Chapter 2
The Biology of IgE: Molecular Mechanism Restraining Potentially Dangerous High Serum IgE Titres In Vivo

Gernot Achatz, Gertrude Achatz-Straussberger, Stefan Feichtner, Sebastian Koenigsberger, Stefan Lenz, Doris Peckl-Schmid, Nadja Zaborsky, and Marinus Lamers

Abstract Our knowledge about the regulation of the expression of IgE and its biological function is at best limited. We do, however, know that the production of IgE is tightly regulated which is reflected by the fact that the steady-state serum levels of IgE in mice and humans are 3–4 orders of magnitude lower if compared to IgG1, which is an immunoglobulin isotype expressed in response to the same cytokine milieu. What are the rate-limiting steps responsible for this discrepancy? In the following chapter six molecular mechanisms restraining IgE levels will be discussed in detail. The understanding of these mechanisms, combined with the analysis of the biological function of the IgE molecule during an immune response, is the prerequisite for the establishment of new systemic IgE-targeted therapeutic strategies in the future.

2.1 Introduction

IgE is an evolutionary conserved member of the immunoglobulin (Ig) family. Compared to all other Ig classes, which are present in concentrations of micrograms to milligrams per ml serum, the titre of IgE is very low (nano- to micrograms per ml range) in plasma of normal healthy individuals and of normal laboratory mouse strains. IgE is most prominent in epitheliae and mucosae where it is bound to specific receptors on highly potent effector cells like eosinophilic granulocytes and mast cells. Bound to these cells IgE has a long half-life (weeks to months), while free in plasma the half-life is very short (~6 hours). This suggests that IgE plays a role in local immune defence mechanisms. However, the core function for IgE is still unknown. From an evolutionary point of view, IgE is conserved and can be found in all mammalia, including monotremata [1]. It therefore originated at least 160 million years ago, possibly even more than 300 million years ago [2], from a gene duplication of IgY, in which the anaphylactic and opsonic activities of IgY were separated,

G. Achatz (✉)
Department of Molecular Biology, University of Salzburg, Salzburg, Austria
e-mail: gernot.achatz@sbg.ac.at

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giving rise to IgE and IgG, respectively [3]. Apparently, in an evolutionary sense, anaphylactic defence mechanisms are needed but at a potentially high price to the organism. The division of anaphylactic and opsonic activities in separate genes allowed principally a tighter and more specific control of both immune mechanisms. In these days IgE is best known for its strong, unwanted effector functions, in the form of allergic reactions [4]. These can range from annoying, local symptoms, like hay fever, to life-threatening, systemic reactions like anaphylactic shock. This underlines the potential hazard of high systemic IgE titres. Remarkably, over the last four decades the incidence of allergic disease has risen. This represents an intriguing problem from a medical, epidemiological, immunological, genetic and evolutionary view. Unfortunately, it is also a major socio-economic problem. One interpretation of these data is that control mechanisms, which were adequate in the past and honed in evolution, are failing.

In the recent past others and we have described several B-cell-specific control mechanisms that indicate a tight control of the IgE response, in agreement with the arguments mentioned above, and that are different from the opsonic type of response (Fig. 2.1):

1. Reduced IL-4-dependent class switch recombination (CSR) to the ε heavy chain (ε-HC) locus in comparison to the γ-1 (γ1)-HC locus [5].
2. Short half-life of free IgE in serum, limiting the risk of a systemic anaphylactic reaction [6].
3. Negative feedback function of CD23, the “low” affinity receptor for IgE, resulting in an in-time and quantity-restricted response [7].
4. Direct impact of the membrane (m)IgE receptor on the quality and quantity of the IgE response in vivo [8, 9].
5. Poor expression of mRNA for the membrane form of both the murine and the human ε-HC, but not for the murine γ1- and the corresponding human γ4-HC [8, 10], resulting in limited expression of IgE as a membrane-bound, antigen-receptor-type molecule [8, 9, 11].
6. Lower chance to contribute to the long-lived plasma cell pool and thus to humoral immunologic memory [12].

In the present review we want to describe these molecular mechanisms and discuss their biological impact on the IgE level in detail.

2.2 Reduced Class Switch Frequency to the IgE Locus

During an immune response, B lymphocytes can switch the Ig isotype from IgM to IgG, IgE, or IgA. This Ig-CSR is based on a DNA recombination event that results in an exchange of the gene segments coding for the constant region of the Ig heavy chain, while retaining the Ig heavy chain variable region. This process changes the effector functions of the corresponding antibody. Much of our current

