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Hidden Memories: Frontline Memory T Cells and Early Pathogen Interception

David Masopust* and Louis J. Picker†

Immunologic memory reflects the ability of a host to more effectively respond to a re-encounter with a particular pathogen than the first encounter, and when a vaccine mimics the first encounter, comprises the basis of vaccine efficacy. For T cells, memory is often equated with the anamnestic response, the ability of secondary lymphoid tissue-based (central) memory T cells to respond to pathogen exposure with a more rapid and higher magnitude production and infection-site delivery of pathogen-specific effector cells than observed in naive hosts. However, increasing evidence supports a fundamentally different kind of T cell memory in which differentiated, long-lived effector memory T cells, prepositioned in sites of potential pathogen invasion or rapidly mobilized to such sites from blood and marginned pools, intercept and potentially control/eliminate pathogen within hours of infection. In this article, we review the evidence for this “hidden” T cell memory and its implication for vaccine development. The Journal of Immunology, 2012, 188: 5811–5817.

Most pathogens are initially encountered at body surfaces. Although innate immune mechanisms may exert immediate control over microbes at the point of entry, elimination and/or control of microbes with pathogenic potential often requires the enlistment of adaptive, pathogen-specific T cell responses. Compared with immediate innate immune responses, T cell responses are slow to develop upon a first-time infection because in the naive host, pathogen-specific T cells are extraordinarily low in frequency, manifest restricted anatomic localization (secondary lymphoid tissue [SLT] only), and lack differentiated effector function (1). Before contributing to pathogen control, the rare, quiescent naive T cells specific for a pathogen not previously encountered must be activated within SLTs that drain sites of infection and then undergo a relatively prolonged period of proliferation and differentiation to both expand the size of the population and provide it with relevant effector functions. Moreover, because T cell effector functions, such as production of antiviral cytokines, killing of host cells harboring cytoplasmic infections, or Th1-mediated control of phagosomal infections, act locally, the expanded, differentiated, pathogen-specific T cells arising in SLT must also migrate to all sites of infection (2). This process can take anywhere from a few days to a few weeks in primary infection, an inherent delay that provides a temporal window of opportunity for continued pathogen replication and, for some pathogens, time for full implementation of immune evasion strategies that permit establishment of persistent infection (see later). However, the majority of first-time infections are ultimately cleared by these primary immune responses, and the host T cell system retains a long-term “memory” of the initial pathogen encounter manifested by elevated frequencies of pathogen-specific T cell clones (3–5).

These memory T cell populations also exhibit phenotypic differences from their naive counterparts (e.g., increased expression of adhesion molecules) (6) that allow them to more efficiently respond to Ag a second time. Early models for T cell-dependent immunity highlighted the contribution of quiescent populations of memory T cells in SLTs that, in the event of secondary Ag exposure, would reactivate a second round of expansion and differentiation, the so-called anamnestic response. Because of the increase in frequency and enhanced intrinsic responsiveness of pathogen-specific (SLT-based) memory populations over their naive counterparts, anamnestic T cell responses were more rapid and higher in magnitude than primary responses, and thus more efficient in controlling infection (7). However, such memory responses were viewed largely as just a faster and larger recapitulation of the primary response, still reliant on expansion and reacquisition of effector functions each time the pathogen is encountered.

Although this system of “reserve” memory with rapid anamnestic mobilization is an efficient mechanism of increasing the efficiency of secondary T cell responses, it has now become clear that this process is only part of the story. Further characterization of T cell populations in extralymphoid tissues has revealed novel memory subsets that are poised for immediate effector function, rather than expansion and differentiation (8). These memory T cell populations are anatomically

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Abbreviations used in this article: bTEM, blood-borne effector memory T cell; HEV, high endothelial venule; IEL, intraepithelial lymphocyte; mTEM, migratory effector memory T cell; NHP, nonhuman primate; rTEM, resident effector memory T cell; SLT, secondary lymphoid tissue; TCM, central memory T cell; TEM, effector memory T cell.

