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RESEARCH ARTICLE | MAY 01 2021

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Henrique Borges da Silva

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Navigating in Deep Waters: How Tissue Damage and Inflammation Shape Effector and Memory CD8+ T Cell Responses

Henrique Borges da Silva

Department of Immunology, Mayo Clinic, Scottsdale, AZ

ABSTRACT

Memory CD8+ T cells promote protective immunity against viruses or cancer. Our field has done a terrific job identifying how CD8+ T cell memory forms in response to Ag. However, many studies focused on systems in which inflammation recedes over time. These situations, while relevant, do not cover all situations in which CD8+ T cell memory is relevant. It is increasingly clear that CD8+ T cells with a memory phenotype form in response to infections with extensive or prolonged tissue inflammation, for example, influenza, herpes, and more recently, COVID-19. In these circumstances, inflammatory mediators expectedly affect forming memory CD8+ T cells, especially in tissues in which pathogens establish. Notwithstanding recent important discoveries, many outstanding questions on how inflammation shapes CD8+ T cell memory remain unanswered. We will discuss, in this review, what is already known and the next steps to understand how inflammation influences CD8+ T cell memory. *ImmunoHorizons*, 2021, 5: 338–348.

INTRODUCTION

Immunological memory can be characterized by the presence of Ag-specific adaptive immune cells with enhanced ability to respond to secondary Ag encounter. The acquisition of immunological memory is paramount for the protection against pathogen reinfections and is the desired goal of vaccination protocols (1–3). Although the development of humoral immunity (i.e., B cell–dependent) promotes the protection against many infections and is the basis of most existing vaccines, there are diseases for which either humoral immunity is less relevant (e.g., tuberculosis) or B cell–inducing vaccines do not exist (e.g., HIV, malaria) (4). In situations for which the relevant Ag is present inside cells, the development of cytotoxic memory CD8+ T cells is fundamental, given CD8+ T cells are key in cell-mediated immunity and the clearance of intracellular pathogens (2). This is also true for cancer, for which the elimination of tumor cells requires CD8+ T cells in many cases, and the harnessing of CD8+ T cells with memory-like characteristics promotes enhanced tumor control (5).

Understanding how CD8+ T cell memory forms has been and still is a fundamental part of the cellular immunology field. Thanks to seminal works, we have a consensual view of how Ag-specific memory CD8+ T cells are generated. Notwithstanding these fundamental discoveries, they mostly used model infections and immunizations for which acute inflammation is present. Acute inflammation, albeit a relevant factor, recedes swiftly over time because of quick pathogen or Ag elimination. It has been increasingly appreciated, also, that elements of the tissue microenvironment help shape CD8+ T cell responses (6–9). In response to infections that induce increased tissue inflammation, memory CD8+ T cells are found. This is true in the context of influenza (10–12) or herpes (13, 14). Therefore, it is likely that the quality, duration, and intensity of the

Abbreviations used in this article: DC, dendritic cell; KLRG1, killer cell lectin-like receptor G 1; LCMV, lymphocytic choriomeningitis virus; LLEC, long-lived effector cell; MP, memory precursor; Tcm, central memory CD8+ T cell; TE, terminal effector; Tem, effector memory CD8+ T cell; Trm, tissue-resident memory CD8+ T cell; Tscm, stem cell–like memory CD8+ T cell.

https://doi.org/10.4049/immunohorizons.2000102

inflammatory context will differentially affect memory CD8$^+$ T cell generation and maintenance. How and whether memory CD8$^+$ T cells form and respond to distinct inflammatory stimuli is currently being investigated by many groups, and we are only now beginning to understand these concepts. This is especially important nowadays, as COVID-19 (caused by the SARS-CoV-2 virus) protection may rely on CD8$^+$ T cell memory responses (15), and this disease is characterized by intense tissue inflammatory responses (16, 17). In this review, we will focus on how inflammation affects the establishment and function of memory CD8$^+$ T cells. We will also discuss how established memory CD8$^+$ T cell populations are influenced by systemic or local inflammation. Finally, we will convey the next steps needed for our complete understanding of how inflammation shapes the memory CD8$^+$ T cell pool, highlighting the main unexplored information "seas" on this matter.

