Seminars in Immunology 28 (2016) 368–376

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

Natural killer cell memory in context

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ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form 23 May 2016
Accepted 24 May 2016
Available online 25 June 2016

Keywords:
Immunological memory
NK cell
Mechanisms
CMV
Adaptive
Epigenetic

ABSTRACT

Immune memory has traditionally been considered a hallmark of vertebrate T and B lymphocytes. However, given the advantage in mounting quicker and more robust responses to recurrent infection, it is unsurprising that alternative strategies of memory are found in various immune cells throughout the evolutionary tree. In this context, a variety of NK cell memory subsets have recently been identified. Mouse models of cytomegalovirus infection have been instrumental in revealing the kinetics and molecular mechanisms of long-lived NK cell memory. Moreover, murine liver-resident memory NK cell subsets have been identified that potentially harbour antigen-specificity. Phenotypic counter-parts have recently been characterised in the human liver, adding to the mounting evidence suggesting that a spectrum of NK cell memory subsets exist in primates. These include cytomegalovirus-associated peripheral blood NK cell expansions that in humans have been shown to harbour epigenetic alterations that impact cellular phenotype and function. Here we discuss some general mechanisms of non-classical immune memory. We highlight themes of commonality that may yield clues to the molecular mechanisms of NK cell memory, whilst emphasising some outstanding questions.

Contents

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; BM, bone marrow; CMV, cytomegalovirus; CRISPR, clustered regularly-interspaced short palindromic repeat; crRNA, CRISPR RNA; DTH, delayed-type hypersensitivity; HSCT, haematopoietic stem cell transplantation; ITAM, immunoreceptor tyrosine-based activation motif; NK, natural killer; PAM, protospacer adjacent motif; PI3K, phosphoinositide 3-kinase; PKCη, protein kinase C isoform eta; R protein, resistance protein; rasiRNA, repeat associated small interfering RNA; ROS, reactive oxygen species; RISC, RNA-induced silencing complex; SAR, systemic acquired resistance; SLEC, short lived effector cell; TLR, toll-like receptor; TF, transcription factor; VLR, variable lymphocyte receptors.

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http://dx.doi.org/10.1016/j.smim.2016.05.008
1044-5323/

1. Introduction

Immune memory is defined as more rapid and robust responses towards previously encountered antigens. Historically, immune memory was considered to be the preserve of T and B lymphocytes that possess unique antigen-specific receptors. During T and B lymphocyte development, a vast, clonally distributed, antigen receptor repertoire is generated by RAG-mediated somatic recombination of antigen receptor genes. This receptor diversity forms the basis for cellular selection, expansion and differentiation processes that underlie so-called classical, "adaptive" immune memory. The Rag1/Rag2 gene complex is almost exclusive to jawed vertebrates – a structural homologue also exists in purple sea urchin – originating from horizontal transfer of the Rag1 transposase into a common ancestor [1,2]. As such, adoption of Rag genes may have supported the evolutionary success and radiation of vertebrates. In contrast, natural killer (NK) cells were initially described in mice as a lymphocyte subset reactive to tumour cells without prior sensitisation [3,4]. Their inherent ability to reject tumour cells or bone marrow cells from MHC class I mismatched hosts distinguished them from adaptive T and B cells, that required antigen priming. Instead, NK cell activity is controlled by a repertoire of germ-line encoded receptors [5]. NK cells are therefore considered an innate arm of the immune system. However, it has been argued that the terms "adaptive" and "innate" immunity create artificial conceptual barriers [6]. Furthermore, a variety of acquired reactions to allografts or pathogens have been documented in species that lack RAG [7]. Thus, different mechanisms of adaptive immune memory must have arisen throughout evolution.

Recently, molecular mechanisms underlying immune memory have been elucidated in a variety of organisms. NK cell adaptations sit within this wider context of "non-classical" immune memory, which together with the well-studied mechanisms of T and B cell memory, reveal overlapping features that potentially offer molecular insight into NK cell memory formation. Here, we briefly review key molecular aspects forming cytotoxic $CD8^+$ T cell memory, an MHC class I-restricted lymphocyte subset representing "classical" immune memory that forms a functional complement to cytotoxic NK cells and therefore offers a platform for comparison within this review. Moreover, we discuss insights to the molecular mechanisms governing non-lymphoid immune memory in a range of different organism, providing a framework for understanding so-called "non-classical" immune memory. In greater detail, we review the growing body of work concerning NK cell memory. We aim to emphasise the phenotypic characteristics that define a spectrum of NK cell memory subsets and highlight some of the key questions that remain outstanding.

