

Regulation and deregulation of human IgE synthesis

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The IgE antibody system is among the most sophisticated of immune defense mechanisms. IgE molecules bind specifically and avidly to receptors localized on the surface of tissue mast cells and circulating basophils. These cells can produce and release several potent mediators after antigen interaction with a small number of surface-bound IgE molecules. The enormous amplification power of the IgE antibody system not only provides an important defense mechanism against parasites, but is also responsible for a number of clinical disorders. The human pathological condition most commonly associated with hyperproduction of IgE is atopy, the familial allergic disorder of immediate-type hypersensitivity to environmental allergens. In this paper Sergio Romagnani summarizes current understanding of the mechanisms involved in IgE regulation. Such studies are of primary importance in defining alterations responsible for the pathological conditions characterized by hyperproduction of IgE.

Early studies in rodents suggested that IgE production could be regulated by antigen-specific helper and suppressor T cells, and by isotype-specific factors showing affinity for IgE (the so-called IgE-binding factors)¹. More recently a further pathway of IgE regulation, essentially based on the reciprocal activity of interleukin 4 (IL-4) and gamma-interferon (IFN- γ), has been discovered in mice^{2,3}. Further research has provided substantial information on the mechanisms of regulation of human IgE synthesis, and the alterations responsible for its loss of regulation in disorders characterized by hyperproduction of IgE.

IL-4 and IFN- γ reciprocally regulate human IgE synthesis *in vitro*

The first unambiguous demonstration of *in-vitro*-induced IgE synthesis in normal B cells was provided by assaying the activity of selected alloreactive and autoreactive T-cell clones⁴⁻⁷. In subsequent studies, it was shown that a significant proportion of phytohemagglutinin (PHA)-induced T-cell clones, obtained from either atopic or nonatopic individuals, could support IgE synthesis in either autologous or allogeneic normal B cells^{8,9}. Supernatants of PHA- or anti-CD3 antibody-stimulated T-cell clones, selected for their helper activity for IgE synthesis, also induced IgE production¹⁰. Interestingly, the helper activity of these supernatants was strongly inhibited by the addition of recombinant IFN- γ ^{10,11}. When PHA-induced T-cell clones or their supernatants were assayed for their ability to induce IgE synthesis and to produce IL-2, IL-4 and IFN- γ , a significant positive correlation between helper function for IgE and production of IL-4 was found¹². In contrast, there was a significant inverse correlation between the IgE helper activity of T-cell clones (or supernatants derived from them) and their ability to produce IFN- γ (Fig. 1)^{12,13}. This opposite regulatory role for IL-4 and IFN- γ in the synthesis of human IgE was confirmed by the observations that (1) human recombi-

nant IL-4 can induce the synthesis of IgE in peripheral blood mononuclear cells (PBMCs) and (2) this effect is inhibited by addition of recombinant IFN- γ ^{12,14,15}. More importantly, an anti-IL-4 antibody consistently abolished the IgE synthesis induced by all active T-cell clones or their supernatants tested, whereas it had little, if any, inhibitory effect on the synthesis of IgM and IgG¹².

A two signal model for the induction of human IgE synthesis

Is the presence of IL-4 sufficient for the induction of human IgE synthesis? Both recombinant IL-4 and IL-4-containing supernatants are ineffective in inducing IgE synthesis in highly purified tonsillar B-cell suspensions containing less than 1% T lymphocytes and monocytes¹². The IL-4-dependent IgE synthesis can be restored by the readdition of appropriate concentrations of autologous or allogeneic T cells, and the inclusion of monocytes potentiates this response^{14,16}.

