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Review

Memory T lymphocytes

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Abstract. Immunological memory protects organisms from recurrent challenge by pathogens. The persistence of a heightened reactive state initiated by antigenic challenge is mediated by long-lived memory lymphocytes. The survival of memory T cells is thought to require stimulation through the T cell receptor (TCR), sometimes by persistent antigen. However, memory T cells can survive in the absence of antigen, in which case TCR stimulation provided by cell surface self-peptide/major histocompatibility complex (MHC) molecules and cytokines are required to sustain memory T cells. Recent work using mouse models has provided insights into the origin of memory T cells. Understanding the mechanisms that underlie the differentiation and persistence of memory T cells may improve the effectiveness of vaccines through the induction of T cell memory.

Key words. Immunological memory; T lymphocyte; antigen; host defense; lymphocyte survival; immunity to infection; vaccine; apoptosis.

Immunological memory

It has been known for some time that infection by a pathogen early in life can give long-lived protection against recurrent infection (reviewed in [1]). Typical immune responses to infectious agents are followed by a state of long-lived memory during which subsequent contact with antigen leads to a more effective response and rapid rejection of the pathogen. Memory is carried by both T and B cells and is due to both an increase in the frequency of specific lymphocytes and a heightened sensitivity to antigen (antigen hyperreactivity).

Both CD4 and CD8 T cell responses can be broken down into three distinct phases: (i) activation and expansion, (ii) death, (iii) stability and memory (fig. 1). During the initial phase, which lasts about a week in vivo, antigen-driven expansion of specific T cells and differentiation into effector cells occurs. In viral systems, 100- to 5000-fold expansion of the virus-specific $CD8^+$ T cells takes place [2]. Subsequently, a period of death ensues (between days 7 and 30 in vivo), during which most of the activated T cells undergo programmed cell death, or apoptosis, and effector activity declines as the amount of antigen declines. This contraction of the T cell response is as dramatic as the expansion, and in most cases greater than 95% of the antigen-specific cells disappear. This phenomenon, termed activation-induced cell death (AICD), thereby regulates cell numbers and maintains homeostasis.

The process of AICD involves several mechanisms that induce apoptosis of activated effector cells. The Fas/

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Fas-ligand pathway can potently induce AICD [3]. However, other mechanisms have also been shown to induce this homeostatic mechanism. Members of the tumor necrosis factor (TNF) play important roles in the induction of AICD [4], as do pro-apoptotic members of the Bcl-2 family [5]. Effector molecules such as perforin have also been implicated in the induction of the apoptosis of cytotoxic effectors [6].

Despite the efficiency of AICD, the expression of several molecules may allow cells to escape apoptosis. Some of these factors are secreted growth factors such interleukin-2 (IL-2), IL-4, IL-7 and IL-15, which have been shown to be antiapoptotic in vitro as well as in vivo [7, 8]. Others are antiapoptotic members of the TNF family, such as CD30 [9] and 4-1BB [10, 11]. In addition, several Bcl-2 family members, such as Bcl-x, have been shown to inhibit apoptosis triggered by a variety of stimuli [12]. The action of these antiapoptotic proteins may allow a cell to escape AICD and form long-living memory cells.

The third phase of the T cell response is characterized by a creation of a pool of memory cells that can persist for many years. Accelerated T cell responses seen upon reexposure to antigen are due to increases in the frequency of antigen-specific T cells (a 5- to 100-fold increase, depending on the system) and also to qualitative changes in memory cells that result in antigen hyperreactivity.

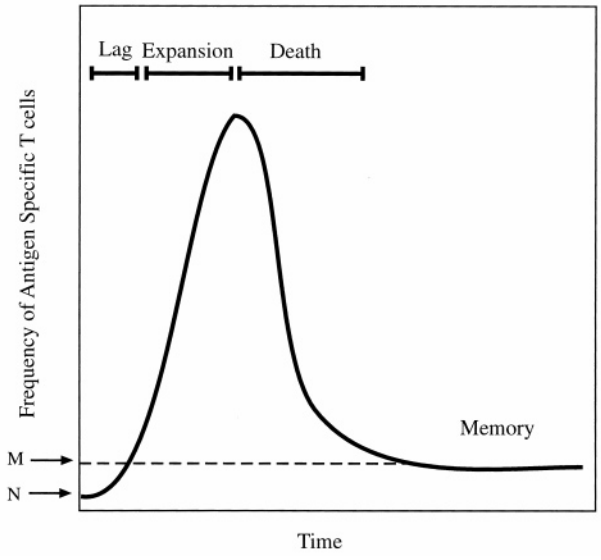

Figure 1. Model of in vivo immune response to an acute viral infection. CD8 + T cell responses to viral infections consist of four different phases: lag phase, expansion, death and memory. The frequency of antigen-specific T cells is represented at the naive level (N) and the memory level (M). Adapted from [1].

Memory T cell phenotype

The phenotype of cell surface markers expressed by T lymphocytes is useful in differentiating between cells at various stages of development and activation (table 1). However, the cell surface molecules used to distinguish memory cells from naive cells are also present on short-lived effector cells. Therefore, to distinguish between memory and effector T cells, it is best to characterize the function and persistence of potential memory cells.

