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Is There Natural Killer Cell Memory and Can It Be Harnessed by Vaccination?

NK Cell Memory and Immunization Strategies against Infectious Diseases and Cancer

Joseph C. Sun[1,2] and Lewis L. Lanier[3]

[1]Immunology Program, Memorial Sloan Kettering Cancer Center, New York, New York 10065

[2]Department of Immunology and Microbial Pathogenesis, Weill Cornell Medical College, New York, New York 10065

[3]Department of Microbiology and Immunology and the Parker Institute for Cancer Immunotherapy, University of California San Francisco, San Francisco, California 94143

Correspondence: sunj@mskcc.org; lewis.lanier@ucsf.edu

Immunological memory is an evolutionary adaptation of the vertebrate immune system that protects the host from repeated pathogen infection. T and B cells possess the specificity and longevity required to generate immune memory, whereas natural killer (NK) cells make up a component of the immune system that was not thought to possess these features. However, much evidence from the last decade has challenged this dogma. The investigators were asked to address the following questions: Is there NK cell memory? And can NK cell memory be harnessed for vaccination? Thus, this article explores the recent literature showing immune memory in NK cells. Along with highlighting these studies, we speculate how NK cell memory can be harnessed in immunization strategies against infectious diseases and cancer.

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

Editors: Shane Crotty and Rafi Ahmed
Additional Perspectives on Immune Memory and Vaccines: Great Debates available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a029538
Cite this article as *Cold Spring Harb Perspect Biol* 2018;10:a029538

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DEFINING IMMUNOLOGICAL MEMORY

Immunological memory is defined by the ability of the host to "remember" and mount a more robust secondary response against a previously encountered pathogen. In vertebrates, immune memory mediated by lymphocytes is typically defined by two distinct features: specificity and longevity. First, these lymphocytes must recognize antigens or antigen fragments derived from pathogens using surface receptors (i.e., specificity), so that they can recognize the same foreign component and respond more efficiently a second time. Second, these lymphocytes must live or survive long enough to encounter the antigen again (i.e., longevity). Without the adaptation of both features, vertebrates could not have evolved an immune system capable of anamnestic responses.

IMMUNE MEMORY IN VERTEBRATES AND INVERTEBRATES

Surprisingly, immune memory has also been described in several models of pathogen infection in invertebrates, including insects, worms, and shellfish (reviewed in Kurtz 2005; Sun et al. 2014). Jawless fishes (e.g., lamprey and hagfish) are the most primitive vertebrates in which lymphoid cells with somatically diversified receptors have been identified (Boehm et al. 2012). Thus, the ability of invertebrates to mount enhanced immunity against previously exposed pathogens predates the evolution of lymphocytes possessing the features of antigen specificity and longevity and likely involves phagocytic cells that can "recall" prior infection with limited specificity. In support of this mechanism, immune memory in myeloid lineages has recently been described in vertebrates (Netea et al. 2016), in which epigenetic changes are proposed to occur in macrophages previously stimulated through pattern-recognition receptors (Saeed et al. 2014).

In higher vertebrates (e.g., mammals and birds), there is little debate that immune memory is mediated by antigen-specific B and T cells of the adaptive immune system. Although memory B cells recognize and recall previously encountered antigens that have not been processed, memory T cells remember antigens in the form of processed peptides presented on major histocompatibility complex (MHC) molecules. Interestingly, the past decade has brought forth a plethora of evidence showing that natural killer (NK) cells possess features of both innate and adaptive immunity (Table 1). NK cells are innate lymphocytes that can rapidly mediate cytotoxicity and secrete proinflammatory cytokines when activated by infected, transformed, or "stressed" cells, with their activation or inhibition controlled by a delicate balance of signals achieved through multiple cell-surface receptors and adapter molecules (reviewed in Lanier 2005). Although NK cells are traditionally found under the domain of innate immunity, they arise from a bone marrow precursor—the "common lymphoid progenitor"—shared with B and T cells (Kondo et al. 1997). Although NK cells do not use the recombination activating gene (RAG) recombinases to rearrange their antigen receptors like B and T cells, NK cells possess a family of receptors (e.g., the highly polymorphic Ly49 in mouse and killer-cell immunoglobulin-like receptor [KIR] in human), some of which

