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Crosstalk between Adaptive and Innate Immune Cells leads to High Quality Immune Protection at the Mucosal Borders

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Abstract

Mucosal effector memory CD8 T cells are located at the epithelium and have a heightened and immediate effector function. By contrast, central memory T cells reside within lymphoid tissues and require proliferation and differentiation to become effector cells that migrate to epithelial surfaces. The accumulation of effector memory T cells at the pathogen entry site(s) is essential for protective immunity, but the mechanisms that drive the differentiation of memory cell subsets are poorly understood. We recently showed that CD8αα, induced selectively on the most highly activated primary CD8αβ T cells, together with its ligand, the thymic leukemia (TL) antigen, induced on mucosal antigen presenting cells and constitutively expressed on intestinal epithelial cells, serve as key components to mediate the selective accumulation of the fittest effector cells to form mucosal effector memory T cells. Therefore, the generation of mucosal effector memory is controlled by an innate-adaptive crosstalk that provides for host defense at the body's largest interface.

Keywords

Protective immunity; effector memory CD8 T cells; central memory CD8 T cells; TCR affinity; CD8αα; Thymic Leukemia Antigen TL; mucosal Dendritic Cells; mucosal epithelium

1. Introduction

The intestine forms the largest entry port for invading pathogens. Many pathogens infect the host through the expanded epithelium of the intestine. Effective immune memory cells residing at this local mucosal site are of great importance for the initial containment and early control of pathogen infection and re-infection (1–3).

2. Effector and Central Memory T cells form distinct subsets

Memory T cells can be broadly separated into central memory (T_{CM}) and effector memory (T_{EM}) cells. T_{CM} express CCR7/CD62L and re-circulate through lymphoid tissues. T_{EM} lack CCR7/CD62L and preferentially home to non-lymphoid tissues such as the intestine epithelium and skin (1–5). T_{CM} are characterized by their ability to proliferate robustly and further differentiate into effector cells upon a secondary stimulation (5), whereas T_{EM} are already fully differentiated effector cells which do not expand much but instead display immediate cytotoxicity and produce functional cytokines upon a secondary challenge (2, 6). Thus, the efficacy of T_{CM} is based on the quantity of memory cells and the efficacy of T_{EM} is based on the quality of memory cells. Immediate responses from local T_{EM} cells may not be sufficient to provide sterilizing protection, but they can efficiently control the local

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infection and delay or even prevent the onset of disease, as well as reducing the potential for secondary transmission. Although T_{CM} are thought of as superior memory cells compared to the T_{EM}, most of the data that support this view are based on biased approaches that focus on T_{CM} characteristics and functions, which often bypass or overlook the contribution of T_{EM}. Nevertheless, the unique characteristics of quality-based T_{EM} allow them to rapidly sense the presence of invading pathogens at the mucosal borders and respond immediately thus preventing the initial infection and/or systemic spreading of the pathogen. The quantity-based T_{CM} on the other hand provide a massive defense once the multiplying pathogens break through the T_{EM} frontline defense or when an infection occurs systemically.

3. An innate-Adaptive Crosstalk drives the selective accumulation of mucosal T_{EM}

The process that drives the specific development and accumulation of T_{EM} at mucosal sites remains poorly defined. Nevertheless, understanding how to induce pre-existing T_{EM} cells at the mucosal interface of the intestine has significant implications for the development of effective vaccines to protect against pathogens that invade via the mucosal interfaces, such as HIV.

Currently much of the knowledge on vaccine-induced T cell-mediated protective immunity has been generated using immunization protocols and analyses that focus on- and favor T_{CM} in lymphoid tissues, which therefore unavoidably miss the specific requirements critical for tissue-resident T_{EM}. Using an oral infection model with *Listeria monocytogenes* (LM), in which bacteria enter the host through mucosal barrier, we investigated the requirements for T_{EM} generation at the intestine epithelium (7). Typically, conventional CD8αβ$^+$ intraepithelial lymphocytes (IEL) have a T_{EM} phenotype and co-express CD8αα homodimers together with CD8αβ heterodimers (1). In our recent study (7), we showed that CD8αα, induced on the most optimally activated primary CD8αβ$^+$ effector T cells, together with its high affinity ligand, the thymus leukemia antigen (TL), a non-classical MHC class I-like molecule induced on dendritic cells (DC) and constitutively expressed on intestinal epithelial cells (IEC), selectively control the survival of high affinity memory precursor cells and mucosal T_{EM} respectively.

3.1. Activation-induced CD8αα rescues CD8αβ primary effector T cells from AICD

Whereas naïve CD8αβ$^+$ T cell do not express CD8αα homodimers, they are readily and transiently induced upon antigen-stimulation (7). The induction of CD8αα is directly controlled by the TCR signal strength and the stronger the signal, the higher the level of CD8αα induction on primary CD8αβ$^+$ effector cells (7). Consequently, high CD8αα expression on primed CD8αβ$^+$ T cells marks those effector cells with the highest affinity/avidity. The induction of CD8αα is controlled by an enhancer ($E8_I$) located in the CD8α promoter (8) and high avidity/affinity $E8_I^{-/-}$ CD8αβ T cells with a deletion of the $E8_I$ enhancer fail to induce CD8αα upon activation (7, 9). Similar to our previous findings using the lymphocytic choriomeningitis virus (LCMV) system (9), also in response to an oral LM infection, antigen-specific $E8_I^{-/-}$ CD8αβ$^+$ T cells did not survive as memory cells in the spleen or the intestine (7). These observations support the notion that activation-induced CD8αα is required for the rescue of activation-induced cell death (AICD) of high affinity CD8αβ$^+$ memory precursor cells (9).

