Regulation of Human IgE Synthesis

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Despite considerable advances in many areas of modern medicine, the fundamental therapeutic alternatives available to patients with allergic diseases have not changed in the past decade. A detailed understanding of the mechanisms regulating the human IgE response will be important in the development of new, effective therapeutic approaches to this group of diseases. Moreover, there is growing evidence suggesting that the IgE antibody plays an important gatekeeper role in the body's defense mechanisms and in facilitating the local deposition of circulating immune complexes. Aside from its well established role in the elimination of parasitic infections, IgE may play an important defense role against exogenous antigens which penetrate the mucosal and epithelial linings of the respiratory tract, gastrointestinal tract, and skin. Following the interaction of such antigens with IgE bound to mast cells, mediators are released which trigger a marked inflammatory response, localization of the antigen, and alteration of vascular permeability to allow the infiltration of other components of the immune system. Treatment of experimental animals with antihistamine prior to the induction of circulating immune complexes has been reported to prevent the deposition of immune complexes into tissues. Such experiments suggest that the IgE-mast cell system may play a role in triggering the inflammatory response of immune complex-mediated vasculitides. Thus, an understanding of the regulation of IgE synthesis has implications not only for the treatment of allergic diseases but for an understanding of the body's sophisticated defense system and in pathologic conditions, the deposition of immune complexes.

This review will focus on current concepts of the mechanisms controlling the human IgE response. Until recently, the investigation of such mechanisms has been hindered by the limited availability of experimental systems which reproducibly activate in vitro IgE synthesis. Most reports have therefore focused on the function of peripheral blood T and B cells from patients with diseases characterized by exceptionally high levels of serum IgE. It was hoped that by understanding the basis for elevated IgE levels in these various pathologic states the role played by the different components of the immune system in generating the human IgE response could be elucidated. Despite the limitations of such studies, it appears that there are striking similarities in the mechanisms by which T cells control IgE synthesis in humans and rodents.

At present, there is substantial evidence to support the concept that the requirements for activation of IgE synthesis differ from those required for synthesis of other immunoglobulin isotypes. Using rodent model systems, Ishizaka [3] has demonstrated that IgE binding factors secreted by T cells which bear Fc receptors for IgE (Fc,R) play an important role in the isotype-specific regulation of IgE synthesis. During the course of this review we will summarize experiments which suggest that the human IgE antibody response is also regulated by T cell-derived soluble factors which bind to IgE.

The role played by T cells in the generation of the IgE antibody response was first demonstrated by a series of experiments carried out in the early 1970s. Thus, Okumura and Tada [4] first demonstrated that neonatally thymectomized
rats were unable to generate IgE antibody responses. Subsequent studies carried out in rodents demonstrated that IgE synthesis was regulated by a balance between two distinct T cell subpopulations (i.e., helper/inducer T cells required for the induction and enhancement of IgE synthesis, and suppressor T cells which inhibit IgE synthesis). Low IgE responder rodents appear to have increased numbers or function of IgE isotype specific suppressor T cells because IgE antibody responses in such animals can be enhanced through experimental manipulations which selectively deplete IgE suppressor T cells. Thus, Tada and co-workers [4,5] used the rat model to demonstrate that sublethal doses of whole body irradiation, or administration of immunosuppressive drugs such as cyclophosphamide, converted rats from their characteristic pattern of transitory, low level IgE production to a pattern of sustained elevated IgE synthesis. The observation that such increased IgE responses in rats could be terminated by passive transfer of syngeneic T cells [6] provided direct evidence that the limited IgE response patterns in unmanipulated rats reflected the dominance of a suppressor T cell regulatory control mechanism that normally serve to minimize the production of antibody of the IgE class. It should be noted that the above experimental measures selectively affected IgE but not IgG responses supporting the notion that the regulation of these two isotypes is qualitatively and/or quantitatively different.

