Molecular Immunology 117 (2020) 180–188

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Control of memory CD8$^+$ T cell longevity and effector functions by IL-15

Jeffrey C. Nolz[a,b,c,*], Martin J. Richer[d,e,*]

[a] Department of Molecular Microbiology & Immunology, Oregon Health & Science University, Portland, OR 97239, United States
[b] Department of Cell, Developmental & Cancer Biology, Oregon Health & Science University, Portland, OR 97239, United States
[c] Department of Radiation Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, United States
[d] Department of Microbiology & Immunology, McGill University, 712 McIntyre Medical Building, 3655 promenade Sir William Osler, Montreal, Quebec, Canada
[e] Rosalind & Morris Goodman Cancer Research Centre, McGill University, Montreal, Quebec, Canada

ABSTRACT

IL-15 is a member of the common gamma chain family of cytokines and plays important roles in regulating several aspects of innate and adaptive immunity. Besides its established role in controlling homeostatic proliferation and survival of memory CD8$^+$ T cells and natural killer cells, recent findings demonstrate that inflammatory IL-15 can also stimulate a variety of effector functions, such as enhanced cytotoxicity, entry into the cell cycle, and trafficking into non-lymphoid tissues. Here, we discuss how IL-15 is critical in regulating many functions of memory CD8$^+$ T cells and how these processes act collectively to ensure optimal protective cellular immunity against re-infections.

1. Introduction

Cytotoxic CD8$^+$ T cells provide host defense and protective immunity by directly engaging and eliminating cells infected with viruses and other intracellular pathogens. After their selection and maturation in the thymus, antigen-naïve CD8$^+$ T cells enter the periphery and begin surveying secondary lymphoid organs for "non-self" peptides presented by MHC-I that will activate their individual, uniquely expressed T cell receptor (TCR). Following activation, CD8$^+$ T cells undergo massive proliferative expansion and differentiate into effector cells that are able to infiltrate non-lymphoid tissues and produce cytokines including IFNγ and TNFα. This transient expansion phase is followed by rapid contraction of the antigen-specific T cell population, where the majority of the clonally expanded effector CD8$^+$ T cells die *via* apoptosis. Effector CD8$^+$ T cells that survive contraction then transition into long-lived memory cells that can provide enhanced protective immunity against re-infection (Harty and Badovinac, 2008).

Besides the overall numerical increase of the antigen-specific T cell population, several other functional properties of memory CD8$^+$ T cells distinguishes them from naïve T cells (Jameson and Masopust, 2018). For instance, memory CD8$^+$ T cells produce cytokines and execute cytolysis immediately following antigen recognition. Memory CD8$^+$ T cells also undergo low levels of basal proliferation, survive independently of any additional TCR-stimulation, and are more broadly distributed compared to naïve T cells; able to traffic into and also become seeded within many non-lymphoid tissues. Thus, memory CD8$^+$ T cells possess a number of specialized properties that ensure both extended longevity and the capacity to rapidly respond to re-invasion of pathogens and nearly all of these specialized functions of memory CD8$^+$ T cells are/can be regulated by interleukin-15 (IL-15).

IL-15 belongs to a family of cytokines that utilize the IL-2 receptor gamma chain (CD132; common gamma chain; γ_c) for signal transduction, which also includes IL-2, IL-4, IL-9, and IL-21 (Lin and Leonard, 2018). Despite sharing this critical signaling molecule, the downstream transcriptional targets and subsequent biological consequences of each of these cytokines varies considerably. One unique feature of IL-15 is that it functions as both a homeostatic cytokine (active during steady-state, non-inflammatory conditions), but also as an inflammatory cytokine, as levels of IL-15 detected in the circulation increase significantly following infections or various forms of inflammatory challenges. Although originally identified as a factor critical for controlling the homeostatic proliferation and survival of memory CD8$^+$ T cells and natural killer (NK) cells (Kennedy et al., 2000), more recent findings have highlighted major roles for IL-15 in regulating a variety of additional specialized effector functions of memory CD8$^+$ T cells (Fig. 1). Here, we discuss the mechanisms that control IL-15 signaling *in vivo*, how IL-15 contributes to the homeostatic proliferation and survival of memory CD8$^+$ T cells, and finally, recent studies that have identified IL-15 as a critical factor that controls a variety of effector functions that collectively optimize the memory CD8$^+$ T cell response against re-infections.

* Corresponding authors.
E-mail addresses: nolz@ohsu.edu (J.C. Nolz), martin.j.richer@mcgill.ca (M.J. Richer).

https://doi.org/10.1016/j.molimm.2019.11.011
Received 11 September 2019; Received in revised form 12 November 2019; Accepted 27 November 2019

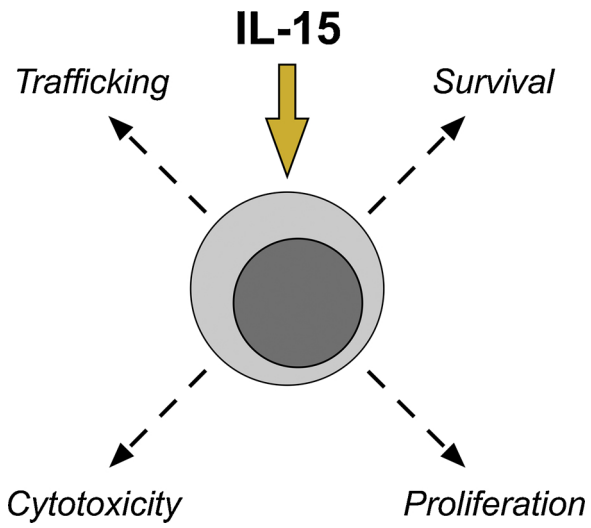

Fig. 1. IL-15 regulates many functional characteristics of memory CD8$^+$ T cells. During both steady-state homeostasis and episodes of infection/inflammation, IL-15 signaling to memory CD8$^+$ T cells can regulate a variety of cellular processes including proliferation, survival, cytotoxicity, and trafficking into non-lymphoid tissues.

2. IL-15 and IL-15 receptor signaling

IL-15 and IL-2 both signal through a shared receptor complex consisting of the IL-2/15Rβ chain (CD122) and the γ_c. Upon activation, most T cells will express IL-2Rα (CD25), resulting in a cell surface heterotrimeric IL-2 receptor complex that exhibits high affinity for IL-2 (Fig. 2A, left). Similarly, IL-15 also signals through a heterotrimeric receptor, consisting of the shared subunits (CD122 and the γ_c) and the unique high affinity receptor, IL-15Rα (CD215). (Giri et al., 1995a, b; Grabstein et al., 1994; Lin and Leonard, 2018). However, unlike IL-2, IL-15 interacts with IL-15Rα intracellularly with very high affinity (Anderson et al., 1995; Giri et al., 1995b) and forms a complex in the endoplasmic reticulum that then traffics to the cell surface of IL-15 expressing cells. These IL-15/IL-15Rα complexes can then be delivered to target cells (*e.g.* memory CD8$^+$ T cell, NK cells) that express CD122 and the γ_c in a unique method of cytokine signaling referred to as trans-presentation (Fig. 2A, middle), which represents the major mode of IL-15 signaling at steady-state (Castillo and Schluns, 2012; Dubois et al., 2002; Duitman et al., 2008; Lodolce et al., 2001). This method of signaling is an important regulatory mechanism to precisely dictate the availability and location of a cytokine which, as will be discussed below, can have a profound impact on various immune cells including memory CD8$^+$ T cells. In addition, the generation of soluble IL-15/IL-15Rα complexes have been reported under certain inflammatory conditions. While the biological significance remains poorly understood, it has been established that these soluble complexes can serve as potent agonists of IL-15 signaling (Fig. 2A, right) (Anthony et al., 2015; Bergamaschi et al., 2012; Mortier et al., 2008; Rubinstein et al., 2006; Stoklasek et al., 2006). Furthermore, soluble IL-15 can signal directly through the intermediate affinity receptor (CD122 and γ_c chain) *in vitro* but this is unlikely to be a major contributor to IL-15 signaling *in vivo*, as soluble IL-15 is rarely, if ever, detected in the absence of the IL-15Rα subunit (Lodolce et al., 2001; Rubinstein et al., 2006).

While none of the IL-15 receptor subunits possess intrinsic signaling capacity, CD122 and the γ_c chain can associate with Janus kinase (JAK) 1 and JAK3 respectively to initiate their signaling cascade (Fig. 2B). Activation of JAK1 and JAK3 leads to the phosphorylation of docking sites for signal transducers and activators of transduction (STAT) 5, and potentially STAT1 and STAT3, albeit to a lesser extent. Recruitment of STAT5 results in its activation *via* tyrosine phosphorylation leading to the formation of STAT5 dimers that can translocate to the nucleus where it can initiate the transcription of numerous target genes. In addition, IL-15 signaling in immune cells has been reported to activate the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (AKT)/mammalian target of Rapamycin (mTOR) pathway (Ali et al., 2015; Fehniger and Caligiuri, 2001; Lin et al., 1995; Miyazaki et al., 1994). Together, these pathways induce a transcriptional program that favors the proliferation, activation, and survival of a variety of lymphocyte populations, including memory CD8$^+$ T cells.

