

# Mechanisms of IgE-Regulation

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## 26.1 Introduction

Currently two different forms of atopic dermatitis can be distinguished: the more frequent extrinsic atopic dermatitis syndrome (EADS) and the less frequent intrinsic atopic dermatitis syndrome (IADS) [1]. These two entities are clinically indistinguishable, however, display different levels of IgE-mediated sensitization to environmental allergens suggesting that the underlying pathophysiological mechanisms are different. In the etiology of EADS IgE-mediated sensitization to allergens undoubtedly plays a significant role. There is a clear age-dependent difference in IgE sensitization to allergens of different origin in patients with extrinsic atopic dermatitis syndrome (EADS) that seems to correlate with the patients' history of exposure-dependent flare-ups of skin symptoms. While during infancy and childhood food allergens such as milk, hen egg, wheat, soy bean, and peanut play a central role, in adolescence and adulthood sensitizations to airborne allergens such as house dust mite or pollen become more prevalent. Recent data suggests that also IgE sensitizations to pollen-associated foodstuffs are relevant.

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## 26.2 Mechanisms of Allergic Sensitization: Allergen Uptake, Processing, and Presentation

Before mechanisms of IgE regulation and sensitization are discussed in more detail, a closer look at the mechanisms of allergic sensitization is necessary. The primary site of antigen/allergen exposure of the body is the epithelium of skin and mucosal surfaces. These epithelial tissues contain highly specialized antigen presenting cells (APC) termed dendritic cells (DC) that act as sentinels of

the immune system [2]. Resident intraepithelial DC form a continuous network of cells that are well equipped to ingest environmental compounds and process complex antigen into short peptides that associate with major histocompatibility complex (MHC) molecules and can be recognized by cells of the adaptive immune response. The migratory capacity of DC allows them to transport antigen/allergen from sites of primary exposure to regional lymph nodes where they can initiate systemic immune responses by presenting processed antigen in the context of MHC molecules to resting T lymphocytes. DC differ from other APC such as monocytes, macrophages, or B cells in that they display a unique capacity to activate naïve T cells and induce the polarization of the ensuing immune response toward a T helper 1 (Th1) or a Th2 phenotype. These two types of T helper cell responses differ on the basis of cytokine production and effector function. Th1 cells are interferon  $\gamma$  (IFN $\gamma$ ) producing effector cells that activate macrophages and cytotoxic T cells and are involved in cellular immune responses against haptens and microbial pathogens, while Th2 cells produce interleukin (IL)-4 and -5 and other mediators that regulate immunoglobulin E (IgE) production, growth, and activation of eosinophils and mast cells and other effector mechanisms relevant for allergic and parasitic diseases. Since Th2 effector lymphocytes play a critical role in orchestrating allergic inflammation and regulating IgE production (see Sect. 26.6) considerable interest has focused on the mechanisms controlling Th activation, polarization and leading to the induction of Th2-dominated immune responses.

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### 26.2.1 Allergen Uptake and Processing

At the interface of environment and organism resident DC are in a functional immature state that is special-

ized to capture and process antigen. Antigen uptake is mediated via a number of mechanisms including macropinocytosis, phagocytosis, and receptor-mediated endocytosis involving clathrin-coated pits. Immature DC display a large panel of cell receptors for patterns associated with foreign antigens, such as the carbohydrate receptors of the C type lectin family (e.g., mannose receptor, langerin, DEC205, DC-SIGN, etc.). These pattern recognition receptors facilitate antigen capture and uptake and lead to an increased effectiveness in antigen presentation [3]. In addition, DC express complement- and Fc-receptors that mediate capture of opsonized or antibody-bound antigens during primary and secondary antigen exposure. Ingested antigen is cleaved into peptides by proteolytic enzymes within the endocytic compartment and loaded onto newly synthesized MHC class II molecules within the acidic MHC class II compartment or onto preformed MHC class II molecules that have been internalized from the cell surface into less acidic endosomal vesicles [4]. Recent reports indicate that at least *in vitro* some of the antigen processing by DC may also occur extracellularly through secretory proteases. Notably, ingested antigen or antigen peptides may also leak into the cytosol and become accessible for the MHC class I presentation pathway. Our current understanding is mostly based on *in vitro* studies using model antigens, while there is still very little data available on the mechanisms involved in uptake and processing of allergens in the *in vivo* setting. Recent *in vitro* data indicate that recombinant allergens such as Phl p1 or Bet v1 are primarily ingested via macropinocytosis [5], a mechanism that may be relevant during the primary sensitization process. In already sensitized individuals uptake is most likely mediated by receptor mediated endocytosis e.g., internalization of IgE-bound allergen via the high affinity IgE receptor that targets the allergen to the MHC class II compartment.

