# A role for CD23 in the suppression of allergy

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**Abstract**

IgE, the key molecule in atopy has been shown to bind two receptors, Fc?RI, 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 Fc?RI triggers allergic reaction, binding of IgE to CD23 is known to play an important role in both IgE synthesis and presentation. Thus, targeting IgE-immune complexes on B cells has shown to 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 matter of debate. Here, we discuss several mechanisms related to IgE and IgE binding to both receptors, as well as the influence of the antigen binding on different immune cells expressing the receptors. One recent paper has shown that free IgE preferentially binds to Fc?RI 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 the antigen presentation by delivering antigen to dendritic cells. The data suggest that CD23 play a multifunctional role in regulating the allergic response pathway.

## 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, FcεRI on allergic effector cells such as mast cells and basophils(6–8).

The second IgE receptor CD23 (FcεRII) 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 has been shown to play a role in the development and growth of normal and leukemic B cells (11,12). Furthermore, it has been studied as a C-type lectin where it was shown to facilitate antimicrobial immunity (13–17) and can even be engaged by sialylated IgG to act as a Fcγ receptor( 18–20). Apart from its form as a membrane receptor, CD23 can be cleaved into soluble fragments (sCD23) which has been studied as a disease marker in allergy, rheumatoid arthritis and leukemia (21–24). Furthermore, sCD23 has been shown to 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, despite the fact that CD23 is a C-type lectin and IgE is heavily glycosylated,

the interaction between IgE and CD23 is independent of carbohydrates (28). Structurally, CD23 presents a short cytoplasmic N-terminus followed by a single transmembrane region and a long C-terminal extracellular domain (29). The extracellular part consists of three regions: 1) an alpha-helical coiled-coil stalk region which mediates the formation of trimers, 2) lectin head which binds IgE and 3) a modified RGD sequence that binds to α5β5 integrin (30). There are two major CD23 isoforms, CD23a and CD23b(31) 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) (32,33).

Structural studies have shown that IgE interacts in different manners with its two receptors, FcεRI and CD23 (34). 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 sub-sides 1 (Cε3A) and 2 (Cε3B) (35,36). In contrast, in 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 differs by one order of magnitude weaker ($K_D$ around 14.4 μM) (37–39). 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 CD21. It was shown that the CD21 binding site on CD23 does not overlap with IgE binding sites (40,41). For CD23 and CD21, a carbohydrate-dependent interaction was reported (42).

### 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 (43) (Fig. 1A and 1B). The leucine zipper region in the stalk was proposed to play an important role in CD23 oligomerisation (44). 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 previous described lectin domain binding site (45). Another important aspect that may regulate CD23 targeting is the valency of IgE. The binding of IgE in complex with allergen (IgE-immune complex) was shown to impact binding of IgE to CD23 (46). 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 (47). The physiological relevance of IgE-allergen immune complexes in healthy and allergic patients is not entirely clear, even though their existence has been described a long time ago (48,49). Similarly to IgE-allergen immune complexes, the well documented presence of natural anti-IgE antibodies could also lead to multivalent IgE complexes that could potentially regulate CD23 versus FcεRI targeting (50–53).

IgE binding to CD23 may also be enhanced by other receptors. The complement receptor CD21, which has been shown to bind 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 immune complex to CD23. It was shown that IgE-immune complexes formed in allergic patients include IgE, IgG1 and IgG4 leading to the activation of the complement system resulting in the fixation of complement components to the complexes that bind to peripheral B cells via CD21 (54) (Fig. 1C). Surprisingly, IgG binding via FcγRII was not found to play a role in that study. 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.

### CD23 as a regulator of IgE levels

A main function attributed to CD23 has been 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 (55,56) while $CD23^{-/-}$ mice show enhanced IgE production (57). Furthermore, anti-CD23 antibodies have been shown to inhibit

antigen-specific IgE responses in mice (58).

In human B cells, it was shown that IgE synthesis can be inhibited*in vitro* by direct targeting of CD23 (59). This supports a model which predicts a positive and a negative feedback mechanism depending on the concentration of IgE and cleavage of membrane CD23 (63). Thus, high levels of IgE or antibodies against the lectin head of CD23 stabilize membrane CD23 preventing its proteolytic cleavage and thereby inhibits IgE synthesis. In turn, the cleavage of CD23 by allergens has been a proposed mechanism of enhanced IgE responses (60). Allergen-cleaved CD23 would lose the ability to suppress IgE synthesis and hence lead to eleveated 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 (61). The fact that IgE and CD21 have distinct binding sites and bind CD23 simultaneously supports this hypothesis (41). In contrast the co-ligation of of membrane IgE and membrane-bound CD23 via allergen-IgE complexes has been suggested as negative feedback mechanism of IgE synthesis but more experiments need to be performed to confirm this hypothesis.

