IgG subclasses determine pathways of anaphylaxis in mice

Héloïse Beutier, PharmD,[a,b,c] Caitlin M. Gillis, BSci,[a,b,c] Bruno Iannascoli, BTS,[a,b] Ophélie Godon, MSc,[a,b] Patrick England, PhD,[d] Riccardo Sibilano, PhD,[e,f] Laurent L. Reber, PhD,[a,b] Stephen J. Galli, MD,[e,f] Mark S. Cragg, PhD,[g] Nico Van Rooijen, PhD,[h] David A. Mancardi, PhD,[a,b] Pierre Bruhns, PhD,[a,b]* and Friederike Jönsson, PhD[a,b]*

Paris, France, Stanford, Calif, Southampton, United Kingdom, and Amsterdam, The Netherlands

Background: Animal models have demonstrated that allergen-specific IgG confers sensitivity to systemic anaphylaxis that relies on IgG Fc receptors (FcγRs). Mouse IgG_{2a} and IgG_{2b} bind activating FcγRI, FcγRIII, and FcγRIV and inhibitory FcγRIIB; mouse IgG_1 binds only FcγRIII and FcγRIIB. Although these interactions are of strikingly different affinities, these 3 IgG subclasses have been shown to enable induction of systemic anaphylaxis.

Objective: We sought to determine which pathways control the induction of IgG_1-, IgG_{2a}-, and IgG_{2b}-dependent passive systemic anaphylaxis.

Methods: Mice were sensitized with IgG_1, IgG_{2a}, or IgG_{2b} anti-trinitrophenyl mAbs and challenged with trinitrophenyl-BSA intravenously to induce systemic anaphylaxis that was monitored by using rectal temperature. Anaphylaxis was evaluated in mice deficient for FcγRs injected with mediator antagonists or in which basophils, monocytes/macrophages, or neutrophils had been depleted. FcγR expression was evaluated on these cells before and after anaphylaxis.

Results: Activating FcγRIII is the receptor primarily responsible for all 3 models of anaphylaxis, and subsequent downregulation of this receptor was observed. These models differentially relied on histamine release and the contribution of mast cells, basophils, macrophages, and neutrophils. Strikingly, basophil contribution and histamine predominance in mice with IgG_1- and IgG_{2b}-induced anaphylaxis correlated with the ability of inhibitory FcγRIIB to negatively regulate these models of anaphylaxis.

Conclusion: We propose that the differential expression of inhibitory FcγRIIB on myeloid cells and its differential binding of IgG subclasses controls the contributions of mast cells, basophils, neutrophils, and macrophages to IgG subclass–dependent anaphylaxis. Collectively, our results unravel novel complexities in the involvement and regulation of cell populations in IgG-dependent reactions *in vivo*. (J Allergy Clin Immunol 2017;139:269-80.)

Key words: *Anaphylaxis, IgG, mouse model, basophil, neutrophil, monocyte, macrophage, IgG Fc receptor, platelet-activating factor, histamine*

Anaphylaxis is a hyperacute allergic reaction that occurs with increasing incidence in the population and can be of fatal consequence. Symptoms include skin rash, hypotension, hypothermia, abdominal pain, bronchospasm, and heart and lung failure, which can lead to asphyxia and sometimes death.[1] The main treatment remains epinephrine (adrenaline) injection to restore heart and lung function. Because anaphylaxis represents an emergency situation, few clinical studies have been possible to address the mechanisms leading to anaphylaxis in patients. Experimental models of anaphylaxis identified mechanisms involving allergen-specific antibodies that trigger activating antibody receptors on myeloid cells, leading to mediator release. These mediators can, by themselves, recapitulate the symptoms of anaphylaxis observed in human subjects.[2,3]

The "classical" mechanism of anaphylaxis states that allergen-specific IgE binds the activating IgE receptor FcεRI on mast cells, which, on allergen encounter, become activated and release histamine, among other mediators. Notably, histamine injection suffices to induce signs of anaphylaxis in animal models.[4] In many cases detectable allergen-specific IgE and increased histamine levels do not accompany anaphylaxis in human subjects (discussed in Khodoun et al[5]), leading to the notion that "atypical" or "alternate" mechanisms of induction could explain these cases. One of these atypical/alternate models proposes a similar cascade of events but instead based on allergen-specific IgG binding to allergen, forming IgG-allergen immune complexes that trigger activating IgG Fc receptors (FcγRs) expressed on myeloid cells (ie, macrophages,

