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1 **The role of IgG subclasses and platelets in experimental anaphylaxis**

2
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11 12 13 14 **Conflict of Interest Statement**

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16 The authors declare no conflict of interest.

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47

48 **Introduction**

49 In 1902, Charles Richet coined the term “anaphylaxis” to describe a “state of heightened
50 sensitivity of a subject to a substance induced by a first injection, that instead of protecting the
51 organism, renders it more fragile and more susceptible”. Since this first description,
52 experimental work led to identification of antibodies, receptors, cells and mediators in this
53 severe allergic reaction, leading to the paradigm that anaphylaxis is an IgE-dependent affliction
54 that is triggered when allergens aggregate cognate IgE antibodies bound to the high-affinity IgE
55 receptor (FcεRI) on the surface of mast cells and basophils. Their activation leads to the release
56 of diverse bioactive mediators, including histamine, which are responsible for the associated
57 clinical signs (1). Seminal works from the Galli, Kinet and Finkelman labs revealed, however,
58 that anaphylaxis can also occur in mice deficient for IgE, FcεRI or mast cells, and suggested
59 that it could be driven by IgG antibodies engaging Fcγ-chain containing receptors (reviewed
60 in (1)). Nowadays the international consensus on anaphylaxis defines anaphylaxis as “a serious,
61 generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or
62 fatal”, which is deliberately generic and excludes any precision on the pathophysiological
63 mechanism involved.

64 In this manuscript we will discuss recent findings on IgG-dependent anaphylaxis with a
65 focus on the role of IgG subclasses and platelets in these reactions.

66

67 **IgG-dependent anaphylaxis in wild-type mice**

68 IgG-dependent passive systemic anaphylaxis (IgG-PSA) can be elicited in mice by the
69 transfer of specific IgG antibodies (of either IgG1, IgG2a/c or IgG2b subclass, but not IgG3)
70 followed by injection of their cognate antigen, or by transfer of pre-complexed IgG (*i.e.* immune
71 complexes (IgG-ICs) or heat-aggregated IgG). IgG-PSA depends on IgG receptor (FcγR)-
72 transduced activation of myeloid cells, leading to mediator release, which notably include
73 platelet-activating factor (PAF) (1, 2). Mice express three activating (FcγRI, FcγRIII and
74 FcγRIV) and one inhibitory FcγRs (FcγRIIB) each having a specific expression profile and
75 distinct affinities for the different IgG subclasses. IgG-PSA in mice is associated with
76 vasodilation, augmented vascular permeability and a reduction in core temperature, motility
77 and awareness (Figure 1). Animals usually return to normal activity and behavior within 1-2
78 hours, but in rare cases cardiopulmonary failure results in death. (IgG)-anaphylaxis can also be
79 triggered by antigen exposure of previously immunized mice that lack key players of the IgE-

80 dependent pathway. IgG-independent immune players may however contribute to the reaction,
81 rendering the interpretation of results more complex. To efficiently engage activating IgG
82 receptors, IgG generally need to be present as multivalent complexes. There is a large consensus
83 that IgG-PSA relies mainly on the engagement of FcγRIII and, to a lesser extent, on FcγRIV
84 and possibly on FcγRI (2, 3).

85 The relative importance of FcγR-bearing effector cells to IgG-PSA remains more debated
86 and is likely to depend on the experimental conditions (1-3). Indeed, all cells of hematopoietic
87 origin express at least one activating FcγR with the exception of T cells, B cells and platelets,
88 and could hence contribute to the reaction. Their involvement in anaphylaxis is often assessed
89 either using depleting antibodies, which is problematic in the context of an antibody-dependent
90 reaction, or using inhibitors, which may not be specific. In a comparative study using mouse
91 IgG1, IgG2a and IgG2b with the same specificity to induce IgG subclass-specific anaphylaxis,
92 we found that IgG1 and IgG2b-PSA shared a common mechanism that involved all tested
93 myeloid cells and in which histamine H1 receptor blockade showed a stronger beneficial effect
94 on PSA-associated temperature drop than PAF receptor blockade (2). IgG1- and IgG2b-PSA
95 were regulated by the inhibitory IgG receptor FcγRIIB present on all myeloid cells and B cells.
96 In contrast in IgG2a-PSA, FcγRIIB-driven inhibition was negligible. IgG2a-PSA was
97 significantly reduced through depletion of neutrophils or monocytes/macrophages and
98 attenuated by both PAF-receptor and histamine H1 receptor antagonists (2). This particularity
99 of IgG2a-PSA may be due to the overall higher affinity of IgG2a to FcγRs (2) that also may
100 explain the relative resistance of IgG2a-PSA to changes in IgG/FcγR affinity induced by
101 modification of IgG-glycosylation (i.e. terminal sialylation) compared to IgG1/IgG2b-PSA (4).
102