A further mechanism by which CD23 may regulate IgE levels, is by acting as a direct decoy receptor for FceRI. It was shown in mice, that B cells regulate serum IgE levels directly by absorbing free IgE molecules, thus preventing FceRI loading and allergic sensitization (47,62,63), This more novel model of IgE regulation fits well with the generally higher IgE levels in CD23 deficient mice.

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

Many functional investigations on CD23 have demonstrated a mechanism triggered by CD23 cross-linking via IgE immune complexes. 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 and CD23b (31). The differential expression of CD23a and b in B cells and monocyte-related cells, respectively has led to several interesting comparative studies showing differential signalling. Specifically, signalling via Fyn and Syk and Akt pathways resulting in IFN-$\gamma$ production was only reported for CD23 cross-linking in B cells whereas cells of the monocytic lineage have been described to signal via I$\varkappa$B and produce inflammatory chemokines and cytokines such as TNF, IL-1$\beta$, IL-1ra, IL-10, IL-8, MCP-1, and MIP-1$\alpha$ (64–68). A recent paper has shown that CD23 as well can negatively regulate BCR activation on B cells by promoting B cell contraction. This provides an explanation for down-regulation of CD23 on memory B cells that mount a higher response of memory B cells to antigenic stimulation (69).

In addition to the differential signalling, the processing of IgE and IgE-immune complexes also depends on the cell type. In monocyte-derived cells or in 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 (70, 71) (Fig. 2). These findings are consistent with studies in mice showing that circulating murine B cells transport IgE immune complexes to the spleen (72–74).

Those findings in B cells fit well to results showing that CD23a expressing human intestinal epithelial cells (75,76) as well as mouse intestinal epithelial cells can shuttle IgE and IgE-immune complexes through the epithelial layer by transcytosis (77). Like in human B cells, food allergens were also shown to be protected from degradation during epithelial transcytosis (78). Interestingly, intestinal epithelial cells (IEC) were also shown to release CCL20 in response to CD23 cross-linking, suggesting that CD23 may act as critical receptor in initiating an allergic response by the release of chemokines capable of recruiting cells of the innate and adaptive immune system (79). 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 (76).

## 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 (73,80). 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 (45,81–84). However, as previously mentioned, experiments with primary B cells have shown that IgE-immune complexes are protected from degradation. This difference in processing between normal B cells and EBV-transformed cells requires more detailed investigations, in order to better understand the mechanism of immunomodulation. Despite the fact that primary human B cells failed to directly induce T cell proliferation, they are able to transfer the IgE-immune complexes to human dendritic cells to induce T cell proliferation (70). Fittingly, it was shown in mice that IgE-mediated antigen presentation was, though initiated by B cells, ultimately dependent on dendritic cells (73, 85). 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 (86,87) (Fig. 3). Independently, it has been described that the CD23 sheddase ADAM10 can mediate sorting of CD23 into B cell-derived exosomes (88,89). The concept of exosome transfer between B cells and dendritic cells has also been put forth in mice (90). 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 (91) as well as negatively regulate allergic airway inflammation (92, 93).

## 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) (94,95). Multiple injections of increasing allergen doses induce the generation of tolerance via regulatory T cells and the induction of protective IgG4 antibodies (96, 97). 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 (98 –100).

A different approach to treat allergic diseases is by anti-IgE therapy (101). Omalizumab, a monoclonal anti-IgE antibody is used for severe allergic asthma and chronic spontaneous urticaria (102,103). Mechanistically, Omalizumab, inhibits both FcεRI:IgE and CD23:IgE interactions (104). A more recent anti-IgE antibody, Ligelizumab, was shown to display increased efficacy in the treatment of allergic asthma (105). Functionally, Ligelizumab was shown to display reduced IgE:CD23 inhibition compared to Omalizumab but enhanced inhibition of IgE:FcεRI binding (106). 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 FceRI pathway (63). 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 (107,108). 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 (109). 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 an 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.

## 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 are lacking, evidence shows that i) CD23 can absorb and clear IgE from the serum in non-inflammatory fashion ii) CD23 reduces the synthesis of IgE from B cells iii) CD23 facilitates antigen-specific IgG and T cell responses (Fig. 4). Together, those factors lead us to believe that CD23 deserves a closer look as a therapeutic target in allergies.