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### 26.3 Activation, Migration, and Maturation of Antigen-Presenting Cells

A key event in the induction of primary immune responses is the migration of allergen-loaded DC from the periphery to the regional lymph nodes [6]. Local activation of DC, e.g., during allergen exposure, leads to a dramatic change in their chemokine receptor pro-

file and allows the directed migration from the epithelium to the afferent lymphatic vessels and on to the T cell-rich areas of the regional lymphoid tissue. The local activation of immature DC is best understood as a response to changes in the local microenvironment. It is easily conceivable that at the site of allergen exposure allergen/allergen carrier-associated molecular patterns (AAMPs) could directly induce the activation and maturation of DC [7]. Alternatively, some allergens may have direct DC activating potential due to their intrinsic enzymatic activity, as it has been recently reported for one of the major house dust mite allergens, the cysteine protease Der p1 [8]. Finally, immature DC may also get activated indirectly. Perturbation of the epithelial homeostasis by allergen exposure may lead to the local release of inflammatory mediators, such as IL-1 or TNF $\alpha$ , which are known agonists of DC maturation [9]. In this context consideration of the natural exposure conditions is of particular relevance. It is well documented that for many aeroallergens the bioavailability depends on the allergen liberation from internal binding sites within the allergen carrier, such as pollen grains [10]. In addition, pollen grains seem to be a rich source of bioactive mediators which get rapidly released upon pollen contact with the aqueous phase. Among others, eicosanoid-like lipid mediators are released within minutes and this release clearly precedes the liberation of protein allergens [11]. Even though the *in vivo* effects of these mediators are still somewhat uncertain, it seems very likely that they may act as adjuvant leading to the activation and modulation of DC function at the site of allergen exposure.

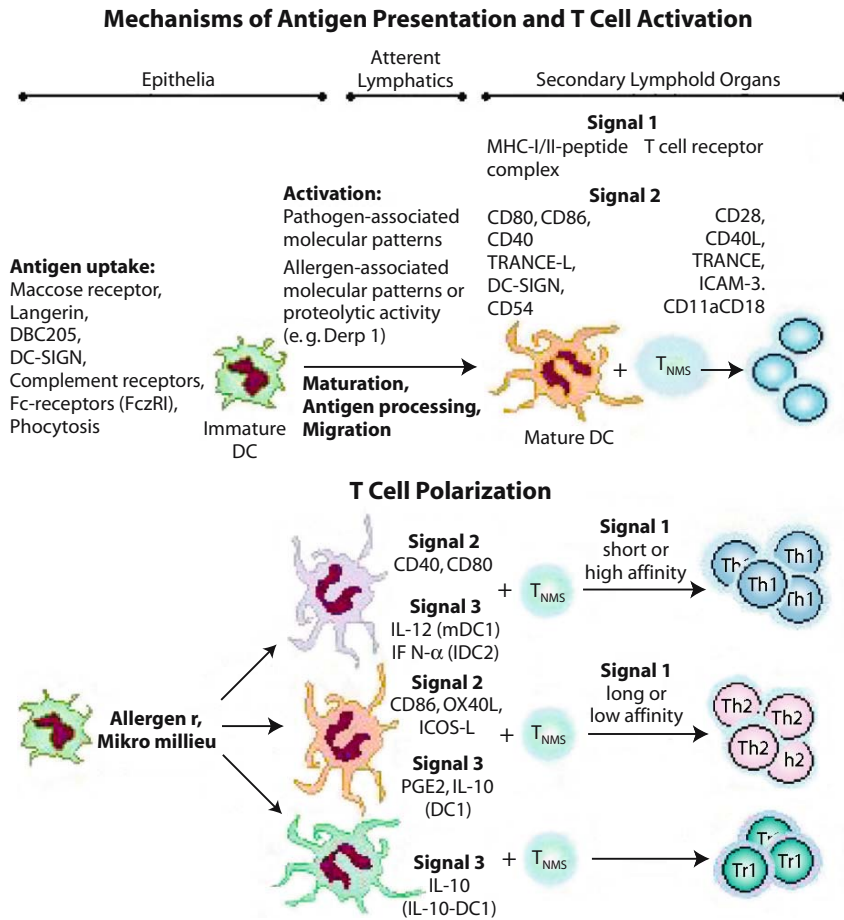
Once activated, DC undergo a functional maturation during which the capacity of antigen uptake and processing is shut down and the machinery for optimal antigen presentation is acquired. This involves increased surface expression of peptide/MHC complexes (signal 1), upregulation of costimulatory molecules such as CD40, CD80, CD86 (signal 2), and the production of cytokines such as IL-12, IL-18, and IL-10, which can polarize T cell responses (signal 3). Upon maturation and migration into the T cell areas of the lymph nodes DC produce chemokines that selectively attract naïve and resting T cells. This process facilitates the interaction with multiple T cells and increases the chances to interact with T cells that recognize the presented antigen.