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based in tissues that can be collectively designated frontline, extralymphoid sites of pathogen exposure (immune “effector” sites, as opposed to immune inductive sites) (9). Indeed, some of these effector site-based memory T cell populations appear to reside permanently within such sites, without evidence of tissue to lymph to blood recirculation, a characteristic that has hidden their existence from conventional analysis (10). These effector site-based, differentiated subsets comprise a long-term memory compartment that makes distinct and crucial contributions to T cell-dependent pathogen control upon re-infection. This review summarizes the known properties of various memory T cell subsets and their development, highlights the intimate relationship between T cell location and function, and hypothesizes how each subset contributes to the integrated process of T cell-dependent pathogen control upon re-infection. The essential parameter of T cell location to rapid infection containment is emphasized. Ramifications for vaccine-elicited memory T cells also are discussed.

**T cell expansion and differentiation: the cellular substrate of memory**

Naive T cells constantly recirculate between SLTs using the blood and lymph as conduits, but are largely, if not completely, excluded from extralymphoid effector sites (11–13). Thus, naive T cells directly scan a relatively small fraction of host tissues, and depend on the Ag acquisition and collection strategies of SLTs to detect pathogen invasion. This restricted naive T cell recirculation pattern is mediated by expression of CD62L and CCR7 (required for migration from blood into lymph nodes across the high endothelial venules [HEVs]), the expression of S1p receptors (allowing T cells to leave lymph nodes by following a chemotactic gradient toward efferent lymph vessels), and the lack of the homing/chemokine receptor combinations required to extravasate into extralymphoid sites (12–15). Naive T cells become activated only after recognition of cognate Ag presented by APCs within lymphoid sites (12, 13, 15). This activated naive T cell response is the redistribution of many of the effector cells developing in the SLTs to these sites (12, 18, 19). This altered T cell trafficking pattern is accomplished via changes in the expression of T cell homing molecules. Most activated T cells downregulate CD62L and CCR7, which prevents re-entry into resting lymph nodes across HEVs (13, 20). In turn, they upregulate various nonlymphoid homing lectins, integrins, and chemokine receptors. These may include receptors that support T cell entry into general sites of inflammation, such as CXCR3 and CCR5, as well as molecules that target T cells to specific organs, such as α4β7 integrin/CCR9 and CLA/CCR4, which mediate selective entry into the small intestinal mucosa and skin, respectively (12, 13, 15). This change in anatomic distribution, from SLT sites of priming to sites of infection, is critical for the exertion of local T cell effector mechanisms.

In situations in which the initial antigenic/microbial challenge is eliminated, 90–95% of the Ag-specific T cell population undergoes apoptosis (although this proportion is highly dependent on the nature of the pathogen or vaccine modality) (4). Those that remain, memory T cells, are diversified into functionally heterogeneous subsets that play distinct, but cooperative roles in protecting the host from reinfection (8). Notably, the functional specializations of each subset are coordinately regulated with homing properties and anatomic distribution (9). Central memory T cells (TCM) are fundamentally defined by their trafficking properties. This subset retains or has re-expressed CD62L and CCR7, lacks CCR5 expression (21), and selectively and constitutively recirculates through SLTs. TCM typically express costimulatory receptors for enhanced reactivation by professional APCs. TCM also retain a great deal of proliferation potential and exhibit a high capacity to secrete IL-2 upon restimulation (9, 22). However, TCM are largely excluded from nonlymphoid effector sites, and thus are anatomically sequestered away from the epithelial surfaces and underlying stroma that constitute the most common sites of pathogen exposure (18, 21). Moreover, TCM require a period of differentiation to acquire certain effector functions, such as the capacity to kill infected host cells within minutes via the targeted secretion of preformed, perforin- and granzyme-containing granules (23, 24). In summary, TCM comprise a population that shares many features with naive T cells; they patrol SLTs rather than frontline sites of infection, and they are subduced in immediate effector function relative to more differentiated effectors. In the event that pathogens are not immediately intercepted at the point of entry by other immune system components, TCM remain poised to proliferate and differentiate upon cognate Ag recognition on APCs that present tissue Ags within the draining SLTs, thus producing a wave of differentiated effector daughter cells. Relative to naive T cells, they exhibit a dramatic increase in clonal abundance and express effector functions more rapidly. Thus, TCM comprise a reserve force of Ag-specific T cell clones that is responsible for recapitulating a primary response in the host, albeit much more quickly, but is not capable of responding immediately to secondary challenges in nonlymphoid tissues. The advantage of TCM-based memory is that a relatively small population of pathogen-specific TCM can “pack a large punch” in terms of the ultimate size of its anamnestic effector response, and therefore a myriad of different TCM specificities can be maintained in an overall SLT T cell compartment of finite size.