103 **IgG-anaphylaxis in FcγR-humanized mice**

104 To approach human pathophysiology, anaphylaxis has been studied in mice carrying
105 human FcγRs, either as a single transgene, as in the case of hFcγRIIA (5-7), or in more complex
106 models expressing several FcγRs (6). Indeed, extrapolating results from IgG/FcγR-dependent
107 reactions from mouse to human pathophysiology is challenging, because both species express
108 very different sets of FcγRs (four in mice, six in humans) that each shows distinct interaction
109 profile with the different IgG subclasses (IgG1-4 in human). Among human FcγRs, only
110 FcγRIIB is inhibitory and expressed at much lower levels than in mice, suggesting that
111 regulation of IgG-driven responses in humans though co-engagement of this inhibitory receptor
112 is less effective than in mice. Furthermore, as an example, whereas IgG3 binds to all human

113 Fc γ Rs, its murine counterpart exclusively engages mouse Fc γ RI. These differences extend
114 through all IgG subclasses, their affinities for Fc γ Rs and their capacity to trigger Fc-dependent
115 effector functions. Studies in Fc γ R-humanized mice revealed that engagement of human Fc γ Rs
116 by IgG-ICs is sufficient to trigger anaphylaxis (5). Among hFc γ Rs, hFc γ RIIA appears to be the
117 major contributor in IgG-PSA (6) and despite its expression on all myeloid cells, hFc γ RIIA-
118 expressing neutrophils and monocytes/macrophages, through their release of PAF, play a
119 predominant role over mast cells, basophils and eosinophils (5). Unexpectedly, hFc γ RIIA-
120 transgenic mice also revealed the critical contribution of a blood component that was until then
121 overlooked in the context of anaphylaxis.

122

123 **Role of platelets in IgG-anaphylaxis**

124 Mouse platelets are devoid of any Fc γ R. Human platelets on the contrary express
125 Fc γ RIIA/CD32A and incubation with IgG-ICs can induce their activation, aggregation and
126 release of granular content. Using hFc γ RIIA-transgenic mice that confer IgG receptor
127 expression to platelets, we and others demonstrated that IgG-induced platelet activation is
128 critical for experimental anaphylaxis, and results in a rapid, severe and prolonged (24 h)
129 thrombocytopenia (6, 7). Activated platelets released serotonin, which determined the severity
130 of anaphylaxis (6, 7). Platelets also contributed to IgG-PSA in a more complex mouse model
131 of cognate hFc γ R expression (6). Recently, platelet-released PAF was similarly proposed to
132 trigger a transient disruption of endothelial integrity and mast cell activation resulting in shock
133 (8). Due to their abundance in blood, it is therefore conceivable that platelets are among the
134 first players to become activated by circulating IgG-ICs triggering a cascade of events that
135 drives the activation and mediator release from various cell types contributing to anaphylaxis
136 (Figure 2).