## 26.4 T Cell Activation and Polarization of the T Cell Response

Signals that lead to T cell activation are generated during the cognate interaction in specialized areas of contact between the T cell and the DC – the so-called immunological synapse. In DC costimulatory molecules and peptide/MHC complexes are concentrated into lipid rafts on their membrane surfaces at sites of T cell contact. Similarly in T cells adhesion molecules, T cell receptors (TCR) and components of the signal transduction machinery concentrate in supramolecular activation complexes at the site of the interaction with the DC. The formation of this DC-T-cell synapse allows prolonged interaction between the cells and results in sustained signal transduction via the TCR that eventually leads to the induction of T cell division. T cells interact with DC in a highly dynamic environment where they have to compete to achieve a level of TCR stimulation sufficient to drive their activation and differentiation. A sustained TCR stimulation is not only required for naïve T cells to proliferate but also for proliferating T cells to differentiate into effector cells. Signals during this cognate interaction of DC and T cell play a critical role in determining the polarization of T helper cell responses toward a Th1 or a Th2 phenotype [12]. A number of regulatory mechanisms seem to be operative. Not too long ago it was suggested that the preferential induction of either Th1 or Th2 responses is determined by the lineage of DC utilized for antigen presentation. According to this concept, DC of myeloid origin (designated as DC1) induced IL-12 dependent Th1 responses, while DC derived from plasmacytoid precursor cells of lymphoid origin (plasmacytoid DC, DC2) preferentially induced Th2 responses. However follow-up studies have demonstrated that depending on the type of stimulus present during DC activation both types of DC can be induced to polarize either toward a Th1 or a Th2 response. The resulting Th polarization seems to be predominantly regulated at the level cytokines present during antigen presentation (signal 3) with DC-derived IL-12 favoring Th1 and DC-derived IL-10 (and IL-6) favoring Th2 development. The degree and type of costimulation (signal 2) also modulates the outcome of T cell response with CD40 and CD80 favoring Th1, while CD86, OX40L, and ICOS-L have more of a Th2-promoting effect. In addition, Th polarization can be regulated at the level of duration

and affinity of TCR-MHC interaction (with sustained interactions of low affinity favoring Th2 induction, while short interactions with high affinity preferably induce Th1 responses) and at the ratio of DC to responder T cells (with low stimulator/responder ratios promoting Th2, while high ratios favor the Th1 development). To add to the level of complexity, the timing at which the naïve T cells get to interact with the DC may also be of relevance [13]. Early after LPS-mediated activation DC produce transiently large amounts of IL-12 and induce Th1 responses, while at later time points the same DC lose the capacity to produce IL-12 and preferentially prime Th2 responses (Fig. 26.1).