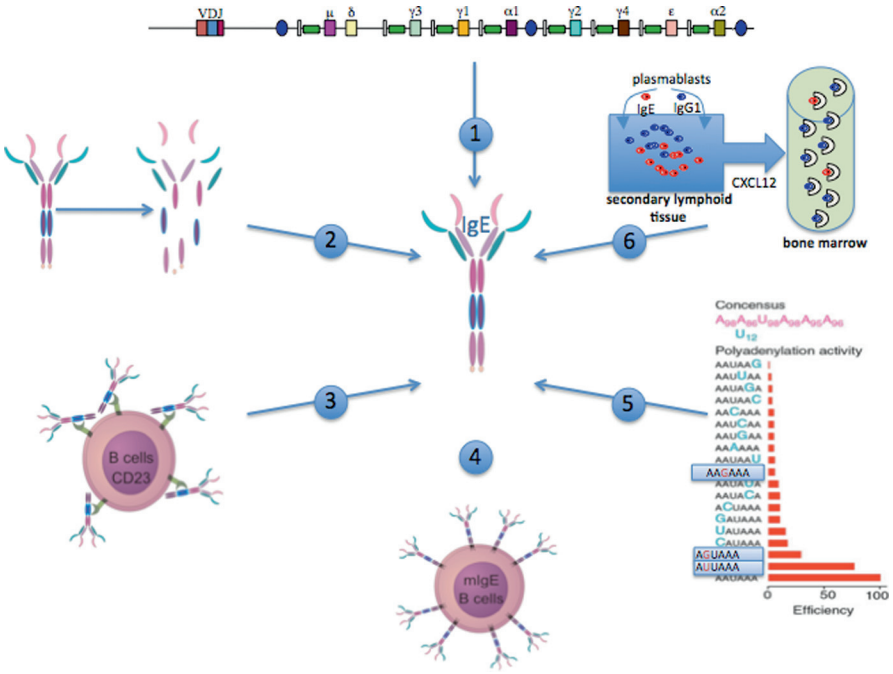

Fig. 2.1 Schematic overview of B-cell-specific control mechanisms, tightly regulating IgE expression in vivo (1) class switch recombination: Although class switching to IgE and IgG1 is induced by the same cytokine milieu followed by similar signal transduction pathways, a 6-fold reduced switching frequency to IgE is observed. (2) Serum half-life: IgE was reported to degrade between 5 and 12 hours, thus displaying the shortest half-life of all immunoglobulin isotypes. (3) Negative feedback regulation by CD23: CD23-knockout mice show a 6-fold increase in serum IgE level. (4) The IgE antigen receptor: Regulation of quantity and quality of the IgE response directly correlates with the surface expression of mIgE. (5) Alternative polyadenylation: In contrast to all other isotypes, the mIgE-RNA gets polyadenylated by three cryptic poly(A) sites. (6) Plasmablast migration: IgE plasmablasts have an intrinsic lower chance to contribute to humoral memory than IgG1 plasmablasts

understanding of the molecular mechanisms of CSR is based on the analysis of in vitro switched B cells where murine and human naïve B cells can be activated by bacterial lipopolysaccharides (LPS), anti-CD40, or CD40L to undergo CSR. Cytokine signals can direct CSR to distinct classes, e.g. interleukin-4 (IL-4) will target murine IgG1 and IgE, and human IgG4 and IgE, respectively. Class switch to IgE is a very rare process [5], which is tightly regulated and can thus be considered as a further means to keep serum IgE low.

CSR (Fig. 2.2) requires transcription of the S regions, which are located upstream of each isotype constant exon and which subsequently become a substrate for the activation-induced deaminase (AID). AID was first discovered by Muramatsu et al. [13] and soon turned out to be the central enzyme in CSR and hypermutation [14]. AID belongs to the RNA editing deaminase family. It could be shown that AID actually acts on DNA of Ig VDJ and S regions rather than on RNA, thereby deaminating

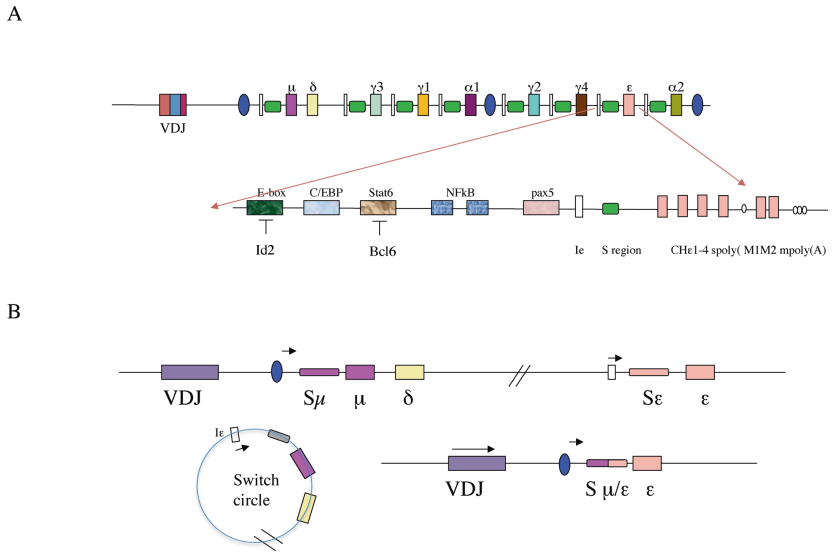

Fig. 2.2 The human immunoglobulin locus exhibits an upstream VDJ arrangement followed by several constant regions of different isotypes (**A**). Each isotype (except IgD) consists of a switch region, which has an upstream promoter/I exon region and downstream constant exons for the secreted Ig molecule followed by a poly(A) site for secreted antibody followed by exons M1 and M2 coding for transmembrane and cytoplasmic domains of the respective isotype and a poly(A) site for the membrane version. Also indicated are the promoters of the V, D and I exons and the internal enhancer elements as well as the 3′ enhancer. Identified transcription factor sites for the Iε promoter are indicated. (**B**) Upon transcription of the S region, RNA and DNA form a stable R-loop and AID gets access to the S regions and deaminates them causing U/G lesions. These lesions are causing DNA breaks, which ultimately lead to DNA recombination and excision of the intervening DNA as a switch circle

C to U [15]. The generated uracils are subjected to general repair mechanisms, which cause single- and double-stranded DNA breaks [16]. Joining of these ends, presumably by non-homologous end joining mechanisms, ultimately leads to CSR and the excision of the intervening DNA in a switch circle [17]. The central role for AID in CSR and hypermutation was not only shown in AID knockout mice [14] but also in patients who harbour defective AID gene expression or non-functional AID mutants [18]. Further elements are thought to contribute to the Ig isotype-specific targeting of CSR, such as the exact composition of the S region—including stem loop structures, chromatin and DNA modifications, promoter regions and germline transcription (GLT) levels (*cis*-acting elements) – as well as *trans*-acting factors that target the CSR machinery to distinct S regions.