Blocking experiments were performed to determine how T cells and monocytes collaborate with IL-4 in the induction of IgE synthesis. Both anti-IL-2 and anti-IL-6 antibodies inhibit the synthesis of IgE induced by IL-4 in PBMC suspensions, which suggests that these cytokines may have a role in the induction of IL-4-dependent IgE synthesis¹⁶. Indeed it has previously been suggested that endogenously produced IL-6 is essential for the synthesis of IgE¹⁷, a finding that may explain the potentiating effect of monocytes¹⁶. However, the fact that IL-2 and IL-6 influence T cells and B cells makes it difficult to establish whether they act directly on B cells, or merely increase the survival of, or enhance the secretion of other cytokines by, T cells. We¹⁶, and others¹⁸, have been unable to reconstitute IgE synthesis by highly purified B cells using mixtures of optimal concentrations of IL-4, IL-2, IL-6, IL-1 and tumor necrosis factor α (TNF- α). This finding suggests that T cells and monocytes do not support IL-4-dependent IgE synthesis solely via the production of other cytokines.

Direct evidence that a physical interaction between T and B cells is required for IL-4-dependent IgE synthesis to occur is provided by assaying IgE synthesis in a double chamber system. When T and B cells are cultured in different chambers separated by a millipore membrane that is permeable to molecules but not to cells, IL-4 cannot induce the synthesis of IgE. IgE synthesis occurs only when T and B cells are cultured in the same chamber^{18,19}. Kinetic studies have provided evidence that the physical interaction with T cells is required before the signal provided by IL-4: IgE synthesis does not occur when B cells are cultured with IL-4 for three to four days before the addition of T cells, while enhancement of IgE synthesis is obtained when the cells are cocultured before the addition of IL-4^{19,20}.

This suggests that IgE synthesis is dependent on two main signals provided by T cells – the first is mediated by physical interaction between T and B cells, and the second

by T-cell-derived (or exogenously added) IL-4. A role for other factors, such as low molecular weight B-cell growth factor (LMW-BCGF)²¹, IL-5 (Ref. 22) and the soluble Fc ϵ RII (CD23)²³, in the synthesis of IL-4-dependent IgE synthesis has also been suggested. However, at least as far as LMW-BCGF and soluble CD23 antigen are concerned, more recent data obtained by assaying the activity of recombinant molecules do not confirm those obtained with the semipurified preparations (author's unpublished data and T. Kishimoto, pers. commun.). Recently it has been shown that infection with Epstein-Barr virus (EBV) in the presence of IL-4 enables B cells to produce IgE²⁴, suggesting that EBV infection can mimic the signal usually provided by T cells for the induction of IL-4-dependent IgE synthesis.

Both cognate and noncognate T cell-B cell interaction can support IL-4-dependent IgE synthesis

It has recently been suggested that cognate interaction between T and B cells (recognition by the T-cell receptor (TCR) of major histocompatibility complex (MHC) class II antigens in association with self or foreign peptides) is an absolute requirement for IL-4-dependent IgE synthesis¹⁸. However, data obtained in our laboratory suggest that both noncognate and cognate interactions with T cells render B cells susceptible to the activity of IL-4. First, most PHA-induced CD4⁺, and even some CD8⁺, T-cell clones can support the synthesis of IgE in B cells from randomly selected donors, if exogenous IL-4 is added in culture¹⁹. Additional evidence is provided by assaying the activity of an alloreactive T-cell clone (TR46). This clone can produce IL-4, but not IFN- γ , and can induce the synthesis of IgE when cultured with B cells possessing the appropriate alloantigen (HLA-DR4). When the DR4-positive B cells are irradiated, IgE synthesis does not occur, but it can be restored by the addition of DR4-negative unirradiated B cells. Furthermore, in the presence of exogenously added IL-4, TR46 enables B cells from all donors tested to produce IgE, irrespective of whether they possessed the DR4 alloantigen¹⁹. In all these experiments IgE synthesis was inhibited by the addition of either anti-IL-4 antibody or IFN- γ (Table 1)^{19,25}.

Several T-cell clones specific for soluble antigens, such as *Bordetella pertussis* exotoxin, tetanus toxoid (TT) and *Dermatophagoides pteronyssinus* (DP) extract components have been assessed for their profile of cytokine production and their ability to induce IgE synthesis in autologous B cells after stimulation with the specific antigen. Only T-cell clones producing IL-4 and little or no IFN- γ provided helper function for IgE synthesis under conditions of cognate interaction. However, many T-cell clones, including those producing IFN- γ but not IL-4 in response to the specific antigen, induced IgE synthesis when cultured with autologous B cells without antigen, but in the presence of exogenously added IL-4 (Ref. 26). This is in contrast to the results reported by Vercelli *et al.*¹⁸, who failed to induce IgE synthesis in bystander B cells cultured with T-cell clones plus IL-4. These authors, however, assessed the activity of only two T-cell clones under these experimental conditions, whereas many T-cell clones have been tested in our laboratory.

