



ELSEVIER

Differentiation of memory B and T cells

Vandana Kalia¹, Surojit Sarkar¹, Tania S Gourley¹, Barry T Rouse² and Rafi Ahmed¹

In the past few years progress has been made in understanding the molecular mechanisms that underlie the initial generation, and the ensuing differentiation and maintenance, of humoral and cellular immunity. Although B and T cell immunological memory contribute to protective immunity through fundamentally distinct effector functions, interesting analogies are becoming apparent between the two memory compartments. These include heterogeneity in function, anatomical location and phenotype, which probably relate to differential environmental cues during the early priming events as well as the later differentiation phases. Detailed definition of the molecular and cellular signals involved in the development of immunological memory, and the relative contributions of different memory subsets to protective immunity, remains an important goal.

Addresses

¹ 1510 Clifton Road, Rollins Research Center G211, Emory University, Atlanta, GA 30322, USA

² Department of Microbiology and Immunology, The University of Tennessee, Knoxville, TN 37996-0845, USA

Corresponding author: Ahmed, Rafi (ra@microbio.emory.edu)

Current Opinion in Immunology 2006, **18**:255–264

This review comes from a themed issue on
Lymphocyte activation
Edited by Bernard Malissen and Janet Stavnezer

0952-7915/\$ – see front matter

© 2006 Elsevier Ltd. All rights reserved.

DOI 10.1016/j.coi.2006.03.020

Introduction

Immunological memory is a cardinal feature of adaptive immunity, whereby the first encounter with a pathogen is imprinted indelibly into the immune system. Subsequent exposure to the same pathogen then results in accelerated, more robust immune responses that either prevent reinfection or significantly reduce the severity of clinical disease. Both humoral and cellular immune responses comprise important arms of immunological memory, and have evolved to perform distinct effector functions. Humoral immune responses include pre-existing antibody, memory B cells (MBCs) and long-lived plasma cells (LLPCs). The antibodies provide the first line of defense by neutralizing or opsonizing free extracellular pathogens. T cells (CD8 and CD4), by contrast, cannot

recognize free pathogens, but instead identify infected cells and exert effector functions including direct cytotoxic effects on target cells and/or release of cytokines to inhibit growth or survival of the pathogen. CD4 T cells further provide help for antibody production and the generation and maintenance of CD8 T-cell memory. Owing to their distinct complementary functions of tackling free pathogens versus infected cells, it is important for a successful vaccine strategy to stimulate both B and T cell immunity. In this review, we discuss the distinct roles played by humoral and cellular responses in protective immunity and provide an overview of our current understanding of memory B and T cell differentiation.

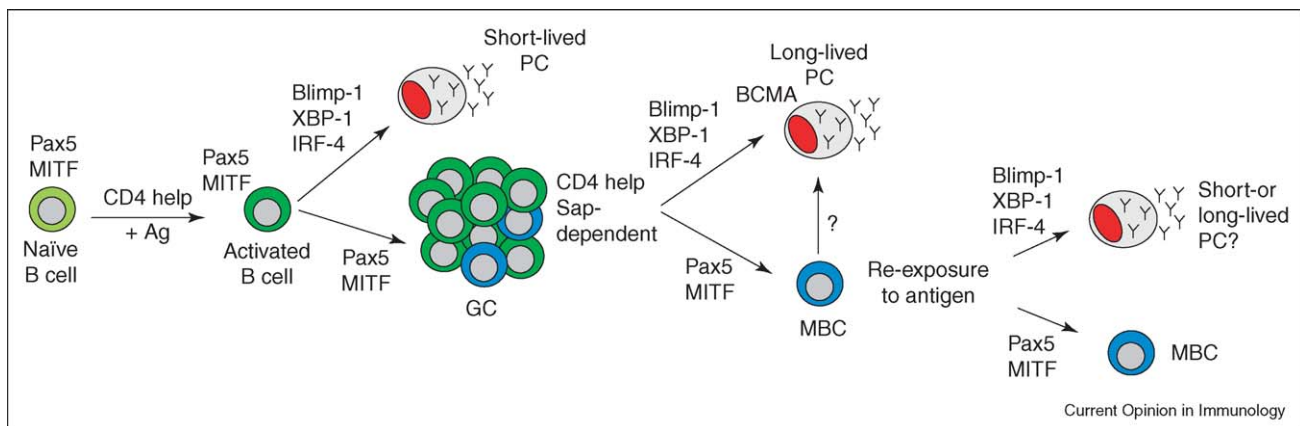
B-cell immunological memory

Prolonged antibody production lasting for years after infection or vaccination provides the first line of defense against pathogens and is key to humoral protection. In addition to pre-existing antibody, immunological memory in the B-cell compartment consists of two distinct cell-types: MBCs and LLPCs. Primarily located in secondary lymphoid organs, antigen-specific MBCs are present at much higher frequencies relative to naïve B cells specific for the same antigen, and although they do not actively secrete antibody they express a higher affinity B-cell receptor (BCR). They mediate rapid recall responses to infection by quickly dividing and differentiating into antibody-secreting plasma cells, while simultaneously replenishing the MBC pool. In contrast, LLPCs reside mainly in the bone marrow and constitutively produce and secrete antibody. Unlike MBCs, they contain minimal levels of BCR or none at all, and cannot be stimulated to divide or to boost the rate of antibody production. Thus, plasma cells are terminally differentiated cells that continuously elaborate effector functions (i.e. constitutively produce antibody) in the absence of antigenic stimulation. It is worth noting that there is no true equivalent to the plasma cell within the T-cell compartment, in which antigen is the main regulator of effector function.

The B-cell response and development of humoral memory to thymus (T)-dependent antigens

The lineage relationships between naïve B cells, MBCs and plasma cells are shown in Figure 1. Following initial stimulation (by antigen and T-cell help), naïve B cells proliferate at the margins of the T-cell zone or periarteriolar sheaths in the lymph nodes and spleen. Activated B cells then continue down one of two divergent pathways:

Figure 1



Distinct sets of transcriptional regulators control commitment to the plasma cell differentiation pathway during the humoral immune response. Naïve B cells are activated by antigen (Ag) in the presence of CD4 T-cell help. The activated B cells then continue down one of two divergent pathways: plasma cell (PC) differentiation, or initiation of a GC reaction. MBCs and LLPCs are generated in the GC. When MBCs are re-exposed to antigen they divide rapidly and differentiate into either PCs or more MBCs. The commitment of B cells to the PC differentiation pathway is regulated by the transcription factors Blimp-1, XBP-1 and IRF-4. These factors represent the gene-expression program that defines B-cell identity (Pax5, MITF etc.) and activate a program that drives terminal differentiation and antibody secretion.

they either remain in the marginal zone and differentiate into short-lived plasma cells, or migrate into the B-cell follicles and, with further CD4 T-cell help, initiate a germinal centre (GC) reaction. Somatic hypermutation, affinity maturation and selection occur in the GC, which results in the generation of high affinity MBCs and probably LLPCs or their precursors [1]. In the absence of CD4 T cells, or if there is impaired CD40, CD28 or inducible costimulatory molecule signaling, humoral responses are highly compromised and exhibit an impaired ability to generate GCs and MBCs [2–5]. Interestingly, although CD4 T-cell help is also crucial for the generation of short-lived plasma cells, the presence of the Slam-associated protein (SAP or Src homology 2 D1A) in CD4 T cells is not essential for this early T-cell-dependent antibody response. However, the presence of SAP in CD4 T cells is required for the GC reaction, and SAP plays a major role in the generation of MBC and LLPC and in the maintenance of long-term humoral immunity [6].