Evidence for the necessity of GLT preceding CSR has come from studies in which deletion of promoter elements that abolished GLT also impaired CSR [19]. Vice versa, enforced transcription of S regions by constitutive or inducible promoter elements leads to induced CSR. This could be shown in knock-in experiments [20] as well as in artificial switch substrates introduced into B-cell lines and even in non-B cells that ectopically express transgenic AID [21]. In any S region, GLT initiates

from a promoter upstream of the germline CSR region (S region). The GLTs comprise a small 5′ exon—termed I exon, which is located upstream of the respective S region—spliced to the normal constant heavy chain exons with the intervening S region spliced out from the primary transcript [22]. To exploit GLT as a regulatory mechanism in isotype specificity of CSR, each germline promoter consists of a unique set of transcription factor (TF)-binding sites. In case of the ε germline promoter, it could be shown that treatment of primary B cells with the mitogen LPS and IL-4 is sufficient to trigger GLT from IgE [23].

Mitogenic signals like LPS or stimulation of CD40 [24] or signals transmitted by BAFF/April interacting with BAFFR/TACI/BCMA on B cells [25] lead to activation of NF-κB, which binds to the ε promoter together with the TF Stat6 that becomes activated upon IL-4/IL-13 signalling [26]. As shown in Fig. 2.2, several other TFs were identified, which can bind to the ε GL promoter like B-cell-specific activation protein (BSAP or Pax5) [27], c-Rel [28], C/EBP and AP1. AP1 only transactivates ε GLT from the mouse, but not from the human promoters [29]. TFs that repress transcription from the ε promoter are B-cell lymphoma 6 (Bcl-6) and Id2. Bcl-6 was shown to repress IL-4-induced CSR by competing for Stat6-binding sites within the ε and γ1 promoters [30] and Id2 binds to E2A TFs, thereby inhibiting their binding to ε promoter elements [31]. Possibly, TFs of the E2A group (E12 and E47) might also play a role in targeting AID to distinct promoter elements of the Ig locus [32] where AID might interact with the transcriptional complex to deaminate S regions [33]. In mouse cell lines, also the TF Ikaros was shown to dampen IgE and IgG GLT by binding to the germline promoter [34]. Schaffer et al. [35] showed that the homeodomain proteins HoxC4 and Oct-1 could bind to Iγ and Iε promoters to decrease levels of GLT and thus diminish CSR to IgG and IgE [35, 36]. There is also evidence for the 3′ enhancer of the Ig locus to selectively interact with promoter regions of the GLTs, in particular with the GL ε and γ2b promoters, which might help to target the recombination machinery to the distinct switch regions [37–39]. However, GLT without splicing of the primary transcript is not sufficient to target switch recombination as deletion of the splice donor site of the Iγ1 exon impaired CSR to IgG1.This shows that CSR also requires processing of the GLTs [40]. Stimulation of B cells with mitogenic signals and IL-4 not only induces GLT from the IgE—but also from IgG1−promoter, which exhibits similar TF-binding sites in its promoter region [41].

The observation that in single B cells more than one isotype-S regions are transcribed [42], together with the fact that AID-mediated DNA deamination is primarily restricted to the Ig locus and is not coupled to all genes that are transcribed in the B cell [22], implies that there have to be further levels of isotype-specific CSR regulation. Initially, it was proposed that due to the high GC contents, S regions are forming stable RNA–DNA hybrids (R-loops) upon transcription, in which the non-template strand remains single stranded and thus serves as a substrate for AID-mediated deamination [43]. However, AT-rich S regions, which are not prone to stable R-loop formation, are also effectively targeted by the CSR machinery, which implies the existence of R-loop-independent AID-recruiting mechanisms [44]. Larson et al. [45] propose that the tertiary G4 DNA structure of transcribed S regions allows specific attraction of repair proteins to S regions, thereby promoting

DNA synapsis and recombination. In addition, histone modifications such as phosphorylation, acetylation and methylation were found to occur in S regions accessible for CSR [33, 46, 47], which were not necessarily coupled to changes in the level of GLT [48]. Additionally, S region length was shown to affect the efficiency of CSR [49]. From these data, it is tempting to speculate that slight differences in S region length, composition and tertiary structures might generate isotype-specific protein-binding sites responsible for isotype-specific targeting of AID to individual S regions. In addition, the C-terminal domain of AID was found to be important for CSR but not for hypermutation, which leads to the assumption that CSR-specific factors might interact with the C-terminal domain of AID to either target AID to specific S regions or to mediate specific DNA synapsis and recombination [50]. Currently, the only published interaction partner for AID is the DNA-binding protein RPA (replication protein A) [51], which binds to AID upon phosphorylation by protein kinase A [52]. Binding of RPA to AID in vitro enhances the ability of AID to deaminate cytidines within transcribed double-stranded DNA and probably targets AID to the S region DNA. Further factors that are important in regulating CSR by yet obscure mechanisms, which do not exclude physical interaction with AID/CSR machinery, are the TF bach2 [53], E47 [32] and swap70, the latter could be shown to have a positive effect specifically on the IgE response in mice [54].

The puzzling phenotype of patients with Job′s or hyper IgE syndrome [55–57] (chronic eczematous dermatitis, recurrent skin and sinopulmonary tract infections, mucocutaneous candidiasis, coarse facies and a remarkably elevated serum IgE level) now seems to be solved and sheds additional light on the complexity of IgE immune response. Job′s syndrome is caused by mutations in the DNA-binding domain or the SH2 domain of the TF Stat3 [58, 59]. Whereas the infectious traits of Job′s syndrome can be explained by a deficiency in Th17-cell development [60, 61], which severely impairs immune responses to certain bacteria and fungi, the extremely high IgE levels are more diversely discussed. Stat3 is involved in many signalling pathways [62] and the most important TF in IL-21 signalling. In the mouse IL-21 or IL-21R deficiency has been correlated with low levels of serum IgG1 and high levels of IgE [63]. This may be due to an inhibition of CSR to IgE, because IL-21 induces ID2 expression [64]. Stat3, however, also transduces signals for the IL-6 family and the IL-10 family of cytokines and can induce several effector cells, like T and NK cells to produce IFN-γ [62]. All these factors can by themselves influence CSR to the IgE locus and influence the amount of IgE produced [62]. The influence of many ILs and cytokines on the level of expression of IgE clearly incorporates IgE in ongoing immune responses, yet without a clear hint to its core function.