Ishizaka [3] has reported that IgE-specific regulatory T cells bear Fc receptors for IgE. These T cells secrete low molecular weight glycoproteins which bind to IgE (i.e., IgE binding factors). These IgE binding factors act on IgE-bearing memory B cells and regulate their differentiation into IgE-secreting plasma cells. IgE-specific regulatory T cells are activated by several signals following antigen activation. The first signal causes T cells bearing Fc receptors for IgE to display a receptor for the FC portion of IgE and to synthesize and secrete IgE binding factors. These factors, however, have no biologic activity. Their biologic activity is dependent on the presence of additional signals which regulate glycosylation of the IgE binding factors. These glycosylation signals are derived from a discrete subset of T cells and can be induced by administration of the appropriate adjuvants. Adjuvants such as alum or parasitic antigens result in the secretion of glycosylation-enhancing factors. This factor acts on the T cells that produce the IgE binding factors to promote the glycosylation of these factors. Glycosylated-IgE binding factors potentiate IgE synthesis. In contrast, adjuvants such as complete Freund’s adjuvants cause a discrete subpopulation of T cells to secrete a glycosylation-inhibition factor which promotes the secretion of poorly glycosylated IgE binding factors that suppress IgE but not IgE synthesis. A comparison of the properties of these two IgE binding factors is shown in Table I.

**Table I. Properties of rat T cell-derived IgE binding factors**

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>IgE potentiating factor</th>
<th>IgE suppressive factor</th>
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</thead>
<tbody>
<tr>
<td>13,000-15,000</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Affinity for IgE</td>
<td>+</td>
<td>+</td>
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<td>Affinity for lentil lectin</td>
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<tr>
<td>Affinity for concanavalin A</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Affinity for peanut agglutinin</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Sensitivity to trypsin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensitivity to neuraminidase</td>
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Despite the extensive data available in rodent models concerning the mechanisms by which IgE synthesis is regulated, similar experiments have not been carried out in humans because analogous in vivo experiments are not possible. The most convincing in vivo evidence that T cells play an important role in the regulation of human IgE synthesis is derived from the frequent observation of elevated serum IgE levels in patients with T cell immunodeficiencies [7]. Thus, increased serum IgE levels have been reported in patients with Di George’s syndrome, ataxia-telangiectasia, and Wiskott-Aldrich syndrome. It has been postulated that these patients may have sufficient numbers of helper T cells to initiate IgE synthesis but an inadequate number of suppressor T cells to inhibit IgE synthesis, thus, resulting in increased production of IgE. This hypothesis is supported by the observation that several diseases characterized by decreased number and function of suppressor T cells are accompanied by extremely high serum IgE levels. Thus, patients with the hyper IgE syndrome (HIE) (extremely elevated serum IgE, recurrent infections, chronic pruritic dermatitis) have been reported to have a selective deficiency of T3+ T8+ suppressor/cytotoxic T cells but not of T3+ T4+ helper/inducer T cells in their circulation. Evaluation of peripheral blood mononuclear cells (PBMC) from patients with HIE have also revealed an inability to generate functional suppressor T cell activity following a 48-h incubation with concanavalin A [8]. Similarly, patients with severe atopic dermatitis and elevated serum IgE levels have also been found to have decreased numbers of circulating T8+ suppressor/cytotoxic T cells [9,10]. Using enumeration of the Fc receptor for IgG (Fc, R) as a marker for suppressor T cells, Cooper et al [11] reported a decreased number of circulating T cells in AD. Furthermore, these investigators found a direct correlation between decreased number of Fc, R+ T cells and elevations in serum IgE.

Finally, close monitoring of serum IgE levels following allogeneic bone marrow transplant reveals that recipients develop extremely high serum IgE levels at the onset of acute graft-versus-host (GVH) disease [12]. The IgE levels return to normal with resolution of GVH disease. The basis for increased IgE levels in patients with acute GVH is believed to be due in part to an imbalance of T cell help and T cell suppression because patients with acute GVH have increased numbers of circulating T cells expressing the HLA-DR activation antigen and decreased numbers of suppressor T cells [13]. These experiments of nature are compatible with observations made in rodent models which suggest that T cells play an important role in the regulation of human IgE synthesis.

