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Understanding Memory CD8⁺ T cells

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Abstract

Memory CD8⁺ T cells were originally thought to exist as two populations (effector and central memory). In recent years, a third population called resident memory T cells has been discovered and further to this these populations are being divided into different subtypes. Understanding the function and developmental pathways of memory CD8⁺ T cells is key to developing effective therapies against cancer and infectious diseases. Here we have reviewed what is currently known about all three subsets of memory CD8⁺ T populations and as to how each population was originally discovered and the developmental pathways of each subpopulation. Each memory population appears to play a distinct role in adaptive immune responses but we are still a long way from understanding how the populations are generated and what roles they play in protection against invading pathogens and if they contribute to the pathogenesis of inflammatory diseases.

Introduction

Broadly speaking, the immune system is divided into the innate and adaptive components. With innate immunity encompassing the initial rapid response of the body to a pathogen and the adaptive response following soon after, which ultimately leads to a long lasting immunological memory. In this review we will focus on the different types of CD8⁺ T memory subsets.

The first evidence for differentiating the two distinct populations of CD8⁺ T cells, effector and memory, was demonstrated through studies using lymphocyte choriomeningitis virus (LCMV) infection in mice [1,2]. Here the authors discovered that a large population of antigen specific effector CD8⁺ T cell population could be found in lymphoid organs early between 7 and 9 days after LCMV infection. They also identified another population that was found to survive long after the infection had cleared. This second memory population was shown to have an increased ability to restrict viral replication upon secondary infection,

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and thus indicated the importance and potency of memory T cells compared to naïve or effector T cells [2]. These seminal studies led the way for investigations to understand how T cell memory is generated.

Naïve CD8⁺ T cells are continuously circulating throughout the body migrating through the blood and secondary lymphoid tissues, such as the lymph nodes, spleen and the Peyer's Patches, and one school of thought indicates that naïve cells may also migrate through non-lymphoid organs and then back into the blood via the afferent lymph [3–6]. Once a naïve T cell encounters its cognate antigen on an antigen presenting cell (APC) within a secondary lymphoid organ (SLO), the CD8⁺ T cell undergoes a number of molecular changes leading to the T cell being in an activated state and differentiating into a number of different subpopulations [7,8]. Upon activation, antigen specific CD8 T cells undergo three distinct phases: 1) clonal expansion during which the cells acquire effector functions, 2) contraction of the effector population through activation induced cell death (AICD) with the concomitant survival of a small percentage of memory population, and 3) maturation of the memory population [9–12]. It should be noted that contraction and the formation of memory are independent of each other because in the absence of contraction, memory cells still form. The contraction phase is controlled by early inflammation [13].

The definition of immunological memory remains contested [14]. In general, memory CD8⁺ T cells are a long-lived population that are antigen specific and provide an enhanced protective response when the same antigen is encountered again [15,16]. These cells persist in the absence of antigen but maintain a distinct phenotype, and elevated precursor frequency, which is one way of distinguishing them from the naïve CD8⁺ T cell population [12], thus indicating that this population of cells is ready and waiting to act rapidly upon reencountering the antigen. Memory T cells respond consistently to stimulation to distinguish them from the random manner in which a host may respond to a given antigen and this response thus provides an evolutionary advantage to the host in that the host is less likely to fall sick or die upon re-encountering the same antigen and this important trait is passed down through the germline [14]. Recently, this view of immunological memory being a hallmark of the adaptive immune response is being broadened to encompass some innate immune cell populations, such as NK cells, $\gamma\delta$ T cells [17,18] or myeloid cells [14], therefore with this in mind it ought to be stated that in this review we will focus on the adaptive immunological memory with specific reference to the CD8⁺ $\alpha\beta$ T cell population.

Identifying CD8⁺ T Memory Cells

Since the advent of technologies such as monoclonal antibodies, MHC class I tetramers, flow cytometry, fluorescence-activated cell sorting (FACS), and RNA-Sequencing (RNA-Seq), investigators have been able to identify unique subsets of CD8⁺ T cell memory populations since they express different cell surface markers. It was not until two decades ago when multiple varieties of memory CD8⁺ T cells were identified [19]. In mice and in humans certain distinct cell surface markers can be used to distinguish memory T cells from effector (T_{EFF}) or naïve cells. In mice, typically increased expression of adhesion molecules such as CD11a and CD44 distinguishes effector and memory CD8 T cells from naïve CD8 T cells (which express lower levels of CD11a and CD44). Naïve CD8 T cells express higher

levels of CD62L, CCR7 and CD127 (IL-7R α). However, activated effector CD8 T cells downregulate these three proteins. CD127 is an important protein that is used to distinguish effector cells from memory T cells [20]. During the early phase of an antimicrobial immune response the majority of effector CD8 T cells express high levels of killer cell lectin-like receptor G1 (KLRG1) and low levels of CD127, which marks the cells as terminally differentiated and are called short lived effector cells (SLECs). Conversely, a small population of T_{EFF} cells retain CD127 expression, but fail to express KLRG1, and survive the contraction phase to become memory T cells, and are labeled as memory precursor effector cells (MPECs).

