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REVIEW

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Molecular regulation of human IgE synthesis

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Abstract Understanding the induction and regulation of IgE synthesis in human B cells is crucial to elucidate the molecular pathogenesis of IgE-dependent diseases. Experimental data, in part supported by clinical observations, suggests that IgE regulation is a complex process involving several cellular and molecular interactions. A two-signal model is accepted for the induction of IgE synthesis in human B cells. The first signal is provided by the cytokines interleukin 4 or 13, which are secreted by T cells, mast cells, and basophils. The second signal for the induction of IgE synthesis requires cell contact between T and B cells. Engagement of the B cell antigen CD40 by the CD40 ligand (CD40L) expressed on T cells leads to subsequent isotype switching during immunoglobulin synthesis in B cells. The CD40-CD40L interaction is well established as a key signal for the induction of isotype switching while the elucidation of the role of other cell-cell interactions, for example, through adhesion molecules, needs further study. An important counteracting cytokine for IgE synthesis is interferon (IFN) γ which is produced mainly by T lymphocytes. Several cell-contact molecules, cytokines, and various hormones have been shown to modulate IgE synthesis in vitro, suggesting a complex network of molecular events to be involved in the production of IgE. However, the relevance of these factors for IgE production in vivo requires further elucidation. Here we describe the molecular mechanisms known to be involved in the induction and regulation of human IgE synthesis and discuss the role of various molecules during this process. Furthermore, evidence is presented that the understanding of IgE synthesis provides a potential key for new therapeutic strategies in patients with IgE mediated diseases including atopic dermatitis.

Key words IgE-synthesis · Interleukin 4 · CD40 · B cells · CD40L

Abbreviations *CD40L* CD40 ligand · *IL* Interleukin · *IFN* Interferon · *STAT* Signal transducers and activators of transcription · *TGF* Transforming growth factor · *TNF* Tumor necrosis factor

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Introduction

IgE-dependent stimulation of tissue mast cells and their circulating counterparts, the blood basophils, constitutes one of the major effector systems of the immune response. Binding of allergen to IgE is followed by the rapid release of a variety of mediators, including histamine, leukotrienes, prostaglandins, and proteases which induce the rapid-onset, marked symptoms of immediate hypersensitivity reactions [1]. Clinically different organ reactivity results

in diverse clinical diseases such as hay fever (allergic rhinitis), allergic asthma, and urticaria as classical manifestations of IgE-dependent immediate hypersensitivity reactions [1]. Understanding the basic mechanism of IgE synthesis and its regulation are currently considered a key to unravel the pathogenesis of these diseases.

Production of IgE and other immunoglobulins is thought to be the result of reciprocal activation of T and B cells [2]. As a key initial step in the chain of events necessary for the induction of Ig production, resting B cells must bind allergens through their membrane bound antigen-specific Ig. After internalization of the allergen receptor complex allergens are processed and presented to T cells as peptide fragments in association with MHC II [3]. The MHC II complex is recognized by the T cell receptor, leading to antigen-specific T-B cell interaction in the presence of costimulatory molecules, an event which causes the activation of both T and B cells [4]. The interaction of these activated B and T cells then results in molecular and cellular events which provide signals necessary for Ig induction and the subsequent development of Ig-producing plasma cells [5]. The initial steps for the development of IgE-producing plasma cells are discussed below in further detail. The relevance of the cytokines interleukin (IL) 4 and 13 and the interaction between CD40 and the CD40 ligand (CD40L) for induction of IgE production is elucidated. Furthermore, the role of modulating effects by various molecules on IgE synthesis is illustrated. Finally, potential new therapeutic approaches to intervene with increased IgE production in atopic diseases are described.

Isotype switching and Ig synthesis

The antigen-binding specificity of an Ig molecule is determined by the NH_2 terminus of the Ig heavy and light chains, which is highly variable. By contrast, the COOH terminus of the heavy chain has a constant amino acid sequence which determines the effector functions of the Ig molecule, such as binding to Fc receptors on various cell types. The variable region of Ig is encoded by multiple germline elements which are assembled into complete V(D)J variable regions during B cell differentiation by a common enzymatic activity (recombinase) [6].

