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The widening spectrum of immunological memory

Colleen M Lau[1] and Joseph C Sun[1,2]

Immunological memory is broadly understood as the underlying mechanism by which an organism remembers previous encounters with pathogens, aberrant cells, or self-antigens to produce a more rapid or robust secondary response upon re-encounter. This phenomenon is widely accepted as the hallmark feature of the adaptive immune system. However, work within the last decade has continuously challenged this viewpoint and opened up the idea that immunological memory extends beyond just conventional B cells and T cells. Along with critical studies on natural killer cells, recent evidence suggest that innate B and T cells, innate lymphoid cells, and even myeloid cells are capable of varying degrees of immune memory. In this article, we review recent work describing memory-like features within the innate immune system, and provide evidence that immunological memory may be more nuanced than previously appreciated.

Addresses
[1] Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[2] Department of Immunology and Microbial Pathogenesis, Weill Cornell Medical College, New York, NY 10065, USA

Corresponding author: Sun, Joseph C (sunj@mskcc.org)

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Introduction

Immunology textbooks in general still maintain a strict dichotomy between innate and adaptive immunity [1,2]. Traditionally, innate immunity is characterized by rapid and non-specific responses, conferred by such short-lived cells as granulocytes, monocytes, macrophages, dendritic cells, and innate lymphoid cells (ILCs) such as natural killer (NK) cells. Adaptive immunity includes the hallmark feature of immunological memory and is thought to be mediated exclusively by long-lived T cells and B cells. Strictly defined, immunological memory is the process in which a naïve lymphocyte recognizes an immunogen (e.g. pathogen protein or peptide) through its antigen receptor and undergoes a clonal expansion of effector cells to resolve the primary insult. This process of antigen recognition and clonal expansion eventually yields a pool of long-lived antigen-specific clones that can respond more robustly to secondary encounter. Because of the theoretically infinite array of antigens, only T cells and B cells that can generate an equally diverse set of antigen recognition receptors through somatic recombination are believed to be capable of memory formation. However, exceptions to these rules have recently been accumulating: innate cells can be long-lived [3,4], adaptive T and B lymphocytes can be 'innate', and innate immune cells can acquire memory-like features.

Thus, research within the last decade has shifted our understanding towards broadening the definition of immune memory to be more inclusive of phenomena that occur outside of the canonical adaptive immune branch. New studies have emerged that aim to enhance our mechanistic understanding of what constitutes innate immune memory, and the parameters that currently define immune memory in general. In this review, we highlight recent advances that characterize memory populations among innate immune cells using features of classic adaptive responses as a reference (Table 1), in order to highlight the widening definition of immunological memory.

Memory features of innate B cells

B1 cells are self-renewing innate B lymphocytes that recognize a broad range of self antigens and pathogens, and are primarily responsible for the rapid secretion of natural antibodies (antibodies generated without exogenous antigen stimulation) as a first line of defense [5]. Unlike their more conventional B2 counterparts, B1 cells are primarily derived from the fetus, do not require T cells for antibody production, have more restricted immunoglobulin repertoires, and are primarily found in the peritoneum and pleural cavities in mice [6–8]. Murine B1 cells are generally categorized into two groups, B1a and B1b, which are distinguished by the presence or lack of CD5, respectively. The former is often associated with autoimmunity; however, both can engage in natural and antigen-induced antibody production depending on context [8].

Evidence for immune memory in innate B lymphocytes largely derives from studies on B1b cells. An early study revealed that mice were protected from *Borrelia hermsii* infection even in the absence of canonical adaptive immunity and B1a cells [9]. A stable expanded population of B1b cells was observed in the peritoneal cavity and remained for at least 230 days. Importantly, primed B1b cells that were transferred into B/T-deficient hosts

Table 1

Features of immunological memory throughout the innate and adaptive immune systems