2.3 Serum IgE Has the Shortest Half-Life of All Serum Immunoglobulins

The half-lives of several sets of murine monoclonal antibodies (mAbs) expressing the same V region in combination with all isotypes of serum Igs were determined by Vieira et al. [6] (Table 2.1). IgE was reported to degrade between 5 and 12 hours

Table 2.1 Serum half-lives of immunoglobulins in rodents and humans

Immunoglobulin isotype	Serum half-life ($t^1/_2$)		
	Mouse[a]	Rat	Human[c]
IgM	2 days	1 days[e]	5–10 days
IgG1	6–8 days	2 days[e], 9–10 days[f]	21–24 days
IgG2	–	–	21–24 days
IgG2a	6–9 days	4–5 days[e], 9–10 days[f]	–
IgG2b	4–6 days	2–3 days[f]	–
IgG2c	–	4 days[f]	–
IgG3	6–8 days	–	7–8 days
IgG4	–	–	21–24 days
IgA	17–22 hours	27 hours[e]	–
IgA1	–	–	5.9 days
IgA2	–	–	4.5 days
IgE	12 hours[a], 5–8 hours[b]	13.1 ± 5.7 hours[d]	1–5 days

[a]Vieira et al. [6], [b]Haba et al. [65], [c]Leffell et al. [168], [d]Hanashiro et al. [67], [e]Peppard and Orlans [169] and [f]Medesan et al. [170].

[6, 65], thus displaying the shortest half-life of all Ig isotypes. Additionally, alterations in the half-life of IgE were reported in dependency of the site of application. Hirano et al. [66] published that intravenously injected murine anti-DNP-IgE persisted for 12 hours whereas intradermally injected IgE was stable for at least 6 days. Similar half-lives for rat IgE (13.1 ± 5.7 hours) were published by Hanashiro et al. [67].

Waldmann et al. [68] hypothesized that an increased catabolic rate of IgE is dependent on the existence of intravascular and/or extravascular compartments. Human IgE is metabolized mainly in the extravascular compartment and the catabolism of IgE is related to the interaction of IgE with Fcε-receptor (FcεR)-bearing cells. In contrast, it has also been speculated that the vascular endothelium represents a site of catabolism of IgE. Interestingly, an FcRn (Brambell receptor [69]) knockout reduced the serum half-life of IgG1 in mice from 9 to 1.4 days. Thereby, IgG1 in FcRn-knockout mice has roughly the same half-life as all other Ig isotypes in mice [70]. Moreover, Lu et al. [71] generated transgenic mice that overexpressed the bovine FcRn (bFcRn) in their lactating mammary glands. Significantly increased IgG levels were observed in the sera and milk from transgenic animals, suggesting that the overexpressed bFcRn binds and protects endogenous mouse IgG and thus extends its life span. These results indicate that the main reason for the difference in the half-life time between IgG and IgE is explained by the stabilizing interaction between IgG and FcRn. Additionally, the MHC class I-related protein FcRn, originally identified by Simister and colleagues [72, 73] plays a critical role in IgG homeostasis by protecting IgG from normal protein catabolism, which results in a substantial increase in the half-life of IgG.

Similarly, the interaction between IgE and FcεRI stabilizes both partners, increasing the half-life of cell-bound IgE to months. The decreased sensitivity to decay

is accompanied by a conformational change in the three-dimensional structure of IgE: binding to the FcεRI causes the protein to open up from a bent shape into a more stretched shape, leaving the antigen-binding sites intact [4]. The majority of IgE in the body is probably bound to FcεRI on basophils and mast cells, whereas IgG is primarily found in the free, circulating form. Nevertheless, the short half-life of unbound (free) IgE in the blood limits the danger of a systemic anaphylactic reactions.

2.4 CD23 Influences IgE Expression by a Negative Feedback Inhibition

In humans two isoforms, CD23a and CD23b, differing in the first six cytoplasmic amino acids [74, 75] were described. While CD23a is constitutively expressed on B cells and follicular dendritic cells, CD23b, after IL-4 stimulation, is expressed on a variety of hematopoietic cell types like B cells, monocytes, eosinophils and Langerhans cells [75–77]. For a long time only one CD23 isoform was known in mouse, corresponding to human CD23a, but recent studies also described the existence of the CD23b isoform. However, CD23 expression in mouse is restricted to B cells (CD23a) and follicular dendritic cells (CD23a and CD23b) [78–80].

Unlike other Fc receptors, CD23 does not belong to the Ig superfamily of proteins, but is a 45 kDa type II transmembrane glycoprotein comprising a C-terminal lectin domain, followed by a stalk region, a transmembrane domain and a short cytoplasmic tail [81, 82]. The lectin domain binds IgE via the Cε3 domain in a calcium-dependent way [83, 84]. CD23 is expressed on the cell surface as trimers [82, 85]. Oligomerization mediates high-affinity binding to IgE, where two lectin heads bind to one IgE molecule [82]. CD23 binds IgE with both a medium affinity ($4–10 \times 10^7\ M^{-1}$) and a low affinity ($4–10 \times 10^6\ M^{-1}$) [86]. Besides this membrane-bound form (mCD23), CD23 also exists as soluble fragments of different sizes (sCD23) when cleaved by an autocatalytic mechanism mediated by the metalloprotease ADAM10 [87, 88]. With the exception of one soluble fragment, all of them contain the IgE-binding lectin domain and can bind IgE with low affinity in the range from 10^5 to $10^6\ M^{-1}$ [89].

