(1) Regulation of the IgE Antibody Response

organ where T lymphocytes differentiate. With development of monoclonal antibody the differentiating antigens on human thymocytes and T lymphocytes have been studied. A subset of $T_{1,3,5}$ lymphocytes exerts suppressor function and cytotoxicity whereas another subset of $T_{1,3,4}$ lymphocytes mounts the proliferative response to soluble antigens and helper function.

Regulatory T cells are known to be heterogeneous. They are antigen-specific or antigen-nonspecific. Some are isotype-, allotype- or idio-type specific helper or suppressor. IgE-specific Th and Ts were first found by Dr T. Kishimoto who will present the results on IgE-specific immune responses and its possible regulations.

An individual elicits a regulated immune response to an antigenic stimulation via cell-to-cell interaction. The duration and magnitude of the immune response are controlled by an immune network. An antigen stimulation activates Th to help B lymphocytes proliferate and differentiate into antibody-producing cells. On the other hand it also causes activation of suppressor inducer with phenotype of Lyt, 1, Qa-1 which results in induction of suppressor effector with Lyt, 2, 3 via activation of acceptor

cells with phenotype of Lyt, 1, 2, 3, Qa-1. In turn the suppressor effector inactivates Th and thus feedback suppression circuit is formed. Although various mechanisms concerning the pathogenesis of autoimmune diseases are postulated, much attention has recently been paid to the polyclonal B cell activation and abnormality of feed back suppression. From the view point of these consideration, Drs Sakane and Tanimoto will present the papers on immune dysfunction of lymphocytes of SLE and other related diseases. Abnormality of the immune network also results in the immuno-deficiency. Dr Mitsuya will present the data on cellular defects and dysfunction of primary immunodeficiencies.

Immunoglobulin combines an antigen to its combining site that exhibits unique antigenic determinants called idio-type. An idio-type is also recognized by an anti-idio-type antibody. Recently an idio-type is also found on T cells. Thus a idio-type and anti-idio-type system including immunoglobulins, B and T cells forms a closed network that regulate the immune response. Dr Sugai will present the papers on the clinical significance of idio-type in monoclonal hypergammaglobulinemia.

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I. INTRODUCTION

The identification of IgE as a carrier of reagenic antibody activity has greatly contributed to the understanding of the mechanism of reagenic hypersensitivity reactions. A crucial role of IgE antibody in allergic diseases suggests to us that understanding of the controlling mechanisms operating in the IgE response is the goal that must be

reached for the development of new therapeutic approaches to allergic diseases.

In the last decade, cellular mechanisms of the IgE antibody formation has been much revealed in experimental animals. As observed in IgM or IgG antibody formation, it was shown in mice, rabbits and rats that collaboration of T and B lymphocytes was essential for the induction of the IgE antibody response. Moreover, in the IgE anti-

body response, the existence of IgE class-specific regulatory T cells that exert their influence selectively on the IgE response has been suggested. Certain characteristic features of the IgE response that are not easily demonstrated in the IgG or IgM antibody response may be explained by assuming the presence of IgE class-specific helper or suppressor T cells. If the IgE antibody response *in vivo* is really regulated by the balance of IgE class-specific helper and suppressor T cells, it is conceivable that induction of an increased number of IgE class-specific suppressor T cells may result in the selective diminution of the IgE antibody production, while sparing the antibody productions with other immunoglobulin isotypes.

II. INDUCTION OF IgE CLASS-SPECIFIC SUPPRESSOR T CELLS

Selective suppression of the IgE antibody response was shown by preadministration of DNP-conjugated mycobacterium (DNP-Myc) into BALB/c mice. As shown in Fig 1, preadministration of DNP-Myc completely inhibited the induction of anti-DNP IgE response against DNP-OVA without an in-

hibitory effect on anti-DNP IgG response. Cell transfer experiment clearly showed that the selective suppression of the IgE response was due to the induction of IgE class-specific suppressor T cells.

In the experiment described in Fig 2, the suppressor function of DNP-Myc-primed T cells was shown to be mediated by IgE class-specific suppressor factors. DNP specific stimulation of T cells induced the production of IgE class-specific suppressor factors and the factors was shown to have the determinants encoded by the H-2 gene complex. The IgE class-specific suppressive activity of the factor could be absorbed with IgE-conjugated Sepharose column but not with IgM or IgG, indicating that IgE class-specific suppressor factor could bind with IgE and the factor showed its selective influence on the IgE response by binding with IgE molecules on the surface of B₆ cells.

III. ESTABLISHMENT OF IgE CLASS-SPECIFIC SUPPRESSOR T HYBRIDOMA

Introduction of somatic cell hybridization technique into immunological fields by

Fig. 1. Selective suppression of anti-DNP IgE response to DNP-OA by preadministration of DNP-Myc. Solid lines (○—○) represent anti-DNP IgE (left) and anti-DNP IgG (right) response in normal mice and dotted lines (×····×) show anti-DNP IgE (left) and IgG (right) response in DNP-Myc-pretreated mice.

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Fig. 2. Selective suppression of in vitro anti-DNP IgE response of DNP-OA-primed spleen cells by the addition of culture supernatants from coculture of DNP-Myc-primed T cells and DNP-HSA-pulsed macrophages.

Köhler and Milstein has provided a revolutionary tool for studies in this field. Their experiments suggested to us that the establishment of a T hybrid cell line with IgE class-specific suppressor function could be attained by the hybridization of DNP-Myc-primed T cells with a T lymphoma cell line and that establishment of a such cell line would provide a powerful strategy for

Fig. 3. Establishment of IgE class-specific suppressor T hybridomas by cell hybridization technique.

the isolation and chemical or immunological characterization of IgE class-specific suppressor factor. By employing the experimental procedures described in Fig 3, we have succeeded in the establishment of a T hybrid clone secreting IgE class-specific suppressor function. Some characterizations of the suppressor factor obtained from T hybridomas were carried out and the result is as follows, i.e. i) suppress the IgE response but not the IgG response, ii) antigen non-specific, iii) absorbed with anti-H-2^d antibody, iv) inactivate B_s cells but not T cells, v) absorbed with IgE but not with IgG or IgM.

A monoclonal T cell line secreting IgE class-specific suppressor factor will be utilized for the isolation and characterization of the suppressor factor. Messenger RNA specific for the suppressor factor will be isolated from a cell line and DNAs encoding the suppressor factor will be cloned. By employing the chemically purified factor, the suppressive mechanisms of the factor will be revealed. If these studies are successfully attained, we will be able to wilfully manipulate human IgE response in a desired fashion.