IL-15 mRNA can be detected in a variety of hematopoietic and non-hematopoietic cells, however, expression of IL-15 protein at steady-state is much more restricted (Fehniger and Caligiuri, 2001). This is due to several post-transcriptional mechanisms, including numerous start sites for translation, negative elements in the c-terminus of the protein and splice variants that are poorly secreted, which severely restrict the production of IL-15 protein (Bamford et al., 1996; Bamford et al., 1998; Gaggero et al., 1999; Tagaya et al., 1997). Removal of these three major restraints for IL-15 translation resulted in a 250-fold increase in IL-15 expression demonstrating the importance of these three mechanisms in regulating the availability of IL-15 (Bamford et al., 1998). Among hematopoietic cells, IL-15 is mostly expressed by monocytes and dendritic cells (DC) and is rarely expressed by T cells themselves. Using reporter mouse models, the Kedl and Lefrançois groups highlighted specialization for IL-15 production amongst DC subsets, with CD8$^+$ DCs representing the major producers of IL-15, while plasmacytoid DCs were found to express negligible levels (Colpitts et al., 2013; Sosinowski et al., 2013). These reporter mouse models have identified other immune cell types, including eosinophils and granulocytes, that can express high levels of IL-15, although the biological role of IL-15 expression by these cell types remains poorly described (Colpitts et al., 2013). In addition to its expression at steady-state, IL-15 can be further induced during inflammatory conditions. IL-15 expression has been observed following toll-like receptor signaling stimulation by bacterial lipopolysaccharide (LPS) or the double-stranded RNA mimic Poly I:C and downstream of type I interferon signaling over the course of viral infections (Castillo and Schluns, 2012; Colpitts et al., 2012; Mattei et al., 2001; Tough et al., 1996; Zhang et al., 1998). While these stimuli induced IL-15 mRNA transcription in all DC subsets, reporter mice established that only CD8α$^+$ DCs upregulated IL-15 protein expression under these inflammatory conditions, further highlighting specialization amongst DC subsets for the production of IL-15 (Colpitts et al., 2012; Mattei et al., 2001). However, additional cell types including inflammatory monocytes, macrophages and, potentially, tumor associated neutrophils have also been reported to upregulate IL-15 expression within a variety of other inflammatory environments (Anthony et al., 2016; Santana Carrero et al., 2019; Santana Carrero et al., 2019; Soudja et al., 2012). As we discuss in further details later, it is becoming increasingly clear that this inflammatory or induced IL-15 plays a critical role in regulating CD8$^+$ T cell mediated immune responses.

3. IL-15 regulates homeostatic proliferation and survival of memory CD8$^+$ T cells

One classic feature of memory CD8$^+$ T cells is their low level of basal proliferation that occurs *in vivo* independent of any new antigen encounter, a process often referred to as homeostatic proliferation. IL-15 is the primary driver of memory CD8$^+$ T cell homeostatic proliferation and extended BrdU incorporation analyses in mice suggest a “doubling-rate” of approximately nine weeks (Parretta et al., 2008), which is estimated to result in the complete renewal of the memory CD8$^+$ T cell population every two to three months, but may be slower in humans (Akondy et al., 2017; Choo et al., 2010; Parretta et al., 2008). The majority of IL-15-mediated homeostatic proliferation occurs within the bone marrow (Becker et al., 2005), although this still remains controversial, with a recent study arguing that homeostatic proliferation occurs primarily within the spleen (Siracusa et al., 2017).

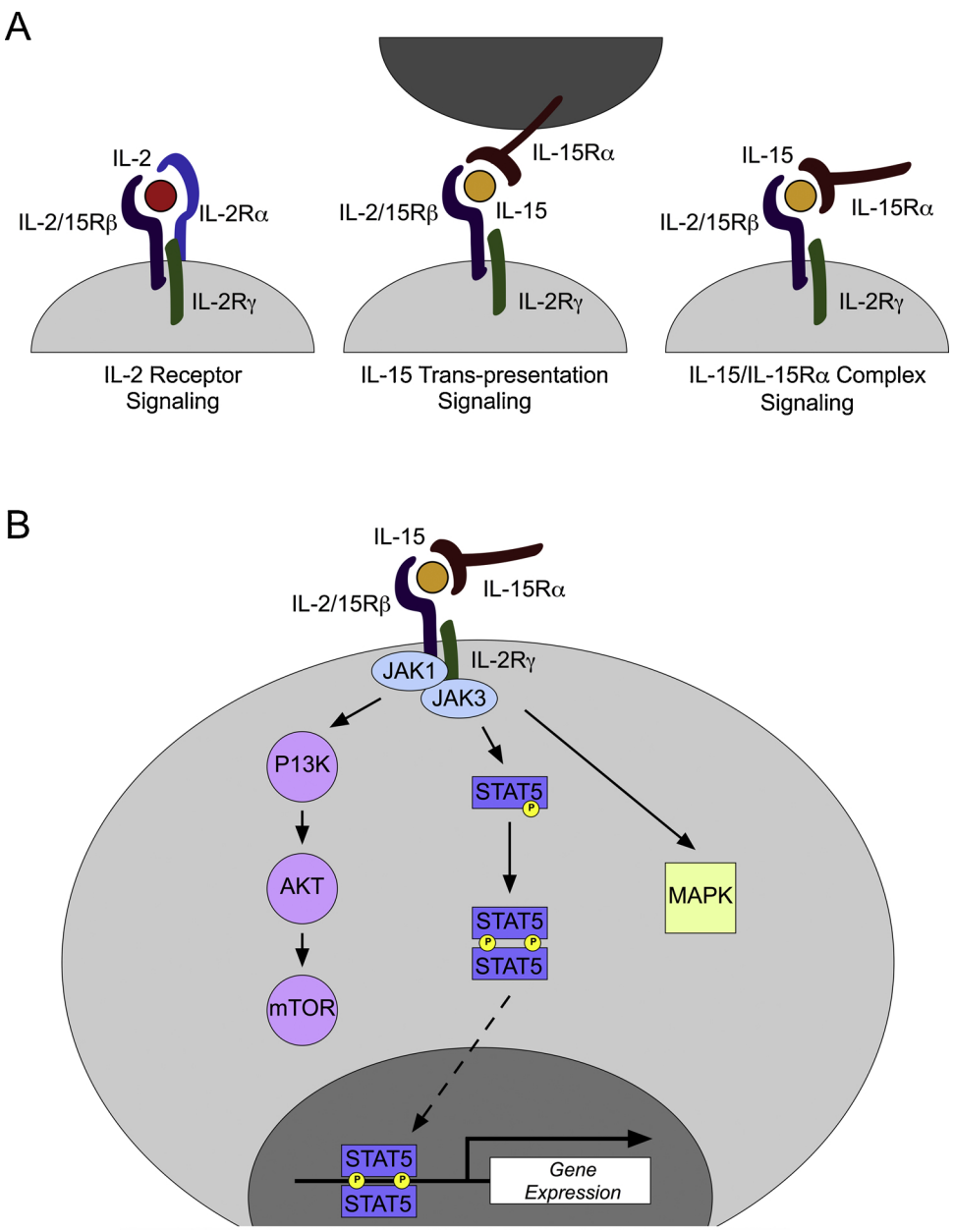

Fig. 2. Comparison of IL-2 and IL-15 signaling to memory CD8$^+$ T cells. (A) IL-2 signals through a heterotrimeric receptor composed of the IL-2Rγ common chain, the IL-2/IL15Rβ chain and the IL-2Rα chain which increases the affinity of IL-2 for the receptor (left panel). IL-15 signals through a similar heterotrimeric receptor composed the IL-2Rγ common chain and the IL-2/IL15Rβ chain and the unique IL-15Rα IL-15 is usually found complexed with IL-15Rα at the surface of other cells where it can be trans-presented to memory CD8$^+$ T cells (middle panel) or in soluble complexes that can also engage signaling pathways in memory CD8$^+$ T cells (right panel). B) IL-15 induces JAK-STAT signaling along with the PI3K-AKT-mTOR and MAPK pathways to induce the transcription of several genes that regulate the function of memory CD8$^+$ T cells.

Despite this low rate of proliferation, individual memory CD8$^+$ T cell populations do not inflate. Rather, homeostatic proliferation is coupled with an equal rate of programmed cell death (Nolz et al., 2012), thereby maintaining a constant number of memory T cells (Fig. 3A).