Studies in humans indicated the importance of CD45RA and CD45RO, as well as a few other markers, as a way of distinguishing circulating effector and memory T cells. In a study by Hamann *et al.*, the authors identified circulating memory population as CD45RA⁻ CD27⁺ and expressed high levels of CD95 (Fas Ligand), CD11a, CD18, CD29, and secreted interleukin-2 (IL-2) and interferon gamma (IFN- γ). In contrast T_{EFF} cells were identified as being CD45RA⁺ CD27⁻ CD62L⁻ but still expressed high levels of CD11a, CD11b, CD18, CD49d, CD95, perforin and granzyme B and were shown to produce IFN- γ and tumor necrosis factor alpha (TNF- α). Interestingly, the effector population had high cytolytic activity without requiring stimulation thus setting one of the differences between effector and memory T cells [21].

Pioneering work by Sallusto *et al.* showed that the expression of CCR7, a chemokine receptor that regulates homing of CD8⁺ T cells to SLOs, revealed the difference between naive, central and effector memory T cell subsets. Their work showed that in humans naive CD8⁺ T cells were CD45RA⁺ CCR7⁺, T_{EFF} cells were CD45RA⁺ CCR7⁻, central memory cells (T_{CM}) were CD45RA⁻ CCR7⁺ and effector memory cells (T_{EM}) were CD45RA⁻ CCR7⁻. This highlighted that there was a difference in memory CD8⁺ T cells that were found to circulate in the blood and readily available to act versus those that remained in the SLOs and once stimulated are able to efficiently generate a new population of effector cells [19]. Following this study, these two distinct sets of memory CD8⁺ T cells were identified in the blood of Epstein Barr virus infected patients. In this study, Tussey *et al.* identified CD8⁺ T memory cells that were CD62L⁺ CCR7⁺ but were unable to immediately produce IFN- γ , similar to T_{CM}, and another set that were CD62L⁻ CCR7⁻ and were able to rapidly produce IFN- γ , similar to T_{EM} cells [22]. More recently, other markers, such as CXCR3R1, have been identified that could further distinguish between different CD8⁺ T cells populations thus indicating that there are a variety of ways to distinguish between the different subsets [23,24].

For some time, it was hypothesized that memory cells existed only in the blood and SLOs. The study by Kim *et al.* provided the first evidence that memory cells were found in non-lymphoid tissues. Using an OT-I TCR transgenic CD8⁺ T cell adoptive transfer system, the authors showed that memory cells were localized within the lamina propria and intraepithelial compartments of the intestinal mucosa [25]. Masopust *et al.* showed that memory cells in mice were present in both lymphoid and non-lymphoid tissues, with a preference of residing in non-lymphoid tissues. The antigen specific CD8⁺ T cells that were

residing in non-lymphoid tissues were able to exert immediate effector functions, similar to T_{EM}, whereas those that were in SLOs, such as the spleen, were not [26].

Soon after the understanding that memory cells resided in non-lymphoid tissues, it became clear that these memory cells were not all the same. A mouse study that focused on T cells found in the lamina propria (LP), indicated that memory cells that resided in this tissue were made up of a distinct set of memory cells that were not found elsewhere and that did not migrate elsewhere, indicating the presence of a different type of memory that is similar to T_{EM} but distinct to T_{CM} [27]. The T_{EM} cells identified in the LP expressed high levels of CD69 which was not seen in T_{EM} cells found in the spleen or blood [28]. Similar high expression of CD69 on memory cells was also found in cells in the lung following a respiratory virus infection [29,30]. Unlike splenic memory CD8 T cells (which were a combination of T_{CM} and T_{EM} cells), those found in the small intestines expressed high levels of granzyme B, CD69, CD103 and β_7 . Splenic memory CD8 T cells expressed high levels of CD27, CD62L, IL-15R β and Ly6C, while the intraepithelial mucosal cells (IELs) expressed low levels of these proteins. Both populations of memory cells expressed high levels of TNF- α and IFN- γ , although surprisingly, IEL memory cells produced much lower levels of IL-2 when compared to splenic memory cells [31].

