

FcεRI-Mediated Activation of Transcription Factors in Antigen-Presenting Cells

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Key Words

IgE receptor · Antigen-presenting cells · NFAT · NF-κB · Transcription

Abstract

Professional antigen-presenting cells (APC) such as monocytes and dendritic cells (DC) bearing high-affinity IgE receptors (FcεRI) efficiently present IgE-bound antigens to T cells. FcεRI expression is upregulated on APC from atopic donors, especially in inflamed tissues. These data suggest a pathophysiological concept of an IgE-mediated delayed-type hypersensitivity reaction in atopic diseases. However, FcεRI ligation also leads to the synthesis of proinflammatory cytokines and other molecules involved in inflammatory reactions. The investigation of transcription factors mediating these effects has only recently commenced. In general, members of the NF-κB family are known to regulate APC function and differentiation, with the RelB subunit being especially important in DC generation. In addition, Ikaros and PU.1 have also been shown to be essential factors for DC differentiation, whereas Oct-2 is upregulated by differentiation towards macrophages. Recently, FcεRI has been demonstrated to induce NF-κB activation via IκB-α serine phosphorylation and degradation in monocytes and DC. Inhibitors of NF-κB activation such as N-acetylcysteine or N-tosyl-L-phenylalanine chloromethyl ketone can sup-

press FcεRI-induced TNF-α and MCP-1 release. Interestingly, in human epidermal Langerhans' cells (LC), NF-κB activation can only be observed when large amounts of FcεRI are present. In addition, the composition of NF-κB complexes differs between monocytes, monocyte-derived DC and LC, suggesting a cell type-specific regulation. Moreover, the transcription factor NFAT is induced upon FcεRI ligation in human APC. The elucidation of further transcription factors involved in FcεRI signaling in APC should contribute to the employment of new inhibition strategies for the treatment of atopic and other inflammatory diseases.

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Introduction

For a long time, studies on FcεRI function focused on effector cells of anaphylaxis such as mast cells and basophils. FcεRI on these cells has been identified as the central structure of immediate-type hypersensitivity reactions such as allergic rhinitis, urticaria or anaphylactic shock. Cross-linking of FcεRI on these cells by IgE and antigen induces a well-characterized cascade of signaling events terminating in the activation of various transcription factors, e.g. members of the AP-1 and NFAT family. The cellular events putatively controlled by these mechanisms are the release of preformed mediators such as his-

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tamine and heparin, as well as the synthesis of prostaglandins and cytokines [1, 2].

In the past decade, expression of FcεRI has also been detected on professional antigen-presenting cells (APC) such as dendritic cells (DC), including epidermal Langerhans' cells (LC) [3, 4] and blood DC [5], as well as peripheral monocytes [6]. These cells differ from mast cells and basophils in their function. They do not release preformed mediators but are suggested to control immune responses by very efficient antigen uptake followed by MHC-restricted presentation to T cells [7]. The FcεRI structure on APC consists of one α chain for IgE binding and two γ chains involved in signal transduction. In contrast to mast cells and basophils, APC lack the signal-enhancing β chain. FcεRI on epidermal LC is upregulated in atopic donors, with maximum expression found in lesional skin of patients with atopic dermatitis [8]. Together with several APC models showing that FcεRI on these cells can be used for effective antigen uptake and presentation to T cells [5, 9–11], these observations led to the concept of an 'IgE-mediated delayed-type hypersensitivity reaction' underlying atopic diseases [12]. However, the study of FcεRI signal transduction in APC, especially the activation of transcription factors responsible for FcεRI-mediated gene activation, has only very recently commenced.

Transcription Factors in APC and DC Function and Differentiation

Since human APC, and especially DC, exhibit various subpopulations with different functions, e.g. myeloid versus lymphoid DC or Th1-polarizing versus Th2-polarizing DC, and the pathways of their differentiation are not fully elucidated, studying the transcription factors that control these processes has become increasingly important. At present, only four major transcription factor families affecting APC/DC function and/or differentiation are known.