At the surface: Molecular and cellular basis of memory CD8$^+$ T cell differentiation and survival

In the past few decades, many papers unveiled how Ag-specific CD8$^+$ T cells clonally expand and differentiate into terminal effectors (TEs) or multiple memory cell subsets. Memory CD8$^+$ T cells survive in the long-term and display enhanced responsivity to secondary Ag encounter. Many cell-intrinsic and -extrinsic signals are instrumental in the effector-to-memory transition and memory CD8$^+$ T cell survival.

Metabolic and transcriptional regulation of CD8$^+$ T cell effector expansion and memory precursor generation. Naive CD8$^+$ T cells are generated in the thymus and migrate to the periphery. After engagement with cognate Ag (together with costimulatory pathways and tertiary signals), CD8$^+$ T cells display many metabolic and transcriptional changes (18). Recently activated CD8$^+$ T cells first increase oxidative phosphorylation, quickly followed by a switch to aerobic glycolysis, a metabolic state characterized by diversion away from mitochondrial respiration pathways (19). These changes are accompanied by activation and robust clonal expansion (20). Increased aerobic glycolysis in effector cells allows energy production to be quicker in response to stimulation and simultaneously promotes the biosynthesis of proteins and other molecules needed to produce effector molecules (19).

Throughout the acute Ag effector phase, Ag-specific CD8$^+$ T cells expand but not uniformly. Already at the early effector phase, effector CD8$^+$ T cells can be distinguished by the expression level of IL-2Rα or CD25. CD25^{hi} early effectors are sensitive to IL-2. As a result, they proliferate more extensively but are more prone to apoptosis. In contrast, CD25^{lo} early effectors are less sensitive to IL-2. These cells, conversely, increase the expression of IL-7Rα or CD127 and L-selectin (CD62L) (21). CD127, for instance, marks a subset of effector CD8$^+$ T cells that can survive T cell contraction and give rise to memory CD8$^+$ T cells; these cells are deemed "memory precursors" (MPs) (22, 23). Conversely, effector CD8$^+$ T cells that

express the killer cell lectin-like receptor G 1 (KLRG1) will mostly contract; these effector CD8$^+$ cells are called TEs (23). Distinct molecules drive the fate of effector CD8$^+$ T cells into the MP versus the TE phenotype. For example, expression of the transcription factors Blimp-1 and ZEB2 promote the TE phenotype in CD8$^+$ T cells (24, 25). In contrast, the transcription factors TCF1, LEF-1, and Bcl-6 induce the MP phenotype in these cells (26–28). Overall, the terminal differentiation of CD8$^+$ T cells is reliant on an increase in pathways related to effector function. Conversely, the induction of an MP phenotype is correlated with the acquisition of quiescence and stemness at the expense of effector function. Thus, both effector CD8$^+$ T cell groups are important, one for the direct pathogen elimination during acute responses and the other for generation of memory CD8$^+$ T cells.

Circulating memory CD8$^+$ T cell subsets. After Ag clearance, most TE CD8$^+$ T cells die. It should be noted that CD8$^+$ T cell contraction does not depend on Ag clearance because it also occurs when pathogen is not completely eliminated (29, 30). Distinct memory CD8$^+$ T cell subsets arise from MP cells, and they can be divided based on distinct aspects. There is currently much talk about how we as a scientific community should define these subsets (31, 32). In this study, we will focus on migratory properties to subdivide memory CD8$^+$ T cells (Table I). Two memory CD8$^+$ T cell subsets were initially defined. Central memory CD8$^+$ T cells (Tcm), which express the secondary lymphoid organ-homing molecules CCR7 and CD62L, are mainly found within the spleen and lymph nodes, lack immediate effector function and have increased ability to generate secondary immune responses. Effector memory CD8$^+$ T cells (Tem) lack expression of these markers, displaying receptors that promote the migration back and from other tissues and have a better ability to readily produce cytokines (33–35). The current view of circulating memory CD8$^+$ T cells is much more complex. The Tcm subset is still somewhat homogeneous, but they are not the only subpopulation of memory CD8$^+$ T cells with quiescence and stemness. In humans and nonhuman primates, a population of stem cell–like memory CD8$^+$ T cells (Tscm) has similar functional characteristics as Tcm but is phenotypically similar to naive CD8$^+$ T cells (36). As for the previous Tem pool, they currently comprise an amalgam of three main subsets. Many of the cells found in nonlymphoid tissues reside long-term in these sites; these cells are now denominated tissue-resident memory CD8$^+$ T cells (Trm); there is more on this subset below. Among the non-Tcm found in the circulation and lymphoid organs, two subsets are found. Tem are derived from MPs, do not express lymph node–homing molecules, and have the characteristics previously described (i.e., lower stemness and half-life and quicker cytokine production) (37). More recently, a new population of non-Tcm was described to have an identical phenotype as TE cells but was found long after Ag clearance. These cells, called "long-lived effector cells" (LLECs) (38, 39), perform superior recall responses against Ag, despite decreased proliferation (38). Tcm, Tem, and LLEC all rely on