CD23 is a pluripotent molecule; its biological functions include cell activation and proliferation, cell adhesion, IgE-dependent antigen transport, processing and presentation as well as regulation of IgE synthesis and expression. However, the most striking phenomenon is CD23′s ambiguous function on IgE regulation, both in activation and/or inhibition of IgE production. Several studies with CD23-deficient and CD23-overexpressing mice clearly demonstrated CD23′s role as a negative feedback regulator of IgE production [90–95]. Yu et al. [7] showed that disruption of the CD23 gene led to increased specific IgE levels after immunization with TD antigens. While IgG1 levels were twice as high after immunization with 2,4-dinitrophenyl-ovalbumin (DNP-OVA), specific IgE levels were 6–12 times higher in these mice. In contrast, mice overexpressing CD23 produce much lower amounts of IgE, confirming CD23 as a potent regulator of IgE production. Experiments with

New Zealand black mice, which cannot form trimers of CD23 and therefore show impaired high-affinity binding of IgE, also have an exaggerated IgE response [96]. Furthermore, anti-CD23 antibody treatment inhibits specific IgE responses and anti-stalk antibodies enhance IgE production and promote cleavage of mCD23 [97–102]. This increase can be attributed to the prevention of cooperative association of the IgE-binding lectin domains, therefore interfering with oligomerization and high-affinity binding of CD23 [85, 98]. Kilmon et al. [98] demonstrated that RAS1, an anti-stalk antibody, not only prevents oligomerization of CD23 but also inhibits the release of mCD23 [98]. Mice treated with RAS1 and immunized with KLH-DNP/Alum with pertussis toxin also expressed higher levels of IgE, comparable to $CD23^{-/-}$ mice. mAB 19G5 also inhibited high-affinity IgE binding and led to increased IgE levels, but unlike RAS1, 19G5 favoured cleavage of mCD23, leading to elevated sCD23 levels (100–150-fold) [85, 103]. Kinetics of the IgE response were comparable with a primary immune response. Thus, here the elevated serum levels were simply the result of cytophilic release of CD23-bound IgE. Ford et al. [103] also showed that IgE levels are increased even in the absence of Ag-alum, indicating that CD23′s negative regulation of IgE can be abrogated by destabilizing CD23. These results clearly revealed CD23′s ambiguous function on IgE regulation: while stabilized mCD23 negatively regulates IgE production, destabilization of mCD23 leads to an increase of IgE.

Summarizing, in the early phase, IL-4 activates expression of both IgE and CD23, whereas later on, when IgE levels have reached a certain threshold, binding of IgE to CD23 stabilizes and prevents degradation of CD23. This inhibits ongoing IgE synthesis and dampens the immune reaction. However, CD23 seems to play only a role in regulating moderate amounts of IgE: first, helminth-infected wild-type and $CD23^{-/-}$ mice showed the same IgE response [7] and second, destabilization of mCD23 via 19G5 treatment did not lead to an increase of IgE in helminth-infected mice [103].

Many studies have been performed to address the mechanisms behind CD23′s regulatory function. Aubry et al. [104] showed that sCD23 enhances IgE synthesis by binding to CD21 on peripheral blood B cells. Christie et al. [105] prevented autocatalytic cleavage of mCD23 and measured reduced IgE levels. In contrast, Texido et al. [92] showed that transgenic mice for sCD23 exhibited no phenotype, indicating that it is the membrane-bound form of CD23 that regulates IgE production. Ford et al. [103] investigated the role of CD21, a natural ligand for CD23. By using CD21-deficient mice it could be demonstrated that the 19G5-induced IgE response is independent of CD21 signalling, suggesting that increased IgE levels can be attributed to the loss of mCD23 and the release of CD23-bound IgE and not to the accumulation of sCD23 [103]. Recent studies from McCloskey et al. [106] showed that sCD23 both inhibits and stimulates IgE production, depending on the structure of the fragments: while sCD23 monomers inhibit IgE synthesis in human B cells, oligomers stimulate synthesis by co-ligating IgE and CD21 on IgE^{+} B cells.

Summarizing, binding of IgE to mCD23 stabilizes the trimer and prevents its degradation, thus inhibiting the autocatalytic release of sCD23 fragments, which stimulate (in oligomeric form) IgE synthesis. Data from McCloskey et al. [106]

confirmed the competition model between CD23 and CD21 for membrane-bound IgE on the B-cell surface proposed by Hibbert et al. [107]. Co-cross-linkage of mCD23 and mIgE by an IgE/Ag complex results in a decrease of IgE; co-cross-linking of CD21 and mIgE by sCD23 leads to an increase of IgE [107]. Still, the mere absence of CD23, as we have seen, suffices to increase IgE responses.

2.5 The Biological Function of the mIgE Antigen Receptor on IgE Synthesis In Vivo

The B-cell receptor (BCR) is undoubtedly the most important component of a B cell′s interface regarding communication with the local environment. Main developmental steps taking place in the bone marrow like signalling through the pre-BCR as well as avoiding autoreactivity by clonal deletion or receptor editing utterly rely on the expression of a functional receptor. In the periphery, the BCR is one of the driving forces establishing antibody responses addressing invading pathogens and it has been shown to be essential for maintaining peripheral B-cell tolerance in the case of B-cell anergy [108]. Regarding mIgE, the relevance of the receptor seems restricted to responding secondary lymphoid organs like the spleen, lymph nodes and Peyer′s patches. Here, the decision to switch to $mIgE^+$ plasmablasts and finally to IgE-producing antibody-secreting cells (ASCs) is being made in an adequate cognate T-cell-help and cytokine context [109].

