cled material has been degassed and cannot contain primordial noble gases but will generate a substantial amount of radiogenic noble gases. To produce the observed high $^3He/^4He$ ratios at ocean islands, it is necessary to add material with a high ^3He concentration. Some models place the high ^3He in an even lower layer separated from the convecting mantle by a seismically invisible density contrast, or in the *D''* layer at the bottom of the lower mantle, or in the core. Other models advocate islands of heterogeneity in the lower mantle, or small-scale heterogeneity distributed throughout the mantle and sampled preferentially by the relatively small volume of partial melts at ocean islands.

Understanding how the mantle may have assimilated primordial noble gases provides an important perspective on these models. For example, equilibration of a dense early atmosphere with a magma ocean (see the figure) can readily generate the ^3He concentrations required for a high ^3He silicate mantle (*7*). With such a high early mantle ^3He concentration and our poor understanding of noble gas partitioning between silicate and metal, we cannot rule out a high ^3He core that may provide a ^3He source for the present-day mantle (*8*). Alternatively, material that survived degassing during accretion may have been buried in the deep mantle, providing the ^3He source.

Ne isotopes in the mantle provide a test for these different concepts (*9*). Noble gases introduced into the silicate mantle or core by way of a magma ocean will reflect the solar nebula gases that formed the early atmosphere and should therefore have a solar Ne isotopic composition ($^{20}Ne/^{22}Ne = 13.8$). In contrast, Ne trapped in extraterrestrial material has an isotopic value of $^{20}Ne/^{22}Ne = 12.5$. Upper limits for mantle Ne are similar to implanted solar values (*9*) but cannot yet be distinguished unambiguously from air contamination during the eruptive process (*10*).

For heavier noble gases, distinguishing air contamination from the real mantle signature is also critical. No solar component in the isotopes of Ar, Kr, or Xe has yet been resolved from an air-like composition in any basaltic sample (*9*). If the noble gases in the mantle-atmosphere system evolved from an early atmosphere, buffered by magma ocean degassing, we might expect some trace of this early system in the heavier noble gases. Either this trace never existed and we must reconsider the atmosphere-magma ocean equilibration model, or recycling of atmosphere-derived heavy noble gases back into the mantle has masked it.

Could remixing of fractionated heavy noble gases have occurred in the early Earth, or did it happen over time as a consequence of ocean crust recycling? The observation that these gases may be ubiquitous in both ocean island and mid-ocean ridge volcanism illustrates that resolving this question will be a key factor for future mantle models addressing the mixing of volatiles from different sources.

A first clue comes from an unexpected source. Isolated from the convecting mantle for long periods of time, the mantle beneath the continents has sampled snapshots of the mantle volatile composition over the last 2 to 3 billion years. Magmatic CO_2 occurs in many natural gas reservoirs (*11*) but is often subject to atmospheric contamination; however, in a few gas fields this contamination is minimal. The recent resolution of a solar Xe component in CO_2 well gas from New Mexico (*12*) is the first indication that the convecting mantle may have evolved from a solar-like composition.

The subcontinental mantle remains one of the least explored parts of the mantle with respect to the heavy noble gas tracers. Yet it may contain a unique, time-integrated signal from other mantle domains. Some exciting work is ahead.

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PERSPECTIVES: IMMUNOLOGY

A Pathogen Receptor on Natural Killer Cells

Eric Vivier and Christine A. Biron

Vertebrates have both an innate and an adaptive immune system to protect themselves against pathogen infection. Adaptive immunity depends on specialized lymphocytes, the T and B cells, that recognize pathogens and support the development of immune memory. These lymphocytes express antigen-specific receptors called T cell receptors (TCRs) or B cell (immunoglobulin) receptors (BCRs). The enormous diversity of this antigen-recognition repertoire is effected by rearrangements of multiple gene segments clustered in the TCR and BCR loci of the genome. Yet, it is unclear how cells of the innate immune system, such as Natural Killer (NK) cells, that lack the recombination machinery necessary for gene rearrangement, recognize pathogens. On page 1323 of this issue, Arase *et al.* (*1*) demonstrate that NK cells recognize a mouse cytomegalovirus (MCMV) protein, m157, through an activating Ly49H receptor. This receptor is related to inhibitory Ly49 receptors that are responsible for inducing tolerance to self antigens.