It is still a matter of debate whether allergens by themselves can lead to a DC activation that preferentially induces Th2 priming. A recent report suggested that the enzymatic activity of Der p1, a cysteine protease, can induce DC activation with a selective upregulation of CD86—a Th2-promoting costimulatory molecule [8]. However, this effect was only observed in DC from Der p1-sensitive patients and not in DC from healthy controls or grass pollen-sensitive patients, suggesting that the pre-existing sensitization was relevant for the observed effects. It remains to be determined whether other allergens with enzymatic activity have a similar impact on DC maturation and influence the T cell response during primary sensitization. A different level at which allergens may modulate the outcome of Th polarization is the degree of DC activation under natural exposure conditions. In contrast to pathogens which via triggering of pattern recognition receptors induce profound DC activation [14], allergens may just lack this capacity and induce activation in only a small subset of DC. Mobilization of low numbers of DC from the site of allergen exposure would lead to a low stimulator responder ratio in the regional lymph node which at least *in vitro* would promote the development of Th2 responses. Finally, under natural exposure conditions organisms are rarely exposed to isolated allergens but rather to a complex mixture of multiple allergens in conjunction with potential adjuvants. The recent report of bioactive eicosanoid-like lipid mediators rapidly released from allergen carriers, such as grass pollen, upon contact with the aqueous phase [10, 11], suggests that these mediators may exert direct or indirect effects on DC function in the microenvironment at the site of allergen exposure. In this context prostaglandin E-like phytoprostanes seem to be prime candidates, which similar to prostaglandin E2 may inhibit DC IL-12 pro-



**Fig. 26.1.** Schematic diagram of factors involved in antigen presentation and T cell polarization (Adapted from [34])

Type of variable	Favoring Th1	Favoring Th2
Antigen dose	High dose	Low dose
Characteristics	Microbial products, TLR ligands	Parasite products, Der p1
Adjuvants	CpG oligodeoxynucleotide Gram-positive cell wall	
Timing	Early after LPS stimulation	Late after LPS stimulation (exhausted DC)
MHC-TCR Interaction	High affinity Short interaction	Low affinity Sustained interaction
APC/T cell ratio	High stimulator/responder	Low stimulator/responder
Costimulatory molecules	Low CD80/CD86 ICAM-1 CD40	High expression of CD86 OX40-L ICOS-L (B7RP-1 or -2)
DC maturation	Mature Monocyte-derived DC	Immature
DC lineage	Myeloid DC	Plasmacytoid DC
DC localization		Mucosal DC
Cytokine production	High IL-12 Low IL-10	Low IL-12 High IL-10, IL-6

**Table 26.1.** Factors influencing T helper cell polarization by dendritic cells (adapted from [7])

duction and result in a propensity to induce Th2 rather than Th1 immune responses [15].

In summary, an enormous plasticity in the response profile of dendritic cells to different activation signals exists and multiple factors determine the outcome of the cellular response that leads to a Th2-dominated immune response and production of allergen-specific IgE (compare Table 26.1)

## 26.5 Origin and Maturation of B Cells

Allergen-specific IgE, like other isotypes, are produced by plasma cells that are derived from B-lymphocytes. For a better understanding of the regulation of IgE production, a short description of the origin and maturation of B cells is presented. B cells are derived from pluripotent stem cells of the bone marrow. Their development starts between the 8th to 9th week of pregnancy in the hemopoietic tissue of the liver and shifts at week 20 of pregnancy towards the bone marrow where the postnatal development is also located. By using the expression profiles of surface molecules and the rearrangement of the germline, the development of B cells can be divided into different stages: pro-B cells, pre-B cells, immature B cells, and naïve B cells. The further development of B cells results in antigen-specific memory B cells and antigen-specific antibody-producing plasma cells [16, 17]. For the production of immunoglobulins, the rearrangement is necessary and starts with the heavy chain in pre-B cells. Rearrangement of the light-chain follows within the pre-B cell and subsequently the complete IgM membrane molecule characterizes the immature B cells. Mature B cells are characterized by the expression of membrane IgM and/or IgD.