mIgE, in contrast to its soluble form, contains three additional structural features encoded by exon M1 and M2, namely the *EMPD* (extracellular membrane-proximal domain) domain, the *transmembrane domain*, which anchors the receptor in the cell membrane and serves as interaction domain for the CD79α/β sheath to form the BCR [110, 111] and the *cytoplasmic domain*. The EMPD regions of the five isotypes differ in length and amino acid composition. In human IgE two functional forms of ε_{EMPD}, namely ε_{short} and ε_{long}, exist composed of 14 and 66 amino acids, respectively [112–114]. According to a study of Poggianella et al. [115] carried out in the mature murine B cell line A20, the presence of the EMPD region is of critical importance for mobilizing intracellular Ca^{2+}, with the EMPD′s length apparently being the "sensor" of caspase-independent apoptosis sensitivity. A similar phenomenon of inhibition of proliferation has been reported in murine WEHI-231 cells transfected with the shorter human version of mIgE [116]. This study also showed that the rate of transport by which the two forms are brought to the cell surface as well as the association with CD79α and the kinetics of protein tyrosine phosphorylation in response to receptor cross-linking differs between the short and the long version. Thus, the form of the EMPD region might have an essential function in shaping the repertoire of $mIgE^+$ plasmablasts selected towards the long-lived plasma cell fate.

A step forward in the understanding of the role of mIgs other than mIgM or mIgD was achieved with two mouse lines with mutations in the ε-HC gene. In the first, the intracellular domain of IgE was removed except for three amino acids (Lys, Val and Lys) (KVKΔtail line). The cytoplasmic domain of IgE in these mice is the same as

that of mIgM and mIgD. In the second line both the intracellular and the transmembrane domains of IgE (ΔM1M2 line) are lacking [9]. In ΔM1M2 mice serum IgE is reduced to less than 10% of normal mice, while KVKΔ tail mice show a reduction of 50%, reflecting a serious impairment of the IgE-mediated immune response. Class switch to IgE was not impaired by the targeting event. Upon stimulation of isolated spleen cells of wild-type, ΔM1M2 and KVKΔtail mice with LPS and IL-4 in vitro, concentrations of IgE and IgG1 in the culture supernatants were comparable in wild-type and mutant mice. These results imply that the reduced IgE titres found in both mutant lines are solely a reflection of the loss of biological activities associated with the transmembrane and cytoplasmic domains of IgE. These data clearly show that the transmembrane domain of IgE is indispensable for a T-cell-dependent IgE-mediated immune response and that the cytoplasmic tail not only determines the absolute amount of IgE produced but also the quality of the antibodies. How does this work?

Two hypotheses can be brought forward. The first implies that signals generated via membrane-bound Ig are needed at all times, not only for the maturation process, but also for the expansion of antigen-specific cells. The second hypothesis postulates that antigen presentation to T-helper cells is necessary at all times during an antibody response and that the antigen receptor is the only device for an effective antigen presentation. The hypotheses are not necessarily mutually exclusive. All Ig classes can associate with the Ig-α/Ig-β heterodimer [117], the signal-transducing unit of the BCR. Recent experiments have shown that an intact antigen receptor on B cells is elementary for the survival of B cells [118]. It is not clear from these experiments which function the antigen receptor performs: interactions with external ligands, maintenance of a tonic signal generated by the mere presence of the receptor in the membrane, or capture of antigen. Both the Ig-α/Ig-β sheath and the cytoplasmic tail of mIg [119] have been implied in guiding antigen bound via the receptor to the antigen-processing compartments. Key residues for internalization are present in the tails in the form of an YxxI/M motif. This could be a prerequisite for processes that are highly dependent on T–B cell interactions like somatic mutation and affinity maturation and the generation of memory cells, but also processes like the rescue from apoptosis and the induction of plasma cells. These considerations predict that the results we obtained in the KVKΔtail and ΔM1M2 lines can be extended to the IgG isotypes and perhaps to IgA. Indeed, Kaisho et al. [120] reached matching conclusions, studying mice carrying similar mutations in the γ1 gene. The phenotype of the mIgG mutants is, however, more prominent.

Further studies showed that upon receptor ligation, the mere cytoplasmic tails of γ and ε but not μ, δ, or α are capable of inhibiting CD22 phosphorylation and SHP-1 recruitment [121, 122]. Due to the fact that none of the cytoplasmic tails of mIgs contain full ITAM/ITIM motifs [123], tail-interacting proteins may influence downstream B-cell signalling cascades. A study of Batista et al. [116] identified two proteins, namely εBAP37 and εBAP41, being exclusively associated with the cytoplasmic tail of mIgE. Those two molecules were shown to be glycosylated and form disulphide-bonded complexes, with each having an extracellular domain. Recently, we described another protein, involved in mIgE-mediated

signalling, HS1-associated protein X-1 (HAX-1). HAX-1 turned out to be associated with the mIgE tail, being indispensable for the internalization of the receptor by linking it to the cytoskeleton via its interaction with HS1 [124].

Additionally, Erazo et al. [125] suggested a model, in which IgE^+ cells exhibit a plasma cell programme from early onwards, with signs of somatic hypermutation despite their exclusion from GCs, with repression of Bcl6 and upregulation of Blimp-1, a central TF in plasma cell differentiation [126]. They further hypothesized that expression of mIgE requires an intermediate $IgG1^+$ cellular phase, leading to high-affinity IgE antibodies without requiring a prolonged IgE^+ GC phase. In contrast, Kelly et al. [127] claimed that in their system of administering phOx-BSA into the footpad of mice and monitoring the response in brachial lymph nodes, the majority of IgE^+ cells are localized in GCs. The notion that CSR to IgE is an actively inhibited process, as was revealed in IL-21- and IL-21R-knockout mice, which are characterized by low IgG and high IgE titres [63], does not support a consecutive switch model. In respect to additional partially controversial literature [128, 129] one can speculate that not only the type and the amount of administered antigen, but also the route of administration and the involved cytokines seem to be of critical importance concerning the nature of the response.

