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INFLUENCE OF KIR DIVERSITY ON HUMAN IMMUNITY

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1. INTRODUCTION

Killer cell immunoglobulin-like receptors (KIR) are expressed on natural killer (NK) cells and on subpopulations of T cells, mostly CD8 cells, that have memory phenotype. KIR thus have the potential to contribute to both the innate immune response, through the action of NK cells, and the adaptive immune response, through the action of memory T cells. KIR were first defined functionally in the context of alloreactive human NK cells that showed specificity for polymorphic HLA class I determinants. Identified in this manner were inhibitory KIR with specificity for HLA-A, B and C determinants. Cloning of cDNA for these KIR led to the identification of additional KIR, some of which are activating receptors with HLA class I specificity and others — including both inhibitory and activating KIR — for which ligands have yet be defined (reviewed in [1]).

2. DIVERSITY OF KIR EXPRESSION WITHIN THE INDIVIDUAL

The human genes encoding KIR comprise a compact family which are part of the leukocyte receptor complex (LRC) on human chromosome 19 (reviewed in [2]). A consequence of the program of human NK-cell development is that individual NK cells express different numbers of KIR genes and in different combination [3]. Such patterns of expression appear stable over time and determined by the methylation status of the genes [4,5]. This differential expression of KIR genes creates heterogeneity of receptor expression within a person's NK-cell population: a repertoire that has the potential to impart clonal specificity to the NK-cell response to pathogens.

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Mechanisms of Lymphocyte Activation and Immune Regulation X
Edited by Gupta *et al.*, Springer, 2005

3. DIVERSITY OF KIR GENOTYPE WITHIN THE HUMAN POPULATION

Human KIR haplotypes differ in gene content [6]. The genes that define the center of the locus (KIR2DL4) and the two ends (KIR3DL3 and KIR3DL2) are almost always present but that is not so for the other KIR genes. The number of KIR haplotypes defined by differences in gene content is approaching one hundred (reviewed in [7]. These haplotypes are further diversified by the allelic polymorphism that is a feature of most of the KIR genes [8]. The combined effect of diversity due to gene content and allelic polymorphism ensures that unrelated individuals rarely (<1%) have identical genotype. KIR genotype diversity thus individualizes NK-cell repertoires. The KIR haplotypes form two groups: the group A haplotypes are shorter having relatively few genes encoding activating receptors (0 or 1), whereas the group B haplotypes are longer because of the presence of more genes encoding activating receptors. Consequently, within the population there is considerable variation in the extent to which activating KIR are present, less so for the inhibitory KIR.

4. POPULATION DIFFERENCES IN KIR DIVERSITY

Populations differ in the relative frequency of group A and B KIR haplotypes: Caucasoid populations have even frequencies, while group A haplotypes predominate in the Japanese and group B haplotypes in Aboriginal Australians. In general there appears to be considerable population specificity in KIR genotype with relatively few KIR genotypes being common to populations and a majority being population-specific. Thus the KIR locus has undergone considerable evolution during the history of the human species (reviewed in [7]).

5. SPECIES-SPECIFICITY OF KIR

The picture of human KIR as a rapidly evolving system of immunoreceptors is fully endorsed by the analyses of KIR in other primate species. Comparison of human KIR with their counterparts in chimpanzee, bonobo, gorilla, orangutan and rhesus macaque shows that every species has a distinct set of KIR genes, with only a minority of them being common to any other species (see [9] and references therein). A major distinction can be made between the hominoids (humans and apes) and the Old World monkeys, represented by the rhesus macaque. Only KIR2DL4, the gene present in the middle of the human KIR locus, is shared by these species; the other rhesus macaque KIR representing a distinct lineage from those found in the hominoids. Given the extent of KIR diversification over relatively short periods of evolutionary time it now comes as little surprise that cattle and mouse KIR genes represent totally different lineages, which in the case of the mouse are known to be present on the X chromosome, not in the LRC [10]. Neither do they account for the dominant alloreactivities of mouse NK cells, a role that is played by the diverse and rapidly evolving lectin-like receptors encoded by the Ly49 genes of the natural killer complex (NKC) (reviewed in [11]).

6. KIR GENES EVOLVE RAPIDLY THROUGH RECOMBINATION

New KIR genes and haplotypes appear to be the work of asymmetric recombination, a mechanism that is likely facilitated by the high sequence similarity between KIR genes and the short intergenic regions that separate them. The only unique intergenic region is that separating the KIR2DL4 gene from the KIR3DP1 pseudogene, and which is of ~14kb. This regions appears a favored site for homologous recombination; it divides the locus roughly into two halves, within each of which there is high linkage disequilibrium (reviewed in [7]).

7. DIFFERENCES IN KIR REPERTOIRES OF EXPRESSION ARE DETERMINED PRINCIPALLY BY THE KIR GENES BUT WITH SOME INFLUENCE OF HLA GENES

When two siblings are genotyped for KIR and HLA they form four groups: KIR and HLA matched; KIR and HLA mismatched; KIR matched, HLA mismatched; and KIR mismatched, HLA matched. The patterns of KIR expression by the NK cells of siblings matched for KIR and HLA are very similar, whereas they range widely for siblings who are KIR and HLA mismatched. Most of the difference is due to the KIR genes, as evidenced by the similarity between KIR matched, HLA mismatched siblings, but there is a lesser effect due to HLA [12]. The latter contribution correlates with the observation that NK cell populations develop to be tolerant of all autologous, but not all allogeneic, HLA class I allotypes [3].

8. A MAJORITY OF ALLOGENEIC BONE MARROW TRANSPLANTS INVOLVE KIR MISMATCH

In matching donors and recipients for clinical allogeneic bone-marrow transplantation the 'gold standard' is for the donor to be a healthy, HLA-identical sibling (reviewed in [13]). Because the HLA and KIR loci are situated on different chromosomes, only one quarter of such gold-standard donors will also be matched for KIR. (For unrelated HLA-matched donors those that are KIR-matched number less than 1%.) When the bone marrow donor is HLA-identical and KIR mismatched the recipient reconstitutes an NK-cell repertoire like that of the donor and different from that of the patient prior to transplantation [14]. The kinetics of the reconstitution differ: some patients are fully reconstituted within one year while others take much longer. The results point to KIR mismatch being beneficial for both quicker recovery of KIR expression and good clinical outcome.

9. CONCLUSION

The extent of human KIR diversity and its rapid evolution point to these genes being subject to natural selection by pathogens. One likely contributor is balancing selection, which provides responsiveness to pathogens through activating receptors, while maintaining tolerance to self through inhibitory receptors. Consistent with this model are the studies correlating activating KIR both with better response to infection [15] and with

susceptibility to autoimmunity [16,17]. Another likely contributor is directional selection, which causes the system to continuously change. This can be conceived in terms of successive pathogen-specific selections. Variant activating receptors could be selected for their capacity to direct pathogen-specific NK-cell responses; variant inhibitory receptors could be selected for their capacity to engage variant HLA class I molecules that have themselves been selected for their capacity to direct pathogen-specific T-cell responses. Anothre and quite distinct biological function of NK cells also has a strong potential to select for improvements in NK-cell function. This is the function that NK cells in the decidua serve in implantation at the beginning of pregnancy (reviewed in [18]).

10. REFERENCES

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