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EDITORIAL

# Anaphylaxis: Spotlight on Inflammation

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Anaphylaxis is a medical condition for which several definitions have been proposed (Table 1 is available in the repository information at https://osf.io/sc2ey/?view_only=f66e841be31b42418eecf639caa0b24d). Charles Richet and Paul Portier coined the term 'anaphylaxis' in 1902. If discovered earlier, it might have invigorated the ongoing scientific debate in the late 19th century between Rudolf Virchow and Iliá Méchnikov on the detrimental versus beneficial nature of inflammation [1]. While inflammation typically serves as a response to tissue damage or infection, to restore homeostasis, anaphylaxis is a classic example of an immunopathological reaction in which an exaggerated and inappropriate response can lead, although rarely, to potentially fatal outcomes. Precisely, the role of inflammation has been underlined as central in several atopic diseases, but, surprisingly, not in anaphylaxis.

The most common triggers of anaphylaxis are foods, insect stings and medications, but the aetiology may be unknown in some cases (idiopathic). This reaction is a multisystem condition that may involve different findings from the skin/mucosal, respiratory, cardiovascular and/or gastrointestinal systems. However, patients may rarely present isolated respiratory or cardiovascular involvement, and skin/mucosal participation may be absent. In addition, anxiety about the possibility of a new episode of anaphylaxis significantly impairs the quality of life of patients and their relatives, restricting daily activities and increasing the state of constant alertness [2]. The foundations of acute anaphylaxis management are removing the trigger, proper patient positioning, immediate administration of adrenaline and repeat adrenaline injections if severe clinical manifestations do not resolve. Moreover, this treatment can be supplemented with

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the use of second-line medications (e.g., β2-adrenergic agonists), as well as with the administration of supportive treatments (e.g., oxygen) [2, 3]. Most patients treated with adrenaline experience prompt resolution of symptoms and signs. However, a minority of patients may require three or more doses of adrenaline (refractory anaphylaxis) or have recurrence after an asymptomatic period (biphasic anaphylaxis) [4, 5].

Different signalling pathways can mediate anaphylaxis (Figure 1). Among them, the classical one is mediated by immunoglobulin (Ig)E. In sensitised individuals, secreted IgE binds to its high-affinity receptor (FcεRI) on effector cells (mainly mast cells and basophils), which store preformed pro-inflammatory granules. Then, allergen binding by cell-bound IgE triggers effector cell activation, leading to the immediate release of potent pro-inflammatory mediators, such as histamine, tryptase, platelet-activating factor (PAF), prostaglandins, leukotrienes and TNF-α, which are responsible for the rapid clinical manifestations of anaphylaxis [6]. However, in some cases, anaphylaxis occurs without detectable levels of specific IgE, suggesting the presence of alternative molecular pathways contributing to the inflammatory response of the reaction, such as IgG-mediated anaphylaxis. Although this pathway is well characterised in murine models [7], clinical evidence for its contribution to human anaphylaxis is limited and plausibly restricted to clinical settings involving systemic administration of drugs (e.g., protamine, dextran) because it seems to require a higher concentration of antigen compared to the classical pathway [8, 9]. Nevertheless, antigen-IgG binding to FcγR on myeloid cells (such as mast cells, basophils, neutrophils, monocytes and macrophages) can lead to their activation and the release of pro-inflammatory mediators. In addition, Ig-independent mechanisms can trigger anaphylaxis. For example, certain medications, such as neuromuscular blocking agents or contrast media, can directly induce the release of inflammatory mediators from mast cells by binding to the Mas-related G protein-coupled receptor member X2 (MRGPRX2) on their surface. Moreover, extrinsic (exercise, alcohol, drugs, etc.) and intrinsic (genetic, hormones, comorbidities such as uncontrolled asthma, etc.) factors can directly and indirectly modulate the release of inflammatory mediators and the severity of an anaphylactic reaction. Furthermore, the complement system, when activated, produces anaphylatoxins (C3a, C4a and C5a), which bind to their receptors on effector cells triggering their degranulation and promoting inflammation. In turn, these receptors are also present in endothelial cells, the principal component of the vascular endothelium and a critical player of anaphylactic reactions [8].

Therefore, the complex inflammatory mechanisms of anaphylaxis are multifaceted and involve Ig-dependent and