**Suppressor T Cells and Human IgE Synthesis**

The potential importance of suppressor T cells in the regulation of IgE synthesis in man is based on the following observations: (1) selective deletion of suppressor T cells in low IgE responder rodents by either total body irradiation or immunosuppressive agents result in marked enhancement of IgE synthesis; (2) serum IgE levels are frequently elevated in the presence of normal IgG levels in many primary T cell immunodeficiencies; and (3) certain disorders such as the HIE, severe AD, and acute GVH disease are associated with marked elevation in serum IgE and decreased numbers of suppressor T cells.

To examine the role of suppressor T cells in atopic individuals several laboratories have attempted to develop in vitro models of IgE synthesis. To date, the most common approach has been to study spontaneous IgE synthesis by cultured PBMC from atopic and nonatopic donors. Numerous studies have reported that PBMC from patients with diseases characterized by elevated IgE levels synthesized abnormally large amounts of IgE spontaneously in vitro whereas PBMC from nonatopic donors failed to synthesize IgE [14–18]. This increased secretion of IgE was isotype restricted as concurrent IgG secretion was not increased [8,14]. Furthermore, IgE synthesis by PBMC from allergic rhinitis donors is higher following exposure to allergens such as grass pollen or ragweed pollen [19,20].

Assuming that up-regulation of expression, an increase in number of the suppressor T cell population, or both contribute to the induction and maintenance of atopic dermatitis, a successful therapy might be to reduce levels of T cells in the atopic skin. It should be noted, however, that several investigators have reported that as much as 40–50% of IgE released into the super-
natants of cultured PBMC from hyper IgE patients may represent IgE preformed in vivo. Therefore any experiments involving the measurement of de novo IgE synthesis by cultured atopic PBMC must include appropriate background controls for measurement of preformed IgE. Treatment of PBMC with protein inhibitors such as cycloheximide, freeze-thawing PBMC on day 0 followed by a 7-day culture period, and acid treatment of cell pellets at day 0 have all been suggested as appropriate methods to be used for assessment of background IgE secretion [21,22]. Nevertheless, regardless of the cell conditions used, all investigators have reported that B cells from atopic donors make substantially more IgE than normal B cells in vitro. The basis for this difference is not well understood but has important implications for understanding the basis of the human reaginic response.

Several laboratories have examined the effects of normal T cells on IgE production by cultured PBMC from patients with severe AD and/or the HIE. In each case, unfractionated T cells from haploidentical or normal T cells suppressed spontaneous de novo IgE production by cultured PBMC from patients with the HIE and/or severe AD [8,15–18]. Since patients with HIE and severe AD have a selective deficiency of circulating T8+ cells, Geha et al [8] investigated the effects of normal T8+ suppressor/cytotoxic T cells and T4+ helper/inducer T cells on IgE synthesis by PBMC from these patients. It was found that spontaneous de novo IgE synthesis by cultured PBMC from these patients could be suppressed by normal parental T8+ T cells but not T4+ T cells. However, since Katz [23] has demonstrated that allelogeneic interactions result in the production of IgE-specific suppressor factors, the possibility that results from the latter co-culture studies were due to allelogeneic effects could not be excluded. In this regard, we observed that abnormally elevated IgE synthesis by cultured PBMC from patients with acute GVH disease could be suppressed by T8+ cells from normal histoidentical siblings [14]. Furthermore, T cells from patients who had recovered from acute GVH disease could effectively suppress IgE synthesis by thawed autologous cultured PBMC that has been cryopreserved during acute GVH.

These results supported the hypothesis that the elevated serum IgE levels in severe AD, acute GVH disease and HIE were due in part to a relative deficiency of suppressor T cells bearing the T8 surface antigen.