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The multigenic and multiallelic Ly49 family is encoded by genes clustered in a locus termed the NK complex on mouse chromosome 6. Ly49 genes encode two distinct types of receptor: one activating, the other inhibitory. These two types functionally correspond to the activating and inhibitory killer cell immunoglobulin-like receptors (KIR) of the human immune system. Inhibitory Ly49 receptors interact with class I major histocompatibility complex (MHC) molecules and are thus important for inducing self tolerance of NK cells. Their inhibitory function depends on an intracytoplasmic region of the receptor called the immunoreceptor tyrosine-based inhibition motif (ITIM), which is absent from activating Ly49 receptors (*2*). The extracytoplasmic domains of inhibitory and activating Ly49 receptors are highly homologous. As a consequence of a charged amino acid residue in the transmembrane domain, activating Ly49 receptors associate with the signaling polypeptide KARAP/DAP12 that harbors an immunoreceptor tyrosine-based activation motif (ITAM) (*3*, *4*). Similarly, all ITIM-bearing molecules coexist with activating "counterparts" that associate with an ITAM-bearing molecule (CD3ζ, FcRγ, or KARAP/DAP12) (*5*).

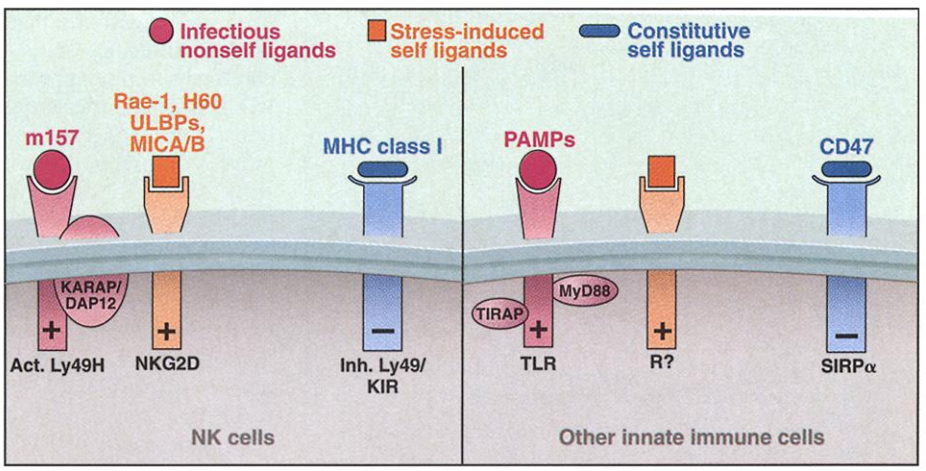
Despite the high degree of homology in their extracytoplasmic domains, activating Ly49 receptors do not bind, or else bind with greatly reduced affinity, to ligands that interact with their inhibitory counterparts. The demonstration by Arase *et al.* (*1*) that the MCMV protein m157 not only interacts with activating Ly49H in B6 mice, but also with inhibitory Ly49I in 129/J mice, indicates that activating and inhibitory receptors sometimes share the same ligand. However, the binding affinities of m157 for Ly49H and Ly49I have not yet been measured. The Ly49I allele from 129/J mice also recognizes the mouse histocompatibility antigen H-2K^d, whereas Ly49H does not recognize any known H-2 ligand. These findings support the notion that activating and inhibitory receptors of NK cells usually differ in their ligand repertoires.

The ability of NK cells to protect the host against pathogen attack has been best documented in humans and rodents infected with herpes group viruses (*6*). Defects in NK cell activity, such as reduced production of interferon-γ (IFN-γ) and decreased cytotoxicity, render mice more susceptible to infection with MCMV, a member of the herpesvirus family (*6*–*8*). Moreover, a gene promoting resistance to MCMV infection, *Cmv-1*, found in some strains of mice, is expressed by subsets of NK cells and encodes the activating Ly49H receptor (*9*–*12*). After exposure to m157 in vitro, Ly49H$^+$ NK cells from mice that are resistant to MCMV exhibit an increased ability to lyse target cells and to produce IFN-γ. How the interaction between Ly49H and m157 contributes to MCMV resistance in select mouse strains in vivo has yet to be elucidated.