Further mouse studies showed that memory cells were found in all non-lymphoid tissues irrespective of the site of initial infection. When memory cells from distinct non-lymphoid tissues were transferred into naïve mice they were found to migrate to most tissues, except the LP, with some preference to their original location. This indicated that a number of memory cells in these non-lymphoid tissues are made up of a pool of circulating memory cells whereas others home to a specific tissue, with the exception of LP memory cells that appeared not to circulate outside of the intestinal mucosa [28]. Parabiosis experiments reinforced the idea that some memory cells were able to migrate to lymphoid and some non-lymphoid tissues (such as lung and liver) but other memory cells found in some non-lymphoid tissues, such as the brain, peritoneal cavity and the LP, were less likely to migrate to out of their resident organs indicating the presence of distinct sets of memory cells [32]. Studies using Herpes Simplex Virus type 1 (HSV-1) indicated the presence of a similar type of antigen specific CD8⁺ T cells that expressed CD69 in the trigeminal ganglion that had the ability to suppress HSV-1 reactivation from latency without killing the neurons harboring the virus [33].

Interestingly, cytotoxic chemotherapy leads to the deletion of circulating T cells, leading to the thought that patients undergoing this type of therapy would be vulnerable to severe infections as their circulating memory T cells would be absent. A study that followed such patients found that they were rarely susceptible to these diseases thus indicating that a subset of non-circulating memory T cells was able to provide an effective immune response to protect these patients from succumbing to infection [34].

This subset of memory T cells that resided permanently within the mucosal tissues and failed to enter the circulation but were similar to, yet distinct from T_{EM} cells were eventually labeled as tissue resident memory T cells (T_{RM}) [35,36].

Since these studies, T_{RM}s have been identified in human tissues as well as mice. The study by Sathaliyawala *et al.* showed that CD45RO, CD69 and CCR7 expression can be used to identify different populations of T_{EM}, T_{CM} and T_{RM}s, whereas CD45RO and CD103 expression can identify mucosal memory CD8⁺ T cells in humans [37]. Hombrink *et al.* identified lung resident memory CD45RA⁻ CD8⁺ T cells from healthy lung tissues from patients undergoing lung resection [38]. Circulating memory cells were in the blood were CD103⁻CD27⁺ (T_{CM} cells), and CD103⁻CD27⁺CCR7⁻ (T_{EM} cells), while in the lung, the majority of the cells were CD69⁺CD103⁻; with a smaller proportion that were CD69⁺CD103⁺. In this study the authors chose to focus on the CD69⁺CD103⁺ population and used the T_{EM} population found in the blood as a baseline for the transcriptomic comparison. From their analysis they showed that the differences between these two populations were found in genes associated with cytokine signaling, chemokine receptor signaling, active transport of ions and small molecules, apoptosis, TNF receptor signaling, the proinflammatory immune response, glucose deprivation and hypoxia. Migratory receptors that distinguished T_{RM}s from T_{EM}s were high expression of CXCR3, CXCR6, CCR5 and CCR6 and low expression of CX3CR1. High expression of CCR6 and CXCR6 in lung T_{RM}s was not unexpected given that this receptor recognizes CCL20 and CXCL16, respectively, produced by lung epithelial cells. Lung T_{RM}s also expressed high levels of adhesion molecules: CD103, CD51 (also known as VTNR), CD44, CD97, VCAM and Claudin19; as well as chemokines: CCL3 (important for attracting macrophages, CD8⁺ T cells and CD4⁺ T cells), CCL4 (important for attracting NK cells and monocytes), CCL20 and XCL1. After *in vitro* stimulation with phorbol ester, PMA, and ionomycin lung T_{RM}s secreted IFN- γ more rapidly than blood T_{EM} cells reflecting data derived from mouse models. Interestingly, Hombrink *et al.* showed that T-bet and eomesodermin (EOMES) were not expressed in the human lung CD69⁺CD103⁺ T_{RM} population, which is the opposite of what has been observed in mouse skin T_{RM} cells [39]. Along similar lines, the authors identified Notch signaling, through Notch1 and Notch2 receptors, as a key component to maintaining constitutive expression of IFN- γ in human lung T_{RM}'s independent of TCR stimulation, whereas inhibition of Notch signaling in mice did not reduce expression of IFN- γ in mouse lung T_{RM}s.

Even with these differences between human and mouse lungs, the core gene signature of CD103⁺ T_{RM} versus T_{EM} in human was similar to the core gene signature of CD69⁺ T_{RM} versus CD69⁻ T_{RM} in mouse lungs. The authors showed that Notch signaling in T_{RM} cells is required for the control of metabolism [38].

