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Divergent behavior of mucosal memory T cells

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Memory CD4 T cells are strategically positioned at mucosal surfaces to initiate a robust adaptive immune response. The detection of specific antigen via the T-cell receptor causes these memory T cells to unleash a potent antimicrobial response that includes rousing local innate immune populations for tissue-specific defense. Paradoxically, these same memory T cells can also be stimulated by nonantigen-specific signals that are generated by the activity of local innate immune cells. This versatility of mucosal memory T cells in both the initiation and the sensing of local innate immunity could be a vitally important asset during pathogen defense but alternatively could be responsible for initiating and maintaining chronic inflammation in sensitive mucosal tissues.

INTRODUCTION

Mucosal tissues contain numerous cells of the innate and adaptive immune system that are strategically positioned to protect sensitive organs against damage from microbial pathogens or the consequences of uncontrolled inflammation.[1] During the resolution of a primary infection, memory lymphocytes are distributed to mucosal tissues where they can generate a rapid local response to reinfection.[2] This mucosal memory pool contains some recirculating T cells that transit in and out of the tissue and other T-cell populations that simply settle down permanently within the mucosa itself. Given the capability of memory lymphocytes to respond rapidly via T-cell receptor (TCR) ligation, conceptual models of T-cell restimulation are often uncoupled from non-TCR signals generated by the innate immune system. However, recent reports have demonstrated that the stimulation of mucosal memory T cells and the response of local innate immune populations remain highly interconnected.

Tissue resident memory (Trm) T cells are a recently defined lineage that populate barrier tissues but are strikingly absent from peripheral blood.[3] These T cells occupy common sites of infection and are thought to provide immediate defense by scanning the local tissue for evidence of reinfection.[4,5] Trm T cells can retain antimicrobial functions that were critical for resolving a primary infection, and upon subsequent TCR ligation, can recall this ability to effectively combat secondary infection.[6,7] However, the functional capability of Trm T cells extends well beyond the concept of an immediate effector population that can directly kill previously encountered pathogens in isolation. Recent work has shown that the restimulation of Trm T cells serves to modify the local endothelium and chemokine milieu to recruit other circulating memory T cells and B cells. In addition, these local Trm cells effectively activate local dendritic cells and natural killer (NK) cells populations to provide non-specific tissue-wide defense.[8,9] These effects of mucosal memory T cells on innate immune populations are a consequence of local TCR ligation, demonstrating that innate immunity can be initiated downstream of local adaptive responses. Paradoxically, mucosal memory T cells can also be stimulated in a TCR-independent manner, often as a direct consequence of local inflammatory signals generated by infection or tissue stress. Thus, memory T cells interact with innate immune cells in a bidirectional process that can alternatively initiate, or sense, the local inflammatory context in the mucosa **Figure 1**.

Holmkvist *et al.*[10] describe a population of human memory CD4 T cells that express interleukin (IL)-18Rα and DR3 and produce multiple cytokines if exposed to a cocktail of IL-12, IL-18, IL-15, and the DR3 ligand, TL1a. It has long been appreciated that memory T cells secrete effector cytokines in

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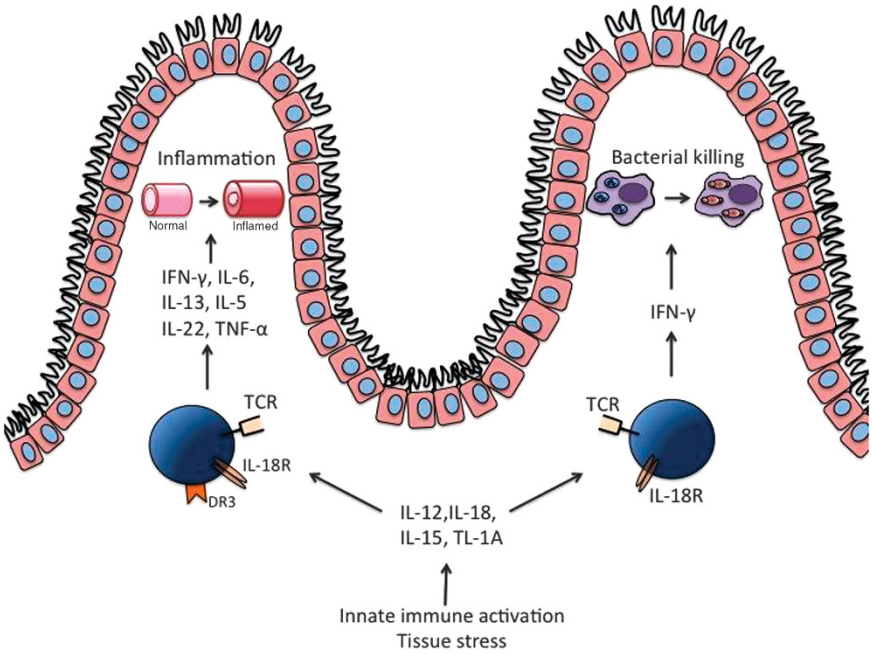

