NATURAL KILLERS

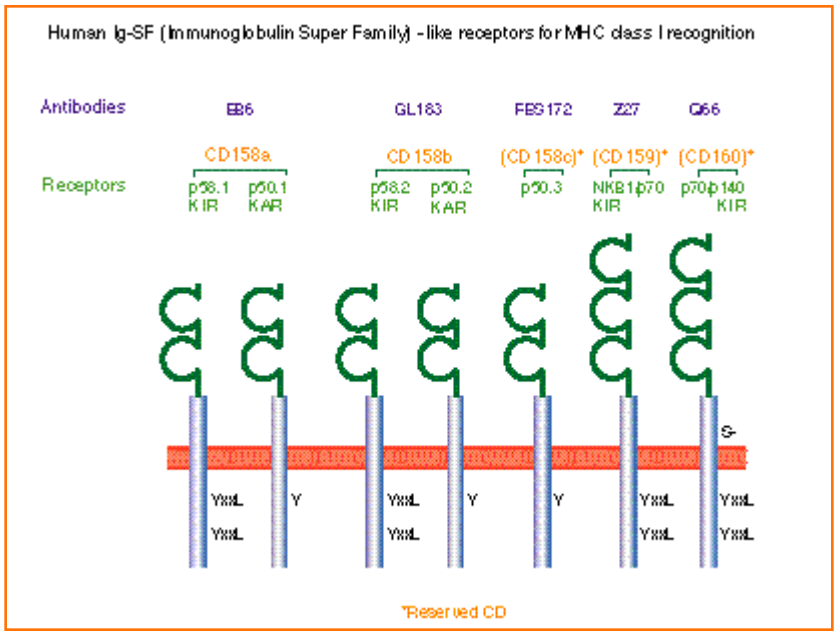
NK Cells and MHC (Major Histocompatibility Complex) Restriction

Natural killer (NK) cells are crucial as a first line of defense in the body because they can exert cytotoxicity without prior sensitization by antigen. These large granular lymphocytes (LGL) kill antibody-coated cells through a mechanism called antibody-dependent cell cytotoxicity (ADCC). This is mediated by the low-affinity Fcγ receptor, CD16. A second mechanism, called natural cytotoxicity, is used to kill many different targets such as tumor cells and virus-infected cells. Therefore, it was believed for a long time that NK cells were not major histocompatibility complex (MHC) restricted (1). Recently, the concept of NK killing has profoundly changed and it is now clear that NK cells are truly complementary to cytotoxic T cells. T cells recognize foreign peptides in the context of self, while NK cells recognize the absence of self (2).

Several receptors on NK cells have been identified in the last few years. This technical breakthrough came with the ability to obtain individual NK clones (3) and the production of monoclonal antibodies against the receptors themselves (4). Analysis at the clonal level shows that individual NK cells discriminate between different targets, by means of MHC restriction. NK clones from a single donor as well as from distinct donors can be divided into MHC Class I allele-specific groups.

However, the picture is actually more complex. NK receptors with MHC-restriction are not homogeneous. They belong to two very distinct families of proteins: the immunoglobulin superfamily (IgSF) and the lectin-like type II transmembrane proteins which have a C-type lectin domain. These lectin-like receptors have been known in rodents for some time (5), but murine counterparts of the Ig superfamily NK receptors had not been detected. Therefore, it was surprising when two groups, using different approaches (6, 7), simultaneously obtained the cDNAs of human MHC-restricted NK receptors and found them to be of the immunoglobulin superfamily.

Receptors of the Immunoglobulin Superfamily (IgSF)



Several receptors of the IgSF have been identified by monoclonal antibodies (4). Two such receptors contain 2 Ig-domains and are specific for HLA-C (group 1: Cw2, Cw4, Cw5, Cw6; group 2: Cw1, Cw3, Cw7, Cw8). Two others contain 3 Ig-domains, one of which is specific for HLA-Bw4. The last, which is always expressed as a homodimer, recognizes HLA-A3 and A11. Thus, individual HLA alleles are not recognized, but rather epitopes shared by several alleles. These have been named killer inhibitory receptors (KIR) because they block NK killing upon engagement with the right self-MHC. A varying percentage of NK cells (less than 50% in certain individuals) express these receptors (8). However, all NK clones express at least one MHC specific receptor. If it is not an IgSF KIR, it is a lectin-like receptor and co-expression of both types is frequent.