Similar to dendritic cells, B cells can also function as antigen-presenting cell (APC). In contrast to most APC, B cells can only present specific antigen that is bound via the specific membrane-bound immunoglobulin as part of the B cell receptor complex [18]. This binding leads to the internalization of the antigen-receptor complex and towards antigen-processing processes by enzymes within the endosome of the cells. The peptide fragments will be bound to HLA-molecules and transported towards the cell surface. Within the MHC complex those fragments will be recognized by the specific T cell receptor on T helper cells.

The BCR is characterized by membrane bound IgM or IgD (mIgM, mIgD) for the specific binding and the Ig $\alpha$  and Ig $\beta$  (CD79) heterodimers, which are important transducers of signals. The BCR is associated with different cell surface receptors like CD19, CD5, and CD32.

Besides the BCR, HLA-II is the most important molecule for the B cell-associated antigen-presentation and is upregulated on B cells by IL-4 and IL-5 [19]. The highly variable binding region for the peptide binding is formed by the  $\alpha$ - and  $\beta$ -chain. In contrast to HLA-I, this binding region is relatively open and larger antigen fragments of 12–24 amino acids can be presented.

In contrast to other APC, B cells react towards small amounts of antigen concentrations. This is highly important since the origin of the APC significantly influences the development of an immune response. B cells promote, like mast cells, mainly a TH2 response and therefore support IgE production, whereas other APCs favor more a TH1 immune response [18].

The interaction between B and T cells if a specific TCR is binding the MHC-II-AG-complex is supported by several costimulatory molecules, mainly CD80/86, CD40, CD54, LFA-1, and LFA-3 [19] (Table 26.2). The interaction between CD40 on B cells and its ligands on T cells plays a central role for the switching process. If this interaction between T and B cells is disrupted the switching process will be completely diminished and no development of IgA-, IgG-, or IgE-producing B cells or plasma cells is possible. However, also several costimulatory molecules influence the T/B cell interaction and also a large amount of cytokines which increases or decreases the switching process and subsequently the immunoglobulin production (Table 26.2).

**Table 26.2.** Induction and modulation of IgE synthesis. (After [20])

	Surface molecules	Cytokines
Inducing signals	CD40-CD40L (Signal 2)	IL-4, IL-13 (Signal 1)
Positive modulators	CD23-CD21 CD28-B7 CD58-CD2	TNF- $\alpha$ LT $\alpha$ IL-5 IL-6
Negative modulators	CD54-LFA3	IL-8, IL-10, IL-12 IFN $\alpha$ , IFN $\gamma$ TGF- $\beta$



## 26.6 Immunoglobulins

Immunoglobulins exist in different forms; one is the membrane-bound form on early B cell surface (mIg) and the other form is the secreted and soluble immunoglobulin which occurs throughout the body fluid (sIg). Immunoglobulins are bifunctional, which is reflected in their molecular structure. The high-variable N-terminal part presents the antigen-binding site, whereas the C-terminal part is characterized by a constant amino acid sequence which promotes the effector functions of the Ig such as the interaction with cells of the immune system and binding of components of the complement system.

Ramirez (1919) and Prausnitz, Küstner (1921) first discovered that allergic reactions are transmitted by blood components and serum. The responsible factor was named reagin and was identified many decades later by Ishizaka and Johansson [20]. The classification of immunoglobulin E was given because these molecules lead to the development of an erythema after local application. Like any other immunoglobulin, IgE consists of two heavy and two light chains. The heavy chains are characterized by an additional constant domain ( $\epsilon 4$ ). Through the Fc-portion of domain  $\epsilon 3$  IgE binds to its specific receptors. In nonallergic healthy donors only small amounts of IgE are detected in the serum (<0.001% of total Ig) and its half-life in this compartment is only 2–5 days. By contrast, the receptor-bound form of IgE is detectable over months on mast cells and basophils. The physiological relevance of IgE remains elusive besides its known functions in parasite infections and type-I-allergies where increased serum IgE-levels are present. Within the type-I-allergic context an additional immunoglobulin might be relevant, namely IgG4, which is considered to play a protective role within IgE-mediated hypersensitivity reactions. The hypothesis of blocking antibodies was based on observations that patients with parasitic infections exhibit very high sIgG4 levels (50%–95% of total IgG, norm. value <4%). These patients rarely develop allergic reactions despite having high IgE-titer. By removing IgG4 molecules, the blocking ability of the sera was completely abolished determined by histamine-releasing assays [20].

