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## The role of CD23 in the regulation of allergic responses

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### Abstract

IgE, the key molecule in atopy has been shown to bind two receptors, FcεRI, the high-affinity receptor, and FcεRII (CD23), mostly found on B cells and that binds IgE with lower affinity. Whereas cross-linking of IgE on FcεRI triggers the allergic reaction, binding of IgE to CD23 plays an important role in both IgE regulation and presentation. Furthermore, IgE-immune complexes on B cells enhance antibody and T cell responses in mice and humans. However, the mechanisms that regulate the targeting of the two receptors and the respective function of the two pathways in inflammation or homeostasis are still a matter of debate. Here, we focus on CD23 and discuss several mechanisms related to IgE binding, as well as the impact of the IgE/antigen-binding on different immune cells expressing CD23. One recent paper has shown that free IgE preferentially binds to FcεRI whereas IgE immune complexes (IgE-ICs) are preferentially captured by CD23. Binding of IgE-ICs to CD23 on B cells can, on one hand, regulate serum IgE and prevent effector cell activation and on the other hand facilitate antigen presentation by delivering the antigen to dendritic cells. These data argue for a multifunctional role of CD23 for modulating IgE responses.

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## 1. Introduction

Allergic diseases are a rising global health threat and economic burden(1–3). In classical type I hypersensitivity, Immunoglobulin E (IgE) is the key molecule in the development of allergic reactions towards allergens(4,5). Specific IgE reacting with allergens triggers the release of inflammatory mediators through allergen-mediated cross-linking of the high-affinity receptor, Fc $\epsilon$ RI on allergic effector cells such as mast cells and basophils(6–8).

Another IgE receptor CD23 (Fc $\epsilon$ RII) has largely been overlooked as a potentially important molecule in the field of allergy research(9). This is possibly the case because CD23 is involved in a complex variety of different immunological processes(10). Besides its role as an IgE receptor, CD23 plays a role in the development and growth of normal and leukemic B cells(11,12). Furthermore, it acts as a C-type lectin facilitating antimicrobial immunity(13–17) and can even be engaged by sialylated IgG to act as an Fc $\gamma$  receptor(18–20). Apart from its form as a membrane receptor, CD23 can be cleaved into soluble fragments (sCD23) which was studied as a disease marker in allergy, rheumatoid arthritis, and leukemia(21–24). Furthermore, sCD23 can activate monocytes via CD11b and CD11c integrins(25–27).

Here, we focus on CD23 as an IgE receptor, particularly in the allergic context where CD23 acts as a regulator of IgE levels and modulator of immune responses. Even though the book on CD23 is still far from closed, several recent findings have shed light on the function of CD23 and show that CD23 could become a key molecule to investigate current treatment options in allergy and to develop novel strategies.

## 2. CD23: A lectin as an Fc receptor for IgE

The CD23 molecule is a trimeric glycoprotein member of the calcium-dependent (C-type) lectin family with a 45 kDa subunit. However, even though CD23 is a C-type lectin and IgE is heavily glycosylated, the interaction between IgE and CD23 is independent of carbohydrates and takes place for CD23 in the lectin-like head domain in a non-lectin manner (28). An early study showed that non-glycosylated recombinant IgE fragment has a high binding activity to CD23 even higher than that of myeloma IgE(29). This is also true for enzymatic deglycosylation of human hybridoma or myeloma IgE which does not show decreased binding to CD23 (not published data). CD23 presents a short cytoplasmic N-terminus followed by a single transmembrane region and a long C-terminal extracellular domain(30). The extracellular part consists of three regions: 1) an alpha-helical coiled-coil stalk region which mediates the formation of trimers, 2) a lectin head that binds IgE, and 3) a modified RGD sequence that binds to  $\alpha$ 5 $\beta$ 5 integrins(31). There are two major CD23 isoforms, CD23a and CD23b(32) which only differ in their intracellular region only 21 or 22 amino acids long for CD23a and CD23b, respectively.

CD23 is expressed initially as a membrane-bound molecule but it may be cleaved from the cell surface by metalloproteinases such as ADAM-10 resulting in soluble CD23 fragments (sCD23) of different molecular weights (37,33, 25 and 17 kDa)(33,34).

Structural studies have shown that IgE interacts in different manners with its two receptors, FcεRI and CD23(35). IgE binds to FcεRI with high affinity ( $K_D$  between 0.01 nM to 0.1nM). This occurs through the Cε3 domain in an open conformation allowing the binding of the FcεRI to a binding pocket formed by two subsites 1 (Cε3A) and 2 (Cε3B) (36,37). In previous work, Shade et al. demonstrated the importance of glycans to IgE biology and identified a key glycan in the Cε3 domain that was required for IgE folding and IgE binding to FcεRI(38). By investigating the glycan patterns of IgE, they demonstrated that sialylation of the Fc part of IgE is associated with allergic pathogenicity and might be important for regulating atopic disease (39). In contrast, in the case of CD23, the crystal structure of the complex shows the interaction of two CD23 heads binding to Cε3 and Cε4 domains of a single IgE molecule with different affinities. One binding site has an affinity of around 1 μM whereas the other one is weaker by one order of magnitude ( $K_D$  around 14.4 μM)(40–42). This interaction is characterized by bringing two Cε3 domains together in a “closed” conformation incompatible with the binding to FcεRIα.

The second major ligand of CD23 is the complement receptor, CD21. It was shown that the CD21 binding site on CD23 does not overlap with IgE binding sites and is of low affinity within micromolar range ( $K_D \sim 8 \cdot 7 \times 10^{-7}$  M)(43, 44). The interaction of CD23 to CD21 occurs in short repeats in CD21 and by using CD21 mutants carrying extracellular point mutations an early study has shown that it involves both carbohydrate-dependent and independent interactions (45).

### **3. IgE targeting to the CD23 pathway**

The importance of CD23 as a target of IgE is not entirely clear. However, even though CD23 binds IgE with clearly lower affinity compared to FcεRI, it was shown that CD23 can oligomerize on the surface of B cells leading to enhanced IgE binding through an avidity effect(46) (Fig. 1A and 1B). The leucine zipper region in the stalk was proposed to play an important role in CD23 oligomerization(47). In turn, a more recent study has suggested a direct involvement of the CD23 stalk region in IgE binding potentially explaining why IgE binds well to B cells despite the relatively poor affinity binding to the previously described lectin domain binding site(48). A further mechanism that was reported to enhance IgE binding to CD23 is the presence of calcium, which induces structural changes in CD23 (49). A less studied aspect that could be very important in regulating CD23 targeting is the valency of IgE. The binding of IgE in complex with an allergen (IgE-immune complex) was shown to impact the binding of IgE to CD23(50). Furthermore, we recently showed that IgE in complex with allergen is preferentially bound by CD23, whereas the binding to FcεRI is diminished by IgE complexation(51). However, those findings are rather new and require confirmation specifically in regards to different IgE/antigen systems. Furthermore, no direct structural evidence for such a relationship between IgE-immune complexes and FcεRI has yet been published. Moreover, the

physiological relevance of IgE-allergen immune complexes (IgE-ICs) in healthy and allergic patients is not entirely clear, even though their existence has been described a long time ago(52,53). Similar to IgE-ICs, the well-documented presence of natural anti-IgE antibodies could also lead to multivalent IgE complexes that could potentially regulate CD23 versus FcεRI targeting(54–57).