During an immune response a B lymphocyte can express different heavy chain isotypes sharing the same VDJ region. This phenomenon (heavy-class switching) allows a single B cell clone to produce antibodies that retain variable region specificity in association with a different CH region gene, i.e., with a different effector function. Before the switching event occurs, B cells express IgM or IgD on their surface. Class switching to IgA, IgE, or IgG results from a recombination event which juxtaposes a downstream constant heavy-chain gene (CH) to the expressed V(D)J genes [7]. Intervening sequences including the previously expressed CH gene are deleted (Fig. 1). Switch regions (S) flanking the CH genes (μ, γ, α, and ε) at the 5′ end serve as recognition sequences for joining DNA segments during the process of switch recombination (Fig. 1).

Ig class switching is always preceded by synthesis of germline Ig RNAs. Germline transcripts contain not only the spliced CH coding exons, but also a 100–500 bp up-

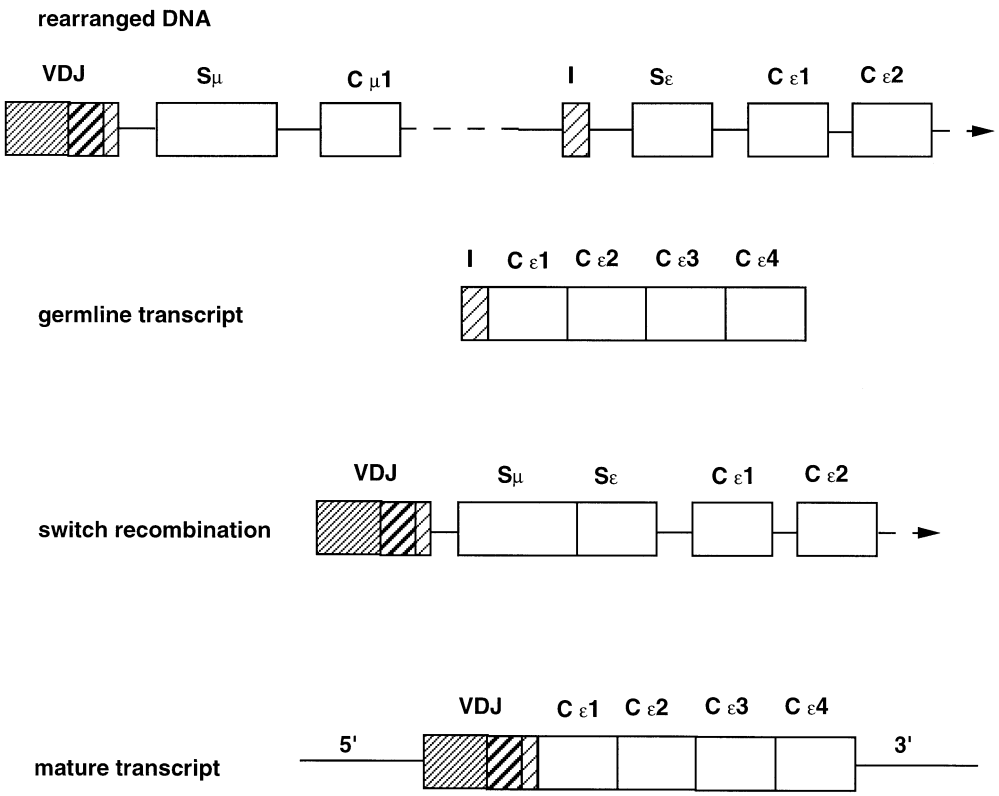

Fig. 1 Mechanism of heavy-chain isotype switching

stream exon [8] (Fig. 1). Germline transcripts are not translated because the upstream exon (I exon) contains stop codons in the reading frame. It is therefore called a sterile transcript. Although sterile transcripts are not translated into a mature protein, they are important for initiating isotype switching. It has recently been shown that deletion of the Igγ1 and Igγ2b exons in mice prevented class switching to IgG1 and IgG2b [9]. By contrast, deletion of the Iε region significantly impairs class switch to IgE, indicating that transcription per se is not sufficient for class switch recombination, although transcription still occurs through the switch region [10]. Isotype switching is regulated by many different molecules, including mitogens and cytokines. Cytokines are thought to control class switching by modulating the accessibility of particular S regions to the recombinase, whereas mitogens activate recombination. In reality the process is more complex, but this distinction may be valuable for a better understanding.