In general, the antigen-driven proliferative expansion of antigen-specific CD8$^+$ T cells during most acute viral or bacterial infections does not require IL-15, although one notable exception is that IL-15 is critical for optimal CD8$^+$ T cell expansion following subunit vaccination combined with adjuvant (Klarquist et al., 2018). However, in both IL-15$^{-/-}$ and IL-15Rα$^{-/-}$ mice, homeostatic proliferation of memory CD8$^+$ T cells is significantly reduced and the overall number gradually diminishes over time (Becker et al., 2002; Goldrath et al., 2002; Schluns et al., 2002; Tan et al., 2002), suggesting that IL-15-mediated homeostatic renewal is critical for maintaining the long-term survival of memory CD8$^+$ T cells. IL-15Rα$^{-/-}$ memory CD8$^+$ T cells transferred into WT recipients proliferate and survive, demonstrating that in contrast to IL-2 receptor signaling, memory CD8$^+$ T cells do not require cell-intrinsic expression of IL-15Rα to mediate high-affinity IL-15 signaling. Importantly, additional experimental evidence using mixed bone marrow chimeras have shown that hematopoietic cells must express both IL-15 and IL-15Rα for the biological activity of this cytokine to occur *in vivo* (Burkett et al., 2004), further supporting the model that memory CD8$^+$ T cells receive IL-15 complexed with IL-15Rα directly from other immune cells. In addition to homeostatic proliferation, IL-15 has also been shown to promote the survival of memory CD8$^+$ T cells by inducing the expression of the costimulatory molecule 4-1BB which can subsequently increase expression of anti-apoptotic molecules, by directly inducing the expression of the anti-apoptotic molecules Bcl-2 and Bcl-X_L, and by modifying metabolic programming (Berard et al., 2003; Kurtulus et al., 2011; O'Sullivan et al., 2014; Pulle et al., 2006; Tripathi et al., 2010). Although the requirement for IL-15 for promoting memory CD8$^+$ T cells survival is not as critical as IL-7 (Schluns et al., 2000), these studies demonstrate that IL-15 regulates the proliferative renewal and long-term maintenance of memory CD8$^+$ T cells.

Another prominent feature of memory CD8$^+$ T cells is the extent of heterogeneity that exists within an antigen-specific population. Memory CD8$^+$ T cells are often most broadly defined based on the expression of receptors that allow for adhesion and the direct

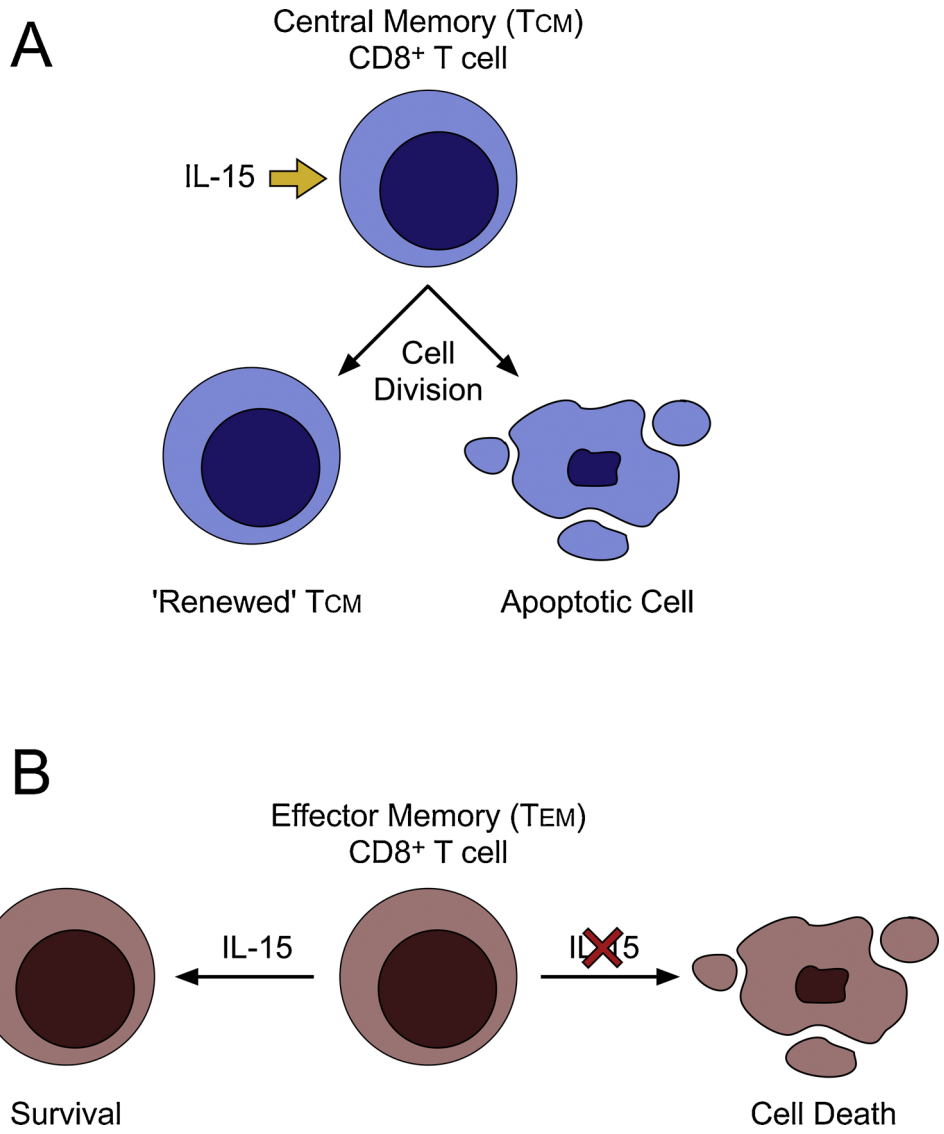

Fig. 3. IL-15 controls homeostatic proliferation and survival of memory CD8$^+$ T cells. (A) IL-15 promotes the homeostatic proliferation of central memory (T_{CM}) CD8$^+$ T cells, where cell division is balanced by an equal rate of programmed cells death. (B) Most effector memory (T_{EM}) CD8$^+$ T cells require IL-15 for survival and undergo cell death in IL-15$^{-/-}$ mice or when IL-15 is neutralized *in vivo*.

infiltration of lymph nodes by crossing high endothelial venules. Central memory (T_{CM}) CD8$^+$ T cells express L-selectin (CD62L) and the chemokine receptor CCR7, whereas effector memory (T_{EM}) CD8$^+$ T cells do not, and accordingly, T_{CM} can be found surveying lymph nodes, but T_{EM} are essentially excluded (Wherry et al., 2003). However, there are several other functional properties that are unique to these two broadly defined subsets. T_{EM} CD8$^+$ T cells express more granzymes and exhibit stronger cytotoxicity than T_{CM} (Wolint et al., 2004), whereas T_{CM} CD8$^+$ T cells express higher levels of CD122 and undergo more homeostatic proliferation (Fig. 3A). Lineage tracing experiments by adoptive transfer have found that at least some T_{EM} CD8$^+$ T cells (typically KLRG1^{Lo}/CD27^{Hi}/CX3CR1$^{Lo/Int}$) become T_{CM} over time and this may be linked to IL-15-mediated proliferation *in vivo* (Gerlach et al., 2016). Another unique subset of memory CD8$^+$ T cells, tissue-resident memory (T_{RM}), become seeded within non-lymphoid tissues such as the skin and do not re-enter the circulation. It has been reported that T_{RM} CD8$^+$ T cells require IL-15 for survival in some cases (Mackay et al., 2015), but not in others (Schenkel et al., 2016), suggesting there may be microenvironment-specific requirements for T_{RM} longevity with a variable dependence on IL-15. Finally, IL-15 is sufficient to convert naïve CD8$^+$ T cells into "virtual" memory cells and this unique subset of memory CD8$^+$ T cells is absent in IL-15$^{-/-}$ mice (White et al., 2016). Thus, IL-15 plays a critical role in the maintenance of diverse subsets of memory CD8$^+$ T cells by promoting their capacity to self-renew through homeostatic proliferation and/or by enhancing their survival.

Because it was originally reported that IL-15 controlled both the homeostatic proliferation and longevity of memory CD8$^+$ T cells, it was therefore assumed that proliferative renewal mediated by IL-15 must be required for long-term survival. However, there are several pieces of evidence that contradict this assumption. As mentioned previously, T_{CM} undergo more homeostatic proliferation than T_{EM}, but a number of studies have reported that T_{EM} (and not T_{CM}) is the memory CD8$^+$ T cell subset most dependent on IL-15 for survival (Fig. 3B). In a study comparing the requirement for IL-2 and IL-15 signaling in regulating the formation and survival of memory CD8$^+$ T cells, it was found that IL-15 was necessary to maintain KLRG1^{Hi} effector memory T cells after the clearance of an acute viral infection (Mitchell et al., 2010). Furthermore, using models of prime-boost vaccination, "secondary" memory CD8$^+$ T cells become predominantly KLRG1^{Hi} T_{EM} and their survival becomes largely dependent on IL-15 (Sandau et al., 2010). Similarly, transient neutralization of IL-15 in rhesus macaques results in

the rapid depletion of T_{EM} $CD8^+$ T cells from the circulation, whereas the numbers of naïve and T_{CM} $CD8^+$ T cells remain unaffected (DeGottardi et al., 2016). Finally, the inflationary effector memory $CD8^+$ T cells that persist during the latent stage of MCMV infection also require IL-15 for their survival (Baumann et al., 2018). Thus, while it is clear that the survival of non-dividing T_{EM} that initially form following infection or vaccination requires IL-15, whether homeostatic proliferation is also necessary for the "renewal" and/or long-term survival of T_{CM} $CD8^+$ T cells remains less clear.