There are two main effector functions which have been shown to be mediated by memory T lymphocytes: cytokine secretion (both $CD4^+$ and $CD8^+$ subsets), and cytolytic function (the $CD8^+$ subset). Memory T cells are able to carry out effector function more efficiently than naive T lymphocytes. In many cases, the memory cells secrete cytokines more quickly, in greater amounts and require less antigenic stimulation than naive cells to do so. The ability to detect the secretion of cytokines from single cells has allowed researchers to measure the numbers of memory cell precursors taken directly ex vivo, allowing them to quantitate the number of antigen-reactive precursors [13]. These studies are performed by examining activated cells for the expression of phenotype surface markers, then determining the patterns and efficacy of cytokine secretion after antigenic challenge. In murine studies, $CD8^+$ memory T cells secrete a greater amount of interferon γ (IFN-γ) more quickly than naive cells after restimulation [14–16]. Similar studies on human memory T cells have also shown faster secretion of IFN-γ, tumor necrosis factor α (TNFα) and interleukin-4 (IL-4) [17–20]. Interestingly, in one such study, memory cells were shown to be capable of secreting IFN-γ within 6 hours of antigen contact, indicating that, in contrast to naive cells, memory cells are capable of effector function without further cell division or differentiation [13]. In addition, the cytokine expression pattern of memory T cells remains stable in the memory pool. Thus, cells that have acquired either a T helper cell 1 (Th1) or T helper cell 2 (Th2) cytokine profile will secrete the same cytokines after antigen rechallenge [21], and furthermore, memory CD8 T cell cytokine secretion profiles are also maintained [22].

In addition to their cytokine production, memory T cells have other mechanisms that allow them to respond better to antigen rechallenge. In both human and murine systems, memory cells have been shown to proliferate more vigorously to antigen than naive cells [17, 23]. This proliferation was induced by much lower antigen doses (10- to 50-fold less) than naive cells [24, 25]. Upon reactivation, murine memory T cells migrated to the sites of infection more effectively than naive cells [26]. Perhaps most important, memory $CD8^+$ T cells retain the expression of effector molecules such as intracellular perforin, Fas ligand and

Table 1. Summary of the expression of surface markers on murine and human T lymphocyte phenotypic surface markers on cells of different activation states (x, lowest expression; xxxx, highest expression).

Molecule	Naive	Effector	Memory	Reference
Mouse				
CD44	x	xxx	xxx	[23, 25, 29, 42]
Ly-6C	x	xx	xxx	[14, 24, 25]
CD69	xxx	x	xx	[24, 25]
CD62L	xxxx	x	xx	[23, 29, 42]
CD25	x	xxx	xx	[24, 25]
CD45RB	xxx	xx	x	[29]
ICAM-1	x	xx	xxx	[76]
LFA-1	x	xx	xxx	[76]
CD43	x	xx	xxx	[76]
a4b1 (VCAM-1)	x	xx	xxx	[76]
a4b7	x	xx	xxx	[76]
CD95 (Fas)	x	xxx	xxx	[25]
Human				
CD45RA	xxx	xxx	x	[17, 77, 78]
CD45RO	x	x	xxx	[17, 77, 78]
CD44	x	xxx	xxx	[19]
CD62L	xxxx	x	x	[18]
CD11a	x	xxx	xxx	[18]
CD18	x	xxx	xxx	[18]
CD29	x	xxx	xxx	[18]
CD49e	x	xxx	xxx	[18]
CD49d	x	xxx	xxx	[18]
LFA-2	x	xxx	xxx	[18]
CD95	x	xxx	xxx	[18]
LFA-1	x	xxx	xxx	[78]

granzyme B [17, 27, 28]. The retention of these effector molecules in memory $CD8^+$ T cells may account for the observation that memory cells are capable of cytolysis more rapidly than naive cells. It has been reported by several groups that memory phenotype cells are capable of direct cytolysis without restimulation [26–30]. In contrast, others have shown that memory cells actually respond poorly without reactivation, but upon reactivation they exhibit potent cytolytic activity [18, 22, 31, 32]. It is interesting to note that in the latter studies, unlike naive cells, memory cells did not require cell division to perform effector function [31, 32]. Differences in the cytotoxic function of memory $CD8^+$ cells may reflect differences in the antigens used to generate them.

Despite some controversy in the field, most researchers agree that antigen hyperresponsiveness and persistence are hallmarks of memory T cells that distinguish them from quiescent naive and short-lived effector cells [33].

The role of persistent antigen in the survival of memory T cells

Determining what factors generate and maintain memory T cells is critical for our understanding of immunological memory. One model postulates that long-term memory is dependent on persistent antigenic stimulation [2, 34]. This view is based on experiments in which adoptively transferred $CD8^+$ memory T cells could not be detected for more than a few weeks in naive recipient mice without secondary challenge. In the case of viral infections, antigen may well persist over a prolonged period of time, particularly following DNA viral infections [2]. Therefore, as is the case for B cell memory [35], small amounts of antigen, derived from an initial infection, persist in specialized depots such as follicular dendritic cells, ensuring that a small subset of T cells is maintained in an activated state long after a pathogen is cleared. However, persistence of antigen is unlikely to explain the long-term memory established by immunization with toxoids or killed organisms. Furthermore, prolonged T cell memory is found for viruses that are unlikely to be reencountered and which do not persist in the host genome, implying that $CD8^+$ T cell memory might be independent of continued antigen exposure [36, 37].

Several reports indicate that memory $CD8^+$ T cells appear to persist in the absence of antigen [38–40]. In these experiments, $CD8^+$ T cells were activated with antigen, then carefully purified away from virally infected, antigen-bearing cells and adoptively transferred to antigen-free mice. After a period of time (usually at least 10 weeks), these recipients were rechallenged with antigen and the potency of the cytotoxic T lymphocyte (CTL) response measured.

Adoptively transferred $CD8^+$ T cells that retained the expression of activation markers and generated a CTL response more vigorous than naive $CD8^+$ T cells were designated memory T cells. More recently, the persistence of TCR-transgenic $CD8^+$ memory cells in the absence of antigen has been demonstrated [23, 41]. Since the $CD8^+$ T cells activated in these experiments expressed a transgenic TCR, it was possible to purify greater numbers of cells and detect the presence of memory cells on the basis of TCR expression as well as antigen reactivity. The use of TCR-transgenic models for memory $CD8^+$ T cell persistence has also allowed investigators to activate naive cells in vitro with peptide antigen [42]. Antigen-peptide/class I MHC complexes on the surface of cells are short lived (half-life is about 8 h), therefore the contribution of peptide antigen to the long-term persistence of memory $CD8^+$ T cells is negligible. In addition, similar experiments in T helper cell models lead to the conclusion that memory $CD4^+$ T cells also do not require antigen for long-term persistence [21].