Features	Type of memory		Type of memory cell						
	Classic	Trained immunity	αβ-T cell	B-2 cell	B-1 cell	γδ-T cell	NK cell	ILC2	MΦ
Specificity	+	−	+	+	+	?	+	−	−
Clonal expansion	+	−	+	+	+	+	+	?	?
Long-lived progeny	+	−	+	+	+	+	+	+	−
Recall response	+	+	+	+	+	+	+	+	+
Receptor rearrangement	+	−	+	+	+	+	−	−	−
Epigenetic reprogramming	+	+	+	?	?	?	+	?	+

provided better protection compared to naïve B1b cells [9]. The antigen specificity behind this response was later uncovered in a study that identified factor H binding protein A as the putative *B. hermsii* antigen recognized by the B1b cells [10]. Similar results were observed in clonally-restricted models using a BCR (IgH) transgenic system that recognizes bacterial polysaccharide α-1,3 dextran. Stable levels of dextran-specific B1b cells were maintained for at least 90 days, and B1b cells harvested from mice immunized with dextran were shown to have an increased capacity for secondary expansion when challenged with a heat-killed DEX-expressing pathogen [11].

Together, these studies provide evidence that T cell-independent B cell memory can be acquired in innate B1 cells similar to conventional B cells. These antigen-specific B1b cells can undergo clonal expansion, become long-lived, and provide enhanced protection when rechallenged with antigen. However, whether this B1b cell memory may be translated into the clinic remains uncertain, as the existence of a B1 population in humans remains controversial [12]. Further studies on the intrinsic molecular mechanisms driving the B1 cell memory program may aid the accurate identification of a human analog.

Memory features of innate T cells

The complex behavior of innate T cell populations such as γδ T cells, natural killer T (NKT) cells, and intraepithelial lymphocytes (IELs) places them at the border of innate and adaptive immune arms. γδ T cells are thymically-derived lymphocytes that are most frequently found in non-lymphoid barrier tissues including the skin, intestinal epithelium, reproductive tracts, and lung [13]. Like their αβ counterparts, they undergo RAG-mediated VDJ recombination to generate a diverse T cell receptor (TCR) repertoire [14]. However, the observed repertoire in tissues actually shows a more limited and biased TCR usage, as exemplified by invariant γδ TCR clones found in the epidermis [15]. Unlike the peptide-MHC restriction of most αβ T cells, activation of γδ T cells can occur via a broad range of molecules including MHC molecules, lipids, soluble and surface-bound proteins, and phosphoantigens [13]. At tissue sites, γδ T cells can be rapidly activated independent of clonal expansion, are sensitive to stress-associated stimuli, can promote tissue repair, and in some cases have antigen-presenting capabilities [16]. Collectively, these features are reminiscent of innate immune qualities, and thus γδ T cells have been categorized as 'innate' T cells [17].

The existence of γδ T cell memory came initially from observations in primates. γδ T cells from Bacillus Calmette–Guerin (BCG)-vaccinated humans showed the greatest increase of all T cells in the blood in response to mycobacterial lysates compared to non-vaccinated controls [18]. Consistent with this, a subset of γδ T cells exhibited expansion patterns analogous to canonical αβ T cell responses in BCG-vaccinated macaques, including a more rapid secondary response upon a challenge with *Mycobacterium tuberculosis* that coincided with protective immunity [19]. Recent advances in single-cell sequencing have provided more precise resolution of these expanded populations, and has allowed for the identification of expanded γδ T cell clones in hematopoetic stem cell transplant patients that reactivate human cytomegalovirus (HCMV) and those expanded during ontogeny [20••,21]. Although these human and nonhuman primate γδ T cells showed kinetic patterns consistent with memory responses, it remains to be determined whether these T cells can actually confer protective responses upon rechallenge.

More recently, studies in mouse models have provided supporting evidence that γδ T cells provide protective immunity during secondary responses. In models of *Staphylococcus aureus*, primed γδ T cells that had persisted for 3 weeks after bacteria clearance exhibited higher IL-17 production compared to naïve γδ T cells when co-cultured with infected macrophages [22]. Adoptive transfer of *S. aureus*-primed γδ T cells were sufficient to reduce bacterial load following challenge *in vivo*, although it is unclear how they directly compare to naïve γδ T cells in this setting [22,23•]. In a model of dermal inflammation, skin sensitized with imiquimod yielded a population of IL-17-producing γδ T cells that persisted in distal skin sites for at least 7 months [24•]. Upon rechallenge, more of these γδ T cells produced IL-17, and this was associated with an exacerbated inflammation that was dependent on these cells [24•]. In an oral model of *Listeria*