Studies of Lymphocyte Subpopulations and Their Clinical Implications

Advances in our basic understanding of immunoregulation have led to the realization that individual subsets of lymphocytes play distinctive roles in the immune response and in immune effector mechanisms and that delicate networks of interactions among these cells as well as with macrophages determine the outcome of the immune response.[1] These advances were made possible by our ability to distinguish the various subpopulations of lymphocytes with phenotypic markers; to trace their interrelated linages of development; and to define their modes of interactions. Moreover, in the mouse, the availability of inbred and congeneic strains have allowed the dissection of roles played by individual classes of genes of the Major Histocompatibility Complex (MHC) in cell to cell interactions and in the control of the immune response.[1] Selective expression of the I region genes and the roles played by individual gene products and other phenotypic markers in cell interaction have been well defined in the mouse.[2] Thus functional subpopulations of T lymphocytes can now be readily defined, separated and their interactions tested *in vitro* through the use of antisera and monoclonal antibodies to well defined marker systems, powerful cell separation procedures and meticulous cell culture techniques and *in vitro* assays.

These advances in mouse immunology have been applied to the studies of human immunology with amazingly short lag time. Students of human immunology have been able to elucidate the human equivalent of mouse MHC; to define the various genes and gene products and a growing number of phenotypic surface and enzyme markers. Data on genetic association of the allotypic markers, particularly the MHC and the immunoglobulin allotypes, with disease states have grown rapidly. Among the clinical conditions that have been shown to be associated with these allotypic markers are, not surprisingly, the autoimmune and collagen diseases in which abnormality in immunoregulation is likely to play an important pathophysiological role. However, such genetic association between a given allotypic marker and a diseased condition does not necessarily mean a direct predisposition of that particular allele to pathophysiological development of the disease. In fact, it is more often an association without a direct pathophysiological role. Recognition of linkage disequilibrium in MHC and in HLA typings suggests that in fact a given allotype found associated with a disease may simply be linked in frequent haplotypes to other genes that together may be predisposing factors. Therefore, the possible predisposing role of a given allotypic marker to a disease must be worked out individually, as have been attempted in a number of diseases. For those diseases, in which an association with an allotype of the HLA-D/DR region can be shown, e.g., autoimmune and collagen diseases and persistent infection, an obvious approach is to investigate abnormality in immunoregulation, simply because of the supposed roles of these genes in the control of immune response. In this approach, it is usually presumed that the association of an allotypic marker to a disease can be reflected in an immunoregulatory change, e.g., shift in number and/or function of the subpopulations of T lymphocytes.

In the past five years studies of lymphocyte subpopulations in diseases have been intensified by the availability of a number of discriminating marker systems. The most widely used include assays for receptors for immunoglobulins of various classes;[3] assays using monoclonal antibodies;[4] functional tests based on Con-A induced suppressor activity of PWM activated B cells;[5] sensitivity to agents affecting cAMP metabolism,[6] etc. While these studies have been useful in allowing us to begin assessing gross changes in immunoregulation in various clinical conditions, e.g., systemic lupus erythematosus (SLE), multiple sclerosis, persistent viral and bacterial in-

fection, pregnancy[7-9] (see also Ratanavongsiri, J. and Matangkasombut, P., Lulitanond, V. et al.; Vidhidharm, A. et al.; and Sriwatana, B., Vongsakul, M. and Matangkasombut, P. in "Abstracts of the 5th International Congress of Immunology" 21-27 August 1983, Kyoto) etc., caution must be exercised in the interpretation of the results. Much too often premature conclusions drawn from such data have led to unnecessary controversies. The fact remains that while the available marker systems can distinguish T cell subpopulations, none of them could be said to have an unequivocal correlation with functional tests. The marker system based on cell surface Fc receptors for immunoglobulins of different classes, had good correlation with *in vitro* functional tests at least when normal T cells were studied.[3] Similarly, the marker system identified by monoclonal antibodies of the OKT series have had good correlation with functional tests.[4] Thus, initially it appeared that either marker system could be used in assessing changes in suppressor and helper cells in various clinical entities. However, difficulties soon arose in that there was usually poor correlation when these T cell subpopulations were assessed by both systems of markers in the same groups of subjects.[10] In our own laboratories, the coefficient of correlation between OKT-8$^+$ and T_G assessed in substantial number of normal subjects was found to be rather low. Whether one system is more accurate than the other cannot be concluded at this stage of the game. What can be said is that either alone cannot be depended on with confidence. This is particularly the case when these techniques were extended for use in assessing diseased conditions without concurrent functional assessment. When the T_G, T_M system was used alone to assess shift in T cell subpopulations in SLE, there appears to be agreement among various reports, i.e., a decrease in T_G and a normal level of T_M.[11,12] On the other hand, when the OKT monoclonal antibodies were used alone, the results were conflicting, i.e., some showing a decrease in OKT-8$^+$ among active SLE,[13] others not.[14] In fact, a number of recent reports suggested that not all OKT-8$^+$ cells are functionally suppressors and that a small fraction of OKT-8$^-$ but OKT-4$^+$ cells are functionally suppressors.[15-17] These discrepancies are further aggravated when results obtained from the use of other series of monoclonal antibodies could not be easily compared with either the OKT markers or the receptors for immunoglobulins. Fortunately, these can be worked out and it is likely that within a couple of years we may settle on a panel of assays that can truly reflect functional subpopulations of T lymphocytes. In the meantime one would only ask that results are not over-interpreted.

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