This blocking ability of IgG4 is related through the direct competition to antigen binding with the high-affinity IgE receptor-complexed IgE molecules. IgG4, like IgE, cannot bind complement factors and has a low

affinity towards Fc-receptors resulting in non-life-threatening reactions in case of antigen-binding.

## 26.7 Isotype Switching

Isotype switching occurs during a humoral immune response resulting in a switch from IgM or IgD to IgG-, IgA-, or IgE-producing B cells. This process involves somatic recombination with persistence of antigen specificity.

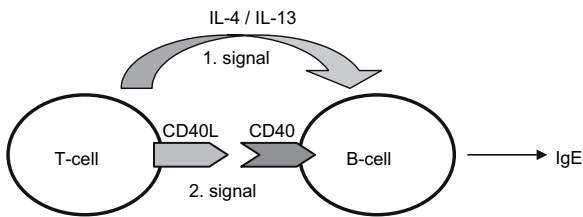
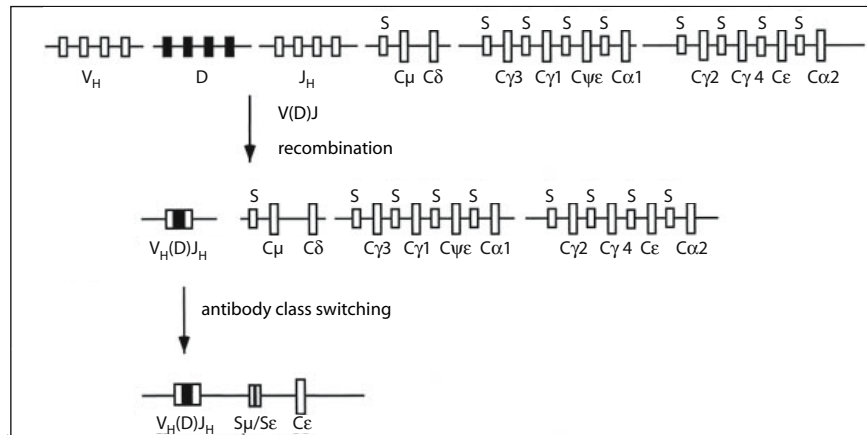
The genes for the constant regions of the heavy chain are 3' from the genes of the variable regions (VDJ-segments) on chromosome 14 and are characterized by  $C\mu$ ,  $C\delta$ ,  $C\gamma 3$ ,  $C\gamma 1$ ,  $C\psi\epsilon$  (pseudogen),  $C\alpha 1$ ,  $C\psi\gamma$ ,  $C\gamma 2$ ,  $C\gamma 4$ ,  $C\epsilon$ ,  $C\alpha 2$  [20]. The switching regions are on genomic level and are summarized in Fig. 26.2.

Apart 5' from this region several GC-rich motives are localized which represent the switch regions. One exception is  $C\delta$ , which does not have its own switch region since IgD is produced through alternative splicing of the  $C\mu$ - and  $C\delta$ -transcript. After activation of the recombination system the looping-out deletion results in class switching, i.e., from IgM to IgE through association of  $S\mu$  to  $S\epsilon$  (Fig. 26.2) [18]. In principle, the isotype switching can also occur sequentially, i.e., from IgM through IgG4 to IgE. However, switching is only possible towards C-regions 3' to the translated C regions.