The signals that initiate the pathways of short-lived plasma cell versus MBC differentiation appear to be distinct. For example, CD40 signaling within the GC favors MBC generation. Conversely, selective expression of transcription factors B-lymphocyte-induced maturation protein 1 (Blimp-1) and X-box binding protein 1 (XBP-1) drive the differentiation of plasma cells (both short- and long-lived) [7–9]. This transcriptional program putatively results from specific interactions (e.g. OX-40, CD23) during activation [10,11]. It is believed that when B cells commit to the plasma cell differentiation pathway, the gene expression program that defined their naïve B-cell

identity is repressed and a program that drives them on a one-way street to terminal differentiation is turned on. The paired box protein 5 (PAX5) is crucial for maintaining naïve and memory B-cell identity [12], as it activates genes required for maintenance of B-cell identity (e.g. CD19 and adaptor protein B-cell linker, BLNK) [13], while simultaneously repressing genes required for plasma cell differentiation and antibody secretion (e.g. XBP-1) [14]. The microphthalmia-associated transcription factor (MITF) also prevents plasma cell differentiation [15]. In the absence of MITF, key regulators of plasma cell differentiation (Blimp-1, XBP-1 and interferon regulatory factor 4 [IRF4]) are induced to drive plasma cell differentiation and to repress genes required for B-cell identity (e.g. PAX5, CD19, MHC class II and CD86) [7–9,16]. Unlike MBCs, plasma cells are terminally differentiated, in part owing to the repression of c-Myc by Blimp-1, leading to impaired cell-cycle progression [17]. How these distinct transcriptional programs are elicited to orchestrate two divergent outcomes, and the mechanisms by which SAP regulates CD4 help, remain exciting avenues of exploration.

Maintenance of humoral memory

Serum and mucosal antibody levels are maintained long-term by multiple mechanisms. Pathogen re-exposure or booster vaccination is clearly the most effective way to boost specific antibody and MBCs. A latent or low-grade chronic infection in which sporadic or continuous antigenic stimulation occurs also drives B-cell receptor (BCR)-dependent differentiation of B cells into antibody-secreting plasma cells. In the absence of antigenic re-exposure, however, LLPCs and MBCs can still be

maintained for decades [18,19]. Although antigen is not needed for the survival of MBCs, the presence of a BCR on MBCs as well as on naïve B cells is required [20]. B-cell activating factor, a member of the tumor necrosis factor (TNF) family, is important for the survival of naïve B cells [21] as well as plasmablasts derived from MBCs [22]. However, it is unknown if B-cell activating factor, or another family member, plays a similar role in MBC maintenance.

In the bone marrow, LLPCs are present that secrete specific antibody for, potentially, the lifetime of an individual [23–25], but how these cells survive and function for such extended periods remains unresolved. Candidate factors involved include Blimp-1, a transcription factor crucial also for plasma cell differentiation [26]. The bone marrow niche itself clearly provides extrinsic survival signals for plasma cells. *In vitro*, the bone marrow stromal cell-derived interleukin (IL)-6 and interactions with the very late antigen (VLA)-4 promote survival [27]. CD44, TNF- α , IL-5, stromal cell-derived factor 1 and TNF family member B-cell maturation antigen are also implicated in the survival of LLPCs [28^{*}]. In addition, BCR-independent polyclonal stimulation by, for example, CpG DNA or bystander T-cell help can also drive proliferation and differentiation of MBCs to replenish the plasma cell pool and to maintain themselves [29].

CD8 T-cell memory

Before delving into the details of CD8 T-cell memory differentiation, it is important to reiterate that B-cell memory is usually manifested by continuous antibody production even after resolution of the disease. This is in stark contrast to the T-cell response, which has a relatively short effector phase. Effector T cells, generated following antigenic stimulation of naïve cells, extravasate into peripheral tissues to rapidly control infection by elaboration of effector functions (i.e. cytokine production and killing of infected cells). Interestingly, effector functions are executed only in the presence of antigen, which apparently acts as a switch for this on–off lifestyle of effector T cells [30]. Discontinuation of effector functions following antigen clearance makes teleological sense, because sustained elaboration of effector functions could result in immunopathological damage. Thus, instead of maintaining pre-existing effector T cells to provide protection, memory CD8 T cells, which are strategically located in the mucosa at the sites of pathogen entry, have the potential to rapidly develop into effector cells upon reencounter with a pathogen.

Accelerated recall responses of memory T cells to reinfection result from quantitative and qualitative changes in antigen-specific T cells [31]. Quantitatively, owing to substantial clonal expansion during primary infection, the precursor frequency of antigen-specific T cells is higher in immune animals (increases of 100–1000-fold

are possible, depending on the system) compared with naïve animals [32]. Qualitatively, memory T cells exhibit striking rapidity and efficiency in elaboration of effector functions upon secondary challenge. This functional superiority of memory T cells is associated with reprogramming of gene expression profiles by epigenetic changes (DNA methylation, histone modifications or reorganization of chromatin structure) ([33] and Ahmed and co-workers, unpublished; see Update) and acquisition of a signature panel of active transcription factors [34]. Not only are memory cells better equipped to assimilate TCR stimulatory signals [35] and to elaborate effector functions with increased rapidity and sensitivity, but they are also precharged with factors that facilitate G(1)-to-S phase transition during cell cycle progression [36,37]. Moreover, unlike naïve T cells, which are located mostly in the lymphoid tissues, a subset of memory T cells, effector memory (T_{EM} ; $CD62L^- CCR7^-$) [38,39], are present in non-lymphoid and mucosal sites and can immediately confront the invading pathogen. Thus, increased numbers of antigen-specific memory cells, accelerated responsiveness and localization near sites of microbial entry form the basis of T-cell protective immunity.

Memory CD8 T-cell subsets

Whereas MBCs and LLPCs represent the two major subtypes of post-GC memory B-cell compartment, the memory CD8 T-cell compartment is characterized by significant heterogeneity with respect to effector functions, gene expression, proliferative potential, surface protein expression and trafficking. The main cell-types involved in CD8 T-cell memory are T_{EM} and central memory (T_{CM} ; $CD62L^+ CCR7^+$) cells [31,40]. Analogous to MBCs, T_{CM} cells are concentrated in secondary lymphoid tissues and have little or no effector functions. Moreover, they both possess stem cell like qualities of self-renewal and respond to antigen by rapidly dividing and differentiating into effector cells. T_{EM} cells, by contrast, can migrate to peripheral tissues [38,39] and mount a more pronounced immediate cytolytic activity compared with T_{CM} cells. Because T_{EM} cells are functionally charged, but remain reticent in the absence of antigen, they do not represent a ‘true’ equivalent of LLPCs that constitutively produce antibody. Moreover, unlike plasma cells, which cannot be stimulated by antigen to divide, T_{EM} cells undergo modest proliferation upon antigenic stimulation, albeit to lower levels than T_{CM} cells [41,42]. Together, both T_{EM} and T_{CM} cells contribute to protective immunity depending on the nature and route of infection [41,43–47].