TABLE I. Main characteristics of the distinct memory CD8$^+$ T cell subsets

Memory Subset	Main Characteristics	Phenotypic Markers
Tcm	Quiescence, stemness, quick reactivation and proliferation upon secondary Ag, recirculate between lymphoid organs and blood	CD44$^+$, CD62L$^+$, CCR7$^+$, TCF1^{hi}, IL-7Ra$^+$, CD45RA$^-$ (humans)
Tscm	Development occurs early after clonal activation, phenotypic characteristics resembling naive CD8$^+$ T cells, highly, quiescent, stemness, recirculate between lymphoid organs and blood	CD44^{lo}, CD62L$^+$, CD45RA$^+$ (humans)
Tem	Heightened capacity to produce cytokines upon secondary Ag, recirculate between lymphoid organs, blood and nonlymphoid organs, shorter lived, decreased stemness	CD44$^+$, CD62L$^-$, IL-7Ra$^+$, KLRG1$^-$
LLECs	May arise from TEs, highest ability to respond to secondary Ag, do not enter nonlymphoid tissues (mostly confined to blood and spleen red pulp)	CD44$^+$, CD62L$^-$, IL-7Ra$^-$, KLRG1$^+$, CX3CR1^{hi}
Trm	Do not recirculate (mostly found in nonlymphoid organs, some in lymphoid organs), quick mediators of secondary immunity to local insults (e.g., barrier infections), high expression of tissue residency markers and transcriptional signatures (e.g., Hobit/Blimp1), can be defined (in mice) by lack of recirculation upon parabiosis surgery or negative intravascular labeling	CD44$^+$, CD62L$^-$, intravascular Ab$^-$ (mice), CD69/CD103$^+$ (tissue dependent), KLF2^{lo}, Hobit/Blimp1$^+$ (tissue dependent)

IL-15 for their survival (38, 40). Tcm and Tem also display IL-7R in their surfaces and rely on this cytokine for survival, mainly through the antiapoptotic protein Bcl-2 and expression of Aquaporin-9 (41–44).

Tissue-resident memory CD8$^+$ T cells. Over the last two decades, important studies defined that some memory CD8$^+$ T cells permanently reside in nonlymphoid tissues (45, 46). Trm can be defined, in many cases, by tissue residency markers, such as CD69 and/or CD103, with a concomitant lack of CD62L and KLRG1 (30). Trm are defined in mouse models through either lack of intravascular Ab staining (47) or by lack of recirculation after parabiosis surgery (48). The notable exception for intravascular labeling is the liver, where Trm (defined as resident by parabiosis) are positioned in the intravascular sinusoids (49). Trm function by patrolling their respective tissues, searching for cognate peptides from secondary exposure. Therefore, they act as the first layer of defense in barrier tissues, inducing a state of immune alert via quick cytokine production after Ag re-encounter (50–53).

Trm can be found virtually everywhere in the organism. This includes epithelial and nonepithelial sites (10, 30, 48, 54) and secondary lymphoid organs (55). Trm widely vary in their phenotype. Although, in epithelial sites, most Trm coexpress CD69 and CD103, in other nonlymphoid tissues, CD103$^+$ cells are mostly absent, and many Trm do not express CD69 as well (54). Liver Trm, for instance, are gated based on CXCR6 expression (56). These variations in the expression of "residency" markers likely reflect the distinct microenvironments of each organ.

