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Inflammatory interference of memory formation

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Abstract

CD8⁺ memory T cells are critical for immunity against intracellular pathogens. Epidemiological evidence demonstrates that bystander infection can impact immune responses to co-infection or vaccination. A recent paper in *Immunity* demonstrates that persistent bystander inflammation can negatively impact CD8⁺ T cell effector to memory transition and protection from subsequent infection.

Immunological memory, or the ability of the immune system to efficiently recognize and respond to a secondary encounter with a pathogen, protects the host from subsequent disease after vaccination or natural infection. CD8⁺ memory T cells are essential mediators of protection against viral and intracellular bacterial infections. While there is a detailed understanding of how CD8⁺ memory T cells form and function in response to specific pathogens in isolation¹, it is less clear how these responses develop in the context of concurrent infection. This becomes an important distinction since approximately one third of the world's population harbors a persistent infection.

Persistent infections such as HIV, malaria and tuberculosis not only directly cause morbidity and mortality, but are also thought to indirectly influence unrelated immune responses. Although epidemiological and observational studies have increasingly drawn attention to immunological cross talk between unrelated immune responses, the underlying mechanisms are complex, varied and only beginning to be understood. While in some cases immunological cross-talk has been shown to enhance protection to an unrelated infection, the majority of studies have shown a negative impact of persistent infection on subsequent immunity to infection or vaccination (reviewed in Stelekati and Wherry, 2012)². Therefore, understanding the impact of these chronic bystander infections on the development of immune memory is essential for enhancing vaccine efficacy and immunity during co-infection.

Epidemiological, and in some cases experimental, evidence demonstrate that bystander infection can affect either the function of previously formed CD8⁺ memory T cells or the development of novel immune responses. Both in clinical and murine studies, inflammation from an antigen-specific immune response can activate unrelated (non-antigen-specific) memory CD8⁺ T cells through a process known as bystander activation^{3, 4}. Recent studies have further demonstrated that bystander activation of preformed memory CD8⁺ T cells can induce granzyme-mediated cytolytic function⁵ and recruitment of memory CD8⁺ T cells into infected tissue⁶. There is currently a growing literature that rapid, innate-like functions of bystander activated memory CD8⁺ T cells can enhance either immune protection or lead to immune pathology⁷.

Although there is evidence of reduced rates of vaccination in individuals with certain chronic infections², how a persistent infection affects the development of a novel immune response is less clear. Naive CD8⁺ T cells are activated through a tightly regulated process that involves three distinct signals: T cell receptor (TCR) recognition of cognate peptide presented on MHC Class I, co-stimulation and exposure to inflammatory cytokines⁸. This activation leads to extensive clonal expansion and the differentiation of antigen-specific effector CD8⁺ T cells. Effector CD8⁺ T cells then undergo a precipitous contraction phase where approximately 90% of the cells die by apoptosis with the remaining cells maturing into long-lived memory populations. The surviving memory pool is enriched for cells derived from memory precursor effector cells (MPECS) that express high levels of the IL-7 receptor alpha chain (CD127) and low levels of the killer cell lectin-like receptor G1 (KLRG1)⁹. Long-lived memory CD8⁺ T cells that survive the transition from effector to memory can persist in the lymphoid organs, blood and tissues where they can rapidly mediate protection to subsequent infection. In the context of persistent infection however, there is the potential for this well-orchestrated process to be derailed at any one of these steps. Chronic infection can lead to altered innate cell function including antigen presentation, enhanced inflammatory cytokine expression that can affect acquisition of effector function or disrupted epithelial or lymphoid organ integrity that can affect migration or access to pathogens. Understanding the stages of CD8⁺ T cell memory differentiation that are affected by persistent infection and the underlying mechanisms is important for developing better vaccines and therapies in developing countries in which persistent infections are prevalent. A recent article in *Immunity* by Stelekati *et al.*, provides fundamental insights into how a persistent infection affects the dynamics of CD8⁺ T cell memory development and sheds light upon some of the underlying mechanisms involved¹⁰.

