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Heterogeneity and Cell-Fate Decisions in Effector and Memory CD8+ T Cell Differentiation during Viral Infection

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Abstract

Heterogeneity is a hallmark of the adaptive immune system. This is most evident in the enormous diversity of B and T cell antigen receptors. There is also heterogeneity within antiviral T cell populations, and subsets of effector and memory T cells now permeate our thinking about specialization of T cell responses to pathogens. It has been less clear, however, how heterogeneity in developing virus-specific effector and memory T cells is related to cell-fate decisions in the immune response, such as the generation long-lived memory T cells. Here we discuss recent findings that might help redefine how heterogeneity in antiviral T cell populations gives rise to T cell subsets with short- and long-lived cell fates.

Cardinal Features of Memory T Cells

Immunological Memory (IM) is a defining characteristic of the adaptive immune system that, during primary infection, produces long-lived plasma cells and memory T and B cells. These memory B and T cells are endowed with unique properties that permit more vigorous and specific responses upon reinfection to protect against pathogens. These key memory B and T cell properties are central to our current understanding of IM, yet the pathways that give rise to optimal memory B and T cells remain poorly understood. This review will focus principally on the development of memory T cells during viral infection. The accompanying review by Dörner and Radbruch covers recent work on antiviral B cell responses (Dörner and Radbruch, 2007). Here we focus on recent advances in our understanding of antiviral memory $CD8^+$ T cell differentiation and, although the majority of the discussion focuses on viral systems, selected data from nonviral experimental models are also discussed, where relevant to antiviral immunity.

Over the last ten years, the innovation of major histocompatibility complex (MHC) class I and II tetramers, the use of T cell receptor (TCR) transgenic mice, and other techniques have led to the detailed quantitation, isolation, and characterization of virus-specific T cell populations in mice, nonhuman primates, and humans during infection. This work outlined the kinetics of virus-specific responses with great precision (Figure 1). A T cell response to a typical acute viral infection can be characterized by three distinct phases: expansion and effector T cell differentiation (profound clonal expansion and acquisition of effector functions), contraction (death of the majority of activated effectors T cells via apoptosis), and stable memory (formation of a numerically stable long-lived population of memory T cells) (Ahmed and Gray, 1996; Williams and Bevan, 2007; Zinkernagel et al., 1996). Virus-specific T cells can expand as much as 10^4-fold to 10^5-fold, in as little as 8 days, from as

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few as 100–200 naive precursors (Arstila et al., 1999; Blattman et al., 2002). This massive T cell proliferation is critical to long-term immunity because the magnitude of the initial clonal burst typically determines memory T cell numbers (Hou et al., 1994; Murali-Krishna et al., 1998). Moreover, extensive cellular differentiation occurs as these newly activated T cells become potent antiviral effector T cells and ultimately memory T cells. Effector T cells migrate to virtually all tissues and eliminate the pathogen by killing infected cells, producing cytokines, and recruiting other leukocytes via chemokine production. In general, effector $CD8^+$ T cells control infection through cytotoxic activity (via perforin and granzymes) and the secretion of interferon (IFN)-γ and tumor necrosis factor (TNF)α (Kaech et al., 2002b; Wherry and Ahmed, 2004; Williams and Bevan, 2007). Effector $CD4^+$ T cells take on a diverse set of roles and inhibit viral replication through the production of antiviral cytokines (and perhaps cytotoxicity), but they also activate dendritic cells (DCs) and provide help to B cells and $CD8^+$ T cells (Seder and Ahmed, 2003).

After the expansion and contraction phases, a fraction (i.e., typically 5%–20%) of virus-specific T cells survives, forming a pool of memory T cells. Unlike most somatic cells in which terminal differentiation results in a functional, but a nonmitotic cell, the major product of memory T cell differentiation is a population of T cells that retains stem cell-like qualities. That is, after *acute* viral infections, long-lived memory T cells are endowed with multipotency, a high proliferative potential, telomerase expression, and self renewal (Williams and Bevan, 2007). These memory T cells persist in an antigen-independent, but cytokine-dependent (namely interleukin-15 [IL-15] and IL-7), manner, and slowly divide (referred to here as homeostatic turnover) (Surh et al., 2006). But almost immediately upon reinfection, memory T cells begin to produce effector molecules, undergo dramatic clonal expansion, and differentiate into secondary effector T cells. This qualitatively and quantitatively enhanced memory T cell response results in faster control of infection compared to a primary response (Figure 1). Thus, the cardinal features of memory T cells are maintenance of (1) high proliferative potential, (2) a multipotent state, meaning that memory T cells can maintain memory T cell identity but also rapidly reactivate antiviral effector functions upon reinfection, and (3) long-term survival and self renewal in the absence of antigen via IL-7- and IL-15-driven homeostatic turnover.

This fairly customary description of effector and memory T cell differentiation during viral infection, however, does not incorporate the complexity of the multiple subpopulations of T cells that are now known to exist. These effector and memory T cell subsets differ not only in their effector functions, migratory properties, and proliferative potential, but also in their long-term persistence and ability to form protective memory T cells. How these distinct effector and memory T cell subsets form, function, and persist is a matter of great interest and will be the main topic of this review.

Effector and Memory T Cell Development and Fate Decisions

Models of Memory T Cell Development during Viral Infection

Despite tremendous advances in our characterization of memory T cells in the last decade, we still do not know *when and how* memory T cells actually form after infection. The answers might largely depend on how one defines a memory T cell. One of the oldest but still most widely used definitions is based simply on time after infection; once antigen-specific T cell numbers stabilized (several weeks to months after infection), these cells were typically deemed memory T cells. However, this definition does not take into account the more concrete functional aspects and subsets of memory T cells described above. When considering the development of T cell memory on the basis of measurable memory T cell properties (i.e., high proliferative potential, multipotency, rapid recall, and homeostatic turnover), at least four possible models can be envisioned (Figure 2).

Model 1 — Uniform Potential—The first model is rooted in an extrinsic viewpoint. Here, the effector T cell pool is relatively homogenous, with each cell having acquired effector functions and memory T cell developmental potential equivalently. Competition for, or withdrawal from, nutrients, cytokines, growth factors, antigen, or other environmental resources limits the number of T cells that can survive contraction and enter the memory T cell pool (Freitas and Rocha, 2000). However, this simple model of memory T cell formation is insufficient to explain the heterogeneity within effector and memory T cell populations and also does not help define *when* memory T cell properties are acquired.

Model 2—Decreasing Potential—In the second model, the early effector T cells also start off with relatively equal memory T cell developmental potential. However, the effector T cells progressively lose memory cell potential and are pushed toward terminal differentiation in a linear fashion as TCR stimulation is increased or prolonged (Ahmed and Gray, 1996). This second model provides a mechanism for creating a heterogeneous pool of effector T cells in various stages of differentiation according to their stimulation history during infection. This model might be particularly useful in explaining the properties of latecomers in the T cell response (Catron et al., 2006; D'Souza and Hedrick, 2006; Jelley-Gibbs et al., 2007) and T cell fates during chronic or latent infections or repetitive stimulation (Wherry and Ahmed, 2004). Although this model was originally based mostly on the effects of antigenic signaling, it does not rule out that exposure to other signals might be involved.