It might be suggested that under the above experimental conditions IgE synthesis is the result of cognate interaction between B cells and a few autoreactive T cells contaminating the B-cell population, rather than noncog-

nate interaction. Against this possibility, it has been shown that cells of a subclone of the mouse EL-4 thymoma can support synthesis of IgM, IgG and IgA by human B cells in the presence of phorbolmyristate acetate (PMA). When B cells are added to EL-4 cultures at an average of one per well, the pattern of Ig secreted by the B-cell clones is found to be similar, thus excluding requirements for human T cells for the EL-4/PMA-dependent

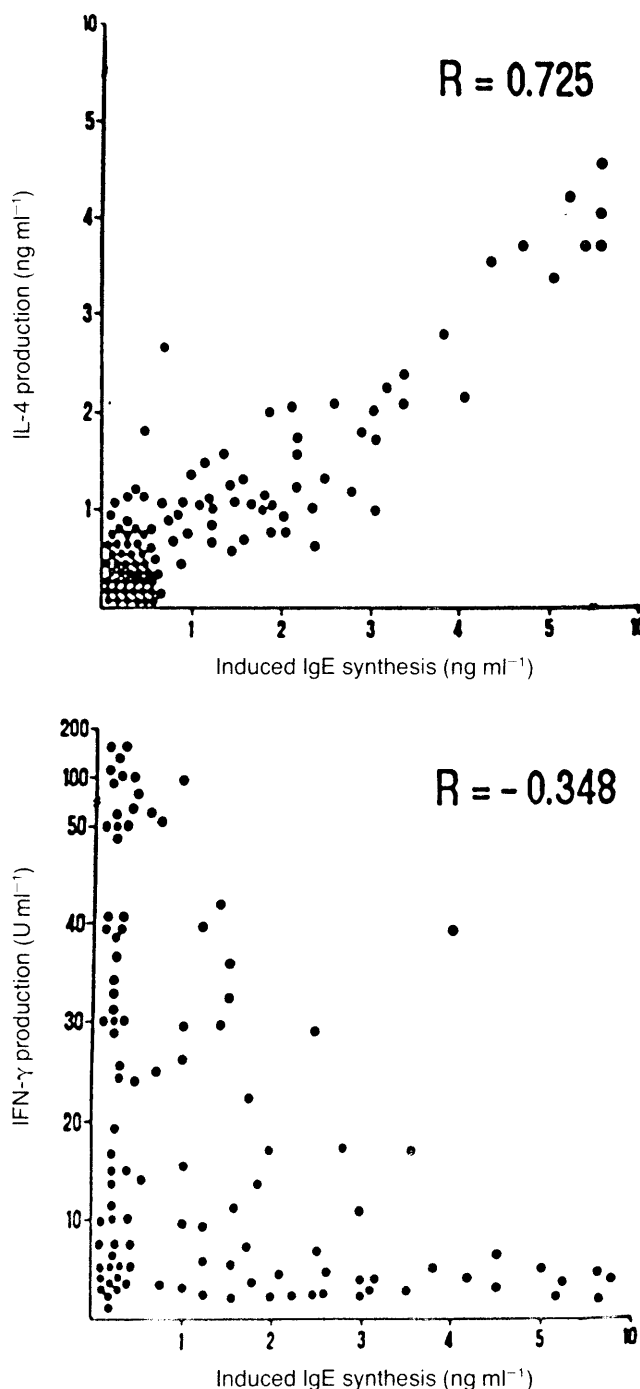


Fig. 1. The ability of human T-cell clones to induce IgE synthesis versus their ability to produce IL-4 or IFN- γ . Each clone (1×10^6 blasts ml^{-1}) was stimulated for 24 h with PHA (1% vol vol⁻¹) and the cell-free supernatant assayed for IL-4 by ELISA and for IFN- γ by RIA. T blasts from each clone were also cultured for 10 days with B cells from two different donors and supernatants from these cultures assayed for their IgE content by calibrated RIA. Mean values from duplicate IL-4 or IFN- γ determinations were plotted against mean IgE values of duplicate determinations performed on B-cell cultures from two different donors. Data from Ref. 12.