Firstly, a major role of NF-κB family transcription factors has been established. These molecules control the expression of many genes involved in inflammatory responses, e.g. genes for cytokines, chemokines, adhesion and costimulatory as well as HLA molecules [13, 14]. Upon stimulation, the five known NF-κB subunits p50, p52, p65/RelA, RelB and c-Rel form various hetero- and homodimers able to bind to specific promoter sequences in target genes. Initial evidence of the presence of NF-κB subunits in APC was provided by Feuillard et al. [15],

who showed p50 and p65 expression in human follicular DC, and Granelli-Piperno et al. [16], who showed p50, p65, RelB and c-Rel expression in human and mouse DC. An essential role of the RelB subunit in the differentiation of myeloid DC has been demonstrated using knockout studies [17, 18]. The RelB subunit also seems to be associated with an enhanced APC function of DC, since mature DC, which represent potent T cell stimulators, exhibit nuclear RelB, whereas immature DC do not [19]. Upregulation of nuclear p50, p52, RelB and c-Rel during DC maturation was also reported by another group [20]. In addition, NF-κB inhibition prevents lipopolysaccharide-induced final maturation of DC determined by MHC class II and costimulatory molecule upregulation [21].

Secondly, using mouse models, the transcription factors Ikaros and PU.1 have been shown to be essential for the development of DC [22, 23]. Furthermore, high Oct-2 expression seems to be characteristic for monocytes and macrophages, whereas during DC differentiation and maturation, a continuous downregulation can be observed [20]. However, most of the other known transcription factors have not been investigated with respect to a potential effect on APC/DC differentiation and function.

NF-κB: A Cell-Specific Regulator of FcεRI-Mediated Inflammatory Responses in APC

The central position of NF-κB in APC/DC function and differentiation on the one hand and the role of NF-κB in the regulation of immune responses and inflammatory processes on the other hand led us to question whether FcεRI ligation on human APC is able to induce NF-κB activation [Kraft S, Novak N, Katoh N, Bieber T, Rupec RA: Aggregation of the high affinity IgE receptor FcεRI on human monocytes and dendritic cells induces NF-κB activation, submitted]. We showed that FcεRI ligation induces rapid NF-κB activation in human APC such as monocytes, monocyte-derived DC (MoDC) and epidermal LC. It is controlled by serine phosphorylation of the inhibitory IκB-α molecule, followed by its degradation (fig. 1). Degradation of other IκB family members such as IκB-β could not be detected. This suggests that NF-κB activation in this case is self-limiting, since NF-κB is known to induce IκB-α but not IκB-β resynthesis [13]. Various inhibitors of NF-κB activation, such as the antioxidants N-acetylcysteine (NAC) and pyrrolidinedithiocarbamate as well as the protease inhibitor N-tosyl-L-phenylalanine chloromethyl ketone, are able to inhibit the

