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From the Thymus to Longevity in the Periphery

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Abstract

An important attribute of the adaptive immune system is the ability to remember a prior encounter with a pathogen; an ability termed immunological memory. *Bigger, better* and *stronger* responses are mounted upon a secondary encounter with the pathogen potentially resulting in clearance of the infection before the development of disease. We will review recent advances in the field of memory CD8⁺ T cell differentiation focusing on both intrinsic and extrinsic factors that govern the development of T cell memory.

Where it all begins

T cell development begins within the thymus from bone marrow derived progenitor cells and involves the acquisition of a T cell receptor (TCR) that fits with the allelic forms of the MHC molecules expressed in the individual. TCR diversity is vast arising from the imprecise random rearrangement of inherited gene segments for each chain. Prior to egress from the thymus the majority of cells that bear either self reactive or non-functional TCR rearrangements are purged from the repertoire. Positive selection results in the survival of cells that express a TCR capable of interacting weakly with self MHC plus self peptide while negative selection deletes cells that express TCRs that recognize self peptide/MHC ligands with too high affinity. Thus, naïve T cells that exit the thymus and enter the blood stream are self tolerant and self MHC restricted.

Naïve T cells are long-lived resting cells and their rate of attrition is matched by the output of new thymus emigrants [1]. Their survival and slow rate of division is dependent on the recognition of MHC-self peptides and exposure to homeostatic cytokines, such as IL-7 [2]. Fibroblastic reticular cells, a component of lymph node stroma located within the T cell zone, were recently demonstrated to be a major source of peripheral IL-7 [3]. Infection generally results in the massive expansion of naïve T cells bearing a TCR capable of recognizing pathogen-encoded peptide ligands. Many factors influence the magnitude of the developing T cell response, including antigen dose, [4] the duration of antigen presentation [5] and the affinity of the TCR-ligand interaction. Using a panel of *Listeria* recombinants expressing peptide variants with varying affinity to the OT-I TCR, it was demonstrated that T cells with low avidity for antigen are activated during a primary response. However, they are expelled from lymphoid organs earlier than T cells with higher avidities and thus generate smaller cohorts of effector T cells and subsequently contract into smaller fractions of the memory pool [6]. T cells, unlike B cells do not undergo classical affinity maturation by mutation of their antigen receptors. Nonetheless during the course of the immune response there does appear to

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be a preferential expansion of T cells bearing the highest affinity TCR which ultimately results in an increase in the overall affinity of the T cell response [7–9].

Following clearance of the pathogen, generally 90–95% of the effector T cell population undergoes Bim dependent apoptosis during the contraction phase. The remaining 5–10% of cells that survive enter the memory pool [10]. What determines if a cell lives or dies? Actively dividing cells are dependent on cytokines such as IL-4, IL-2, IL-7 and IL-15 for survival. During a primary T cell response, as antigen is cleared there is a reduction in the levels of cytokines that support T cell survival. This famine in pro-survival cytokines is thought to drive the death of large numbers of effectors. Indeed, the exogenous introduction of pro-survival cytokines (IL-15 and IL-2) during the contraction phase can increase the size of the developing memory T cell population [11,12]. Conversely, removal of IL-15 receptor from the surface of macrophages results in a more profound loss of effectors [13]. Nonetheless, it has been demonstrated that the fate of effector T cells is predetermined prior to contraction suggesting that competition for limited resources is not the major factor dictating survival. The effector population is heterogeneous, and subsets of effectors that are fated to die can be distinguished from others that contribute to memory [14]. When the number of effector cells competing for survival is artificially increased, this has no effect on the rate or extent of contraction, again arguing that competition for survival factors is not the cause of effector cell death [15].

New flavors of memory

Seminal work by Sallusto and Lanzavecchia introduced the concept that memory T cells are heterogeneous [16]. This was first observed in human blood, although the murine counterparts were discovered soon after. Central memory T cells circulate between secondary lymphoid organs, express the LN homing molecules CCR7 and CD62L, do not exhibit immediate effector functions but can undergo significant recall proliferation upon antigen re-encounter. Effector memory T cells classically lack LN homing molecules and are thus generally deposited in and circulate through peripheral tissues. They exhibit immediate effector function upon antigen recognition (Figure 1) [17]. With time following an infection, the memory pool gradually changes converting from an effector memory dominated pool to a more stable and long lived central memory population. It has been more than a decade since it was first shown that memory T cells come in different flavors, but the past year has seen the characterization of two new memory CD8⁺ T cell subsets which fall outside the effector and central memory dichotomy.