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**Figure Legends**

**Figure 1.**

Regulation of IgE binding 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-antigen complexes 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; in human 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 in cooperation with B cells.

**Figure 3**

Model: The antigen-specific immune response via CD23 in mice. IgE-antigen immune complexes (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-immune complexes by B cells via CD23 allows 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 4**

CD23 as an inhibitor of allergic sensitisation. CD23 plays different roles during the allergic response including A) clearance of serum IgE that counteracts the allergic pathway to prevent IgE sensitization on FceRI B) negative feedback regulation of IgE synthesis by binding of IgE-ICs to CD23 on B cells C) T cell proliferation and antibody production induced by binding of IgE-ICs to CD23 on B cells.

**Figure 1**

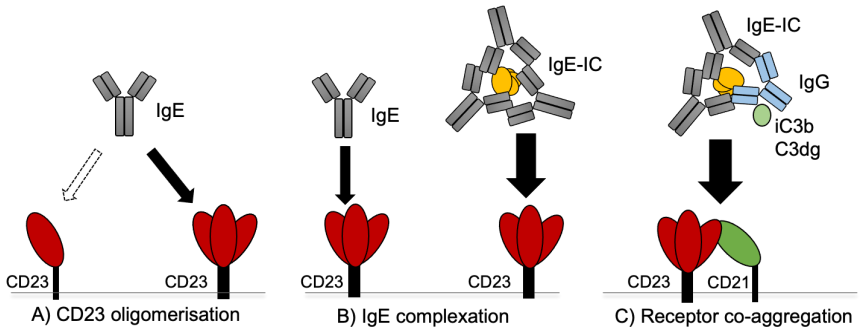


**Figure 2**

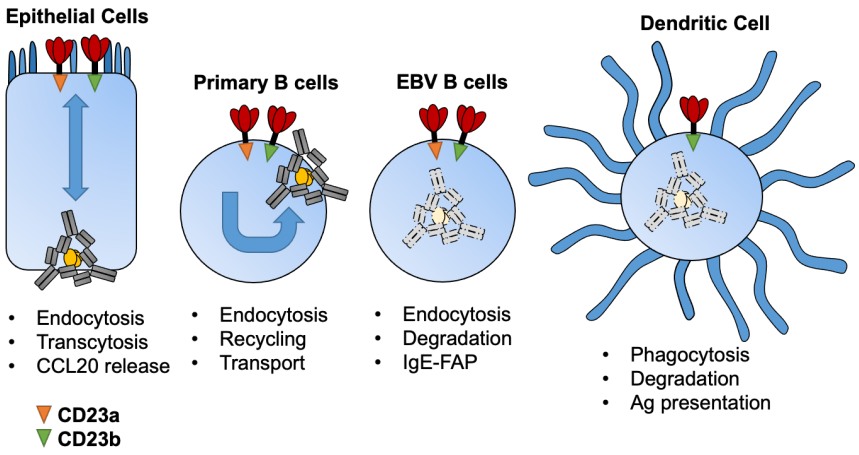



**Figure 3**

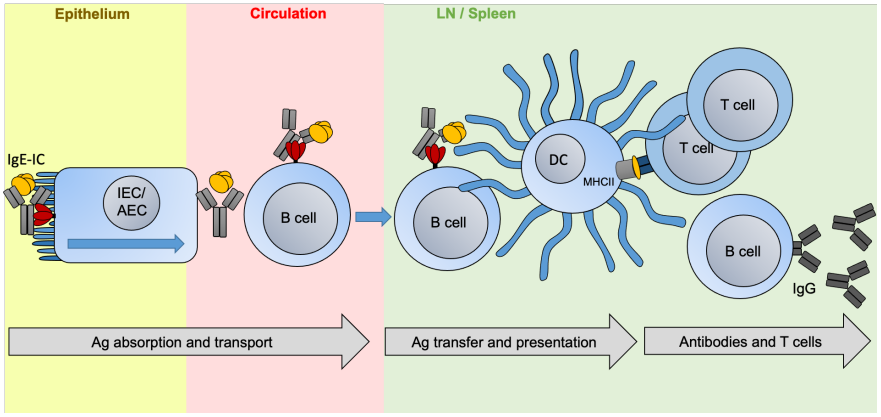



**Figure 4**

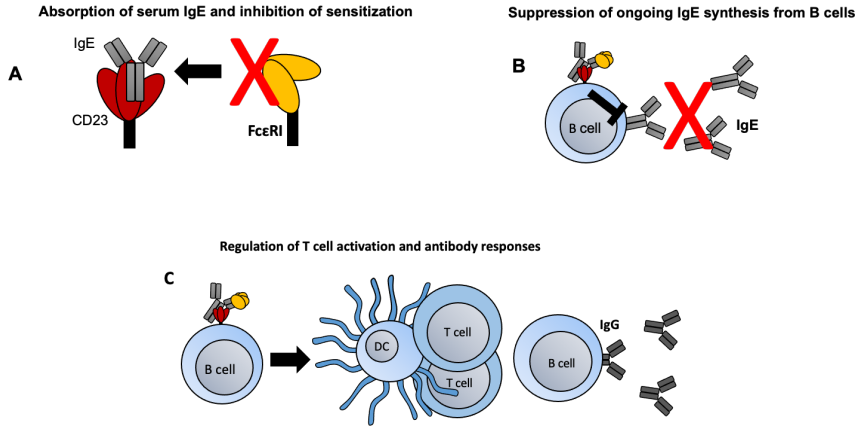


**Figure 1**

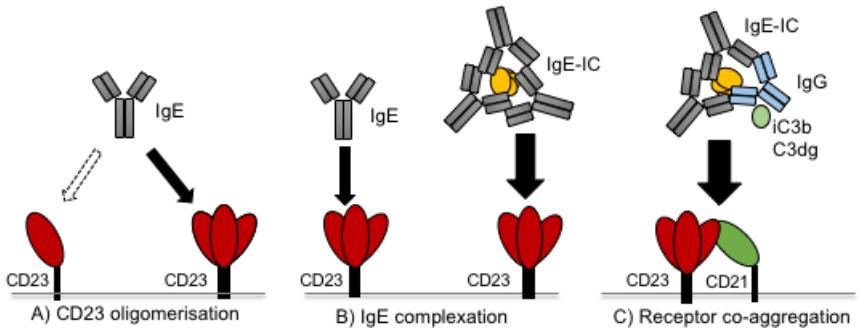
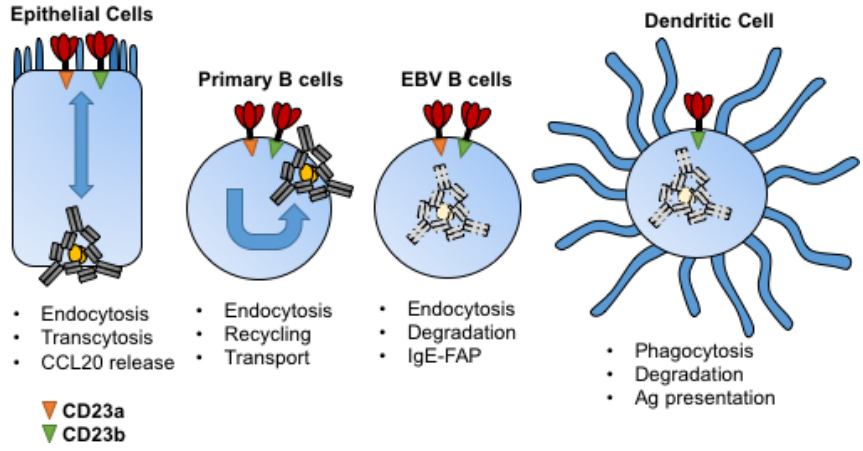



**Figure 2**

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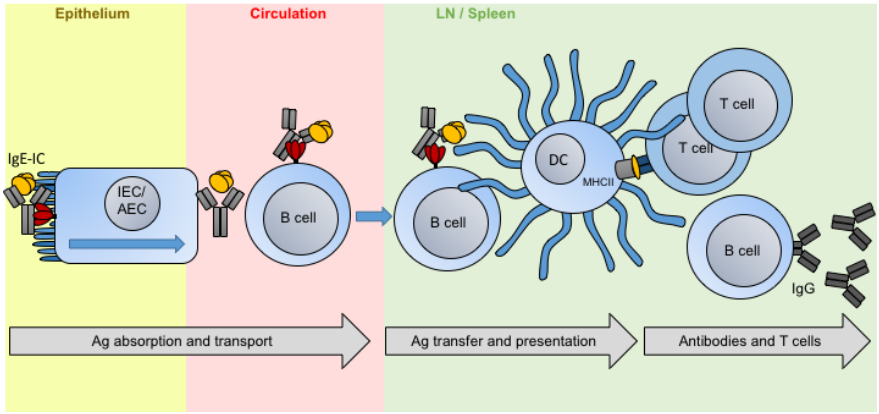

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