IgE binding to CD23 may also be enhanced by other receptors. CD21, which binds CD23, is an interesting co-receptor for IgE-IC. Even though IgE itself does not fix complement, the inclusion of complement-fixing IgG could impact the immune complex binding to CD23. It was shown that IgE-ICs formed in allergic patients include IgE, IgG1, and IgG4(58).The binding of immune complexes to B cells via CD23 could therefore be regulated by the IgG subclass present in the complex. As IgG4 does not fix complement well, higher IgG4 content versus IgG1 could reduce CD23/CD21 interaction and thus B cell targeting of the immune complex. (Fig. 1C). Surprisingly, IgG binding via FcγRII was not found to play a role in that study. Potentially, the co-ligation of FcγR with CD23 could impact complex binding and subsequent cellular activation or inhibition of signaling via immunoreceptor tyrosine-based activation (ITAM) or inhibition (ITIM) motifs, depending on the involved FcγR(59).Overall, the role of IgG and complement factors in regulating IgE-IC binding to CD23 on B cells or other cell types requires more detailed investigations.

#### **4. CD23 as a regulator of IgE levels**

A main function attributed to CD23 is the regulation of IgE synthesis. Both *in vitro* and *in vivo* studies have shown that CD23 plays a central role in regulating IgE synthesis. However, the exact mechanism of IgE down-regulation is a matter of debate.It was shown quite some time ago that mice overexpressing CD23 display reduced IgE levels after primary immunization with antigen in alum(60,61)while CD23<sup>-/-</sup> mice show enhanced IgE production(62).Furthermore, anti-CD23 antibodies inhibit antigen-specific IgE responses in mice(63).

In human B cells, IgE synthesis can be inhibited *in vitro* by direct targeting of CD23(61).This supports a model of either positive or negative feedback mechanism depending on the concentration of IgE and cleavage of membrane CD23 (64). Thus, high levels of IgE or antibodies against the lectin head of CD23 stabilize membrane CD23 preventing its proteolytic cleavage and thereby inhibit IgE synthesis.In turn, the cleavage of CD23 by allergens has been a proposed mechanism of enhanced IgE responses(65). Allergen-cleaved CD23 would lose the ability to suppress IgE synthesis and hence lead to elevated IgE levels. CD23 binding by antibodies recognizing the stalk region of CD23 or metalloproteinases such as ADAM10 are additional ways in which CD23 cleavage and production of soluble CD23 can occur.

It has been proposed that CD23 cleavage not only prevents negative regulation but may even enhance IgE synthesis by acting on other cells as soluble CD23. However, the mechanisms by which sCD23 enhances IgE synthesis are unclear. Potentially, released soluble CD23 may up-regulate IgE synthesis by cross-linking membrane IgE and CD21. The activity of the soluble fragments depends on their oligomeric state namely soluble CD23 monomers inhibit whereas oligomers stimulate IgE synthesis(66).The fact that IgE and CD21 have distinct binding sites and bind CD23 simultaneously supports this hypothesis(44). In

contrast, the co-ligation of membrane IgE and membrane-bound CD23 via allergen-IgE complexes has been suggested as a negative feedback mechanism of IgE synthesis but more experiments need to be performed to confirm this hypothesis.

A recent paper has shown that CD23 as well can negatively regulate BCR activation on B cells by promoting B cell contraction. This explains the down-regulation of CD23 on memory B cells that mount a higher response of memory B cells to antigenic stimulation (75). In contrast, up-regulation of CD23 on switched memory B cells correlates with antigen-specific IgE levels and may be involved in some pathologies such as allergic rhinitis (76).

A further mechanism by which CD23 may regulate IgE levels is by acting as a direct decoy receptor for FcεRI. It was shown in mice, that B cells regulate serum IgE levels directly by absorbing free IgE molecules, thus preventing FcεRI loading and allergic sensitization(51,67,68), This more novel model of IgE regulation fits well with the generally higher IgE levels in CD23 deficient mice. CD23 cleavage could then be a mechanism to suppress this serum clearance and thereby enhance IgE levels.

## **5. CD23 in the activation of B cells and monocytes**

Many functional investigations on CD23 have demonstrated mechanisms triggered by CD23 cross-linking. The role of CD23 in monocyte-related cells is generally tricky to assess, as they can also express FcεRI. For example, human monocytes express FcεRI, whereas IL-4 stimulation up-regulates CD23 on those cells(69). Therefore, anti-CD23 antibodies were often used for specific CD23 cross-linking. It has been known for quite some time that CD23 cross-linking leads to internalization. The mechanism of uptake is different for the two CD23 isoforms, CD23a facilitates endocytosis and CD23b phagocytosis(32). The differential expression of CD23a and CD23b in B cells and monocyte-related cells, respectively has led to several interesting comparative studies showing differential signaling. Specifically, signaling via Fyn and Syk and Akt pathways resulting in IFN-γ production was only reported for CD23 cross-linking in B cells whereas cells of the monocytic lineage have been described to signal via IκB and produce inflammatory chemokines and cytokines such as TNF, IL-1β, IL-1ra, IL-10, IL-8, MCP-1, and MIP-1α (69–74).

In addition to the differential signaling, the processing of IgE and IgE-ICs also depends on the cell type. In monocyte-derived cells or dendritic cells only expressing CD23b, IgE and allergen are targeted to a degradative pathway after CD23 cross-linking. In contrast, human primary B cells expressing CD23a in addition to CD23b, protect IgE and allergen from degradation and recycle IgE-immune complexes via CD23 allowing transfer to other immune cells (77,78)(Fig. 2). These findings are consistent with studies in mice showing that circulating murine B cells transport IgE immune complexes to the spleen(79–81).

Those findings in B cells fit well to results showing that CD23a expressing human intestinal epithelial cells(82,83) as well as mouse intestinal epithelial cells can shuttle IgE and IgE-immune complexes through the epithelial layer by transcytosis(84). Like in human B cells, food allergens were also shown to be

protected from degradation during epithelial transcytosis(85). Interestingly, intestinal epithelial cells (IEC) were also shown to release CCL20 in response to CD23 cross-linking, suggesting that CD23 may act as a critical receptor in initiating an allergic response by the release of chemokines capable of recruiting cells of the innate and adaptive immune system (86). Furthermore, CD23-dependent transcytosis of IgE immune complexes was described for human airway epithelial cells (AEC), however, in contrast to B cells and IEC, CD23b was the reported isoform involved in AEC(83).

## 6. CD23 mediated immune response

The consequence of CD23 mediated IgE- immune complex processing or trafficking is still not understood in detail. However, it is thought that IgE modulates immune responses to an antigen via CD23, as was shown in mice for antibody and T cell responses(80,87). The mechanism of antigen presentation mediated by CD23 has been referred to as IgE-facilitated antigen presentation (FAP) (Fig. 3). As B cells are antigen-presenting cells expressing MHC class II, B cells could potentially also degrade antigen and display peptides on MHC class II for antigen presentation. This was indeed shown using EBV-transformed human B cells which directly present IgE-immune complexes to T cells (48,88–91). However, as previously mentioned, in primary B cells, IgE-immune complexes are protected from degradation. This difference in processing between normal B cells and EBV-transformed cells requires more detailed investigations, to better understand the mechanism of immunomodulation. Although primary human B cells fail to directly induce T cell proliferation, they can transfer the IgE-immune complexes to human dendritic cells to induce T cell proliferation(77). Fittingly, in mice, IgE-mediated antigen presentation was, though initiated by B cells, ultimately dependent on dendritic cells(80,92). The mechanism by which antigen could be transferred from B cells to other cell types is not entirely clear. A potential role in CD23-induced IgE or antigen shipping between immune cells could be attributed to exosomes. It was shown that B cell-derived exosomes can play a role in presenting allergen peptides to activate T cells (92,93) (Fig. 3). Independently, it has been described that the CD23 sheddase ADAM10 can mediate the sorting of CD23 into B cell-derived exosomes(94,95). The concept of exosome transfer between B cells and dendritic cells has also been put forth in mice(96). The consequence of CD23-mediated T cell proliferation and whether it is pro- or anti-inflammatory in the allergic context has not been resolved yet, and evidence is generally conflicting. In mouse models of allergic asthma, it was both postulated that CD23 could positively(98) as well as negatively regulate allergic airway inflammation (99,100).