4. Regulation of memory $CD8^+$ T cell effector functions by IL-15

While the role of IL-15 in regulating memory $CD8^+$ T cell longevity during homeostasis has long been appreciated, several recent studies have begun to highlight an important role for IL-15 that is induced during inflammatory conditions. In fact, IL-15 can impact several features of memory $CD8^+$ T cells that confer them a functional advantage compared to naïve $CD8^+$ T cells, including the exhibition of effector functions, priming proliferation and promoting trafficking into non-lymphoid tissues. Here, we will discuss how IL-15 is critical in regulating or even dictating several of the functional characteristics of memory $CD8^+$ T cells and how this plays a central role in enhancing host protection against re-infection.

4.1. Regulation of cytotoxicity and cytokine production

One important functional characteristic of memory $CD8^+$ T cells is the capacity to rapidly secrete effector cytokines and express cytolytic molecules such as perforin and granzymes. Recent studies have begun to establish that this property of memory $CD8^+$ T cells can be regulated by a number of cytokines, including IL-15, in the absence of cognate antigen recognition (Beadling and Slifka, 2005; Freeman et al., 2012; Kohlmeier et al., 2010; Soudja et al., 2012). In fact, IL-15 is sufficient to cause human memory $CD8^+$ T cells to become highly cytolytic and increase expression of perforin, granzyme B, as well as IFNγ (Fig. 4A) (Cheuk et al., 2017; Liu et al., 2002). Using various infection models, Soudja and colleagues demonstrated that IL-15 expression by inflammatory monocytes (in complex with IL-15Rα) was sufficient to induce expression of granzyme B by memory $CD8^+$ T cells regardless of their antigenic specificity (Soudja et al., 2012). In addition, IL-15 also contributed, albeit to a lesser extent, to the production of effector cytokines such as IFNγ from memory T cells in the absence of antigen recognition and was sufficient to provide partial protection against the intracellular bacterial pathogen *Listeria monocytogenes* (Soudja et al., 2012). This form of "bystander" protection has also been described for virtual memory $CD8^+$ T cells, which also occurs in an IL-15-dependent manner (White et al., 2016). Thus, antigen-independent induction of granzyme B and IFNγ (and perhaps activating receptors such as NKG2D) by memory $CD8^+$ T cells may represent a first line of defense that contributes to host protection against pathogens for which they remain immunologically naïve. Nevertheless, the relative contribution of these IL-15 stimulated effector functions of memory $CD8^+$ T cells over the course of a secondary infection with a previously encountered pathogen remains poorly understood and should be the subject of future investigations.

4.2. Primed proliferation of memory $CD8^+$ T cells

Another key functional advantage of memory $CD8^+$ T cells is the capacity to divide more rapidly than their naïve counterparts. However, under non-inflammatory conditions, memory $CD8^+$ T cells were shown to have a higher threshold for cell cycle entry compared to naïve T cells (Mehlhop-Williams and Bevan, 2014). This suggested that cell extrinsic factors may regulate the increased proliferative capacity of memory $CD8^+$ T cells. Early studies had demonstrated that TLR stimulation could induce production of IL-15 in a type I interferon-dependent manner leading to the proliferation of memory phenotype $CD8^+$ T cells (Tough et al., 1996; Zhang et al., 1998). However, these experiments could not differentiate whether this is a characteristic of "bona-fide" antigen-specific memory $CD8^+$ T cells and was simply a bystander effect or whether it played an important biological role during the course of infection.

Using TCR transgenic T cells or MHC-class I tetramers to study antigen-specific memory $CD8^+$ T cells, we observed that an unrelated viral infection induced a transcriptional program that was dominated by the induction of cell cycle related genes (Richer et al., 2015). Interestingly, this was associated with the cell cycle entry and a few cycles of division for most memory $CD8^+$ T cells in the lymph node and the spleen independently of antigen encounter. Cell cycle entry was dependent on the induction of IL-15 in a type I interferon-dependent manner (Fig. 4A). IL-15 induction of cell-cycle entry was linked to the activation of the mTOR pathway as cell-cycle entry could be inhibited by rapamycin treatment (Ali et al., 2015; Marcais et al., 2014; Richer et al., 2015). As opposed to the cell division induced by secondary infection with a pathogen expressing cognate antigen, the proliferation induced by inflammatory IL-15 did not result in any cellular accumulation despite increased cell division compared to basal homeostatic proliferation (Fig. 4B). This suggests that increased IL-15 induced following infection simply enhances homeostatic division, which likely remains balanced by an equal induction of cell death and is not sufficient to engage the cellular pathway necessary to lead to accumulation. More importantly, "primed" proliferation of memory $CD8^+$ T cells represented more than a bystander effect but rather played an important biological role which is linked to the increased protection afforded by memory $CD8^+$ T cells (Fig. 4B). Antigen-specific memory $CD8^+$ T cells lost their proliferative advantage over naïve T cells when secondary infection occurred in an IL-15 deficient host, resulting in diminished protective immunity (Richer et al., 2015). Together, these data demonstrated that "primed" proliferation induced by IL-15 allows all memory $CD8^+$ T cells to prepare for rapid division and accumulation if cognate antigen is encountered to provide enhanced protection against re-infection.

4.3. Regulation of memory $CD8^+$ T cell trafficking and migration

Unlike naïve $CD8^+$ T cells which are primarily confined to the circulation, spleen, and lymph nodes, memory $CD8^+$ T cells acquire the capacity to directly infiltrate non-lymphoid tissues from the circulation without needing to be (re)-activated by antigen-presenting cells. One of the mechanisms that allows memory $CD8^+$ T cells to extravasate across activated vascular endothelium and into non-lymphoid tissues is their capacity to generate ligands for the adhesion molecules P- and E-selectin in an antigen-independent manner. Enzymatic synthesis of core 2 O-glycans is critical for generating functional ligands for all leukocytes to bind to the vascular adhesion molecules P- and E-selectin and extravasate into non-lymphoid tissues (Hobbs and Nolz, 2017). Naïve $CD8^+$ T cells are unable to synthesize core 2 O-glycans, thereby preventing these cells from infiltrating most non-lymphoid tissues. However, following T cell activation, core 2 O-glycans can be found decorating a variety of surface proteins (*e.g.* PSGL-1, CD43, *etc.*) that now function as P- and E-selectin ligands, which allows effector and memory $CD8^+$ T cells to traffic out of the circulation and into non-lymphoid tissues to combat infections (Nolz et al., 2011).

During steady-state, non-inflammatory conditions, core 2 O-glycan synthesis activity is inactive in most memory $CD8^+$ T cells, but can be strongly induced by IL-15 both *in vitro* and *in vivo* (Nolz and Harty, 2014). Memory $CD8^+$ T cells increase expression of a number of glycosyltransferases downstream of IL-15 signaling that collectively act to facilitate the synthesis of core 2 O-glycans required for P- and E-selectin ligand formation and trafficking into non-lymphoid tissues (Fig. 5) (Osborn et al., 2017). Inhibition of the transcription factor STAT5 antagonizes the development of core 2 O-glycans, but whether there is