Another human study by Wong *et al.* analyzed the expression profiles of CD8⁺CD69⁻CD103⁻, CD8⁺CD69⁺CD103⁻ and CD8⁺CD69⁺CD103⁺ across several tissues. As expected CD69⁺CD103⁻ T_{RM}s were present in all non-lymphoid tissues but the blood. Using bioinformatics algorithm on total CD8⁺ T cells from several different tissues, the authors identified four subtypes of CD69⁺CD103⁺ T_{RM}s. CCR5⁺CD49a⁺CD45RA⁺ and CCR5⁺CD49a⁺CD45RO⁺ populations were found at high frequencies in the colon and lung likely due to the high expression of CCL5 (a chemokine that is highly expressed in the lungs and colon). CCR5⁺CD45RO⁺CD161⁺ T_{RM}s that are found in the colon; these are likely to be the mucosal-associated invariant T (MAIT)-like cells. The final subtype was mainly

present in the tonsil and spleen and was CXCR5⁺PD-1⁺, which are a subtype of cells that were recently identified in the spleens of mice infected with LCMV clone 13 that respond rapidly to treatment with anti-PD-L1 blocking antibody [40]. This study highlighted the diversity between the CD8⁺ T_{RM} populations in various tissues in humans indicating the necessity of utilizing multiple surface markers to identify specific populations [41].

Similarities and differences between the different types of memory CD8⁺ T cells

Physiologically, having these three different flavors of memory CD8⁺ T cells is very advantageous. Due to the presence of very few naive CD8⁺ T cells that can respond to a given pathogen [42], the time in which a primary response is generated in the draining lymph nodes is large enough the infecting pathogen can cause serious damage to the host. Epithelial and mucosal tissues represent those most vulnerable to attack by pathogens, therefore the presence of resident memory CD8⁺ T cells that can respond efficiently and rapidly to infection are necessary for protecting animals against debilitating infections. Some pathogens move directly into lymphatic vessels and draining lymph nodes and therefore the presence of memory cells that are either circulating (T_{EM}) or that reside within the lymphoid organs (T_{CM}) are a necessary component of the immune response to previous infections. Thus, T_{RM} appear to exclusively reside within non-lymphoid tissues and do not reenter circulation whereas T_{CM} while mostly residing in SLOs are seen within circulation. T_{EM} cells are motile and recirculate throughout the body. These cells were previously conflated as non-lymphoid tissue resident cells, however, it was later discovered that these cells were in fact present in blood vessels and not in tissue parenchyma [43]. While both T_{EM} and T_{CM} can be found in the spleen T_{EM} are primarily located with the red pulp whereas T_{CM} are mostly located within the white pulp [44].

All types of memory CD8⁺ T cells respond rapidly to reinfection and are all CD127^{hi} CD44^{hi} CD11a^{hi}, but they are distinct from each other with respect to the expression of the transcriptome and cell surface proteins [45]. T_{EM} and T_{CM} cells are known to be CD69⁻ CD103⁻, whereas T_{RM} CD8⁺ T cells are mostly CD69⁺ CD103⁺, although there is some evidence of T_{RM} CD8⁺ T cells that are CD103⁻ [46]. It should also be noted that there are some T_{RM} cells that have been found to be both CD69⁻ CD103⁻ and so while these prove to be useful markers for T_{RM}s, it is critical to identify T_{RM}s based on their inability to recirculate [47]. CD103 (α chain of α4β7 integrin) binds to E-cadherin, which is mainly expressed on epithelial cells, and has been implicated in mediating survival, retention and localization of T_{RM} cells [36,45,48–51]. Both T_{EM} and T_{RM} are CD62L⁻ CCR7⁻ due to their exclusion from the lymph nodes and therefore it is only T_{CM} that are CD62L⁺ CCR7⁺, which remain in the lymph nodes. One study also identified another population of migratory memory T cells, termed T_{MM}, that were defined as CD62L⁻ CCR7⁺. These were found to be circulating in healthy human skin and were confined to the dermis. T_{MM}s produced an intermediate levels of cytokines compared to T_{EM} and T_{CM} cells and appeared to recirculate more slowly than T_{CM}s [52]. T_{CM} have a much higher proliferative potential than T_{EM} and express CD27 whereas T_{EM} do not. Furthermore, T_{CM} need a much longer period of reactivation in order to express cytolytic markers such as perforin, whereas T_{EM} respond

immediately and contain high levels of perforin [53]. After TCR activation, T_{CM} express IL-2 but once they have differentiated into effectors cells they stop producing IL-2 [53]. Interestingly *in vitro* when activated CD8⁺ T cells are exposed to IL-2 they are more likely to become T_{EM}, whereas if the activated CD8⁺ T cells are exposed to IL-15 they acquire a T_{CM} phenotype [3]. CXCR3 is required for the correct amount of T_{EM} formation, in its absence reduced numbers of T_{EM} cells are generated but the recall response is better due to greater numbers of T_{CM} [54]. It has also been shown that T_{CM} express CXCR3 which is important in the recall response and distinguishes them from naïve T cells [55].