Table 1. The alloreactive T-cell clone TR46 induces 'bystander' B cells to synthesize IgE in the presence of endogenously or exogenously added IL-4

Stimulator B cells (DR 4,5)	Bystander B cells (DR 3,7)	TR46 T-cell clone DR4-specific	Exogenous IL-4 (200 U ml ⁻¹)	Medium	IgE synthesis (ng ml ⁻¹) IFN- γ (100 U ml ⁻¹)	Anti-IL-4 Ab (1:250)
+	+	-	+	<0.3	<0.3	<0.3
+	-	+	-	11.0	1.3	2.5
-	+	+	-	<0.3	<0.3	<0.3
+ ^a	+	+	-	5.0	0.6	0.8
+ ^a	-	+	-	<0.3	<0.3	<0.3
-	+	+	+	7.5	1.2	0.9

The T-cell clone TR46 was obtained by a cloning technique described in Ref. 5. This clone recognized the HLA-DR4 alloantigen and was selected because of its ability to produce high levels of IL-4 and no IFN- γ in response to PHA (1% vol vol⁻¹) or to the original mitomycin-C-treated stimulatory cells. In the assay for IgE synthesis 2×10^5 T blasts were cultured with 2×10^5 B cells for 10 days. ^aB cells were irradiated with 5 000 rads. Data from Refs 19 and 25.

B-cell response²⁷. The addition of IL-4 to such a system also results in the production of large amounts of IgE²⁸. These data have recently been confirmed in our laboratory. Furthermore, we have shown that treatment of PMA-prestimulated EL-4 thymocytes with cyclosporin A or paraformaldehyde (to block the release of cytokines) had no inhibitory effect on the IgE synthesis induced under these experimental conditions (unpublished results).

Taken together, these data clearly suggest that cognate interaction is required to induce T cells to produce IL-4, but is not essential for providing the first (physical) signal to B cells. Noncognate, contact-dependent B-cell activation can also function as an efficient signal for IL-4-dependent IgE synthesis^{19,25}. This conclusion is consistent with recently reported findings showing that both MHC class-II-restricted and MHC class-II-unrestricted physical interaction with helper T cells can lead B cells into cell