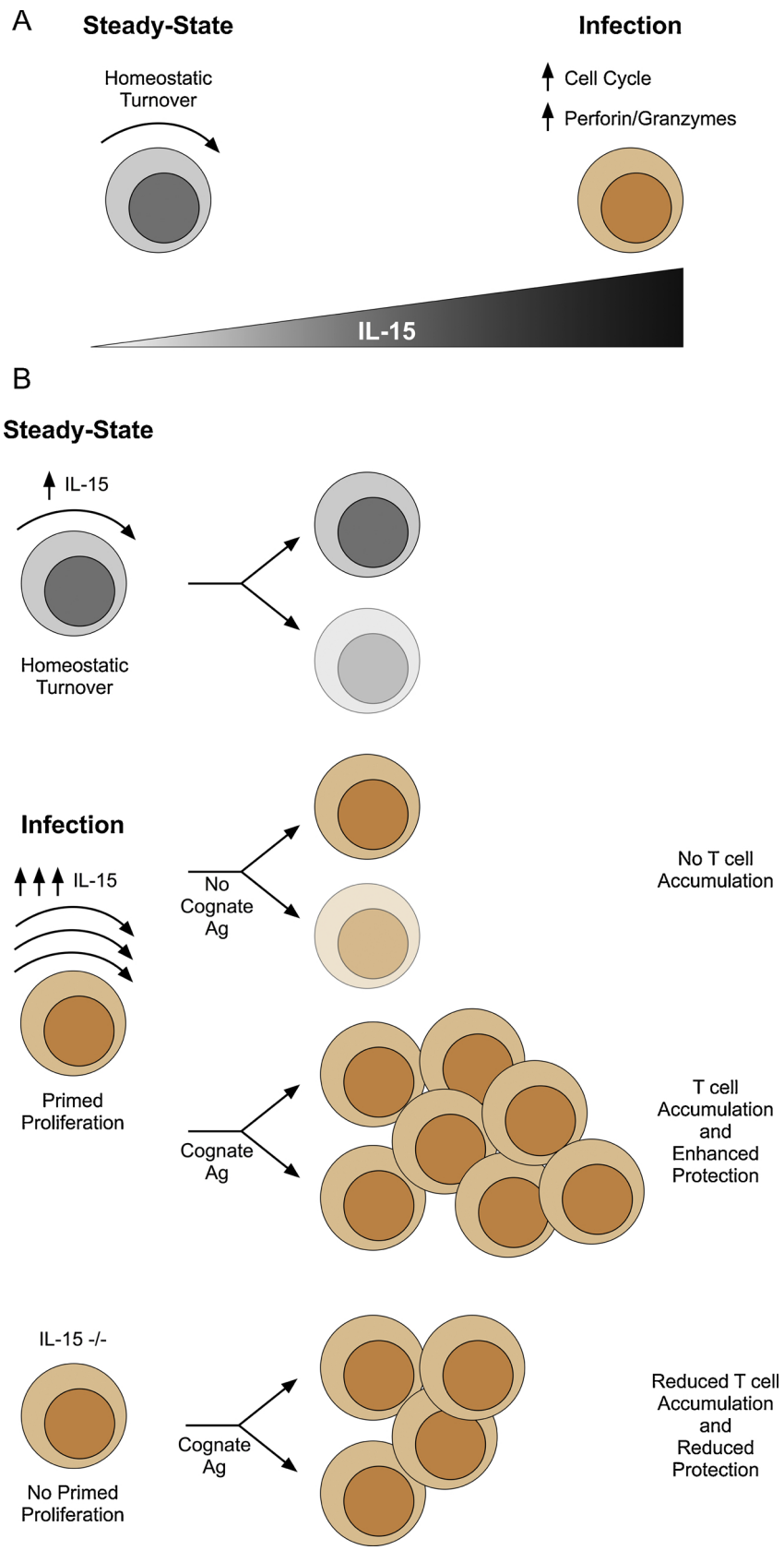

Fig. 4. IL-15 primes effector functions and rapid proliferation of memory CD8$^+$ T cells during infection. (A) In addition to its important homeostatic role, IL-15 can be induced in various inflammatory settings leading to the priming of memory CD8$^+$ T cell effector functions. (B) During infection, "inflammatory" IL-15 induces cell cycle entry of all memory CD8$^+$ T cells without leading to cellular accumulation. Importantly, this "primed" proliferation is responsible for the enhanced proliferative capacity of memory CD8$^+$ T cells upon antigenic encounter and is directly linked to their protective capacity.

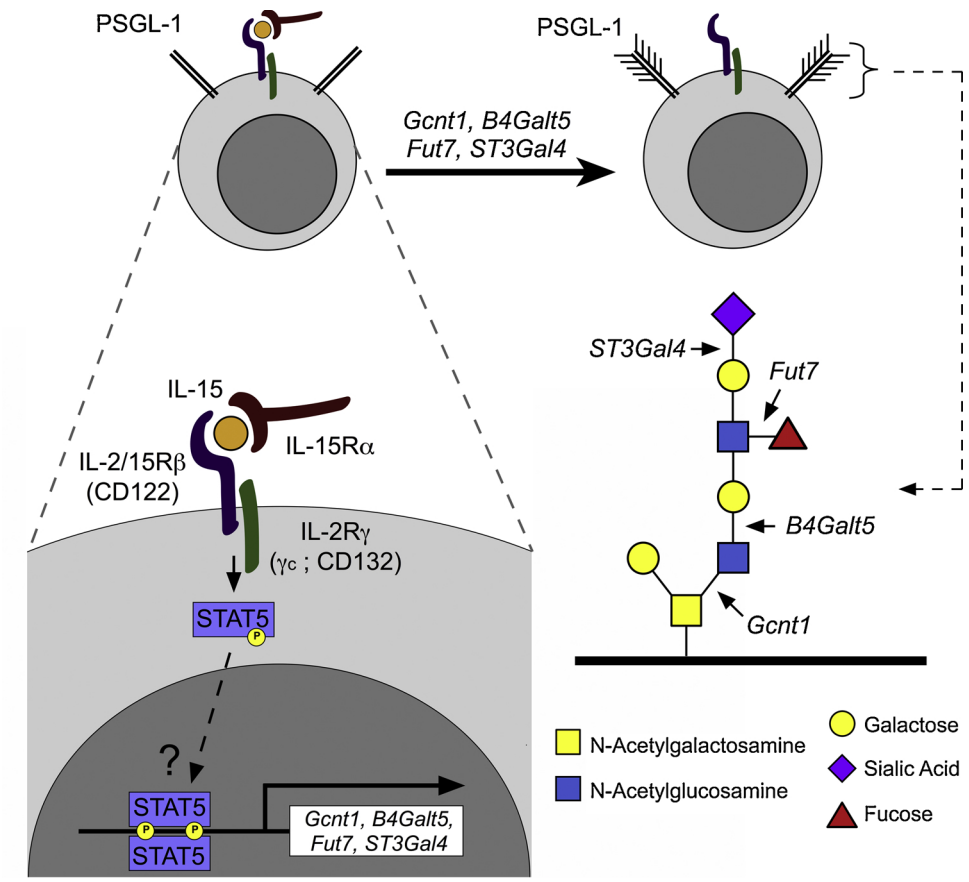

Fig. 5. IL-15 promotes core 2 O-glycan synthesis of P- and E-selectin ligands on memory CD8$^+$ T cells. IL-15 signaling to memory CD8$^+$ T cells increases expression of several glycosyltransferases including core 2 β1,6 N-acetylglucosaminyltransferase-I (*Gcnt1*), β1,4-galactosyltransferase-V (*B4Galt5*), α1,3-fucosyltransferase-VII (*Fut7*) and ST3 β-galactoside α2,3-sialyltransferase IV (*ST3Gal4*). Expression of these glycosyltransferases promotes the synthesis of core 2 O-glycans on surface proteins such as PSGL-1 that now function as P- and/or E-selectin ligands to facilitate extravasation into non-lymphoid tissues such as the skin and lung. Inhibition of STAT5 blocks IL-15-mediated core 2 O-glycan synthesis, but whether there is direct transcriptional regulation of these glycosyltransferases by STAT5 is currently unknown.

direct transcriptional regulation of this set of glycosyltransferases by STAT5 is currently unknown. Thus, inflammatory IL-15 can function as a systemic "warning signal" to circulating memory CD8$^+$ T cells, facilitating core 2 O-glycan synthesis that allows them to rapidly infiltrate inflamed, non-lymphoid tissues during infections.

One assumption of the T_{CM}/T_{EM} classification discussed previously is that because T_{CM} CD8$^+$ T cells express the receptors required to survey lymph nodes, then T_{EM} must be the memory CD8$^+$ T cells that that traffic into and survey peripheral tissues. However, there have been several recent reports suggesting that T_{EM} (especially the most terminally differentiated CD62L^{Lo}/KLRG1^{Hi}CX3CR1^{Hi} subset) are unable to infiltrate most non-lymphoid tissues, but rather are confined within the circulation (Gerlach et al., 2016; Osborn et al., 2017; Smith et al., 2014). As mentioned earlier, T_{CM} CD8$^+$ T cells express higher levels of CD122 compared to T_{EM} CD8$^+$ T cells and thus, we have found that IL-15-mediated core 2 O-glycan synthesis is a primarily a feature of the T_{CM} CD8$^+$ T cell subset (Osborn et al., 2019, 2017). In agreement with this, T_{CM} CD8$^+$ T cells traffic to the skin during viral infection better than T_{EM}; whereas all T cell trafficking into the skin is inhibited when P- and E-selectin are blocked. Studies of memory CD8$^+$ T cell-mediated protective immunity agree with these findings as T_{EM} are more protective against pathogens that infect the spleen (*e.g.Listeria monocytogenes* delivered intravenously) (Jabbari and Harty, 2006; Nolz and Harty, 2011), but T_{CM} are more protective against viral skin infection (*e.g.* Vaccinia virus delivered by skin scarification). Overall, these studies suggest that defined lineages of memory CD8$^+$ T cells form to provide optimal host defense against re-infection and that IL-15 (and potentially other activators of STAT5) plays a critical role in controlling the trafficking of the T_{CM} subset.

Besides promoting core 2 O-glycan synthesis, IL-15 has been reported to control the migration and/or trafficking of memory CD8$^+$ T cell through additional mechanisms. IL-15 promotes CD8$^+$ T cell trafficking to the lung during a primary viral infection (Verbist et al., 2011) and treatment of immune mice with IL-15-IL-15Rα complexes also causes memory CD8$^+$ T cells to infiltrate the lung (Sowell et al., 2017), but whether this form of mucosal trafficking is dependent on core 2 O-glycan activity is currently unknown. Besides trafficking into non-lymphoid tissues such as the skin and lung, IL-15 complexes have also been shown to cause memory CD8$^+$ T cells to migrate into B cell follicles within the spleen (Webb et al., 2018), which could imply that IL-15 may also influence chemokine receptor expression and/or signaling to promote or inhibit migration within lymphoid organs. Interestingly, *in vitro* experiments have also found that IL-15 suppresses expression of CCR7 and the sphingosine-1-phosphate receptor (S1PR1; $S1P_1$) (Gattinoni et al., 2011; Osborn et al., 2017; Setoguchi, 2016). Because both of these receptors contribute to T cell egress from non-lymphoid tissues and into draining lymph nodes, one intriguing notion is that IL-15 signaling to memory CD8$^+$ T cells causes a transient state of memory CD8$^+$ T cell accumulation within inflamed non-lymphoid tissues, by both increasing the rate of extravasation through core 2 O-glycan synthesis, while also limiting the rate of egress through reduced expression of CCR7 and S1PR1.