Although persistent antigen may not be an absolute requirement for CTL memory in organs of the central immune system such as the spleen, the presence of antigen-enhanced, antiviral CTL memory has been demonstrated in mucosal tissues [43]. It may be possible that the factors that ensure the survival and activation of memory T cells may be different in nonmucosal versus mucosal tissues. Resolution of the issue of the role of antigen in T cell memory persistence is important for practical reasons (vaccine design) and because it defines how we view immunological memory. If continuous antigenic stimulation is essential for maintaining memory, then one may question the very existence of immunological memory [23].

Role of self-reactivity in maintaining T cell memory

Although persistent antigen is not required to deliver the TCR stimulation that ensures the survival and activation of memory T cells, recent work has indicated that cross-reactive interaction between the TCR and self-MHC may be important in maintaining memory T cells [33]. Several groups of researchers have reported the requirement of class I [41, 44, 45] and class II [42, 46–48] MHC expression for the in vivo survival of naive $CD8^+$ and $CD4^+$ T cells. These findings imply that the survival of naive T cells requires a low level of stimulation through the TCR by contact with self-MHC. There is general agreement that naive T cells are quiescent cells that rarely enter the cell cycle unless confronted with a specific antigen [49], so the stimulus delivered by the TCR expressed on naive T cells with self-MHC probably does not lead to T cell activation. How such signaling maintains cell survival without entry into the cell cycle remains unclear.

The requirement of class I MHC expression has been demonstrated for the survival and maintenance of the activated phenotype for male-specific (anti-H-Y) TCR transgenic $CD8^+$ memory cells [42]. Mature T cells express TCRs which are weakly reactive to self-peptide/MHC molecules as a result of thymic positive selection [50, 51]. Thus, memory T cells could persist not because they have an inherently longer lifespan, but because they receive constant low-level stimulation from the self-peptide/MHC molecules in the absence of antigen, which provides the signaling for positive selection during development (fig. 2). Although there is evidence to suggest that thymic self-peptides are specifically recognized during the positive selection of T cells [52, 53], the degree of specificity of TCR cross-reactivity with self-peptide/MHC complexes remains to be determined.

Role of growth factors in the survival of memory T cells

It is presumed that T cell proliferation in vivo reflects a TCR-mediated polyclonal response to antigen. However, the massive proliferation of T cells seen in viral infections is suggestive of a bystander reaction driven by cytokines instead of the TCR [54, 55]. The antigen specificity of antiviral memory CTLs following infection with heterologous viruses appears to be cross-reactive [56]. This antigen-independent cytolytic activity of memory CTLs may at least in part be due to bystander activation brought about by infection with unrelated virus. In an elegant set of experiments, Tough et al. [57] demonstrated that bystander proliferation of memory $CD8^+$ T cells is mediated by type I interferon (IFN I). In mice, T cell proliferation after viral infection preferentially affected a subset of $CD8^+$ cells that had a memory phenotype ($CD44^{hi}$) but not naive $CD8^+$ T cells ($CD44^{lo}$). This proliferation was mimicked by injection of an inducer of IFN I [poly (I:C)] and also by purified IFN I. After the stimulation of antigen-specific $CD8^+$ T cells, IFN I potentiated the clonal expansion and survival of $CD8^+$ T cells responding to specific antigen. Stimulation of these cells appeared to be TCR-independent, because equivalent proliferation occurs when $CD8^+$ T cells are exposed to Poly I:C and transferred to β2-microglobulin-negative mice (class I MHC-negative). Lipopolysaccharide (LPS), another strong inducer of IFN I, protected T cells from AICD [58] and induced the selective stimulation of $CD44^{hi}$ $CD8^+$ cells in vivo [59]. Therefore, IFN I may play a role in the generation and maintenance of specific memory. Since IFN I inhibits proliferation of $CD8^+$ T cells, IFN I-induced proliferation of $CD8^+$ T cells in

vivo presumably occurs indirectly through production of secondary cytokines by non-T cells. One such cytokine, IL-15, when injected into mice closely mimicked the effects of IFN I in causing strong and selective stimulation of memory-phenotype $CD44^{hi}$ $CD8^+$ T cells [60]. IL-15 has been shown to protect against Fas-induced apoptosis in vivo, as well as by in vitro death induced by anti-Fas, anti-CD3 or dexamethasone of activated T cells [8]. This finding has been confirmed in mice deficient in the IL-15 receptor α subunit gene which have a lower number of $CD44^{hi}$ $CD8^+$ T cells [61].

As well as IL-15, other inflammatory cytokines can protect T cells from AICD in vitro and so may have a potential role in the development and survival of memory T cells. The cytokines IL-2, IL-4 and IL-7 prevented the death in vitro of in vivo activated T cells, and IL-2 and IL-4 can protect T cells from AICD in vivo [7]. These cytokines share a component of their receptors, the common γ chain (γc). Therefore, their collective ability to protect T cells from AICD may be mediated by signals involving γc. Consistent with a role in rescuing activated T cells from apoptosis, various cytokines have also been implicated in the survival of naive T cells. The cytokines IL-6 [62], IL-4 and IL-7 [63] prolong the life span of resting T cells in vitro, whereas IL-4 and IL-7, but not IL-6, protect T cells from radiation-induced apoptosis [64]. It is now well established that cytokines that are secreted by non-T cells play a role in maintaining activated and naive T cell homeostasis (fig. 2).