2.6 Impaired Splicing and Polyadenylation Restricts the Generation of a Mature mIgE Transcript

Both of the mRNAs for the secreted and the membrane form of IgHCs are generated from the same precursor mRNA by means of alternative splicing and polyadenylation. The third (IgD and IgGs) or fourth (IgM and IgE) constant exon, which is located 5′ of the transmembrane and the cytoplasmic exons, is a composite exon: it contains an internal splice donor site which is used when mRNA for membrane-bound Ig is made. It is also followed by an "internal" polyadenylation-addition site that is used when mRNA for secreted Ig is made. A 3′ "external" polyadenylation-addition site is found downstream of the membrane exons. With the exception of IgE, the consensus sequence AATAAA is used for the "internal" and the "external" polyadenylation signals. Looking at the mRNA levels of both forms in the course of B-cell development, a shift in the membrane-to-secreted ratio can be observed [130]. While resting B cells produce similar amounts of both mRNA′s, the ratio changes in favour of the secreted form in activated B lymphoblasts and in the terminally differentiated B cell, the plasma cell, mRNA for the secreted form is 20–100 times higher abundant than mRNA for the membrane form. This change in the membrane-to-secreted ratio does not seem to be caused by an increase in transcription rate, since the heavy chain enhancer is already completely active in the pre-B-cell stage [131]. This shift is far more likely generated by a selective increase in the processing rate and in the stability of secretory mRNA [132]. It is known for a long time that polyadenylation has a paramount effect on mRNA stability, nuclear export and translation. The process of polyadenylation requires numerous factors responsible for the

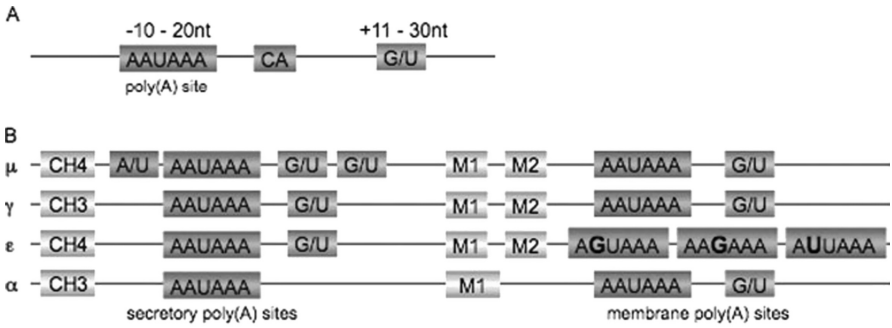

Fig. 2.3 Polyadenylation consensus sequences of mouse immunoglobulin isotypes. (**A**) An ideal polyadenylation consensus sequence (AAUAAA) and a perfectly positioned GU-rich region is shown. "CA" marks the site of actual cleavage and subsequent polyadenylation. (**B**) The secretory and membrane poly(A) sites of the immunoglobulin isotypes in mouse are shown. All sites except ε membrane poly(A) have a single AAUAAA consensus sequence. The ε membrane poly(A) site is made up of three "cryptic"-poly(A) sites. The μ secretory poly(A) site depicts a distinct dual structure, which is not found in the other isotypes. It has an upstream AU-rich region and two suboptimally placed GU-rich motifs, weakening the μ secretory poly(A) site

recognition, cleavage and addition of the poly(A) tail. Two multisubunit complexes, designated cleavage-polyadenylation specificity factor (CPSF) [133–135] and cleavage stimulation factor (CstF) [136], cooperate with each other to define the site of polyadenylation [137, 138]. They recognize the highly conserved AAUAAA hexanucleotide (Fig. 2.3) [137, 139] and a more divergent GU-rich sequence located downstream of the actual cleavage site [140–142]. Two additional factors, cleavage factor I and II (CFI and CFII), are further necessary for the cleavage reaction [135]. For the poly(A) synthesis itself, CPSF and poly(A) polymerase [143–145], together with poly(A)-binding protein II (PAB II), are sufficient, although CstF was recently shown to enhance this reaction [146]. A subunit of the CstF, CstF-64, was shown to be expressed in a stage-specific manner in B cells expressing IgM [141, 147]. It was speculated that in resting B cells, where CstF-64 is less abundant, the poly(A) site for the membrane form of μ (μm poly(A) site) is preferred over that of the secreted form (internal or μs poly(A) site). The higher amount of CstF in activated plasma cells leads to the better recognition of the "weaker" internal μs poly(A) site [147]. A supposed mechanism for this phenomenon is that polyadenylation of the μs poly(A) site takes place before transcription over the μm poly(A) site can proceed. However, this phenomenon was found to be valid for IgM [148–150] but not for IgG and IgA [151–153]. For IgG2b, not the increasing amount of CstF-64 during B-cell development is important but rather the improved binding and polyadenylation efficiency [154]. Further, Yan et al. [44] postulated a specific activity in B-cell extracts that selectively impairs the formation of a μs poly(A) site processing complex, suggesting that the function of this poly(A) site may be regulated by both positively and negatively acting factors. Additionally, the sequence of the intron 5′ of the M1 exon can influence the polyadenylation/splicing balance. For IgA a specific sequence in

the Cα3-Mα1 intron is recognized by a 58 kDa protein and leads to a predominant usage of the αs poly(A) site [153, 155]. In this special case, the ratio of αs-to-αm IgA in resting B cells is about 2. Therefore it is possible that *cis*-acting elements unique to each HC gene act upon a common mechanism regulation Ig mRNA processing.