Figure 1 Innate stimulation of T cells in mucosal tissues. Local innate immune activation or tissue stress can initiate a cytokine milieu capable of stimulating nearby memory T cells in the absence of T-cell receptor (TCR) ligation. The synergy of interleukin (IL)-15 and TL1a in the presence of IL-12 and IL-18 can increase the expression of multiple pro-inflammatory cytokines from memory T cells. Such innate stimulation of CD4 and CD8 T cells has been observed in bacterial infection models in which IL-18 R signaling contributes to the production of interferon-γ (IFN-γ) and host protection against pathogenic bacteria (right). This noncognate pathway might be particularly for the host if a pathogen evades antigen presentation or if a coinfection is present. However, innate stimulation of memory T cells in mucosal tissues might also induce or perpetuate harmful inflammatory responses (left).

Table 1 Cytokine-induced cytokine production of T cells

Mediator cytokine	Effector cytokine	Reference
IL-12, IL-18	IFN-γ,	11,12
IL-33	IL-13	13
IL-1	IL-17A, IL-22	13,14
IL-15, IL-7, IL-2	IFN- γ	16
TL-1A	IFN-γ	10,17
ISG15	IFN-γ	19

IFN-γ, interferon-γ; IL, interleukin.

response to other cytokines, and IL-18 was originally termed IGIF (interferon gamma-inducing factor) in recognition of the capacity to induce interferon-γ (IFN-γ) production from NK cells and Th1 cells.[11,12] Th2 and Th17 subsets can also respond to IL-33 and IL-1, respectively,[13,14] suggesting that the IL-1 family are key mediators in cytokine-induced cytokine production from memory T cells.[15] However, the stimulation of memory T cells by cytokines also extends beyond T helper subset responsiveness to IL-1 family members (**Table 1**). Although memory CD8 T cells secrete IFN-γ in response to IL-12 and IL-18, this effect can also be elicited to varying degrees by IL-12/IL-2, IL-12/tumor necrosis factor-α (TNF-α), IL-12/IL-33, or IL-18/IFN-β, as well as other cytokine pairs.[16] Cytokines such as IL-7, IL-15, TL1A, and ISG15 have also been reported to elicit immediate IFN-γ production from different populations of effector or memory CD4 or CD8 T cells.[16–19] Holmkvist *et al.* extend these observations to show that memory T-cell exposure to IL-15 and/or TL1a dramatically enhances cytokine production elicited by IL-12 and IL-18.[10] Importantly, this enhancing effect was observed across a wide range of T-cell-derived effector cytokines, including IFN-γ, TNF-α, IL-5, IL-6, IL-13, IL-22, and granulocyte macrophage colony-stimulating factor, suggesting that cytokine-induced cytokine production is not restricted to any individual effector response. The exact mixture of stimulating cytokines was critical for determining the effector response elicited, with IL-12 more important for IFN-γ, TNF-α, and IL-6 production, while other cytokines were efficiently induced by IL-18/IL-15/TL1a in the absence of IL-12.[10] It will be important to examine the synergistic nature of IL-15/TL1a in mouse models of inflammatory and infectious disease in order to determine whether this mixture of cytokines drives protective or pathological responses in a variety of settings. However, it seems clear that a wide variety of cytokines can be elicited from memory T-cell populations at barrier surfaces, depending on the exact mixture of local cytokines that is available within the local tissue.

Holmkvist *et al.*[10] identify a subset of IL-18Rα/DR3-expressing T cells that effectively respond to this mixture of cytokines and demonstrate that IL-15/TL1a drive selective proliferation of this population in vitro. These IL-18Rα+ DR3+ memory cells were identified in human peripheral blood, nasal polyps, and skin, and were particularly enriched in the small intestine and colon where they represent the majority of CD4 T cells. Given the broad array of cytokines that can elicit cytokine production from memory T cells,[16] there will undoubtably be additional receptors that initiate similar effects. Greater understanding of the diversity of cytokine receptor expression on mucosal memory cells is warranted. It seems possible that the initial stimulation conditions in the lymph node might determine the range of subsequent cytokine receptor

expression and thus control the ability of memory T cells to respond to local inflammatory conditions. Alternatively, the anatomical context that memory cells find themselves might alter cytokine receptor expression and thus regulate the threshold of responses that can occur in each tissue. It is also worth noting that several cytokines can actually inhibit cytokine-induced cytokine production from memory T cells, including IL-4, IL-10, and TGF-β.[16,20] Indeed, Holmkvist *et al.* show that TL1a can inhibit IL-15-mediated induction of IL-10 in both IL-18Rα + and IL-18Rα − T cells, perhaps suggesting an additional role for this cytokine in perpetuating inflammatory responses by effectively decreasing local anti-inflammatory responses.