Model 3—Fixed Lineage—A third model posits that memory or effector T cell lineage commitment occurs very early after the initial T cell stimulation, such that fully mature memory T cells and effector T cells coexist within the effector T cell population (Farber, 1998; Sallusto and Lanzavecchia, 2001). According to this model, these preformed memory T cells might bypass the effector stage, possess all characteristic traits of memory T cells, and survive the contraction phase, whereas the effector T cells die. Some evidence for this model is that at the peak of clonal expansion, a minority of T cells bears phenotypic resemblance to memory T cells found several weeks later (Lefrancois and Marzo, 2006). Also, it is possible to isolate $CD4^+$ T cells early in the immune response that do not have full effector function, but can persist long term (Wu et al., 2002). Furthermore, this model might more accurately portray the events that occur when naive T cells are primed under noninfectious conditions, such as with DC vaccines (Badovinac et al., 2005). In another recent study, asymmetric separation of daughter cells at the first T cell division was observed, and one daughter T cell adopted a memory cell fate and the other an effector T cell fate (Chang et al., 2007), suggesting that lineages might be fixed as early as the first cell division. It remains to be determined, though, how this 50:50 split in cell fates after division one leads to only 5%–20% of the clonal T cell burst entering the memory T cell pool.

Model 4—Fate Commitment with Progressive Differentiation—The fourth model builds on the first three, but differs in several important respects. One distinction is that it postulates the existence of memory precursor effector cells (MPECs). These MPECs are not fully mature memory T cells, as in the third model, but rather they possess effector properties (hence MP*E*C) and require further differentiation to gain quintessential memory T cell properties, such as a high proliferative potential and the ability to undergo homeostatic turnover. Also, the effector T cell pool is heterogeneous and contains many short-lived effector cells (SLECs) that will die after infection, and a smaller fraction of MPECs with the potential to become long-lived memory T cells. The SLECs are a terminally differentiated cell population, but, unlike in the third model, the MPEC fate is not fixed. That is, the MPECs retain plasticity to develop into SLECs if additional strong stimulatory signals are encountered (e.g., persisting antigen and/or inflammation). This model is also consistent

with early fate commitment in the first T cell division (Chang et al., 2007) if the memory-fated daughter T cells require further differentiation events to mature into a long-lived memory T cell.

In this model, the primary basis for the cell-fate decision is the magnitude of the overall strength of signal, which includes the combined effects of antigen, costimulation, and inflammation (signals 1, 2, and 3). High or excessively strong signals drive greater clonal expansion but also promote terminal effector T cell differentiation. The fourth model differs from the decreasing-potential hypothesis in that different cell fates can be specified early according to the intensity of the signals received (Gett et al., 2003) but do not require multiple rounds of stimulation to create heterogeneous cell fates.

Distinguishing which of the models of memory T cell development occurs during viral infections has been a difficult and controversial challenge. Indeed, these models are not mutually exclusive, and it is possible that multiple pathways exist for generating effector T cells and long-lived memory T cells depending on the T cell priming conditions. We will now discuss our current understanding of effector and memory T cell heterogeneity and the implications for T cell memory with these models as a guide.

Identification of Memory Precursors and Defining Their Progressive Differentiation

Initially, several reports suggested that the entire Naive → Effector → Memory (N → E → M) differentiation process could run on autopilot after a brief (~24 hr) stimulation with antigen (Williams and Bevan, 2007). Subsequent work has shown that $CD4^+$ T cell help, IL-2, inflammation, and persisting antigen can greatly influence memory T cell differentiation. Moreover, functional, phenotypic and gene-expression profiling of antigen-specific T cell populations during the course of an antiviral T cell response has led to the notion that fully competent memory T cells develop gradually after the clearance of acute viral infection (as referred to in models 1 and 4) (Kaech et al., 2002a). After most acute viral infections, the memory T cell pool slowly converts from a population containing mostly effector memory T (T_{EM}) cells (e.g., $CD62L^{Lo}$, $CCR7^{Lo}$, $IL\text{-}2^{Lo}$) to one containing central memory T (T_{CM}) cells (e.g., $CD62L^{Hi}$, $CCR7^{Hi}$, $IL\text{-}2^{+}$) that exhibit a high proliferative potential and can homeostatically turn over (Wherry and Ahmed, 2004). A number of other important phenotypic changes also occur gradually in the memory pool, resulting in memory T cells with a more mature phenotype ($IL\text{-}7R^{Hi}$, $CD27^{Hi}$, $CD122^{Hi}$, $Bcl\text{-}2^{Hi}$, $KLRG1^{Lo}$, $CXCR3^{Hi}$, and $CD43^{Lo}$) that differs considerably from the starting effector T cell population (Figure 3 and Table 1) (Badovinac et al., 2007; Hikono et al., 2007; Kaech et al., 2003; Wherry et al., 2004; Wherry et al., 2003). Because this process is gradual, a snapshot taken at one or two time points early after infection might be insufficient to appreciate the full dynamics and timeframe of these changes. The phenotypic changes in the memory T cell population could result from selective survival of different subsets (model 3), actual cellular conversion (models 1 and 4), or both.

The progressive changes in memory T cell function (e.g., high proliferative potential, homeostatic turnover) that accompany the E → M transition help to delineate when memory T cells form after acute infection. These data alone, however, do not distinguish whether the effector T cell population is homogenous or heterogeneous with regard to the potential to form memory T cells (model 1 versus models 2, 3, and 4). The examination of gene and surface marker expression has demonstrated that, like the memory T cell population, the effector T cell population is rich in cellular and functional heterogeneity (Wherry and Ahmed, 2004). In particular, a subset of effector $CD8^+$ T cells can be identified that already expressed certain features of memory $CD8^+$ T cells, such as increased IL-7R expression (Huster et al., 2004; Kaech et al., 2003). However, these $IL\text{-}7R^{Hi}$ effector $CD8^+$ T cells did not appear to be preformed memory T cells (model 3), but rather they were more like

MPECs (model 4). The IL-7R^{Hi} T cells had full effector function and expressed cytotoxic molecules (e.g., granzyme B) and IFN-γ, but, similar to their IL-7R^{Lo} counterparts, the IL-7R^{Hi} effector T cells had a relatively low proliferative capacity compared to mature memory T cells (Huster et al., 2004; Kaech et al., 2003). The IL-7R^{Hi} effector T cells, however, had a substantially increased ability to become self-renewing memory T cells compared to the IL-7R^{Lo} effector T cells (Huster et al., 2004; Kaech et al., 2003). A number of subsequent studies in infectious models support the idea that the IL-7R^{Hi} fraction of effector CD8$^+$ T cells contains MPECs, though in some cases (e.g., low inflammatory conditions), not all IL-7R^{Hi} effector T cells are destined to populate the memory pool (Castellino and Germain, 2007; Hand et al., 2007; Huster et al., 2004; Kaech et al., 2003; Lacombe et al., 2005). Taken together, it appears that by approximately 1 to 2 weeks after viral infection, effector CD8$^+$ T cells have committed to short-lived or long-lived cell fates.