It has also been postulated that CD23-mediated FAP can lead to IgG responses to unrelated allergens in a possible scenario of epitope spreading (8,101). Thus, CD23-expressing B cells will behave as presenting cells binding to antigens, regardless of the cell's specificity, just as is the case with dendritic cells which can bind to different unrelated antigens via Fc $\gamma$  receptors and induce antibody response to unrelated allergens. By this, CD23-FAP might explain the development of allergen polysensitivity to multiple allergens. CD23-mediated FAP is indeed as efficient as Fc $\gamma$  receptors to induce antigen presentation even higher than BCR

on the surface of B cells (102). This mechanism might play a role in IgE autoreactivity where low cross-reactive IgE autoantibodies can develop via FAP into high-affinity IgE autoantibodies (103). Even though this mechanism has been postulated as a potential cause of different IgE-mediated autoimmune diseases such as atopic dermatitis where the presence of IgE autoantibodies has been associated with allergen sensitization it still requires a lot of further evidence (104).

## **7. CD23 in current allergy therapy approaches**

As long as the biology of CD23 is not completely understood, the potential use for CD23 as a therapeutic target is limited. However, several recent studies have begun to shed light on how current allergy therapies affect CD23.

The only disease-modifying therapy for allergies is allergen-specific immunotherapy (AIT) (105,106). Multiple injections of increasing allergen doses induce the generation of tolerance via regulatory T cells and the induction of protective IgG4 antibodies (107,108). The role of CD23 in the generation of such IgG responses is unclear. However, the tolerogenic IgG induced by AIT was shown to inhibit IgE binding to CD23 and hence antigen presentation by EBV-transformed B cells (109–111).

A different approach to treat allergic diseases is by anti-IgE therapy (112). Omalizumab, a monoclonal anti-IgE antibody is used for severe allergic asthma and chronic spontaneous urticaria (113,114). Mechanistically, Omalizumab inhibits both FcεRI:IgE and CD23:IgE interactions (115). A more recent anti-IgE antibody, Ligelizumab, was more efficacious in the treatment of allergic asthma (116). Functionally, Ligelizumab displayed reduced IgE:CD23 inhibition compared to Omalizumab but enhanced inhibition of IgE:FcεRI binding (117). A different anti-IgE antibody referred to as MEDI4212 is mimicking CD23 binding to IgE and was shown to inhibit allergic responses in mice and inhibit the FcεRI pathway (68). A further interesting anti-IgE termed (8D6), an anti-IgE Fab bound to IgE-Fc through a mixed protein-carbohydrate epitope, was shown to inhibit FcεRI while retaining CD23 binding (118,119). The monoclonal anti-CD23 antibody Lumiliximab, which specifically targets CD23 was shown to inhibit allergen-induced response in allergen-presenting cells and reduced Th2 response (120). However, anti-CD23 never lead to particularly significant clinical outcomes in patients with asthma suggesting that blocking CD23 does not reduce allergic symptoms. Hence, studying the type of immune response elicited by CD23 is essential to understanding its role in allergy and immunotherapy as it could very well be of benefit to target IgE towards the CD23 pathway instead of blocking this interaction.

## **8. Conclusion**

The general goal of disease-modifying allergy immunotherapy is to reduce IgE responses while enhancing IgG and regulatory T cell responses. While evidence from experimental disease models as well as allergic patient studies on CD23 is lacking, evidence shows that i) CD23 can absorb and clear IgE from the serum

in a non-inflammatory fashion ii) CD23 reduces the synthesis of IgE from B cells iii) CD23 regulates antigen-specific IgG and T cell responses. Together, those factors lead us to believe that CD23 deserves a closer look as a therapeutic target in allergies.

## References

1. Devereux G. The increase in the prevalence of asthma and allergy: food for thought. *Nat Rev Immunol*. 2006;6(11):869–74.
2. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J [Internet]*. 2014;7(1):12. Available from: <https://doi.org/10.1186/1939-4551-7-12>
3. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ [Internet]*. 2000;321(7253):88–92. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=27429&tool=pmcentrez&rendertype=abstract>
4. Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med [Internet]*. 2012;18(5):693–704. Available from: <http://dx.doi.org/10.1038/nm.2755>
5. Galli SJ, Kalesnikoff J, Grimaldeston M a, Piliponsky AM, Williams CMM, Tsai M. Mast Cells as “Tunable” Effector and Immunoregulatory Cells : Recent Advances. *Annu Rev Immunol*. 2005;23:749–86.
6. Finkelman FD, Khodoun M V, Strait R. Human IgE-independent systemic anaphylaxis. *J Allergy Clin Immunol [Internet]*. 2016 Jun 1;137(6):1674–80. Available from: <https://doi.org/10.1016/j.jaci.2016.02.015>
7. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature [Internet]*. 2008;454(7203):445–54. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3573758&tool=pmcentrez&rendertype=abstract>
8. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol [Internet]*. 2008 Mar [cited 2014 Mar 19];8(3):205–17. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18301424>
9. Conrad DH, Ford JW, Sturgill JL, Gibb DR. CD23: An overlooked regulator of allergic disease. *Curr Allergy Asthma Rep [Internet]*. 2007;7(5):331–7. Available from: <https://doi.org/10.1007/s11882-007-0050-y>
10. Acharya M, Borland G, Edkins a L, Maclellan LM, Matheson J, Ozanne BW, et al. CD23/FcεRII:



molecular multi-tasking. Clin Exp Immunol [Internet]. 2010 Oct [cited 2014 Mar 25];162(1):12–23. Available from:

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2990925&tool=pmcentrez&rendertype=abstract>