Currently, a two-signal hypothesis is postulated for the switching process (Fig. 26.3) [18, 20]. IL-4 and/or IL-13, which are mainly produced by TH2 cells, deliver the first signal to induce isotype switching to IgE. IL-4 binds to the IL-4-receptor, which in turn results in several phosphorylation steps by JAKs and finally STAT-6 builds a homodimer and translocates to the nucleus. Within the nucleus, STAT-6 binds towards specific DNA sequences within the promoter region of IL-4-dependent genes. Upstream of  $S\epsilon$  STAT-6 binds the germline  $\epsilon$  region. After the splicing process of introns the  $\epsilon$ -germline-transcript is produced. The  $I\epsilon$  region contains several stop codons preventing  $\epsilon$ -GLT from translation. Therefore, this transcript is called „sterile.“ The exact mechanism of the  $\epsilon$  GLT is currently not known; it is speculated that it builds a part of the switching recombinase system [18, 20].

The second signal towards IgE switching is provided by CD40/CD40-ligand interaction (Fig. 26.3). CD40 is a

**Fig. 26.2.** Genes from the constant regions of immunoglobulins (Modified after [18]) VDJ: genes of the variable region; S: switch region; C $\mu$ : gene for the constant region of IgM; C $\delta$ : gene for the constant region of IgD (etc.) By isotype switching the S $\mu$  region will associate to S $\epsilon$  subsequently and the VDJ region and the heavy chain of IgE are synthesized



**Fig. 26.3.** Two signal hypothesis for the induction of IgE production in B cells (modified after [20])

45–50 kDa membrane glycoprotein of the tumor necrosis factor receptor superfamily. It is constitutively expressed on B cells, but also on dendritic cells. The physiological ligand is CD40-ligand which is expressed on activated T cells [18, 20]. The CD40-CD40-ligand interaction results in upregulation of several B cell activation molecules but also in the deletion of the DNA region between S $\mu$  and S $\epsilon$  by induction of a loop-out process. This results in proximity of the VDJ-segment to the C $\epsilon$  segment. After further deletion of unnecessary regions the mature DNA-transcript is produced and can finally be translated into the proteins (immunoglobulin E) [7].

## 26.8 Additional Factors of IgE Regulation

Besides the main two signals to induce the IgE-switching process several further molecules like CD23, CD86, and CD54 play an important role for the modulation of

IgE production [6, 29, 33] (Table 26.1). CD23 is expressed by lymphocytes, macrophages, and monocytes. On B cells CD23 is induced by IL-4 and inhibited by IFN $\gamma$  [22]. Besides its membrane-bound form, CD23 exists also in a soluble form. Additional ligands of CD23 are CD21, CD11b/CD18, and CD11c which implicates its several immunomodulatory effects. Regarding IgE synthesis, CD23 has been reported to exert increasing, but also decreasing effects on IgE production.

CD86 is the natural ligand of CD28 and CTLA-4 and plays an important role as a costimulatory molecule for T cell activation. [23]. It is constitutively expressed on professional APCs and only weakly on nonactivated B cells and is rapidly upregulated after cell activation. An agonistic anti-CD86-Ab increases anti-CD40+IL-4-mediated IgE and IgG4 synthesis [18]. The binding of anti-CD86 leads furthermore to an increased B cell proliferation, increased CD23 expression and a moderate CD54 expression.

Also the adhesion molecule CD54 seems to influence IgE production [18] (Table 26.2). Its main function is the cell contact-dependent adhesion. CD54 is regulated in a cell-specific manner. On B cells it is induced by IL-4 and after CD40-CD40-ligand interaction. CD54 is expressed in association with MHC-II on all APCs including B cells and acts as a costimulatory molecule for T cell activation, e.g., through the induction of costimulatory molecules. It has been shown previously that anti-CD54-Abs promote the anti-CD40+IL-4-induced IgE production by enhancing the  $\epsilon$ -germline transcripts.

## 26.9 Therapeutic Implications

The treatment of atopic diseases is currently dominated by symptomatic measures including, e.g., the usage of antihistamines or corticosteroids. Specific immunotherapy (SIT) is currently the only causal treatment of atopic diseases. A recent study using a dermatophagoides p./f. extract in AD patients indicates a therapeutic impact of SIT also for the treatment of AD (Werfel et al. personal communication).