In contrast with TCM, effector memory T cells (TEM) lack CD62L and/or CCR7 expression, molecules directing lymph node entry via HEVs, and express chemokine receptors such as CCR5 that are associated with homing to inflammatory sites (9, 21). Accordingly, TEM are preferentially distributed within nonlymphoid tissues and/or remain blood associated, either circulating or contained within margimated pools in splenic red pulp and hepatic sinusoids (2, 25). Further definition of TEM is challenging because they comprise a re-
fully differentiated TEM recirculate through lymphatics slowly corresponding to more durable Ag presentation, increase the maintenance of TCM, and over time, the recombination in which foreign Ag is rapidly eliminated, mainly in the naive population, all favor the production of TEM to TCM maintained at various stages of the immune response against any particular pathogen. Under priming conditions in which foreign Ag is rapidly eliminated, maintenance of TCM is favored over TEM, and over time, the response becomes increasingly TCM biased (28). For example, vaccination with replication-deficient vectors, infection with agents that are very modestly pathogenic, or experimental situations in which mice contain particularly abundant Ag-specific T cells in the naive population, all favor the production of TEM (29–31). More pathogenic infections, typically corresponding to more durable Ag presentation, increase the number of resulting TEM. Preferential differentiation of TEM is enhanced when pathogens are not immediately contained or Ag exposure is recurrent, resulting in iterative waves of T cell activation and proliferation, a process exploited by heterologous prime-boost vaccination (32, 33). TEM differentiation and long-term maintenance of large TEM populations is particularly pronounced during certain persistent infections, such as CMV, typified by continuous, low-level or repeated recruitment pathogen replication that is controlled but never eliminated (26, 34). More pathogenic infections, typically corresponding to more durable Ag presentation, increase the number of resulting TEM. Preferential differentiation of TEM is enhanced when pathogens are not immediately contained or Ag exposure is recurrent, resulting in iterative waves of T cell activation and proliferation, a process exploited by heterologous prime-boost vaccination (32, 33). 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Considerable effort has been made to delineate the mechanisms responsible for the development and maintenance of TCM versus TEM. The theme that has emerged is that the degree of tissue damage and inflammation, and the density and persistence of Ag play a major role in setting the ratio of TEM to TCM maintained at various stages of the immune response against any particular pathogen. Under priming conditions in which foreign Ag is rapidly eliminated, maintenance of TCM is favored over TEM, and over time, the response becomes increasingly TCM biased (28). For example, vaccination with replication-deficient vectors, infection with agents that are very modestly pathogenic, or experimental situations in which mice contain particularly abundant Ag-specific T cells in the naive population, all favor the production of TEM (29–31). More pathogenic infections, typically corresponding to more durable Ag presentation, increase the number of resulting TEM. Preferential differentiation of TEM is enhanced when pathogens are not immediately contained or Ag exposure is recurrent, resulting in iterative waves of T cell activation and proliferation, a process exploited by heterologous prime-boost vaccination (32, 33). TEM differentiation and long-term maintenance of large TEM populations is particularly pronounced during certain persistent infections, such as CMV, typified by continuous, low-level or repeated recruitment pathogen replication that is controlled but never eliminated (26, 34). Teleologically, one may surmise that only under conditions in which infections are particularly pathogenic, persistently or repetitively experienced, and/or exert a high fitness cost without rapid control, is it evolutionarily advantageous to maintain large numbers of TEM.