Pathways That Induce Effector and Memory T Cell Heterogeneity

What are the signals and genetic pathways that affect T cell longevity and specify different effector and memory T cell lineages? Although we are far from a complete understanding of these pathways, a substantial body of work has outlined some key factors, including (1) the role of CD4$^+$ T cell help, (2) common gamma-chain cytokines, and (3) the strength of antigenic and inflammatory signals during T cell priming.

CD4$^+$ T Cell Help and IL-2

CD4$^+$ T cells, CD40-CD40L signals, and IL-2 help to maximize effector CD8$^+$ T cell expansion, an effective E → M transition, and long-term maintenance after acute viral infections (Northrop and Shen, 2004; Rocha and Tanchot, 2004; Williams and Bevan, 2007). The result of defective CD4$^+$ T cell help is the generation of a population of anti-viral CD8$^+$ T cells that largely resembles T$_{EM}$ cells, responds poorly to rechallenge, and in some cases expresses the death receptor, Trail (Badovinac et al., 2006; Janssen et al., 2005). Interestingly, IL-2 acts early during infection to instill robust recall capacity in the memory CD8$^+$ T cells that develop later (Williams et al., 2006). An early source of IL-2 during CD4$^+$ T cell priming is also required for optimal memory CD4$^+$ T cell differentiation (Dooms et al., 2007). One possible mechanism for early CD4$^+$ T cell help for CD8$^+$ T cells is by the enhancement of naive CD8$^+$ T cell chemotaxis to helped DCs (Castellino et al., 2006). In addition, there is some evidence that the high-affinity antibodies produced by the CD4$^+$ T:B cell collaboration may indirectly help memory CD8$^+$ T cell development because passive immune therapy can improve memory CD8$^+$ T cell function in CD4$^+$-deficient animals (Bachmann et al., 2004). There might also be an interesting connection between elevated T-bet expression in unhelped CD8$^+$ T cells and the enrichment of T$_{EM}$-phenotype cells. (Intlekofer et al., 2007) Thus, CD4$^+$ T cells appear to modulate the developing effector and memory T cell subpopulations through mechanisms that include APC activation, CD40:CD40L, IL-2, neutralizing antibody, Trail, and T-bet.

IL- 7 and IL-15

IL-7 and IL-15 are important for both antiviral memory CD8$^+$ and CD4$^+$ T cell generation and homeostasis (Purton et al., 2007; Surh et al., 2006). In vitro priming in the presence of IL-2 or IL-15 can lead to T$_{EM}$ cell-like or T$_{CM}$ cell-like populations of CD8$^+$ T cells, respectively (Manjunath et al., 2001). IL-7 and IL-15, however, do not appear to play major instructive roles in the actual MPEC- versus SLEC-fate decision in vivo. Most data indicate that reducing or enhancing IL-7 or IL-15 signals during the N → E or E → M stages does not greatly alter the number IL-7R^{Hi} MPECs or memory CD8$^+$ T cells that ultimately form (Hand et al., 2007; Klonowski et al., 2006; Sun et al., 2006; Tripathi et al., 2007) (S.M.K., unpublished data). Treatment with IL-2, IL-7, and IL-15 during the contraction phase will

substantially protract effector T cell death, but it does not seem to affect the memory $CD8^+$ T cell population quantitatively or qualitatively (Blattman et al., 2003; Hand et al., 2007; Klonowski et al., 2006; Melchionda et al., 2005; Sun et al., 2006; Tripathi et al., 2007) (S.M.K., unpublished data). Moreover, the forced expression of IL-7R on all effector $CD8^+$ T cells does not save the terminally differentiated IL-$7R^{Lo}$ SLECs from death (Hand et al., 2007). Altogether, these data suggest that IL-7R downregulation is symptomatic, not causal, to effector $CD8^+$ T cell contraction after infection and that, although IL-7 and IL-15 can clearly provide survival signals, these important homeostatic cytokines are unlikely to provide differentiation signals for the generation of subsets of effector and memory T cells in vivo.

Strength of Signal: Antigen, Costimulation, and Inflammation

In general, there are three major classes of signals necessary for T cell activation and differentiation: signal 1 from antigen, signal 2 from costimulation, and signal 3 from inflammation. The strength (magnitude and/or duration) of signal 1 can influence the size of the virus-specific T cell response (Bullock et al., 2000; Wherry et al., 1998; Wherry et al., 1999). What has remained less clear is how the strength of TCR signaling during infection qualitatively influences memory T cell differentiation. Limiting the strength or duration of signals received by T cells during priming can alter both the types of effector T cell subsets produced and their rate of memory cell maturation. In general, blunting the infection, reducing the duration of stimulation, or increasing intraclonal T cell competition leads to enhanced formation of effector T cells expressing high amounts of IL-7R and CD62L and low amounts of KLRG1 (Badovinac et al., 2007; Badovinac et al., 2005; Joshi et al., 2007; Marzo et al., 2005; Williams and Bevan, 2004) (E.J.W., unpublished data). In some experiments, this effect was accompanied by more rapid, but not necessarily more abundant, memory T cell development (Badovinac and Harty, 2007; Badovinac et al., 2005). Together, these observations demonstrated that the strength or duration of infection is a critical factor regulating the quality and rate of memory $CD8^+$ T cell differentiation, but it was unclear how the strength of antigenic, costimulatory, or inflammatory signals was individually involved.

Costimulatory signals (signal 2) from receptors such as CD28, CD40, 41BB, CD27, ICOS, and OX40 clearly impact the size of the antiviral effector and memory T cell populations, with some notable differences in their effects on $CD4^+$ versus $CD8^+$ T cells (Greenwald et al., 2005; Watts, 2005). Interestingly, the expression levels of some costimulatory receptors, including CD27, CD28, and others, are often used to distinguish subsets of antiviral T cells, especially in humans (van Lier et al., 2003). Costimulation certainly plays an important role in effector and memory T cell survival during infection, but what influence these signals have, if any, on instructing effector versus memory T cell-fate determination is not clear.

Although inflammation can augment the expression of costimulatory molecules, inflammatory cytokines can also directly impact effector T cell expansion and differentiation (Mescher et al., 2006). For example, type I IFN, IL-12, and IFN-γ signals can act directly on T cells for optimal effector T cell expansion and survival (Badovinac et al., 2000; Curtsinger et al., 2003; Haring et al., 2005; Kolumam et al., 2005; Mullen et al., 2001; Whitmire et al., 2005a; Whitmire et al., 2005b). An interesting point that emerged from these studies is that the nature of the pathogen can determine which cytokine will be most influential for developing effector T cells (Cousens et al., 1999). For instance, lymphocytic choriomeningitis virus (LCMV) specific $CD8^+$ T cell responses are critically dependent on type I IFN, but do not require IL-12, whereas the opposite is true for $CD8^+$ T cells responding to *Listeria monocytogenes* infection (Way et al., 2007).

