

Molecular Basis for Downregulation of C5a-Mediated Inflammation by IgG1 Immune Complexes in Allergy and Asthma

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Abstract Allergy and asthma are triggered primarily by the binding of allergen-specific immunoglobulin E (IgE)–allergen complexes to their receptors, recognition of the allergens by antigen-presenting cells, and allergen presentation to the T cells. These events lead to mucus secretions, runny nose, itchy eyes, sneezing, airway hyperresponsiveness, and nasal congestion. Complement 5a (C5a) has emerged as a central molecule that mediates these allergic reactions. Many allergens and allergen-specific IgG immune complexes (IgG-ICs) cause complement activation and C5a generation. C5a interaction with its receptor (C5aR) leads to the infiltration and activation of several immunologic cell types and the secretion of pathogenic inflammatory and proinflammatory mediators. However, IgG1-IC binding to the IgG inhibitory Fc gamma receptor (FcγRIIB) suppresses C5aR-mediated inflammatory signaling and, hence, may reduce the inflammatory immune responses through this FcγRIIB-mediated pathway. Reviews of the IgG1-IC interactions with C5a-mediated inflammatory immune responses suggest that IgG1-IC–C5a inhibitory therapy may reduce inflammation in allergic diseases.

Keywords Allergen · Glycosylated IgG · Cytokines · Immunologic cells · Fcγ receptor · Complement-5a receptor · Allergen immunotherapy · Allergy · Asthma · Leukocytes

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Introduction

Allergic and asthmatic diseases affect 300 million people worldwide [1] and are caused by common allergens, including house dust mites (HDMs), cockroaches, animal dander, fungi, and pollens [2]. Complement 5a (C5a) generation results from exposure to a variety of allergens (Table 1) and the formation of allergen-specific immunoglobulin G complexes (IgG-ICs) [3]. The production of C5a recruits macrophages (MΦs), basophils (BAs), polymorphonuclear neutrophils (PMNs), eosinophils (EOs), and mast cells (MCs) to exposure sites and production of inflammatory mediators, i.e., interleukin (IL)-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [4–6]. C5a interaction with its receptor (C5aR) triggers a cascade of intracellular signaling through the Ras-Raf, MEK1/2, and ERK1/2 pathways [7, 8]. Such signaling causes recruitment of inflammatory cells that are important for increased production of a variety of inflammatory and proinflammatory mediators, i.e., IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF, IL-1, IL-6, tumor necrosis factor-α (TNF-α), histamine, leukotrienes, myeloperoxidase, and platelet-activating factors [4–8]. These inflammatory mediators cause the pathophysiology of allergy and asthma, i.e., airway hyperresponsiveness (AHR), airway eosinophilia, goblet cell hyperplasia, recurrent episodes of wheezing, breathlessness, and chest tightness [3, 9, 10].

In contrast to the generation of allergen-specific IgG2a, IgG1 (analogous to IgG4 in humans) antibodies have been shown to suppress the inflammatory immune responses in murine models of allergy and asthma (Tables 2, 3).

IgGs isolated from sera of normal, healthy individuals show a high degree of galactosylation, which preserves the anti-inflammatory state [11]. Conversely, the degree of galactosylation of the IgG N-glycan chains was reported to be lower in patients with inflammatory diseases such as rheumatoid arthritis [12–19], osteoarthritis [18, 20], Crohn's disease [18, 21],

Table 1 Influence of C5a in allergy and asthma

Allergen and allergic diseases	Species	Site of increased releases of C5a	Immunologic inflammation	Studies
HDM, <i>Aspergillus fumigatus</i> , and perennial ryegrass	Mice	Sera	Aggregation of PMNs and IgE-mediated responses	[87]
<i>Dermatophagoides</i> species (Der p 3 and Der f 3)	Mice	Sera	Increased histamine secretion and PMNs chemotaxis	[88]
Ragweed allergen	Human	Sera	Harshness of allergic rhinoconjunctivitis symptoms	[89, 90]
Cowshed dust extracts	Mice	BAL	–	[91]
<i>Candida albicans</i>	Human	PBMC	Activation of PBMCs and increased release of IL-6 and IL-1 β	[92, 93]
Thrombin	Mice	BAL	Increased vascular leakage, PMNs infiltration, and lung injury	[94]
β -Tryptase	Human	Skin MCs	Enhanced tissue damage	[95]
Allergic respiratory disease	Human	Plasma	Increased histamine secretion	[96]
Asthma	Human	BAL	Increased IL-8 secretion	[97]
Asthma	Human	BAL	Increased infiltration of EOs and PMNs	[19]
COPD and asthma	Human	Sera	Increased disease severity	[98]
Chronic urticaria	Human	Blood and sera	Increased infiltration of CD4 ⁺ T cells, MOs, PMNs, EOs, and BAs; enhanced secretion of IL-4 and IL-5	[99]
Allergic rhinitis	Human	Nasal lavage fluid	Increased nasal symptoms	[100]