Evidence for effector site-based memory

TEM are present in blood, splenic red pulp, and comprise the dominant, if not exclusive, T cell population within nonlymphoid tissues (2, 18, 19, 35). In healthy adult nonhuman primates (NHPs), fully differentiated (CD28+ TEM are highly represented in blood and spleen, but comprise a very modest component of CD8+ T cells in lymph node and thoracic duct lymph (<20% of blood levels), suggesting that the majority of fully differentiated TEM recirculate through lymphatics slowly or not at all (36) (L.J.P., unpublished observations). In addition, these observations suggest that blood or compartments of organs that are contiguous with blood and contain large populations of memory T cells (e.g., splenic red pulp and liver sinusoids) comprise a distinct compartment that may be rapidly recruitable to sites of pathogen invasion. Recent evidence adds to this paradigm by demonstrating that certain tissue compartments are populated by resident TEM (rTEM) that do not exit nonlymphoid tissues in the resting host (37–46). We refer to this recently identified “resident memory” T cell subset (10) as “rTEM” to emphasize their location in nonlymphoid tissues and conceptual relationship with other populations of TEM. Such rTEM populations typically adopt tissue-specific differentiation states, and they are not identified by peripheral blood analysis. Tissue TEM within the small intestinal epithelium, which comprise a population of CD8αβ+ memory intraepithelial lymphocytes (IELs), have been particularly well characterized in mice. Months after clearance of infection in mice, pathogen-specific small intestinal memory IELs constitutively retain cytolytic function and express high levels of granzyme B, yet express relatively low levels of the costimulatory ligand CD27 and cytokine receptors for IL-15 and IL-7 (47, 48). In addition, they constitutively maintain CD103/B7 integrin expression, as well as CD69 (47–49). This CD103/CD69+ phenotype was not expressed among pathogen-specific memory CD8 T cells in blood, and this discordance was later explained by the observation that small intestinal IELs are resident and do not recirculate through blood (37, 38). In mice, stable populations of nonrecirculating CD8+ rTEM have been identified within intestinal epithelium, the CNS, the skin epidermis, and potentially the salivary gland and a subset of cells within the respiratory mucosa (37–46). Although functional properties vary, rTEM isolated from any of these compartments typically express CD69 and often CD103/B7 integrin. Interestingly, pathogen-specific memory CD8+ T cells isolated from pancreas, stomach, kidney, heart, and female reproductive tract also contain CD69+/CD103− and CD69+/CD103+ subsets (50). Evidence supports the hypothesis that CD69 prevents S1P-mediated egress from tissues (51, 52), and that CD103/B7 integrin enforces maintenance in epithelia via E-cadherin binding (50, 53, 54), suggesting that CD103/CD69 expression may be a defining feature of nonrecirculating rTEM within many nonlymphoid tissues.

Questions regarding rTEM ontogeny remain. These populations may be very long-lived; for example, mouse and NHP studies reported minimal decay over ~1–2y (18, 55). CD69 expression is often interpreted as a surrogate for recent TCR engagement, and recent studies have proposed that CD103 expression by rTEM is induced or maintained by local cognate Ag (39, 43). Removal of pathogen-specific rTEM from small intestinal IELs can permit redifferentiation into TCM and loss of immediate cytolytic function, suggesting that the population exhibits developmental plasticity, and maintenance of an effector-like phenotype is dependent on anatomic location (47). In situations in which Ag is cleared, it remains possible that the effector-like properties of rTEM are maintained by local cross-reactivity with environmental Ags at body surfaces. Alternatively, certain tissue compartments may regulate T cell effector differentiation state independently of TCR ligation (50). Discriminating between these possibilities has obvious ramifications for generating long-lived rTEM through vaccination.