11. Schwarzmeier JD, Hubmann R, Döchler M, Jäger U, Shehata M. Regulation of CD23 expression by Notch2 in B-cell chronic lymphocytic leukemia. Leuk Lymphoma [Internet]. 2005 Jan 1;46(2):157–65. Available from: <https://doi.org/10.1080/10428190400010742>
12. Fournier S, Rubio M, Delespesse G, Sarfati M. Role for low-affinity receptor for IgE (CD23) in normal and leukemic B-cell proliferation. Blood. 1994;84(6):1881–6.
13. Guo Y, Chang Q, Cheng L, Xiong S, Jia X, Lin X, et al. C-Type Lectin Receptor CD23 Is Required for Host Defense against *Candida albicans* and *Aspergillus fumigatus* Infection. J Immunol [Internet]. 2018;ji1800620. Available from: <http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1800620>
14. Zhao X, Guo Y, Jiang C, Chang Q, Zhang S, Luo T, et al. JNK1 negatively controls antifungal innate immunity by suppressing CD23 expression. Nat Med [Internet]. 2017;23(3):337–46. Available from: <https://doi.org/10.1038/nm.4260>
15. Jégouzo SAF, Feinberg H, Morrison AG, Holder A, May A, Huang Z, et al. CD23 is a glycan-binding receptor in some mammalian species. J Biol Chem. 2019;294(41):14845–59.
16. Kijimoto-Ochiai S. CD23 (the low-affinity IgE receptor) as a C-type lectin: a multidomain and multifunctional molecule. Cell Mol Life Sci C [Internet]. 2002;59(4):648–64. Available from: <https://doi.org/10.1007/s00018-002-8455-1>
17. Mossalayi MD, Vouldoukis I, Mamani-Matsuda M, Kauss T, Guillon J, Maugein J, et al. CD23 mediates antimycobacterial activity of human macrophages. Infect Immun [Internet]. 2009 Dec [cited 2014 Jul 21];77(12):5537–42. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2786469&tool=pmcentrez&rendertype=abstract>
18. Wang TT, Maamary J, Tan GS, Bournazos S, Davis CW, Krammer F, et al. Anti-HA Glycoforms Drive B Cell Affinity Selection and Determine Influenza Vaccine Efficacy. Cell [Internet]. 2015;162(1):160–9. Available from: <http://dx.doi.org/10.1016/j.cell.2015.06.026>
19. Maamary J, Wang TT, Tan GS, Palese P, Ravetch J V. Increasing the breadth and potency of response to the seasonal influenza virus vaccine by immune complex immunization. Proc Natl Acad Sci [Internet]. 2017;201707950. Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.1707950114>
20. Sondermann P, Pincetic A, Maamary J, Lammens K, Ravetch J V. General mechanism for

- modulating immunoglobulin effector function. *Proc Natl Acad Sci* [Internet]. 2013 Jun 11;110(24):9868 LP – 9872. Available from: <http://www.pnas.org/content/110/24/9868.abstract>
21. Platzer B, Ruiter F, van der Mee J, Fiebiger E. Soluble IgE receptors - elements of the IgE network. *Immunol Lett*. 2012;141(1):36–44.
22. Sarfati M, Chevret S, Chastang C, Biron G, Stryckmans P, Delespesse G, et al. Prognostic importance of serum soluble CD23 level in chronic lymphocytic leukemia. *Blood* [Internet]. 1996;88(11):4259–64. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8943862>
23. Boccafogli a, Vicentini L, Lambertini D, Scolozzi R. Soluble CD23 is increased in allergy. *Allergy* [Internet]. 1997 Apr 29;52(3):357–8. Available from: <https://doi.org/10.1111/j.1398-9995.1997.tb01009.x>
24. Moura RA, Quaresma C, Vieira AR, Gonçalves MJ, Polido-Pereira J, Romão V, et al. A2.12 Increased CXCR5 B cell expression, CXCL13 and SCD23 serum levels in untreated early rheumatoid arthritis patients support B cell activation since the initial phase of the disease. *Ann Rheum Dis* [Internet]. 2016 Feb 1;75(Suppl 1):A20 LP-A20. Available from: [http://ard.bmj.com/content/75/Suppl\\_1/A20.1.abstract](http://ard.bmj.com/content/75/Suppl_1/A20.1.abstract)
25. Rezzonico R, Chicheportiche R, Imbert V, Dayer J-M. Engagement of CD11b and CD11c  $\beta 2$  integrin by antibodies or soluble CD23 induces IL-1 $\beta$  production on primary human monocytes through mitogen-activated protein kinase–dependent pathways. *Blood* [Internet]. 2000 Jun 15;95(12):3868 LP – 3877. Available from: <http://www.bloodjournal.org/content/95/12/3868.abstract>
26. Lecoanet-Henchoz S, Gauchat J-F, Aubry J-P, Graber P, Life P, Paul-Eugene N, et al. CD23 Regulates monocyte activation through a novel interaction with the adhesion molecules CD11b-CD18 and CD11c-CD18. *Immunity* [Internet]. 1995;3(1):119–25. Available from: <http://www.sciencedirect.com/science/article/pii/1074761395901647>
27. Lecoanet-Henchoz S, Plater-Zyberk C, Graber P, Gretener D, Aubry JP, Conrad DH, et al. Mouse CD23 regulates monocyte activation through an interaction with the adhesion molecule CD11b/CD18. *Eur J Immunol*. 1997;27(9):2290–4.
28. Sun PD. Human CD23: Is It a Lectin in Disguise? *Structure*. 2006;14(6):950–1.
29. Vercelli D, Helm B, Marsh P, Padlan E, Geha RS, Gould H. The B-cell binding site on human immunoglobulin E. *Nature*. 1989;338(6217):649-651.
30. Delespesse G, Sarfati M, Wu CY, Fournier S, Letellier M. The Low-Affinity Receptor for IgE. *Immunol Rev* [Internet]. 1992 Feb 1;125(1):77–97. Available from: <https://doi.org/10.1111/j.1600-065X.1992.tb00626.x>
31. Borland G, Edkins AL, Acharya M, Matheson J, White LJ, Allen JM, et al.  $\alpha$ 5 $\beta$ 1 integrin

sustains growth of human Pre-B cells through an RGD-independent interaction with a basic domain of the CD23 protein. *J Biol Chem*. 2007;282(37):27315–26.

32. Yokota A, Kikutani H, Tanaka T, Sato R, Barsumian EL, Suemura M, et al. Two species of human Fc epsilon receptor II (Fc epsilon RII/CD23): tissue-specific and IL-4-specific regulation of gene expression. *Cell* [Internet]. 1988 Nov 18;55(4):611–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2972386>
33. Weskamp G, Ford JW, Sturgill J, Martin S, Docherty AJP, Swendeman S, et al. ADAM10 is a principal “shedase” of the low-affinity immunoglobulin E receptor CD23. *Nat Immunol*. 2006;7(12):1293–8.
34. Lemieux GA, Blumenkron F, Yeung N, Zhou P, Williams J, Grammer AC, et al. The low affinity IgE receptor (CD23) is cleaved by the metalloproteinase ADAM10. *J Biol Chem* [Internet]. 2007/03/27. 2007 May 18;282(20):14836–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/17389606>
35. Sutton BJ, Davies AM. Structure and dynamics of IgE-receptor interactions: FcεRI and CD23/FcεRII. *Immunol Rev*. 2015;268(1):222–35.
36. Holdom MD, Davies AM, Nettleship JE, Bagby SC, Dhaliwal B, Girardi E, et al. Conformational changes in IgE contribute to its uniquely slow dissociation rate from receptor FcεRI. *Nat Struct Mol Biol* [Internet]. 2011;18(5):571–6. Available from: <http://dx.doi.org/10.1038/nsmb.2044>
37. Wurzburg BA, Garman SC, Jardetzky TS. Structure of the human IgE-Fc C epsilon 3-C epsilon 4 reveals conformational flexibility in the antibody effector domains. *Immunity* [Internet]. 2000;13(3):375–85. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11021535>
38. Shade KT, Platzer B, Washburn N, et al. A single glycan on IgE is indispensable for initiation of anaphylaxis. *J Exp Med*. 2015;212(4):457-467.
39. Shade KC, Conroy ME, Washburn N, et al. Sialylation of immunoglobulin E is a determinant of allergic pathogenicity. *Nature*. 2020;582(7811):265-270.
40. Borthakur S, Hibbert RG, Pang MOY, Yahya N, Bax HJ, Kao MW, et al. Mapping of the CD23 binding site on immunoglobulin e (IgE) and allosteric control of the IgE-FcεRI interaction. *J Biol Chem*. 2012;287(37):31457–61.
41. Dhaliwal B, Pang MOY, Yuan D, Yahya N, Fabiane SM, McDonnell JM, et al. Conformational plasticity at the IgE-binding site of the B-cell receptor CD23. *Mol Immunol* [Internet]. 2013;56(4):693–7. Available from: <http://dx.doi.org/10.1016/j.molimm.2013.07.005>
42. Dhaliwal B, Pang MOY, Keeble AH, James LK, Gould HJ, McDonnell JM, et al. IgE binds asymmetrically to its B cell receptor CD23. *Sci Rep* [Internet]. 2017;7(November 2016):45533. Available from: <http://www.nature.com/articles/srep45533>