BAL bronchoalveolar lavage; PBMCs peripheral blood mononuclear cells; – not reported

systemic lupus erythematosus [18, 22], Sjögren's syndrome [21], ankylosing spondylitis [18], ulcerative colitis [18, 23], infective endocarditis [18], tuberculosis [21], liver fibrosis and cirrhosis in hepatitis C infection [24], HIV infection [25], and ovarian cancer [26].

It is important to note that glycan composition of the IgG1-IC molecules comprise a branched *N*-glycan in their Fc portion. This form of IgG showed high heterogeneity due to terminal

sialic acid, galactose, or *N*-acetylglucosamine residues, causing dectin-1 to cooperate with the Fc gamma receptor (Fc γ RIIB) [27–29]. Indeed, the inhibitory impact of IgG1 has been shown in mouse models of autoimmune disease, in which IgG1-ICs engaged dectin-1 molecules together with Fc γ RIIB to cause Syk phosphorylation. This phosphorylated Syk promotes the subsequent phosphorylation of the immunoreceptor tyrosine-based inhibition motif (ITIM) and SH2 domain phosphatases

Table 2 Allergen-specific IgGs and their association with decreased inflammation in a murine model of allergy and asthma

Immunization	Murine strains	Allergen-specific antibodies	Immunologic inflammation	Studies
OVA	WT ^M	IgG1 (Abs-Rx)	Protection from asthma	[101]
OVA	WT ^M	IgG1 (Abs-Rx)	Reduction of IgE-mediated inflammation	[102]
OVA	WT ^R	IgG1 (Abs-Rx)	Changed immediate airway response to late airway response	[103]
Birch (Bet v 1) and grass pollen (Phl p 1 and Phl p 5)+rabbit IgG (Ab-P)	WT ^M	IgG1	Reduced allergen-specific IgE binding affinity and BAs degranulation	[104]
OVA+anti-OVA IgG1 (Ab-P)	WT ^M	(-.)	Reduced total cell and EOs numbers, T-cell proliferation, and secretion of Th2 cytokines followed by AHR	[105]
OVA+anti-OVA IgG (Ab-P)	Fc γ R ^{-/-} M	IgG1	Decreased eosinophilia followed by decreases in IL-5, IL-13, eotaxin, mononuclear cell proliferation, and AHR	[106]
OVA+anti-OVA IgG (Ab-P)	Fc γ R ^{-/-} M	(-.)	Decreased DCs activation, CD4 ⁺ T-cell proliferation, and AHR	[107]
OVA	Fc γ R ^{-/-} M	(-.)	Decreased leukocyte counts	[108]

Ab-P Antibody administered passively; Abs-Rx Antibody generated during the course of vaccination; Bet v 1 *Betula verrucosa* 1; M Mice; R Rat; (-.) not measured; OVA Ovalbumin; Phl p *Phleum pratense*; rHM Recombinant hybrid molecule; WT Wild-type; Fc γ R Fc - gamma receptor

Table 3 Allergen-specific IgGs and their association with elevated immunologic inflammation in a murine model of allergy and asthma

Immunization	Murine strains	Allergen-specific antibodies	Immunologic inflammation	Studies
Engraftment of retrovirally transduced birch pollen allergen (Bet v 1)–GFP-expressing bone marrow cells	WT ^M	IgG2a (Abs-Rx)	Increased BAs degranulation	[109]
rHM	WT ^M	IgG2a >>> IgG1 (Abs-Rx)	Increased secretion of IFN- γ and IL-10 but diminished secretion of IL-13	[110]
OVA+anti-OVA IgG (Ab-P)	WT ^M	–	DCs activation; CD4 ⁺ T cell proliferation; increased secretion of EOs, TNF- α , IL-6, and Th2 cytokines followed by AHR	[107]
Ragweed extract	WT ^M and Fc γ RIIB ^{−/−} M	–	Increased infiltration of EOs and increased secretion of IL-4, IL-5, and IL-13	[23]
OVA+anti-Ova IgG (Ab-P)	Fc γ RIII ^{−/−} M	–	Increased infiltration of immunologic cells (EOs, CD4 ⁺ T cells, and CD8 ⁺ T cells) and augmented secretion of cytokines, i.e., IL-4, IL-5, IL-10, IL-12, IL-13, MCP-1, followed by AHR	[111]