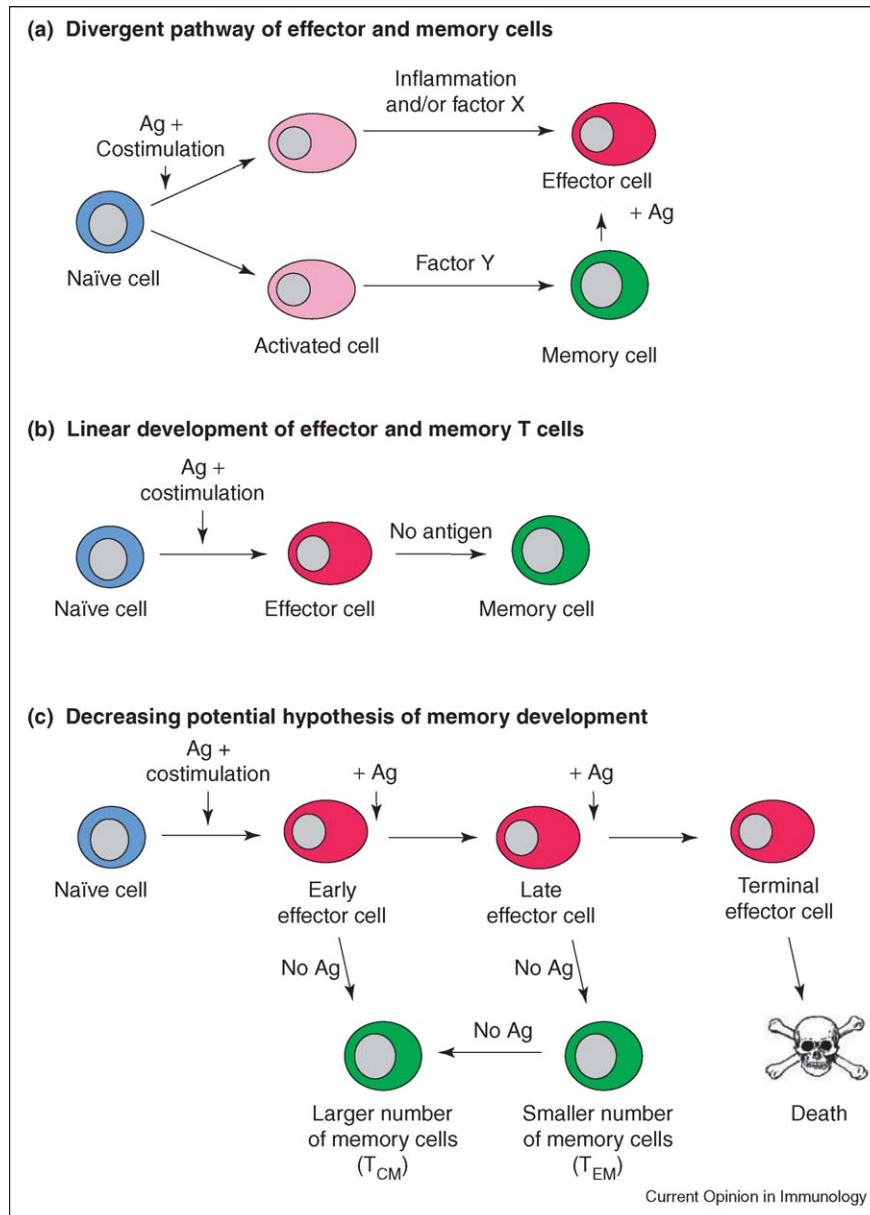
In addition to this well-defined T_{EM}/T_{CM} dichotomy of recirculating memory CD8 T cells, additional levels of complexity in memory CD8 T-cell phenotypes exist between distinct peripheral tissues and in different infectious models [48^{*}]; for example, pathogen-specific

lymphocytes that reside in the gut, lung-airways or brain retain CD69 expression [48^{••},49]. Similarly, existence of developmental and functional subdivision of MBCs (e.g. pre-plasma MBCs) is also becoming apparent [10]. Such functional, anatomic and phenotypic heterogeneity in the CD8 T-cell memory pool has important consequences for immunity, and the factors that govern this cell fate decision are of major interest.

Memory CD8 T-cell differentiation

Although it is well-established that effector plasma cells and MBCs differentiate along separate pathways, the lineage of memory T-cell development is not fully understood. The conventional model of memory CD8 T-cell differentiation is the linear differentiation model (Figure 2) [32], which proposes that memory cells are derived directly from effector cells. The use of CRE/

Figure 2



Models of memory cell differentiation. A simplistic rendering of the currently popular models of B-cell and T-cell differentiation are presented. **(a)** The first model represents the B-cell paradigm of divergent pathways traced by effector and memory cells. T-cell differentiation into effector and memory cells might also be driven along these divergent pathways, depending on antigen (Ag) dose or inflammatory stimuli. **(b)** The second model is a representation of the more conventional linear pathway of differentiation of naïve T cells into effector cells and ultimately into memory cells. **(c)** The third model is a variation of the linear differentiation theme that allows effector cells that die to be distinguished from those that survive and differentiate into long-lived memory T cells. It is based on the decreasing potential hypothesis, which states that the duration and level of antigenic stimulation largely govern the effector and memory T-cell balance.

LOXP recombination system in transgenic mice to 'mark' virus-specific effector T cells showed that marked effectors were maintained in the memory T-cell pool [50], which indicates that memory cells are direct descendants of effector cells. Several studies have shown that T-cell activation and proliferation are tightly coupled to effector cell and eventually memory cell differentiation [51–55]. Moreover, recent identification of a memory precursor population within the effector T-cell pool further supports the paradigm that memory T cells pass through an effector phase [56,57,58]. Thus, in contrast to plasma cell and MBC differentiation, it is unlikely that the divergent pathway represents a major pathway of memory T-cell differentiation.

However, in certain cases (e.g. activation with heat-killed bacteria or *in vitro* stimulation with high doses of IL-2 or IL-15 cytokines) [59] memory T cells might also develop without passing through an effector-cell stage, depending on the priming milieu [32]. Thus, antigen plus costimulation in the presence of an inflammatory milieu early during an infection (e.g. IL-12 [60,61], type-I interferon [62,63] and IL-21 signals [64]) might favor differentiation of effector T cells, whereas antigen plus costimulation in the absence of inflammation (as antigen and infection are waning) might lead to memory T-cell differentiation [57,65]. Therefore, it is important to consider that memory T-cell development might occur in a non-linear fashion, and that it can result in qualitatively different memory T-cell subsets.