A number of transcription factors have been implicated in differentiating memory T cell populations from effector T cells (Table 1). For example, MPECs (which are the precursors to memory cells) are associated with high expression of EOMES ([56–58]), inhibitor of DNA binding 3 (ID3, [59,60]), B cell lymphoma 6 (BCL-6, [61]), Signal transducer and Activator of Transcription 3 (STAT3, [62,63]), forehead box protein O1 (FOXO1, [64,65]), serine protease inhibitor 2A (Spi2A, [66]) and transcription factor 1 (TCF-1, [67]). It has also been shown that high expression of Fas ligand (FasL) leads to formation of T_{CM} over T_{EM} [68]. Similarly the differential expression of ID2 and ID3 leads to the formation of either TEM or TCM [60]. Expression of the transcription factor Blimp-1 is required for TEM formation over T_{CM}, although the study by Kallies *et al.* showed that Blimp-1 expression is more important for efficient recall responses. One possibility is that Blimp-1 maybe important for early programming of memory T cells as its expression is control by IL-2 [69]. Eomes and TCF-1 is required for T_{CM} cells formation over T_{EM}, with TCF-1-Wnt signaling pathway inducing expression of Eomes [56,67]. T_{RM} cells express low levels of Kruppel Like Factor 2 (KLF2) leading to downregulation of the sphingosine 1-phosphate receptor-1 (S1PR1) [70]. The downregulation of KLF2 in T_{RMS} is due to the phosphatidylinositol-3-OH kinase - Akt pathway [70]. Downregulation of S1PR1 allows for increased expression of CD69 and thus, prevents egress of T_{RM} cells from non-lymphoid tissues [71]. Recently it was shown that the transcription factor Homolog of Blimp1 in T cells (Hobit) is specifically upregulated in all T_{RM} cells [72]. Table 1 provides a list of known transcription factors that are important for the formation of MPECs and memory CD8⁺ T cells.

Ultimately expression of the various transcription factors leads to the expression of cytokines such as IL-2, IL-7 and IL-15, or receptors that respond to the presence of specific cytokines, such as CD122, which is the receptor for responding to the presence of IL-15. Indeed, the local milieu provides the instructive signals to cells indicating what type of memory T cell is generated [73,74]. It is known that if CD8⁺ T cells are exposed to IL-15 they are more likely to form memory T cells versus effector T cells, whereas exposure of cells to IL-2 produces poor memory [3,75]. Memory CD8⁺ T cells also required IL-7 for survival [76]. It has been shown that IL-15, TGF- β , IL-33 and tumor necrosis factor (TNF) are required for the formation and survival of skin T_{RMS}. *In vitro*, TGF- β and IL-33 combined led to downregulation of KLF2 and interestingly so did the combination of IL-12 and IL-18, overall indicating that these combination of cytokines could be important for the formation of T_{RMS} [45,70]. TGF- β is known to signal mainly through the Smad pathway. A recent study shows that signaling via that TGF- β -Smad4 pathway is not required for the

formation of T_{RM}s but interestingly, TGF- β is not necessary for development of circulating memory cells but Smad4 is [77]. Furthermore, the downregulation of T-bet and Eomes is necessary for TGF- β signaling to occur for the formation of T_{RM} cells but that a low levels of T-bet expression is still required to enable the T_{RM}s to be responsive to IL-15 [39].

The origin of the different memory cells has been subject of much discussion [73,78–83] and so we will briefly cover some of the most recent advances in this manuscript. Recent evidence points towards T_{CM} and T_{RM} having the same clonal origin [80], although it should be noted that this study did not pursue the origin of T_{EM} cells. A microarray study comparing the transcriptional profile of skin, gut and lung T_{RM}s, to splenic naïve, T_{CM} and T_{EM} indicated that these circulating cells have a very different transcriptional profile compared to the T_{RM}s. Even more interesting was the finding that T_{RM}s found in the skin had a transcriptional profile that is different from the gut and lung T_{RM}s. This study identified 37 transcripts that were common to T_{RM}s but were different from the T_{CM} and T_{EM} cells including the transcription factors, such as lipopolysaccharide-induced tumor-necrosis factor (Litaf) and nuclear receptor subfamily 4 group A, member 1 (Nr4a2) were upregulated in T_{RM}s compared to T_{CM} and T_{EM} cells. This study came to the conclusion that T_{RM} cells originated from the same precursors of T_{CM} and T_{EM} and that T_{RM}s develop due their location and environmental milieu [45].

Memory T cells and Disease

To date relatively little is known about how aberrant memory CD8⁺ T cell responses can lead to specific inflammatory diseases.