From [a]the Department of Immunology, Unit of Antibodies in Therapy and Pathology, Institut Pasteur, Paris; [b]INSERM, U1222, Paris; [c]Université Pierre et Marie Curie, Paris; [d]Institut Pasteur, Plate-Forme de Biophysique Moléculaire, Centre d'Innovation et Recherche Technologique (CiTech), CNRS-UMR3528, Paris; [e]the Department of Pathology and [f]the Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine; [g]the Antibody and Vaccine Group, Cancer Sciences Unit, University of Southampton Faculty of Medicine, Southampton General Hospital; and [h]the Department of Molecular Cell Biology, VU Medical Center, Amsterdam.

*These authors contributed equally to this work.

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Corresponding author: Friederike Jönsson, PhD, and Pierre Bruhns, PhD, Unit of Antibodies in Therapy and Pathology, Department of Immunology, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris, France. E-mail: joensson@pasteur.fr. Or: bruhns@pasteur.fr.

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Abbreviations used
FcγR: IgG Fc receptor
FcRn: Neonatal IgG receptor
FITC: Fluorescein isothiocyanate
Gfi1: Growth factor independence 1
K_A: Affinity constant
K_D: Dissociation equilibrium constant
K_{off}: Dissociation rate
K_{on}: Association rate
mMCP-1: Mast cell protease 1
PAF: Platelet-activating factor
PSA: Passive systemic anaphylaxis
RU: Resonance units
TNP: Trinitrophenyl
TRIM21: Tripartite motif-containing protein 21
WT: C57Bl/6 wild-type

basophils, and/or neutrophils), which in turn release platelet-activating factor (PAF).[2,3] Importantly, PAF injection suffices to induce signs of anaphylaxis in animal models.[6] IgG-induced anaphylaxis can be elicited by intravenous injection of allergen-specific IgG followed by allergen administration and is termed IgG-induced passive systemic anaphylaxis (PSA).

IgG receptors in the mouse comprise 4 "classical" IgG receptors termed FcγRs but also the neonatal IgG receptor (FcRn) and the intracellular FcR tripartite motif-containing protein 21 (TRIM21).[7,8] Although FcRn and TRIM21 both participate in the intracellular routing of IgG and FcRn in protection from catabolism and distribution to tissues,[9] FcγRs control cell activation in the presence of immune complexes. FcγRs in mice are subdivided into (1) activating FcγRs (ie, FcγRI, FcγRIII, and FcγRIV), which lead to cell activation on immune complex binding, and (2) an inhibitory FcγR (ie, FcγRIIB), which inhibits cell activation when coengaged by an immune complex with an activating FcγR coexpressed on the same cell.[10] Thus inhibition of cell activation by FcγRIIB requires that the immune complex contains IgG bound by both the activating and inhibitory FcγR.

Four IgG subclasses exist in mice: IgG_1, IgG_{2a}, IgG_{2b}, and IgG_3. Among those, only IgG_{2a} and IgG_{2b} bind to all FcγRs, whereas IgG_1 binds only to FcγRIIB and FcγRIII. It remains under debate whether IgG_3 binds to FcγRs, particularly FcγRI.[11,12] The affinities of these FcγRs toward IgG subclasses are strikingly different (Table I),[11-14] leading to the notion of high-affinity receptors that retain monomeric IgG and low-affinity receptors that do not.[8] However, the avidity of IgG-immune complexes enables both types of receptors to retain IgG-immune complexes, leading to receptor clustering, intracellular signaling events, and, eventually, cell activation. FcγRI is a high-affinity receptor for IgG_{2a},[15] and FcγRIV is a high-affinity receptor for IgG_{2a} and IgG_{2b}.[16] All other FcγR-IgG interactions are of low affinity (reviewed in Bruhns[7]).