Memory T cell heterogeneity

What is the source of memory T-cell heterogeneity? Is this continuum of differentiation states and/or lineages programmed via unique transcriptional regulation that is cell autonomous, and can cell extrinsic factors be manipulated to dictate the final outcome of the differentiation process? We have come to realize that early priming events strongly influence the number, location and functional properties (quality) of memory CD8 T cells. In contrast to the antigen-driven affinity maturation of MBCs, which is central to memory B-cell differentiation, antigen exposure is needed only briefly (20–24 hours) to initiate T-cell development. However, the type of effector and memory CD8 T-cell response eventually generated is further influenced by the duration and/or dose and the 'context' of antigenic stimulation (e.g. cytokine milieu, chemokine signals and costimulation — as determined by the nature and activation state of APCs [66]). Under some conditions, signals from concomitantly stimulated helper T cells, and perhaps from regulatory cells, also impact on the eventual memory response.

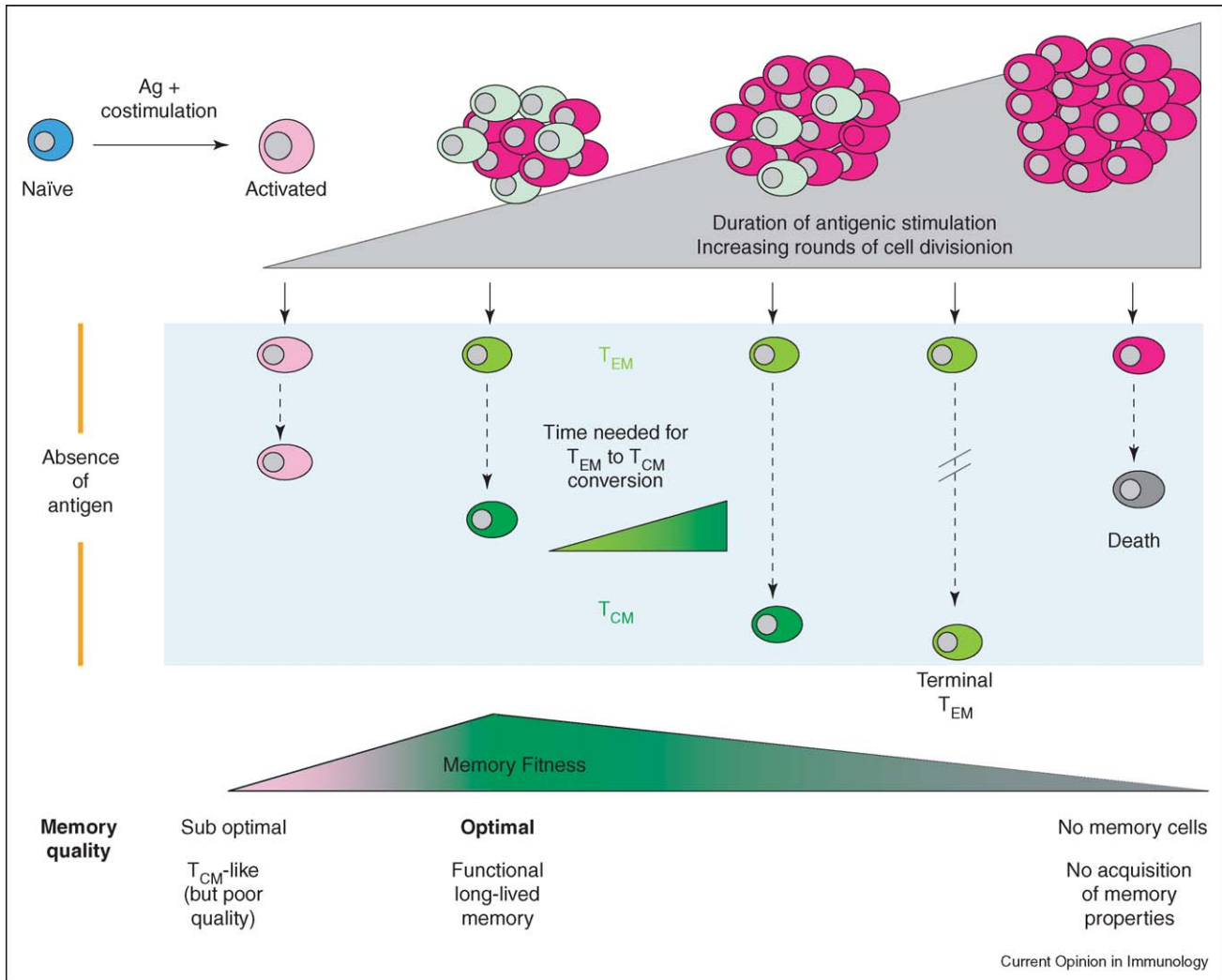
Distinct lymphoid environments have been shown to program T cells to adopt different trafficking properties [49,67], thereby implicating unique environmental cues in dictating memory outcome. Additionally, following

emigration from secondary lymphoid tissue, inductive signals unique to distinct anatomical compartments might further regulate memory CD8 T-cell differentiation. Recent studies demonstrate that acquisition of the unique phenotype of memory cells within the intraepithelial compartment of intestinal mucosa (intraepithelial lymphocytes [IELs]) occurs gradually *in situ* within the gut. Following their differentiation, memory IELs remained CD62L⁻ indefinitely within the mucosa, but could be reprogrammed to form T_{CM} upon restimulation and memory differentiation within the spleen [48]. Thus, analogous to the situation with B cells, whereby microenvironments such as GCs and plasma foci represent the sites in which affinity maturation of developing MBCs and the generation of short-lived antibody-forming cells occur, the tissue microenvironment of a developing T cell also significantly impacts the memory T-cell differentiation program by providing a unique milieu of cytokines, costimulation, immune accessory cells and antigen persistence.

It is believed that the balance between effector and memory cells and the heterogeneity in memory population is directly related to the extent and frequency of TCR stimulation and to the division history of the cells (probably conditioned by the dose of the antigen) [32,68] (Figure 3), such that functionally fit memory cells arise only under optimal stimulation conditions in which antigen load is effectively controlled. Consistently, reduced stimulation of CD8 T cells during infection primarily promotes the generation of T_{CM} cells [41,69]. In addition, reduction in antigen load by antibiotics [57] or use of higher CD8 T-cell precursor frequencies [70] might lead to a more rapid conversion to T_{CM} phenotype (CD62L⁺). It is noteworthy that initial TCR stimulation results in rapid shedding of CD62L from the cell-surface by proteolytic cleavage, but continued TCR stimulation leads to transcriptional silencing of CD62L-encoding locus [31]. Therefore, it is interesting to speculate that the rate of generation of T_{CM} cells, as evaluated by reacquisition of CD62L expression, might correlate with the level of antigenic stimulation during priming.