3.2. Activation-induced CD8αα rescues CD8αβ primary effector T cells from TICD

The marked presence of CD8αα-expressing CD8αβ$^+$ T cells at the mucosal interface of the intestine suggested that there must be a mechanism in place that drives the selective accumulation of high affinity/avidity T_{EM} at this mucosal border. Because of the high

affinity interaction between CD8αα and its ligand TL, induced on the priming mesenteric lymph node (MLN) $CCR7^+/CD103^+$ migratory DC (7), and constitutively expressed on the intestinal epithelial cells in close proximity of the $CD8\alpha\alpha^+$ IEL (10, 11), we postulated that a crosstalk between the T cells and the innate immune cells (DC and IEC) initiated by this receptor-ligand pair, CD8αα-TL, might be involved in the selective accumulation of the $CD8\alpha\alpha^+$ (high affinity/avidity) effector cells at the mucosal interface. Surprisingly however, in contrast to the absolute requirement for CD8αα expression, we found that, in $TL^{-/-}$ animals, $CD8\alpha\beta^+$ memory cells persist at an increased frequency, indicating a negative role of TL for the survival of activated $CD8\alpha\beta^+$ T cells (7). Consistent with this, in TL-Tg mice, forced expression of a TL transgene driven by an MHC class I promoter interfered with the survival of activated $CD8\alpha\beta^+$ T cells and completely prevented the formation of $CD8\alpha\beta^+$ memory cells in the intestine as well as in the lymphoid tissues. The TL induced cell death (TICD) of activated $CD8\alpha\beta^+$ T cells also occurred using $E8_I^{-/-}$ $CD8\alpha\beta^+$ T cells, indicating that TICD is the result of TL interaction with CD8αβ (7). The selective survival of CD8αα-expressing $CD8\alpha\beta^+$ T cells primed by TL-expressing migratory DC indicated that this adaptive-innate crosstalk drove the rescue of high affinity/avidity $CD8\alpha\beta^+$ primary effector cells that home to the intestine.

3.3. Activation-induced CD8αα rescues CD8αβ secondary effector T cells from TICD

TL constitutively expressed on the IEC in the intestine, forms a second checkpoint and eliminates weak secondary effector cells, which escaped TICD initially during their initial priming by TL negative peripheral antigen-presenting cells (APC). In support of this, we showed that adoptive transfer of sorted $CD8\alpha\alpha^{-/low}$ or $CD8\alpha\alpha^{high}$ effector cells initially primed *in vitro* in the absence of TL, to either WT or $TL^{-/-}$ hosts resulted in the accumulation of $CD8\alpha\alpha^{high}$ but not $CD8\alpha\alpha^{-/low}$ derived T_{EM} in the TL-expressing intestine epithelium of the WT mice, whereas both $CD8\alpha\alpha^{high}$ and $CD8\alpha\alpha^{-/low}$ effector cells survived as T in the EM intestine of $TL^{-/-}$ recipient mice (7). This suggested that, in addition to the crosstalk between the primary T cells and the antigen-presenting cells (APC), TL expressed on gut epithelial cells forms a second checkpoint to selectively eliminate effector cells with weak affinity/avidity for the antigen and prevent them from accumulating as T_{EM} at the mucosal borders. Consistent with this, we also showed, using altered peptide ligands (APLs) with varied affinities, that priming with low affinity peptides led to the generation of sub-optimal primed memory cells in the lymphoid tissues, but not to the accumulation of T_{EM} in the intestine (7).

4. Conclusion

The activation marker CD8αα, induced on high-affinity/avidity effector $CD8\alpha\beta^+$ T cells together with TL, induced on APC and constitutively expressed on the intestinal epithelium, establish an adaptive-innate crosstalk, which prevents weak primary and secondary effector cells from accumulating at the mucosal interface. This selective process also preserves the most sensitive effector cells, which are able to respond rapidly and resist the initial infection and consequently also prevent excessive and potentially damaging inflammatory immune responses.

5. Future Prospective

Our data demonstrate that an affinity/avidity-based selective crosstalk between innate and adaptive immune cells is essential for the generation and preservation of memory T cells that form the critical first line of defense at mucosal interfaces. These new findings, define a fundamentally new concept for our understanding of immune memory and for the design of strategies to induce effective vaccine-induced immunity. It is evident from recent advances, including our study here and other published data (4, 7, 12, 13), that in order to generate

successful vaccines, it is important to mirror the endogenous immune responses and adapt the design based on the nature of pathogens and the route of infection. For example, most infections, including HIV and SIV infections, are acquired across mucosal barriers, and several studies have demonstrated that local $CD8^+$ CTL responses play a crucial role in the initial containment and early control of pathogen replication (14–18). Therefore, for successful vaccination-induced pre-existing protective immunity, it is of utmost importance to induce a local and highly sensitive and effective $CD8^+$ T_{EM} layer in addition to T_{CM} cells that reside in lymphoid tissues. Based on our findings, this would imply that for strategies, which aim to induce protective immunity at mucosal sites, it is important to screen for vaccines, which mediate strong induction of CD8αα during the initial immunization. This will warrant the selective accumulation of high affinity/avidity mucosal T_{EM} that can sense low doses of the pathogen and respond rapidly and with enhanced efficacy to provide effective protection against pathogens that invade via the largest yet most vulnerable interfaces of the body.

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