Given that infectious organisms can spread through many different host tissues, the immune response needs to be multifaceted. During MCMV infection, Ly49H-m157 interactions may make different contributions to antiviral defense depending on the site of virus infection. In the spleen, engagement of Ly49H with m157 may be the primary recognition event leading to NK cell cytotoxicity directed against MCMV-infected targets (*6*, *9*, *13*). In contrast, production of IFN-γ by NK cells is essential for preventing the spread of MCMV infection in liver tissue (*7*, *8*). IFN-γ production by NK cells can be induced by interaction of Ly49H with viral proteins, but also in response to different cytokines, particularly interleukin-12 (IL-12) and IL-18, made by other cells of the innate immune system (*6*, *7*). It remains to be seen whether innate cytokine-dependent and Ly49H-dependent pathways cooperate to induce NK cell activation. The Ly49H-m157 interaction may also be important for maintaining sufficient numbers of activated NK cells after innate cytokine responses have subsided. Consistent with this possibility, a preferential expansion of the Ly49H$^+$ NK subset has been documented in the late phases of MCMV infection (*14*). Whether the interaction of Ly49H with m157 is indicative of the interactions of other activating isoforms of MHC class I–specific inhibitory receptors with their ligands remains to be seen.

The recognition of a virus-encoded molecule by a germ line–encoded NK receptor is strikingly similar to other strategies of innate immune recognition (see the figure). Innate immune cells express a variety of primary recognition structures whose engagement initiates their activation programs. In pioneering work, Medzhitov and Janeway identified evolutionarily conserved receptors, such as Toll-like receptors (TLRs), that recognize pathogen-associated molecular patterns (PAMPs) (*15*). These receptors have been defined as pattern recognition receptors (PRRs), and Ly49H may be a new member of this family. It will be interesting to see whether Ly49H can interact with pathogen-encoded ligands other than m157. Alternatively, MCMV may have exerted selective pressure on the host, which imposed the shaping of a dedicated NK cell activating receptor specifically for the m157 protein.

Finally, through their cell surface NKG2D receptors, NK cells recognize multiple self molecules expressed by stressed cells (*16*). NK cells seem to have evolved two complementary pathways for handling immune defense and self-tolerance. They recognize infectious nonself and stress self molecules through activating receptors, such as Ly49H and NKG2D, respectively, and normally expressed self molecules through inhibitory receptors, such as those of the Ly49 family.



The two faces of Ly49. Strategies of innate immune recognition. **(Left)** Despite their lack of conventional antigen-specific receptors, NK cells identify pathogen proteins and discriminate "normal cells" from virus-infected, allogeneic, or tumor cells. NK cells have two types of receptor for this purpose. Inhibitory receptors, such as those of the Ly49 family, recognize self MHC class I molecules and exert inhibition through ITIM. Activating NK cell receptors include the activating isoforms of MHC class I–specific inhibitory receptors: six KIR-S receptors in human and 10 Ly49 receptors in mouse, including Ly49H. Activating Ly49 receptors recognize microbial proteins: for example, Ly49H recognizes the m157 protein of MCMV. NK cells also have other activating receptors, such as NKG2D which recognizes multiple molecules expressed by stressed cells (H60 and Rae-1 in mouse; MICA, MICB, and ULBP in human). **(Right)** Other innate immune cells—neutrophils, macrophages, and dendritic cells—express pattern recognition receptors, such as TLRs, that recognize PAMPs and are linked to signaling pathways through the adaptor molecules MyD88 or TIRAP. These cells also recognize stress-induced self antigens (such as heat shock proteins), but the receptors involved have not been fully characterized (R?). The self molecules expressed by normal cells are recognized by ITIM-bearing receptors, such as SIRPα, that induce tolerance by preventing immune cell activation.

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