Resident memory T cell (Trm)

It is well appreciated that peripheral tissues house a large proportion of the memory T cell pool [18] although it was thought that these were simply effector memory T cells trafficking through the tissue as part of their immunological surveillance. Carbone and colleagues defined a population of peripherally deposited memory T cells that are both phenotypically and functionally distinct from memory T cells within the circulation - they were coined resident memory T cells (Trm) [19]. Memory CD8⁺ T cells can persist long term in sensory ganglia harboring latent herpes simplex virus (HSV) [20] as well as in healed HSV skin lesions [19, 21]. These cells were shown to be permanently resident within the skin and sensory ganglia. In general, Trm cannot leave the tissue in which they reside and thus have a limited role in protecting a local site from either secondary infection or reactivation of a local latent infection. Their retention appears linked to the up-regulation of certain adhesion molecules which fasten them to the extracellular matrix [22]. Upon secondary encounter with their pathogen Trm rapidly acquire effector function [23] and in certain situations can undergo extensive proliferation *in situ* in response to antigen presented by inflammatory dendritic cells [24]. The factors maintaining these T cells within the tissue for long periods have yet to be elucidated.

The T memory stem cell (Tscm)

In many ways all memory cells are stem cells. At least, when they are labeled with CFSE, transferred and challenged with antigen they all proliferate. Whether every proliferating memory cell produces effector and memory progeny is not known. The cardinal feature of a stem cell is the ability to self renew. Gattinoni et al [25] demonstrate that CD8⁺ T cells can acquire stem cell like properties if they receive signaling through the Wnt- β -catenin pathway during activation. Activation of the Wnt signaling pathway in naïve T cells during stimulation impeded T cell proliferation and the acquisition of effector function but the memory population that did form could self-renew and differentiate into various effector and memory CD8⁺ T cell subsets- this population was termed T memory stem cells (Tscm). Patients receiving repeated bouts of lympho-ablative chemotherapy retain protective T cell memory against EBV and CMV. This finding led Turtle et al [26] to identify a phenotypically and functionally distinct subset of memory T cells, CD161^{hi}, IL-18R⁺, with high expression of ABC-transporters that conferred resistance to chemotherapeutic drugs. The defined subset exists in the central and effector memory pool. Whether they form a stable subset of memory and have a memory maintenance role outside reconstitution following immune ablation awaits analysis.

Intrinsic factors that govern memory development

Two key transcription factors, T-bet and Eomesodermin (Eomes), greatly influence memory CD8⁺ T cell development [27,28]. How these transcription factors influence the T cells fate appears linked to their control of the expression of IL-7R and IL-15R [29,28]. Signaling through these receptors is known to promote memory T cell survival and homeostasis. Expression of these transcription factors is regulated by inflammatory cytokines, particularly IL-12. Elevated levels of IL-12 promote T-bet expression and suppress eomes expression favoring the development of short lived effector cells. Low levels of IL-12 result in repression of T-bet and expression of eomes this combination of gene expression favors the generation of memory T cells [29,30].

Inhibitor of DNA binding 2 (Id2), was identified as another transcription factor important in memory T cell development. An antagonist of E protein transcription factors, Id2 is upregulated in CD8⁺ T cells during infection and remains elevated in memory CD8⁺ T cells. Although Id2-deficient naïve CD8⁺ T cells undergo normal proliferation following pathogen encounter, effector CD8⁺ T cells exhibited elevated expression levels of Bim and CTLA-4 and reduced levels of Bcl-2 which made these cells more prone to apoptosis [31]. More recently Blimp-1, a transcription repressor, initially identified as a critical regulator of plasma cell differentiation has been linked to T cell homeostasis and memory development [32,33]. Blimp-1 promotes the formation of short lived effector cells and promotes the trafficking of these cells into peripheral tissues [34,35].