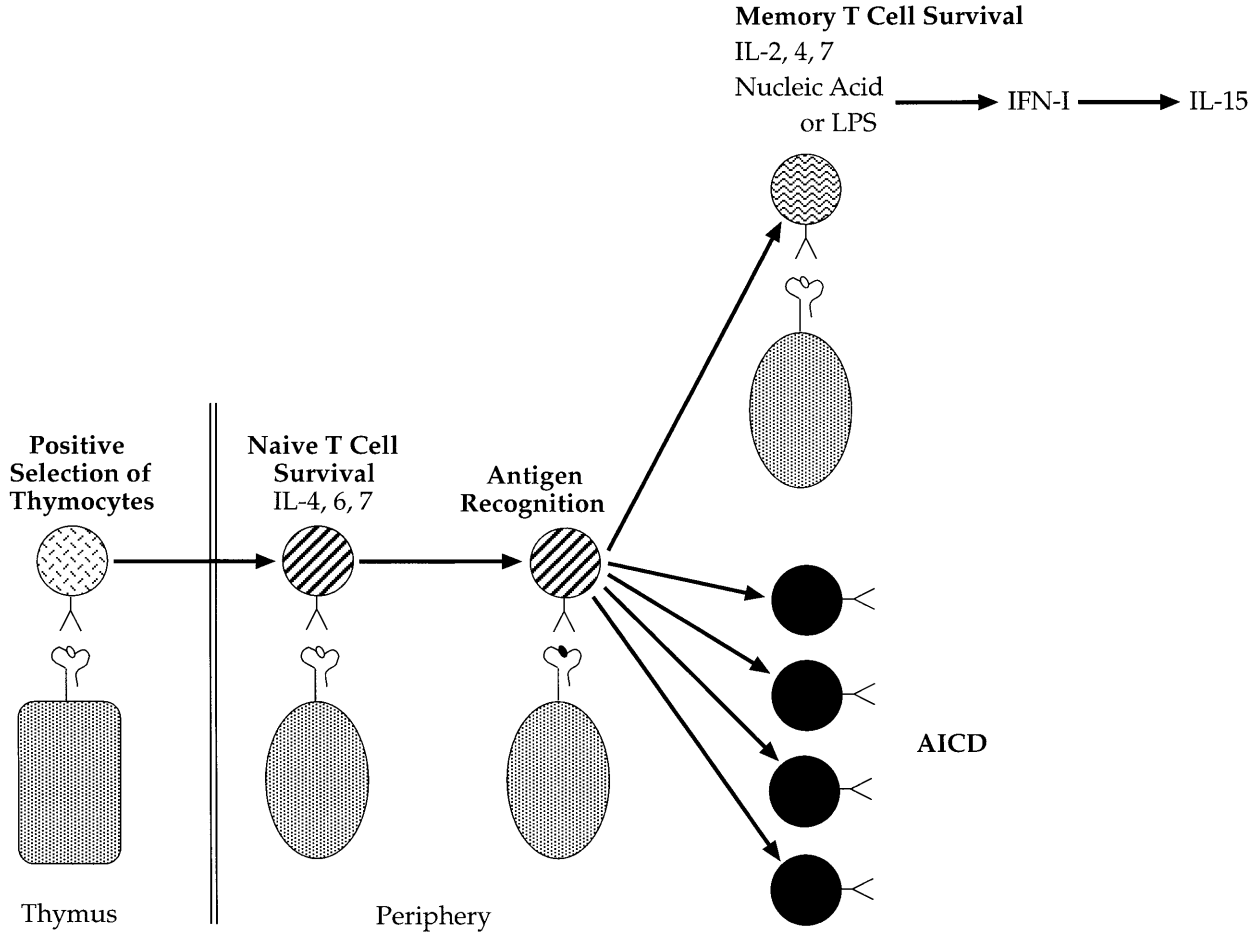

Figure 2. Model for the survival of T lymphocytes. Recognition of self-peptide/MHC molecules (self-peptide: open circle) on the surface of thymic stromal cells by the TCRs of thymocytes rescues thymocytes from apoptosis and leads to positive selection of T cells which express self-reactive TCRs. Engagement of self-peptide/MHC by TCRs on naive T cells is required for survival, as are certain cytokines. Recognition of antigen-peptide/MHC (antigen-peptide: filled circle) triggers the proliferation of activated T cells and the differentiation into effector cells, most of which die through apoptosis (AICD), and memory T cells. The survival of activated T cells (presumably including memory T cell precursors) is enhanced by IFN I following bacterial [via lipopolysaccharide (LPS)], or viral infection (via nucleic acid) which leads to the production of IL-15. Other cytokines have also been implicated in the survival of activated T cells.