Ab-P antibody administered passively; *Abs-Rx* antibody generated during the course of vaccination; *Bet v 1* *Betula verrucosa* 1; *GFP* green fluorescent protein; *IFN* interferon; *M* mice; –, not measured; *OVA* ovalbumin; *Phl p* *Phleum pratense*; *rHM* recombinant hybrid molecule; *WT* wild-type; *Fc γ R* Fc-gamma receptor

predominantly called SHIP. These signaling molecules block the C5aR-mediated extracellular signal-regulated protein kinase 1 and 2 (ERK1/2) phosphorylation, phospholipase C- γ (PLC- γ), and phosphoinositol-3,4,5-triphosphate [PI(3,4,5)P₃]-mediated pathway of inflammation [30]. However, high-galactosylated IgG-ICs in dectin-1^{−/−} mice and agalactosylated or low-galactosylated IgG-ICs in vitro and in vivo mouse models of autoimmune disease have not shown the ability to inhibit C5a-induced inflammation [30]. Thus, it is possible that IgG1 antibodies, which showed their association with suppression of inflammatory immune responses in allergy and asthma (Table 3), might be a result of the change in IgG glycosylation pattern.

However, the exact mechanism by which IgG1 antibodies reduce the immunologic inflammation in allergic and asthmatic diseases is not clear. In this review, the C5a-mediated inflammatory immune responses and their possible control by IgG1-ICs are reviewed, and the potential of IgG1-IC therapy being used therapeutically to inhibit several of the C5a-mediated inflammatory functions in allergy and asthma is proposed.

Complement Activation and C5a-mediated Functions

There are three major complement pathway systems (classical, alternative, and lectin) that cause complement activation and C5a production [31]. C5a is a small (11-kDa) protein fragment that exerts its effector functions upon binding to its main functional receptor, C5aR, a member of the large family of G protein-coupled receptors (GPCRs) [32, 33]. C5aR is distributed widely on a variety of immunologic cells, i.e., PMNs, monocytes (MOs), M Φ s, dendritic cells (DCs), EOs, BAs, MCs, and T cells [31, 34]. Several studies have

documented the association of these cells with an increased generation of C5a [35, 36] and up-regulation of C5aR in allergy and asthma [6, 37–39]. The following C5a-mediated functions are critical for immunologic inflammation in allergy and asthma.

Recruitment of Leukocytes

C5a acts as a chemoattractant that causes the infiltration of immunologic cells toward the sites of inflammation [31]. The role of C5a in the recruitment of BAs, PMNs, EOs, and MCs and the increased secretion of proinflammatory mediators, i.e., histamine, leukotrienes, platelet-activating factor, IL-1, IL-6, and TNF- α , have been observed as key events in the induction of allergic and asthmatic disease manifestations [5]. These include cellular degranulation, enhanced smooth muscle contraction, vascular permeability, mucus secretion, and AHR in allergic and asthmatic diseases [4, 5, 35, 36, 40, 41].

Adaptive Immune Responses

C5a interaction with C5aR on antigen-presenting cells (APCs) and T cells causes the up-regulation of stimulatory and costimulatory molecules, which triggers the production of a variety of cytokines [42–44]. Indeed, ligation of the C5aR by C5a causes the release and up-regulation of stimulatory and costimulatory molecules on APCs and T cells to trigger Th2 and Th17 cytokines in allergic asthma [45, 46]. These cytokines cause B cell activation and production of allergen-specific IgE antibodies. These antibodies bind with their

receptors on different immunologic cells and cause the increased secretion of histamine and leukotrienes, followed by mucus secretion and AHR [47–51]. Pharmacologic targeting of C5a/C5aR-mediated signaling significantly suppressed airway inflammation [6, 52], suggesting that C5a acts as a positive regulator in the development of inflammation in these diseases [6, 52–54].

FcγR-mediated Inflammation

C5a-mediated functions are important in causing the up-regulation of activating FcγRs and down-regulation of inhibitory FcγRIIB [55]. These classes of FcγRs are the receptors for IgG, which are present on many immunologic cells, have distinct IgG binding affinity, and participate in complement activation (Table 4).

