Immunology Letters 141 (2011) 36–44

Contents lists available at SciVerse ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Soluble IgE receptors—Elements of the IgE network

Barbara Platzer[a,b], Floortje Ruiter[a,b], John van der Mee[a,b], Edda Fiebiger[a,b,*]

[a] Division of Gastroenterology and Nutrition, Children's Hospital, Boston, MA 02115, United States
[b] Department of Pediatrics, Harvard Medical School, Boston, MA 02115, United States

ARTICLE INFO

Article history:
Received 22 July 2011
Received in revised form 15 August 2011
Accepted 27 August 2011
Available online 6 September 2011

Keywords:
IgE
Fc receptors
FcεRI
CD23
FcεRII
Galectin-3

ABSTRACT

Soluble isoforms of three human IgE Fc receptors, namely FcεRI, FcεRII, and galectin-3, can be found in serum. These soluble IgE receptors are a diverse family of proteins unified by the characteristic of interacting with IgE in the extracellular matrix. A truncated form of the alpha-chain of FcεRI, the high affinity IgE receptor, has recently been described as a soluble isoform (sFcεRI). Multiple soluble isoforms of CD23 (sCD23), the low affinity IgE receptor also known as FcεRII, are generated via different mechanisms of extracellular and intracellular proteolysis. The second low affinity IgE receptor, galectin-3, only exists as a secretory protein. We here discuss the physiological roles of these three soluble IgE receptors as elements of the human IgE network. Additionally, we review the potential and current use of sFcεRI, sCD23, and galectin-3 as biomarkers in human disease.

1. Introduction

Antibodies of the immunoglobulin E isotype (IgE) are key regulators of host defense against parasitic infections. Over the last three decades, IgE additionally gained undesirable fame as a central mediator of allergic responses. Allergic responses, however, are not regulated by IgE alone, but rather by a complex protein network including transmembrane and soluble IgE receptors and a variety of co-receptors that do not even bind IgE directly (for a detailed review on the human IgE network see Gould et al. [1]).

Soluble IgE receptors are constituents of the human IgE network and are part of feedback mechanisms that regulate IgE production. Therefore, the physiology of these serum components is highly interesting as they are potential *in vivo* modulators of allergic responses. Thus far, three human soluble IgE receptors have been described, namely, soluble FcεRI (sFcεRI), soluble CD23 (sCD23), and galectin-3 (Table 1 and Fig. 1). The focus of this review is to compare and contrast the role of these three soluble IgE receptors in the context of the human IgE network. We discuss the possible physiological roles of the soluble IgE receptors, clinical implications, and elaborate on the potential and current use of soluble IgE receptors as biomarkers of disease.

2. Generation of soluble IgE receptors

2.1. Soluble FcεRI, sFcεRI

sFcεRI is a single-chain receptor isoform of FcεRI, the high affinity IgE receptor. In humans and mice, robust levels of tetrameric FcεRIαβγ$_2$ are constitutively expressed on the cell surface of mast cells and basophils. This receptor isoform is well known for its function as a key regulator of allergic responses [2]. Under physiological conditions, FcεRIαβγ$_2$ is preloaded with IgE. When IgE-specific antigen crosslinks the receptor, the release of preformed inflammatory mediators and cytokines is triggered. Thus, IgE-FcεRI mediated activation of mast cells and basophils is considered a hallmark of immediate allergic reactions [2]. The following subunits assemble cotranslationally to form tetrameric FcεRI [3]: an IgE-binding α-chain, FcεRIα, and two signaling subunits, FcεRIβ and FcεRIγ; the latter is commonly referred to as the common FcRγ-chain and dimerizes. In addition to the tetrameric isoform, human antigen presenting cells (APCs), such as Langerhans cells of the skin and various other peripheral blood dendritic cell subpopulations, constitutively express a trimeric αγ$_2$ isoform of the FcεRI [2,4–6]. In contrast, murine APCs lack constitutive expression of the receptors, but an inducible version of FcεRIαγ$_2$ has been described in mice after viral infection or challenge with house dust mite [7,8]. Trimeric FcεRIαγ$_2$ is considered to be an antigen uptake receptor and has been shown to be involved in the regulation of Th2-type allergic tissue inflammation [5,9].

In allergic individuals, induction of FcεRI expression has also been described for many other cell types, including monocytes,

* Corresponding author at: 300 Longwood Avenue, EN630, Boston, MA 02115, United States. Tel.: +1 617 919 2549; fax: +1 617 730 0498.
E-mail address: edda.fiebiger@childrens.harvard.edu (E. Fiebiger).

0165-2478/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.imlet.2011.08.004

Table 1
Soluble IgE receptors in human serum.

Soluble IgE receptor	Main source *in vivo*	Regulation of production
sFcεRI-soluble alpha-chain of FcεRI	Not defined	IgE-mediated FcεRI activation
sCD23	B cells	Surface expression of membrane CD23 and accessibility of cleavage sites Expression and activity of shedding enzymes ADAM10, ADAM8, ADAM33, MMP9
Galectin-3	Macrophages	Induction via IL-4 and IL-13 Inhibition by LPS and INF-γ

eosinophils, platelets, and gastrointestinal epithelial cell [10–14]. Immunoprecipitation studies from human serum show that sFcεRI consists of a smaller FcεRI alpha-chain with a molecular weight of ~40 kDa compared to the ~60 kDa full length protein [15]. The lower molecular weight is likely explained by the lack of the transmembrane and cytosolic domains [16]. This is also supported by the fact that FcεRIβ and FcεRIγ$_2$ require the alpha-chain transmembrane region to form a receptor complex and fail to co-immunoprecipitate with sFcεRI. Therefore, ultimately, mass spectrometric analysis is needed to precisely define the protein sequence of sFcεRI.