The pathways needed for Trm establishment are still being unveiled, and akin to their phenotype, they are likely distinct between tissues. For most epithelial sites, signaling through TGF-β is necessary (11, 30, 57, 58). In contrast, Trm generation in the liver is less dependent on this cytokine (49, 59). The need for cognate Ag signaling inside the tissue is also organ-dependent. Whereas in the skin, female reproductive tract, and gut their microenvironment, signals are sufficient to support Trm generation (50, 60, 61), lung Trm require Ag inside the tissue (62, 63). The long-term survival of Trm may also have organ-dependent requirements, and this is perfectly exemplified by the role of IL-15. After lymphocytic choriomeningitis virus (LCMV) infection, whereas IL-15 promotes Trm survival in the salivary gland and kidney, it is dispensable for their maintenance in the small intestine, female reproductive tract, and pancreas (64). These findings, in many cases, are the result of studies that used either immunization Ag plus adjuvant or the model virus LCMV. In both these models, only a transient inflammatory response occurs, rather than what happens in response to pathogens of medical relevance, such as ones directly infecting barrier tissues.

Submerging: effect of inflammatory environment on CD8$^+$ T cell function

CD8$^+$ T cell activation occurs in lymph nodes or spleen through Ag presentation by dendritic cells (DCs). DCs can

either be resident in these organs or migrate from barrier tissues where they picked up Ag (65–68). The microanatomical relocalization of DCs to T cell–rich areas is a fundamental step of CD8$^+$ T cell activation (69–73). Past research has defined that, in most cases, DCs recognize and capture cognate Ag in the port of entry (systemic or local), migrate to proximal lymphoid organs toward T cell–rich areas, and present Ag (72, 73). Whether inflammation affects this was not entirely clear, although lymph node inflammation is important for the full activation of CD8$^+$ T cells (74). Moreover, inflammatory cytokines are considered an additional signal to TCR and costimulation for maximal CD8$^+$ T cell proliferation (75). A recent study has investigated this, using sophisticated imaging tools. Surprisingly, in response to type I inflammation induced by TLR, lymph node-resident DCs (rather than migratory ones) are crucial for Ag delivery and initial activation of CD8$^+$ T cells. Resident DCs relocate to T cell zones through CCR7 signaling, which allows for quick Ag presentation. Further highlighting the importance of inflammation, upon type I signals, monocytes infiltrate lymph nodes via CCR2 through local blood vessels. Inside lymph nodes, monocytes enter the T cell zone and secrete inflammatory cytokines to boost T cell activation (76), confirming previous studies showing the ability of these cells to infiltrate Ag-draining lymph nodes (77, 78). Importantly, these inflammatory monocytes do not distribute equally inside the T cell zone. This promotes distinct microenvironments within these lymphoid organs that are based on the intensity of inflammatory signals. Consequently, effector CD8$^+$ T cells with distinct phenotypes can be found in these intranodal microenvironments, showing that inflammatory signals not only help CD8$^+$ T cell effector function but also direct their heterogeneity (76). This divergent early CD8$^+$ T cell effector programming may also impact the generation of CD8$^+$ T cell memory. This is suggested by the clear distinction in TCF1, a promemory transcription factor (79), observed between CD8$^+$ T cells in distinct microenvironments (76). The interplay between inflammatory signals, TCR engagement, and CD8$^+$ T cell function is also highlighted by studies showing that a concerted action of both pathways shape how some early effector CD8$^+$ T cells undergo Bim-dependent apoptosis (80). TCR signal strength and Ag availability, conversely, can dictate how effector CD8$^+$ T cells develop intracellular proinflammatory pathways (3).

The intensity and quality of inflammation dictate not only the magnitude of CD8$^+$ T cell effector expansion but also fine-tune their phenotype and impact their different functional aspects (23, 81–83). This is important to promote the elimination of infected cells, given inflammation-induced chemokine and integrin ligand upregulation promote effector CD8$^+$ T cell infiltration into nonlymphoid tissues and pathogen killing (84–88). Consequently, the phenotype and function of effector CD8$^+$ T cells vary depending on the type of infection. For example, whereas in response to vesicular stomatitis virus a greater proportion of effector CD8$^+$ T cells differentiate into MP cells, in response to *Listeria*, almost all effector CD8$^+$ T cells have a TE phenotype

(89). Because inflammation is dependent on pathogen load, in many cases, the infection intensity is the defining feature of the effector CD8$^+$ T cell response. A relevant example is COVID-19, in which the presence of polyfunctional SARS-CoV-2–specific CD8$^+$ T cells are associated with recovery from disease (90, 91) and the magnitude of Ag-specific CD8$^+$ T cells correlates with viral load (91). However, the correlation between inflammatory molecules and the expression of effector molecules in SARS-CoV-2–specific CD8$^+$ T cells was weak (91). This suggests a more complex interplay between lung inflammation, Ag load, and effector CD8$^+$ T cell responses during COVID-19.