Three of the 4 IgG subclasses in the mouse, IgG_1, IgG_{2a}, and IgG_{2b}, have been reported to enable the induction of systemic anaphylaxis, inducing mild-to-severe hypothermia.[5,17,18] This is rather surprising for IgG_1, considering that inhibitory FcγRIIB binds IgG1 with a 10-fold higher affinity (affinity constant [K_A], 3.3×10^6 M^{-1}) than activating FcγRIII (K_A, 3.1×10^5 M^{-1}; Table I),[13] implying that inhibition should dominate over activation. C57Bl/6 wild-type (WT) mice experience a very mild anaphylactic reaction during IgG_1-induced PSA compared to FcγRIIB$^{-/-}$ mice,[19] indicating that inhibition

TABLE I. Affinities of mouse FcγR-IgG subclass interactions (K_A values in M^{-1})

	IgG_1	IgG_{2a}	IgG_{2b}	IgG_3
FcγRI	−	1×10^8	1×10^5	(+)
FcγRIIB	3.3×10^6	4.2×10^5	2.2×10^6	−
FcγRIII	3.1×10^5	6.8×10^5	6.4×10^5	−
FcγRIV	−	2.9×10^7	1.7×10^7	−

Data were compiled from Nimmerjahn and Ravetch[13] and Nimmerjahn et al.[14]
−, No detectable affinity; *(+)*, under debate.[11,12]

by FcγRIIB occurs in WT mice during IgG_1-induced PSA, reducing but not protecting against anaphylaxis. IgG_1-dependent PSA has been reported to rely on basophils[20] that coexpress FcγRIIB and FcγRIII.[21] In this apparently simple situation, only 1 activating receptor and 1 inhibitory receptor are engaged on a single cell type that, once activated, produces an anaphylactogenic mediator, such as PAF.[20]

However, IgG_{2a} and IgG_{2b} bind 3 activating FcγRs and inhibitory FcγRIIB with different affinities, ranging over 2 logs. In particular, the affinity of FcγRIIB for IgG_{2a} is significantly lower than that for IgG_{2b}, whereas the activating IgG receptors FcγRIII and FcγRIV bind IgG_{2a} and IgG_{2b} with similar affinities, respectively (Table I). Notably, FcγRIV is not expressed on basophils but on monocytes/macrophages and neutrophils,[14] which have both been reported to contribute to experimental anaphylaxis.[18,22-24] In addition, mice expressing only FcγRIV can develop IgG-dependent PSA.[16] Therefore, together with expression and binding data, one would hypothesize that FcγRIV contributes predominantly to IgG_{2a}- and IgG_{2b}-induced PSA.

In this work we present evidence contrary to this hypothesis and reveal which activating FcγR on which cell types releasing which mediators are responsible for IgG_{2a}-dependent PSA and IgG_{2b}-dependent PSA and the differential regulation of these models of anaphylaxis by FcγRIIB. Our results unravel a complex balance determined by FcγR expression patterns, inhibition potential by FcγRIIB, and respective affinities of activating and inhibitory FcγRs for IgG subclasses that, together, regulate the contribution of cells and anaphylactogenic mediators to a given model of IgG-induced anaphylaxis.

METHODS

Mice

Female C57Bl/6J mice (herein referred to as WT mice) were purchased from Charles River (Wilmington, Mass), female BALB/cJRj mice were from Janvier Labs (Le Genest-Saint-Isle, France), and FcγRIIB$^{-/-}$ (MGI:1857166), FcγRIII$^{-/-}$ (MGI: 3620982) and Rosa26-YFP mice were from Jackson Laboratories (Bar Harbor, Me). FcγRI$^{-/-}$ mice (MGI: 3664782) were provided by J. Leusen (University Medical Center, Utrecht, The Netherlands), FcγRIV$^{-/-}$ mice (MGI: 5428684) were provided by J. V. Ravetch (Rockefeller University, New York, NY), growth factor independence 1 (Gfi1)$^{-/-}$ mice were provided by T. Moroy (Montreal University, Montreal, Quebec, Canada), and MRP8-cre mice were provided by Clifford Lowell (University of California at San Francisco, San Francisco, Calif). MRP8-cre and Rosa26-YFP mice were intercrossed to generate MRP8-cre; Rosa26-YFP mice. Cpa3-Cre; Mcl-1$^{fl/fl}$ mice[25] (backcrossed for at least 9 generations on a C57Bl/6J background) were kept in the Stanford University animal facility. All mouse protocols were approved by the Animal Ethics committee CETEA (Institut Pasteur, Paris, France) registered under #C2EA-89 and/or the Institutional Animal Care and Use Committee of Stanford University.

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