The alpha-chain of the multimeric FcεRI complex is a type I membrane protein that contains the receptor's IgE-binding site [17]. The soluble alpha-chain, sFcεRI, likewise contains an IgE binding site as it is precipitated with IgE and forms IgE-complexes in serum [15]. Dissociation studies [18] as well as subsequent analysis of the crystal structure [19] of FcεRI–alpha and IgE revealed an extraordinarily high affinity of this ligand–receptor interaction. As the crystals analyzed were generated with a recombinant soluble version of FcεRI–alpha, it is likely that serum sFcεRI has a high affinity for IgE consistent with reports in the literature [19].

It has not yet been characterized how the production of sFcεRI is induced *in vivo*. *In vitro* data show that sFcεRI can be generated after IgE-mediated crosslinking of surface-expressed FcεRI when the trimeric isoform of the receptor is expressed in MelJuso cells [15], which are a common model for non-professional antigen presenting cells [20]. This set of data suggests that production of the soluble isoform is induced by FcεRI crosslinking-induced receptor activation. Since these data were generated with a stable cell line generated with full length FcεRI–alpha cDNA, sFcεRI could not be produced as a splice variant, but rather must be a product of a posttranslational modification such as cleavage by a protease. Nonetheless, several *in vivo* mechanisms for generating sFcεRI could be operating in parallel as discussed for the other sIgE receptors later in this review.

Currently, many more questions about sFcεRI remain open. For example, the cell types that release or shed this protein in humans remain to be defined. No *in vivo* modulators of sFcεRI production are as of yet known. Furthermore, experiments are needed to investigate whether activation of tetrameric FcεRI also induces the release of sFcεRI. Such experiments will answer the question as to whether mast cells and basophils contribute to the generation of the serum pool of sFcεRI. Another important issue not yet resolved is whether sFcεRI exists in mice. If it does not, murine models might be inadequate for studying the potential physiological role of this receptor isoform. Initial experiments to detect sFcεRI from supernatants of IgE-activated RBL-2H3 cells, a rat basophilic leukemia cell line that expresses the tetrameric isoform of the receptor, and murine dendritic cells from a human FcεRIα-transgenic animal that express a chimeric form of FcεRIαγ$_2$ have failed (Fiebiger lab, unpublished observation and [9]). It is conceivable that expression of the sFcεRI isoform is different between humans and mice, comparable to the dissimilar expression patterns of trimeric sFcεRI between the two species [21]. However, more studies on the topic need to be performed before any conclusions are warranted.

2.2. Soluble FcεRII, sCD23

Soluble CD23 (sCD23) molecules result from proteolytic cleavage of the 45 kDa transmembrane form of the low affinity receptor for IgE, FcεRII (CD23). Unlike FcεRI, this IgE Fc receptor does not belong to the immunoglobulin receptor family. Its large extracellular globular C-type lectin domain places CD23 in the C-type lectin superfamily. Various cell types including B cells, T cells, NK cells, monocytes, macrophages, follicular dendritic cells, Langerhans cells, bone marrow stromal cells, neutrophils, eosinophils, platelets, and epithelial cells express CD23 at the cell surface. For a more detailed insight to the biology of transmembrane CD23, we refer the reader to Gould et al. and Acharya et al. who discussed this topic in their reviews in great detail [1,22].

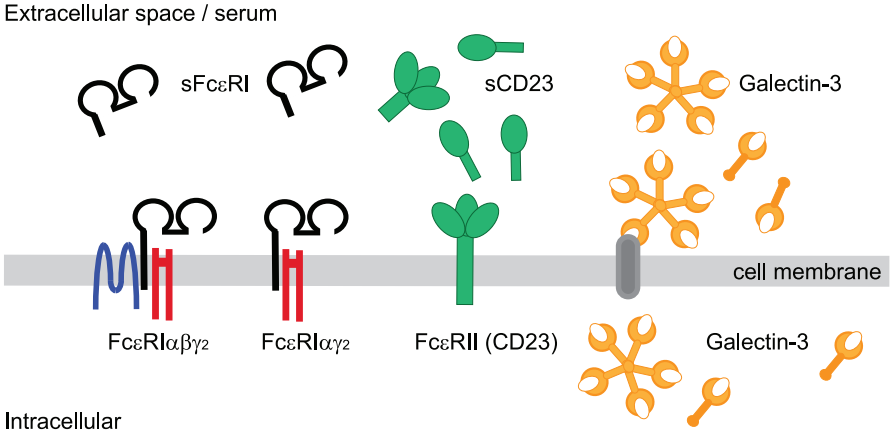

Fig. 1. Human IgE Fc-receptors and their soluble isoforms. The high affinity IgE Fc receptor, FcεRI (FcεRI), has two transmembrane isoforms, FcεRIαβγ$_2$ and FcεRIαγ$_2$. The soluble isoform, sFcεRI, is a single chain receptor consisting of a truncated version of the IgE-binding FcεRIα subunit. Several different soluble isoforms of the transmembrane low affinity IgE Fc receptor, FcεRII or CD23, have been described. A detailed summary of soluble CD23 (sCD23) isoforms and their cleavage sites is provided in Table 2. Galectin-3 is a secretory IgE Fc receptor. After secretion, galectin-3 can attach to cell membranes via interacting with a large number of carbohydrate structures displayed by cell surface proteins. Additionally, an intracellular pool of galectin-3 can be found in the cytoplasm and the nucleus.