Cytokine-mediated stimulation of T cells is often referred to as "innate responsiveness", as it can occur in the absence of TCR ligation. Indeed, this "innate-like" capability represents an underappreciated functional overlap between memory T cells and innate lymphocytes in mucosal tissues.[15] It is likely that many microbial pathogens can generate a cytokine milieu that would be capable of activating tissue memory T cells independent of TCR stimulation. Indeed, innate stimulation of CD4 and CD8 T cells has been documented in viral and bacterial infection models, although this is often visualized by providing additional PAMP stimulus.[21–24] One recent study demonstrated that TLR and inflammasome signaling have essential roles in innate CD4 and CD8 T-cell responsiveness to *Salmonella* infection,[25] which fits with the accepted role of these pathways in the production and processing of IL-1-like family members and their importance in defense against *Salmonella*.[26] It is less clear whether this inherent capacity for T-cell innate responsiveness actively contributes to bacterial clearance, especially since exogenous PAMPS are often required to detect these responses *in vivo*.[21–24] However, mice containing T cells that lack the ability to respond to IL-1 family members displayed higher bacterial burdens after *Salmonella* infection.[25] Furthermore, previous studies have shown that OVA-specific memory T cells can respond to IL-12 and IL-18 and provide some protection against *Listeria* infection.[22,27] Therefore, it seems likely that innate stimulation of memory T cells represents a mechanism that can contribute to pathogen clearance from mucosal tissues. The exact role of TL1a and IL-15 in amplifying T-cell-mediated host defense against infectious agents now deserves some attention. Such noncognate pathways might be critically important for defense against pathogens that efficiently impede antigen presentation, perhaps forcing the host to activate T cells solely via non-TCR-dependent mechanisms. Similarly, having T cells that can simply respond to local inflammation might be advantageous in combating rapidly dividing pathogens or during coinfections where one pathogen initiates a response that can actively participate in the clearance of a second pathogen occupying the same tissue.[25] Additional work is needed to examine each of these possibilities in relevant infection models.

Although the presence of a memory T-cell population that responds to innate stimuli might be beneficial in some situations, it could also perpetuate harmful inflammatory responses in sensitive mucosal tissues. In a macaque model of *Salmonella* infection, much of the early inflammatory response to intestinal infection is elicited by local T cells and can be blunted in animals where T cells were lost due to simian immunodeficiency virus infection.[28] Other models have shown that exposure of virally infected mice to endotoxin initiates cytokine production from T cells that can ultimately prove fatal.[21,29] This heightened sensitivity to endotoxin during viral infection is IL-12 and IL-18 dependent and might provide a model for understanding the severity of bacterial coinfections during existing respiratory viral disease.[30] Similarly, the synergy detected between IL-15 and TL1a in driving pro-inflammatory cytokine production from IL-18Rα + DR3 + memory T cells could be a critical step in the pathogenesis of inflammatory bowl disease.[31,32] Indeed, Holmkvist *et al.*[10] detected IL-18Rα + DR3 + T cells within lymphoid aggregates present in the inflamed intestines of patients with Crohn's disease. Furthermore, these memory T cells were identified in close proximity to cells expressing IL-18. Thus, cytokine-induced cytokine production by mucosal memory T cells may contribute to the pathogenesis of inflammatory bowel disease and thus understanding the capacity of IL-15 and TL1a to synergistically enhance inflammatory responses could be helpful for future intervention strategies.

In conclusion, mucosal memory T cells remain intimately connected to innate immune populations in the local tissue and have the capacity to initiate or to sense local innate responses. If the correct cytokine milieu is generated by innate activation, these memory T cells can be reactivated and perhaps contribute to host defense or to aggravating a developing inflammatory condition. Greater understanding of the cytokines that drive these "innate responses" from T cells and the individual memory populations that are able to respond to these different cytokine cocktails should clarify the exact role of this innate functionality of memory lymphocytes in contributing to pathogen clearance and immune pathology in mucosal tissues.

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DISCLOSURE

The authors declared no conflict of interest.

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