Fixed-drug eruption occurs when a patient is treated with a specific drug whose adverse reaction leads to the formation of a cutaneous lesion, which may recur in the same location (as well as new locations) if the patient is treated with the same drug. Interestingly, while a fixed drug eruption manifests as a skin lesion it does not lead to systemic symptoms indicating that it is caused by cells that do not circulate and reside in the skin. Recent studies have indicated that fixed drug eruptions are due to the presence of large numbers of T_{EM} cells that express CD69 and are found in the intraepidermis. Considering the location of these cells in the skin, and that they were distinguished from dermal and circulating CD8⁺ T cells, indicates that they are actually T_{RM} cells rather than T_{EM} cells. Mizukawa *et al.* showed that T_{RM}s isolated from coetaneous lesions produced high levels of IFN- γ . This led to localized epidermal injury, thus indicating that the T_{RM} cells are the cause of the fixed drug eruption [84].

Similarly, plaque psoriasis is a chronic inflammatory skin disease, caused by infiltration of T cells into the epidermis. While current treatments can lead to remission of the disease, it can recur in the same location when treatment is stopped. This led to the concept that the disease is due to activated T cells that reside within the areas where the lesions occur. The study by Cheuk *et al.* showed that a high proportion of the epidermal T cells in diseased lesions are CD103⁺ CD49a⁺ CD8⁺ T compared to those in normal skin. The CD8⁺ T cells isolated from the epidermis of psoriasis plaques expressed high levels of IL-12, IL-22, IFN- γ , granzyme A, granzyme B and perforin compared to healthy skin, indicating that they were highly

active cells. Furthermore, high numbers of these CD103⁺ CD49a⁺ CD8⁺ T cells remained in the same region of the lesions even after the psoriasis was successfully treated, and were capable of being reactivated to produce inflammatory cytokines. This indicated that pathogenic T_{RM} cells survived long-term at the site of the inflammatory disease and were active participants in the pathogenesis and persistence of psoriasis [85]. A similar role for T_{RM} cells was found in the study of patients with cutaneous T cell lymphoma (CTCL) [52]. Together, these studies indicate that pathogenic T_{RM}s may lead to inflammatory disease in humans.

Memory subsets other than T_{RM} cells have also been implicated in human diseases. Patients who receive allogeneic hemopoietic stem cell transplantation to cure hematologic malignancies, such as acute and chronic leukemia and lymphoma, are susceptible to graft versus host disease (GVHD) due to the transplantation of donor T cells. A report by Chen *et al.* indicated that while donor T_{CM} cells do respond to alloantigens they do not cause GVHD disease in the B6(H-2^b) → BALB/c (H-2^d) fully mismatched allogeneic bone marrow transplant model [86]. However, in another study T_{CM} cells were shown to only partially participate in the development of GVHD [87]. Thus, the precise role of these memory subset of T cells in GVHD pathogenesis remains to be fully elucidated.

The role for memory CD8 T cells in the pathogenesis of other inflammatory diseases such as asthma has also been investigated. Several studies have implied a role of IL-6, IL-15, IL-13 and CD8⁺ T cells in the development of asthma [88–90]. Indeed, a distinct population of T_{EM} cells expressing high levels of IL-6R α (also known as CD126) was found at a greater frequency in asthma patients. Although it was unclear whether their increased presence led to higher disease severity [91], these cells were shown to produce high levels of IL-15, IL-13, IFN- γ and GATA3 compared with T_{EM} cells that express low levels of IL-6R α . Furthermore, this population also expressed higher levels CCR4, which is important in recruiting T cells into the airways of asthma patients [91]. While the biological significance of these subsets of T_{EM}s in asthma patients needs to be fully determined, this study did suggest that T_{EM} cells may have a role in the pathogenesis of asthma.

Conclusion

Over the years, immunologists have identified a number of circulating and resident CD8⁺ memory T cells. Each subset of memory T cells appears to have a discrete and important role in ensuring that we are protecting from pathogens. With better technologies that are available we are realizing that there may be many more memory populations present than the original two circulating populations that were discovered by Volkert *et al* in 1974 [1]. While we have identified several important populations (T_{EM}, T_{CM} and T_{RM}) much about them remains a mystery.

It seems surprising that very few diseases have been associated with aberrant memory CD8⁺ T cells and more studies into this need to be performed. While we know about a number of transcription factors, cytokines and cell surface markers that are associated with each memory subset, much more information needs to be uncovered to help us understand the molecular pathways and the necessary environment that lead to the formation of these T

cells. This information is critical to enable us to develop highly effective and long-lived therapeutics.

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Highlights

- Memory CD8 T cell differentiation is a complex process
- Several subset of memory CD8 T cells have been identified
- Here we discuss the most current understanding of different subsets of memory CD8 T cells and their role in antimicrobial immune responses

Table 1

Table of important Transcription Factors. Unless indicated the listed transcription factors are highly expressed in the specific populations. The gene name and protein names are how these genes are identified in the mouse genome, unless indicated as human.