In chronic infections where antigen persists, effector T cells do not differentiate into durable memory cells [71,72,73,74], and might survive in an antigen-dependent manner as dysfunctional cells (exhaustion) or could eventually die (deletion) [72]. The degree to which CD8 T cells become defective appears to correlate with antigen load and can range from partial loss of cytokine production to complete loss of cytolytic function and cytokine secretion. Understanding if effector T-cell dysfunction induced by antigen persistence is reversible is important in vaccine strategies against chronic infections and/or tumors that aim to restore CD8 T-cell function in the face of continued antigenic stimulation. Recent studies [75] have identified increased expression of an

Figure 3



The decreasing potential model of memory CD8 T-cell development. Optimal antigenic stimulation triggers a developmental program of expansion and differentiation of naïve T cells into effectors. Following antigen clearance, a fraction (5–10%) of the cells progressively differentiate into potent long-lived memory cells in the absence of antigen [41,47,86] (light blue shaded box). Whereas suboptimal stimulation might lead to limited CD8 T cell expansion and/or impaired memory development and function [49,87], the decreasing potential model postulates that prolonged antigenic stimulation impairs memory generation potential by driving the cells towards a terminally differentiated effector phenotype with each successive stimulus and cell division. This is accompanied by an increasing susceptibility to apoptosis, and cells receiving the highest magnitude of stimulation bear the lowest potential to survive and differentiate into memory cells. Furthermore, the generation of T_{EM} and T_{CM} lineages, and the time needed for differentiation into T_{CM} cells (represented by the length of dotted line), are also regulated by the duration and/or strength of antigenic stimulation. Whereas a short duration of antigenic stimulation favors development of T_{CM} , longer stimulation promotes the differentiation of terminal T_{EM} cells. Apart from antigen, additional cell-extrinsic variables including the cytokine and chemokine milieu, costimulatory and inhibitory signals (dependent on the type and activation state of the APC), interaction with other cell-types (e.g. CD4 T cells), and the anatomic location might further impact the qualitative and quantitative aspects of a developing T-cell response and the ensuing memory differentiation and maintenance. Key: terminal effectors, dark pink; suboptimal memory, light pink; memory precursors, light green; effector memory, intermediate green; central memory, dark green.

inhibitory receptor programmed death 1 (PD-1) on the surface of antigen-specific CD8 T cells in mice chronically infected with lymphocytic choriomeningitis virus. PD-1 is known to be an inhibitory receptor for T cells and belongs to the CD28 family [76]. Interestingly, blockade of PD-1 interaction with its ligand PD-L1, which is highly expressed on chronically infected cells, relieved the

inhibitory effect such that the exhausted T cells recovered their proliferative ability in response to antigen, regained cytolytic function, exhibited improved cytokine secretion ability (interferon- γ and TNF- α), and rapidly reduced the viral loads. These studies represent an important step towards designing therapies to revive T-cell function through blockade of inhibitory receptors, which

might serve an immunoregulatory function in balancing anti-viral immune responses and immunopathology.

Transcription factors that regulate memory T-cell differentiation

Knowing how various developmental cues are interpreted by a developing T cell to institute specific patterns of gene expression, and the timing during which a differentiating cell is amenable to epigenetic changes, is crucial to understanding the lineage relationships between memory T-cell subsets and their role in protection. Although it is clear that the differentiation of effector plasma cells and MBCs is orchestrated by a well-defined growing list of molecular signals and transcriptional factors, a detailed molecular delineation of the differentiation path of memory T cells is a topic that requires further investigation. The recent demonstration that tissue-specific T-box transcription factors T-bet and comsodermin, which regulate CD8 T-cell effector functions, also regulate the maintenance of IL-15-dependent memory CD8 T cells [77**] is an important step in providing a molecular link between programming of effector and memory CD8 T cells. These studies exemplify a framework in which transcription factors that specify lineage function can also specify responsiveness to growth and/or survival signals [78].

Maintenance of CD8 T-cell memory

It is now clear that both memory CD8 T cells and B cells can persist in the absence of antigen. Longevity of memory T cells, perhaps indefinite, is attributed to their ability to replenish their numbers in the absence of antigen by way of homeostatic proliferation. It is clear that factors that enhance cell division (IL-15) or promote cell survival (IL-7) [31] are important in maintaining the numbers of memory T cells in the absence of antigen. Recent studies have identified the bone marrow as a preferential homing site for memory T cells, where they proliferate more extensively than in secondary lymphoid organs [79,80] in response to self-renewal signals. Whether constitutive production of such cytokines by specific cell-types within the bone marrow makes it a preferred niche for homeostatic proliferation is not known.

In MBCs, polyclonal activation of innate pathways (by way of Toll-like receptors [TLRs]) or bystander CD4 T-cell help are also believed to contribute to their long-term maintenance and/or generation of plasma cells in the absence of antigen. Although our understanding of innate signaling pathways in memory T cells is minimal, it is intriguing to speculate that TLR-signaling might modulate homeostatic proliferation of memory T cells. It is well-established that CD4 T cells are crucial for the maintenance of functional CD8 T-cell memory, such that memory cells generated in the absence of CD4 help are unstable, exhibit diminished cytokine production

and proliferation upon secondary challenge [81,82], and undergo TNF-related apoptosis inducing ligand (TRAIL)-mediated death [83*]. The nature of help and the mechanism by which CD4 T cells regulate memory CD8 T-cell differentiation (direct CD4–CD40L interactions between CD4 and CD8 T cells [82,84], cognate licensing of DCs [82,85], or soluble factors) remain intriguing avenues of further investigation.

Conclusions

Although the nature of humoral and cellular immunity is fundamentally different, interesting analogies exist between B-cell and CD8 T-cell memory. The generation of both memory types is dependent on differentiation signals during a primary response; both processes are progressive, depend on CD4 T-cell help and costimulation, and are largely maintained long-term in absence of antigenic stimulation. Moreover, interesting functional correlates between effector and central memory CD8 T cells, and between LLPCs and MBCs, exist. Elucidation of when and how commitment to memory lineage is specified remains an exciting area of immunology and is crucial to manipulating the quality and quantity of antigen-specific memory cells in the design of preventative and therapeutic vaccines. Many questions remain before we have a thorough molecular definition of a memory cell. For example, what are the factors that regulate lineage decisions and the differentiation program of memory cells? What are the determinants that regulate the functional superiority and longevity of the memory cells? Answers to these and many other questions will continue to shape our understanding of the cellular and molecular mechanisms that regulate immunological memory.

Update

The study cited in the main body of text as Ahmed and co-workers, unpublished, has now been accepted for publication [88].

Acknowledgements

This work was supported by grant funding from the National Institutes of Health (to RA and BTR), the Elizabeth Glaser Pediatric AIDS Foundation (to VK and SS), and the Leukemia and Lymphoma Society (to TSG).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. O'Connor BP, Cascalho M, Noelle RJ: **Short-lived and long-lived bone marrow plasma cells are derived from a novel precursor population.** *J Exp Med* 2002, **195**:737-745.
2. Ferguson SE, Han S, Kelsoe G, Thompson CB: **CD28 is required for germinal center formation.** *J Immunol* 1996, **156**:4576-4581.
3. Kawabe T, Naka T, Yoshida K, Tanaka T, Fujiwara H, Suematsu S, Yoshida N, Kishimoto T, Kikutani H: **The immune responses in CD40-deficient mice: impaired immunoglobulin class switching and germinal center formation.** *Immunity* 1994, **1**:167-178.