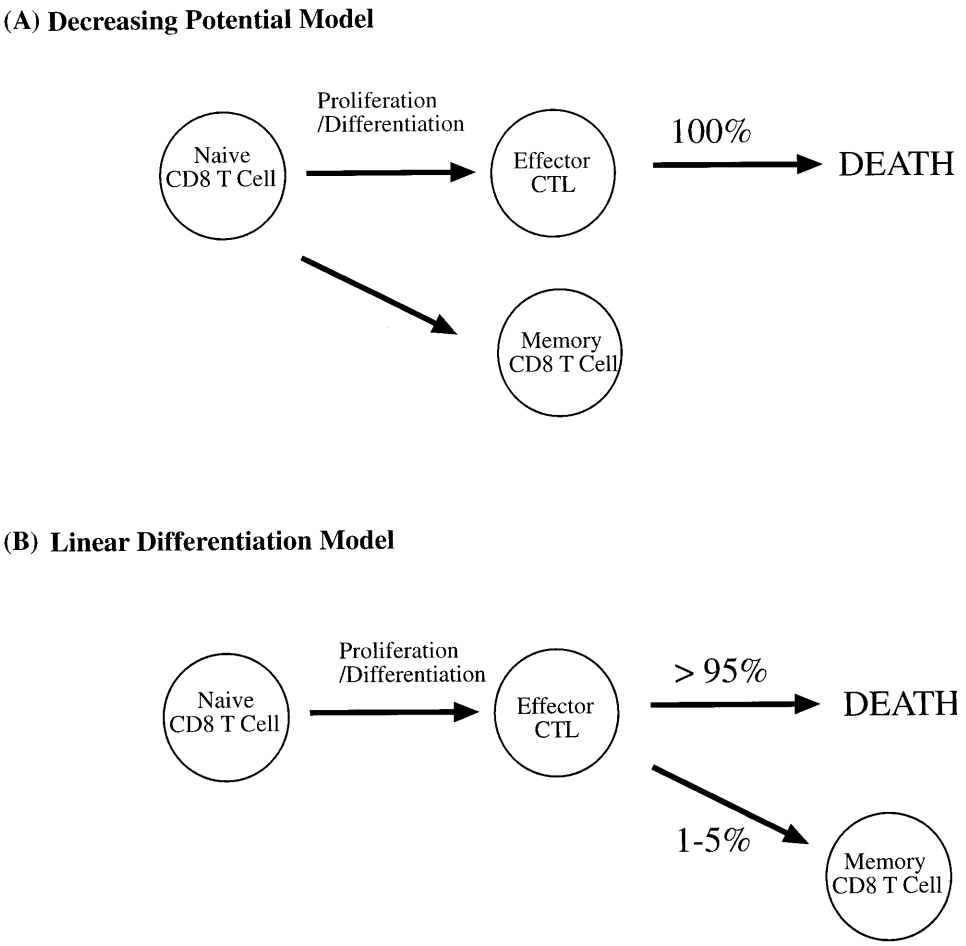

Figure 3. Models for memory cell differentiation. (*A*) The decreasing potential model states that memory cells originate from cells that do not become effectors. (*B*) The linear differentiation model states that memory cells are derived from effector cells that escape death. Adapted from [1, 66].

Experiments in which mice were infected with different viruses revealed that although the size of the memory cell pool remained constant, the composition of the pool changed after infection with heterologous virus [65]. This resulted in an overall decrease in the frequency of memory cells specific for an individual virus. Thus, the effect of cytokines in memory T cell survival may be to generate the microenvironment that supports the survival of a defined pool size of memory cells.

Differentiation of memory T cells

The precise lineage relationship between memory and effector cells is not well understood. One possibility is that the presence of large amounts of antigen plus costimulation, in the appropriate cytokine environment, leads to the differentiation into effector T cells, all of which eventually die (fig. 3). This model, known as the decreasing potential model [1, 66], proposes that memory T cells are generated when one or more signals necessary for terminal differentiation into effector cells are lacking, as antigen and infection are waning. Therefore, memory cells arise from precursors that are not fully differentiated effector cells. Another model of memory cell differentiation, the linear differentiation model, predicts that memory cells arise directly from the few surviving effector cells which evade AICD after antigen stimulation. The decreasing potential model has to provide a mechanism for the differential stimulation of precursors into either effector or memory cells, whereas the linear differentiation model has to incorporate a mechanism for discriminating between effectors that die and those that live to become memory cells.

The dichotomy of effector B cell and memory B cell differentiation is well established [1, 35, 66–72]. Differences in antigen dose and cytokine concentrations favor the differentiation of naive B cells into antibody-secreting plasma cells or memory B cells. Unlike B cells, T cells lack a convenient marker that allows the discrimination between effector and memory cells. Therefore, effector and memory T cells have to be defined functionally. The key difference between and effector and memory $CD8^+$ T cells is that memory T cells can survive in the absence of antigen, whereas effector cells can not. Experiments investigating the costimulatory requirements for production of memory or effector $CD8^+$ T cells in vivo provide evidence that suggests that effector and memory T cells may differentiate along separate pathways. Using mice which lack the expression of genes encoding costimulatory receptors (heat-stable antigen [HSA] or CD28 [73, 74]), it was shown that costimulation through either HSA or CD28 could give memory $CD8^+$ T cells, but the production of effector $CD8^+$ T cells required costimulation through CD28 [75]. In this study, the generation of memory T cells was studied in the presence of persistent antigen in the form of virus; therefore, the possibility exists that the cytolytic activity detected upon rechallenge was not due to the reactivation of resting memory $CD8^+$ T cells but rather due to a low level of persistently activated CTLs. Support for the linear differentiation model comes from adoptive transfer experiments with TCR-transgenic cells that are activated with antigen, then adoptively transferred to antigen-free recipient mice [23]. Activated $CD8^+$ T cells give rise to a pool of resting memory T cells that survive for up to 100 days in the absence of antigen. However, it is still unclear whether the memory T cells were the direct descendants of activated $CD8^+$ T cells that had undergone full differentiation into effector CTLs. Recently researchers used a novel cell division 'counting' system to examine the origin of $CD8^+$ memory cells. Using an adoptive transfer system, they tested whether pre- or posteffector CD8 cells give rise to memory cells [28]. These studies concluded that memory CD8 cells were the progeny of postcytolytic effector cells that had escaped AICD and therefore support a linear differentiation model of memory cell development.

Conclusion

Although the field of T cell memory is an area of intense research, for the most part our understanding is limited. However, recent work has allowed us to draw some general conclusions. Memory T cells are long-lived cells which exhibit antigen hyperreactivity and can survive in the absence of antigen. In the absence of antigen, signals provided by self-peptide/MHC complexes are required for the persistence of long-term memory cells. Memory $CD8^+$ cells are the progeny of posteffector cells that escape AICD. These findings provide a framework to allow researchers to address unanswered questions concerning memory cell development: How do memory cell precursors escape AICD? How is memory cell hyperresponsiveness generated? And how is the homeostasis of the memory cell pool maintained? A better understanding of these issues may lead to improvements in the design of vaccines which can be used to generate potent protective T cell memory against pathogens and tumors.