Although new evidence points to the broad distribution of rTEM, other TEM populations appear to constitutively recirculate through nonlymphoid tissues. The dichotomy between these subsets was elegantly illustrated in a recent report on murine skin memory T cell populations (41). In vivo dynamic imaging revealed that during the resting state, memory CD8
T cells within the epidermis were resident and exhibited little motility. In contrast, memory T cells within the underlying dermis (mostly containing memory CD4 T cells) lacked CD103/β7 integrin expression, and were motile and recirculated between blood and tissue. Indeed, migratory memory CD8 and CD4 T cells can be isolated from the afferent lymphatics of primary lymph nodes, suggesting constitutive T cell recirculation occurs through certain tissue compartments (11, 56, 57). Thus, two pathways exist for routine surveillance of nonlymphoid compartments, manifested by the maintenance of both resident and recirculating migratory memory T cells. Further work is required to catalog the complete distribution and numerical contribution of rTEM and migratory TEM (mTEM) to the memory T cell pool. Importantly, analysis of blood will not reveal rTEM populations; thus, these populations will remain hidden from view without the direct examination of nonlymphoid tissues.

Function of effector site-based memory

T cell-dependent protective immunity likely results from the concerted actions of multiple memory subsets, and identifying the distinct roles of TCM, blood-borne TEM (bTEM), tissue recirculating mTEM, and sessile rTEM is experimentally arduous. However, recent evidence supports the hypothesis that discrete memory T cell subsets operate at different phases of reinfection. We propose that rTEM and tissue recirculating mTEM already present at the site of infection are the only subsets poised to provide an immediate (within minutes to hours) contribution to protective immunity in situ. Local inflammation resulting from infection would promote a second wave of early (after several hours) adaptive effector functions via the local recruitment of preformed bTEM. In the event that immediate and early responses contain, but do not eliminate, the infection, TCM would then undergo a period of proliferation and effector differentiation within SLTs, and provide a late (days to weeks) wave of abundant effectors that would contribute to control of pathogens that escape TEM-mediated elimination (Fig. 1).

Mounting evidence highlights the particular role of effector site-based memory to rapid protection from reinfection. For instance, after contraction of the T cell response, systemic memory T cells remain stable, whereas those within the lung airways gradually wane (25). This loss of local memory correlates with a gradual loss of T cell-dependent protective immunity against a heterosubtypic respiratory influenza virus challenge, providing evidence for a site-based role in protection (58). This interpretation was strengthened by later studies demonstrating that transfer of memory CD4 T cells directly into the lung airways of naive mice conferred partial, but rapid, protection against a local viral challenge (59). A recent study demonstrated the potential to generate tissue-retentive influenza virus-specific memory CD4+ T cells within the lung tissue. Interestingly, this population preferentially homed to lung upon transfer to naive mice, and conferred more rapid

![FIGURE 1.](http://www.jimmunol.org/)
and efficacious control in response to local challenge compared with memory T cells derived from spleen (46). Studies by Swain and colleagues demonstrated that lung CD4 T cell memory may contribute to early influenza control by enhancing the magnitude of innate responses, highlighting the integration of frontline adaptive T cell memory with the innate immune system (60). A protective role for effector site-based memory has been demonstrated in several models of skin infection in mice. rTEM established within epidermis are essential for rapid protective immunity against epidermal rechallenge with either HSV-1 or vaccinia virus (40, 44, 45). Importantly, TCM make little contribution to immediate protection in these models, although they do make late contributions to virus control in the event the infection is not controlled rapidly at the site of infection.