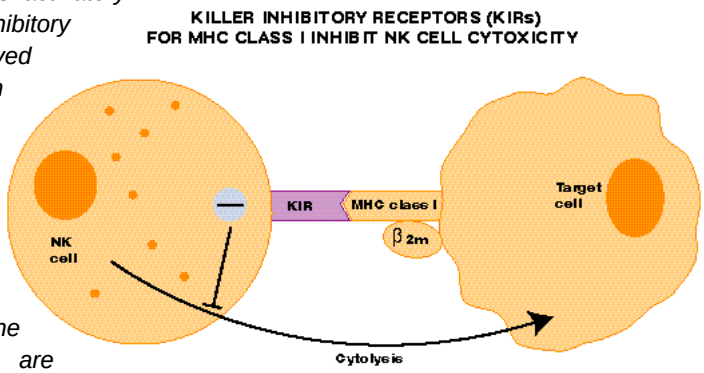
Lectin-like Receptors

Lectin-like receptors in the human are mainly represented by the CD94/NKG2 complex (9). CD94 (with a typical lectin-like structure) seems to be unable to bind HLA alleles by itself. But it can be assembled with different NKG2 proteins to form variable dimers that have HLA specificity (8). NKG2, type II transmembrane proteins again with a lectin-like domain, are encoded by a whole family of genes. In general, lectin-like receptors are of broader specificity, need a higher threshold of HLA protein expression for their function, and are expressed on a much larger fraction of NK cells than the IgSF receptors.

NKR-P1 (CD161) is another lectin-like molecule which is expressed on most NK cells. It is probably involved in activating the natural cytotoxicity pathway (10), but no HLA specificity has been demonstrated for this receptor (11).

Inhibitory and Activatory Receptors

NK receptors are found in two functionally different forms–activatory and inhibitory, which differ in their cytoplasmic tail. Inhibitory receptors (both IgSF and lectin-type) contain two conserved motifs called immunoreceptor tyrosine-based inhibition motifs (ITIM) which are missing in activatory receptors (12). For most known receptors both forms exist, but there are exceptions.



Inhibitory receptors prevent NK killing if the corresponding MHC Class I molecule is present; lysis of the target cell occurs if the MHC Class I molecule is absent. Activatory forms of receptor (usually stained by the same antibody that recognizes the inhibitory form) are expressed in some donors only. A cell with activatory receptors will have inhibitory receptors of a different MHC Class I specificity, and the inhibitory signal dominates the activatory one.

NK Receptors Expressed on T Cells

All NK receptors (inhibitory as well as activatory, lectin-like as well as IgSF) can also be expressed on T cells (13). In general, these T cells are CD8+ and can be either TCR αβ or γδ. They have an activated phenotype with low CD28, high CD45RO, CD18, CD57, CD29, and no expression is found in the thymus and in cord blood (4). Expression of NK receptors is found on the T cells of almost all individuals, but to a varying extent. In contrast to NK cells, T cells are positive for only one receptor protein per cell. There is evidence that CD3+, NK receptor+ cells represent oligoclonal expansions, maybe after chronic antigen stimulation (14). The role of coexpression of NK and T cell receptor is not yet clear; probably it allows adjustment and fine tuning of the response (15).

Recently research studies show that Cytomegalovirus, a life-long latent virus, has adapted perfectly to the NK and T cell defense. It down-regulates MHC Class I expression on the cells it infects, preventing presentation of viral peptides. It also expresses an MHC Class I homologue of its own which binds CD94, evading NK cytotoxicity (16, 17).

Many questions remain to be answered in this growing field. Not only basic ones such as the identification of additional receptors, their mode of action, their distribution, and the presence or absence of selection processes; but also practical questions such as their possible role in transplant rejection.

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