43. Aubry J-P, Pochon S, Graber P, Jansen KU, Bonnefoy J-Y. CD21 is a ligand for CD23 and regulates IgE production. *Nature* [Internet]. 1992 Aug 6;358:505. Available from: <https://doi.org/10.1038/358505a0>
44. Hibbert RG, Teriete P, Grundy GJ, Beavil RL, Reljic R, Holers VM, et al. The structure of human CD23 and its interactions with IgE and CD21. *J Exp Med*. 2005;202(6):751–60.
45. Aubry JP, Pochon S, Gauchat JF, Nueda-Marin A, Holers VM, Graber P, et al. CD23 interacts with a new functional extracytoplasmic domain involving N-linked oligosaccharides on CD21. *J Immunol* [Internet]. 1994 Jun 15;152(12):5806 LP – 5813. Available from: <http://www.jimmunol.org/content/152/12/5806.abstract>
46. Kilmon MA, Ghirlando R, Strub MP, Beavil RL, Gould HJ, Conrad DH. Regulation of IgE production requires oligomerization of CD23. *J Immunol*. 2001 Sep;167(6):3139–45.
47. Munoz O, Brignone C, Grenier-Brossette N, Bonnefoy J-Y, Cousin J-L. Binding of Anti-CD23 Monoclonal Antibody to the Leucine Zipper Motif of FcεRII/CD23 on B Cell Membrane Promotes Its Proteolytic Cleavage: EVIDENCE FOR AN EFFECT ON THE OLIGOMER/MONOMER EQUILIBRIUM . *J Biol Chem* [Internet]. 1998 Nov 27;273(48):31795–800. Available from: <http://www.jbc.org/content/273/48/31795.abstract>
48. Selb R, Eckl-Dorna J, Neunkirchner A, Schmetterer K, Marth K, Gamper J, et al. CD23 surface density on B cells is associated with IgE levels and determines IgE-facilitated allergen uptake, as well as activation of allergen-specific T cells. *J Allergy Clin Immunol*. 2015;139(1):290–9.
49. Yuan D, Keeble AH, Hibbert RG, Fabiane S, Gould HJ, McDonnell JM, et al. Ca<sup>2+</sup>-dependent structural changes in the B-cell receptor CD23 increase its affinity for human immunoglobulin E. *J Biol Chem* [Internet]. 2013/06/17. 2013 Jul 26;288(30):21667–77. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23775083>
50. Reginald K, Eckl-Dorna J, Zafred D, Focke-Tejkl M, Lupinek C, Niederberger V, et al. Different modes of IgE binding to CD23 revealed with major birch allergen, Bet v 1-specific monoclonal IgE. *Immunol Cell Biol* [Internet]. 2013 Feb 1;91(2):167–72. Available from: <https://doi.org/10.1038/icb.2012.70>
51. Engeroff P, Caviezel F, Mueller D, Thoms F, Bachmann MF, Vogel M. CD23 provides a noninflammatory pathway for IgE-allergen complexes. *J Allergy Clin Immunol* [Internet]. 2020 Jan 1;145(1):301-311.e4. Available from: <https://doi.org/10.1016/j.jaci.2019.07.045>
52. Brostoff J, Carini C, Wraith DG, Johns P. Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium chromoglycate. *Lancet* [Internet]. 1979;313(8129):1268–70. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673679922293>
53. Brostoff J, Johns Dennis P, Stanworth R. COMPLEXED IgE IN ATOPY. *Lancet* [Internet].

1977;310(8041):741–2. Available from:

<http://www.sciencedirect.com/science/article/pii/S0140673677902409>

54. Jensen-Jarolim E, Vogel M, de Weck AL, Stadler BM. Anti-IgE autoantibodies mistaken for specific IgG. *J Allergy Clin Immunol* [Internet]. 1992 Jan 1 [cited 2018 Jun 13];89(1):31–43. Available from: <https://www.sciencedirect.com/science/article/pii/S0091674905800387?via%3Dihub>
55. Bracken SJ, Adami AJ, Rafti E, Schramm CM, Matson AP. Regulation of IgE activity in inhalational tolerance via formation of IgG anti-IgE/IgE immune complexes. *Clin Mol Allergy* [Internet]. 2018;16(1):13. Available from: <https://doi.org/10.1186/s12948-018-0091-x>
56. Chan Y-C, Ramadani F, Santos AF, Pillai P, Ohm-Laursen L, Harper CE, et al. Auto-anti-IgE<sup>+</sup>: Naturally occurring IgG anti-IgE antibodies may inhibit allergen-induced basophil activation. *J Allergy Clin Immunol* [Internet]. 2014 Dec 1 [cited 2018 Jun 13];134(6):1394-1401.e4. Available from: <https://www.sciencedirect.com/science/article/pii/S0091674914008951?via%3Dihub>
57. Engeroff P, Plattner K, Storni S, Thoms F, Boligan KF, Muerner L, et al. Glycan-specific IgG anti-IgE autoantibodies are protective against allergic anaphylaxis in a murine model. *J Allergy Clin Immunol*. 2020. Available from: <https://doi.org/10.1016/j.jaci.2020.11.031>
58. Meulenbroek LAPM, de Jong RJ, den Hartog Jager CF, Monsuur HN, Wouters D, Nauta AJ, et al. IgG Antibodies in Food Allergy Influence Allergen – Antibody Complex Formation and Binding to B Cells: A Role for Complement Receptors. *J Immunol*. 2013;191(7):3526–33.
59. Nimmerjahn F, Ravetch J V. Fcγ receptors as regulators of immune responses. *Nat Rev Immunol*. 2008;8(1):34–47.
60. Payet M, Conrad DH. IgE regulation in CD23 knockout and transgenic mice. *Allergy Eur J Allergy Clin Immunol*. 1999;54(11):1125–9.
61. Payet-Jamroz M, Helm SLT, Wu J, Kilmon M, Fakher M, Basalp A, et al. Suppression of IgE Responses in CD23-Transgenic Animals Is Due to Expression of CD23 on Nonlymphoid Cells. *J Immunol* [Internet]. 2001 Apr 15;166(8):4863 LP – 4869. Available from: <http://www.jimmunol.org/content/166/8/4863.abstract>
62. Yu P, Kosco-Vilbois M, Richards M, Köhler G, Lamers MC. Negative feedback regulation of IgE synthesis by murine CD23. *Nature*. 1994;369(6483):753–6.
63. Flores-Romo L, Shields J, Humbert Y, Graber P, Aubry JP, Gauchat JF, et al. Inhibition of an in vivo antigen-specific IgE response by antibodies to CD23. *Science (80- )* [Internet]. 1993 Aug 20;261(5124):1038 LP – 1041. Available from: <http://science.sciencemag.org/content/261/5124/1038.abstract>

