Lymphokines and Immediate Type Allergy*

The demonstration of immediate type allergy in humans dates back to 1865 when Blackley performed the first allergy skin test by placing pollen from an anther of Italian rye grass on abraded skin and observed a wheal and flare reaction,[1] although in 1819 Bostock[2] had already noted that sensitive individuals would develop a sharp attack of hay fever after inhaling pollen from grass or ragweed.

The presence of a skin-sensitising antibody in the serum of allergic patients was first described by Prausnitz and Kustner in 1921.[3] They showed that an intracutaneous injection of fish extract into a sensitive individual produced a wheal and flare reaction; they also showed that such sensitivity could be transferred to the skin of a normal recipient via the patient's serum. Coca and Grove in 1925 first named this skin-sensitising factor as atopic reagin (or reaginic antibody) because of its association with hereditary conditions and their uncertainty as to the exact nature of this factor.

The nature of reaginic antibody remained a mystery during the ensuing 40 years in spite of extensive studies by numerous investigators. In 1966, Drs. K. and T. Ishizaka[4] characterised the antibody from the serum of highly ragweed-allergic patients and called the protein "immunoglobulin E" (IgE) because of its unique physicochemical properties and biological functions when compared with IgG, IgA, IgM and IgD. The finding of a patient with IgE myeloma by Johansson[5] in 1967 made possible the routine measurement of total serum IgE and specific IgE antibody in allergy practice.[6]

Although the mast cell had been described by Ehrlich in 1879,[7] its biological function became clear only after the discovery of IgE. Treatment of tissues and peripheral blood with ^{125}I-labelled anti-IgE showed that only mast cells and basophils possess IgE receptors.[8] Furthermore, it has been well established that the immediate type allergic reaction is initiated with the bridging by antigens of two cell-bound specific IgE antibody molecules resulting in the release of histamine, eosinophil chemotactic factor of anaphylaxis (ECF-A), neutrophil chemotactic factor (NCF), platelet-activating factor (PAF) and leukotrienes from mast cells in tissue and basophils in the blood.[9]

In recent years, it has been increasingly realised that the occurrence of the immediate type allergy in humans and animals is influenced by a group of proteins secreted by activated lymphocytes, i.e. lymphokines. Moreover, the lymphokines affect nearly every step of the allergic reaction during its development. This article attempts to summarise some of the most interesting findings of recent research in this exciting area.

Lymphokines regulating IgE synthesis

Just like plasma cells secreting IgG, IgA and IgM, IgE-producing plasma cells may be differentiated from pleuripotential haematopoietic stem cells through pre-B cells; each B cell is committed to a certain antigenic specificity in the pre-B cell stage without the influence of any antigens and/or T cells. Resting B cells in the Go phase can be activated by anti-IgM, B-cell stimulating factor-1 (BSF-1, a T-cell factor),[10] antigens and mitogens, with the result that they reach a proliferating state, a state which can be maintained in the presence of B-cell growth factor (BCGF).[11] However, the differentiation of activated B cells into immunoglobulin – producing B cells requires the presence of other T-cell-derived factors, i.e. early-acting and late-acting B-cell differentiation factors (BCDF), the latter very possibly being interleukin 2 (IL-2).[11,12] Finally, the proliferation and differentiation processes must be regulated since uncontrolled antigen-driven expansion of an individual B-cell clone could threaten the integrity of the immune system and result in immunologically mediated diseases.

However, the IgE antibody response shows unique features which are not observed in the IgM- or IgG-response, i.e. the IgE antibody responses in experimental animals or normal humans (except atopic patients) are either not evident or just transient following normal immunisation. Studies by several laboratories strongly suggest that although IgE is similar to other Ig

*This study was supported partly by a grant No. NSC74-0412-B002-68 from The National Science Council of The Republic of China.

classes and is controlled by antigen-specific helper and suppressor T cells, it appears that the IgE response is also regulated by an isotype-specific help and suppression mechanism.[13-15] In 1980, Ishizaka et al.[16,17] first demonstrated the existence of two rat T-cell factors which have an affinity for homologous IgE and selectively regulate the isotype-specific IgE response, the so-called IgE-binding factor. One of the factors specifically potentiates the IgE response (IgE-potentiating factor), while another suppresses the response (IgE- suppressive factor). Both factors are glycoproteins having comparable molecular weights of 13,000 to 15,000 and share a common gene and precursor polypeptide. The major difference between the two factors is in the carbohydrate moieties of their molecules. The IgE-potentiating factor has both an N-linked, mannose-rich oligosaccharide and an O-linked oligosaccharide. The terminal sugar residue of both of these oligosaccharides is sialic acid. In contrast, IgE-suppressive factor contains only 0-linked oligosaccharide, the terminal sugar of which is galactose. Their more recent studies show that the effective substance inducing IgE-binding factor during immune response comprises interferon-like molecules released when macrophages are activated by complete Freund's adjuvant (CFA) or *Bordetella pertussis,* or when antigen-primed T cells are stimulated with antigen. However, the inducers of IgE-binding factor do not determine the nature of factors produced by the Lyt 1^+, Fcϵ and/or Fcγ receptor-positive T cells.[18,19] In the selective formation of IgE-potentiating factor, another T-cell factor from Lyt 1^+ T cells, called glycosylation- enhancing factor (GEF), is involved. This factor enhances the assembly of N-linked oligosaccharides to IgE-binding factors during their biosynthesis and provides the factor with IgE-response-enhancing capability. To the contrary, antigen-primed Lyt 2^+, I-J^+ T cells release glycosylation-inhibiting factor (GIF) which inhibits the assembly of the N-linked oligosaccharide and thereby provides IgE-binding factors with suppressive activity. It was further found that GEF is a kallikrein-like protease and GIF is a fragment of phosphorylated lipomodulin.