**REQUIREMENTS FOR THE INDUCTION OF IgE SYNTHESIS BY NORMAL B CELLS**

**Role of Soluble Factors From Hyper IgE T Cells**

To date, most studies of human IgE synthesis in vitro have been restricted to the detection of spontaneous IgE synthesis by in vivo activated lymphocytes from atopic donors. Such studies have been fraught with difficulties because the amounts of IgE secreted into culture supernatants are extremely small (in the picogram to few nanogram range). Since these same cultures frequently have 100–1000 times more IgG present in them, it is crucial that highly specific antisera to IgE be used in the assays for IgE. Furthermore, as mentioned above, preformed IgE bound to cell membranes of basophils, monocytes, T and B cells has to be accurately determined and its value subtracted from the total IgE measured in cultures. Finally, it is likely that a significant proportion of IgE produced in such cultures are secreted by terminally differentiated IgE plasma cells which are not subject to the same degree of T cell regulation as resting B cells. Thus, to further our understanding of the mechanisms controlling the human IgE response there has been considerable interest in developing model systems in which in vitro IgE production can be induced in nonatopic subjects and augmented in atopic subjects.

Since pokeweed mitogen (PWM) is a potent T cell dependent activator of B cells for IgG, IgA, and IgM synthesis, numerous laboratories have studied the ability of PWM to induce human PBL to synthesize IgE. Conflicting results were obtained primarily because some laboratories utilized antisera to IgE myeloma P.S. which cross-reacted with idiotypic determinants on polyclonal immunoglobulin of other isotopes [24]. In most studies including our own [14], when appropriately specific antisera was used, PWM failed to stimulate IgE synthesis by normal PBMC and inhibited IgE synthesis by atopic PBMC [14–18]. Furthermore, T cell independent B cell activators such as *Staphylococcus aureus* Cowan strain and Epstein-Barr virus has also failed to induce normal B cells to produce IgE in vitro [14].

The failure of normal PBL to synthesize IgE was not due to the presence of suppressor T cells of the T8 phenotype. Indeed, elimination of T8+ suppressor T cells from PBMC by treatment with OKT8 antibody and complement enhanced IgG production but did not reverse the inability of normal lymphocytes to synthesize IgE following stimulation with PWM or Epstein-Barr virus [14]. These results suggested two possibilities: (1) IgE precursor B cells were not present in the circulation of normal donors; and (2) the activation of IgE B cells require T cell signals not generated by normal T cells under experimental conditions known to generate T cell for the differentiation of IgG B cells. The recent finding by Lanzaetveca [25] that alloreactive T cell clones can induce normal peripheral blood B cells to produce large amounts of IgE, IgG, and IgM suggests that IgE precursor B cells are present in the circulation.

Since PBMC from patients with the HIE, severe AD, and acute GVH disease spontaneously synthesize high levels of IgE in vitro, we evaluated their T cells for the secretion of soluble factors capable of inducing IgE synthesis by normal B cells [14,26]. Purified peripheral blood T cells of patients suffering from these 3 hyper IgE states were cultured at 1.0 × 10^4 cells/ml in RPMI-1640 culture medium supplemented with 10% fetal calf serum. After 24 h, the culture supernatants were collected and assessed for their ability to induce immunoglobulin synthesis in cultures of normal B cells. Supernatants of T cells from patients with elevated serum IgE induced significant IgE synthesis by normal B cells whereas supernatants from the T cells of normal subjects did not induce IgE synthesis by normal B cells. In contrast, supernatants from T cells of hyper IgE patients and normal patients enhanced IgG synthesis by normal B cells to the same degree. These results suggest an isotype specific helper factor(s) for IgE was released by T cells from patients with elevated serum IgE. Recently, Romagnani et al [27] have also reported that T cells from patients with severe AD secrete soluble factors which stimulate IgE but not IgG production in vitro by B cells from normal or grass pollen sensitive patients with allergic rhinitis. These results suggest that T cells from hyper IgE patients but not normal donors secrete helper factors that are required for the induction of IgE synthesis by normal B cells.

Characterization of this immune IgE-specific helper factor revealed that it shared several physiochemical characteristics with the IgE-potentiating factor described by Yodoi et al [3,28]: (refer to table I). Treatment of the hyper IgE T cells with tunicamycin, a glycosylation inhibitor, or cycloheximide blocked the generation of IgE helper factor. Furthermore, treatment of T cell supernatants containing IgE helper factor with insolubilized trypsin or insolubilized neuraminidase markedly reduced the capacity of these supernatants to induce IgE synthesis in cultures of normal B cells.