IgG-IC ligation with activating FcγRs causes the tyrosine phosphorylation of immunoreceptor tyrosine-based activating motifs by the SRC family kinases [56, 57]. The latter molecules lead to the recruitment of SyK family kinases, followed by the activation of various downstream targets, i.e. linker for activation of T cells (LAT), multimolecular adaptor complexes (MACs), and phosphoinositide 3-kinase (PI3K). These molecules generate the membrane-docking sites for Bruton's tyrosine kinase (BTK), which recruit phosphoinositide base (PI) and PLC-γ. The latter molecule is a multidomain phosphodiesterase that converts PI(3,4,5)P₃ to three byproducts: phosphoinositol-4,5-diphosphate [PI(4,5)₂], inositol-1,4,5-triphosphate (IP₃), and diacylglycerol (DAG). These downstream products cause Ca⁺⁺ mobilization and activation of the RAS-RAF-MAPK pathway for cellular activation and inflammation (Fig. 1a) [58–60].

In contrast, IgG-IC ligations with inhibitory FcγRIIB cause the tyrosine phosphorylation of ITIM by Lyn kinase, which recruits the SHIP. The latter molecule gets phosphorylated and reacts with PI(3,4,5)P₃. Phosphorylated SHIP inhibits the PI(3,4,5)P₃-mediated induction of other inflammatory messengers, as discussed earlier [61] (Fig. 1b).

Thus, the proportion of activating versus inhibitory FcγRs (A/I ratio) determines the magnitude of IgG-IC-induced inflammatory responses. Conversely, FcγR activation enhances the synthesis of C5 through the binding of IgG antibodies and, consequently, promotes the signaling for generation of C5a, which increases the A/I ratio [29, 62]. Because of this phenomenon, both C5a and FcγRs have been valued for their role in inducing inflammation in many diseases [63, 64].

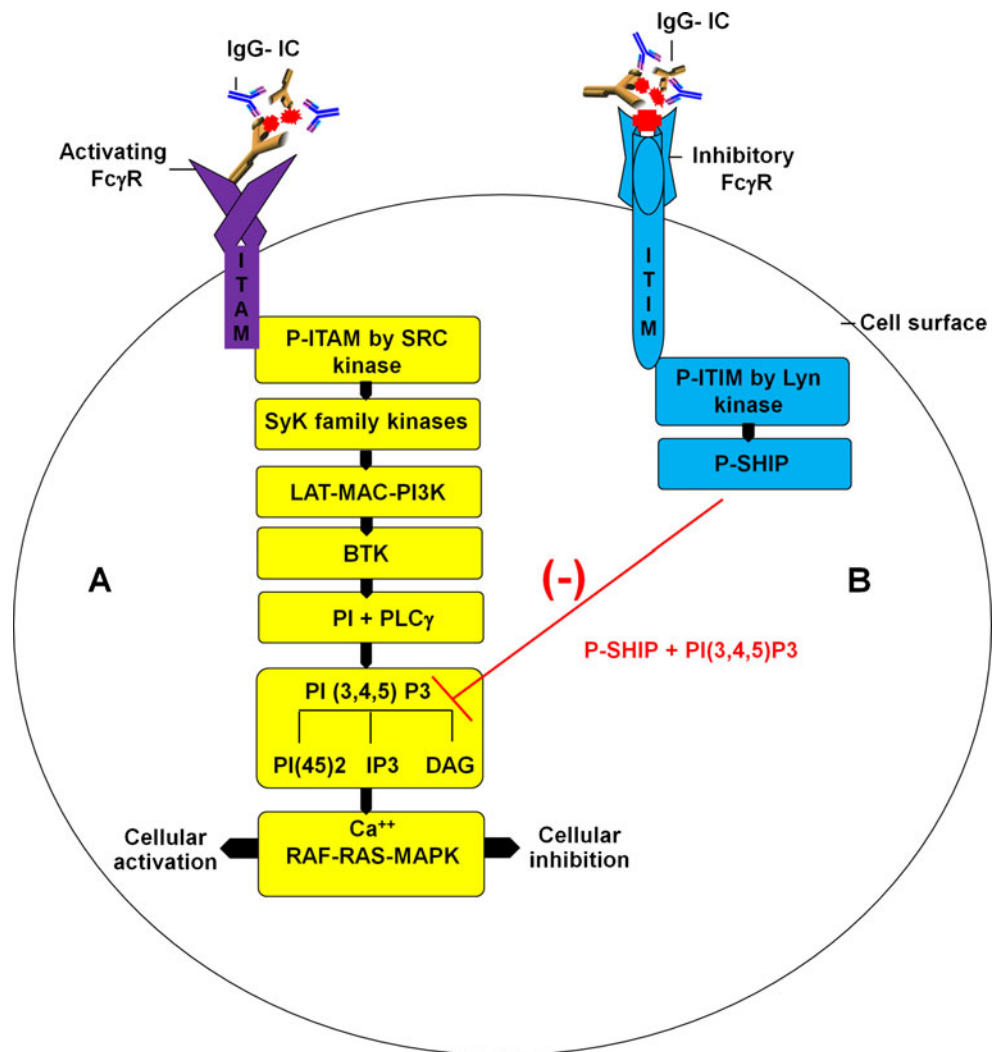
Deposition of IgG-ICs and their impact on C5a-mediated airway inflammation have been observed in mouse models of acute lung injury [3]. Several studies showed the increased expression of activating FcγRs [65–69] and allergen-specific IgG and their association with increased immunologic inflammation in murine