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1 Ahmed R. and Gray D. (1996) Immunological memory and protective immunity: understanding their relationship. Science **272:** 54–60
2 Oehen S., Waldner H., Kundig T. M., Hengartner H. and Zinkernagel R. (1992) Antivirally protective cytotoxic T cell memory to lymphocytic choriomeningitis virus is governed by persisting antigens. J. Exp. Med. **176:** 1273–1281
3 Chinnaiyan A. M. and Dixit V. M. (1997) Portrait of an executioner: the molecular mechanism of FAS/APO-1-induced apoptosis. Sem. Immunol. **9:** 69–76
4 Wong B. and Choi Y. (1997) Pathways leading to cell death in T cells. Curr. Opin. Immunol. **9:** 358–364
5 Minn A. J., Swain R. E., Ma A. and Thompson C. B. (1998) Recent progress on the regulation of apoptosis by Bcl-2 family members. Adv. Immunol. **70:** 245–279
6 Spaner D., Raju K., Radvanyi L., Lin Y. and Miller R. G. (1998) A role for perforin in activation-induced cell death. J. Immunol. **160:** 2655–2664
7 Vella A. T., Dow S., Potter T. A., Kappler J. and Marrack P. (1998) Cytokine-induced survival of activated T cells in vitro and in vivo. Proc. Natl. Acad. Sci. USA **95:** 3810–3815
8 Bulfone-Paus S., Ungureanu D., Pohl T., Lindner G., Paus R., Ruckert R. et al. (1997) Interleukin-15 protects from lethal apoptosis in vivo. Nature Med. **3:** 1124–1128
9 Duckett C. S. and Thompson C. B. (1997) CD30-dependent degradation of TRAF2: implications for negative regulation of TRAF signaling and the control of cell survival. Genes Dev. **11:** 2810–2821
10 Nocentini G., Giunchi L., Ronchetti S., Krausz L. T., Bartoli A., Moraca R. et al. (1997) A new member of the tumor necrosis factor/nerve growth factor receptor family inhibits T cell receptor-induced apoptosis. Proc. Natl. Acad. Sci. USA **94:** 6216–6221
11 Hurtado J. C., Kim Y.-J. and Kwon B. S. (1997) Signals through 4-1BB are costimulatory to previously activated splenic T cells and inhibit activation-induced cell death. J. Immunol. **158:** 2600–2609
12 Boise L. H., Minn A. J., June C. H., Accavitti M. A., Lindsten T. and Thompson C. B. (1995) CD28 costimulation can promote T cell survival by enhancing the expression of Bcl-xL. Immunity **3:** 87–98
13 Lalvani A., Brookes R., Hambelton S., Britton W., Hill A. V. S. and McMicheal A. J. (1997) Rapid effector function in $CD8^+$ memory T cells. J. Exp. Med. **186:** 859–865
14 Walunas T. L., Bruce D. S., Dustin L., Loh D. Y. and Bluestone J. A. (1995) Ly-6C is a marker of memory $CD8^+$ T cells. J. Immunol. **155:** 1873–1883

