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Editorial

The evolution of NK cell diversity

Natural killer (NK) cells play pivotal roles in immune defence against invading viruses and cellular transformation leading to cancer. More recently, a role for NK cells has been found during pregnancy. How do NK cells mediate these diverse functions? While the 'end' of the answer to this question involves mechanisms inducing cell-death and cytokine/chemokine production, its 'beginning' is proving much more complicated to explain. This is because of the highly diverse repertoires of receptors used by NK cells to sense the status of the other cells in the body that surround them. The evolution of NK cell functions has selected for conserved, semi-conserved, and quickly evolving genes encoding cell surface receptors. A common, but not exclusive, theme linking the ligands is that they are class I MHC or closely related molecules.

Most conserved is the NKG2 family of lectin-like receptors, which are very similar in humans and mice. The most divergent member of this family, NKG2D, recognizes induced MHC I-like ligands on 'stressed' cells. A single *Nkg2d* gene is present in the genomes of all vertebrates analyzed to date. Although sufficiently interesting in its own right to have been the subject of a recent issue of *Seminars in Immunology* (volume 18, issue 3, June 2006), NKG2D is not the focus for this one. The semi-conserved genes we refer to above are the *Nkrp1* family, which along with the *Ly49* and *Nkg2* families form the majority of the genes located in the NK gene complex (NKC). *Nkrp1* gene numbers are variable between species but constant within a species. In contrast to the NKG2, Ly49, and KIR ligands, the Clr/Ocil ligands for NKRP1 are not related to MHC but to the receptors themselves. Whereas the genes for NKG2D and Ly49/KIR are on different chromosomes from the genes for their ligands, the *Clr/Ocil* and *Nkrp1* genes are closely linked on the same chromosome (and in fact are interdigitating). This situation is analogous to that seen for some self-recognition systems in plants.

The least conserved NK cell receptors, and the main focus of this issue, are the hyper-polymorphic Ly49 and KIR families of class I MHC receptors. The extreme diversity of these MHC receptors arises from the combination of four factors: (1) the number of genes on a single chromosome (haplotype) varies wildly between individuals of the same species leading to qualitative loss and gain of functions by the NK cells of the individuals carrying haplotype combinations; (2) genes common to different haplotypes, or even duplicated on the same haplotype, can exhibit extensive allelic polymorphism with significant functional consequences; (3) within the placental mammals different species have expanded diversity in different and unrelated receptor proteins (lectin-like Ly49 vs. Ig-related KIR) to perform the same job: positive and negative regulation of NK cell development and effector function by binding to class Ia MHC ligands; and (4) individual NK cells express different combinations of KIR (human) or Ly49 (mouse) receptors, leading to a highly heterogenous population of NK cells with which the mammalian host can respond to diverse microbial infections and malignancies. In contrast, individual NKG2 and NKRP1 family members are expressed on most NK cells.

Although KIR and Ly49 are structurally unrelated, both receptor families have evolved similar ways of dealing with their NK cell responsibilities. The gene families encoding KIR and Ly49 have both followed an evolutionary strategy in which 'different is good' for haplotype structure, gene content and allelic polymorphism as well as the combinatorial expression of receptors by NK cells. Both types of receptors use similar signaling adaptors for the positive and negative regulation of NK cell function and maintaining a balance between tolerance of self and responsiveness to missing self. Such commonality for receptors with divergent origin and different evolutionary histories is a remarkable example of convergent evolution and the power of natural selection. But what are the pressures that cause the continual selection of new diversity? In this issue of *Seminars in Immunology* several of the leading researchers in this field of immunology give their answers.

Dr. Peter Parham (Stanford University School of Medicine, Stanford, CA) describes the different mammalian species for which KIR/Ly49 usage has been determined. Also discussed are the evolutionary paths taken in different species by an often overlooked member of the KIR-containing leukocyte receptor complex: the IgA receptor (CD89) encoded by *FCAR*. Finally, Dr. Parham describes the balancing selection between pathogen immunity and reproduction resulting in the maintenance of type A vs. type B KIR haplotypes in all human populations.

Drs. John Trowsdale and Ashley Moffett (University of Cambridge, Cambridge, UK) expand on the role of KIR diversity during pregnancy. In particular the usage of particular KIR by intrauterine NK cells and the unusual HLA expression by fetally derived trophoblast cells infiltrating the maternal extravillous tissues and how these interactions potentially affect reproduction. The random nature of the allograft fetus MHC expression in particular is an enticing explanation for polymorphic NK cell receptors.

Drs. Andrew Makrigiannis (IRCM, Montreal, Canada) and James Carlyle (University of Toronto, Toronto, Canada) contrast Ly49 haplotype variability with Nkrp1 haplotype stability. Extremes of Ly49 haplotype diversity include the BALB/c mouse with 8 genes and the NOD mouse with 22 genes. On the other hand Nkrp1 gene numbers are constant among characterized strains. Two closely related and closely linked gene families are evolutionary opposites in terms

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of variability. Possible mechanisms explaining this discrepancy are discussed.

Drs. Silvia Vidal, Agnieszka Kielczewska, and Michal Pyzik (McGill University, Montreal, Canada) discuss both MHC-dependent and MHC-independent strategies used by NK cells to combat viral infection with specific reference to MCMV. The two activating receptors, Ly49P and Ly49H, are both necessary for resistance to MCMV in MA/My and C57BL/6 mice respectively, but the mechanisms are entirely different.

Drs. Mary Carrington, Maureen Martin, and Smita Kulkarni (National Cancer Institute, Frederick, USA) review the latest knowledge of the contribution of specific KIR to autoimmunity and infectious disease. KIR haplotypes with specific activating KIR may be useful in combating pathogen infections, but having many activating KIR is counterbalanced by increased risk of autoimmunity.

Dr. Jim Kaufman (University of Cambridge, Cambridge, UK) provides an evolutionary perspective on NK cell receptors based on the chicken. A look into the possible evolutionary history of NK cell receptors is described. With multiple Ig-related receptors in an LRC-syntenic region and relatively few lectin-like receptor encoding genes, the strategy employed by this tasty model organism is uncomfortably close to that used by humans.

Drs. Anthony Scalzo (University of Western Australia, Western Australia, Australia) and Michael Brown (University of Virginia, Virginia, USA), two pioneers in NK cell-MCMV immunity and Ly49 genetics research, respectively, provide a keen perspective into the microscopic arms race between host and pathogen that has resulted in the receptor diversity we see today.

Finally, Dr. Eric Dissen (University of Oslo, Oslo, Norway) describes NK cell receptor diversity in rats and cattle. Interestingly, the only species apart from primates that possess an expanded KIR repertoire are cattle. In addition, Dr. Dissen addresses the close co-evolution of activating and inhibitory receptors.

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