Inflammatory cytokines also appear to play a key role in some cell-fate decisions in the developing T cell response by altering the distribution of effector T cells that have memory T cell potential (i.e., MPECs) versus terminally differentiated cells (i.e., SLECs) (Badovinac et al., 2005; Joshi et al., 2007; Pearce and Shen, 2007). Under low inflammatory conditions, fewer IL-7R^{Lo} effector T cells are generated. As inflammation increases, the formation of more IL-7R^{Lo} effector T cells is favored. It appears that for a constant dose of antigen, increasing inflammatory signals can increase the SLEC to MPEC ratio. IL-12 and IFN-γ are two primary players in this process, but other signals are undoubtedly involved in this process because IL-12 and IFN-γ amounts can vary between different infections (Cousens et al., 1999), and likely candidates are type I IFNs (Curtsinger et al., 2005; Kolumam et al., 2005; Way et al., 2007), other IL-12 family members, or even Toll-like receptor ligands that act directly on T cells (Hervas-Stubbs et al., 2007). For the purposes of vaccination, one might predict that the type of inflammatory signal will be as important as the amount. Indeed, some recent evidence for this concept is emerging from vaccine studies (Wille-Reece et al., 2006), and this issue of the recognition of viral infection by the innate immune system and subsequent inflammatory response is covered in the accompanying review by Pichlmair and Reis e Sousa (2007).

Although a dose-dependent inflammation model suggests that for a given dose of antigen lower inflammatory conditions favor memory T cell development, this should not be incorrectly interpreted to mean that the absence of inflammation enhances memory T cell formation. The priming of T cells without any inflammation leads to tolerance and/or clonal deletion (Redmond and Sherman, 2005). Thus, some inflammation is clearly required for optimal T cell expansion, effector T cell development, and memory T cell generation. It is not clear, however, whether increased inflammation would induce greater numbers of SLECs at the expense of MPECs or whether MPEC numbers are determined by other factors. Moreover, if the SLEC versus MPEC decision is based on an overall strength of signal, then the effects of inflammation might vary according to the degree of TCR stimulation. This idea should be testable by varying inflammation at constant doses of antigen and vice versa, and then examining SLEC versus MPEC fates and memory T cell formation. In addition, it will be interesting to examine whether inflammation can act in a bystander manner with or without TCR signaling during memory T cell differentiation. To rationally apply these principles to vaccination, one might need to determine the optimal inflammatory signals for a given dose or regimen of antigen exposure.

Balancing Effector T Cell Differentiation and Memory T Cell Fates

Additional heterogeneity, other than simply short-term and long-term fates, exists in the functional specification of T cells during infection. This point is more obvious for CD4$^+$ T cells, compared to CD8$^+$ T cells, where a diverse array of effector cell types (Th1, Th2, Th17, T_{FH}, Treg, etc.) exists. Thus, T cell fate decisions might exist in layers: Activated T cells commit to (1) which type of effector cell to become and (2) whether to be long lived or not. The specification of different effector CD4$^+$ T cell populations is based on key innate immune cytokines that induce the appropriate effector T cell response for the given pathogen or adjuvant (IFN-γ and IL-12 → T-bet → Th1; IL-4 → GATA3 and c-maf → Th2; IL-6 and TGFβ → rorγ → TH17 and TGFγ → FoxP3 → Treg). It is unclear whether every effector T cell lineage produces long-lived, self-renewing memory T cells, and if so, whether common or separate pathways are used. For example, some evidence implies that IL-7R might also be a marker for Th1 CD4$^+$ T cells (Dooms et al., 2007; Kondrack et al., 2003; Li et al., 2003; Purton et al., 2007), but it remains to be seen whether this will apply to all effector T cell lineages (e.g., Th2 or Th17).

Some data suggest that effector function specification and memory T cell potential are intertwined, but the precise mechanism is unclear (Intlekofer et al., 2005; Joshi et al., 2007; Takemoto et al., 2006; Wu et al., 2002). For example, Th1 cells with the potential to form memory T cells versus terminally differentiated effector Th1 could be distinguished based on low and high levels of IFN-γ production, respectively (Wu et al., 2002). It is worth pointing out that virus-specific IFN-γ-producing $CD4^+$ T cells can efficiently populate the memory T cell pool (Whitmire et al., 2006), though the attrition of these cells has been documented in some infections (Homann et al., 2001). Another example is that recent work in $CD8^+$ T cells suggests that memory T cell potential is inversely linked to T-bet expression. In LCMV infection, SLECs contain higher amounts of T-bet than do MPECs, and the overexpression of T-bet in these effector $CD8^+$ T cells could induce an SLEC fate (Joshi et al., 2007). T-bet expression can be regulated by inflammatory cytokines in a dose-dependent manner, and hence these data provide a mechanism for how some inflammatory signals can influence the MPEC- versus SLEC-fate decision (Joshi et al., 2007; Takemoto et al., 2006). Also, it is not clear how T-bet and eomesodermin (Eomes), another T-box transcription factor involved in effector $CD8^+$ T cell differentiation, cooperate to regulate effector $CD8^+$ T cell fates (Takemoto et al., 2006).

The control of innate cytokines on T cell expression of lineage-determining transcription factors, such as T-bet, that can specify both effector functions and memory fates creates a sensible way for the innate immune system to influence T cell homeostasis long term. It will be interesting to examine whether this model applies to other key transcription factors involved in lymphocyte differentiation.

Memory T Cell Subsets

T cell heterogeneity also has considerable implications for the protective immunity afforded by memory T cells. Indeed, it was the seminal work of a few groups in the late 1990s that first outlined the existence of specific memory T cell subsets (coined T_{EM} and T_{CM} cells) and alerted us to the importance of heterogeneity within antigen-specific T cell populations (Hamann et al., 1997; Sallusto et al., 1999). However, it is quite evident today that memory T cell heterogeneity is more complex than simply T_{CM} and T_{EM} cells. Nonetheless, the concept of T_{EM} and T_{CM} cells remains an important paradigm, though a number of important questions remain unresolved with regard to these memory T cell subsets. These include understanding how T_{EM} and T_{CM} cells contribute to protective immunity to different pathogens, the precise lineage relationships between these cell types, and how the heterogeneity in the memory T cell pool is related to the early effector T cell heterogeneity discussed above.

T_{EM} and T_{CM} cells were first distinguished in humans based on lymph node (LN) homing receptor CD62L and CCR7 expression, effector functions, and proliferative capacity (Sallusto et al., 1999). These studies gave rise to the original views of T_{EM} and T_{CM} cells in which T_{EM} cells exist at the portals of pathogen entry and possess immediate effector functions and a reduced proliferative capacity, and T_{CM} cells exist mainly in lymph nodes, express effector function upon restimulation, and mount robust secondary responses. Although these largely accepted definitions persist, it is worth noting that one important caveat of using strictly $CD62L^{Lo}$ and $CCR7^{Lo}$ to define T_{EM} cells is that recently activated effector T cells share this phenotype, thus blurring the line between true effector T cells and resting T_{EM} cells. In general, T_{EM} cells are not in LNs, but they can be found in spleen, blood, and a variety of nonlymphoid tissues, whereas T_{CM} cells are found in LN, spleen, and blood, and they also enter nonlymphoid tissues, albeit less efficiently than do T_{EM} cells (Marshall et al., 2001; Masopust et al., 2001; Reinhardt et al., 2001; Wherry et al., 2003). In addition, some of the functional differences first noted in $CD4^+$ T_{EM} and T_{CM} cells do not

hold up as well in memory $CD8^+$ T cell subsets because $CD8^+$ T_{EM} and T_{CM} cells are nearly equivalent in their production of effector cytokines and cytotoxicity (Barber et al., 2003; Ravkov et al., 2003; Unsoeld et al., 2002; Wherry et al., 2003). However, the augmented capacity of T_{CM} cells to proliferate to antigen and homeostatic signals and to produce IL-2, compared to T_{EM} cells has held true in most analyses (Wherry and Ahmed, 2004). The ability of T_{CM} cells to undergo homeostatic turnover in response to IL-7 and IL-15 is a key factor in the longevity of these memory T cells.