Mouse studies have made highly reductionist comparisons of i.v. transferred CD8 TCM versus TEM to protect against various pathogen challenges. It is important to note that transferred TCM will not reconstitute rTEM populations but may comprise mTEM and/or bTEM. Nevertheless, transferred CD8 TCM elicited a greater degree of protection than TCM against a variety of infectious challenges when measured within a few days of challenge (61–63). In cases in which the pathogen was rapidly eliminated, TCM were sufficient and faster than TCM on a per cell basis. However, in cases where the pathogen overwhelmed the number of transferred memory T cells, TCM exhibited far greater control than TEM when measured 7 d or more postinfection, almost certainly because of the enhanced ability of TCM to proliferate and differentiate into a second wave of effectors that migrate to sites of infection (28, 61). Thus, the relative contributions of TEM and TCM to protective immunity will depend on the dose, route, replication rate, and pathogenesis of the infectious agent in question, as well as the quantity, function, and anatomic distribution of memory T cells throughout the host (8).

The theme that emerges from these studies is that the contribution of each memory T cell subset is mandated by their function and specialization, and varies at each phase of an anamnestic response (Fig. 1). For “immediate” responses (which may commence as soon as foreign peptide has been presented on host MHC molecules), location is critical, as is rapid effector function. In contrast, proliferation potential is completely irrelevant. Only rTEM and mTEM that are actually present at the peripheral site of infection can contribute to “immediate” protection, and their local quantity is a critical determinant of immediate pathogen control. If pathogen is not immediately eliminated at the point of entry, inflammation (which may be augmented by reactivation of tissue TEM) will result in the specific extravasation of greater numbers of mTEM, as well as bTEM, at the site(s) of infection. In principle, this “early” mTEM/bTEM recruitment would greatly increase the local density of TEM, an augmentation of effector potential that would almost certainly be critical for rapid control of all but the most low-dose (or benign) infections. At the same time of this early TEM response, tissue Ags will localize to draining lymph nodes, and if presented on activated APCs in sufficient quantity, will elicit a second round of activation, proliferation, and differentiation among TCM. This process, which takes several to many days, will result in a numerically robust dissemination of new effectors (even from a rare population of TCM) into the site of infection. This “late” phase of the anamnestic effector response may explain why TCM make little impact on protective immunity until several days after challenge. However, TCM can ultimately make very potent contributions to protective immunity, and suffice under conditions in which very rapid control is unnecessary.

Implications of effector site-based memory for vaccination

The goal of any prophylactic vaccine is to safely mimic an initial pathogen encounter so as to elicit protective immune memory: Ab and/or T cell responses that prevent infection with the bona-fide pathogen or abrogate such infection prior to overt disease. For pathogens that are highly susceptible to Ab or T cell-mediated mechanisms, typically those agents that naturally cause acute infections, any vaccine that is capable of maintaining protective Ab responses or eliciting robust anamnestic Ab and T cell responses upon pathogen exposure will usually meet this goal. Indeed, none of the vaccine approaches in clinical use today specifically target high-frequency, TEM-biased T cell responses, and given the dependence of the generation and maintenance of such responses on higher/longer Ag exposure and/or increased tissue damage/inflammation, such targeting would almost certainly increase vaccine complexity, and potentially pose safety and tolerability issues. However, conventional vaccine approaches have not yielded highly protective vaccines for a number of critical human pathogens, in particular, pathogens with sophisticated immune-evasion capabilities that allow chronic infection. Notably, three such pathogens—HIV, Mycobacterium tuberculosis, and the Plasmodium species responsible for malaria—are among the top 5 most deadly global infectious diseases. HIV, in particular, has resisted vaccine development for >25 y. HIV and its simian counterpart SIV combine an intrinsic resistance to Ab-mediated neutralization with a replication strategy that provides for rapid establishment of a large, systemic viral population, capable of overwhelming or dynamically adapting/evading almost all immune selection pressures (64). Although many conventional vaccines, most notably approaches using replication-deficient vectors, have proved capable of eliciting TCM-biased, virus-specific memory that generates robust anamnestic T cell responses upon viral exposure, these responses, though considerably more rapid and of higher magnitude than primary responses in naive subjects, have largely failed to mediate long-term control of HIV/SIV infection (64). Significantly, when highly augmented effector T cell responses occur only after peak systemic viral replication, they are still subject to the dynamic immune-evasion mechanisms operating in naive individuals.