The ε-HC gene differs from the Ig genes as to its 3′ external εm poly(A) site (Fig. 2.3). Here, three kryptic "external" polyadenylation signals (AGTAAA, AAGAAA and ATTAAA) are found, which are in considerable disagreement with the consensus sequence (AATAAA). As we have seen, the ratio of transcripts for the secreted and the membrane form of Ig reflects the usage of either polyadenylation signal. The poor 3′ polyadenylation sites in the ε gene unfavourably influence the production of mRNA for the membrane form of ε [10]. One of the consequences of the restricted polyadenylation of the εm transcript is a limited stable pool of εm mRNA which further influences the poor expression of the membrane-associated IgE-BCR on switched B cells. Surface expression of the membrane form of IgE is paramount to the survival of IgE switched B cells [9]. Therefore, weak 3 ́processing of mε-mRNA seems to be a way to keep numbers of IgE-positive B cells and thus the titre of secreted IgE in the serum low.

Another interesting feature is that the human ε gene in vitro generates more than two mRNAs for the secretory and the membrane-associated forms, generated via alternative splicing and polyadenylation. Burrone et al. have found and characterized two functional membranes and two functional secretory isoforms out of six possible isoforms. All four heavy chains seem to assemble into proper Igs, although with different kinetics, and are functionally active as a receptor or as a mediator of a humoral immune response [116, 156, 157].

2.7 IgE Plasmablasts Have an Intrinsic, Lower Chance to Contribute to the Long-Lived Plasma Cell Pool

It is generally accepted that the switch of B cells expressing membrane-bound Igs, which serve as antigen receptors, to antibody-secreting plasmablasts and finally non-dividing, long-lived plasma cells, marks the terminal differentiation of a B cell. Thus, besides memory B cells, antibody-secreting plasma "memory" cells represent the key cell type for the maintenance of humoral immunological memory. Although some populations of long-lived plasma cells persist in the spleen, most of them return to their "place of birth" and invade the bone marrow or inflamed tissues where they survive as resident, immobile cells in survival niches up to several months [158–160]. However, the life span of plasma cells is limited by the immigration of newly formed migratory plasmablasts that compete with old plasma cells for their survival niches. In these niches, resident long-lived plasma cells are resistant to therapies targeting activated and/or proliferating lymphocytes, for example, by radiation [161] or cyclophosphamide [162]. The permanent and antigen-independent secretion of antibodies specific for allergens or autoantigens makes these cells key players in allergic and autoimmune diseases and obviously key targets for possible therapeutic interference.

The migration of plasmablasts to the bone marrow is a critical differentiation step for long-lived plasma cells. Little is known about the migration of ASCs in general and ASCs of IgE in particular. Chemokines and their receptors are crucially involved in the control of lymphocyte trafficking. Hauser et al. [163, 164] showed that migratory cells lose responsiveness to many chemokines, with the exception of chemokine ligand (CXCL) 12 and CXCL9. The corresponding receptors, sensitive for CXCL12 and CXCL9, were identified as chemokine receptor (CXCR) 4 and CXCR3, respectively. It has recently been suggested that the chemokine receptor CXCR4 is required for normal accumulation of plasma cells in the bone marrow [165], as demonstrated by the increased sensitivity of the CXCR4 receptor for its ligand CXCL12, which is mainly expressed in the splenic red pulp, the lymph node medullary cords and the bone marrow.

Muehlinghaus [166] first pointed out the importance of the antigen receptor for migration behaviour of memory B cells. It was shown that CXCR3 is preferentially expressed on a fraction of human memory B cells, in particular on those expressing IgG1. Further, $CXCR3^{-}$ memory B cells upregulate CXCR3 and migrate towards concentration gradients of its ligand only when co-stimulated with interferon γ but not with IL-4.

In order to analyse the migratory behaviour of memory B cells in the dependence of the isotype of the antigen receptor, we constructed "knock-in" mouse strain KN1, where we completely exchanged the membrane ε-genomic region downstream of the secretory poly(A) site for the membrane γ1-region [167]. Thus, in KN1 the IgE immune response develops under the regulation of γ1-specific cytoplasmic signalling. KN1 not only showed a significant increase in mRNA for the membrane and secreted ε-transcripts, but also a 6-fold increase in serum IgE. The continually accumulating serum IgE titre is the result of a selection advantage of chimeric mIgE-expressing B cells in KN1 mice for their immigration to the bone marrow. The γ1-based signalling in chimeric mIgE-B cells indicates the existence of an isotype-specific, antigen-receptor-dependent developmental programme for B cells to become long-lived plasma cells.

Summarizing, our data strongly support the concept that BCR-mediated signalling continues in the plasmablast stage and has an isotype-specific component: γ1-like signalling, in contrast to ε-like signalling, facilitates migration of plasmablasts towards the chemokine CXCL12, allowing them to settle in plasma cell niches, like in the bone marrow, and (thus) more efficiently induces progression towards the fully matured plasma cell stage. Our observations also lead to the conclusion that during a Th2-mediated immune response, in normal wild-type mice, IgE plasmablasts have an intrinsic lower chance to contribute to the long-lived plasma cell pool and thus to humoral immunologic memory than IgG1 plasmablasts.

2.8 Conclusions

Our knowledge about the regulation of the expression of IgE is at best limited. Unfortunately, a similar statement can be made regarding the function of membrane-bound IgE. We do, however, know that the production of IgE is tightly regulated.

This regulation is evident on the level of DNA (switch) recombination, transcription and RNA processing. It is not inconceivable that also post-translational processes may influence the expression of membrane-bound IgE. The consequences of a possible disregulation, i.e. uncontrolled IgE secretion, warrant an in-depth study of these processes.

Summarizing, IgE antibodies may have strong effector functions, but this contrasted with the slow IgE response and the limited development of memory responses. Together these observations represent mechanisms to restrain potentially dangerous, but apparently necessary, because present, high serum IgE titres at many different levels in a biological process.

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