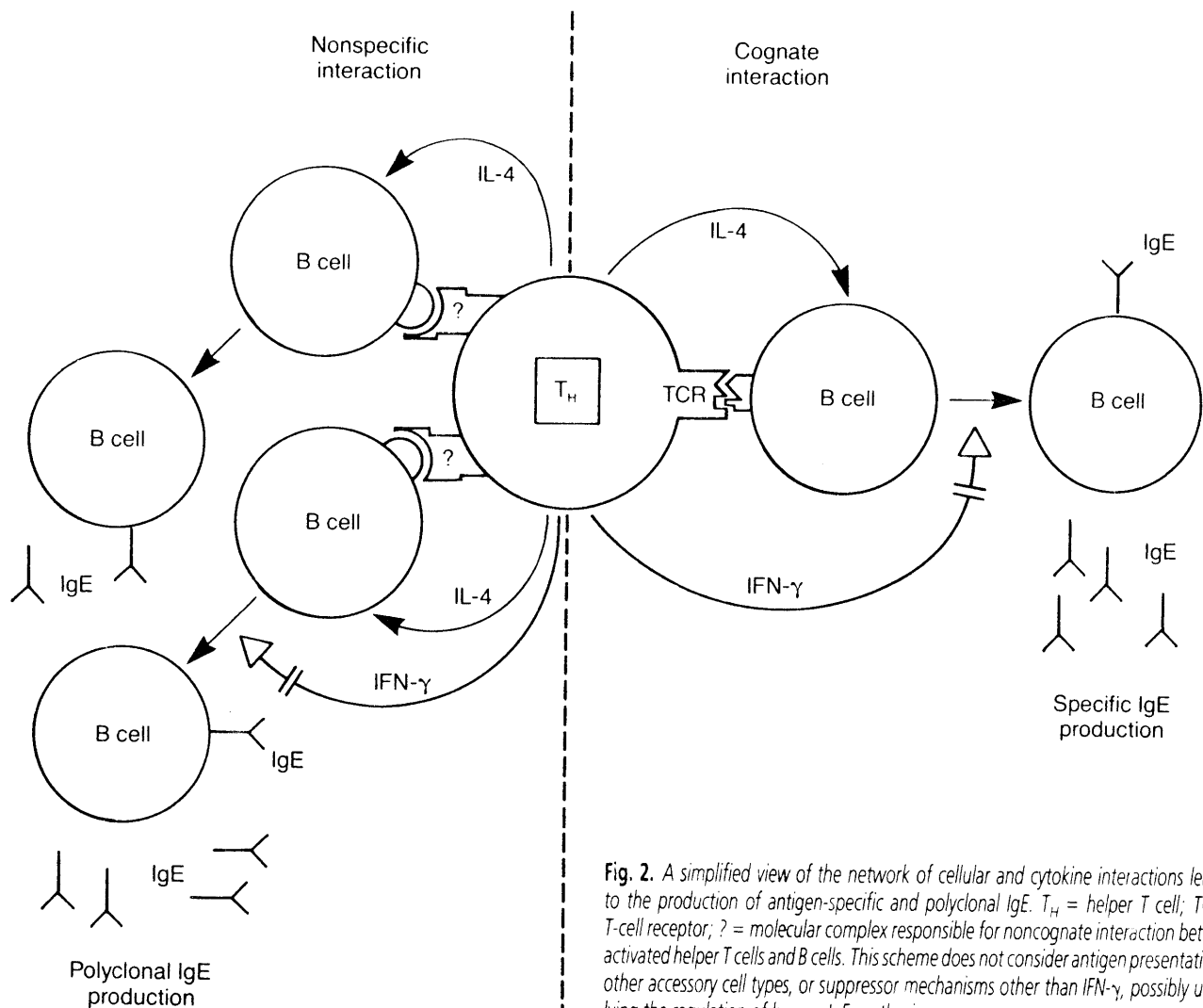


Fig. 2. A simplified view of the network of cellular and cytokine interactions leading to the production of antigen-specific and polyclonal IgE. T_H = helper T cell; TCR = T-cell receptor; ? = molecular complex responsible for noncognate interaction between activated helper T cells and B cells. This scheme does not consider antigen presentation by other accessory cell types, or suppressor mechanisms other than IFN- γ , possibly underlying the regulation of human IgE synthesis.

cycle, rendering them susceptible to the action of cytokines²⁹⁻³¹. The nature of molecule(s) that are responsible for nonspecific physical interaction occurring between T and B cells is still unclear. In preliminary experiments, we have shown that such a molecule is distinct from the TCR-CD3 complex, but fully (even if transiently) expressed on the membrane of TCR-CD3-activated T cells¹⁹.

The pathophysiological implications of these findings are noteworthy. When a B cell acts as an antigen-presenting cell for the helper T cell, cognate interaction occurs and provides the first signal to the B cell. If the T cell can release IL-4, in the absence of inhibitory amounts of IFN- γ , production of antigen-specific IgE results. However, B cells specific for other antigens present in the microenvironment can receive both a physical nonspecific signal, and IL-4, from activated T cells, thus being induced to produce IgE (Fig. 2). This may explain why in some pathological conditions, such as parasitic infestations or the acute phase of graft-versus-host disease (GVHD), strong polyclonal IgE production occurs. Obviously this is an oversimplified view of the mechanisms involved in the regulation of IgE synthesis. It does not consider that antigens can be presented by other accessory cell types, such as macrophages and dendritic cells. Furthermore, the demonstration that in the EL-4-PMA-IL-4 model IgE production is much higher than in models with human T-cell clones that cannot produce IFN- γ indicates other suppressive activities.