Maximum depth: formation of memory CD8$^+$ T cells in the presence of systemic or tissue inflammation
Beyond affecting their effector expansion, the inflammatory context induced by various diseases can determine how and whether CD8$^+$ T cell memory is formed. In addition, memory CD8$^+$ T cells face distinct levels of inflammation in different tissues that also affects their long-term survival and secondary function.

How inflammation shapes memory CD8$^+$ T cell generation. The effector-to-memory transition typically occurs during the peak of effector response, when MP cells arise (22). Even in the context of LCMV infection, the presence of proinflammatory cytokines (namely, prolonged IL-2, type I IFN, and IL-12 stimulation) divert effector CD8$^+$ T cells away from the memory phenotype (23, 92, 93). The sensing of these cytokines, however, cannot be interpreted separately from cognate Ag. Indeed, reduced TCR signal strength resulted in increased MP accumulation even in the presence of inflammatory cytokines (3). The effect of inflammation on MP cells may also be context-dependent. Different from acute viral infection, immunization with inflammation-inducing adjuvants (e.g., CpG) do not affect the numbers of MPs, rather they promote an increase of TE cells (94).

In contrast, another signal typically associated with tissue inflammation, eATP, was shown by us to promote the MP phenotype and transition to memory in CD8$^+$ T cells through the P2RX7 receptor (95). The role of eATP sensing for CD8$^+$ T cells is likely complex and may involve autocrine release of eATP by CD8$^+$ T cells via the hemichannel Pannexin-1 (95, 96). In this case, inflammation-derived eATP may not be relevant for memory generation, at least in the presence of less aggressive pathogens. Whether this is true in the presence of infections that induce enhanced or prolonged tissue inflammation, such as influenza in the lung or *Yersinia* in the gut, remains to be defined. In addition, despite preferential expression of P2RX7 in MP cells, many early effector CD8$^+$ T cells also express P2RX7 (59, 95), and it is reasonable to assume that not all of them will become MP cells. What is the effect of eATP sensing on effector CD8$^+$ T cells that do not become MP cells? Like MPs, are these cells able to release eATP via

Pannexin-1? These will be important questions to be answered and may help us understand whether CD8$^+$ T cells rely on eATP for memory generation in the context of excessive inflammation-derived eATP.

Another inflammatory signal likely sensed by forming memory CD8$^+$ T cells is DNA from viral origin or from host/CD8$^+$ T cells themselves. Recognition of DNA and engagement of the cGAS–STING pathway can induce cell death in certain cell types (97). Contrary to this, CD8$^+$ T cell cGAS–STING activation promotes the generation of Tcm phenotype CD8$^+$ T cells in humans (98). Cytosolic DNA can accumulate in effector CD8$^+$ T cells, and simultaneous engagement of DNA repair pathways is likely important for memory CD8$^+$ T cell generation. Indeed, a DNA repair gene signature is associated with memory CD8$^+$ T cell generation (99). This may suggest that increased DNA repair helps curb the intensity of the cGAS–STING activation to prevent undesirable effects (i.e., cell death).

Many pathogens induce a localized immune response. Protective immunity in these cases relies on Trm, and tissue inflammation context influences how and whether Trm are formed. In the small intestine, two major inflammation-modulating factors affect Trm generation: the local microbiota and the presence of regulatory T cells (Tregs). The gut microbiota contains specific bacteria that can promote the accumulation of intestine Trm (100). Moreover, Trm specific for microbiota Ags found in the gut can promote protection against certain oral infections and tumors (101). In different circumstances, however, microbiota may diminish Trm accumulation and responses. For example, transient elimination of microbiota favors CD8$^+$ Trm responses to *Listeria*-encoded Ags (102).

