EDITORIAL

HLA SYSTEM AND CANCER

Cancer cells, along with bacteria, viruses, unicellular and multicellular pathogens, have the potential of mounting harmful challenges to the body. The body, through the process of evolution, has developed the immune system as its active defense mechanisms. The human immune system is composed of a wide range of distinct cell types, with Iymphocytes playing a major role through provision of the specificity of immune recognition.

The immune system is armed with various appendages as means through which it is capable of interacting directly or indirectly with virtually every cell in the body. Its two broad branches are the humoral and cellular branches. The first is largely composed of B Iymphocytes and their products, and the second, T Iymphocytes. Whereas B cells recognise antigen not presented in the form of other molecules, T cells are not capable of recognising non-protein antigens. They recognise antigens in the form of a "self" major histocompatibility complex (MHC), the human leukocyte antigen (HLA) system. They utilise T cell receptors on their surfaces to recognise antigen/MHC molecule complexes. As opposed to B cells which have the ability to recognise antigen in its native conformation, T cells recognise antigen that has been processed by other cells and presented to their surfaces by MHC molecules.

The MHC molecules themselves are receptors for peptide antigens. The HLA gene system is divided into two classes - class I and class II. Those in class I are named A, B and C while those in class II are named DP, DQ, DR. MHC molecules from these major subregions are codominantly expressed, and the extent of MHC polymorphism present in the gene pool usually results in heterozygosity for most individuals at every major class I and class II locus.

Most of tumour cells in the body express class I peptide complexes, which are the ligands for CD8+ T cells. Some tumour cells clearly present antigenic peptides in the context of class I, because specific recognition of tumour cells by cytolytic CD8+ T cells results in their destruction *in vitro* and *in vivo*. Tumour cells which cannot process or present antigen recognisable by T cells may enjoy selective advantage by escaping elimination by the immune system. A number of mechanisms exist for tumour cells to escape the immune system recognition. Some tumour cells of epithelial origin express either greatly reduced or absent levels of class I molecules on their surfaces. Demonstration of down regulation of class I antigen expression has been used as a poor outcome indicator. In this category are tumours such as embryonal carcinomas, choriocarcinoma, cervical carcinoma, mammary carcinoma, and small cell carcinoma of the lungs. Others are neuroblastoma, some types of colorectal carcinoma, and some types of malignant melanoma(1).

In this issue of the journal, Tamiolakis and colleagues have demonstrated progressive downregulation of class I antigen expression from dysplasia, carcinoma-*in situ* of the gall bladder, and invasive carcinoma(2). Downregulation of the expression of particular class *I Loci* or loss of genes for particular class I-alpha chains is another escape mechanism, and yet another is downregulation of certain proteasome component molecules as exhibited by small cell lung carcinoma. These concepts can be employed in approach to anticancer treatment. Observations that renal cell carcinoma and malignant melanoma can undergo spontaneous regression have strengthened the belief that enhanced immune system is capable of eradicating established tumour cells(3). With recent advances in immunology, the biologic basis for antitumour immunity is beginning to unfold. T Iymphocytes can respond to the tumour antigens presented as peptides in association with MHC molecules and tumour cells or on "professional" antigen presenting cells such as dendritic cells, mounting on immune response to keep tumour proliferation in check(4).

This approach to treatment has however not yet become established because in spite of the fact that immune T cell responses can be readily demonstrated *in vitro* and *in vivo,* such responses typically do not eliminate established tumour. Fortunately today, immunocompetent T-lymphocytes that mediate antitumour effects in cancer patients is practicable and represents a successful form of adoptive immunotherapy. Antitumour effects are mediated directly by Iysis of tumour targets or indirectly through subsequent recruitment and activation of other immune effects. These processes can mediate clinically relevant regression of cancer. Time will tell whether current efforts in this rather nebulous area will be translated into reproducible and meaningful therapeutic armamentaria.

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