Disregulation of cytokine production in disorders characterized by hyperproduction of IgE

The findings reported above encouraged investigations into whether alterations in IgE-regulatory mechanisms are involved in the genesis of human diseases characterized by hyperproduction of IgE. Some interesting results have been obtained in patients with the hyper-IgE (or Buckley's) syndrome, parasitic infestations, vernal conjunctivitis and common atopic diseases.

Hyper-IgE syndrome

We first examined the ability of PBMC from four children with the hyper-IgE syndrome to produce different cytokines in response to stimulation with PHA. PBMC from all four children produced lower concentrations of IFN- γ than PBMC from eight age-matched healthy controls, particularly at lower cell concentrations³². Other groups have not shown such a difference, but have tested only high PBMC concentrations^{33,34}. Analysis at clonal level revealed that patients with the hyper-IgE syndrome had significantly lower proportions of circulating T cells that can produce IFN- γ and TNF- α (but not of T cells producing IL-2 or IL-4) in comparison with controls³¹. In addition, all four children with the hyper-IgE syndrome showed high proportions of circulating CD4⁺ helper T cells that can induce IgE synthesis in allogenic normal B cells. This helper activity for IgE synthesis correlated positively with IL-4 production by T cells and negatively with the ability of the same T cells to produce IFN- γ .

IFN- γ inhibits the synthesis of IgE and both IFN- γ and TNF- α play an important role in cell-mediated immune reactions and in the defense against infectious agents^{35,36}. It is reasonable to suggest, therefore, that the defective production of IFN- γ accounts for hyperproduction of IgE and that the combined defect of IFN- γ and

Table 2. Altered proportions of T cells that can be induced to produce IL-4 or IFN- γ in the peripheral blood of patients with parasitic infestations

Diagnosis	Number of CD4 ⁺ T-cell clones tested	Number of T-cell clones producing:		
		IL-4	IFN- γ	IL-2
Filariasis	38	19 (50%)	21 (55%)	20 (53%)
Filariasis	41	24 (58%)	24 (58%)	28 (68%)
Toxocariasis	37	21 (57%)	6 (16%)	20 (54%)
Toxocariasis	40	27 (67%)	15 (38%)	29 (72%)
Toxocariasis and Ascaridiasis	38	32 (84%)	21 (55%)	n.t.
All cases	194	123 ^a (63%)	87 ^c (45%)	
Healthy controls (4)	158	41 ^b (26%)	109 ^d (69%)	86 (54%)

T-cell clones were established from peripheral blood T-cell suspensions by stimulating single T cells with PHA (1% vol vol⁻¹) in the presence of irradiated feeder cells and IL-2, as described in Ref. 12. T blasts (1×10^6 ml⁻¹) were then stimulated for 24 h with PHA (1% vol vol⁻¹) and the supernatants assayed for the presence of IL-4, IFN- γ and IL-2, as described in Ref. 12. Supernatants containing more than 200 pg ml⁻¹ of IL-4, 10 U ml⁻¹ IFN- γ and 0.5 U ml⁻¹ of IL-2 were regarded as positive. ^aversus ^b: $\chi^2 = 49.0$; $p < 0.0005$. ^cversus ^d: $\chi^2 = 20.6$; $p < 0.0005$. n.t. = not tested. Data from Ref. 40.

TNF- α may contribute to the susceptibility to infections found in patients with the hyper-IgE syndrome³¹. It has recently been reported that *in vivo* injection of IFN- α or IFN- γ induces the reduction of serum IgE levels and results in the improvement of clinical manifestations in patients with the hyper-IgE syndrome or with atopic dermatitis^{37,38}.

Parasitic infections

It is well known that parasitic infection induces a marked production of IgE antibodies, most of which are not specific for parasite antigens. The mechanisms by which parasites stimulate IgE production are still unknown. Filarial parasite-specific T-cell lines release soluble factors that can induce IgE synthesis in normal B cells³⁹, but the nature of these factors has not been specified. Recently, we have examined a large number of PHA-induced T-cell clones established from the peripheral blood of five patients with parasitic infestations (two with filariasis, two with toxocariasis and one with toxocariasis and ascaridiasis) for their profile of IL-4 and IFN- γ production. Patients infested with parasites showed significantly higher proportions of IL-4-producing, and significantly lower proportions of IFN- γ -producing, CD4⁺ T-cell clones in comparison with controls (Table 2)⁴⁰. It is not known whether the IL-4-producing T-cell clones present in the circulation of these patients are specific for parasite antigen.