Population	Gene encoding Transcription Factor	Protein Name of Transcription Factor	Reference
MPEC (Memory Precursor Effector Cell)	Eomes	Eomesodermin	Banerjee et al. J. I. (2010) Pearce et al. Science (2003) Intlekofer et al. Nature Immunology (2005)
	ID3	ID3	Ji et al. Nature Immunology (2011) Yang et al. Nature Immunology (2011)
	BCL-6	BCL-6	Yoshida et al. J. I. (2006)
	STAT3	STAT3	Cui et al. Immunity (2011) Siegel et al. Immunity (2011)
	FOXO1	FOXO1	Hess Michelini et al. J.E.M. (2013) Kim et al. Immunity (2013)
	Serpina3g	Spi2A	Liu et al. Nature Immunology (2004)
	TCF-7	TCF-1	Zhou et al. Immunity (2010)
Memory (Effector and Central Memory combined)	Fos	Fos	Kaech et al. Cell (2002), Wherry et al. Immunity (2007)
	ATF-2	ATF-2	Kaech et al. Cell (2002)
	ROR- α	ROR- α	Kaech et al. Cell (2002)
	Jun B	Jun B	Kaech et al. Cell (2002), Wherry et al. Immunity (2007)
	BHLHE40	SHARP-2	Wherry et al. Immunity (2007)
	Eomes	Eomesodermin	Wherry et al. Immunity (2007)
	Fosb	Fosb	Wherry et al. Immunity (2007)
	Hopx	Hop	Wherry et al. Immunity (2007)
	ID2	ID2	Wherry et al. Immunity (2007)
	Klf4	Klf4	Wherry et al. Immunity (2007)
	Runx2	Runx2	Wherry et al. Immunity (2007)
	Cebpb	Cebpb	Wherry et al. Immunity (2007)
	Myb (downregulated)	Myb	Wherry et al. Immunity (2007)
T _{CM} (Central Memory)	FasL	FasL	Dudani et al. J.I. (2008)
	ID3	ID3	Yang et al. Nature Immunology (2011)
	Eomes	Eomesodermin	Banerjee et al. J.I. (2010)
	TCF-7	TCF-1	Zhou <i>et al.</i> Immunity (2010)
	Forced expression of Bcl-6 + inactivation of Tbx21, Prdm1 and ID2	T-bet (Tbx21) Blimp-1 (Prdm1)	Cannarile, et al (2006) Ichii et al (2004) Intlekofer et al (2007) Rutishuaser et al. (2009)
	KLF2	KLF2	Skon et al. Nature Immunology (2013)
T _{EM} (Effector Memory)	Prdm1 [not necessary for maintenance of memory but required for efficient recall response; and migration of cells to the lung for influenza infection]	Blimp1	Kallies et al. Immunity (2009)

Population	Gene encoding Transcription Factor	Protein Name of Transcription Factor	Reference
	KLF2	KLF2	Skon et al. Nature Immunology (2013)
	ASCL2 (human)	MASH2 or ASH2	Hombrink et al. Nature Immunology (2016)
	RUNX1 (human)	Runx1	Hombrink et al. Nature Immunology (2016)
	LEF1 (human)	TCF10	Hombrink et al. Nature Immunology (2016)
	FOXP1 (human)	Foxp1	Hombrink et al. Nature Immunology (2016)
	KLF12 (human)	AP2 repressor	Hombrink et al. Nature Immunology (2016)
	ZNF511 (human)	Znf511	Hombrink et al. Nature Immunology (2016)
	IKZF5 (human)	Znf1A5 or PEGASUS	Hombrink et al. Nature Immunology (2016)
	GTF2H2 (human)	TFIIH or BTF2 or P44	Hombrink et al. Nature Immunology (2016)
	RERE (human)	Arp or Arg	Hombrink et al. Nature Immunology (2016)
	KLF7 (human)	Klf7	Hombrink et al. Nature Immunology (2016)
	ZNF318 (human)	Zfp318 or Tzf	Hombrink et al. Nature Immunology (2016)
	TFDP2 (human)	Dp2	Hombrink et al. Nature Immunology (2016)
	BBX (human)	HBP2 or ARTC1	Hombrink et al. Nature Immunology (2016)
	HOXB7 (human)	Hox2	Hombrink et al. Nature Immunology (2016)
	ZNF274 (human)	Zf2 or Zscan51	Hombrink et al. Nature Immunology (2016)
	ZNF638 (human)	Np220 or Zfml	Hombrink et al. Nature Immunology (2016)
	ZNF365 (human)	Talanin or Uan	Hombrink et al. Nature Immunology (2016)
	EWSR1 (human)	Ews	Hombrink et al. Nature Immunology (2016)
	ZNF18 (human)	Zfp535 or Kox11	Hombrink et al. Nature Immunology (2016)
	CNOT7 (human)	Hcaf-1	Hombrink et al. Nature Immunology (2016)
	ZNF22 (human)	Zfp422 or Kox15	Hombrink et al. Nature Immunology (2016)
	ZNF428 (human)	Zfp428 or C19orf37	Hombrink et al. Nature Immunology (2016)
	FOXN3 (human)	C14orf116 or Ches1	Hombrink et al. Nature Immunology (2016)
	ZNF83 (human)	Znf816B or HPF1	Hombrink et al. Nature Immunology (2016)