**Induction of IgE Synthesis by Human Alloreactive T Cell Clones**

It has been firmly established that T cells can activate B cells during the course of a mixed lymphocyte reaction. However, the low frequency of alloreactive T cells and the concomitant activation of alloreactive suppressor/cytotoxic T cells has limited the usefulness of allogeneic systems for the activation
of B cells. Recently, Lanzavecchia [25] reported that alloreac­
tive T cell clones can trigger human peripheral blood B cells to
proliferate and secrete high levels of immunoglobulin of all
isotypes including IgE antibody. This report, however, did not
identify whether atopic or nonatopic B cells were being used as
stimulator cells in their experiments.

We have found that B cells from both nonatopic donors as
well as atopic donors synthesize IgE, IgG, IgM, and IgA in large
quantities when cultured with alloreactive helper T cell clones
that recognize determinants expressed by the stimulator B cells.
However, only B cells from allergic donors but not from normal
subjects can be induced to secrete IgE via a bystander effect
when cultured with T cell clones which are stimulated by
antigenic determinants not expressed by the indicator B cells.
On the other hand, IgG, IgM, and IgA synthesis could be
enhanced to the same levels in both atopic and normal donors
via the same bystander conditions used in the latter experi­
ments.

These results suggest that precursor IgE B cells are present
in normal peripheral blood although probably at lower numbers
than found in atopic subjects. Furthermore, precursor IgE B
cells circulating in nonatopic donors are in the resting or G0
phase and require cognate stimulation (direct T-B cell inter­
action) to induce IgE synthesis. In contrast, atopic B cells can
be stimulated to produce IgE either under conditions of cognate
recognition or innocent bystander where soluble factors se­
creted during the course of an alloreaction drive preactivated
IgE B cells to produce more IgE (Table I). These experiments
suggest that both resting and preactivated precursor IgE B cells
are present in atopic donors. Further studies using purified B
subpopulations and better characterized soluble T cell
factors are in progress to clarify the various stages and signals
which allow precursor IgE B cells to differentiate into IgE
secreting plasma cells.

ISOTYPE SPECIFIC REGULATION OF THE HUMAN
IgE RESPONSE BY T CELL-DERIVED
IgE-BINDING FACTORS

The observations made in rodents that IgE-binding factors
secreted by FcR+ T cells play an important role in the
specific regulation of IgE synthesis have stirred considerable
interest in the culture of human peripheral blood FcR+ T
and the isolation of IgE-binding factors from such cells. The
subpopulation of human peripheral blood T cells that bear Fc
receptors for IgE as detected by rosette formation with IgE-
coated ox erythrocytes is usually less than 0.1% of isolated T
cells from nonatopic donors [29, 30]. Ragweed-sensitive patients
with allergic rhinitis, however, have been reported to have levels of
FcR+ T cells as high as 0.5–1.4% of isolated T cells [31].
Furthermore, Yodoi and Ishizaka [32] demonstrated that FcR+ lymphocytes could be induced in vitro by activation of lymphocytes
from ragweed-sensitive patients with ragweed antigen E followed
by incubation with IgE. A subsequent report by Ishi­
zaka and Sandberg [33] found that peripheral blood lymphocytes
from ragweed-sensitive patients formed IgE binding fac­
tors when they were incubated with ragweed antigen E in the
presence of human myeloma IgE. Culture filtrates of these cells
inhibited rosette formation of FcR+ RPMI-8866 lymphoblas­
toid cells with IgE-coated ox red cells and could be absorbed
with IgE-Sepharose. IgE binding factors were also obtained with
human T cells activated by alloantigen or cultured in IL-
2 containing medium with IgE. The functional activity of these
IgE binding factors was not defined. Nevertheless, if the regu­
lation of human IgE synthesis is analogous to the rodent model,
one would expect to find that FcR+ T cells from patients with
hyper IgE states are responsible for the secretion of IgE-
potentiating factors.