Although peripheral Treg expansion may be deleterious for gut Trm accumulation in determined contexts (103), in response to infections inducing type I inflammation, expansion of type 1 Tregs is important for the induction of CD8$^+$ Trm by increasing the availability of bioactive TGF-β in the small intestine microenvironment (104). Treg depletion also leads to reduced Trm numbers in the CNS upon viral infection (105). The apparent lesson from these studies is that tissue inflammation is, in many cases, important for Trm development, but in controlled levels; in a somewhat similar manner as for circulating memory CD8$^+$ T cells, excessive type 1 inflammation diverts tissue-seeding CD8$^+$ T cells to a terminal phenotype. Agreeing with this notion, disproportionate inflammation limits the acquisition of memory traits and favors terminal exhaustion in CD8$^+$ T cells during chronic LCMV infection (106). Moreover, CD8$^+$ T cell diversion toward terminal exhaustion relies on expression of inflammation-associated transcriptional features, including T-bet and Tox upregulation (107).

Excessive inflammation may be deleterious for the generation of memory CD8$^+$ T cells. Response to SARS-CoV-2, however, may induce a more complex relation between inflammation and CD8$^+$ T cell memory. Many studies suggest that CD4$^+$ and CD8$^+$ T cell memory, elicited by past exposure or immunization, is crucial to promote long-term protection against the virus (90, 108–111). Aside from a potential contribution of pre-existing memory CD8$^+$ T cells specific for cross-reactive coronavirus Ags (112), much of the CD8$^+$ T cell response to SARS-CoV-2 is mediated by newly activated clones (91). In convalescent patients, SARS-CoV-2–specific CD8$^+$ T cells are enriched for the Tscm pool. In high-prevalence clones, these cells are skewed toward a Temra (i.e., effector memory cells re-expressing CD45RA) and Tem phenotypes, with a low prevalence in quiescent cells. In airway samples from patients, CD8$^+$ T cells with a Trm phenotype can be found, and higher frequency of these cells correlated with younger age and survival (113). Future studies focusing on how memory CD8$^+$ T cells form and function in both circulation and tissues of SARS-CoV-2–infected hosts will be needed.

Role of inflammation in memory CD8$^+$ T cell maintenance and reactivation. Inflammatory signals can affect not only the generation of memory CD8$^+$ T cells but also their maintenance. In many circumstances, bystander infections or insults lead to increased secretion of inflammatory mediators that can affect existing memory CD8$^+$ T cells. A straight-forward example is sepsis, which induces preferential attrition of memory CD8$^+$ T cells (114). The effect of bystander inflammation is usually more prevalent in barrier tissues, which are often the sites of new infections. An example is the lung, where epithelial cells infected with influenza increase their production and secretion of TSLP. TSLP, despite positively modulating naive CD8$^+$ T cell survival in vitro, negatively impacts existing lung CD8$^+$ Trm (115). TSLP directly represses the expression of the transcription factors Runx2 and Egr2, both important for antiviral CD8$^+$ T cell homeostasis (116, 117). TSLP activity also diminished the expression of Pannexin-1, which can influence CD8$^+$ T cell mitochondrial homeostasis in the context of IL-15 (95) and may influence memory CD8$^+$ T cell maintenance (96). Pannexin-1, as explained above, mediates the export of eATP in CD8$^+$ T cells. We have found the eATP signaling through P2RX7 promotes the long-term maintenance of established Trm by using mouse LCMV (59), which does not, however, induce relevant lung Trm populations (63). Future studies will be necessary to assess whether P2RX7 (and Pannexin-1) are required for the maintenance of lung Trm populations. If this is true, it will be important to assess whether TSLP also influences eATP sensing pathways in lung Trm. Mirroring circulating memory CD8$^+$ T cells (118), lung Trm maintenance relies on mitochondrial fitness, more specifically on the expression of the transcription factor Bhlhe40 (10). The lung, like other mucosal tissues and tumors, displays limited nutrients (e.g., glucose) and increased baseline inflammation (119, 120). The induction of stress pathways in lung Trm is likely important for the tissue-specific function of Bhlhe40, which is a stress-responsive protein.

