

Unexpected Functions of FcεRI on Antigen-Presenting Cells

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Key Words

IgE receptor · Antigen-presenting cells · Apoptosis · NF-kappa B · Dendritic cells

Abstract

In contrast to mast cells and basophils, the high affinity IgE receptor (FcεRI) on antigen-presenting cells (APC) shows structural and functional differences. It consists only of a minimal structure of one α- and two γ-chains and enables APC to efficiently take up and present antigen in IgE-mediated delayed-type hypersensitivity reactions that are thought to play a pivotal role in atopic diseases. However, recent studies of FcεRI signal transduction and function on APC suggest additional mechanisms by which FcεRI engagement on APC could affect inflammatory reactions. FcεRI ligation is able to induce major signaling events like protein tyrosine kinase activation including p72^{syk} leading to PLC-γ1 phosphorylation and consecutive calcium influx. Late signaling events like the activation of transcription factors such as NF-κB provide a link to the release of proinflammatory cytokines and chemokines, Th-polarizing factors such as IL-12 and the induction of antiapoptotic factors. FcεRI-mediated IL-10 production in monocytes could also influence their differentiation. Since there are hints that in vivo a functional FcεRI signaling pathway only exists in

individuals from an atopic background, we suggest that these unexpected mechanisms may have an effect on inflammatory reactions in atopic diseases.

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Introduction

For decades, studies on FcεRI focused on effector cells of anaphylaxis such as mast cells and basophils. FcεRI on these cells is essential for immediate-type hypersensitivity reactions like allergic rhinitis, urticaria or anaphylactic shock. Ligation by IgE and antigen induces a complex and well-characterized cascade of signaling events. This leads to the release of preformed mediators such as histamine and heparin as well as synthesis of prostaglandins and cytokines [1].

In the past decade, FcεRI has also been detected on professional antigen-presenting cells (APC) such as dendritic cells (DC) including epidermal Langerhans cells (LC) [2, 3] and blood DC [4] as well as peripheral monocytes [5]. These cells differ from mast cells and basophils. They do not release preformed mediators but are very efficient in antigen uptake followed by MHC-restricted presentation to T cells [6]. FcεRI on APC consists only of one IgE-binding α-chain and two signal-transducing γ-chains lacking the β-chain. On LC it is upregulated in

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atopic donors with a maximum in the lesional skin of atopic dermatitis (AD) [7]. Together with models showing that FcεRI on APC is used for antigen uptake/presentation [4, 8, 9], these observations led to the concept of an 'IgE-mediated delayed-type hypersensitivity reaction' underlying atopic diseases [10]. However, studies on FcεRI signaling and other functions in APC have just been started recently.

Insights into the FcεRI-Associated Activation Pathway and Putative Consequences

Studies on basic signaling mechanisms in LC demonstrated that FcεRI ligation leads to tyrosine phosphorylation and a calcium influx [11] which are controlled by the phosphatase CD45 [12]. A calcium influx can also be detected after FcεRI ligation on monocytes [5]. In recent studies to further elucidate early FcεRI signaling events in APC, we could show that LC [13], monocytes and monocyte-derived DC express a broad array of src family protein tyrosine kinases (PTK) and the p72^{syk} PTK, enabling them to transduce early signals induced by antigen receptors. In addition, we could show that upon FcεRI ligation p72^{syk} is phosphorylated on tyrosine (data not published). This PTK is essential for central FcεRI-induced events in effector cells of anaphylaxis [1], suggesting an equally important role in APC. Following FcεRI ligation, tyrosine phosphorylation of PLC-γ1 (which induces IP₃ generation followed by cellular calcium influx) could also be detected.