Table 4 Properties of different FcγRs in mice and humans [28, 61, 112–115]

Mice	Activating FcγRs FcγRI	FcγRIII	FcγRIV	Inhibitory FcγR (FcγRIIB)	IgG ability to fix complement
IgGs	IgG2a >> IgG2b > IgG3	IgG2a = IgG2b > IgG1	IgG2a = IgG2b > IgG1	IgG1 = IgG2b > IgG2a	IgG3 ≥ IgG2a = IgG2b >> IgG1
Cell types	MOs, MΦs, DCs, PMNs, ECs	MOs, MΦs, DC, PMNs, NKs cells, BAs, ECs, MCs	MOs, MΦs, DCs, MCs, PMNs	MOs, MΦs, DCs, B cells, BAs, ECs, MCs	
Human	Activating FcγRs FcγRI	FcγRIIA	FcγRIIC	Inhibitory FcγRs (FcγRIIB)	IgG ability to fix complement
IgGs	IgG3 = IgG1 > IgG4	IgG1 >> IgG3 > IgG2 > IgG4	IgG1 >> IgG3 > IgG4 > IgG2	IgG3 > IgG1 > IgG4 >> IgG2	Unknown function (FcγRIIB) IgG1 = IgG3 ≥ IgG2, 4 IgG3 > IgG1 > IgG2 ≥ IgG4
Cell types	MOs, MΦs, DCs, PMNs, MCs	MOs, MΦs, DC, PMNs, ECs, BAs, MCs	PMNs, NKs	MOs, MΦs, DCs, PMNs, BAs, B cells	PMNs

IgGs immunoglobulins-G; FcγR Fc-gamma receptor; MOs monocytes; MΦs macrophages; DCs dendritic cells; PMNs polymorphonuclear neutrophils; ECs eosinophils; BAs basophils; MCs mast cells; NKs natural killer cells

Fig. 1 IgG ligation with activating FcγR causes the tyrosine phosphorylation of ITAM by SRC kinases in its cytoplasmic region. This leads to the recruitment of SyK family kinases, followed by the activation of various downstream targets, e.g., LAT, MAC, and PI3K. These molecules generate the membrane-docking sites for BTK to recruit PI and PLC-γ. PLC-γ converts PI(3,4,5)P₃ to three by-products termed PI(4,5)₂, IP₃, and DAG. These downstream products activate the calcium ion mobilization and RAS-RAF-MAPK pathway and, in turn, cause cellular activation and inflammation (a). In contrast, IgG-IC ligations with inhibitory FcγRIIB cause the tyrosine phosphorylation of ITIM by Lyn kinase that recruits SHIP. When binding to PI(3,4,5)P₃, the latter molecule gets phosphorylated and inhibits the PI(3,4,5)P₃-mediated production of other inflammatory messengers (b)



models of allergy and asthma (Table 3). Mechanistically, allergen-specific IgG, which forms during sensitization, might react to the allergen upon its secondary exposure and form the IgG-ICs. These IgG-ICs might activate the complement system to generate the C5a. Indeed, studies have shown the interaction of IgG-ICs with activating FcγRs, which triggers C5a production [70, 71]. Furthermore, FcγR association with the mannose receptor [72–74], dectin-1 (receptor for β-glucans) [28, 30, 75, 76], and dectin-2 (receptor for different species of HDMs, e.g., *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, and mold, e.g., *Aspergillus fumigatus*) have been recognized as critical for induction of Th2 cytokine-mediated inflammation in allergic and asthmatic diseases [77]. Moreover, C5a affects FcγR-mediated function [78], and the latter receptor influences dectin-1 [30] and dectin-2 [75]. Thus, it is entirely possible that combined signaling among the receptors of IgG, C5a, and lectin is crucial for the pathogenesis of allergy and asthma.