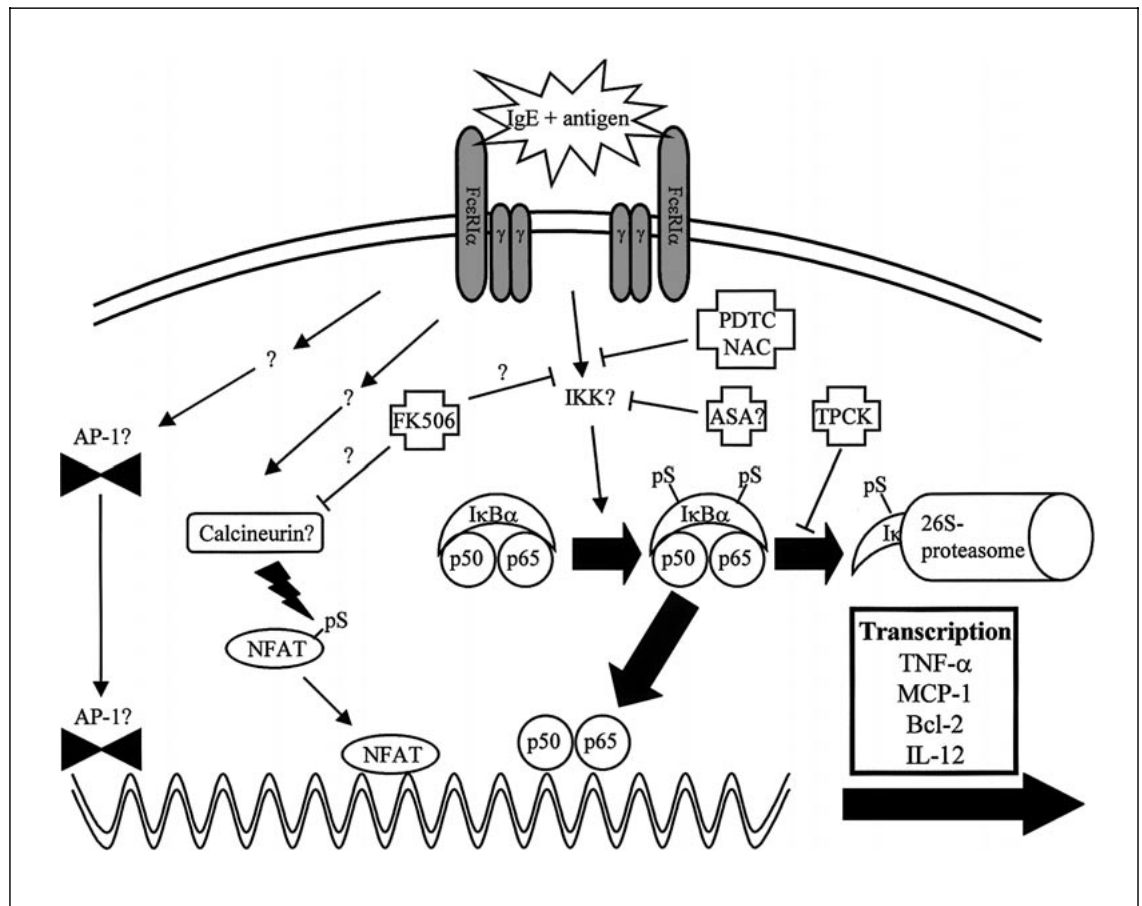


Fig. 1. Model for FcεRI-mediated transcription factor activation in APC. Ligation of FcεRI by IgE and antigen leads to binding of the transcription factors NF-κB, NFAT and putatively AP-1 to specific regulatory promoter sequences of target genes. These processes may lead to the transcription of target genes such as TNF-α, MCP-1, Bcl-2 and IL-12. FcεRI-induced NF-κB activation is a result of serine phosphorylation and proteasomal degradation of inhibitory IκB-α molecules. This step is sensitive to multiple inhibitory compounds and

putatively involves activation of IκB kinases (IKK). FcεRI-mediated NFAT activation is induced via presently unknown signaling molecules, potentially terminating in calcineurin-induced dephosphorylation at phosphoserine (pS) residues. The role of FcεRI-induced AP-1 activation is unknown, but it is probably required for cooperative NFAT activation. PDTC = Pyrrolidinedithiocarbamate; ASA = acetylsalicylic acid; TPCK = N-tosyl-L-phenylalanine chloromethyl ketone.

FcεRI-mediated production of the proinflammatory cytokine TNF-α and the chemokine MCP-1 in human APC. These data suggest a role of FcεRI-mediated NF-κB activation in the control of inflammatory reactions, e.g. in atopic diseases. Since FcεRI ligation on monocytes also induces synthesis of the Th1-polarizing cytokine IL-12 and prevents spontaneous apoptosis by upregulation of Bcl-2 family proteins and TNF-α (which are both known to be regulated by NF-κB), it is tempting to speculate about a regulatory role of NF-κB in these processes.