64. Fellmann, M., Buschor, P., Röthlisberger, S., Zellweger, F. Vogel M, Fellmann M, Buschor P, Röthlisberger S, Zellweger F, Vogel M. High affinity targeting of CD23 inhibits IgE synthesis in human B cells. *Immunity, Inflamm Dis* [Internet]. 2015;3(4):339–49. Available from: <http://www.ncbi.nlm.nih.gov.proxy.library.uu.nl/pmc/articles/PMC4693728/>
65. Schulz O, Sutton BJ, Beavil RL, Shi J, Sewell HF, Gould HJ, et al. Cleavage of the low-affinity receptor for human IgE (CD23) by a mite cysteine protease: Nature of the cleaved fragment in relation to the structure and function of CD23. *Eur J Immunol*. 1997;27(3):584–8.
66. McCloskey N, Hunt J, Beavil RL, Jutton MR, Grundy GJ, Girardi E, et al. Soluble CD23 monomers inhibit and oligomers stimulate IGE synthesis in human B cells. *J Biol Chem*. 2007;282(33):24083–91.
67. Cheng LE, Wang Z-E, Locksley RM. Murine B Cells Regulate Serum IgE Levels in a CD23-Dependent Manner. *J Immunol* [Internet]. 2010;185(9):5040–7. Available from: <http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.1001900>
68. Jabs F, Plum M, Laursen NS, Jensen RK, Mølgaard B, Miehe M, et al. Trapping IgE in a closed conformation by mimicking CD23 binding prevents and disrupts FcεRI interaction. *Nat Commun* [Internet]. 2018;9(1). Available from: <http://dx.doi.org/10.1038/s41467-017-02312-7>
69. Pellizzari G, Hoskin C, Crescioli S, Mele S, Gotovina J, Chiaruttini G, et al. IgE re-programs alternatively-activated human macrophages towards pro-inflammatory anti-tumoural states. *EBioMedicine* [Internet]. 2019 May 1;43:67–81. Available from: <https://doi.org/10.1016/j.ebiom.2019.03.080>
70. Yokota A, Yukawa K, Yamamoto A, Sugiyama K, Suemura M, Tashiro Y, et al. Two forms of the low-affinity Fc receptor for IgE differentially mediate endocytosis and phagocytosis: identification of the critical cytoplasmic domains. *Proc Natl Acad Sci U S A*. 1992;89(11):5030–4.
71. Peng W, Grobe W, Walgenbach-Brünagel G, Flicker S, Yu C, Sylvester M, et al. Distinct Expression and Function of FcεRII in Human B Cells and Monocytes. *J Immunol* [Internet]. 2017;1601028. Available from: <http://www.jimmunol.org/content/early/2017/03/08/jimmunol.1601028?papetoc>
72. Chan M a, Gigliotti NM, Matangkasombut P, Gauld SB, Cambier JC, Rosenwasser LJ. CD23-mediated cell signaling in human B cells differs from signaling in cells of the monocytic lineage. *Clin Immunol* [Internet]. 2010 Dec [cited 2014 Oct 20];137(3):330–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20805040>
73. Ten RM, McKinstry MJ, Trushin S a, Asin S, Paya C V. The signal transduction pathway of CD23 (Fc epsilon RIIB) targets I kappa B kinase. *J Immunol* [Internet]. 1999 Oct 1;163(7):3851–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10490984>

74. Gosset P, Tillie-Leblond I, Oudin S, Parmentier O, Wallaert B, Joseph M, et al. Production of chemokines and proinflammatory and antiinflammatory cytokines by human alveolar macrophages activated by IgE receptors. *J Allergy Clin Immunol* [Internet]. 1999;103(2):289–97. Available from: <http://www.sciencedirect.com/science/article/pii/S009167499970504X>
75. Liu C, Richard K, Wiggins M, Zhu X, Conrad DH, Song W. CD23 can negatively regulate B-cell receptor signaling. *Sci Rep* [Internet]. 2016;6(May):25629. Available from: <https://doi.org/10.1038/srep25629>
76. Yao Y, Wang N, Chen CL, et al. CD23 expression on switched memory B cells bridges T-B cell interaction in allergic rhinitis. *Allergy*. 2020;75(10):2599-2612.
77. Engeroff P, Fellmann M, Yerly D, Bachmann MF, Vogel M. A novel recycling mechanism of native IgE-antigen complexes in human B cells facilitates transfer of antigen to dendritic cells for antigen presentation. *J Allergy Clin Immunol*. 2018;142(2):557–68.
78. Karagiannis SN, Warrack JK, Jennings KH, Murdock PR, Christie G, Moulder K, et al. Endocytosis and recycling of the complex between CD23 and HLA-DR in human B cells. *Immunology* [Internet]. 2001 Jul;103(3):319–31. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1783243&tool=pmcentrez&rendertype=abstract>
79. Hjelm F, Karlsson MCI, Heyman B. A novel B cell-mediated transport of IgE-immune complexes to the follicle of the spleen. *J Immunol*. 2008;180(10):6604–10.
80. Ding Z, Dahlin JS, Xu H, Heyman B, Heyman B, Heyman B, et al. IgE-mediated enhancement of CD4+ T cell responses requires antigen presentation by CD8α- conventional dendritic cells. *Sci Rep* [Internet]. 2016;6(February):28290. Available from: <http://www.nature.com/articles/srep28290>
81. Xu H, van Mechelen L, Henningsson F, Heyman B. Antigen conjugated to anti-CD23 antibodies is rapidly transported to splenic follicles by recirculating B cells. *Scand J Immunol* [Internet]. 2014 Oct 30 [cited 2014 Nov 5]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25359575>
82. Tu Y, Salim S, Bourgeois J, Di Leo V, Irvine EJ, Marshall JK, et al. CD23-Mediated IgE Transport Across Human Intestinal Epithelium: Inhibition by Blocking Sites of Translation or Binding. *Gastroenterology* [Internet]. 2005 Sep 1;129(3):928–40. Available from: <https://doi.org/10.1053/j.gastro.2005.06.014>
83. Palaniyandi S, Tomei E, Li Z, Conrad DH, Zhu X. CD23-dependent transcytosis of IgE and immune complex across the polarized human respiratory epithelial cells. *J Immunol* [Internet]. 2011 Mar 15 [cited 2014 May 8];186(6):3484–96. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21307287>
84. Yang P-C, Berin MC, Yu LCH, Conrad DH, Perdue MH. Enhanced intestinal transepithelial antigen