5. Concluding remarks and perspectives

Here, we discussed a variety of mechanisms by which IL-15 controls multiple fundamental features of memory CD8$^+$ T cell biology, but many open questions still remain. As described, trans-presentation seems to be the primary mechanism that delivers IL-15 to memory CD8$^+$ T cells during steady state conditions to promote homeostatic proliferation, but how IL-15 signals to memory CD8$^+$ T cells during infection and a complete characterization of transcriptional targets remains relatively ill-defined. One potential mechanism would be that IL-15/IL-15Rα complexes are formed and shed into the circulation during infection (Tamzalit et al., 2014), which could cause distal biological effects without requiring cell – cell contact. In fact, it has been proposed

that all of the IL-15 found in the serum following an inflammatory challenge is complexed with IL-15Rα (Bergamaschi et al., 2012). Whether IL-15 or IL-15/IL-15Rα soluble complexes play a major in IL-15 signaling *in vivo* remains to be thoroughly defined, but both have been the subject of intense investigation for their potential role in manipulating immune responses to various infectious diseases and cancer (Waldmann, 2018). In fact, IL-15 complexes can be detected within the tumor microenvironment and promote the accumulation of $CD8^+$ T cells (Santana Carrero et al., 2019). On the other hand, inhibiting IL-15-mediated signaling could reduce the cytotoxicity and trafficking of memory $CD8^+$ T cells into non-lymphoid tissues such as the skin during inflammatory diseases such as contact dermatitis or psoriasis. This is supported by recent data demonstrating that blocking IL-15 signaling with anti-CD122 antibodies was sufficient to revert vitiligo and reduced the production of IFNγ by T_{RM} $CD8^+$ T cells (Richmond et al., 2018). Similarly, it has been found that targeting CD122 could be an effective strategy in preventing transplant rejections (Mathews et al., 2018). Overall, in addition to its critical homeostatic role, inflammatory IL-15 has profound impacts on the protective function of memory $CD8^+$ T cells. In fact, accumulating data suggest that many, if not all, of the functional advantages that memory $CD8^+$ T cells possess over naïve T cells are, at least in part, dictated by IL-15. Thus, any vaccination or immunotherapy approaches aimed at manipulating the function of memory $CD8^+$ T cells will need to consider the capacity of these cells to respond to this critical cytokine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the members of the Nolz and Richer labs for helpful discussions and Dr. Stephanie A. Condotta for generating figures and critical reading of the manuscript. Research in the Nolz lab is supported by the National Institutes of Health (R01-AI132404). Research in the Richer Lab is supported by the Canadian Institutes of Health Research (PJT-152903, PJT-162212); the Natural Sciences and Engineering Research Council of Canada (RGPIN-2016-04713); and the Canada Foundation for Innovation. MJ Richer is supported by salary awards from the Canadian Institutes of Health Research and the Fonds de Recherche du Québec – Santé.

References

Akondy, R.S., Fitch, M., Edupuganti, S., Yang, S., Kissick, H.T., Li, K.W., Youngblood, B.A., Abdelsamed, H.A., McGuire, D.J., Cohen, K.W., Alexe, G., Nagar, S., McCausland, M.M., Gupta, S., Tata, P., Haining, W.N., McElrath, M.J., Zhang, D., Hu, B., Greenleaf, W.J., Goronzy, J.J., Mulligan, M.J., Hellerstein, M., Ahmed, R., 2017. Origin and differentiation of human memory CD8 T cells after vaccination. Nature 552, 362–367.

Ali, A.K., Nandagopal, N., Lee, S.H., 2015. IL-15-PI3K-AKT-mTOR: a critical pathway in the life journey of natural killer cells. Front. Immunol. 6, 355.

Anderson, D.M., Kumaki, S., Ahdieh, M., Bertles, J., Tometsko, M., Loomis, A., Giri, J., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., et al., 1995. Functional characterization of the human interleukin-15 receptor alpha chain and close linkage of IL15RA and IL2RA genes. J. Biol. Chem. 270, 29862–29869.

Anthony, S.M., Howard, M.E., Hailemichael, Y., Overwijk, W.W., Schluns, K.S., 2015. Soluble interleukin-15 complexes are generated in vivo by type I interferon dependent and independent pathways. PLoS One 10, e0120274.

Anthony, S.M., Rivas, S.C., Colpitts, S.L., Howard, M.E., Stonier, S.W., Schluns, K.S., 2016. Inflammatory signals regulate IL-15 in response to Lymphodepletion. J. Immunol. 196, 4544–4552.

Bamford, R.N., Battiata, A.P., Burton, J.D., Sharma, H., Waldmann, T.A., 1996. Interleukin (IL) 15/IL-T production by the adult T-cell leukemia cell line HuT-102 is associated with a human T-cell lymphotrophic virus type I region /IL-15 fusion message that lacks many upstream AUGs that normally attenuates IL-15 mRNA translation. Proc Natl Acad Sci U S A 93, 2897–2902.

Bamford, R.N., DeFilippis, A.P., Azimi, N., Kurys, G., Waldmann, T.A., 1998. The 5' untranslated region, signal peptide, and the coding sequence of the carboxyl terminus of IL-15 participate in its multifaceted translational control. J. Immunol. 160, 4418–4426.

Baumann, N.S., Torti, N., Welten, S.P.M., Barnstorf, I., Borsa, M., Pallmer, K., Oduro, J.D., Cicin-Sain, L., Ikuta, K., Ludewig, B., Oxenius, A., 2018. Tissue maintenance of CMV-specific inflationary memory T cells by IL-15. PLoS Pathog. 14, e1006993.

Beadling, C., Slifka, M.K., 2005. Differential regulation of virus-specific T-cell effector functions following activation by peptide or innate cytokines. Blood 105, 1179–1186.

Becker, T.C., Coley, S.M., Wherry, E.J., Ahmed, R., 2005. Bone marrow is a preferred site for homeostatic proliferation of memory CD8 T cells. J. Immunol. 174, 1269–1273.

Becker, T.C., Wherry, E.J., Boone, D., Murali-Krishna, K., Antia, R., Ma, A., Ahmed, R., 2002. Interleukin 15 is required for proliferative renewal of virus-specific memory CD8 T cells. J. Exp. Med. 195, 1541–1548.

Berard, M., Brandt, K., Bulfone-Paus, S., Tough, D.F., 2003. IL-15 promotes the survival of naive and memory phenotype CD8+ T cells. J. Immunol. 170, 5018–5026.

Bergamaschi, C., Bear, J., Rosati, M., Beach, R.K., Alicea, C., Sowder, R., Chertova, E., Rosenberg, S.A., Felber, B.K., Pavlakis, G.N., 2012. Circulating IL-15 exists as heterodimeric complex with soluble IL-15Ralpha in human and mouse serum. Blood 120, e1–8.

Burkett, P.R., Koka, R., Chien, M., Chai, S., Boone, D.L., Ma, A., 2004. Coordinate expression and trans presentation of interleukin (IL)-15Ralpha and IL-15 supports natural killer cell and memory CD8+ T cell homeostasis. J. Exp. Med. 200, 825–834.

Castillo, E.F., Schluns, K.S., 2012. Regulating the immune system via IL-15 transpresentation. Cytokine 59, 479–490.

Cheuk, S., Schlums, H., Gallais Serezal, I., Martini, E., Chiang, S.C., Marquardt, N., et al., 2017. CD49a expression defines tissue-resident CD8(+) t cells poised for cytotoxic function in human skin. Immunity 46, 287–300.

Choo, D.K., Murali-Krishna, K., Anita, R., Ahmed, R., 2010. Homeostatic turnover of virus-specific memory CD8 T cells occurs stochastically and is independent of CD4 T cell help. J. Immunol. 185, 3436–3444.

Colpitts, S.L., Stoklasek, T.A., Plumlee, C.R., Obar, J.J., Guo, C., Lefrancois, L., 2012. Cutting edge: the role of IFN-alpha receptor and MyD88 signaling in induction of IL-15 expression in vivo. J. Immunol. 188, 2483–2487.

Colpitts, S.L., Stonier, S.W., Stoklasek, T.A., Root, S.H., Aguila, H.L., Schluns, K.S., Lefrancois, L., 2013. Transcriptional regulation of IL-15 expression during hematopoiesis. J. Immunol. 191, 3017–3024.

DeGottardi, M.Q., Okoye, A.A., Vaidya, M., Talla, A., Konfe, A.L., Reyes, M.D., Clock, J.A., Duell, D.M., Legasse, A.W., Sabnis, A., Park, B.S., Axthelm, M.K., Estes, J.D., Reiman, K.A., Sekaly, R.P., Picker, L.J., 2016. Effect of Anti-IL-15 administration on t cell and NK cell homeostasis in Rhesus macaques. J. Immunol. 197, 1183–1198.