4. Mombaerts P, Clarke AR, Rudnicki MA, Iacomini J, Itohara S, Lafaille JJ, Wang L, Ichikawa Y, Jaenisch R, Hooper ML *et al.*: **Mutations in T-cell antigen receptor genes alpha and beta block thymocyte development at different stages.** *Nature* 1992, **360**:225-231.
5. Wong SC, Oh E, Ng CH, Lam KP: **Impaired germinal center formation and recall T-cell-dependent immune responses in mice lacking the costimulatory ligand B7-H2.** *Blood* 2003, **102**:1381-1388.
6. Crotty S, Kersh EN, Cannons J, Schwartzberg PL, Ahmed R: **SAP is required for generating long-term humoral immunity.** *Nature* 2003, **421**:282-287.
7. Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, Gravalles EM, Friend D, Grusby MJ, Alt F, Glimcher LH: **Plasma cell differentiation requires the transcription factor XBP-1.** *Nature* 2001, **412**:300-307.
8. Turner CA Jr, Mack DH, Davis MM: **Blimp-1, a novel zinc finger-containing protein that can drive the maturation of B lymphocytes into immunoglobulin-secreting cells.** *Cell* 1994, **77**:297-306.
9. Shaffer AL, Lin KI, Kuo TC, Yu X, Hurt EM, Rosenwald A, Giltman JM, Yang L, Zhao H, Calame K *et al.*: **Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program.** *Immunity* 2002, **17**:51-62.
10. McHeyzer-Williams LJ, McHeyzer-Williams MG: **Antigen-specific memory B cell development.** *Annu Rev Immunol* 2005, **23**:487-513.
11. McHeyzer-Williams MG, Ahmed R: **B cell memory and the long-lived plasma cell.** *Curr Opin Immunol* 1999, **11**:172-179.
12. Nutt SL, Eberhard D, Horcher M, Rolink AG, Busslinger M: **Pax5 determines the identity of B cells from the beginning to the end of B-lymphopoiesis.** *Int Rev Immunol* 2001, **20**:65-82.
13. Horcher M, Souabni A, Busslinger M: **Pax5/BSAP maintains the identity of B cells in late B lymphopoiesis.** *Immunity* 2001, **14**:779-790.
14. Reimold AM, Ponath PD, Li YS, Hardy RR, David CS, Strominger JL, Glimcher LH: **Transcription factor B cell lineage-specific activator protein regulates the gene for human X-box binding protein 1.** *J Exp Med* 1996, **183**:393-401.
15. Lin L, Gerth AJ, Peng SL: **Active inhibition of plasma cell development in resting B cells by microphthalmia-associated transcription factor.** *J Exp Med* 2004, **200**:115-122.
This study illustrates the antagonistic effect of MITF expression in naïve cells on the process of terminal differentiation through the repression of IRF-4. In the absence of MITF activity, spontaneous antibody secretion occurred.
16. Mittrucker HW, Matsuyama T, Grossman A, Kundig TM, Potter J, Shahinian A, Wakeham A, Patterson B, Ohashi PS, Mak TW: **Requirement for the transcription factor LSIRF/IRF4 for mature B and T lymphocyte function.** *Science* 1997, **275**:540-543.
17. Lin Y, Wong K, Calame K: **Repression of c-myc transcription by Blimp-1, an inducer of terminal B cell differentiation.** *Science* 1997, **276**:596-599.
18. Manz RA, Lohning M, Cassese G, Thiel A, Radbruch A: **Survival of long-lived plasma cells is independent of antigen.** *Int Immunol* 1998, **10**:1703-1711.
19. Maruyama M, Lam KP, Rajewsky K: **Memory B-cell persistence is independent of persisting immunizing antigen.** *Nature* 2000, **407**:636-642.
20. Lam KP, Kuhn R, Rajewsky K: **In vivo ablation of surface immunoglobulin on mature B cells by inducible gene targeting results in rapid cell death.** *Cell* 1997, **90**:1073-1083.
21. Hsu BL, Harless SM, Lindsley RC, Hilbert DM, Cancro MP: **Cutting edge: BLyS enables survival of transitional and mature B cells through distinct mediators.** *J Immunol* 2002, **168**:5993-5996.
22. Avery DT, Kalled SL, Ellyard JI, Ambrose C, Bixler SA, Thien M, Brink R, Mackay F, Hodgkin PD, Tangye SG: **BAFF selectively enhances the survival of plasmablasts generated from human memory B cells.** *J Clin Invest* 2003, **112**:286-297.
23. Manz RA, Thiel A, Radbruch A: **Lifetime of plasma cells in the bone marrow.** *Nature* 1997, **388**:133-134.
24. Slifka MK, Antia R, Whitmire JK, Ahmed R: **Humoral immunity due to long-lived plasma cells.** *Immunity* 1998, **8**:363-372.
25. Manz RA, Hauser AE, Hiepe F, Radbruch A: **Maintenance of serum antibody levels.** *Annu Rev Immunol* 2005, **23**:367-386.
26. Shapiro-Shelef M, Lin KI, McHeyzer-Williams LJ, Liao J, McHeyzer-Williams MG, Calame K: **Blimp-1 is required for the formation of immunoglobulin secreting plasma cells and pre-plasma memory B cells.** *Immunity* 2003, **19**:607-620.
27. Minges Wols HA, Underhill GH, Kansas GS, Witte PL: **The role of bone marrow-derived stromal cells in the maintenance of plasma cell longevity.** *J Immunol* 2002, **169**:4213-4221.
28. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, Lin LL, Mantchev GT, Bram RJ, Noelle RJ: **BCMA is essential for the survival of long-lived bone marrow plasma cells.** *J Exp Med* 2004, **199**:91-98.
This study defines B-cell maturation antigen as one of the molecular determinants for the long-term survival of plasma cells.
29. Bernasconi NL, Traggiai E, Lanzavecchia A: **Maintenance of serological memory by polyclonal activation of human memory B cells.** *Science* 2002, **298**:2199-2202.
30. Slifka MK, Rodriguez F, Whitton JL: **Rapid on/off cycling of cytokine production by virus-specific CD8⁺ T cells.** *Nature* 1999, **401**:76-79.
31. Kaech SM, Wherry EJ, Ahmed R: **Effector and memory T-cell differentiation: implications for vaccine development.** *Nat Rev Immunol* 2002, **2**:251-262.
32. Ahmed R, Gray D: **Immunological memory and protective immunity: understanding their relation.** *Science* 1996, **272**:54-60.
33. Wilson CB, Makar KW, Shnyreva M, Fitzpatrick DR: **DNA methylation and the expanding epigenetics of T cell lineage commitment.** *Semin Immunol* 2005, **17**:105-119.
34. Manders PM, Hunter PJ, Telaranta AI, Carr JM, Marshall JL, Carrasco M, Murakami Y, Palmowski MJ, Cerundolo V, Kaech SM *et al.*: **BCL6b mediates the enhanced magnitude of the secondary response of memory CD8⁺ T lymphocytes.** *Proc Natl Acad Sci USA* 2005, **102**:7418-7425.
35. Kersh EN, Kaech SM, Onami TM, Moran M, Wherry EJ, Miceli MC, Ahmed R: **TCR signal transduction in antigen-specific memory CD8 T cells.** *J Immunol* 2003, **170**:5455-5463.
36. Latner DR, Kaech SM, Ahmed R: **Enhanced expression of cell cycle regulatory genes in virus-specific memory CD8⁺ T cells.** *J Virol* 2004, **78**:10953-10959.
37. Veiga-Fernandes H, Rocha B: **High expression of active CDK6 in the cytoplasm of CD8 memory cells favors rapid division.** *Nat Immunol* 2004, **5**:31-37.
38. Sallusto F, Lenig D, Forster R, Lipp M, Lanzavecchia A: **Two subsets of memory T lymphocytes with distinct homing potentials and effector functions.** *Nature* 1999, **401**:708-712.
39. Masopust D, Vezys V, Marzo AL, Lefrancois L: **Preferential localization of effector memory cells in nonlymphoid tissue.** *Science* 2001, **291**:2413-2417.
40. Lanzavecchia A, Sallusto F: **Understanding the generation and function of memory T cell subsets.** *Curr Opin Immunol* 2005, **17**:326-332.
41. Wherry EJ, Teichgraber V, Becker TC, Masopust D, Kaech SM, Antia R, von Andrian UH, Ahmed R: **Lineage relationship and protective immunity of memory CD8 T cell subsets.** *Nat Immunol* 2003, **4**:225-234.
42. Bouneaud C, Garcia Z, Kourilsky P, Pannetier C: **Lineage relationships, homeostasis, and recall capacities of central- and effector-memory CD8 T cells in vivo.** *J Exp Med* 2005, **201**:579-590.