Lineage Development of Memory T Cell Subsets and Relationship to Early Effector Heterogeneity

There is ongoing debate about the development and lineage relationship of memory T cell subsets. Some studies suggest that T_{CM} and T_{EM} cells are fixed populations that do not convert over time (Manjunath et al., 2001; Marzo et al., 2005; Sallusto and Lanzavecchia, 2001) (model 3), whereas others propose that T_{EM} cells can convert to T_{CM} cells in the absence of antigen (Badovinac et al., 2007; Bouneaud et al., 2005; Wherry et al., 2004; Wherry et al., 2003; Zaph et al., 2006) (model 4). On the basis of recent work, we propose that after acute viral infection, there are at least three distinct T cell populations in the early memory T cell pool. First, there exist T_{EM} cells derived from IL-$7R^{Hi}$ MPECs that represent a transitional or convertible T cell population, which can further differentiate and transform slowly into T_{CM} cells (Badovinac et al., 2007; Marzo et al., 2005; Wherry et al., 2004; Wherry et al., 2003) (E.J.W., unpublished data). Second, there is a population of T_{CM} cells primarily derived from these convertible T_{EM} cells. These memory T cells have acquired the ability to efficiently self renew via homeostatic turnover (Wherry et al., 2004; Wherry et al., 2003) (E.J.W., unpublished data). Some T_{CM} cells might descend directly from $CD62L^{Hi}$ MPECs present at the peak of clonal expansion. Whether T_{CM} cells that arise as a result of conversion from T_{EM} cells are functionally equivalent to T_{CM} cells derived from $CD62L^{Hi}$ MPEC is unclear. Third, there remain some terminally differentiated IL-$7R^{Lo}$ $KLRG1^{Hi}$ $CD62L^{Lo}$ SLECs that can enter the memory phase and downregulate markers of effector activation (e.g., granzyme B). These resting SLECs in the memory pool, however, do not efficiently persist long term, self renew, or undergo conversion to T_{CM} cells (Joshi et al., 2007) (E.J.W., unpublished data). These resting SLECs seem to represent an end-stage T_{EM} cell population.

The segregation of the memory T cells into self-renewing T_{CM} cells, transitional T_{EM} cells, and end-stage T_{EM} cells fits with a number of experimental observations and might help to explain some apparently disparate results in the field. For instance, such a model helps to account for the differences in phenotypic heterogeneity and protective immunity in T_{EM} cell subsets across different studies (Bachmann et al., 2005a; Bachmann et al., 2005b; Huster et al., 2006; Roberts et al., 2005; Roberts and Woodland, 2004; Wherry et al., 2003). These results might reflect differing proportions of transitional, end-stage T_{EM} cells, depending on the infection and time of analysis. Lastly, reducing the overall strength of T cell stimulation by increasing naive $CD8^+$ T cell precursor frequency and T cell competition appears to enrich the development of transitional T_{EM} cells (Badovinac et al., 2007) (E.J.W., unpublished data), increasing the evidence that these T cells occupy a particular stage of memory T cell differentiation.

Protective Immunity

One of the major implications of memory T cell subsets with different functional properties or anatomical localization is for protective immunity. Relatively few studies, however, have directly compared the protective capacity of T_{CM} and T_{EM} cells. Mouse studies demonstrated that $CD8^+$ T_{CM} cells conferred greater protective immunity compared to T_{EM}

cells after systemic, local, and respiratory challenge infections, and this was associated with a greater proliferative burst of T_{CM} cell-derived secondary effector T cells (Wherry et al., 2003). Evidence is accumulating that T_{CM} cells also correlate with more favorable responses against simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV) (Seaman et al., 2004; Vaccari et al., 2005) and protect better against tumors (Klebanoff et al., 2005). A recent study delineated multiple memory $CD8^+$ T cell subsets to Sendai virus that do not conform to the strict T_{EM} and T_{CM} cell definitions. With additional phenotypic markers, including CXCR3, CD27, CD43 (high MW form), and KLRG1, a hierarchical series of subsets was described with varying degrees of recall potency (Hikono et al., 2007). However, other studies using respiratory viruses found interesting kinetics in which T_{EM} cells responded better than did T_{CM} cells at early time points after infection, but in which at later time points, T_{CM} cells mounted the more vigorous secondary responses (Roberts et al., 2005; Roberts and Woodland, 2004), perhaps consistent with the gradual change in the composition of transitional versus end-stage T_{EM} cells over time.

There might be an advantage to maintaining end-stage T_{EM} cells for finite lengths of time after viral clearance because this is the most likely period for reinfection to occur. Indeed, immunity to respiratory Sendai virus or influenza virus infection correlates best with the persistence of T_{EM} cells in the lungs (Hogan et al., 2001; Liang et al., 1994). However, if the end-stage T_{EM} cells gradually disappear, the host could still be protected for longer periods by transitional T_{EM} cells that have become T_{CM} cells. It is interesting to consider whether functional, but relatively senescent, T_{EM} cells are not preferentially maintained in the lung and intestinal mucosa to optimally balance immunological protection and immunopathological damage to delicate mucosal tissues.

Altered Memory T Cell Differentiation during Repetitive or Chronic Infections

Although the above discussion of memory T cell development pertains mostly to events occurring during primary infection with viruses that are completely cleared from the host, there are several situations in which memory T cell differentiation might differ. First, recent work indicates that secondary (2°) and tertiary (3°) memory $CD8^+$ T cells are distinct from primary (1°) memory T cells. More 2° and 3° memory $CD8^+$ T cells persist in a $CD62L^{Lo}$ state, with heightened levels of granzyme B and cytotoxicity, for longer periods of time compared to the 1° memory T cells (Jabbari and Harty, 2006; Masopust et al., 2006). In addition, although a substantially larger number of virus-specific T cells can be generated with repeated infection, the E → M transition appears extended, and longer time might be needed to reach stable memory T cell numbers (Grayson et al., 2002; Masopust et al., 2006). These observations point out that memory T cell phenotype, function, and maintenance can be influenced by stimulation history, and special consideration should be given to this issue when developing prime-boost regimens for vaccination.