IgG1-ICs Are Critical for Suppression of C5a-mediated Inflammatory Functions

In mice, allergen-specific IgG, particularly IgG2a, has been associated with immunologic inflammation in wild-type (WT) and FcγRIIB^{−/−} mice, which have all the activating FcγRs but no inhibitory FcγRIIB (Table 2). In contrast, allergen-specific IgG1 antibodies in WT (which have all the activating and inhibitory FcγRs) and FcγR^{−/−} mice (which have only inhibitory FcγRIIB) were protected from immunologic inflammation (Table 3), even in the presence of C5a, which is known for activation and infiltration of MΦs, PMNs, EOs, BAs, and MCs [4, 5].

C5aR, which is important for C5a-mediated signaling, is a member of the large family of GPCRs and is composed of Gαi and Gβγ subunits. The Gαi subunit is the basis for activation of class IB PI3Kγ, which causes the intracellular signaling for the Ras-Raf, MEK1/2, and ERK1/2 pathways [7]. In contrast, Gβγ subunits directly activate these intracellular signaling pathways

Table 5 Allergen-specific IgGs and their association with decreases in inflammation in human patients with allergy and asthma

Immunization	Allergen-specific antibodies (Abs-Rx)	Immunologic inflammation	Studies
Birch and grass pollen extracts	IgG1, IgG4	No allergic reaction	[116]
Phospholipase extracted from honey bee venom, grass pollen, and HDMs	IgG1 and IgG4	–	[117]
Birch pollen allergen (Bet v 1)	IgG4	Decreased proliferation of Bet v 1-specific T cells and secretion of IL-4, IL-5, IL-10, and IFN- γ	[118]
Grass pollen allergen (Phl p 7)	IgG4	Blocked IgE-mediated allergen presentation and BA activation.	[119]
Grass pollen allergen (Phl p 5)	IgG4	Increased IL-10 secretion	[120]
Grass pollen immunotherapy (Phl p 5)	IgG1, IgG2, IgG4	Clinical recovery	[121]
Birch pollen allergen (Bet v 1)	IgG1	Reduced total symptom score	[122]
Timothy pollen extract (rPhl p 1, 2, 5, 6, 7, 11, 12, and nPhl p 4)	IgG4	Decreased serum EO cationic protein	[123]

Abs-Rx antibody generated during the course of vaccination; *Bet v 1* *Betula verrucosa*; *IFN* interferon; *nPhl p* Phl p native; *Phl p* *Phleum pratense*; *rPhl p* recombinant Phl p; – not reported