Table 1. Versatility of natural killer (NK) cells

Property	Innate immunity	Adaptive immunity	NK cells
Rapid (no prior sensitization)	Yes	No	Yes
Nonspecific response to cytokines	Yes	No	Yes
Early response to heterologous infections	Yes	No	Yes
Specific response to antigens	No	Yes	Yes
Clonal expansion	No	Yes	Yes
Long-lived progeny	No	Yes	Yes
Recall response to same pathogen	No	Yes	Yes

are specific for pathogen-encoded antigens, host "stress"-induced molecules, and MHC class I proteins (Lanier 2005). Furthermore, as with B and T cells, NK cells share a need for cytokines of the common interleukin (IL)-2 γ chain family, the same cytokine family required for longevity in adaptive lymphocytes (Sun and Lanier 2011). This understanding that NK cells shared developmental and homeostatic properties with adaptive lymphocytes set the foundation for several groups to test the hypothesis that antigen-specific NK cells could produce long-lived progeny that contribute to recall responses.

NK CELL MEMORY IN MICE AND HUMANS

NK cell memory has now been described in multiple pathogen and nonpathogenic contexts (reviewed in O'Sullivan et al. 2015). Although the evidence for memory and recall responses of NK cells can be extrapolated from F1 hybrid resistance studies (i.e., the ability of F1 recipients to reject parental bone marrow grafts) performed in the 1960s (Cudkowicz and Stimpfling 1964), more recent direct evidence comes from delayed hypersensitivity studies performed in RAG-deficient mice, which lack B and T cells (O'Leary et al. 2006). These studies showed recall NK cell responses against chemical haptens and viral particles containing antigens from influenza, human immunodeficiency virus (HIV), and vesicular stomatitis virus (VSV) (O'Leary et al. 2006; Paust et al. 2010). Furthermore, virus-specific Ly49H$^+$ NK cells responding to mouse cytomegalovirus (MCMV) infection were shown to possess nearly all of the features of CD8$^+$ T cells, including antigen specificity, clonal expansion, contraction, long-lived memory, and recall responses (Sun et al. 2009). Interestingly, the kinetics of primary, secondary, and even tertiary responses of virus-specific NK cells were comparable to that of T cells exposed to infectious agents (Sun et al. 2009, 2010). However, the magnitude of the clonal expansion of NK cells was not as great as CD8$^+$ T-cell responses against dominant pathogen epitopes (10^5-fold expansion), but more closely resembled subdominant epitopes (10^3–10^4-fold). Additional evidence exists in several other virus models in which NK cells are primed during initial infection, but thus far lack the receptor–ligand specificity inherent to the MCMV model in which molecular mechanisms of NK cell memory are rapidly being elucidated (reviewed in O'Sullivan et al. 2015). Last, "memory-like" NK cells have been described in settings in which NK cells were stimulated with proinflammatory cytokines (e.g., IL-12, IL-15, and IL-18) or lymphopenia (e.g., *Rag*$^{-/-}$ × *Il2rg*$^{-/-}$ or sublethally irradiated mice) in the absence of activating receptor ligation, and this exposure generated long-lived cells that were capable of robust recall responses months later (reviewed in O'Sullivan et al. 2015; Cerwenka and Lanier 2016). Thus, there are now multiple lines of evidence in support of immunological memory within the NK cell compartment.