A second situation that can dramatically alter memory $CD8^+$ T cell differentiation is persisting infection (Klenerman and Hill, 2005; Wherry and Ahmed, 2004) (Figure 3 and Table 1). A substantial body of literature exists on the defects in T cell effector functions that can occur during chronic infections with hierarchical loss in proliferative capacity, cytotoxicity, and the ability to produce cytokines (Lieberman et al., 2001; Shin and Wherry, 2007) and the topic of chronic HIV infection is covered in the accompanying review by Deeks and Walker (2007). Virus-specific $CD8^+$ T cells that persist during chronic infection are quite different from memory T cells found after acute infection. For example, during chronic viral infection, virus-specific T cells remain $CD62L^{Lo}$ $CCR7^{Lo}$, and T_{CM} cells rarely develop (Wherry et al., 2004). These T cells also have a low proliferative capacity, express low amounts of IL-7 and IL-15 receptors, and fail to respond efficiently to these

cytokines (Shin and Wherry, 2007). Rather, long-term maintenance of virus-specific $CD8^+$ T cells during chronic infection depends on periodic bursts of cell division due to persisting antigen (Shin et al., 2007) and, in some cases, the priming of new thymic emigrants (Vezys et al., 2006). The precise details of impaired memory T cell development could differ depending on the whether T cells are subjected to repetitive stimulation, for example by herpes virus infections, or protracted, continuous stimulation (e.g., LCMV, HIV, hepatitis C virus [HCV]).

In addition to the changes in memory T cell differentiation and homeostasis, virus-specific $CD8^+$ T cells can become exhausted and lose effector functions during chronic infection (Shin and Wherry, 2007). The inhibitory receptor PD-1 is highly expressed during many chronic infections and blockade of the PD-1-PD-L1 pathway can restore function in these exhausted T cells (Barber et al., 2006; Day et al., 2006; Petrovas et al., 2006; Radziewicz et al., 2006; Trautmann et al., 2006; Zhang et al., 2007). The extent of PD-1 expression and functional exhaustion in a virus-specific T cells likely depends on the degree of ongoing viral replication, antigen abundance, and inflammation associated with, as well as the anatomical location or cellular tropism of, the persisting virus. Moreover, T cell populations from persistent or latent infections will consist of a mixture of various phenotypes and functional states (i.e., activated versus resting) depending on their recent or history of exposure to antigen, inflammation, and other factors (Figure 3 and Table 1).

Memory T Cell Differentiation in Humans

The above issues are particularly relevant for studying virus-specific T cell populations in humans, and T cell phenotype and function often varies for different pathogens (van Lier et al., 2003). For example, influenza virus (flu)-, respiratory syncytial virus (RSV)-, and vaccinia virus (VV)-specific memory $CD8^+$ T cells, all infections that do not persist, are usually IL-$7R^{Hi}$, $CD62L^{Hi}$, and $CD27^{Hi}$ (van Leeuwen et al., 2005). In contrast, a greater proportion of IL-$7R^{Lo}$, $CD62L^{Lo}$, and $CD27^{Hi/Int}$ cells are found in Epstein-Barr virus (EBV)- and cytomegalovirus (CMV)-specific $CD8^+$ T cell populations (Boutboul et al., 2005; van Leeuwen et al., 2005; Wherry et al., 2006). Further, HIV-specific $CD8^+$ T cells are mainly IL-$7R^{Lo}$ $CD62L^{Lo}$, but they express high amounts of CD27 (Appay et al., 2002; Boutboul et al., 2005; Champagne et al., 2001; Paiardini et al., 2005; Sabbaj et al., 2007; van Leeuwen et al., 2005; Wherry et al., 2006). Overall, the parallels between humans and mice are striking. For example, human memory T cells from acute infections (e.g., flu and RSV) respond substantially better to IL-7 and IL-15 compared to those from latent infections (e.g., EBV and CMV) (van Leeuwen et al., 2005). Thus, pathogen persistence for chronic, highly replicating, as well as latent, reactivating viruses, can substantially impact human memory T cell differentiation. It is important to keep in mind the effects of persistent and latent viral infections on the phenotypic heterogeneity of antiviral T cells in humans, especially when performing cross-sectional rather than longitudinal types of studies (Figure 3 and Table 1).

Conclusions and Implications for Vaccines and Long-Term Antiviral Immunity

Understanding the pathways that lead to optimal generation and maintenance of memory T cells is of considerable importance for both prophylactic and therapeutic vaccines. One would like to define the subsets of T cells that will provide the most robust protective immunity for different types of pathogens and also those capable of persisting independent of repetitive or continual boosting. Defining how the diversity in phenotype and function of effector and memory T cells arises during primary immune responses will likely lead to the discovery of multiple signals and pathways that control the differentiation of T cells with different functions, protective capacities, and long-term fates. Decoding the pathways and

molecules that can be used to therapeutically enhance long-term T cell immunity is a major future goal. Applying emerging new observations such as possible fate-determining signals imprinted by early inflammatory cytokines or the asymmetric separation of daughter T cells (Chang et al., 2007) and other signals should empower and enhance vaccine design. Moreover, the improved ability to implement functional genomic approaches and forward and reverse genetics to study memory T cell differentiation should provide rich opportunities to take our understanding of effector and memory T cell differentiation to a new level of practical application.

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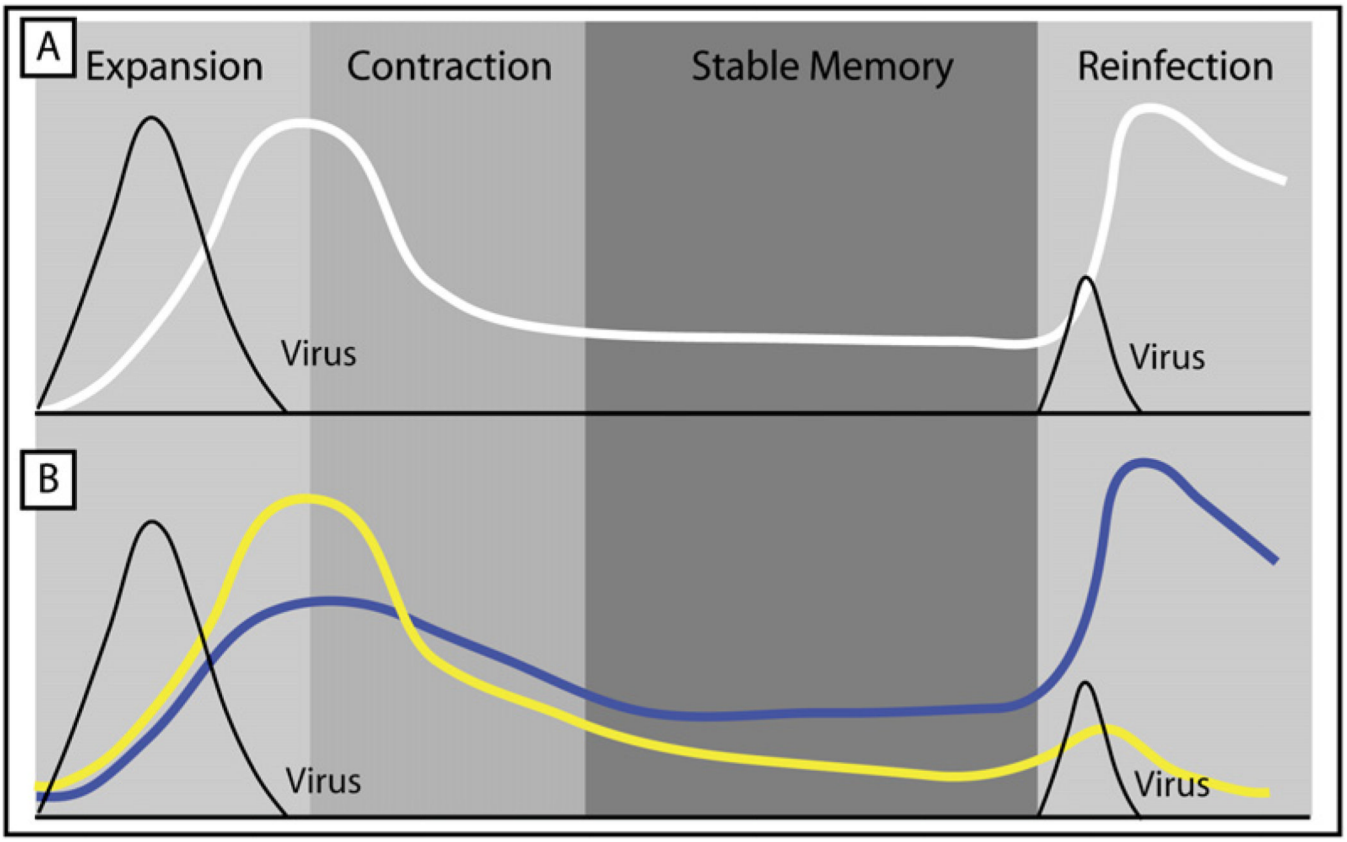