Distal signaling events like the activation of transcription factors have only been studied very recently. The transcription factor NF-κB is essential for the regulation of many genes involved in inflammatory processes [14]. We could detect its FcεRI-induced activation in APC [15], which is not characterized in the mast cell/basophil system. Its activation in the pathway described is mediated by serine phosphorylation of the inhibitor IκB-α followed by its degradation. Interestingly, FcεRI-mediated NF-κB activation seems to link it to the regulation of inflammatory processes, since NF-κB controls the expression of proinflammatory cytokines like IL-6, IL-8, TNF-α or chemokines like MCP-1. Together with antigen focusing via FcεRI, this pathway could represent a second mechanism to influence immunological reactions.

There are hints that in the ex vivo-system human epidermal LC a functional FcεRI signaling pathway is only present in donors expressing high FcεRI levels, who mainly have an atopic background. Expression of src and syk

family PTK is upregulated in LC from inflammatory skin of AD. But there are also differences in FcεRI-mediated PTK activity between donors expressing high FcεRI levels compared to those with low or medium levels. We could show that FcεRI engagement on LC leads to a response measured by PLC-γ1 phosphorylation (which is downstream of src- and syk-PTK) and consecutive PLC-γ1-induced calcium influx [11] only from FcεRI^{high} donors. In addition, FcεRI-induced NF-κB activation was only detected in LC from FcεRI^{high} donors.

A Role for FcεRI in the Regulation of APC Apoptosis and Differentiation

Recently, a new role for FcεRI on APC has been identified: FcεRI is involved in the regulation of apoptosis in monocytes [16]. Monocytes have a limited life span and their homeostasis is regulated by programmed cell death in vivo. Spontaneous apoptosis of human monocytes can be enhanced by serum removal or stimulation via CD95/Fas-Fas ligand. We showed that FcεRI ligation on monocytes was able to prevent apoptosis induced by these stimuli. This induction of antiapoptotic mechanisms can explain why monocytes from patients with severe AD expressing high FcεRI levels may have been activated in vivo, thus displaying the apoptosis dysregulation observed. FcεRI-mediated paracrine secretion of TNF-α seems to be partially responsible for inhibition of apoptosis. The production of Bcl-2 family molecules provides an additional mechanism. Interestingly, both TNF-α and Bcl-2 family proteins are regulated by NF-κB [14, 17], which shows another role for the FcεRI/NF-κB signaling pathway described above. In this work it has also been shown that FcεRI ligation in APC can induce IL-12 production. APC-derived signals can influence T helper cell differentiation, e.g. APC-derived IL-12 is able to induce a Th1 phenotype. Therefore, one may suggest an involvement of FcεRI-induced IL-12 in the chronification of AD lesions being characterized by a switch from a Th2 to a Th1 phenotype sustaining inflammatory reactions. Surprisingly, we have recently shown that FcεRI engagement on monocytes prevents their differentiation in DC resulting in the emergence of macrophage-like cells. This effect might be due to IL-10 production after cross-linking. The cells generated under these conditions are less efficient in T cell stimulation and produce higher levels of TNF-α, MCP-1, MIP1α and IL-8. Modulation of APC differentiation by FcεRI ligation in vitro implies a pivotal role in atopic diseases in vivo: FcεRI engagement through aller-

gens could drive monocytes into macrophages, which then may play a regulatory role in atopic inflammation by secretion of proinflammatory cytokines and chemokines following repeated antigen exposure.

Conclusions

The data reviewed here show that, in addition to its established function in antigen focusing, FcεRI on APC may have further functions. NF-κB-mediated production of proinflammatory cytokines, antiapoptotic and Th-polarizing factors such as IL-12 as well as factors influenc-

ing their own differentiation like IL-10 demonstrate the broad impact FcεRI ligation may exert on immunological reactions *in vivo*. These unexpected functions depend on a sufficient signaling cascade. There are hints from the *ex vivo*-system human epidermal LC that main events defining functional signaling pathways like (1) PTK activation, (2) PLC-γ phosphorylation and consecutive calcium influx as well as (3) activation of transcription factors like NF-κB regulating inflammatory relevant genes may only be functional in donors showing an atopic background. The potential involvement of these unexpected functions in the pathophysiology of atopic diseases shows the importance of studying these mechanisms in detail.

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