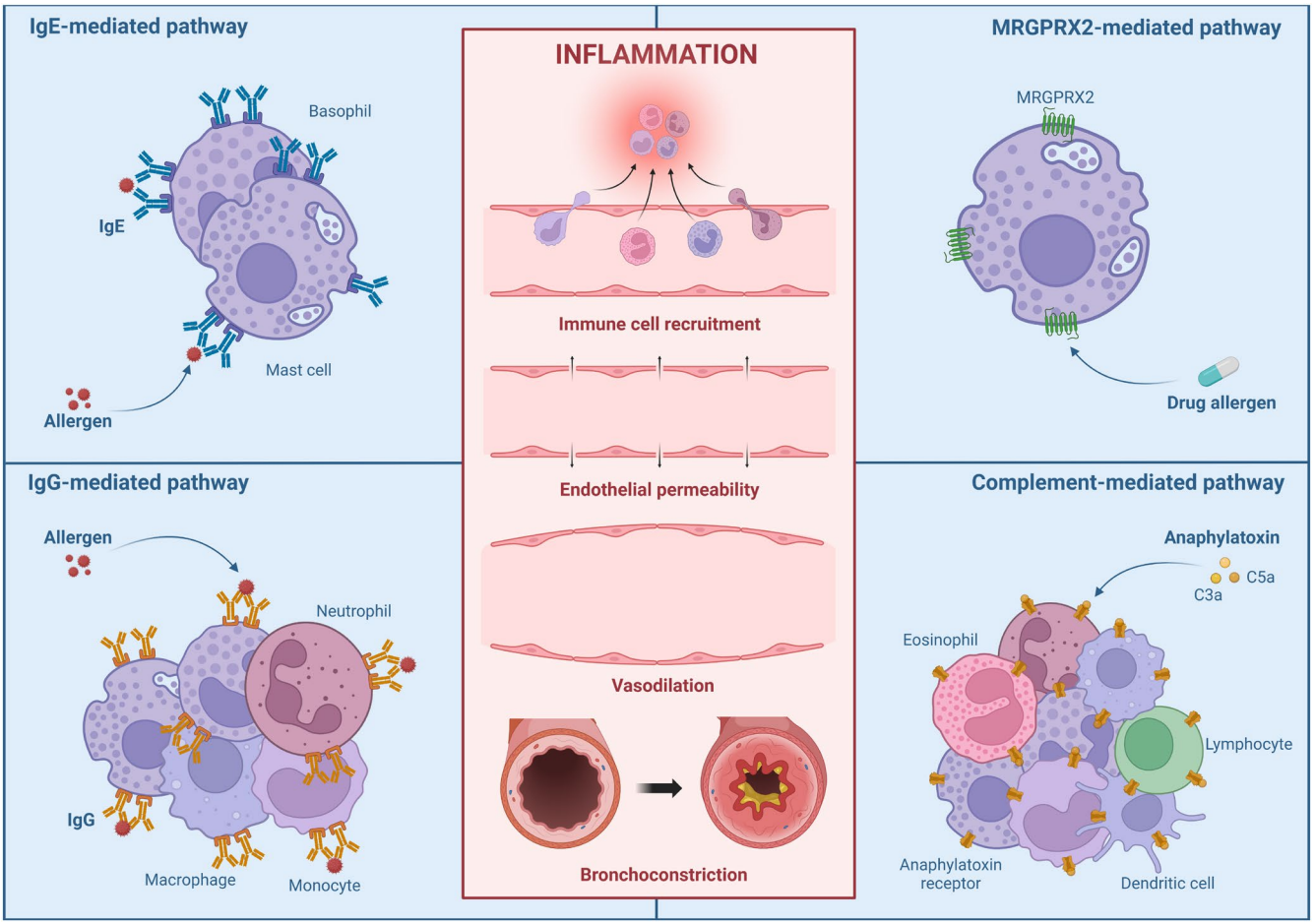


**FIGURE 1** | Inflammation is the main process underlying anaphylaxis, regardless of the molecular pathway involved in the reaction. The activation of the different molecular pathways involved in the reaction results in the release of pro-inflammatory mediators, which leads to the systemic inflammation underlying symptoms and signs of anaphylaxis. Ig, Immunoglobulin; MRGPRX2, Mas-related G protein-coupled receptor member X2. Created with BioRender.com.

Ig-independent pathways, as well as diverse molecular and cellular pathways. However, all of them converge in the release of pro-inflammatory mediators that cause clinical manifestations that are practically indistinguishable (Figure 1). Increasing our knowledge of these biological systems is crucial for the translation to clinical practice, which could improve the diagnosis, treatment and prevention of anaphylaxis. Indeed, there are currently no reliable biomarkers to confirm the diagnosis when it is uncertain, to inform management decision-making and to stratify patient risk. The lack of biomarkers is partly due to the challenge of prospectively enrolling patients, especially children, and obtaining repeated biological samples to capture the dynamic changes that occur during anaphylaxis.

Based on these gaps, there is a pressing need to elucidate the complex interplay between anaphylaxis endotypes and phenotypes, and therapeutic responses to optimise its care and develop novel treatments. For this aim, the central role of inflammation in anaphylaxis should be underlined. Innovative treatments explicitly targeting the inflammatory cascade may pave the way for advances in anaphylaxis management. Indeed, the actual standard of care is based on medications, such as adrenaline, which explicitly target the patient's symptoms and signs, and which have little impact on the underlying immune mechanisms. Thus, we encourage future research, based on the collaboration between scientists and clinicians that could deepen our understanding of these concepts and broaden the options available for patients, especially in severe cases.

### Author Contributions

All authors contributed to the writing and critical revision of the manuscript. M.G. conceived the original idea. R.J.-S. and E.N.-B. led the project, and coordinated the stucture and the writing of the manuscript.

### Conflicts of Interest

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### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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