Role of IL-4 and IL-13 for induction of IgE synthesis

The cytokine IL-4 has been identified as a crucial factor for isotype switching to IgE [11, 12]. The role of IL-4 for the induction of IgE synthesis first became evident in 1986 when it was shown that rIL-4 induces IgE production by lipopolysaccharide-stimulated murine B cells [13]. The absolutely essential presence of IL-4 for IgE production has been demonstrated by the ability of anti-IL-4 antibodies to abrogate IgE production induced by parasites [14]. Similiary, IL-4 knock-out mice are unable to synthesize IgE [15]. More recently another cytokine, IL-13, has been identified as a switch factor to IgE in humans [16]. IL-13 has an approximately 30% homology to IL-4 and shares many of its biological activities. Until now the contribution of IL-13 to human IgE responses in vivo has not been clarified. In mice this cytokine does not promote IgE synthesis since murine B cells do not express a receptor for IL-13. The contribution of IL-4 and IL-13 to IgE production of human B cells in vivo remains to be determined.

Both cytokines are also produced by mast cells and basophils upon appropriate stimulation [17]. Interaction of basophils and B cells through CD40L-CD40 binding, together with basophil-derived IL-4, is able to induce human IgE synthesis in the absence of T cells in vitro. Thus, in addition to T cells, mast cells and/or basophils may also be involved in the induction of IgE synthesis in vivo, and basophil-derived IL-4 may play a role in the differentiation of T cells into the TH2 phenotype. Further evidence is needed to confirm this finding and determine its physiological relevance.

IL-4 and IL-13 are capable of inducing ε-germline transcripts in human B cells, and they provide thus the first signal for the induction of IgE synthesis [11] (Fig. 2). The mechanism by which both cytokines induce germline transcription have recently been unraveled at the molecular level. The promoter region of the Iε exon

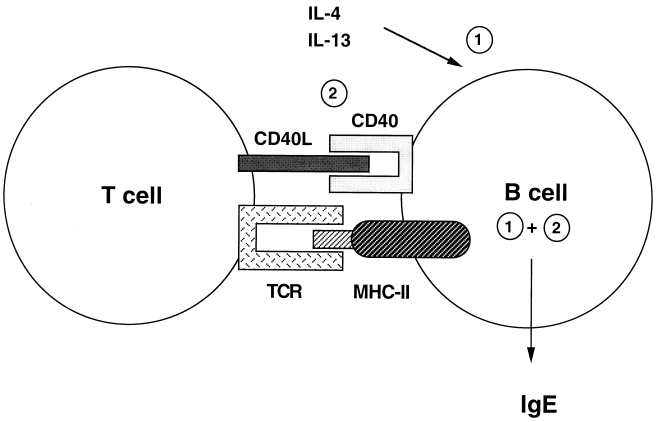

Fig. 2 The induction of IgE synthesis in human B cells requires two signals

contains a binding site for an IL-4 responsive element [18]. This element (TCCNNNGAA) is known to bind a family of transcription factors known as signal transducers and activators of transcription (STAT). STAT proteins are found in the cytoplasm; they are activated after tyrosine phosphorylation, translocate into the nucleus, and activate gene transcription through binding of STAT binding sequences [19]. IL-4 and IL-13 have both been shown to induce STAT6, which binds the STAT binding sequence of the Iε promoter and can induce germline transcription [18, 20]. The biological role of STAT6 binding to the ε germline promoter has recently been demonstrated in vivo. STAT6-deficient mice are unable to make IgE, supporting the hypothesis that STAT6-driven Cε gene transcription is critical for class switching [21].

Role of CD40/CD40L for IgE synthesis

It is well established that the principal molecules for T cell mediated B cell activation are CD40 and CD40L (Fig. 2). CD40 is a 50-kDa glycoprotein and is expressed on all B cells and on other cells such as endothelial, epithelial, dendritic, and monocytic cells [22–24]. CD40 belongs to the nerve growth factor –tumor necrosis factor (TNF) receptor family, which are type I transmembrane proteins. Engagement of CD40 results in switch recombination in human B cells, and the generation of CD40 knock-out mice has demonstrated that the presence of this molecule is crucial for generating a normal immune response, including class switching [25]. Activation of the CD40 molecule is important for isotype switching; however, the presence of cytokines is required. Cross-linking of CD40 on B cells with anti-CD40 antibodies allows for IgE production in the presence of IL-4 or IL-13, and IgA production has been determined in the presence of IL-10 and transforming growth factor (TGF) β [26].

The natural ligand for CD40 is CD40L, which is expressed predominantly on activated T cells and mast

cells [27, 28]. The critical role of CD40 in B cell function has been illustrated by patients with X-linked hyper-IgM syndrome who lack the expression of functional CD40L due to mutations in the gene for CD40L [29, 30]. B cells from patients with hyper-IgM syndrome do not switch from IgM to other Ig classes and do not form germinal centers in the spleen. More recently, several case reports have been published reporting on patients suffering from hyper-IgM syndrome with functionally normal expression of CD40L but with defects in the CD40 signaling pathway [31]. The intracellular mechanisms by which CD40 induces switch recombination in B cells are not yet completely known and are currently under investigation.