Conversely, memory CD8$^+$ T cells can be activated in response to bystander inflammation in certain situations, inducing an effector T cell–like phenotype, including expression of granzyme B (121, 122) and IFN-γ (123, 124). These cells, upon

bystander activation, can eliminate cells infected with noncognate virus and promote quick pathogen control but may promote tissue damage in the presence of a nonrelated chronic infection. The ability of memory CD8$^+$ T cells to engage bystander inflammatory signals increases with additional Ag stimulations but decreases with time after the last Ag encounter (125). This parallels the acquisition of an effector-like phenotype in secondary and tertiary memory CD8$^+$ T cells (126) as well as in mice exposed to pathogen normalization via cohousing with pet store counterparts (127). This contrasts with the progressive enrichment of quiescent Tcm in the absence of serial Ag stimulation. Interestingly, memory CD8$^+$ T cell bystander activation does not happen only in response to systemic inflammation but also occurs in a localized way in response to immunizations (128). The presence of bystander inflammation (e.g., type I IFN) can also promote memory CD8$^+$ T cell proliferation (129), although this seems limited if compared with Ag-driven proliferation (129). Localized bystander inflammation, moreover, can promote the accumulation of Trm quickly after inflammation onset (130). This suggests that inflammation can
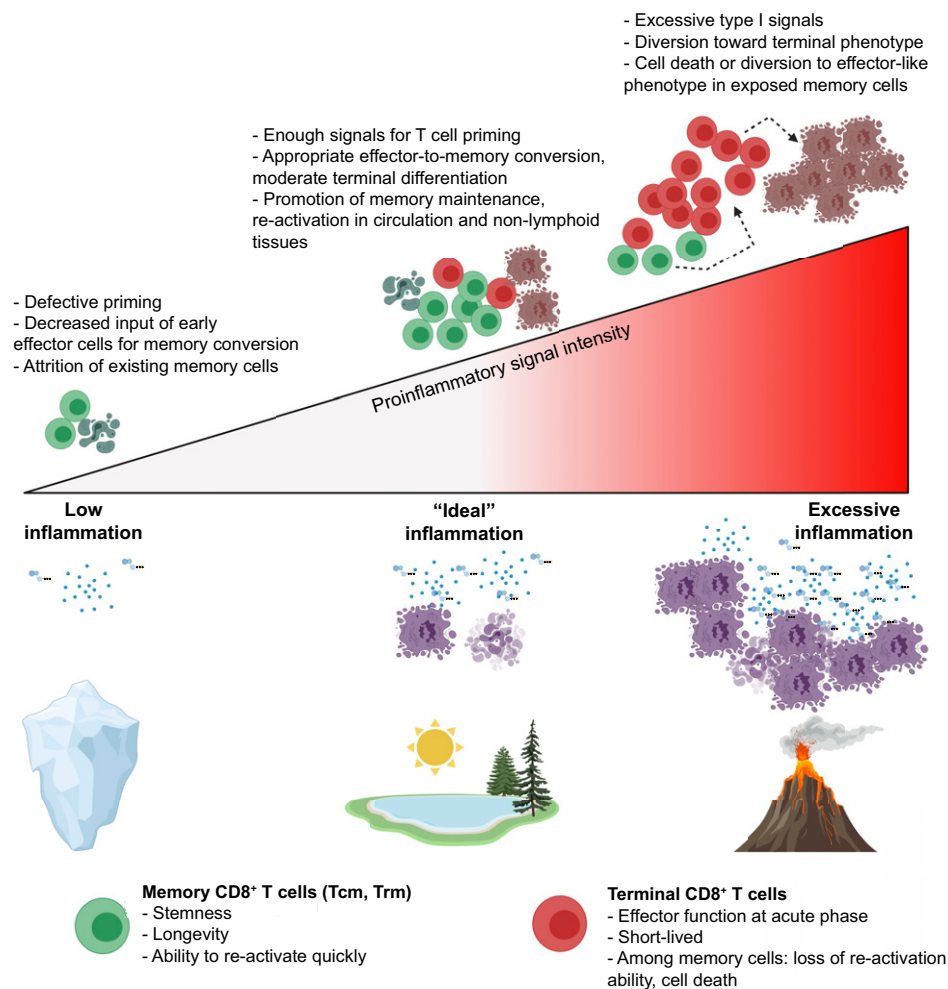

FIGURE 1. How inflammation can affect memory CD8$^+$ T cells.