T cells from patients with the hyper IgE syndrome are
continuously exposed to plasma IgE levels ranging from 10–
100 μg/ml and are frequently undergoing antigenic stimulation
due to repeated severe infections. Based on data derived from
experimental animals, one would expect to find increased num­
bers of circulating FcR+ T cells in patients with the HIE. To
detect FcR+ T cells, we incubated purified T cells from pa­
tients with hyper IgE syndrome and T cells from normal donors
with 10 μg/ml human myeloma IgE followed by immunosorbent
fluorescein-labelled goat anti-human IgE. T cells from 6 nona­
topic donors (serum IgE < 50) had FcR+ T cells ranging from
0–1.0. In contrast, the percentage of FcR+ T cells from 2
patients repeated on several occasions fluctuated from 2.0–
8.5%.

FcR+ T cells and FcR– T cells were sorted on a Becton-
Dickinson FACSV-IV cell sorter and long term T cell lines were
determined by maintaining them in RPMI-10% FCS, interleu­
in-2 and irradiated autologous PBMC [34]. The majority of
donors (75–90%) in the FcR+ T cell lines continued to express
FcR after 2 months of continuous cell culture.

Supernatants from the FcR+ T cell line but not the FcR–
T cell lines secreted factors which potentiated IgE but not IgG
production by B cells from patients with allergic rhinitis but
not B cells from normal nonatopic donors [34] (Table III).
These IgE-potentiating factors bound to immobilized IgE but
not to immobilized IgG, IgA, or bovine serum albumin and lost
their IgE-potentiating activity after incubation with insolubilized
trypsin or neuraminidase. Furthermore, the IgE-potentiating
factor secreted by these cultures acted as a differentiation
signal for IgE B cells rather than an isotype switch factor. A
switch factor would be expected to induce B cells which do not
express IgE on their surface to become IgE bearing B cells and
to secrete IgE. However, the IgE-binding factor present in
culture supernatants from hyper IgE patients was not found to
be a switch factor because: (1) it did not induce normal B cells
to secrete IgE, and (2) because removal of IgE-bearing B cells
obtained from allergic rhinitis patients by absorption over anti-
IgE coated Petri dishes greatly reduced their IgE response to
the IgE-binding factor but not their IgG response to PWM.
Cytotfluorographic analysis of the FcR+ T cell line from hyper
IgE patients revealed a predominance of T cells bearing the
T3, T4, Ia activated helper/inducer T cell phenotype. In this
regard Mitsuya et al [35] reported a patient with Sézary syn­
drome and serum IgE of 563,640 IU/ml whose peripheral T
cells were 98–100% Leu 3a,b positive (same helper/inducer T
cell population stained by the OKT4 monoclonal antibody).
These T cells provided IgE specific help in vitro.

Kishimoto and co-workers have also investigated the func­
tional activity of T cell derived IgE binding factors from pa­

| Table II. Type of interactions required for induction of IgE synthesis by human alloreactive T cell clones |
| --- | --- | --- |
| Type of interaction | IgE production by Atopic B cells | Normal B Cells |
| Cognate stimulation | ++++ | ++ |
| Noncognate bystander | ++ | – |

| Table III. Enhancement of IgE synthesis by supernatants of T Cell lines derived from 2 patients with the hyper IgE syndrome |
| --- | --- | --- | --- |
| Source of supernatant | Supernatant | Net IgE (ng/ml) | Net IgG (ng/ml) |
| Patient #1 | FcR+ line | 1,150 | 1,250 |
| Patient #1 | FcR– | 800 | |
| Patient #2 | FcR+ line | 7,700 | 1,125 |
| Patient #2 | FcR– | 1,700 | 1,300 |

* Reproduced in part from Young MC, Leung DYM, Geha RS: Production of IgE potentiating factor in man by T cell lines bearing Fc receptors for IgE. Eur J Immunol, in press, [34].
* The effect of culture supernatants from FcR+ and FcR– T cell lines were tested on B cells from patients with allergic rhinitis.
patients with pulmonary tuberculosis [36]. T cells from the latter patients incubated with PPD plus IgE for 5 days were found to have suppressive effect on the polyclonal IgE response induced by PWM plus Staphylococcus aureus strain Cowan I. The direct addition of these PPD-activated T cells, as well as the cultured supernatants from the activated T cells, suppressed the IgE response without affecting the IgG response. The IgE-specific suppressive activity in the supernatants was specifically absorbed by an IgE column but not an IgG column and could be eluted with acid buffer. These investigators concluded that T cells from patients with tuberculosis activated with PPD in the presence of IgE secreted IgE binding factors which specifically suppressed IgE synthesis.