Many of the findings in mouse highlighted above have now been reproduced in humans. Analogous to the mouse NK cells bearing the activating Ly49H specific for the MCMV-encoded glycoprotein m157, the activating receptor CD94-NKG2C exists on a small subset of human NK cells that have been observed to undergo vigorous clonal expansion in some human cytomegalovirus (HCMV)-seropositive individuals during reactivation of HCMV in immunosuppressed transplant patients (Lopez-Verges et al. 2011; Della Chiesa et al. 2012; Foley et al. 2012). Several studies have shown that expansion and persistence of NKG2C^{bright} NK cells are accompanied with gene-specific (e.g., interferon [IFN]-γ) and global epigenetic remodeling that impacts the behavior of the memory cells (Luetke-Eversloh et al. 2014; Lee et al. 2015; Schlums et al. 2015). The specificity of this response is shown by the finding that expansion of NKG2C^{bright} NK cells only occurs in individuals who are infected with HCMV and not with other herpesviruses, including Epstein–Barr virus (EBV) (Hendricks et al. 2014) or HSV-2 (Bjorkstrom et al. 2011). NK cells are thought to interact with HLA-E, which is up-regulated during HCMV infection; however, whether HLA-E alone represents the CD94-NKG2C ligand driving NK cell expansion or whether an unknown viral component associates with HLA-E, or alters HLA-E conformation or peptide repertoire, remains to be determined. Current studies are aimed at elu-

cidating the cellular and molecular mechanisms behind the expansion of NKG2C^{bright} NK cells during HCMV infection. In humans homozygous for a null *KLRC2* (NKG2C) allele, NK cells possessing activating KIR appear to respond to HCMV infection, suggesting the existence of a redundant mechanism of recognition against this pathogen (Della Chiesa et al. 2014). However, other studies have reported that the frequency of activating KIR^{+} NK cells and the activating KIR repertoire was equivalent in donors with or without functional *KLRC2* alleles (Liu et al. 2016).

In addition to the abundance of evidence in mouse and man, a recent study provided evidence for antigen-specific NK cell memory in macaques previously immunized by simian immunodeficiency virus (SIV) infection or elicited by vaccination with adenoviral vectors containing HIV-1 Env or SIV Gag antigens (Reeves et al. 2015). All of these studies above collectively imply that NK cell memory is a feature of the mammalian immune system that is evolutionarily conserved across species. Because we can now appreciate the specificity and longevity of NK cells found in mice, monkeys, and humans, the question of whether this innate lymphocyte compartment can be harnessed by vaccination can now be experimentally addressed.

CAN NK CELL MEMORY BE HARNESSED BY VACCINATION?

Although the distinction between innate and adaptive immunity has become blurred in recent years, we do not fully understand whether immune memory in innate lymphocytes is an evolutionary adaptation because of pathogen pressures or an evolutionary remnant of innate lymphocytes that later acquired RAG and became adaptive. A practical question now presents itself: Can we harness NK cell memory in vaccine strategies against pathogens that have been elusive to immunization or treatment thus far? From Edward Jenner's discovery of vaccination against smallpox more than 200 years ago to the current time, the large majority of our immunization protocols have centered around the ability to elicit B cells to produce neutralizing antibodies. Against pathogens, where generation of useful antibody responses have failed (such as HIV), T-cell responses have been targeted in recent vaccine strategies. Where both B- and T-cell-targeted vaccination has failed to produce protection against pathogens, can we now elicit the NK cell compartment? Given the genetic evidence that NK cells and specific receptors (KIR) can strongly influence both plasma HIV RNA abundance and AIDS progression (Bashirova et al. 2011), and resolution of hepatitis C virus (Khakoo et al. 2004), one wonders whether vaccination via the NK cell compartment represents a viable immunization strategy. Particularly because HIV specifically cripples the numbers and responsiveness of T cells, perhaps the recruitment of robust memory NK cell responses in this setting will prove efficacious.

Vaccination of NK Cells against HCMV and Other Viruses?

Because the strongest evidence of antigen specificity, clonal expansion, longevity, and recall responses of NK cells resides in cytomegalovirus (CMV) infection of mice and humans, perhaps CMV (and other herpesviruses) represents the most promising avenue to explore vaccination of the NK cell compartment. CMV can cause serious health problems and life-threatening disease in newborns and immune-suppressed individuals (including cancer and transplant patients) deficient in NK cells (Orange 2006). Specifically, following bone marrow transplantation, in which NK cells are among the first lymphocytes to repopulate the periphery, boosting the recall capacity of NK cells may improve overall host defense against CMV or other infectious diseases. Thus, implementation of new vaccine approaches to augment the generation of NK cell memory could greatly improve current vaccination strategies (and be incorporated in combination with current protocols targeting B or T cells), in particular against viruses known to be specifically recognized by NK cells (Lanier 2008). In scenarios in which antibodies are ineffective or T-cell responses are impaired, it is tempting to speculate that immunization via the NK cell compartment may boost overall immunity and impart protection against infectious diseases.