Where do memory T cells come from?

A study by Stemberger and colleagues demonstrated that the fate of a naïve T cell is not pre-determined prior to activation. Specifically they showed that daughters of a single cell could develop into both effector cells and memory T cells [36]. Whether memory T cells arise directly from naïve T cells or transition through an effector phase prior to adopting their memory status remains controversial. Currently there are two models to describe memory T cell development. The asymmetrical division model proposes that following activation the T cell asymmetrically divides resulting in the unequal distribution of proteins and mRNAs that are important in skewing cell fate [37]. Specifically one daughter, resembles an effector cell which gains cytolytic effector function, loses replicative potential and is doomed to die, while the other daughter displays an opposing phenotype resembling a more quiescent long lived memory cell. Further support for this model comes from Teixeira and colleagues [38] who introduced point

mutations within the TCR β chain of the OT-I TCR. These mutations had no effect on the development of effector cells during primary challenge although there was severe impairment to the memory T cell pool. The defect was attributed to poor localization of the TCR to the immunological synapse which in turn lead to less downstream NF- κ B induction. This work favors a model where effector and memory T cell development represent disparate pathways.

The second model, termed the 'linear differentiation' model proposes that memory T cells develop from effector T cells [39]. Support for this linear model of development has surfaced recently with a study by Bennard et al [40] who endeavor to ascertain whether cells expressing the effector molecule granzyme B (or their progeny) can develop into memory cells. Using a transgenic mouse where granzyme B expressing cells are indelibly marked they show that cells expressing an effector phenotype during the primary infection could form functional memory. Furthermore, Harrington et al show that CD4⁺ T cells expressing IFN γ during the primary response can also progress into the memory phase [41]. Although it seems apparent that cells exhibiting effector function during the primary infection can form memory, whether acquisition of effector function is a prerequisite for a cell to transition into memory is still unclear. The fact that the slow naïve T cell division that occurs under lymphopenic conditions in the absence of pathogen infection results in the differentiation of memory cells might suggest that effector development is not a prerequisite [42,43].

Fading memories?

Every infection severe enough to engage an adaptive immune response alters the composition of the memory T cell pool. Pioneering work by Selin and Welsh demonstrated that subsequent heterologous infections induced the non-specific decay or attrition of pre-existing memory CD8⁺ T cells [44,45]. It was proposed that over time, following infection by a plethora of pathogens, memory T cells specific for past infections are progressively diluted out by memory T cell populations directed against more recently encountered pathogens. A recent study questioned this paradigm [46]. Using a prime-boost immunization strategy it showed that the size of the memory T cell compartment is not fixed and can indeed increase to accommodate newly established memory populations at no numerical expense to any other T cell subset, naïve or memory. Huster et al [47] corroborated these findings demonstrating very little numerical attrition of a pre-existing *Listeria* memory CD8⁺ T cell population following prime-boost vaccination with modified vaccinia Ankara virus. However, the pre-existing memory that persisted was unable to provide immediate protection against high dose *Listeria* challenge. The defect was attributed to an impairment in killing and cytokine production by effector memory cells. Thus, although subsequent infection may not greatly alter the magnitude of the pre-existing memory pool it may alter its functionality. Although further investigations are clearly warranted to decipher if attrition, either numerical or functional is occurring following repeated bouts of infection, cumulatively these studies highlight an important issue, that is, an individuals immunological history will affect how they combat subsequent infections.

Conclusion

Following activation a naïve T cell has two fates become a senescent effector and die or differentiate into a memory T cell and live. When does this fate decision happen during an immune response and what are the extrinsic and intrinsic factors that govern this decision remain important issues.

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Figure 1. The changing faces of a T cell as it progresses through various life stages

Naïve (N) T cells upon interaction with an antigen bearing DCs undergo activation and clonal expansion, forming a large effector (E) T cell pool. The vast majority of effector cells (senescent effector) undergo apoptosis during the contraction phase. Memory (M) T cells are antigen experienced cells that survive the contraction phase and are classically divided into effector (Tem) or central (Tcm) memory. Cell transitions that are still contentious are depicted with a dotted line.