Stekalati *et al.* make the important observation that in the presence of persistent viral infection, the development of an unrelated bacterial-specific CD8⁺ memory T cell response is disregulated. Using a well-characterized mouse model system of chronic viral infection, either uninfected mice or mice infected with lymphocytic choriomeningitis virus (LCMV) were subsequently infected with *Listeria monocytogenes* expressing the model antigen ovalbumin (OVA). Strikingly, the authors found that thirty days after infection, the OVA-specific CD8⁺ T cells generated in the context of bystander persistent viral infection exhibited lower expression of surface molecules associated with memory formation and had a decreased proportion of MPECS. In an effort to avoid complexities associated with pathogen replication or pathogenesis due to altered innate immunity in persistently infected mice, the authors adopted a simplified adoptive transfer approach. Congenically marked TCR transgenic OT1 T cells specific for OVA were primed in one mouse and then adoptively transferred into either persistently infected or uninfected mice, thus enabling direct assessment of the effector to memory transition in the context of persistent bystander infection. Despite being primed in the same environment, CD8⁺ effector cells transferred into mice infected with bystander viral or parasitic infections (*Toxoplasma gondii* or *Heligmosoides polygyrus*) demonstrate defects in survival, function (measured by multifunctional cytokine production) and protective capacity of the CD8⁺ memory T cells. This defect could be directly attributed to the MPEC pool in the post-effector stage as transfer of early MPECS into bystander infected mice decreased their survival in

comparison to transfer into uninfected animals, whereas transferred pre-formed memory cells were far less affected by bystander infection. Thus, the inflammatory environment associated with a persistent infection may divert MPEC cells away from a long-lived fate to a more terminally differentiated effector phenotype.

To interrogate the mechanisms underlying skewed MPEC differentiation, gene array analyses were performed on OT-1 cells in bystander infected mice and CMV-specific CD8⁺ T cells in HCV infected humans. Importantly, shared inflammation-driven gene expression programs were found in murine and human cells exposed to chronic infection. Although no one specific inflammatory signal alone (Type 1 Interferon (IFN), IFN γ or IL-12) was required to drive this inflammation-induced program, these findings suggest that several inflammatory pathways may act synergistically to alter the ability of effector CD8⁺ T cells to efficiently transition to memory.

Taken together, these findings demonstrate that chronic coinfection and inflammation can have deleterious effects on the formation of unrelated memory CD8⁺ T cells, and have important implications for the induction of immunity by vaccination, especially in populations where persistent infections are common. These observations also give rise to many questions. What are the upstream cues that skew MPEC differentiation? Does bystander infection also affect the priming of CD8⁺ memory responses? How does bystander activation affect the development of other types of CD8⁺ memory, such as tissue resident memory cells? Does this skewing apply to CD4⁺ T cell or B cell memory programs? Can non-infectious chronic diseases associated with inflammation, such as heart disease, also affect the development or function of immune memory to infection and vaccination? The answers to these questions will help to understand how immune memory is formed and how it can be manipulated by vaccination or therapeutics.

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Figure 1.

Bystander infection negatively impacts effector to memory transition. There are multiple stages of memory CD8⁺ T cell development that can be negatively impacted by persistent bystander inflammation (**green text**). Naïve CD8⁺ T cells that are primed by antigen presenting cells proliferate and differentiate to form effector cells. In some infections, such as LCMV, short-lived effector cells (SLECs) driven by inflammatory cues express high levels of cytokine and cytolytic activity. Memory precursor effector cells (MPECs) can survive the contraction to form long-lived memory CD8⁺ T cells in the lymphoid organs. *Stelekti et al.* provide evidence that bystander chronic infection negatively impacts the MPEC to memory cell transition. Inflammation from bystander infection skews MPEC differentiation such that survival, cytokine production, and protective capacity of the CD8⁺ memory cells is diminished and gene expression programs associated with chronic inflammation develop (**red text**).