- transport in allergic rats is mediated by IgE and CD23 (Fc $\epsilon$ RII). *J Clin Invest* [Internet]. 2000 Oct 1;106(7):879–86. Available from: <https://doi.org/10.1172/JCI9258>
85. Bevilacqua C, Montagnac G, Benmerah A, Candalh C, Brousse N, Cerf-Bensussan N, et al. Food Allergens Are Protected from Degradation during CD23-Mediated Transepithelial Transport. *Int Arch Allergy Immunol* [Internet]. 2004;135(2):108–16. Available from: <https://www.karger.com/DOI/10.1159/000080653>
86. Li H, Chehade M, Liu W, Xiong H, Mayer L, Berin MC. Allergen-IgE Complexes Trigger CD23-Dependent CCL20 Release From Human Intestinal Epithelial Cells. *Gastroenterology* [Internet]. 2007;133(6):1905–15. Available from: <http://www.sciencedirect.com/science/article/pii/S0016508507016940>
87. Getahun A, Hjelm F, Heyman B. IgE enhances antibody and T cell responses in vivo via CD23+ B cells. *J Immunol*. 2005;175(3):1473–82.
88. van der Heijden FL, Joost van Neerven RJ, van Katwijk M, Bos JD, Kapsenberg ML. Serum-IgE-facilitated allergen presentation in atopic disease. *J Immunol*. 1993;150(8 Pt 1):3643–50.
89. Holm J, Willumsen N, Würtzen PA, Christensen LH, Lund K. Facilitated antigen presentation and its inhibition by blocking IgG antibodies depends on IgE repertoire complexity. *J Allergy Clin Immunol* [Internet]. 2011;127(4):1029–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21377718><http://www.sciencedirect.com/science/article/B6WH4-529SW39-6/2/af2d510097c74576200f2e933d202540>[http://www.sciencedirect.com/science?\\_ob=MIimg&\\_imagekey=B6WH4-529SW39-6-1&\\_cdi=6840&\\_user=533256&\\_pii=S0091674911](http://www.sciencedirect.com/science?_ob=MIimg&_imagekey=B6WH4-529SW39-6-1&_cdi=6840&_user=533256&_pii=S0091674911)
90. van Neerven RJ, Wikborg T, Lund G, Jacobsen B, Brinch-Nielsen A, Arnved J, et al. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum-IgE-facilitated allergen presentation. *J Immunol* [Internet]. 1999;163(5):2944–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10453043>
91. Villazala-Merino S, Rodriguez-Dominguez A, Stanek V, Campion NJ, Gattinger P, Hofer G, et al. Allergen-specific IgE levels and ability of IgE-allergen complexes to cross-link determine extent of CD23-mediated T cell activation. *J Allergy Clin Immunol* 2020; 145(3):958-967; Available from: <http://www.sciencedirect.com/science/article/pii/S009167491931601X>
92. Henningsson F, Ding Z, Dahlin JS, Linkevicius M, Carlsson F, Grönvik K-O, et al. IgE-Mediated Enhancement of CD4+ T Cell Responses in Mice Requires Antigen Presentation by CD11c+ Cells and Not by B Cells. *PLoS One* [Internet]. 2011 Jul 6;6(7):e21760. Available from: <https://doi.org/10.1371/journal.pone.0021760>
93. Admyre C, Bohle B, Johansson SM, Focke-Tejkl M, Valenta R, Scheynius A, et al. B cell-derived



- exosomes can present allergen peptides and activate allergen-specific T cells to proliferate and produce TH2-like cytokines. *J Allergy Clin Immunol*. 2007;120(6):1418–24.
94. Qazi KR, Gehrmann U, Domange Jordö E, Karlsson MCI, Gabrielsson S. Antigen-loaded exosomes alone induce Th1-type memory through a B cell–dependent mechanism. *Blood* [Internet]. 2009 Mar 19;113(12):2673–83. Available from: <https://doi.org/10.1182/blood-2008-04-153536>
95. Mathews JA, Gibb DR, Chen B-H, Scherle P, Conrad DH. CD23 Sheddase A disintegrin and metalloproteinase 10 (ADAM10) is also required for CD23 sorting into B cell-derived exosomes. *J Biol Chem* [Internet]. 2010 Nov 26 [cited 2014 Mar 25];285(48):37531–41. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2988358&tool=pmcentrez&rendertype=abstract>
96. Padro CJ, Shawler TM, Gormley MG, Sanders VM. Adrenergic regulation of IgE involves modulation of CD23 and ADAM10 expression on exosomes. *J Immunol* [Internet]. 2013 Dec 1 [cited 2014 Oct 6];191(11):5383–97. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24140643>
97. Martin RK, Brooks KB, Henningsson F, Heyman B, Conrad DH. Antigen Transfer from Exosomes to Dendritic Cells as an Explanation for the Immune Enhancement Seen by IgE Immune Complexes. *PLoS One* [Internet]. 2014;9(10):e110609. Available from: <http://dx.plos.org/10.1371/journal.pone.0110609>
98. Palaniyandi S, Liu X, Periasamy S, Ma A, Tang J, Jenkins M, et al. Inhibition of CD23-mediated IgE transcytosis suppresses the initiation and development of allergic airway inflammation. *Mucosal Immunol* [Internet]. 2015;8(6):1262–74. Available from: <http://www.nature.com/doifinder/10.1038/mi.2015.16>
99. Cernadas M, De Sanctis GT, Krinzman SJ, Mark DA, Donovan CE, Listman JA, et al. CD23 and Allergic Pulmonary Inflammation: Potential Role as an Inhibitor. *Am J Respir Cell Mol Biol* [Internet]. 1999 Jan 1;20(1):1–8. Available from: <https://doi.org/10.1165/ajrcmb.20.1.3299>
100. Haczku A, Takeda K, Hamelmann E, Oshiba A, Loader J, Joetham A, et al. et al. CD23 Deficient Mice Develop Allergic Airway Hyperresponsiveness Following Sensitization with Ovalbumin. *Am J Respir Crit Care Med* [Internet]. 1997 Dec 1;156(6):1945–55. Available from: <https://doi.org/10.1164/ajrccm.156.6.9701087>
101. Mudde GC, Bheekha R, Bruijnzeel-Koomen CA. Consequences of IgE/CD23-mediated antigen presentation in allergy. *Immunol Today*. 1995;16(8):380-383
102. Carlsson F, Hjelm F, Conrad DH, Heyman B. IgE enhances specific antibody and T-cell responses in mice overexpressing CD23. *Scand J Immunol*. 2007;66(2-3):261-270.

103. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-Mediated Autoimmunity. *Front Immunol.*2018;9:689.
104. Pellefigues C. IgE Autoreactivity in Atopic Dermatitis: Paving the Road for Autoimmune Diseases? *Antibodies (Basel).* 2020;9(3).
105. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol.* 2015;136(3):556–68.
106. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol.* 2016;137(2):358–68.
107. Jutel M, Akdis CA. Immunological mechanisms of allergen-specific immunotherapy. *Nat Rev Immunol.* 2011;66(6):725–32.
108. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol.* 2011;127(1):18–27.
109. Shamji MH, Kappen J, Abubakar-Waziri H, Zhang J, Steveling E, Watchman S, et al. Nasal allergen-neutralizing IgG4 antibodies block IgE-mediated responses: Novel biomarker of subcutaneous grass pollen immunotherapy. *J Allergy Clin Immunol [Internet].* 2019;143(3):1067–76. Available from: <http://www.sciencedirect.com/science/article/pii/S0091674918315951>
110. Wachholz PA, Kristensen Soni N, Till SJ, Durham SR. Inhibition of allergen-IgE binding to B cells by IgG antibodies after grass pollen immunotherapy. *J Allergy Clin Immunol [Internet].* 2003;112(5):915–22. Available from: <http://www.sciencedirect.com/science/article/pii/S0091674903020220>
111. Shamji MH, Wilcock LK, Wachholz PA, Dearman RJ, Kimber I, Wurtzen PA, et al. The IgE-facilitated allergen binding (FAB) assay: Validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. *J Immunol Methods [Internet].* 2006;317(1):71–9. Available from: <http://www.sciencedirect.com/science/article/pii/S0022175906002584>
112. Gasser P, Eggel A. Targeting IgE in allergic disease. *Curr Opin Immunol [Internet].* 2018;54:86–92. Available from: <https://doi.org/10.1016/j.coi.2018.05.015>
113. Lanier B, Bridges T, Kulus M, Taylor F, Berhane I. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic ( IgE-mediated ) asthma. *J Allergy Clin Immunol [Internet].* 124(6):1210–6. Available from: <http://dx.doi.org/10.1016/j.jaci.2009.09.021>
114. Strunk RC, Bloomberg GR. Omalizumab for Asthma. *N Engl J Med [Internet].* 2006 Jun 22;354(25):2689–95. Available from: <https://doi.org/10.1056/NEJMct055184>
115. Pennington LF, Tarchevskaya S, Brigger D, Sathiyamoorthy K, Graham MT, Nadeau KC, et al.