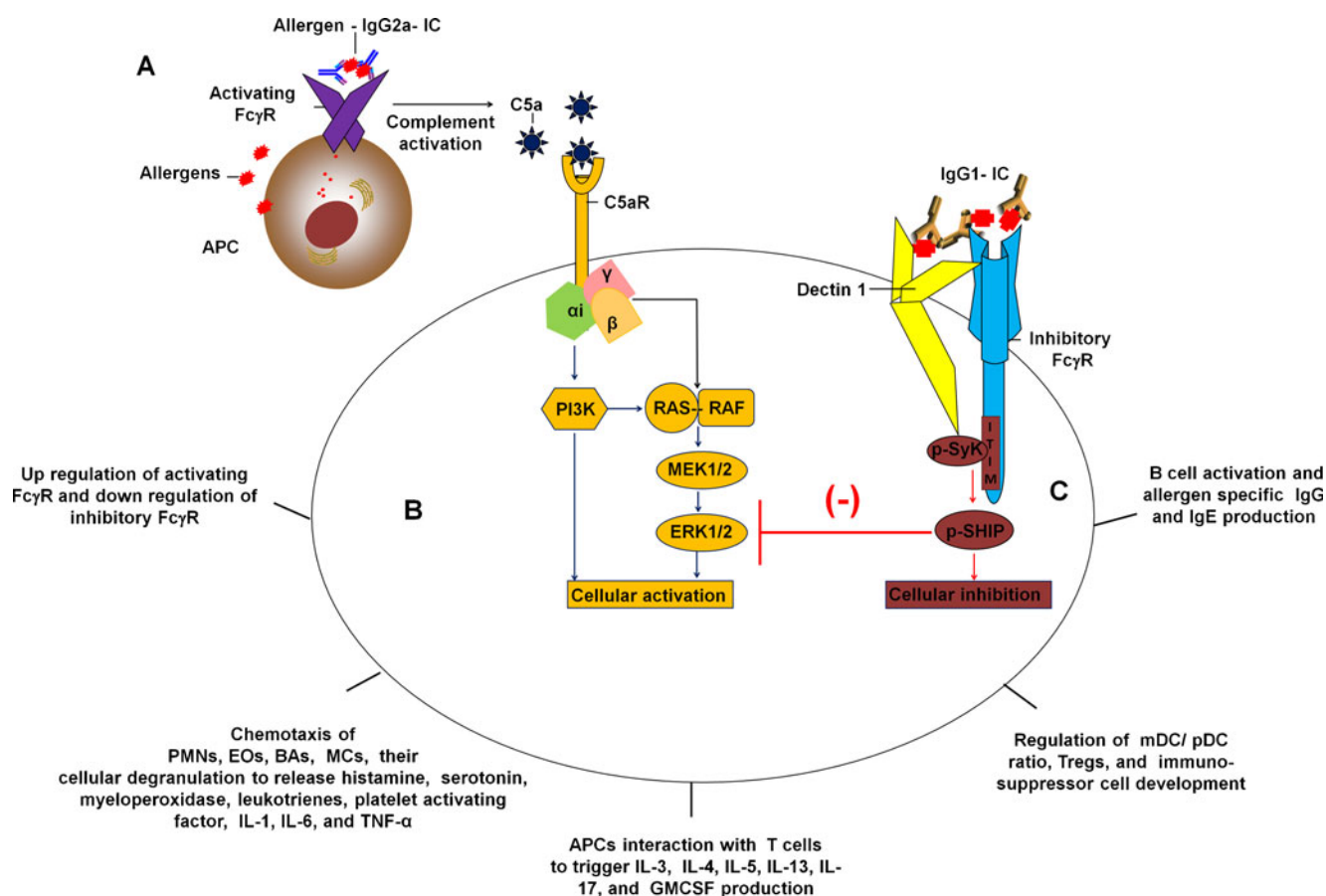


Fig. 2 Allergens or IgG2a-ICs cause complement activation and C5a release (a). C5a ligation with C5aR cascades their signaling event through G α i and G β γ to activate the PI3K γ , Ras-Raf, MEK1/2, and ERK1/2 pathway for cellular activation. Such cellular activation results in: (1) up-regulation of activating Fc γ R and down-regulation of inhibitory Fc γ RIIB; (2) chemotaxis of PMNs, EOs, BAs, and MCs, as well as their degranulation, to secrete histamine, serotonin, myeloperoxidase, leukotrienes, platelet-activating factors, IL-1, IL-6, and TNF- α ; (3)

interaction of DCs with T cells to secrete IL-4, IL-5, IL-13, GM-CSF, and IL-17; (4) regulation of mDC/pDC ratios, and Tregs; and (5) B-cell activation to secrete allergen-specific IgG and IgE antibodies (b). However, ligation of allergen-specific IgG1-IC with Fc γ RIIB and dectin-1 leads to the subsequent phosphorylation of Syk, ITIM, and SHIP. These downstream signaling molecules reduce C5aR-mediated inflammation in allergy and asthma (c)

[8]. The downstream pathways of many C5a-mediated effector functions observed in allergy and asthma include: (1) recruitment of immunologic cells; (2) increased secretion of inflammatory and proinflammatory mediators, e.g., histamine, leukotrienes, platelet-activating factor, IL-1, IL-6, and TNF- α [4, 5, 35, 36, 40, 41]; (3) up-regulation of stimulatory and costimulatory molecules on APCs and T cells that trigger Th2 and Th17 cytokine secretion [45, 46]; (4) modulation of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) ratios for activation of T cells [6]; (5) development of regulatory T cells (Tregs) [79, 80]; (6) regulation of costimulatory molecules, e.g., B7-H1 (PD-L1) and B7-DC (PD-L2) on pDCs, which modulate the function of mDCs and Tregs [81]; and (7) regulation of development of CD11b^{high} CD11c^{int} Gr1⁺ F4/80⁺ immunosuppressive cells [82].

Recent studies have shown the importance of this block of signaling (Ras-Raf, MEK1/2, and ERK 1/2), in which highly galactosylated IgG1-ICs engaged the dectin-1 molecule, which is a receptor of β -glucans [28, 30, 75, 76], together with Fc γ RIIB, resulting in Syk phosphorylation. This promotes the subsequent phosphorylation of the ITIM and SHIP, blocking C5aR-mediated ERK1/2 phosphorylation and PI(3,4,5)P₃ pathway-driven inflammation [28–30].