15 Ernst D. N., Weigle W. O., Noonan D. J., McQuitty D. N. and Hobbs M. V. (1993) The age-associated increase in IGN-γ synthesis by mouse CD8$^+$ T cells correlates with shifts in the frequencies of cell subsets defined by membrane CD44, CD45RB, 3G11 and MEL-14 expression. J. Immunol. **151:** 575–587
16 Tanchot C., Guillaume S., Delon J., Bourgeois C., Franzke A., Surukhan A. et al. (1998) Modifications of CD8$^+$ T cell function during in vivo memory of tolerance induction. Immunity **8:** 581–590
17 de Jong R., Brouwer M., Miedema F. and van Lier R. A. W. (1991) Human CD8$^+$ T lymphocytes can be divided into CD45RA$^+$ and CD45RO$^+$ cells with different requirements for activation and differentiation. J. Immunol. **46:** 2088–2094
18 Hamann D., Baars P. A., Rep M. H. G., Hooibrink B., Kerkhof-Garde S. R., Klein M. R. et al. (1997) Phenotypic and functional separation of memory and effector human CD8$^+$ T cells. J. Exp. Med. **186:** 1407–1418
19 Sanders M. E., Makgoba M. W., Sharrow S. O., Stephany D., Springer T. A., Young H. A. et al. (1988) Human memory T lymphocytes express increased levels of three cell adhesion molecules (LFA-3, CD2 and LFA-1) and three other molecules (UCHL1, CDw29 and Pgp-1) and have enhanced IFN-γ production. J. Immunol. **140:** 1401–1407
20 Picker L. J., Singh M. K., Zdraveski Z., Treer J. R., Waldrop S. L., Berstresser P. R. et al. (1995) Direct demonstration of cytokine synthesis heterogeneity among human memory/effector T cells by flow cytometry. Blood **86:** 1408–1419
21 Swain S. L. (1994) Generation and in vivo persistence of polarized Th1 and Th2 memory cells. Immunity **1:** 543–552
22 Cerwenka A., Carter L. L., Reome J. B., Swain S. L. and Dutton R. W. (1998) In vivo persistence of CD8 polarized T cell subsets producing type 1 or type 2 cytokines. J. Immunol. **161:** 97–105
23 Bruno L., Kirberg J. and von Boehmer H. (1995) On the cellular basis of immunological T cell memory. Immunity **2:** 37–43
24 Curtsinger J. M., Lins D. C. and Mescher M. F. (1998) CD8+ memory T cells (CD44^{high}, LY-6C$^+$) are more sensitive than naive cells (CD44^{low}, Ly-6C$^-$) to TCR/CD8 signaling in response to antigen. J. Immunol. **160:** 3236–3243
25 Pihlgren M., Dubois P. M., Tomkowaik M., Sjogren T. and Marvel J. (1996) Resting memory CD8+ T cells are hyperreactive to antigenic challenge in vitro. J. Exp. Med. **184:** 2141–2151
26 Kedl R. M. and Mescher M. F. (1998) Qualitative differences between naive and memory T cells make a major contribution to the more rapid and efficient memory CD8+ T cell response. J. Immunol. **161:** 674–683
27 Geisberg M. and Dupont B. (1992) Cytolytic effector function is present is resting peripheral T lymphocytes. Int. Immunol. **4:** 1273–1281
28 Opferman J. T., Ober B. T. and Ashton-Rickardt P. G. (1999) Linear differentiation of cytotoxic effectors into memory T lymphocytes. Science **283:** 1745–1748
29 Zimmermann C., Brduscha-Riem K., Blaser C., Zinkernagel R. M. and Pircher H. (1996) Visualization, characterization and turnover of CD8+ memory T cells in virus-infected hosts. J. Exp. Med. **183:** 1367–1375
30 Selin L. K. and Welsh R. M. (1997) Cytolytically active memory CTL present in lymphocytic choriomeningitis virus-immune mice after clearance of virus infection. J. Immunol. **158:** 5366–5373
31 Oehen S. and Brduscha-Riem K. (1998) Differentiation of naive CTL to effector and memory CTL: correlation of effector function with phenotype and cell division. J. Immunol. **161:** 5338–5349
32 Ehl S., Klenerman P., Aichele P., Hentgartner H. and Zinkernagel R. M. (1997) A functional and kinetic comparison of antiviral effector and memory cytotoxic T lymphocyte populations in vivo and in vitro. Eur. J. Immunol. **27:** 3404–3413
33 Beverley P. C. L. (1990) Is T-cell memory maintained by crossreactive stimulation? Immunol. Today **11:** 203–205
34 Gray D. and Matzinger P. (1991) T cell memory is short-lived in the absence of antigen. J. Exp. Med. **174:** 969–974
35 MacLennan I. C. M. (1994) Germinal centers. Annu. Rev. Immunol. **12:** 117–139
36 Doherty P. C., Allan W., Eichelberger M. and Carding S. R. A. (1992) Roles of $\alpha\beta$ and $\chi\delta$ T cell subsets in viral immunity. Ann. Rev. Immunol. **10:** 123–151
37 Demkowicz W. E. and Ennis F. A. (1993) Vaccinia virus-specific CD8$^+$ cytotoxic T lymphocytes in humans. J. Virol. **67:** 1538–1544
38 Hou S., Hyland L., Ryan K. W., Portner A. and Doherty P. C. (1994) Virus-specific CD8$^+$ T-cell memory determined by clonal burst size. Nature **369:** 652–654
39 Lau L. L., Jamieson B. D., Somasundaram T. and Ahmed R. (1994) Cytotoxic T-cells memory without antigen. Nature **369:** 648–652
40 Mullbacher A. (1994) The long-term maintenance of cytotoxic T cell memory does not require persistence of antigen. J. Exp. Med. **179:** 317–321
41 Tanchot C., Lemonnier F. A., Perarnau B., Freitas A. A. and Rocha B. (1997) Differential requirements for survival and proliferation of CD8 naive or memory T cells. Science **276:** 2057–2062
42 Markiewicz M. A., Girao C., Opferman J. T., Sun J., Hu Q., Agulnik A. A. et al. (1998) Long-term T cell memory requires the surface expression of self-peptide/major histocompatibility complex molecules. Proc. Natl. Acad. Sci. USA **95:** 3065–3070
43 Kundig T. M., Bachmann M. F., Oehen S., Hoffmann U. W., Simard J. J. L., Kalberer C. P. et al. (1996) On the role of antigen in maintaining cytotoxic T-cell memory. Proc. Natl. Acad. Sci. USA **93:** 9716–9723
44 Kirberg J., Berns A. and von Boehmer H. (1997) Peripheral T cell survival requires continual ligation of the T cell receptor to major histocompatibility complex-encoded molecules. J. Exp. Med. **186:** 1269–1275
45 Nesic D. and Vukmanovic S. (1998) MHC class I is required for peripheral accumulation of CD8+ thymic emigrants. J. Immunol. **160:** 3705–3712
46 Takeda S., Rodewald H.-R., Arakawa H., Bluetmann H. and Shimizu T. (1996) MHC class II molecules are not required for survival of newly generated CD4$^+$ T cells but affect their long-term life span. Immunity **5:** 217–228
47 Brocker T. (1997) Survival of mature CD4 T lymphocytes is dependent on major histocompatibility complex II-expressing dendritic cells. J. Exp. Med. **186:** 1223–1232
48 Rooke R., Waltzinger C., Benoist C. and Mathis D. (1997) Targeted complementation of MHC class II deficiency by intrathymic delivery of recombinant adenoviruses. Immunity **7:** 123–134
49 Tough D. F. and Sprent J. (1994) Turnover of naive- and memory-phenotype T cells. J. Exp. Med. **179:** 1127–1135
50 Zinkernagel R. M. and Doherty P. C. (1974) Restriction of in vitro T cell mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semi-allogeneic system. Nature **248:** 701–702
51 Bevan M. J. (1977) In a radiation chimera, host *H-2* antigens determine immune responsiveness of donor cytotoxic cells. Nature **269:** 417–418
52 Hogquist K. A., Tomlinson A. J., Keiper W. C., Mc Gargill M. A., Hart M. C., Naylor S. et al. (1997) Identification of a naturally occurring ligand for thymic positive selection. Immunity **6:** 389–399
53 Hu Q., Bazemore Walker C.R., Girao C., Opferman J. T., Sun J., Shabanowitz J. et al. (1997) Specific recognition of thymic self-peptides induces the positive selection of cytotoxic T lymphocytes. Immunity **7:** 221–231
54 Nahill S. R. and Welsh R. M. (1993) High frequency of cross-reactive cytotoxic T lymphocytes elicited during the virus induced polyclonal cytotoxic T lymphocyte response. J. Exp. Med. **177:** 317–327
55 Razvi E. S. and Welsh R. M. (1995) Apoptosis in viral infections. Adv. Virus Res. **45:** 1–60