Structural basis of omalizumab therapy and omalizumab-mediated IgE exchange. *Nat Commun* [Internet]. 2016;7(May):11610. Available from: <http://www.nature.com/doi/10.1038/ncomms11610>

116. Gauvreau GM, Arm JP, Boulet L-PP, Leigh R, Cockcroft DW, Davis BE, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. *J Allergy Clin Immunol* [Internet]. 2016;138(4):1051–9. Available from: <http://dx.doi.org/10.1016/j.jaci.2016.02.027>
117. Gasser P, Tarchevskaya SS, Guntern P, Brigger D, Ruppli R, Zbären N, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun* [Internet]. 2020;11(1). Available from: <http://dx.doi.org/10.1038/s41467-019-13815-w>
118. Chen J-B, Ramadani F, Pang MOY, Beavil RL, Holdom MD, Mitropoulou AN, et al. Structural basis for selective inhibition of immunoglobulin E-receptor interactions by an anti-IgE antibody. *Sci Rep* [Internet]. 2018;8(1):11548. Available from: <https://doi.org/10.1038/s41598-018-29664-4>
119. Shiung Y-Y, Chiang C-Y, Chen J-B, Wu PC, Hung AF-H, Lu DC-S, et al. An anti-IgE monoclonal antibody that binds to IgE on CD23 but not on high-affinity IgE.Fc receptors. *Immunobiology* [Internet]. 2012;217(7):676–83. Available from: <http://www.sciencedirect.com/science/article/pii/S0171298511002567>
120. Poole J a, Meng J, Reff M, Spellman MC, Rosenwasser LJ. Anti-CD23 monoclonal antibody, lumiliximab, inhibited allergen-induced responses in antigen-presenting cells and T cells from atopic subjects. *J Allergy Clin Immunol* [Internet]. 2005 Oct [cited 2014 Mar 25];116(4):780–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16210051>

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## Figure Legends

### Figure 1.

Mechanisms that regulate targeting of IgE to CD23. A) Free IgE binds only weakly CD23 monomer whereas it binds much more strongly to oligomerized CD23 B) IgE-antigen immune complexes (IgE-IC) bind to CD23 much stronger than free IgE C) Binding of antigen-specific IgG to IgE-IC could enable complement fixation via CD21 and lead to co-aggregation of CD23 and CD21

### Figure 2

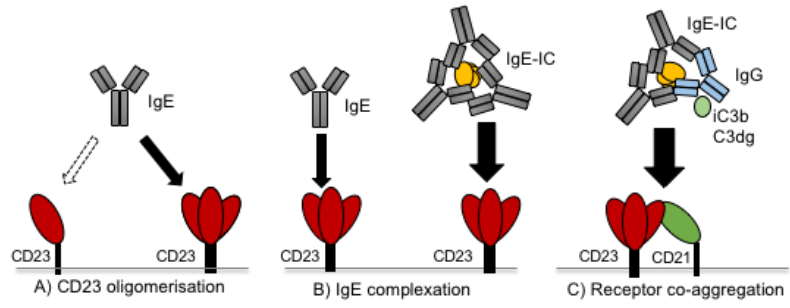
IgE-IC processing by CD23. CD23a and CD23b are expressed in epithelial cells (A) which mediate

endocytosis, transcytosis, and release of the chemokine CCL20 in response to CD23 triggering; inhuman primary B cells (B) which mediate endocytosis, recycling, and transport and in EBV B cells (C) which are capable of antigen degradation and IgE-facilitated antigen-presentation (FAP). In dendritic cells (D) only CD23b is expressed which mediates phagocytosis, antigen degradation, and antigen presentation.

### Figure 3

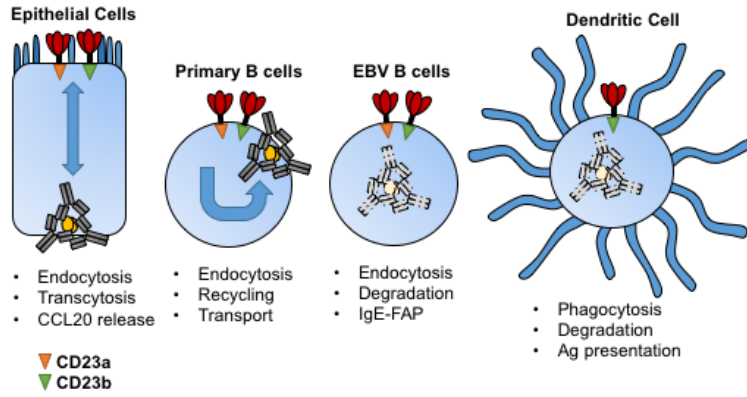
Model: The antigen-specific immune response via CD23 in mice. IgE-ICs are endocytosed via CD23 by intestinal epithelial cell (IEC) or alveolar epithelial cell (AEC) which mediate transport of IgE-immune complexes into the circulation. Alternatively, immune complexes could also be formed directly in circulation. Uptake of IgE-ICs by B cells via CD23 allows the transfer of IgE-ICs to dendritic cells in lymph nodes or spleen. This induces antigen-presentation on the surface of DCs in complex with the MHC complex to the T cells which promotes T cell proliferation and formation of antibodies.

Figure 1



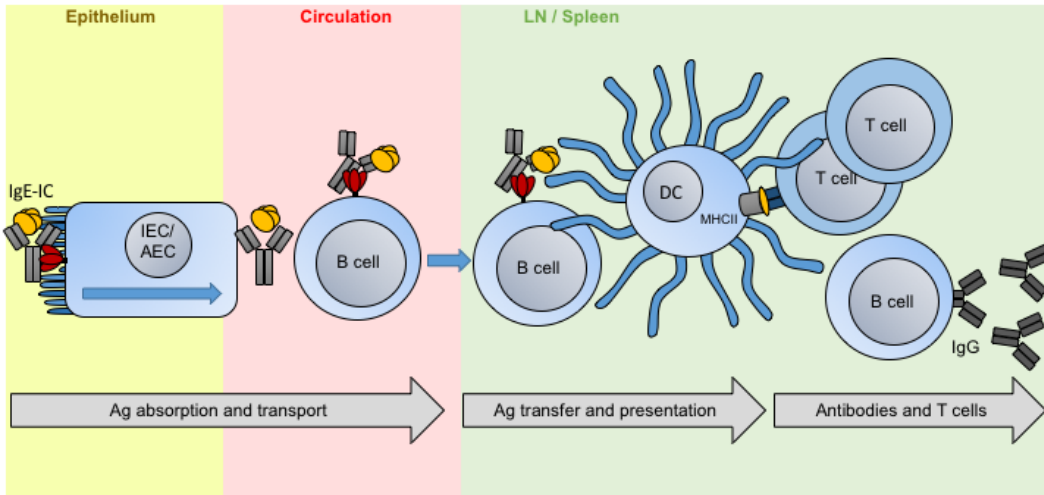
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Figure 2



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Figure 3



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