Since the yield of IgE binding factors from these in vitro culture systems are too small for extensive characterization, several investigators have attempted to derived human T cell hybridomas which produce IgE-binding factors. In a recent report by Huff and Ishizaka [37] normal human T cells proliferating in IL-2 containing medium were incubated with human IgE, and the cells fused with the human T-cell line CEM. Five hybridomas were obtained which formed IgE-binding factors upon incubation with human IgE. The IgE-binding factors formed by 4 hybridomas had a molecular weight between 25,000 and 30,000 whereas one hybridoma formed IgE-binding factors of 30,000 to 15,000 molecular weight, molecular sizes comparable to those formed by rat lymphocytes. All the IgE binding factors obtained by Huff and Ishizaka had affinity for concanavalin A, suggesting that the factor contained N-linked, mannosereich oligosaccharides. Of considerable interest is that these investigators demonstrated low affinity binding of human IgE-binding factors for rat IgE. As a result, they assessed the effect of these purified human IgE-binding factors on the IgE forming cell response of rat mesenteric lymph node cells. These investigators found that purified IgE-binding factor from one of their human T cell hybridomas selectively potentiated the IgE response.

Recently, we successfully established human T cell hybridoma lines derived from T cells of patients with hyper IgE syndrome [38]. Supernatants from T cell hybridomas bearing Fc receptors for IgE were found to secrete significant amounts of soluble factors which enhanced IgE synthesis by B cells from patients with allergic rhinitis. Hybridoma supernatants passed over IgE-conjugated Sepharose but not IgG-Sepharose lost IgE enhancing activity, and the IgE enhancing activity was recovered from the IgE-Sepharose beads by acid elution.

The in vivo significance of these IgE binding factors is suggested by the observation that low molecular weight IgE binding factors can be isolated from sera of patients with HIE [39]. We found that unfraccionated IgE binding factors from 2 of 3 hyper IgE patients enhanced IgE but not IgG production by B cells from patients with allergic rhinitis. Separation of these IgE-binding factors over Sepharose conjugated with concanavalin A revealed a mixture of IgE regulatory activities. IgE suppressor factors passed through the concanavalin A column whereas IgE enhancing factors bound to concanavalin A. In contrast, small molecular weight IgE binding factors from sera of nonatopic donors exclusively contain IgE suppressor activity. In 2 of 3 patients with the HIE infusion with normal plasma resulted in decreased rates of IgE synthesis by their PBMC accompanied by a transitory drop in serum IgE levels [40,41].

CONCLUSION

The data presented in this review suggest that T lymphocytes play an important role in the isotype-specific regulation of the human IgE response (Fig 1). Resting B cells can be activated to secrete IgE and other immunoglobulin isotypes by cognate interaction with alloreactive helper T cell clones. Subsequent isotype-specific IgE antibody secretion is modulated by IgE binding factors derived from FcR+ T cells. The function of these IgE binding factors are determined by their degree of N-glycosylation. IgE-enhancing factors are more highly glycosylated than IgE suppressor factors and require terminal sialic acid for their activity. A balance between these two signals will determine the development of the IgE antibody response. The recent availability of T cell hybridomas which secrete IgE binding factors should make it possible to isolate these factors in sufficient quantity to characterize their physiochemical features and study their mode of action in greater detail. It is hoped that an understanding of the mechanisms underlying isotype specific regulation of IgE synthesis in man will direct us to more effective therapy of IgE mediated disorders.

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FIG 1. Summary of potential cellular interactions involved in the regulation of human IgE synthesis. Starting from left to right, resting precursor IgE B cells are activated by T-B cognate interaction. T cell-derived IgE-binding factors (IgE-BF) act on preactivated IgE bearing B cells to enhance or suppress further differentiation into IgE-secreting plasma cells. (*) denotes lymphocyte activation.


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