Dubois, S., Mariner, J., Waldmann, T.A., Tagaya, Y., 2002. IL-15Ralpha recycles and presents IL-15 in trans to neighboring cells. Immunity 17, 537–547.

Duitman, E.H., Orinska, Z., Bulanova, E., Paus, R., Bulfone-Paus, S., 2008. How a cytokine is chaperoned through the secretory pathway by complexing with its own receptor: lessons from interleukin-15 (IL-15)/IL-15 receptor alpha. Mol. Cell. Biol. 28, 4851–4861.

Fehniger, T.A., Caligiuri, M.A., 2001. Interleukin 15: biology and relevance to human disease. Blood 97, 14–32.

Freeman, B.E., Hammarlund, E., Raue, H.P., Slifka, M.K., 2012. Regulation of innate CD8+ T-cell activation mediated by cytokines. Proc. Natl. Acad. Sci. U. S. A. 109, 9971–9976.

Gaggero, A., Azzarone, B., Andrei, C., Mishal, Z., Meazza, R., Zappia, E., Rubartelli, A., Ferrini, S., 1999. Differential intracellular trafficking, secretion and endosomal localization of two IL-15 isoforms. Eur. J. Immunol. 29, 1265–1274.

Gattinoni, L., Lugli, E., Ji, Y., Pos, Z., Paulos, C.M., Quigley, M.F., Almeida, J.R., Gostick, E., Yu, Z., Carpenito, C., Wang, E., Douek, D.C., Price, D.A., June, C.H., Marincola, F.M., Roederer, M., Restifo, N.P., 2011. A human memory T cell subset with stem cell-like properties. Nat. Med. 17, 1290–1297.

Gerlach, C., Moseman, E.A., Loughhead, S.M., Alvarez, D., Zwijnenburg, A.J., Waanders, L., Garg, R., de la Torre, J.C., von Andrian, U.H., 2016. The chemokine receptor CX3CR1 defines three antigen-experienced CD8 t cell subsets with distinct roles in immune surveillance and homeostasis. Immunity 45, 1270–1284.

Giri, J.G., Anderson, D.M., Kumaki, S., Park, L.S., Grabstein, K.H., Cosman, D., 1995a. IL-15, a novel T cell growth factor that shares activities and receptor components with IL-2. J. Leukoc. Biol. 57, 763–766.

Giri, J.G., Kumaki, S., Ahdieh, M., Friend, D.J., Loomis, A., Shanebeck, K., DuBose, R., Cosman, D., Park, L.S., Anderson, D.M., 1995b. Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. EMBO J. 14, 3654–3663.

Goldrath, A.W., Sivakumar, P.V., Glaccum, M., Kennedy, M.K., Bevan, M.J., Benoist, C., Mathis, D., Butz, E.A., 2002. Cytokine requirements for acute and Basal homeostatic proliferation of naive and memory CD8+ T cells. J. Exp. Med. 195, 1515–1522.

Grabstein, K.H., Eisenman, J., Shanebeck, K., Rauch, C., Srinivasan, S., Fung, V., Beers, C., Richardson, J., Schoenborn, M.A., Ahdieh, M., et al., 1994. Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. Science 264, 965–968.

Harty, J.T., Badovinac, V.P., 2008. Shaping and reshaping CD8+ T-cell memory. Nat. Rev. Immunol. 8, 107–119.

Hobbs, S.J., Nolz, J.C., 2017. Regulation of t cell trafficking by enzymatic synthesis of O-Glycans. Front. Immunol. 8, 600.

Jabbari, A., Harty, J.T., 2006. Secondary memory CD8+ T cells are more protective but slower to acquire a central-memory phenotype. J. Exp. Med. 203, 919–932.

Jameson, S.C., Masopust, D., 2018. Understanding subset diversity in t cell memory. Immunity 48, 214–226.

Kennedy, M.K., Glaccum, M., Brown, S.N., Butz, E.A., Viney, J.L., Embers, M., Matsuki, N., Charrier, K., Sedger, L., Willis, C.R., Brasel, K., Morrissey, P.J., Stocking, K.,