Factors influencing IgE synthesis

Modulation by cytokines

A variety of cytokines can modulate IL-4 and IL-13 mediated IgE synthesis (Table 1). Factors which have been shown to downregulate IgE synthesis in vitro include interferon (IFN) α, IFNγ, IL-8, IL-10, IL-12, and TGFβ [12, 32–35]. IFNγ and IFNα have been demonstrated to be effective in reducing serum IgE levels in vivo, as has been shown in a study of patients with hyper-IgE syndrome in which the administration of IFNα or IFNγ resulted in a rapid but transient reduction of serum IgE levels [36]. In contrast, in vivo administration of IFNα or IFNγ in patients with atopic dermatitis fails to inhibit IgE production [37, 38]. These data suggest that IFNs are able to inhibit IgE production in vivo in some but not all patients and shows that suppression of IgE production in vivo by IFN alone is not sufficient to downregulate IgE synthesis efficiently.

Upregulation of IgE production by some cytokines has also been described. For example, IgE synthesis can be enhanced by the cytokines IL-5 and IL-6 in vitro [39, 40]. An involvement of TNFα and its receptors CD120a and CD120b for the induction of IgE synthesis was suggested by a study of Aversa et al. [41]. They demonstrated that mTNFα expressed on T cells can promote IgE synthesis in vitro.

The mechanisms by which cytokines affect IgE production occur at different levels. Cytokines can modulate IgE synthesis through direct effects on B cells (e.g., germline transcription or switch recombination) or through indirect effects on other cells (e.g., T cells and monocytes). Cytokines which have been shown to act directly at the B cell level by modulating IL-4 induced germline transcription are TNFα and TGFβ. TNFα enhances IgE production by upregulating IL-4 induced ε germline transcription whereas TGFβ inhibits IgE synthesis by downregulating IL-4 induced ε germline transcription in purified B cells [42]. Other cytokines such as IL-5 and IL-6 have been shown not to affect ε germline transcription, and other as yet unclarified mechanisms must apply. IL-10 inhibits ε germline transcription only in the presence of monocytes, indicating that indirect effects through monocytes occur on IgE synthesis in B cells [34]. IFNα and IFNγ in turn fail to block IgE production in the absence of T cells [43]. These observations, together with the finding that INFα and INFγ fail to modulate IL-4 induced ε germline transcription in purified B cells, suggest that IFNα and IFNγ mediate their inhibitory effects through inhibition of costimulatory signals provided by T cells. However, another report has shown that IFNγ represses ε germline transcription and downregulates switch recombination to ε [44]. Considering the fact that the ε germline promoter contains binding sites for IFNγ-induced transcription factors, directs effects of IFNγ on epsilon germline production seem possible. In conclusion, it remains unclear at which level IFNα and IFNγ inhibit IgE synthesis: primarily on the B cell level or mainly through T cells. Most likely, both mechanisms apply under certain circumstances in vivo and can be influenced by many diverse factors as well.

Taken together, the mechanisms by which cytokines modulate IgE synthesis are not completely understood. The data obtained until now indicates that the modulation of IgE production by cytokines can either occur through direct effects on B cells or indirectly through effects on other cells like T cells, monocytes, or natural killer cells. However, the precise role of their involvement in IgE production remains elusive.

Modulation of IgE production by contact molecules

There is solid evidence that a number of other surface molecule pairs on T and B cells are also involved in IgE production [1]. Other signals than CD40 have been described which synergize with IL-4 for the induction of IgE synthesis. Engagement of mouse CD30 by CD30L in the presence of IL-4 and IL-5 results in polyclonal secre-

Table 1 Modulation of IgE synthesis by cytokines and contact molecules

	Cytokines		Contact molecules	
Enhancing IgE synthesis	TNFα, lymphotoxin α	[41]	CD23-CD21	[47–49]
	IL-5, IL-6	[39, 40]	CD28-B7	[53]
			CD30-CD30L	[45]
			CD58-CD2	[52]
Inhibiting IgE synthesis	IL-8, IL-10, IL-12	[32–34]	CD54-LFA3	[68]
	IFNα, IFNγ	[12]		
	TGFβ	[35]		

tion of IgG1, IgA, IgG3, and IgE [45]. The involvement of other family members from the nerve growth factor–TNF receptor familiy in the induction of IgE synthesis may be due to similarities of these molecules within the intracellular portion of the family receptors, leading to the activation of similar signal transduction pathways and subsequent mobilization of common transcription factors participating in the induction of isotype switching. This hypothesis holds because engagement of both CD30 or TNF receptor I and CD40 results in activation of the transcrition factor NF-κB. The importance of this transcription factor promoting isotype switching has been shown by the generation of p50/NF-κB deficient mice. These mice are defective in class switching to IgG3, IgA, and IgE [46].