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NK-Cell-Targeted Vaccine against Cancer?

Although the newly discovered longevity and enhanced responses of previously primed NK cells can be exploited to target viruses and other infectious pathogens, might these features also be manipulated to generate long-lived tumor-specific NK cells, which are better poised to recognize and destroy transformed cells? Bone marrow transplant studies have previously revealed that alloantigen-specific NK cells positively impact leukemia patients by mediating graft-versus-tumor function without exacerbating the harmful graft-versus-host disease commonly associated with transplantation (Ruggeri et al. 2002; Foley et al. 2014). Because leukemia patients undergoing immunoablative treatments before hematopoietic cell transplant often become susceptible to CMV, it could be beneficial to exploit memory NK cells in this setting to eliminate both tumor and virus. Preconditioning of NK cells in vitro using proinflammatory cytokines before in vivo transplantation showed great efficacy in mouse tumor models (Ni et al. 2012), suggesting that a similar formulation to boost longevity and effector function in human NK cells for transplant into leukemic patients may be efficacious. As NK cells are now being incorporated into adoptive cellular immunotherapy strategies to target cancer (Vivier et al. 2012; Morvan and Lanier 2016), the coming years should provide a greater indication of whether it is feasible and/or efficacious to treat or prevent cancer by eliciting these powerful killers.

Can Memory NK Cells Mediate Bystander Responses?

In thinking about how NK cells (or other innate lymphocytes) can be harnessed in the fight against infectious diseases or cancer, it is important to consider the mechanism(s) of action. For memory B- or T-cell responses, one typically thinks of the vigorous clonal expansion by antigen-specific lymphocytes that drive protective immunity against previously encountered pathogens. However, memory B and T cells have been shown to participate in a nonspecific manner as well, secreting antibodies or cytokines (IFN-γ), respectively, in the absence of cognate antigen recognition. These nonantigen-specific responses can be driven by pattern recognition receptors (TLR9 for memory B cells) (Bernasconi et al. 2002) or proinflammatory cytokines (such as IL-12 for memory $CD8^+$ T cells) (Berg and Forman 2006). Interestingly, although antigen-specific memory NK cells can robustly mediate cytotoxicity and produce proinflammatory cytokines during pathogen reencounter, and these are obvious effector functions that should be exploited via vaccination, a recent study found that memory NK cells, compared with naïve NK cells, did not produce greater amounts of IFN-γ as bystanders during heterologous pathogen challenges (Min-Oo and Lanier 2014). Further, both mouse and human memory NK cells are less responsive to bystander cytokine-induced activation than naïve NK cells. However, whether memory NK cells can provide assistance to memory T- or B-cell priming via other mechanisms during either homologous or heterologous pathogen challenge remains to be elucidated.

CONCLUDING REMARKS

The discovery of immunological memory in NK cells has initiated studies to determine whether similar anamnestic responses exist in other innate lymphocytes, or even in myeloid cells and nonhematopoietic cells. Given the importance of immune memory in host defense against infectious disease, these novel insights into the adaptive properties of this innate lymphocyte also has prompted the further elucidation of the cellular, molecular, and microbial influences that drive the generation of NK cell memory. As we increase our basic understanding of the biology of NK cells and innate immune memory, we must also begin to envision how to channel the effector function of these powerful killers toward the prevention and treatment of cancer and infectious diseases.

ACKNOWLEDGMENTS

J.C.S. is a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Disease and

funded by the National Institutes of Health (NIH) (AI100874 and P30CA008748). L.L.L. is an American Cancer Society Professor and funded by the NIH (AI068129).

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Cold Spring Harb Perspect Biol 2018; doi: 10.1101/cshperspect.a029538 originally published online December 18, 2017

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