56 Selin L. K., Nahill S. R. and Welsh R. M. (1994) Cross-reactivities in memory cytotoxic T lymphocyte recognition of heterologous viruses. J. Exp. Med. **179:** 1933–1943

57 Tough D. F., Borrow P. and Sprent J. (1996) Induction of bystander T cell proliferation by viruses and type I interferon in vivo. Science **272:** 1947–1950

58 Vella A. T., Mc Cormack J. E., Linsley P. S., Kappler J. W. and Marrack P. (1995) Lipopolysaccharide interferes with the induction of peripheral T cell death. Immunity **2:** 261–270

59 Tough D. F., Sun S. and Sprent J. (1997) T cell stimulation in vivo by lipopolysaccharide (LPS). J. Exp. Med. **185:** 2089–2094

60 Zhang X., Sun S., Hwang I., Tough D. and Sprent J. (1998) Potent and selective stimulation of memory-phenotype CD8 + T cells in vivo by IL-15. Immunity **8:** 591–599

61 Lodolce J. P., Boone D. L., Chai S., Swain R. E., Dassopoulos T., Trettin S. et al. (1998) IL-15 receptor maintains lymphoid homeostasis by supporting lymphoid homing and proliferation. Immunity **9:** 669–676

62 Teague T. K., Marrack P., Kappler J. W. and Vella A. T. (1997) IL-6 rescues resting mouse T cells from apoptosis. J. Immunol. **158:** 5791–5796

63 Vella A., Teague T. K., Ihle J., Kappler J. and Marrack P. (1997) Interleukin 4 (IL-4) or IL-7 prevents the death of resting T cells: Stat6 is probably not required for the effect of IL-4. J. Exp. Med. **186:** 325–330

64 Boise L. H., Minn A. J., June C. H., Lindsten T. and Thompson C. B. (1995) Growth factors can enhance lymphocyte survival without committing the cell to undergo division. Proc. Natl. Acad. Sci. USA **92:** 5491–5495

65 Selin L. K., Vergilis K., Welsh R. M. and Nahill S. R. (1996) Reduction of otherwise remarkably stable virus-specific cytotoxic T lymphocyte memory by heterologous viral infections. J. Exp. Med. **183:** 2489–2499

66 Farber D. L. (1998) Differential TCR signaling and the generation of memory T cells. J. Immunol. **160:** 535–539

67 Liu Y.-J., Joshua D. E., Williams G. T., Smith C. A., Gordon J. and MacLennan I. C. M. (1989) Mechanism of antigen-driven selection in germinal centres. Nature **342:** 929–931

68 Gray D., Dullforce P. and Jainandunsing S. (1994) Memory B cell development but not germinal center formation is impaired by in vivo blockade of CD40-CD40 ligand interaction. J. Exp. Med. **180:** 141–155

69 Neurath M. F., Max E. E. and Strober W. (1995) Pax5 (BSAP) regulates the murine immunoglobulin 3′ alpha enhancer by suppressing binding of NF-alpha-P, a protein that controls heavy chain transcription. Proc. Natl. Acad. Sci. USA **92:** 5336–5340

70 Stuber E., Neurath M., Calderhead D., Fell H. P. and Strober W. (1995) Cross-linking of OX40 ligand, a member of the TNF/NGF cytokine family, induces proliferation and differentiation in murine splenic cells. Immunity **2:** 507–521

71 Liu Y.-J., Cairns J. A., Holder M. J., Abbot S. D., Jansen K. U., Bonnefoy J.-Y. et al. (1991) Recombinant 25-kDa CD23 and interleukin 1-alpha promote the survival of germinal center B cells: evidence for bifurcation in the development of centrocytes rescued from apoptosis. Eur. J. Immunol. **21:** 1107–1114

72 Turner C. A., Mack D. H. and Davis M. M. (1994) Blimp-1, a novel zinc finger-containing protein that can drive the maturation of B lymphocytes into immunoglobulin-secreting cells. Cell **77:** 297–306

73 Shahinain A., Pfeffer K., Lee K. P., Kundig T. M., Kishihara K., Wakeham A. et al. (1993) Differential T cell costimulatory requirements in CD28-deficient mice. Science **261:** 609–612

74 Letvin N. L. (1998) Progress in the development of an HIV-1 vaccine. Science **280:** 1875–1880

75 Liu Y., Wenger R. H., Zhao M. and Nielsen P. L. (1997) Distinct costimulatory molecules are required for the induction of effector and memory cytotoxic T lymphocytes. J. Exp. Med. **185:** 251–262

76 Butcher E. C. and Picker L. J. (1996) Lymphocyte homing and homeostasis. Science **272:** 60–66

77 Merkenschlager M. and Beverley P. C. (1989) Evidence for differential expression of CD45 isoforms by precursors for memory-dependent and independent cytotoxic responses: human CD8 memory CTLp selectively express CD45RO (UCHL1). Int. Immunol. **1:** 450–459

78 Okumura M., Fujii Y., Inada K., Nakahara K. and Matsuda H. (1993) Both $CD45RA^+$ and $CD45RA^-$ subpopulations of $CD8^+$ T cells contain cells with high levels of lymphocyte function-associated antigen-1 expression, a phenotype of primed T cells. J. Immunol. **150:** 429–437