Schuh, J.C., Joyce, S., Peschon, J.J., 2000. Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice. J. Exp. Med. 191, 771–780.
Klarquist, J., Chitrakar, A., Pennock, N.D., Kilgore, A.M., Blain, T., Zheng, C., Danhorn, T., Walton, K., Jiang, L., Sun, J., Hunter, C.A., D'Alessandro, A., Kedl, R.M., 2018. Clonal expansion of vaccine-elicited T cells is independent of aerobic glycolysis. Sci. Immunol. 3.
Kohlmeier, J.E., Cookenham, T., Roberts, A.D., Miller, S.C., Woodland, D.L., 2010. Type I interferons regulate cytolytic activity of memory CD8(+) T cells in the lung airways during respiratory virus challenge. Immunity 33, 96–105.
Kurtulus, S., Tripathi, P., Moreno-Fernandez, M.E., Sholl, A., Katz, J.D., Grimes, H.L., Hildeman, D.A., 2011. Bcl-2 allows effector and memory CD8+ T cells to tolerate higher expression of Bim. J. Immunol. 186, 5729–5737.
Lin, J.X., Leonard, W.J., 2018. The common cytokine receptor gamma chain family of cytokines. Cold Spring Harb. Perspect. Biol. 10.
Lin, J.X., Migone, T.S., Tsang, M., Friedmann, M., Weatherbee, J.A., Zhou, L., Yamauchi, A., Bloom, E.T., Mietz, J., John, S., et al., 1995. The role of shared receptor motifs and common Stat proteins in the generation of cytokine pleiotropy and redundancy by IL-2, IL-4, IL-7, IL-13, and IL-15. Immunity 2, 331–339.
Liu, K., Catalfamo, M., Li, Y., Henkart, P.A., Weng, N.P., 2002. IL-15 mimics T cell receptor crosslinking in the induction of cellular proliferation, gene expression, and cytotoxicity in CD8+ memory T cells. Proc. Natl. Acad. Sci. U. S. A. 99, 6192–6197.
Lodolce, J.P., Burkett, P.R., Boone, D.L., Chien, M., Ma, A., 2001. T cell-independent interleukin 15Ralpha signals are required for bystander proliferation. J. Exp. Med. 194, 1187–1194.
Mackay, L.K., Wynne-Jones, E., Freestone, D., Pellicci, D.G., Mielke, L.A., Newman, D.M., Braun, A., Masson, F., Kallies, A., Belz, G.T., Carbone, F.R., 2015. T-box transcription factors combine with the cytokines TGF-beta and IL-15 to control tissue-resident memory t cell fate. Immunity 43, 1101–1111.
Marcais, A., Cherfils-Vicini, J., Viant, C., Degouve, S., Viel, S., Fenis, A., Rabilloud, J., Mayol, K., Tavares, A., Bienvenu, J., Gangloff, Y.G., Gilson, E., Vivier, E., Walzer, T., 2014. The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. Nat. Immunol. 15, 749–757.
Mathews, D.V., Dong, Y., Higginbotham, L.B., Kim, S.C., Breeden, C.P., Stobert, E.A., Jenkins, J., Tso, J.Y., Larsen, C.P., Adams, A.B., 2018. CD122 signaling in CD8+ memory T cells drives costimulation-independent rejection. J. Clin. Invest. 128, 4557–4572.
Mattei, F., Schiavoni, G., Belardelli, F., Tough, D.F., 2001. IL-15 is expressed by dendritic cells in response to type I IFN, double-stranded RNA, or lipopolysaccharide and promotes dendritic cell activation. J. Immunol. 167, 1179–1187.
Mehlhop-Williams, E.R., Bevan, M.J., 2014. Memory CD8+ T cells exhibit increased antigen threshold requirements for recall proliferation. J. Exp. Med. 211, 345–356.
Mitchell, D.M., Ravkov, E.V., Williams, M.A., 2010. Distinct roles for IL-2 and IL-15 in the differentiation and survival of CD8+ effector and memory T cells. J. Immunol. 184, 6719–6730.
Miyazaki, T., Kawahara, A., Fujii, H., Nakagawa, Y., Minami, Y., Liu, Z.J., Oishi, I., Silvennoinen, O., Witthuhn, B.A., Ihle, J.N., et al., 1994. Functional activation of Jak1 and Jak3 by selective association with IL-2 receptor subunits. Science 266, 1045–1047.
Mortier, E., Woo, T., Advincula, R., Gozalo, S., Ma, A., 2008. IL-15Ralpha chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation. J. Exp. Med. 205, 1213–1225.
Nolz, J.C., Harty, J.T., 2011. Protective capacity of memory CD8+ T cells is dictated by antigen exposure history and nature of the infection. Immunity 34, 781–793.
Nolz, J.C., Harty, J.T., 2014. IL-15 regulates memory CD8+ T cell O-glycan synthesis and affects trafficking. J. Clin. Invest. 124, 1013–1026.
Nolz, J.C., Rai, D., Badovinac, V.P., Harty, J.T., 2012. Division-linked generation of death-intermediates regulates the numerical stability of memory CD8 T cells. Proc. Natl. Acad. Sci. U. S. A. 109, 6199–6204.
Nolz, J.C., Starbeck-Miller, G.R., Harty, J.T., 2011. Naive, effector and memory CD8 T-cell trafficking: parallels and distinctions. Immunotherapy 3, 1223–1233.
O'Sullivan, D., van der Windt, G.J., Huang, S.C., Curtis, J.D., Chang, C.H., Buck, M.D., Qiu, J., Smith, A.M., Lam, W.Y., DiPlato, L.M., Hsu, F.F., Birnbaum, M.J., Pearce, E.J., Pearce, E.L., 2014. Memory CD8(+) T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development. Immunity 41, 75–88.
Osborn, J.F., Hobbs, S.J., Mooster, J.L., Khan, T.N., Kilgore, A.M., Harbour, J.C., Nolz, J.C., 2019. Central memory CD8+ T cells become CD69+ tissue-residents during viral skin infection independent of CD62L-mediated lymph node surveillance. PLoS Pathog. 15, e1007633.
Osborn, J.F., Mooster, J.L., Hobbs, S.J., Munks, M.W., Barry, C., Harty, J.T., Hill, A.B., Nolz, J.C., 2017. Enzymatic synthesis of core 2 O-glycans governs the tissue-trafficking potential of memory CD8+ T cells. Sci. Immunol. 2.
Parretta, E., Cassese, G., Santoni, A., Guardiola, J., Vecchio, A., Di Rosa, F., 2008. Kinetics of in vivo proliferation and death of memory and naive CD8 T cells: parameter estimation based on 5-bromo-2'-deoxyuridine incorporation in spleen, lymph nodes, and bone marrow. J. Immunol. 180, 7230–7239.
Pulle, G., Vidric, M., Watts, T.H., 2006. IL-15-dependent induction of 4-1BB promotes antigen-independent CD8 memory T cell survival. J. Immunol. 176, 2739–2748.
Richer, M.J., Pewe, L.L., Hancox, L.S., Hartwig, S.M., Varga, S.M., Harty, J.T., 2015. Inflammatory IL-15 is required for optimal memory T cell responses. J. Clin. Invest. 125, 3477–3490.
Richmond, J.M., Strassner, J.P., Zapata Jr., L., Garg, M., Riding, R.L., Refat, M.A., Fan, X., Azzolino, V., Tovar-Garza, A., Tsurushita, N., Pandya, A.G., Tso, J.Y., Harris, J.E., 2018. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. Sci. Transl. Med. 10.
Rubinstein, M.P., Kovar, M., Purton, J.F., Cho, J.H., Boyman, O., Surh, C.D., Sprent, J., 2006. Converting IL-15 to a superagonist by binding to soluble IL-15R{alpha}. Proc. Natl. Acad. Sci. U. S. A. 103, 9166–9171.
Sandau, M.M., Kohlmeier, J.E., Woodland, D.L., Jameson, S.C., 2010. IL-15 regulates both quantitative and qualitative features of the memory CD8 T cell pool. J. Immunol. 184, 35–44.
Santana Carrero, R.M., Beceren-Braun, F., Rivas, S.C., Hegde, S.M., Gangadharan, A., Plote, D., Pham, G., Anthony, S.M., Schluns, K.S., 2019. IL-15 is a component of the inflammatory milieu in the tumor microenvironment promoting antitumor responses. Proc. Natl. Acad. Sci. U. S. A. 116, 599–608.
Schenkel, J.M., Fraser, K.A., Casey, K.A., Beura, L.K., Pauken, K.E., Vezys, V., Masopust, D., 2016. IL-15-Independent maintenance of tissue-resident and boosted effector memory CD8 t cells. J. Immunol. 196, 3920–3926.
Schluns, K.S., Kieper, W.C., Jameson, S.C., Lefrancois, L., 2000. Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. Nat. Immunol. 1, 426–432.
Schluns, K.S., Williams, K., Ma, A., Zheng, X.X., Lefrancois, L., 2002. Cutting edge: requirement for IL-15 in the generation of primary and memory antigen-specific CD8 T cells. J. Immunol. 168, 4827–4831.
Setoguchi, R., 2016. IL-15 boosts the function and migration of human terminally differentiated CD8+ T cells by inducing a unique gene signature. Int. Immunol. 28, 293–305.
Siracusa, F., Alp, O.S., Maschmeyer, P., McGrath, M., Mashreghi, M.F., Hojyo, S., Chang, H.D., Tokoyoda, K., Radbruch, A., 2017. Maintenance of CD8(+) memory T lymphocytes in the spleen but not in the bone marrow is dependent on proliferation. Eur. J. Immunol. 47, 1900–1905.
Smith, C.J., Turula, H., Snyder, C.M., 2014. Systemic hematogenous maintenance of memory inflation by MCMV infection. PLoS Pathog. 10, e1004233.
Sosinowski, T., White, J.T., Cross, E.W., Haluszczak, C., Marrack, P., Gapin, L., Kedl, R.M., 2013. CD8alpha+ dendritic cell trans presentation of IL-15 to naive CD8+ T cells produces antigen-inexperienced T cells in the periphery with memory phenotype and function. J. Immunol. 190, 1936–1947.
Soudja, S.M., Ruiz, A.L., Marie, J.C., Lauvau, G., 2012. Inflammatory monocytes activate memory CD8(+) T and innate NK lymphocytes independent of cognate antigen during microbial pathogen invasion. Immunity 37, 549–562.
Sowell, R.T., Goldufsky, J.W., Rogozinska, M., Quiles, Z., Cao, Y., Castillo, E.F., Finnegan, A., Marzo, A.L., 2017. IL-15 complexes induce migration of resting memory CD8 t cells into mucosal tissues. J. Immunol. 199, 2536–2546.
Stoklasek, T.A., Schluns, K.S., Lefrancois, L., 2006. Combined IL-15/IL-15Ralpha immunotherapy maximizes IL-15 activity in vivo. J. Immunol. 177, 6072–6080.
Tagaya, Y., Kurys, G., Thies, T.A., Losi, J.M., Azimi, N., Hanover, J.A., Bamford, R.N., Waldmann, T.A., 1997. Generation of secretable and nonsecretable interleukin 15 isoforms through alternate usage of signal peptides. Proc. Natl. Acad. Sci. U. S. A. 94, 14444–14449.
Tamzalit, F., Barbieux, I., Plet, A., Heim, J., Nedellec, S., Morisseau, S., Jacques, Y., Mortier, E., 2014. IL-15.IL-15Ralpha complex shedding following trans-presentation is essential for the survival of IL-15 responding NK and T cells. Proc. Natl. Acad. Sci. U. S. A. 111, 8565–8570.
Tan, J.T., Ernst, B., Kieper, W.C., LeRoy, E., Sprent, J., Surh, C.D., 2002. Interleukin (IL)-15 and IL-7 jointly regulate homeostatic proliferation of memory phenotype CD8+ cells but are not required for memory phenotype CD4+ cells. J. Exp. Med. 195, 1523–1532.
Tough, D.F., Borrow, P., Sprent, J., 1996. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. Science 272, 1947–1950.
Tripathi, P., Kurtulus, S., Wojciechowski, S., Sholl, A., Hoebe, K., Morris, S.C., Finkelman, F.D., Grimes, H.L., Hildeman, D.A., 2010. STAT5 is critical to maintain effector CD8+ T cell responses. J. Immunol. 185, 2116–2124.
Verbist, K.C., Cole, C.J., Field, M.B., Klonowski, K.D., 2011. A role for IL-15 in the migration of effector CD8 T cells to the lung airways following influenza infection. J. Immunol. 186, 174–182.
Waldmann, T.A., 2018. Cytokines in Cancer immunotherapy. Cold Spring Harb. Perspect. Biol. 10.
Webb, G.M., Li, S., Mwakalundwa, G., Folkvord, J.M., Greene, J.M., Reed, J.S., Stanton, J.J., Legasse, A.W., Hobbs, T., Martin, L.D., Park, B.S., Whitney, J.B., Jeng, E.K., Wong, H.C., Nixon, D.F., Jones, R.B., Connick, E., Skinner, P.J., Sacha, J.B., 2018. The human IL-15 superagonist ALT-803 directs SIV-specific CD8(+) t cells into B-cell follicles. Blood Adv. 2, 76–84.
Wherry, E.J., Teichgraber, V., Becker, T.C., Masopust, D., Kaech, S.M., Antia, R., von Andrian, U.H., Ahmed, R., 2003. Lineage relationship and protective immunity of memory CD8 T cell subsets. Nat. Immunol. 4, 225–234.
White, J.T., Cross, E.W., Burchill, M.A., Danhorn, T., McCarter, M.D., Rosen, H.R., O'Connor, B., Kedl, R.M., 2016. Virtual memory T cells develop and mediate bystander protective immunity in an IL-15-dependent manner. Nat. Commun. 7, 11291.
Wolint, P., Betts, M.R., Koup, R.A., Oxenius, A., 2004. Immediate cytotoxicity but not degranulation distinguishes effector and memory subsets of CD8+ T cells. J. Exp. Med. 199, 925–936.
Zhang, X., Sun, S., Hwang, I., Tough, D.F., Sprent, J., 1998. Potent and selective stimulation of memory-phenotype CD8+ T cells in vivo by IL-15. Immunity 8, 591–599.