The low-affinity receptor for IgE (CD23) has also been shown to play a role in IgE regulation (Table 1). CD23 is expressed on a variety of cells including B cells, T cells, a subset of thymic epithelial cells, follicular dendritic cells, Langerhans cells, monocytes, eosinophils, and platelets. The importance of CD23 or its soluble fragments in the synthesis of human IgE in vitro has been highlighted by the demonstration that a specific subset of anti-CD23 antibodies blocks both, IL-4 induced IgE production by normal human B cells and the spontaneous production of IgE by B cells from atopic patents [47, 48]. Moreover, CD23 has been shown to modulate the antigen-specific IgE response in an isotype-selective manner in vivo [49]. Studies using inhibitory anti-CD21 antibodies and the binding of CD23 liposomes to recombinant CD21-transfected cells reveal that CD23 binds to a subtype of CD21 which is identical to complement receptor 2 (CR2). Engagement of CD21 on B cells by some anti-CD21 monoclonal antibodies increases IL-4 induced IgE production, as does treatment with recombinant sCD23 in both T cell dependent and T cell independent systems [50]. Considering the fact that IL-4 and allergens induce CD23 expression on T cells, it may be possible that in allergic patients T cell associated CD23 interacts with B cell associated CD21, leading to increased IgE production. Although the data indicate a role for CD23 in IgE synthesis, further evidence is required to define the role and physiological relevance of CD23 in human IgE regulation.

It has been suggested by Vercelli et al. [51] that certain adhesion molecules participate in T-B cell interactions, resulting in IgE synthesis because blocking antibodies directed against either CD2, CD4, or LFA-1 have been shown to inhibit IgE production by B cells stimulated with IL-4 and autologous T cells. In addition, it has been shown that ligation of B cell surface CD58 (LFA-3) provides IL-4 stimulated B cells with a second signal to induce IgE production in the absence of T cells or anti-CD40 [52]. Although there is strong evidence to suggest that costimulatory molecules such as CD28 and CTLA-4 are involved in isotype switching, the role of these molecules in the regulation of IgE synthesis has not yet been well studied. It has been shown that anti-CD28 monoclonal antibodies produce a dose-dependent inhibition of IgE but not of IgG synthesis by tonsillar B cells when driven by an allergen-specific human T cell clone, suggesting involvement of these molecules in the regulation of IgE synthesis [53].

Taken together these results indicate that molecules other than CD40-CD40L may be sufficient to provide T-B cell interaction and are therefore able to induce IgE synthesis in vitro. However, patients with defective CD40L expression or defective CD40 signaling suffering from hyper-IgM syndrome do not switch to IgE isotype production, suggesting that the interaction of molecules other than CD40-CD40L, including adhesion molecules, is not be sufficient for the induction of IgE synthesis in vivo.

Effects of hormones, neuropeptides, and other molecules on IgE production

The fact that hormones may play an important role in the IgE antibody response was demonstrated by a report showing that hydrocortisone and IL-4 induce IgE synthesis in B cells derived from peripheral blood [54]. Furthermore, oral treatment with corticosteroids has been shown in patients with allergic asthma to result in increased IgE production in vivo [55]. The therapeutic effect of steroids in allergic disorders despite their enhancing effects on IgE synthesis in IL-4 supplemented in vitro systems may be explained by the observation that steroids are able to inhibit IL-4 production in vitro and in vivo [56]. No other hormones, including testosterone, β-estradiol, progesterone, aldosterone, gonadotropin, and prolactin, seem to affect IgE synthesis [57]. Thus the effects of hydrocortisone in vitro during the induction of IgE synthesis seem to be selective, although the molecular processes leading to this phenomen have not been elucidated so far.