Population	Gene encoding Transcription Factor	Protein Name of Transcription Factor	Reference
	GTF3A (human)	TFIIIA or AP2	Hombrink et al. Nature Immunology (2016)
T _{RM} (Resident memory)	Litaf	Litaf	Mackay et al. Nature Immunology (2013)
	Nr4a1	Nur77	Mackay et al. Nature Immunology (2013); Hombrink et al. Nature Immunology (2016)
	Nr4a2	Nurr1	Mackay et al. Nature Immunology (2013)
	KLF2 (low levels)	KLF2	Skon et al. Nature Immunology (2013)
	Zfp683	Hobit	Mackay et al. Science (2015)
	ETS1 (human)	Ets-1 or EWSR2	Hombrink et al. Nature Immunology (2016)
	ZFP36L1 (human)	Cmg1 or Brf1	Hombrink et al. Nature Immunology (2016)
	GPBP1 (human)	Gbpv or Vasculin	Hombrink et al. Nature Immunology (2016)
	NFE2L2 (human)	NRF2 or HEBP1	Hombrink et al. Nature Immunology (2016)
	RELA (human)	p65 or NFkB3	Hombrink et al. Nature Immunology (2016)
	FOS (human)	Ap-1 or p55	Hombrink et al. Nature Immunology (2016)
	NFAT5 (human)	NFAT5	Hombrink et al. Nature Immunology (2016)
	ZC3H12A (human)	MCPIP	Hombrink et al. Nature Immunology (2016)
	NOTCH1 (human)	Notch1	Hombrink et al. Nature Immunology (2016)
	MYB (human)	c-Myb	Hombrink et al. Nature Immunology (2016)
	KLF5 (human)	Klf5 OR Bteb2	Hombrink et al. Nature Immunology (2016)
	CITED2 (human)	Mrg1 or VSD2	Hombrink et al. Nature Immunology (2016)
	NR3C1 (human)	GRL	Hombrink et al. Nature Immunology (2016)
	REL (human)	c-Rel	Hombrink et al. Nature Immunology (2016)
	ZNF32 (human)	Kox30	Hombrink et al. Nature Immunology (2016)
	AHR (human)	AhR or BHLHe76	Hombrink et al. Nature Immunology (2016)
	TWIST1 (human)	Twist or BHLHa38	Hombrink et al. Nature Immunology (2016)
	EPAS1 (human)	Epas-1 or Hif2alpha	Hombrink et al. Nature Immunology (2016)
	KLF6 (human)	Bcd1 or ST12 or COPEB	Hombrink et al. Nature Immunology (2016)
	NFKB1 (human)	EBP-1 or p50	Hombrink et al. Nature Immunology (2016)

Population	Gene encoding Transcription Factor	Protein Name of Transcription Factor	Reference
	CREM (human)	CDREM-2 or ICER	Hombrink et al. Nature Immunology (2016)
	NR4A3 (human)	Nor1 or Chn	Hombrink et al. Nature Immunology (2016)
	NFKB2 (human)	Lyt10 or H2TF1 or p52	Hombrink et al. Nature Immunology (2016)
	BATF (human)	Batf or SFA2	Hombrink et al. Nature Immunology (2016)
	IRF4 (human)	Irf4	Hombrink et al. Nature Immunology (2016)
	RBPI (human)	RBPI Kappa or CSL or SUH	Hombrink et al. Nature Immunology (2016)
	PBX4 (human)	Pbx4	Hombrink et al. Nature Immunology (2016)
	ATF3 (human)	Atf3	Hombrink et al. Nature Immunology (2016)
	FOSB (human)	FosB or AP-1	Hombrink et al. Nature Immunology (2016)
	BACH2 (human)	Bach2	Hombrink et al. Nature Immunology (2016)
	RUNX3 (human)	Runx3 or CBFA3	Hombrink et al. Nature Immunology (2016)
	EGR2 (human)	Egr2 or Krox20	Hombrink et al. Nature Immunology (2016)