However, there are cell type-specific differences in the composition of NF-κB complexes even when the same stimulus, i.e. FcεRI ligation, is applied. Whereas 'classi-

cal' p50- and p65-containing complexes can be detected in FcεRI-stimulated monocytes and MoDC, FcεRI-stimulated LC show complexes consisting of p50 and mainly RelB subunits. This difference may be a distinctive feature of various APC/DC types and needs to be examined in appropriate in vitro models.

Recently, weak FcεRI-induced binding of unknown protein complexes to NF-κB sites has also been described in mast cells and the basophilic cell line RBL-2H3 [24, 25]. However, the composition of this complex does not contain known NF-κB subunits [24]. The transcription factor NFAT has been extensively described to be induced by FcεRI ligation in these cells [26–29]. Since the

kb element in the murine TNF- α promoter region preferentially binds NFAT in mast cells, whereas in DC it binds NF- κ B [30], the possibility of a cell-specific regulation of kb sites by different transcription factors must be kept in mind.

The low-affinity IgE receptor Fc ϵ RII/CD23 has also been reported to induce NF- κ B DNA binding in human monocytes and the monoblastic cell line U937 [31, 32]. This further undermines the notion of a central regulatory role for NF- κ B in proinflammatory APC functions. However, due to the absent or low CD23 levels on monocytes and the fact that Fc ϵ RI represents the main IgE binding structure on these cells [6], the in vivo relevance of this phenomenon is still unclear.

Does in vivo NF- κ B Activation Only Occur in LC from Atopic Donors?

LC serve as epidermal outposts of the immune system and thus are potentially confronted with various pathogens and allergens [7]. Their role in the pathophysiology of contact dermatitis is well established. In atopic dermatitis, Fc ϵ RI expression on LC is maximal and allows it to be distinguished from other inflammatory skin diseases [33]. In addition, LC are able to present IgE-mediated antigens [9], thus suggesting a major role for Fc ϵ RI-bearing LC in the pathophysiology of atopic dermatitis. Interestingly, when compared to monocytes and MoDC, only LC exhibiting high amounts (mean $56.7 \pm 16.0\%$) of Fc ϵ RI, termed 'responder LC', show strong NF- κ B induction [Kraft S, Novak N, Katoh N, Bieber T, Rupec RA: Aggregation of the high affinity IgE receptor Fc ϵ RI on human monocytes and dendritic cells induces NF- κ B activation, submitted].

Since Fc ϵ RI expression on these cells clearly correlates with the serum IgE level as a marker of atopic status, we propose that in vivo, the Fc ϵ RI-mediated NF- κ B induction observed may only occur in LC from atopic individuals, thus leaving LC from normal donors hyporesponsive. This discrepancy between LC and monocytes or in vitro generated MoDC, which do not exhibit specific LC markers and thus are believed to correspond to dermal or interstitial DC, could be determined by the epidermal localization of LC. They are potentially exposed to high amounts of mostly harmless antigens upon minimal epidermal damage, so hyporesponsiveness is desirable for LC when compared to interstitial DC or blood monocytes, which are exposed to foreign antigens only upon more serious damage. Moreover, this potential hyporesponsiveness is

also paralleled by the lack of functional mannose receptors and a fully developed endosomal and lysosomal compartment for loading of MHC class II molecules in LC [34].