The question of whether neuropeptides are able to modulate IgE synthesis has been addressed by Kimata et al. [58]. These authors reported that adrenocorticotropic hormone is a potent modulator of human IgE synthesis in vitro. This has been shown to modulate IgE synthesis in a dose-dependent fashion in human peripheral blood mononuclear cells in vitro [58]. Furthermore, the ubiquitous neuropeptides vasointestinal peptide, somatostatin, and substance P have been shown specifically to inhibit IgE production in a T cell and monocyte-dependent fashion [58]. These studies were performed with peripheral blood mononuclear cells and not in pure B cell systems, and indirect effects through cytokine production by other cells must be considered. The physiological role of hormones during IgE production in vivo has not been elucidated and is at this point speculative.

The effects of other immunoregulatory molecules such as prostaglandins and gangliosides on human IgE synthesis is controversial, and, again, their physiological role has not been proven. Prostaglandin E_2 has been shown to enhance IL-4 dependent B cell proliferation but to inhibit IL-4 induced IgE secretion [59]. A recent study

has demonstrated that the gangliosides GM2 and GM3 inhibit IgE production in vitro by inhibiting endogenous TNFα production [60].

These findings demonstrate that the production of human IgE by B cells can be modulated by a number of different factors including neuropeptides and hormones in vitro, indicating a possible interaction between neurological, endocrinological, immunological, and allergic responses during this process in vivo. However, the relevance of these factors in humans remains to be established.

Implications for therapeutic strategies

The treatment of allergies still focuses on the inhibition of mediator release or on blocking the binding of soluble mediators to their receptors. There have, however, been recent attempts to modulate IgE production by pharmacological means. The immunosuppressant cyclosporin A (CsA) has been shown to inhibit T cell dependent IgE synthesis in vitro through downregulation of CD40L expression [61]. By contrast, T cell independent induction of IgE synthesis by anti-$CD40^+$ IL-4 was not affected by cyclosporin A treatment [61]. From clinical studies there is nevertheless convincing evidence that local and systemic administration of cyclosporin A in patients with atopic dermatitis improves the clinical condition in these patients, resulting rather from downregulation of the inflammatory response than from direct interference with IgE synthesis [62].

Another drug which may be useful in preventing allergic disease is disodium cromoglycate (DNCG). It has been demonstrated that disodium cromoglycate inhibits anti-$CD40^+$ IL-4 induced IgE synthesis by targeting CD40-mediated switch recombination. The inhibition occurs at concentrations of disodium cromoglycate readily achievable in the course of asthma therapy, indicating that this drug may be useful in the treatment of IgE mediated diseases [63].

The approach to modulate IgE production by modification of molecular mechanisms which lead to isotype switching from IgM to IgE requires further study. To date the regulatory elements involved in switch recombination are still not completely understood, and this makes the search for new therapies at this molecular level rather difficult.

Because of the central role of IL-4 and IL-13 in the induction of IgE synthesis, on the one hand, and, on the other, the enhanced production of these cytokines by allergen-specific T cells, shown to be associated with increased IgE levels, it is obvious that approaches to block IgE synthesis should include inhibition or neutralization of IL-4 and IL-13. The first step has already been achieved with the development of an IL-4 mutant protein which can sufficiently block IgE synthesis in vitro [64]. More recently it has been shown that the IL-4 mutant protein is also active in inhibiting IgE synthesis in vivo in a hu-SCID mouse system [65]. Further studies with such receptor antagonists are needed, however, to determine their potential place in anti-allergic therapeutic modalities.

A more recent therapeutic strategy in allergic diseases is the induction of tolerance in allergen-specific T cells, the main sources of IL-4 and IL-13. The induction of nonresponsiveness in allergen-specific T cells in vitro is possible by using high immunogenic doses of antigenic peptides in the absence of professional APC. The usefulness of this model has also been demonstrated in vivo [66] since subcutaneous administration of Fel d I peptides in mice decreases T cell responses and induces peripheral T cell tolerance. Because these peptides do not react with IgE antibodies, a reduction of the potentially life-threatening unwanted effects during conventional immunotherapy is to be expected. A clinical trial with Fel d I derived peptides is currently underway and will hopefully provide more information about the potential usefulness of such therapeutic approaches.

Lately the development of chimeric humanized mouse anti-human IgE antibody has shown promising results in a phase II study in adults with allergic asthma. Administration of the antibodies not only significantly lowered serum IgE levels but also increased the allergen threshold for the induction of an early asthmatic response [67]. These studies must be repeated with a larger group of patients and over a longer period of time to confirm their efficacy. The effects of administering such antibodies in patients with atopic dermatitis has not yet been studied yet.

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