Figure 1. A Homogenous and Heterogeneous View on Antiviral Memory T Cell Development

(A) T cells clonally expand and homogeneously differentiate into effector T cells, of which most die, but some persist to become long-lived memory T cells. Upon reinfection, memory T cells re-expand and control infection faster than 1° infection.

(B) Two populations of effector T cells form with different memory T cell potential: short-lived effector T cells (SLECs; yellow line) that do not gain memory T cell potential, and memory precursor effector cells (MPECs; blue line) that do. Upon reinfection, it is primarily the descendents of MPECs that participate in secondary responses because of their enhanced proliferative capacity.

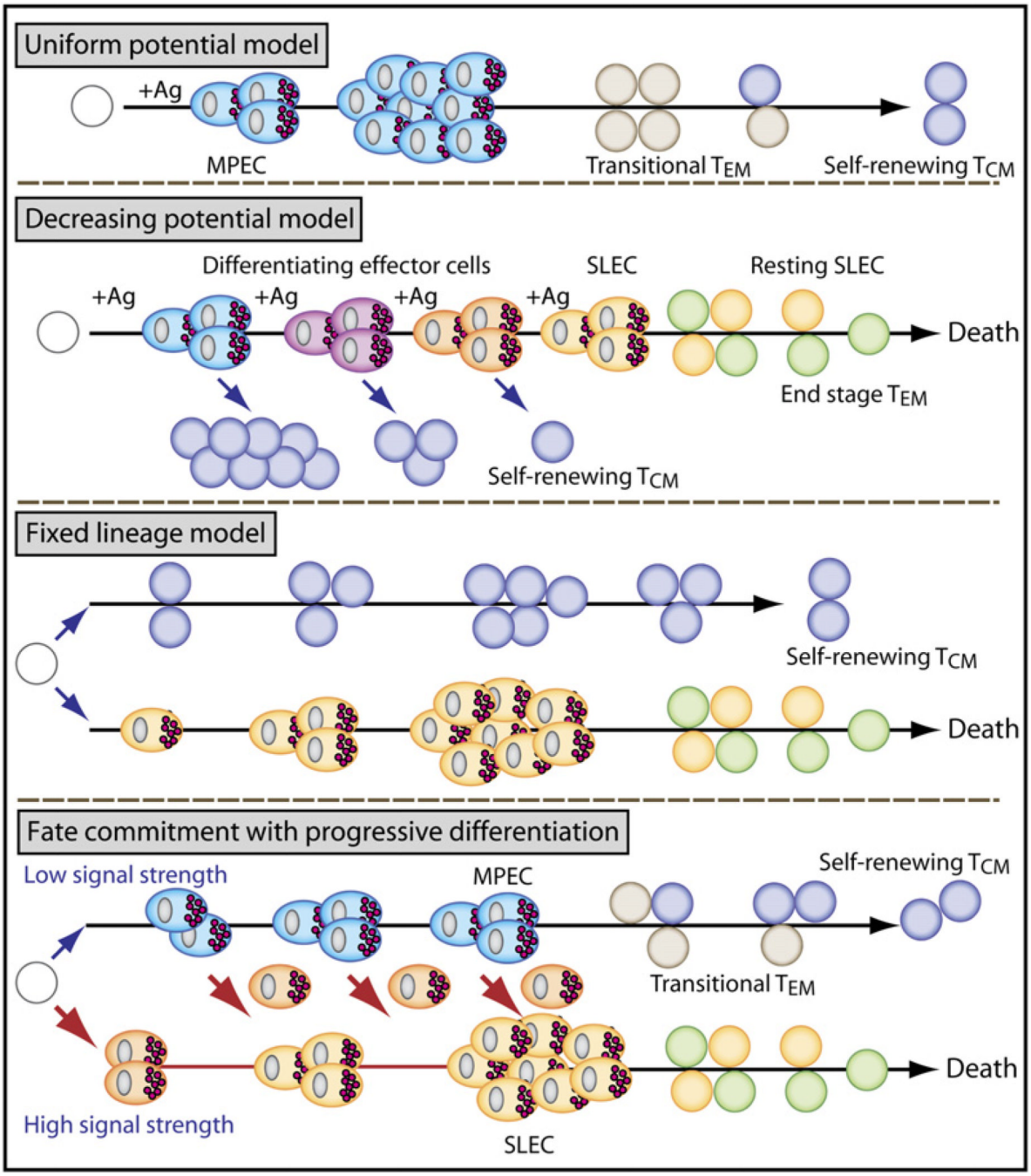

Figure 2. Models of Effector and Memory Cell-Fate Decisions during Acute Viral Infection

Model 1—uniform potential. All activated effector cells develop equal potential to become MPECs (aqua cells), but extrinsic factors limit the number of memory T cells generated. MPECs give rise to transitional T_{EM} cells (gray) that convert into self-renewing T_{CM} cells (dark blue).

Model 2—decreasing potential. Shorter durations of antigenic stimulation favor MPECs that give rise to T_{CM} cells. Longer stimulation promotes terminal differentiation of SLECs (yellow) and end-stage T_{EM} cells (green) that decline over time.

Model 3—fixed lineage. Upon activation, naive T cells develop into either SLECs or fully mature memory T cells. In this model, cells might bypass an effector stage and develop directly into self-renewing T_{CM}.

Model 4—fate commitment with progressive differentiation. According to the strength of signal, either an MPEC or SLEC fate will be adopted early after activation. The MPECs acquire effector functions, but remain multipotent (e.g., can still become memory T cells or SLECs). Most SLECs die, but some persist with a limited lifespan as an end-stage T_{EM} cell. MPECs survive, and give rise to transitional T_{EM} cells that progressively mature into long-lived T_{CM} cells.