Until today, several mechanisms of SIT have been determined including the reduced release of histamine and leukotrienes by basophils, but also a reduction of the cellular infiltrates (eosinophils and T cells) within the allergic inflamed tissue has been reported [24, 25]. In addition, several molecules which are also involved in IgE regulation have been described to be expressed decreased (IL-4 receptor, CD23, and CD40-ligand) while other surface molecules like IL-2 Ra, IL-12R, CD3, CD4, CD8, CD45, and HLA-DR remained unchanged. However, other studies reported also a significant reduction of MHC-II molecules on CD4 and CD8 cells. Furthermore, the decreased expression of CD23 during SIT was observed as well as the reduced expression of CD69, a T cell activation marker. In addition, a shift of cytokine secretion pattern indicates fundamental changes within the effector cells of the immune system during SIT. A clear, reduced secretion of TH2 cytokines like IL-4, IL-5, and IL-13 [24, 25] indi-

cates a shift from the allergen-specific TH2 towards a TH1-response during SIT. These findings are, however, controversial since also an increase of TH2 cytokines and a reduction of the TH1 cytokine IFN $\gamma$  was determined. In addition, IL-10 has been related to the induction of tolerance during SIT [26]. Such changes of IL-10 and also IFN $\gamma$  would explain the reduced histamine and leukotriene secretion from peripheral leukocytes during SIT [27]. Previously the role of B cells during SIT was focused on the measurement of immunoglobulin production. Many studies have reported reduced specific IgE levels and an increase of specific IgG4 levels during SIT [28, 29]. In addition, we could previously show that the cell surface expression of several molecules on B cells during SIT is modulated [30]. On day 6 of SIT, a significant reduction of the expression of several molecules including CD32, CD5, CD23, CD54, and MHC-II was observed. However, these changes were normalized approximately 4 weeks after the initiation of the SIT. CD32 (Fc $\gamma$ -RII) exhibits downregulating effects on B cell activation and binds IgE-containing immune complexes. CD5 reduces signal transduction mechanisms through the B cell receptor and its role in allergic reaction remains unclear. By contrast, CD54 is known to play an important role within inflammatory processes and is, like MHC-II, regulated by IL-4, implying that if IL-4 secretion is reduced, these molecules may be downregulated during SIT. Taken together, these data suggest that SIT is not only modulating immunoglobulin synthesis, but also other B cell functions like antigen presentation and B-/T cell interaction. Whether these changes of the B cell phenotype are of major importance regarding the long-term effects of SIT has to be determined in future studies.

Another new approach to target IgE as an effector molecule of type-I-allergic reactions is the usage of anti-IgE. However, the data from recent studies suggest that anti-IgE is only effective if the serum IgE is completely abolished [31, 32]. Considering that patients suffering from EADS usually exhibit extremely high total serum IgE-levels (above 2000 kU/l) one can easily conclude that such therapy will need a conscientious efficacy and cost analysis before consideration. However, such studies would demonstrate for the first time the exact pathophysiological role of IgE in atopic dermatitis. From experimental data, we also know that molecules from the nuclear hormone receptor family such as peroxisome proliferation acti-

**Table 26.3.** Alterations of immunological parameters during specific immunotherapy

Target cells	Effects
Basophils	↓ Histamine, leukotriene release
Eosinophils	↓ Tissue infiltration
<b>Lymphocytes/monocytes</b>	
Surface markers	↓ IL-4R, CD23, CD40L, CD25, HLA-DR, CD69
Cytokines	↓ IL-4, IL-5, IL-13 ↑ IL-10 ↓↑ IFN $\gamma$
<b>B-lymphocytes</b>	
Ig-secretion	↓ IgE ↑ IgG4
Surface markers	↓ CD32, CD23, CD5, CD54, HLA-DR



vating receptor ligands abolish IgE-production in vitro [33]. Whether such molecules will also be applicable for the treatment of severely affected AD patients will need to be determined by prospective clinical trials.

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