consequences. From these studies, it is clear that a small number of T_{RM} accelerate pathogen control in the event of reinfection or reactivation of latent infections in solid organs, such as the brain, by instructing innate immune cells, such as microglia. Yet, definitive experiments to evaluate the cumulative neurotoxic consequences of antiviral recall responses by bT_{RM} in driving tissue-wide activation of brain-resident glia and its associated neurotoxicity, and subsequent neurocognitive impairment remain to be performed.

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