Mechanistically, restricted Fc ϵ RI-mediated NF- κ B activation in LC highly positive for Fc ϵ RI could be due to several possibilities. Firstly, it could simply be an effect of higher Fc ϵ RI expression on these cells. However, since we observed absolutely no NF- κ B induction in LC expressing low to moderate amounts (mean $18.5 \pm 2.8\%$) of surface Fc ϵ RI, termed 'nonresponder LC', this does not seem to be the sole reason for that observation. Secondly, these results on NF- κ B activation correlate with similar observations we made when analyzing Fc ϵ RI-induced calcium mobilization, a putative upstream signal of NF- κ B activation [35]. A responder status in terms of calcium mobilization was only observed in LC exhibiting very high Fc ϵ RI levels, mostly from lesional skin of patients with atopic dermatitis, whereas LC from the rest of the donors showed no calcium mobilization. So, in addition to enhanced Fc ϵ RI expression, there are several other explanations for that phenomenon. Since the presence of the signal-enhancing β chain of Fc ϵ RI was excluded in these experiments, there is still the possibility of enhanced expression and/or activity of protein tyrosine kinases (PTK) proximal to calcium influx and NF- κ B activation. Indeed, we found enhanced expression levels of nearly all syk and src family members of PTK in lesional skin of atopic dermatitis patients [Kraft S, Wessendorf JHM, Wollenberg A, Bieber T: Expression and activity of protein tyrosine kinases establishes a functional signal transduction pathway in Fc ϵ RI⁺⁺⁺ Langerhans cells, in preparation]. Additionally, we found Fc ϵ RI-induced tyrosine phosphorylation of phospholipase C- γ (which induces calcium influx via IP₃) only in LC highly positive for Fc ϵ RI, which could also be due to enhanced PTK expression and/or activity in responder cells. Taken together, these results hint that an Fc ϵ RI/PTK/calcium/NF- κ B signaling pathway may only be active in LC from atopics in vivo. This phenomenon may be due to multifactorial causes and needs further investigation.

Fc ϵ RI-Mediated NFAT Activation in APC

Activation of NFAT family transcription factors is a well-characterized event after Fc ϵ RI ligation on mast cells and basophils and leads to the transcription of various cytokine genes, e.g. IL-5 [26–29]. However, the role of this transcription factor in human APC is completely unclear.

In recent experiments [unpubl. data], we were able to demonstrate that FcεRI ligation on human APC such as monocytes, but only in a small percentage of DC cultures, leads to DNA binding of protein complexes to an NFAT consensus sequence (fig. 1). Interestingly, the complexes lack well-characterized members of the NFAT family, such as NFATc1 (NFATc) or NFATc2 (NFATp), but variably contain the NFATx variant of NFATc3 (NFAT4) and NFATc4 (NFAT3), which are also broadly expressed in tissues outside the immune system [36]. NFATx is predominantly found in the thymus and at a lower level in leukocytes [37], whereas NFATc4 has recently been implicated to be involved in the pathogenesis of cardiac hypertrophy [38].

Since we were able to show that FcεRI ligation on human monocytes and DC induces the synthesis of various cytokines and chemokines such as TNF-α, IL-12 and MCP-1 [39] [Kraft S, Novak N, Katoh N, Bieber T, Rupec RA: Aggregation of the high affinity IgE receptor FcεRI on human monocytes and dendritic cells induces NF-κB activation, submitted], as well as IL-1β, IL-6 and IL-8 [40], the involvement of NFAT in these processes is possible. FcεRI-mediated AP-1 activation in APC has not been investigated so far. However, for the induction of many genes, NFAT is dependent on cooperative activation of the AP-1 factors Fos and Jun binding to composite NFAT/AP-1 DNA elements [41].

Consequences for the Treatment of Atopic Diseases

Due to their chronicity and complex pathophysiology, atopic diseases are a therapeutic problem involving considerable socioeconomic costs [42, 43]. With respect to atopic dermatitis, reduction of allergen exposure and topical treatment with glucocorticoids are the two main therapeutic principles. The putative central role of FcεRI-mediated presentation of IgE-bound allergens by DC and the increasing knowledge regarding transcription factors activated upon FcεRI ligation may help to define new therapeutic strategies. The immunosuppressant FK506/tacrolimus, together with the related immunophilin cyclosporin, has been used internally for several years in the prevention and treatment of transplant rejection. Recent clinical trials also gave promising results for topical FK506 in the treatment of atopic dermatitis [44], and it is now approved for use in Japan and the USA.