Given that sexually/mucosally transmitted HIV infections in humans and experimental SIV infections in NHPs after limiting dose mucosal challenge are typically initiated by one or very few transmitted/founder viral variants, and that establishment of a systemic, progressive infection capable of dynamic evasion takes many days of local viral amplification and spread (64), it was hypothesized that establishment of a high-frequency, virus-specific TEM response might be an effective way to control these infections. This hypothesis was recently tested with the development of SIV protein-expressing vectors based on the persistent β-herpesvirus rhesus CMV. Rhesus CMV/SIV vectors elicit and indefinitely maintain high-frequency, SIV-specific TEM responses at potential sites of early viral replication after mucosal challenge, and strikingly, >50% of monkeys vacci-
nated with these vectors manifested early, stringent control of mucosally administered SIV (27). This protection, which correlated with the peak SIV-specific CD8+ TEM response magnitude during the vaccine phase, was characterized by an initial peak of viremia of variable, but usually low, magnitude, followed by near-immediate control to below quantifiable levels. Although many of the protected monkeys showed periodic, low-level viral “blips” of measurable viremia over the first 6 mo of follow-up, these blips waned, and after 1 year, replication-competent SIV was not recoverable from the tissues of protected animals. Notably, this early-onset, TEM-mediated protection occurred without an anamnestic response.

Such “windows of TEM opportunity” (periods in early infection with chronic pathogens in which immune-evasion mechanisms are not fully developed and the infection may be relatively susceptible to TEM-mediated control) may exist for other vaccine-resistant pathogens as well. Malaria parasites would be most vulnerable to T cell-mediated immunity during the intrahepatic stage of its life cycle, but the length of this stage (~5 d) is sufficiently short to largely avoid T cell effectors arising from a vaccine-elicted anamnestic response. In keeping with this, recent studies have suggested that protection mediated by malaria vaccines is associated with TEM-mediated responses (65).

Similarly, a vaccine that elicits and maintains high-frequency, Mycobacterium tuberculosis-specific TEM populations in lung might well allow for earlier and more efficient control of this pathogen. Finally, maintenance of robust vaccine-elicted TEM responses might also be effective in therapeutic vaccination against reactivation of latent viruses such as herpes simplex, allowing earlier intercept of reactivation foci, perhaps before clinical manifestations. Taken together, these considerations suggest that vaccines exploiting TEM have the potential to address some of the most pressing problems in clinical infectious disease today, a potential that merits the prioritization of development of safe, potent, TEM-generating vaccine modalities.

Conclusions

A central theme of the immune system is the concentric layering of protective mechanisms of increasing complexity and specificity: adaptive immunity is layered on innate immunity, αβ T cells and B2 B cells are layered over γδ T cells and B1 B cells, and memory populations are layered over naïve populations. As this review indicates, it is increasingly clear that a similar concentric layering exists within the memory T cell compartment itself. Diverse, differentiated, and specialized TEM that form a first line of T cell-mediated defense to pathogen re-encounters are layered over TEM populations that serve as a strategic reserve. T cell memory cannot be equated to the anamnestic effector response, but must be considered a complex composite of functionally and anatomically diverse populations, many of which are hidden from routine analysis of blood, that make distinct contributions to host defense. Understanding the interplay of these populations and their specific functional contribution to immunity will be crucial for definition of the mechanisms underlying protective T cell immunity and for the rational development of next-generation immunotherapeutics, particularly vaccines, that exploit these mechanisms.

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