Lymphocytes from patients with hyper-IgE syndrome and allergic diseases had been reported to produce IgE-binding factor.[20,21] Furthermore, human T-cell hybridoma could be switched from the formation of human IgE- potentiating factor to the formation of IgE-suppressive factor by adding GIF to the cells together with IgE.[22] These findings indicate that mechanisms for the selective formation of human IgE-potentiating factors or IgE-suppressive factors are similar to those of rodent IgE-binding factors. It is speculated that GIF may be useful for clinical purposes in the future because of its capability of producing IgE-suppressive factor.

In addition to a wide spectrum of immunoregulatory functions, interferon (IFN) was reported to suppress the ability of mouse spleen cells synthesising IgE to sensitise rat skin to heterologous adoptive cutaneous anaphylaxis.[23] Our previous study showed that a concentration of human fibroblast IFN (400 IU/ml incubated for six hours) was able to suppress *in vitro* IgE biosynthesis by MNCs from asthmatic children to a degree of 30 per cent. Moreover, the B cells were the targets for the IFN effect. However, the presence of normal T cells could protect B cells from the suppressive effect of IFN on IgE synthesis.[24]

Lymphokines involved in the proliferation and differentiation of mast cells and basophils

Several lines of evidence obtained from recent studies strongly indicate that the growth and maturation of mast cells and basophils, the target cells of allergy which release mediators upon antigenic stimulation, are also lymphokine-dependent.

Interleukin 3 (IL-3) was initially defined as the factor in conditioned media from Con A- stimulated normal splenic lymphocytes that induced the expression of 20-α-hydroxysteroid dehydrogenase (20 α SDH), a specific enzyme marker for a mature T-cell population,[25] on the surfaces of cultured splenic lymphocytes of nu/nu mice.[26] After the discovery of a Thy-1^+ WEHI-3 cell line, which constitutively produces high titres of IL-3,[27] IL-3 has been purified to homogeneity.[28] By using the apparently purified IL-3, Ihle *et al*[29] demonstrated that, in addition to inducing the expression of 20αSDH, IL-3 was found to possess the biological activities of 1) WEHI-3 growth factor, 2) mast cell growth factor (MCGF), 3) P-cell-stimulating factor, 4) histamine-producing-cell-stimulating factor and 5) colony-stimulating factor. These data are consistent with those reported by several other investigators that the growth and differentiation of mast cells/basophils are lymphokine-dependent.[29-27] A more recent study provided evidence for the presence of specific receptors for IL-3 on IL-3-dependent cell lines such as 32 Dc1 and FDC-Pl.[38] Also, a MCGF cDNA, which encodes a multilineage haematopoietic growth factor, was cloned thus providing further evidence for the multiple activities of IL-3.[39]

In humans, lectin-stimulated MNC's supernatants were reported to contain factors supporting the growth of murine IL-3-dependent cell lines.[32,40] More recently, a T-cell-derived factor called basophil-promoting activity (BaPA) was described.[41] This factor, which is different from IL-1, IL-2 and CSF of macrophage/granulocyte both biochemically and biologically, was found to be capable of promoting the growth of basophils in human bone marrow culture.

Thus, T-cell-derived lymphokines can indeed regulate the growth and

maturation of mast cells and basophils.

Lymphokines involved in immediate type allergy

Although the relationship between type I IgE-mediated allergy and type IV cell-mediated immune response is intriguing, several studies strongly suggested that lymphokines are involved in the immediate type allergy. Boetcher *et al*[42,43] reported that human basophil chemotaxis could be enhanced by lymphocyte-derived factors. Moreover, lymphocytes activated by antigen and mitogen could secrete histamine-releasing activity (HRA) and IFN to enhance the IgE-mediated histamine release from human basophils, although HRA exerts such an effect within several minutes,[44,45] IFN requires an induction period to synthesise new RNA to augment basophil releasability.[46,47]

Effect of immunotherapy (hyposensitisation) on lymphokine production

Although immunotherapy has been repeatedly shown since 1911 to be effective in the treatment of respiratory allergies,[48] the working mechanism(s) still remains ill-defined. Generation of antigen-specific suppressor cell activity reflected in diminished lymphoproliferative responses to antigen stimulation after immunotherapy has been postulated to be one of the mechanisms accounting for its clinical effectiveness.[49,50]

In a recent study, we found that after immunotherapy, while the proliferative response of OKT4 helper cells to specific antigen was decreased, that of OKT8 suppressor cells was enhanced.[51] As lymphokine production, especially that of IL-2 (T-cell growth factor, TCGF), is closely correlated to the capability of cells to proliferate,[52] we studied the changes in the production of and responsiveness to IL-2 after immunotherapy in house-dust-sensitive asthmatic children.[53] Our results showed that the production of IL-2 by MNCs and OKT4 cells was markedly depressed while the responsiveness of OKT8 cells was augmented. Although the house-dust we used for treatment was a mixture of several allergenic materials, our data are in agreement with those reported by Gatien *et al*[54] and Evans *et al*[55] that the production of migration-inhibition factor (MIF) and lymphocyte mitogenic factor (LMF), which is the forerunner for IL-2, were decreased after immunotherapy with purer allergen (antigen E).

Therefore, the changes in the production of and responsiveness to IL-2 may be used as a parameter to monitor the efficacy of immunotherapy.

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