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RESEARCH HIGHLIGHT

A "memorable" NK cell discovery

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The host immune system is comprised of many unique cell types that respond to pathogen-derived molecules (foreign antigens) and play key roles in combating infection. Immune cells have been historically classified into two groups. *Innate* immune cells, such as macrophages and dendritic cells, recognize biochemical patterns within compounds or proteins expressed by microorganisms, and upon activation secrete proinflammatory cytokines immediately or within hours following infection. On the other hand, *adaptive* immune cells, such as B and T cells, react with exquisite specificity to small protein determinants encoded by pathogens and clonally expand in numbers over the course of seven to ten days following infection or vaccination.

While similarities exist between innate and adaptive immune cells (activation, proliferation and cytokine production), one longstanding and critical distinction is the formation of immunologic "memory" by cells of the adaptive immune response. For example, following antigen encounter, certain innate immune cell types proliferate at the population level, but their numbers contract and return to baseline following pathogen clearance and resolution of the inflammatory response. In addition, if a host is re-infected with the same pathogen, the kinetics and magnitude of the innate response mirror that which occurred during primary pathogen exposure. In contrast, adaptive immune cells undergo massive clonal expansion following antigen encounter, often increasing their starting numbers by > 10 000-fold. Like the innate response, the adaptive cellular response also undergoes contraction. However, this contraction phase is generally incomplete and some pathogen-specific cells survive and persist in nearly all tissues, generally for the life of the host. The persistence of these pathogen-specific cells comprises the formation and maintenance of immunologic memory. Importantly, because adaptive memory cells are present in greater starting numbers, are widely distributed in the body and have been re-programmed to secrete cytokines or kill target cells more efficiently upon antigen re-encounter, they confer enhanced protective immunity against secondary pathogen exposures [1]. Indeed, the enhanced protection afforded by memory cells of the adaptive immune system underlies the basis for vaccination strategies.

Natural Killer (NK) cells comprise a unique subset of immune cells that exhibit potent inflammatory cytokine production and cytolytic activity, and are believed to participate in tumor surveillance and resistance to pathogens [2]. Both mouse and human NK cells express combinations of cell surface receptors that are classified as either activating or inhibitory. Ligands for the inhibitory receptors are class I major histocompatibility (MHCI) molecules, or related proteins. The ligands for activating NK cell receptors are varied, but also include MHCI-related molecules, and many have yet to be identified [3]. However, for at least one mouse NK cell activating receptor (Ly49H), the ligand is a murine cytomegalovirus (MCMV) encoded protein called m157 [4, 5]. An abundance of experimental data suggest that the balance between activating and inhibitory receptor signaling ultimately determines whether an NK cell becomes activated and exerts cytolytic activity or remains at rest. Indeed, if a mouse Ly49H$^+$ NK cell encounters a MCMV-infected cell, ligation of Ly49H overrides the signaling through inhibitory receptors resulting in target cell elimination.

NK cells have long been categorized as innate immune cells. Consistent with this, early studies revealed that NK cell populations rapidly expand in response to virus infection, but they did so non-specifically. That is, their activation was believed to be induced by altered expression of host cell surface molecules (*e.g.* MHCI). In addition, the expanded NK cell population ultimately contracts to pre-infection levels following virus clearance. Previously it was not known whether NK cells from the expanded population persisted in peripheral tissues, as methods for tracking antigen-experienced NK cells were not available. Thus, experimental data demonstrating the persistence of long-lived, antigen-experienced NK cells was lacking. However, it is now becoming clear that NK cells exhibit characteristics of

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adaptive T cell responses that were until recently unappreciated.

In a recent article in *Nature*, Sun *et al*. [6] established methods to track antigen-experienced (Ly49H$^+$, m157-reactive) mouse NK cells and demonstrated that several features of NK cell biology overlap with those of T cells, including distinct phases of antigen-specific cell activation, expansion, contraction and formation of persistent memory populations. Using a model of MCMV infection of C57BL/6 mice, the authors showed that NK cells bearing Ly49H activating receptors undergo robust expansion and reach maximal frequency and total numbers by 7 days following virus infection. The expansion phase of Ly49H$^+$ NK cells was followed by contraction of total numbers and declines in frequency, which closely mirrors kinetics generally associated with the adaptive immune response of T cells. Importantly, this Ly49H$^+$ NK cell response was not observed following infection of mice with MCMV lacking expression of m157.

The authors went on to demonstrate that antigen-experienced, Ly49H$^+$ NK cells persisted in the spleen, lymph nodes and livers of mice following MCMV infection. Furthermore, these persistent "memory NK" cells were also shown to express several cell surface phenotypic markers associated with memory T cell development, and exhibit enhanced cytokine expression upon activating receptor cross-linking. When the authors adoptively transferred memory NK cells to naïve recipient mice, the NK cells underwent robust secondary expansion when recipient mice were subsequently infected with MCMV. Thus, for the first time Sun *et al*. showed that NK cell expansion, contraction, persistence and secondary expansion are characteristics that mirror those commonly described for T cells of the adaptive immune response. As mentioned above, one of the most striking hallmarks of memory T cell populations is their ability to mediate enhanced protective immunity following secondary pathogen exposure. Indeed, in series of critical experiments, the authors proved that antigen-experienced, memory NK cells are more protective than naïve NK cells against MCMV infection. Collectively, these new data have reshaped our thinking of how NK cells contribute to protective immunity against virus infection.

The implications of these novel findings are potentially far-reaching. For example, these new data suggest that it may be possible to expand pathogen-specific NK cell populations through vaccination. Should the tools for tracking antigen-experienced human NK cells become available, and as new activating ligands are identified, novel vaccines could potentially be formulated to elicit populations of pathogen-reactive memory NK cells that directly contribute to enhanced protective immunity. Thus, the longstanding classification of NK cells as mediators of innate immunity has now been challenged, and collectively the field must begin to "adapt" to a new perspective on the role of NK cells in host-defense.

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