FK506 is known to act on T cells by suppressing calcineurin phosphatase activity, thus leading to the downreg-

ulation of NFAT activity and NFAT-controlled cytokine genes. In addition, FK506 may also suppress APC functions. In a recent study, we were able to show that FK506 suppresses epidermal LC stimulatory capacity as well as the expression of CD25/IL-2R, CD40 and MHC class I and II antigens on these cells [45]. Whether FK506 exerts its therapeutic effect by inhibiting FcεRI-mediated NFAT activation and gene transcription in epidermal LC in vivo is unclear at present. However, FK506 and cyclosporin have been reported to inhibit FcεRI-induced cytokine transcription in effector cells of anaphylaxis by inhibition of calcineurin, which is known to activate NFAT [46, 47]. A direct influence on FcεRI-induced NFAT activation has only been shown for cyclosporin to date [26]. In addition, we were able to demonstrate FK506-induced inhibition of NFAT DNA binding also in human DC [unpubl. data]. However, the expression of most of the above-mentioned FK506-sensitive molecules in human LC is thought to be regulated by NF-κB, which is also known to be susceptible to FK506 inhibition [48].

Moreover, other well-known pharmacological agents have been reported to suppress APC functions via NF-κB inhibition. Firstly, acetylsalicylic acid has been shown to inhibit NF-κB-mediated IL-12 induction in human monocytic cells [49]. Secondly, the antioxidant NAC has been demonstrated to reduce baseline and lipopolysaccharide- or CD40-induced NF-κB activity in DC, as well as inhibiting upregulation of HLA-DR, the costimulatory molecule CD86/B7.2 and CD40 [50]. NAC-treated DC were also less effective in terms of T cell-stimulatory capacity. In the investigations outlined above, we were able to show that NAC also inhibits NF-κB activation and cytokine production induced by FcεRI ligation on human monocytes and DC (fig. 1). In addition to these pharmacological inhibitors of APC transcription factors, peptide inhibitors, e.g. masking the nuclear localization sequence of NF-κB p50 [51] and plasmids carrying mutant dominant-negative IκB-α, thus rendering cells nonresponsive to most NF-κB targeted stimuli, may also represent therapeutic strategies for atopic and other inflammatory diseases.

Future Perspectives

Rapid progress has been made in understanding how APC and especially DC can influence immune responses by tolerizing T cells or by influencing Th profiles [52, 53]. From the T cell system, we know that NFAT activity is essential for the transcription of both Th1- and Th2-spe-

cific factors [54]. Recently, the transcription factor t-bet has turned out to regulate IFN- γ expression and to accumulate during Th1 differentiation. GATA-3, together with c-maf, specifically regulates the expression of cytokines such as IL-4, IL-5 and IL-13, thus driving Th2 differentiation. APC have been reported to direct Th profiles, for example by the IL-12 they produce [55], and distinct subsets of DC have been reported to induce Th1 polarization of Th cells (myeloid 'DC1') or, in contrast, Th2 polarization (plasmacytoid 'DC2') [52]. However, the latest publications do not favor a model in which DC1 and DC2 are separated by lineage specificity. It is suggested that DC2 can also be generated from myeloid DC1 by 'exhaustion' after prolonged activation [53] or simply the ratio of stimulating DC versus T cells drives Th1 or Th2 differentiation [56]. Thus, the nature or amount of the pathogen encountered and not the type of DC should determine the outcome of the immune response.

At this early stage of investigation of Th-polarizing DC subsets, the transcription factors mediating diverse DC

functions are unknown. It is unclear whether there exists a system of 'DC1- and DC2-specific' transcription factors comparable to the observations made in Th1 and Th2 cells described above. The influence of Fc ϵ RI ligation on the DC profile is also unclear. As mentioned above, NF- κ B, which is known to regulate the expression of the IL-12 p40 subunit [57, 58], would represent a promising candidate for DC1 differentiation. However, the demonstration of an essential role of the c-Rel subunit in IL-12 p40 induction in murine macrophages [59] indicates that the individual roles of the distinct NF- κ B subunits also need further investigation. Taken together, the identification of transcription factors regulating functionally distinct DC subsets – and possibly the effect of Fc ϵ RI ligation on their activity – should contribute to a better understanding of their differentiation pathways and of the molecular pathophysiology of diseases characterized by DC-induced polarization of Th subsets.

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