2. Formation of classical immune memory in cytotoxic $CD8^+$ T cells

Studying "classical" memory of T and B cells has provided enormous insight into the molecular mechanisms that generate immune memory. B cell memory for example, is marked by high affinity antibody responses through processes of isotype switching and somatic hypermutation. However, cytotoxic $CD8^+$ T cells most closely resemble NK cells in terms of gene expression profile and ability to kill target cells [8] and therefore invites comparison. In response to pathogens, cytotoxic $CD8^+$ T cells differentiate from naïve to either short-lived effector or long-lived memory cells via characteristic check-point phases of expansion, contraction and memory formation [9,10]. Naïve $CD8^+$ T cells are primed through a sustained interaction with dendritic cells presenting antigen in the context of co-receptor engagement and inflammatory cytokines including IFN-I, IFN-γ, IL-2 or IL-12 [11]. This tripartite signal induces cell proliferation; increasing the frequency of antigen-specific T cells by up to 50,000 fold [10]. During this time, T cell metabolism changes from oxidative phosphorylation to anabolic glycolysis, providing substrates necessary for proliferation and activation. The metabolic switch is regulated through hubs mTORC1/2, key regulators of protein synthesis, induced by upstream PI3K-AKT signalling [12,13].

The majority of expanding $CD8^+$ T cells differentiate into short-lived effector cells (SLECs), which combat the invading pathogen, but quickly recede via apoptosis [14]. The pro-apoptotic BH3 family member Bim appears to be a critical factor in this process [15]. The contraction phase typically removes 95% of expanded cells, leaving a small pool of memory precursor T cells that exhibit a less differentiated $CD62L^{hi}IL\text{-}7R^{\alpha hi}KLRG1^{lo}$ phenotype [9]. Notably, naïve $CD8^+$ T cells do not seem to have a pre-determined fate for either SLEC or memory cell lineages, as single cell experiments reveal the multi-potent potential of individual naïve cells [16].

The initial cues that determine SLEC versus memory precursor cell fate remain controversial, but likely depend on variations in signalling frequency, strength and duration, factors governed by antigen affinity and availability [9,17]. Alternatively, the asymmetric distribution of signalling proteins in dividing daughter cells may also influence $CD8^+$ T cell fate [18]. In this scenario, a synapse with an antigen-presenting cell polarizes the T cell, whereby surface receptors, intracellular signal molecules and possibly transcription factors maybe unequally distributed during cell division.

Several transcription factors drive a memory cell programme, forming a self-reinforcing network that maintains lineage identity [19]. The transcription factors Eomes and T-bet are both important in the early stages of $CD8^+$ T cell differentiation, however the ratio of Eomes to T-bet is critical in deciding a memory versus a SLEC programme [20,21]. Memory precursors dominantly express Eomes, whilst suppressing T-bet. The Wnt pathway and downstream TCF-1 transcription factor is necessary for Eomes expression [22,23]. Whilst the repression of T-bet is in-part mediated by FOXO1 activation [24]. FOXO1 is itself repressed by the PI3K-AKT-mTOR signalling axis that controls metabolic remodelling in expanding/SLEC T cells [24,25]. The induction of PI3K-AKT-mTOR signalling is dependent upon TCR engagement and further sustained by IL-12 through PI3K and STAT4 signalling [21,26]. In contrast, memory $CD8^+$ T cells express FOXO1 as they return to an oxidative phosphorylation energy supply [9], hence FOXO1 is an important sensor that links metabolism to gene regulation and cell fate. FOXO1 also induces KLF2, a transactivator that promotes expression of CCR7, CD62L [27], proteins required for homing.

$CD8^+$ T cell memory precursors express the signature transcription factors ID3 and BCL6. ID3 maintains cell survival [28], while BCL6 antagonises the SLEC specific regulator BLIMP-1 [19]. Whilst STAT4 appears to promote SLEC differentiation, STAT3 signalling via IL-10 and IL-21 play a critical role in driving $CD8^+$ T cell memory by maintaining expression of other transcription factors including Eomes and BCL6 [29].

Memory $CD8^+$ T cells can be classified into central, effector and tissue-resident memory compartments [30,31]. Central memory T cells recirculate through secondary lymph nodes, display a $CD62L^{hi}CCR7^{hi}$ phenotype, have low cytotoxic function, but high proliferative potential [32]. Conversely, effector memory T cells reside in the periphery, are $CD62L^{low}CCR7^{low}$ and constitutively express effector molecules such as granzyme B, but have lower proliferative capacity [32]. Finally, tissue-resident memory T cell subsets closely resemble effector memory T cells but are less migratory. Instead they are retained within tissues such as the lung, skin and gut via receptors CD103 and CD69 as well as other adhesion and chemokine receptors [9,30].

Memory T cells can confer life-long protection, with evidence of vaccination-induced responses lasting for over 85 years [33]. Mem-