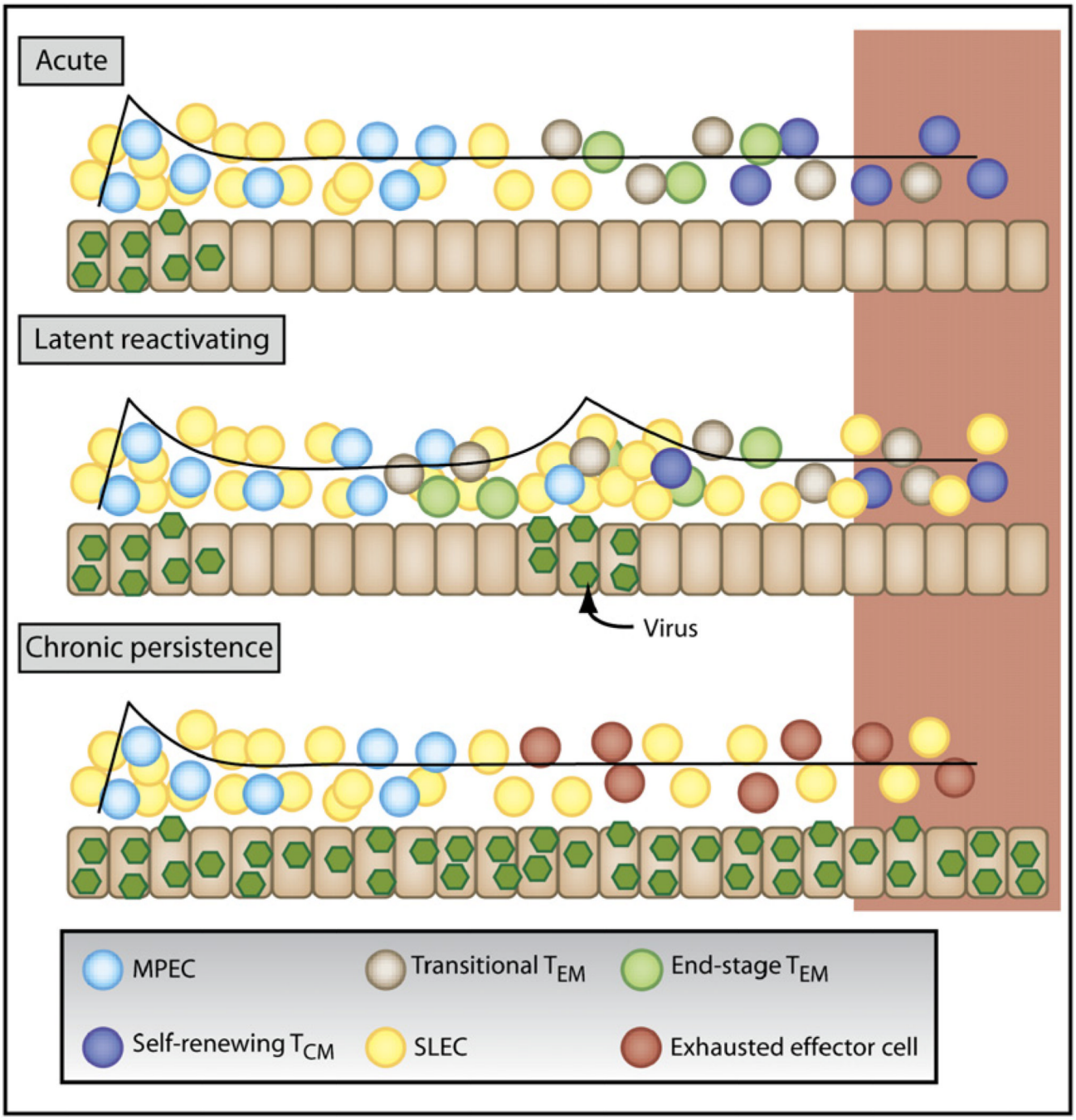

Figure 3. Differential Effects of Acute, Latent or Chronic Viral Infections on Memory T Cell Differentiation

Viral infections fall into three categories based on the duration and pattern of viral infection —(1) acute, (2) latent with reactivation, and (3) chronic or persistent.

Primary acute infection generates SLECs (yellow) and MPECs (aqua). For a description of the cell types, see Figure 2. The majority of SLECs die, but some persist for finite intervals (T_{EM} cells; green). In contrast, MPECs survive and progressively mature from transitional T_{EM} cells (light blue) into protective T_{CM} cells (dark blue).

During latent or reactivating viral infections, a mixed population with a variety of effector and memory differentiate states is formed. Typically, there will be more SLECs and T_{EM}

cells than after acute infection. The abundance of secondary MPECs, resting T_{CM} cells, or transitional T_{EM} cells will likely depend on the frequency and degree of viral reactivation. During persistent or chronic viral infections, with high viremia, T cells can undergo altered differentiation and become exhausted (red). According to the type of infection, the snap-shot of effector and memory T cells present (outlined in red box) is likely to be different. See Table 1 for detailed descriptions of common attributes.

Table 1

Characteristics of T Cells Responding to Different Types of Viral Infections

Type of Infection Phenotype of T Cells	Functional Properties	Examples of Infections
Acute viral Infection (Memory Phase)		
$CD62L^{Hi} > CD62L^{Lo}$	–High proliferative potential	LCMV (Acute Strains)
$CD44^{Hi}$	–Potent effector functions (IFN-γ, TNF-α, IL-2, cytotoxicity)	VSV
$CD27^{Int/Hi}$	–Potent homeostatic turnover	Vaccinia virus
$CD11a^{Hi}$	–Antigen-independent persistence	Influenza virus
$CCR7^{Hi}$		RSV
$CD127^{Hi}$		Sendai Virus
$CXCR3^{Hi}$		
$KLRG1^{Lo}$		
$CD122^{Hi}$		
$CD43^{Lo}$		
$PD\text{-}1^{Lo}$		
$CD69^{Lo}$		
$CD57^{Lo}$		
Latent, Reactivating Infection		
$CD62L^{Lo} > CD62L^{Hi}$	–Intermediate proliferative potential	γHV
$CD44^{Hi}$	–Weaker effector functions (lower IFN-γ, TNF-α, IL-2)	EBV
$CD27^{Lo/Int}$	–Reduced homeostatic turnover	CMV
$CD11a^{Hi}$		HSV
$CCR7^{Lo/Hi}$		
$CD127^{Lo/Int}$		
$CD122^{Lo}$		
$KLRG1^{Hi/Lo}$		
$PD\text{-}1^{Int/Hi}$		
$CD69^{Lo}$		
$CD57^{Hi}$		
Chronic, Persistent Infection		
$CD62L^{Lo}$	–Low proliferative potential	LCMV (chronic strains)
$CD27^{Lo/Int}$	–Poor effector functions (exhausted)	HCV
$CD44^{Hi}$	–Little or no homeostatic turnover	HIV
$CCR7^{Lo}$	–Antigen-dependent persistence	SIV
$CD11a^{Hi}$		
$CD122^{Hi/Lo}$		
$CD127^{Lo/int}$		
$PD\text{-}1^{Hi}$		

Type of Infection Phenotype of T Cells Functional Properties	Examples of Infections
KLRG1$^{Hi/Lo}$	
CD57^{Hi}	
CD69^{Hi}	