This hypothetical scheme highlights the common relation between inflammatory signals and memory CD8$^+$ T cells. Independent of location or nature of memory CD8$^+$ T cells, low or no inflammation mostly hinders memory CD8$^+$ T cell generation (including the input of effector cells needed for effector-to-memory conversion) and survival. Conversely, excessive inflammation usually diverts activated CD8$^+$ T cells toward terminal-like phenotypes, consequently leading to increased population death; this is also true for existing memory CD8$^+$ T cells, in which too high levels of proinflammatory signals lead to both a conversion to a effector-like phenotype and increased attrition. There is a likely sweet spot, where enough type 1 inflammatory signals promote effective priming of CD8$^+$ T cells (together with TCR and costimulation), appropriate MP generation (both in circulation and in tissues), and efficient maintenance and reactivation of memory CD8$^+$ T cells, either in the presence or not of secondary Ag. Manipulations of local and/or systemic inflammation should ideally shape the inflammatory environment to reach this hypothetical sweet spot, which may vary from tissue to tissue and from infection to infection. The figure was created with Biorender.com.

alter the intraorgan trafficking of memory CD8^{+} T cells. Also, cytokine-mediated recruitment of bystander circulating effector and memory CD8^{+} T cells is a hallmark of Ag-reactivated Trm (51–53). This provides further evidence that bystander inflammation promotes differential migration of memory CD8^{+} T cells. Finally, inflammatory signals can also increase memory CD8^{+} T cell functional avidity (131). Overall, memory CD8^{+} T cells are equipped with sensing pathways that allow the recognition of bystander signals, allowing their response modulation.

The reactivation of memory CD8^{+} T cells may also be favored by inflammation associated with their cognate Ag. For example, the accumulation of acetate at sites of reinfection promotes glutaminolysis and cellular respiration, promoting enhanced memory CD8^{+} T cell function and subsequent pathogen clearance (132). A positive role of inflammation can also be found for gut Trm in response to *Yersinia* infection, in which prolonged production of IL-12 and type I IFN within Trm-rich immune clusters promote long-term Trm survival (133). These clusters are found in many nonlymphoid tissues, such as the brain (134), female reproductive tract (135), and lung (47). Therefore, a more detailed assessment is needed of whether the controlled production of inflammatory mediators in these sites can also favor Trm survival. These data once again illustrate a possible scenario in which controlled inflammation may be needed for the optimal survival and function of Trm.

CONCLUSIONS

Our field has made outstanding advancements to define how memory CD8^{+} T cells form, maintain, and act in response to multiple inflammatory environments. Despite these breakthroughs, many knowledge gaps remain, most of them discussed throughout this review. For instance, we now know that type 1 inflammatory signals can influence the quality and spatial distribution of CD8^{+} T cell priming, influencing their effector function and subsequent memory fate (76). However, not much is known about how type 2 stimuli influence CD8^{+} T cell memory. This may be particularly important for Trm, which can express type 2 cytokine receptors (136). Still, about the role of type 1 inflammation for CD8^{+} T cell responses, how does this pan out in the context of systemic inflammation, which induces a strong inflammatory monocyte response? Answering this question, and others, may give us a complete understanding of how different inflammatory responses control the CD8^{+} T cell memory fate.

Nevertheless, a common theme can be depicted about how inflammation affect memory CD8^{+} T cells. Regardless of the site or infection model for memory CD8^{+} T cell generation, maintenance, and secondary function, the presence of a controlled level of inflammatory signals may be ideal (Fig. 1). If inflammation signals are absent or too low, they often result is a decay in memory generation and impaired reactivation. At the other end, exaggerated inflammatory signals typically divert CD8^{+} T cells toward terminal differentiation and death at an effector phase and impaired memory CD8^{+} T cell maintenance. Given that 1) there seems to be a common denominator for how inflammation affects all memory CD8^{+} T cell subsets and 2) inflammation often induces changes in the nature of existing memory CD8^{+} T cells (128), future studies aiming to understand how inflammation affects CD8^{+} T cell memory may benefit from limiting the subdivision in memory subsets. Obviously, the use of subsets to define memory CD8^{+} T cells is valuable because it is hard to understand general tendencies without placing these cells into defined groups. However, if we are considering multiple inflammatory backgrounds, subsets may not capture the complexity of the millions of clones generating a role for long-lived memory CD8^{+} T cells. This is especially true considering that memory cells resultant from one clone are not homogeneous, even when placed in the same subset.

DISCLOSURES

The author has no financial conflicts of interest.

ACKNOWLEDGMENTS

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