Vernal conjunctivitis

Vernal conjunctivitis (VC) is a seasonally recurrent, bilateral inflammation of the conjunctiva, distinguished by cobblestone papillae on the tarsal conjunctiva and by papillar hypertrophy on the limbal conjunctiva. Histological examination reveals infiltration in the substantia propria by lymphocytes, plasma cells, basophils, mast cells and especially eosinophils. Elevated levels of IgE are usually present in both the serum and tears of these

Table 3. CD4⁺ T cells that can be induced to produce IL-4, but not IFN- γ , accumulate in the conjunctival infiltrates of patients with vernal conjunctivitis

Source of CD4 ⁺ T-cell clones	Number of T-cell clones tested	Number of T-cell clones producing:		
		IL-4	IFN- γ	IL-4 and IFN- γ
Peripheral blood	53	9 (17%)	31 (58%)	13 (25%)
Conjunctiva	49	29 (59%)	9 (18%)	11 (33%)

PHA-induced T-cell clones were contemporarily established from peripheral blood and conjunctival infiltrates of three patients with vernal conjunctivitis, as described in Table 2. T blasts (1×10^6 ml⁻¹) were then stimulated for 24 h with PMA plus anti-CD3 antibody and the supernatants assayed for IL-4 and IFN- γ . See Table 2 for additional explanations. Data from Refs 26 and 40.

patients. An allergic etiology has been suggested, but little is known of its specific pathogenesis⁴¹.

We have recently established T-cell clones from cell suspensions of conjunctival fragments from three children with VC subjected to surgery and have assayed these T-cell clones for their helper activity for IgE synthesis and the production of IL-4 and IFN- γ . Most CD4⁺ T-cell clones obtained from the conjunctival infiltrate of the three patients showed helper function for IgE synthesis and could produce IL-4. In contrast, even after maximal stimulation, such as that delivered by PMA plus anti-CD3 antibody, very few CD4⁺ T-cell clones could produce IFN- γ (Table 3)^{26,40}. Recently, eye alterations histologically similar to those of VC have been observed in a cohort of IL-4 transgenic mice expressing IL-4 at the T-cell level (A.K. Abbas, pers. commun.). These findings suggest a role for dysregulation of IL-4 production in the genesis of these VC lesions.

Atopic diseases

Patients with common atopic diseases show an increased production of IgE which is usually limited to antibodies specific for environmental allergens, such as those derived from pollens, house dust mites, pets and fungal spores. Several significant associations have been drawn between particular HLA haplotypes and responsiveness to different purified allergens⁴² but the mechan-

ism behind genetically determined recognition of allergenic epitopes and IgE production is unclear. From the evidence reported above, one possibility is that allergens differ from other antigens in their ability to 'select' helper T cells with peculiar profiles of cytokine production. To explore this possibility, we have recently established DP- and TT-specific T-cell clones from PBMCs of one atopic donor showing both immediate-type hypersensitivity to DP and delayed cutaneous hypersensitivity to TT.

A total of 22 TT- and 12 DP-specific T-cell clones were obtained and assayed for their ability to produce IL-4 and IFN- γ in response to stimulation with either PMA plus anti-CD3 antibody or with specific antigen. Twenty-one of 22 TT-specific T-cell clones produced both IL-4 and IFN- γ in response to PMA plus anti-CD3 antibody. Eight out of 12 DP-specific T-cell clones also produced both IL-4 and IFN- γ , but four T-cell clones failed to produce IFN- γ in response to the same stimulation. When assayed with the specific antigen, the proportion of DP-specific T-cell clones that could produce IL-4, but not IFN- γ , was even higher (six out of 12), whereas only four out of 22 TT-specific T-cell clones showed a similar pattern of cytokine production (Table 4)²⁶. In addition, mean concentrations of IL-4 produced by DP-specific T-cell clones after stimulation with either PMA plus anti-CD3 antibody or specific antigen were significantly higher than those produced by TT-specific T-cell clones, whereas mean concentrations of IFN- γ were significantly lower (see legend of Table 4). These data suggest that in a given (atopic) individual, allergen-specific T-cell clones have a higher probability than T-cell clones specific for microbial antigens of belonging to the IL-4⁺, but not the IFN- γ -producing (IgE-helper) subset.