Several studies have shown that allergen immunotherapy induces highly allergen-specific IgG1 and IgG4 antibodies, as well as an association between these antibodies and decreased inflammatory immune responses in allergy and asthma (Table 5).

Because IgG1 and IgG4 are known to have high degrees of galactosylation patterns [15] and some common structural homology in normal, healthy humans [83, 84], we postulated that anti-allergen IgG antibodies generated during allergen sensitization are shifted toward glycoforms lacking sialic acid (proinflammatory form). Conversely, sialylated IgGs would have anti-inflammatory activity mediated through the induction of inhibitory Fc γ RIIB [11] which is associated with a reduction of inflammation in allergy and asthma [45, 85].

This suggests therapeutic efficacy by IgG1 allergen-specific immune responses associated with their change in glycosylation pattern. This chemical modification of IgG1 allows it to bind to dectin-1 and Fc γ RIIB, which potentially reduces the C5a-mediated inflammation in allergic and asthmatic diseases.

Interestingly, mepolizumab and benralizumab, both of which are undergoing phase 2 and 3 trials for treatment of allergic diseases such as asthma, eosinophilic esophagitis, Churg-Strauss syndrome, nasal polyposis, hypereosinophilic syndromes, rhinovirus-induced asthma, and chronic obstructive pulmonary disease (COPD) are structurally IgG1 [86]. These drugs basically are meant to target the IL-5- and IL-5R α -mediated effector functions critical for inducing eosinophilic inflammation in allergy and asthma. Because both drugs are IgG1, it is possible they might also have some inhibitory impact on C5a-mediated inflammatory functions in these diseases.

The exact mechanisms by which IgG1 and Fc γ RIIB reduce inflammation in allergy and asthma are not clear. Thus, we propose a model in which both allergen and allergen-specific IgG-ICs, predominantly IgG2a-ICs (in mice) formed during the course of allergen sensitization, cause the generation of C5a (Fig. 2a). C5a then interacts with C5aR to initiate downstream signaling through G α i and G $\beta\gamma$ subunits of C5aR and, in turn, trigger the PI3K γ -dependent and independent Ras-Raf, MEK1/2, and ERK1/2 pathway for cellular activation. These cellular activation events include: (1) up-regulation of activating Fc γ R_s and down-regulation of inhibitory Fc γ RIIB; (2) chemotaxis of inflammatory cells (i.e., PMNs, EOs, BAs, and MCs) and their degranulation to release histamine, serotonin, myeloperoxidase, leukotrienes, platelet-activating factors, IL-1, IL-6, and TNF- α ; (3) interaction of DCs with T cells to secrete Th2 and Th17 cytokines; (4) regulatory control upon the balance of mDCs/pDCs ratios and development of Tregs; and (5) B-cell activation to secrete allergen-specific IgG and IgE antibodies (Fig. 2b). In contrast, the allergen-specific IgG1-IC association with Fc γ RIIB and dectin-1 causes the subsequent phosphorylation of Syk, ITIM, and SHIP, which are critical for reducing C5aR-mediated inflammatory signaling in allergy and asthma (Fig. 2c). Thus, using highly galactosylated IgG1-IC therapy might be a potential tool for inhibiting several of the C5a-mediated inflammations in allergic and asthmatic diseases.

Conclusions

Allergens and allergen-linked IgG antibodies, generated as a result of allergen sensitization and repeated allergen contact, cause complement activation and C5a production. C5a then promotes the recruitment of several inflammatory immunologic cells, i.e., M Φ s, PMNs, EOs, BAs, and MCs, and increased secretion of histamine, leukotrienes, platelet-activating factor, and a variety of cytokines. These inflammatory mediators trigger many pathophysiologic features of allergy and asthma. Several allergen-specific immunotherapies, which have been used in murine models and humans with allergy and asthma, have shown the development of allergen-specific IgG1/IgG4 antibodies, their link with inhibitory Fc γ RIIB, and their impact on decreased immunologic inflammation. However, the mechanism by which allergen-specific immunotherapy exerts these effects remains an immunologic mystery. The information emerging in this review suggests that IgG1-ICs, in association with dectin-1 and Fc γ RIIB, potentially reduce the C5a-mediated inflammatory signaling in allergic and asthmatic diseases. Nevertheless, more experimental animal and clinical pilot studies are required to rationalize this in allergic and asthmatic diseases.

Compliance with Ethics Guidelines

Conflict of Interest Manoj Kumar Pandey declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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