43. Unsoeld H, Krautwald S, Voehringer D, Kunzendorf U, Pircher H: **Cutting edge: CCR7⁺ and CCR7⁻ memory T cells do not differ in immediate effector cell function.** *J Immunol* 2002, **169**:638-641.
44. Roberts AD, Woodland DL: **Cutting edge: effector memory CD8⁺ T cells play a prominent role in recall responses to secondary viral infection in the lung.** *J Immunol* 2004, **172**:6533-6537.
45. Bachmann MF, Wolint P, Schwarz K, Jager P, Oxenius A: **Functional properties and lineage relationship of CD8⁺ T cell subsets identified by expression of IL-7 receptor alpha and CD62L.** *J Immunol* 2005, **175**:4686-4696.
46. Bachmann MF, Wolint P, Schwarz K, Oxenius A: **Recall proliferation potential of memory CD8⁺ T cells and antiviral protection.** *J Immunol* 2005, **175**:4677-4685.
47. Roberts AD, Ely KH, Woodland DL: **Differential contributions of central and effector memory T cells to recall responses.** *J Exp Med* 2005, **202**:123-133.
48. Masopust D, Vezys V, Wherry EJ, Barber DL, Ahmed R: **● Cutting edge: gut microenvironment promotes differentiation of a unique memory CD8 T cell population.** *J Immunol* 2006, **176**:2079-2083.
This study suggests that anatomic location impacts the T-cell memory differentiation program. Transfer and *in vivo* restimulation of memory cells from gut or spleen resulted in memory phenotypes unique to their new environment, independent of the original location.
49. Masopust D, Kaech SM, Wherry EJ, Ahmed R: **The role of programming in memory T-cell development.** *Curr Opin Immunol* 2004, **16**:217-225.
50. Jacob J, Baltimore D: **Modelling T-cell memory by genetic marking of memory T cells *in vivo*.** *Nature* 1999, **399**:593-597.
51. Kaech SM, Ahmed R: **Memory CD8⁺ T cell differentiation: initial antigen encounter triggers a developmental program in naive cells.** *Nat Immunol* 2001, **2**:415-422.
52. Opferman JT, Ober BT, Ashton-Rickardt PG: **Linear differentiation of cytotoxic effectors into memory T lymphocytes.** *Science* 1999, **283**:1745-1748.
53. van Stipdonk MJ, Hardenberg G, Bijker MS, Lemmens EE, Droin NM, Green DR, Schoenberger SP: **Dynamic programming of CD8⁺ T lymphocyte responses.** *Nat Immunol* 2003, **4**:361-365.
54. van Stipdonk MJ, Lemmens EE, Schoenberger SP: **Naive CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation.** *Nat Immunol* 2001, **2**:423-429.
55. Wong P, Pamer EG: **Cutting edge: antigen-independent CD8 T cell proliferation.** *J Immunol* 2001, **166**:5864-5868.
56. Kaech SM, Tan JT, Wherry EJ, Konieczny BT, Surh CD, Ahmed R: **Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells.** *Nat Immunol* 2003, **4**:1191-1198.
57. Badovinac VP, Porter BB, Harty JT: **CD8⁺ T cell contraction is controlled by early inflammation.** *Nat Immunol* 2004, **5**:809-817.
Collectively, these studies [57*,61*-64*] illustrate the functional significance of inflammatory cytokines in driving effector T-cell expansion, survival and function.
58. Huster KM, Busch V, Schiemann M, Linkemann K, Kerksiek KM, Wagner H, Busch DH: **Selective expression of IL-7 receptor on memory T cells identifies early CD40L-dependent generation of distinct CD8⁺ memory T cell subsets.** *Proc Natl Acad Sci USA* 2004, **101**:5610-5615.
59. Manjunath N, Shankar P, Wan J, Weninger W, Crowley MA, Hieshima K, Springer TA, Fan X, Shen H, Lieberman J *et al.*: **Effector differentiation is not prerequisite for generation of memory cytotoxic T lymphocytes.** *J Clin Invest* 2001, **108**:871-878.
60. Curtsinger JM, Johnson CM, Mescher MF: **CD8 T cell clonal expansion and development of effector function require prolonged exposure to antigen, costimulation, and signal 3 cytokine.** *J Immunol* 2003, **171**:5165-5171.
61. Curtsinger JM, Lins DC, Johnson CM, Mescher MF: **Signal 3 tolerant CD8 T cells degranulate in response to antigen but lack granzyme B to mediate cytotoxicity.** *J Immunol* 2005, **175**:4392-4399.
See annotation to [57*].
62. Curtsinger JM, Valenzuela JO, Agarwal P, Lins D, Mescher MF: **● Type I IFNs provide a third signal to CD8 T cells to stimulate clonal expansion and differentiation.** *J Immunol* 2005, **174**:4465-4469.
See annotation to [57*].
63. Kolumam GA, Thomas S, Thompson LJ, Sprent J, Murali-Krishna K: **Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection.** *J Exp Med* 2005, **202**:637-650.
See annotation to [57*].
64. Zeng R, Spolski R, Finkelstein SE, Oh S, Kovanen PE, Hinrichs CS, Pise-Masison CA, Radonovich MF, Brady JN, Restifo NP *et al.*: **Synergy of IL-21 and IL-15 in regulating CD8⁺ T cell expansion and function.** *J Exp Med* 2005, **201**:139-148.
See annotation to [57*].
65. Badovinac VP, Porter BB, Harty JT: **Programmed contraction of CD8⁺ T cells after infection.** *Nat Immunol* 2002, **3**:619-626.
66. Pulendran B, Ahmed R: **Translating innate immunity into immunological memory: implications for vaccine development.** *Cell* 2006, **124**:849-863.
67. Mora JR, Bono MR, Manjunath N, Weninger W, Cavanagh LL, Rosenblatt M, Von Andrian UH: **Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells.** *Nature* 2003, **424**:88-93.
68. Lanzavecchia A, Sallusto F: **Progressive differentiation and selection of the fittest in the immune response.** *Nat Rev Immunol* 2002, **2**:982-987.
69. van Faassen H, Saldanha M, Gilbertson D, Dudani R, Krishnan L, Sad S: **Reducing the stimulation of CD8⁺ T cells during infection with intracellular bacteria promotes differentiation primarily into a central (CD62L^{high}CD44^{high}) subset.** *J Immunol* 2005, **174**:5341-5350.
70. Marzo AL, Klonowski KD, Le Bon A, Borrow P, Tough DF, Lefrancois L: **Initial T cell frequency dictates memory CD8⁺ T cell lineage commitment.** *Nat Immunol* 2005, **6**:793-799.
71. Wherry EJ, Barber DL, Kaech SM, Blattman JN, Ahmed R: **● Antigen-independent memory CD8 T cells do not develop during chronic viral infection.** *Proc Natl Acad Sci USA* 2004, **101**:16004-16009.
These three articles [71*,73*,74*] demonstrate that in chronic infections IL-7 and IL-15 receptors on virus-specific CD8 T cells are suppressed and canonical memory properties are impaired.
72. Wherry EJ, Ahmed R: **Memory CD8 T-cell differentiation during viral infection.** *J Virol* 2004, **78**:5535-5545.
73. Fuller MJ, Hildeman DA, Sabbaj S, Gaddis DE, Tebo AE, Shang L, Goepfert PA, Zajac AJ: **Cutting edge: emergence of CD127^{high} functionally competent memory T cells is compromised by high viral loads and inadequate T cell help.** *J Immunol* 2005, **174**:5926-5930.
See annotation to [71*]
74. Lang KS, Recher M, Navarini AA, Harris NL, Lohning M, Junt T, Probst HC, Hengartner H, Zinkernagel RM: **Inverse correlation between IL-7 receptor expression and CD8 T cell exhaustion during persistent antigen stimulation.** *Eur J Immunol* 2005, **35**:738-745.
See annotation to [71*]
75. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ, Ahmed R: **● Restoring function in exhausted CD8 T cells during chronic viral infection.** *Nature* 2006, **439**:682-687.
This study shows that *in vivo* blockade of the inhibitory molecule PD-1 can restore the function of exhausted CD8 T cells during chronic viral infection. This provides a means for generating effective immune responses in the setting of persistent antigen.
76. Greenwald RJ, Freeman GJ, Sharpe AH: **The B7 family revisited.** *Annu Rev Immunol* 2005, **23**:515-548.
77. Intlekofer AM, Takemoto N, Wherry EJ, Longworth SA, Northrup JT, Palanivel VR, Mullen AC, Gasink CR, Kaech SM,

