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Does a Low Level of Expression of HLA Molecules Engender Autoimmunity?

THE immune system can summon a variety of defenses against invaders from the outside. Among these deterrents are three types of killer lymphocytes that attack and lyse cellular targets. One type consists of cytotoxic, or CD8, T cells with α/β antigen receptors that interact with the HLA class I glycoproteins on nearly all cells. These HLA molecules bind to peptides derived from intracellular antigens, such as viral proteins, and display them on the cell surface. Binding of the α/β antigen receptor to complexes of HLA class I molecules and peptide fragments of an invading virus induces the T lymphocyte to kill the infected cell. Another type of killer T lymphocyte expresses receptors for antigen of the γ/δ type. Relatively little is known about the antigens recognized by γ/δ receptors or the role of these receptors in disease, except that in some cases the antigens may be autoantigens that appear when a cell is subjected to stress.[1] Natural killer cells are a third type of killer lymphocyte. They are not T cells and express no T-cell receptors for antigen. Nevertheless, they are cytotoxic and have an important role in combating viral infections, particularly infections by herpesviruses. Natural killer cells may also attack tumor cells,[2,3] but our understanding of the specificity of these kinds of killer lymphocytes is incomplete.

For a cell to be vulnerable to an α/β cytotoxic T lymphocyte, it must display HLA class I molecules. However, the converse is true for natural killer cells: the presence of HLA glycoproteins actually protects the cell from attack by natural killer cells.[4] The way in which HLA molecules defend cells from assault by natural killer cells has recently become clear. Natural killer cells express receptors that bind to HLA class I molecules on other cells.[5] Most of these receptors inhibit cytotoxic function rather than activate it, as in the case of the antigen receptor of the T cell. Consequently, cells that express high levels of HLA molecules generally resist attacks by natural killer cells. The HLA-specific inhibitory receptors are believed to enable natural killer cells to attack cells in which the expression of HLA molecules has been down-regulated as a result of infection or neoplastic transformation.

At least two families of HLA-specific inhibitory receptors have been identified in humans: killer immunoglobulin-like receptors (KIRs) and CD94/NKG2.[5] As a group, the natural killer cells of each person express 10 or more different inhibitory receptors. Each natural killer cell, however, expresses several kinds of inhibitory receptors, but not all of them.[6] Since these variants bind different sets of HLA class I molecules, it takes only one (or a few) of the six or so different HLA glycoproteins on normal cells to inhibit an individual natural killer cell. Consequently, the loss of one HLA molecule (or all of them) can render a cell susceptible to destruction by natural killer cells.

The HLA-specific inhibitory receptors represent only one component of the specificity of natural killer cells. To be killed, a target cell must have two properties relating to natural killer cells: the inability to inhibit them and the capacity to stimulate them. Recently, some of the stimulatory natural-killer-cell receptors have been identified.[5] Tumor cells and cells infected by viruses tend to be the most stimulatory, but even certain normal cells can stimulate natural killer cells. For example, natural killer cells kill bone marrow grafts from mutant mice that fail to express the mouse versions of HLA class I molecules.[7] The molecules that stimulate natural killer cells are in most cases not known.

Some T lymphocytes, including a minority of α/β T cells and a substantial fraction of γ/δ T cells, also express the HLA-specific inhibitory receptors found on natural killer cells.[5,8] The stimulation of such T cells through their antigen receptors can be inhibited if the target cell expresses high levels of HLA

class I antigens. The HLA-specific inhibitory receptors on such T cells may, like the inhibitory receptors on natural killer cells, allow preferential lysis of cells that have down-regulated the expression of HLA class I molecules. In one patient with melanoma it was shown that α/β T cells specific for a melanoma antigen were initially prevented from attacking the tumor cells, because the T cells expressed an inhibitory receptor that bound an HLA antigen expressed by the tumor cells. Later, when variant tumor cells arose that had selectively lost this HLA class I antigen, the T cells were able to attack the tumor cells.[9]

The susceptibility of some normal HLA-deficient cells to natural killer cells has long led scientists to question why natural killer cells do not attack other normal cells that also express low levels of HLA class I molecules, such as erythroblasts, hepatocytes, and neurons. It has been assumed that such cells are spared because they fail to stimulate the natural killer cells. But, as described by Handgretinger et al. in this issue of the *Journal,* lymphocytes may sometimes attack erythroid precursors precisely because they lack HLA antigens.[10]

Handgretinger et al. describe a patient with pure red-cell aplasia, a rare disease in which erythroid precursors are absent in the bone marrow. One form of the syndrome involves an expansion of a population of large granular lymphocytes that can have the phenotype of natural killer cells or T cells. The patient in question had an abnormally large population of γ/δ T cells, which expressed several different HLA-specific inhibitory receptors of the type found on natural killer cells. These T cells failed to kill most normal cells, unless the HLA molecules of the target cells were masked by an antibody. However, these abnormal T cells did kill erythroblasts, which express very low levels of HLA class I molecules. The authors concluded that these T cells are self-reactive but are unable to attack most normal cells because of protective HLA molecules.

A similar phenomenon was recently reported in the case of a distinct set of self-reactive γ/δ T cells, which is present in all people.[11] This strategy of protection fails in the case of erythroblasts because of their low level of expression of HLA antigens. Validation of this hypothesis will require the demonstration that red-cell aplasia is reversed by treatments that inhibit the γ/δ lymphocytes.

These new results suggest that in some cases, pure red-cell aplasia may result from the failure of erythroblasts to inhibit autoimmune lymphocytes. But what antigens on erythroblasts stimulate the lymphocytes, and by means of which killer T-cell receptor? Handgretinger et al. suspect that the γ/δ T-cell receptor is not generally involved, because the larger-than-normal population of lymphocytes in many patients with this form of pure red-cell aplasia does not express γ/δ T-cell receptors. Is there a common erythroid antigen recognized by all the different larger-than-normal populations of lymphocytes found among patients with pure red-cell aplasia? Or, does the antigen differ from patient to patient? In some patients these lymphocytes are not T cells at all but, rather, have a natural-killer cell phenotype. Furthermore, some T cells can, under appropriate conditions, adopt the specificities of natural killer cells.[12] It is possible that such T cells express, in addition to their antigen receptors, the stimulatory receptors normally present on natural killer cells. It is therefore plausible in these patients that the attack on erythroid cells is mediated by the natural killer type of stimulatory receptor rather than the T-cell receptor.

Whatever the answers to these questions prove to be, the results of Handgretinger et al. are important because they represent evidence of autoimmunity associated with a low level of expression of HLA antigens. Unlike erythroid lineage cells in mice, which express relatively high levels of the mouse counterpart of HLA class I antigens, erythroid progenitor cells in humans express low levels of these antigens. This species difference leads to another question: why do human erythroid progenitor cells have such low levels of HLA class I molecules when such a condition could incite an attack by natural killer cells or other lymphocytes?

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