137

138 **Relevance for human anaphylaxis and conclusion**

139 The fact that transgenic expression of a complete set of human Fc γ Rs reproducing
140 mostly the original expression profiles on all hematopoietic cells stimulated with human
141 aggregated IgG is sufficient to induce anaphylaxis in mice (6), is a strong indicator for the
142 relevance of IgG anaphylaxis in humans. Indeed, several lines of evidence support the existence
143 of IgG/Fc γ R-, neutrophil- and PAF-dependent human anaphylaxis. Cases of anaphylaxis were
144 reported after administration of different therapeutic IgG antibodies (1), and serum PAF
145 concentrations correlate with anaphylaxis severity in humans (9). In a clinical study of

146 neuromuscular-blocking agent-induced anaphylaxis, concentrations of anti-drug IgG, markers
147 of Fc γ R engagement and neutrophil activation (upregulation of CD11b and CD18, elevated
148 levels of elastase and DNA-MPO complexes in plasma), as well as reduced activity of PAF-
149 acetyl hydrolase correlated with anaphylaxis severity (10). Notably, neutrophil activation could
150 be observed in patients lacking evidence of classical IgE-anaphylaxis (10). Limited data from
151 these patients further evidenced that platelet activation (upregulation of CD62P) was associated
152 with anaphylaxis severity and that anaphylaxis occurrence was accompanied by a reduction in
153 circulating platelet numbers (6). These findings open new perspectives for the understanding
154 and management of IgE-independent anaphylaxis in humans. In addition to certain drugs that
155 can directly activate mast cells (notably through the recently described MRGPRX2), IgG-
156 dependent reactions may account for or contribute to anaphylaxis, in particular when large
157 amounts of IgG-ICs can form in the circulation. Further clinical studies will allow to determine
158 whether it could be beneficial for patients at risk of developing IgG-driven anaphylaxis (i.e.
159 programmed intravenous administration of certain antibodies or drugs) to transiently receive
160 treatments to block Fc γ Rs (especially Fc γ RIIA) or limit the biological effects of serotonin
161 and/or PAF.

162

163

164 **Author Contributions**

165 All authors have made a substantial intellectual contribution to the manuscript, and approved it
166 for publication.

167

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174

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203

204 **Figure Legends:**

205

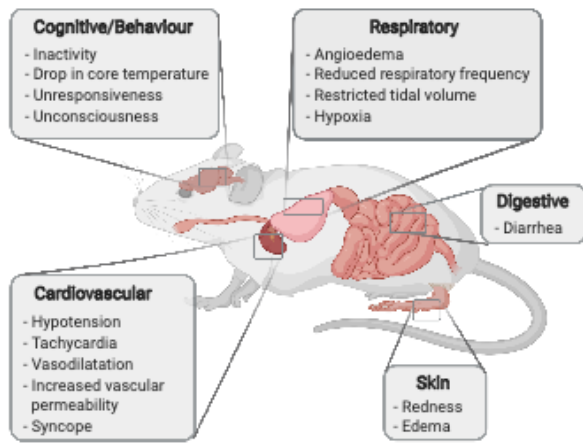
206 Figure 1. Pathophysiologic changes in experimental anaphylaxis in mice. Anaphylaxis is a
207 systemic hypersensitivity reaction that affects multiple organs; the most common clinical signs
208 of anaphylaxis in mice are indicated. Created with BioRender.com

209

210

211 Figure 2. Model of IgG-dependent experimental anaphylaxis in hFcγRIIA-expressing mice in
212 the absence of mouse endogenous FcγRs. Human FcγRIIA expression is conserved in
213 hFcγRIIA-transgenic mice, including its expression on all myeloid cells and platelets. Injected
214 heat-aggregated (HA)-IgG, mimicking IgG-ICs forming inside the circulation, can engage
215 hFcγRIIA on any of these cells, but will have a stochastically higher likelihood to encounter
216 platelets>neutrophils>monocytes>>basophils, leading to their activation. As a consequence
217 platelets will be activated, form aggregates, adhere to circulating leukocytes and degranulate.
218 Platelet-released serotonin can directly trigger anaphylaxis-associated vascular leakage,
219 vasodilation and bronchoconstriction. Platelet-released PAF, or PAF-release by other IgG-IC-
220 activated myeloid cells can fuel the reaction through activation of perivascular mast cells
221 leading to histamine release. PAF and histamine may contribute to clinical signs of hFcγRIIA -
222 PSA in mice. Created with BioRender.com

223 **Figure 1**



224
225 **Figure 2**