Miller JD *et al.*: **Effector and memory CD8⁺ T cell fate coupled by T-bet and eomesodermin.** *Nat Immunol* 2005, **6**:1236-1244.

By studying mice that have compound mutations of the genes that encode the transcription factors T-bet and eomesodermin, this experiment demonstrates the molecular basis for survival of IL-15-dependent memory subsets and natural killer cells, as well as the function of effector cytotoxic T lymphocytes.

78. Yajima T, Yoshihara K, Nakazato K, Kumabe S, Koyasu S, Sad S, Shen H, Kuwano H, Yoshikai Y: **IL-15 regulates CD8⁺ T cell contraction during primary infection.** *J Immunol* 2006, **176**:507-515.
79. Becker TC, Coley SM, Wherry EJ, Ahmed R: **Bone marrow is a preferred site for homeostatic proliferation of memory CD8 T cells.** *J Immunol* 2005, **174**:1269-1273.
80. Di Rosa F, Pabst R: **The bone marrow: a nest for migratory memory T cells.** *Trends Immunol* 2005, **26**:360-366.
81. Khanolkar A, Fuller MJ, Zajac AJ: **CD4 T cell-dependent CD8 T cell maturation.** *J Immunol* 2004, **172**:2834-2844.
82. Northrop JK, Shen H: **CD8⁺ T-cell memory: only the good ones last.** *Curr Opin Immunol* 2004, **16**:451-455.
83. Janssen EM, Droin NM, Lemmens EE, Pinkoski MJ, Bensinger SJ, Ehst BD, Griffith TS, Green DR, Schoenberger SP: **CD4⁺ T-cell help controls CD8⁺ T-cell memory via TRAIL-mediated activation-induced cell death.** *Nature* 2005, **434**:88-93.
- This study provides evidence that memory CD8 T cells generated in the absence of CD4 T-cell help undergo TRAIL-mediated activation-induced cell death during recall responses.
84. Sun JC, Bevan MJ: **Cutting edge: long-lived CD8 memory and protective immunity in the absence of CD40 expression on CD8 T cells.** *J Immunol* 2004, **172**:3385-3389.
85. Smith CM, Wilson NS, Waithman J, Villadangos JA, Carbone FR, Heath WR, Belz GT: **Cognate CD4⁺ T cell licensing of dendritic cells in CD8⁺ T cell immunity.** *Nat Immunol* 2004, **5**:1143-1148.
86. Kaech SM, Hemby S, Kersh E, Ahmed R: **Molecular and functional profiling of memory CD8 T cell differentiation.** *Cell* 2002, **111**:837-851.
87. Williams MA, Bevan MJ: **Shortening the infectious period does not alter expansion of CD8 T cells but diminishes their capacity to differentiate into memory cells.** *J Immunol* 2004, **173**:6694-6702.
88. Kersh EN, Fitzpatrick DR, Murali-Krishna K, Shires J, Speck SH, Boss JM, Ahmed R: **Rapid demethylation of the IFN- γ gene occurs in memory but not naïve CD8 T cells.** *J Immunol* 2006, **176**:4083-4093.



Endeavour

The quarterly magazine for the history and philosophy of science.

You can access *Endeavour* online on ScienceDirect, where you'll find book reviews, editorial comment and a collection of beautifully illustrated articles on the history of science.



Featuring:

Waxworks and the performance of anatomy in mid-eighteenth-century Italy by L. Dacome
Representing revolution: icons of industrialization by P. Fara
Myths about moths: a study in contrasts by D.W. Rudge
The origins of research into the origins of life by I. Fry
In search of the sea monster by K. Hvidtfelt Nielsen
Michael Faraday, media man by P. Fara

Coming soon:

The Livingstone story and the Industrial Revolution by L. Dritsas
Intertwined legacies: Pierre Curie and radium by D.H. Rouvray
Provincial geology and the Industrial Revolution by L. Veneer
The history of computer climate modeling by M. Greene
The history of NASA's exobiology program by S.J. Dick

And much, much more...

Endeavour is available on ScienceDirect, www.sciencedirect.com