Summary and conclusions

This review summarizes current understanding of the role of cellular and molecular signals involved in the regulation of human IgE synthesis. It is well established that IL-4 and IFN- γ are the main regulatory cytokines of IgE production, with opposite effects on the synthesis of this immunoglobulin class. However, a prior physical interaction with activated T cells is required for B cells to synthesize IgE in response to IL-4. Cognate interaction with T cells producing IL-4, but not inhibitory amounts of

Table 4. Profile of IL-4 and IFN- γ production by *Dermatophagoides pteronyssinus* (DP)- and tetanus toxoid (TT)-specific T-cell clones established from the same individual

Antigen specificity	Number of CD4 ⁺ T-cell clones	PMA plus anti-CD3 antibody			Specific antigen (DP or TT)		
		IL-4 and IFN- γ	IFN- γ	IL-4	IL-4 and IFN- γ	IFN- γ	IL-4
TT	22	21	1	0	12	6	4
DP	12	8	0	4	2	4	6

DP- or TT-specific T-cell clones were established from peripheral blood T-cell suspensions of one atopic donor, displaying immediate-type hypersensitivity to DP and delayed cutaneous hypersensitivity to TT, as described in Ref. 43. Only CD4⁺ T-cell clones showing proliferative response to the specific antigen (mitogenic index greater than 10) in the presence of mitomycin-C-treated autologous non-T cells were selected and assayed for their ability to produce IL-4 and IFN- γ in response to either PMA plus anti-CD3 antibody or specific antigen. Mean values of IL-4 produced by TT- (p < 0.01). Mean values of IFN- γ produced under the same experimental conditions were 108 ± 15 and 58 ± 20 U ml⁻¹ (p < 0.05). Mean values of IL-4 produced by TT-specific and DP-specific T-cell clones after stimulation with PMA plus anti-CD3 antibody were 630 ± 117 and 1342 ± 514 pg ml⁻¹, respectively (p < 0.05). Mean values of IFN- γ produced under the same experimental conditions were 49 ± 8 and 16 ± 7 (p < 0.01). For additional explanations, see Table 2. Data from Ref. 26 and from Parronchi et al., submitted.

IFN- γ , leads to specific IgE antibody production. When high numbers of activated helper T cells with this profile of cytokine production are generated, noncognate interaction with B cells showing different specificities results in polyclonal IgE production. Other cytokines, such as IL-2 and IL-6, also contribute to the induction or potentiation of human IgE synthesis, but their role is not yet completely defined.

Imbalances between IL-4-producing and IFN- γ -producing helper T cells seem to be responsible for polyclonal IgE production in patients with the hyper-IgE syndrome and parasitic infestations. In the former there is a large reduction in the number of circulating T cells able to produce IFN- γ (and TNF- α), whereas proportions of circulating T cells that can be induced to produce IL-4 are significantly increased in the latter. Helper T cells that can produce IL-4, but not IFN- γ , and that can provide helper function for IgE synthesis accumulate in the conjunctiva of patients with vernal conjunctivitis. Finally, preliminary observations suggest that allergens may differ, at least in part, from other antigenic molecules in their ability to 'select', in atopic donors, helper T cells inducible to relatively high production of IL-4 and to low or undetectable production of IFN- γ . Thus, it is reasonable to suggest that the accumulation of helper T cells with peculiar profiles of cytokine production in target organs and 'selection' by allergens of this type of cell may contribute to the pathogenesis of IgE-mediated disorders.

This work was supported by grants from CNR (Finalized Project Oncology) and from AIRC.

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