REVIEW

Perspectives in the Molecular Mechanisms Underlying Anaphylaxis

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Abstract

The complexity of anaphylaxis in terms of clinical features and etiology-pathogenesis makes it difficult to establish precise endotypes that correspond to specific phenotypes. Therefore, interest in unravelling the cellular and molecular mechanisms underlying anaphylactic reactions has grown.

A large group of anaphylactic reactions are characterized by the classical immunological mechanism of type I hypersensitivity, which leads to IgE-mediated activation of mast cells and basophils. However, in recent decades, other relevant signaling pathways have emerged. These include IgG-associated neutrophil activation, complement activation, cyclooxygenase metabolism, and direct mast cell activation. In drug-induced anaphylaxis, the Mas-related G protein–coupled receptor (MRGPRX2) plays an interesting role by directly triggering mast cell degranulation. In addition, contact, coagulation, and metabolic systems are activated, while homeostasis is altered, as evidenced by the modulation of proteins such as albumin, phospholipids, and apo- and lipoproteins. In all cases, the release of mediators and/or dysregulation of the systems has an impact on the endothelium, which is actively involved in the pathophysiology of the reactions. Furthermore, recent evidence points to extracellular vesicle- and microRNA-mediated communication between cellular compartments in anaphylaxis, and genetic factors, such as hereditary α-tryptasemia, are associated with risk of severe reaction. In summary, the recognition of cellular and molecular signaling mechanisms will enable better patient phenotyping and management in clinical practice.

Key words: Anaphylaxis. Immunoglobulins. Mechanisms. Epigenetic. Endothelium. Extracellular vesicles. miRNAs. Metabolites. α-Tryptasemia.

Resumen

La complejidad de la anafilaxia promueve el interés por desvelar los mecanismos celulares y moleculares subyacentes. Sin embargo, la heterogeneidad de las características clínicas y la etiopatología de la anafilaxia dificulta establecer endotipos precisos que se correspondan con fenotipos concretos.

Un amplio grupo de reacciones anafilácticas están mediadas por mecanismos de hipersensibilidad tipo I, que conlleva la activación de mastocitos y basófilos mediada por inmunoglobulina E. Sin embargo, en las últimas décadas se han descrito otras vías de señalización relevantes que implican la activación de neutrófilos asociado a inmunoglobulina G, la activación del complemento, el metabolismo de la ciclooxigenasa y la activación directa de los mastocitos. En este último caso adquiere especial relevancia la activación del receptor *Mas-related G protein–coupled receptor X2* (MRGPRX2). Además, en anafilaxia se activan los sistemas del contacto y coagulación, y se alteran sistemas de regulación metabólica y homeostática de proteínas como la albúmina, los fosfolípidos y las apo- y lipo-proteínas. La liberación de mediadores y/o desregulación de los sistemas produce un impacto en el componente endotelial, que participa activamente en la fisiopatología de las reacciones. Además, estudios de la última década sugieren que existe una potencial comunicación celular mediada por vesículas extracelulares y microARNs, y que existen factores genéticos, como la alfa-triptasemia hereditaria, que se asocian con riesgo de sufrir una reacción grave. En resumen, el reconocimiento de los mecanismos de señalización celular y molecular permitirá un mejor fenotipado del paciente y su manejo en la práctica clínica.

Palabras clave: Anafilaxia. Inmunoglobulinas. Mecanismos. Epigenética. Endotelio. Vesículas extracelulares. miRNAs. Metabolitos. Alfa-triptasemia.

Introduction

Anaphylaxis is a severe allergic hypersensitivity reaction that develops rapidly and can be potentially life-threatening if not treated immediately [1]. There has been a significant increase in anaphylactic reactions in hospital emergency departments [2], although fatalities are rare [3]. Clinically, anaphylaxis is a complex syndrome that can involve multiple organs, including the skin, as well as the respiratory, digestive, nervous, and cardiovascular systems [4,5]. While a wide variety of substances can trigger an anaphylactic reaction, the most common etiological agents in adults are drugs, foods, and Hymenoptera stings, while in children, foods are the main culprits [6-8]. At present, the precise etiological association between triggers and molecular mechanisms is unknown, although some evidence supports the direct connection between specific culprits and associated mechanisms (Table).

Classically, it has been reported that the allergen triggers the release of chemical mediators by effector cells (mainly mast cells [MCs] and basophils), leading to onset of symptoms [28,29]. The nature of the allergen seems to determine the molecular mechanism by which the mediators are released, ie, through immunological pathways (immunoglobulin E [IgE]-dependent or -independent) or nonimmunological pathways [30]. However, in recent years, other intrinsic and extrinsic factors have been shown to modulate anaphylaxis [31], and the emergence of new technologies (eg, omics), the discovery of extracellular vesicles, and the increased understanding of the vascular system's role in these reactions have highlighted that anaphylaxis involves more generalized and complex mechanisms [32,33].

Despite these advances, the clinical management of anaphylaxis remains significantly challenging. Currently, no biomarkers can reliably provide a sensitive and specific molecular diagnosis or predict the severity and recurrence risk of reactions. The absence of predictive biomarkers of the severity and etiology of a reaction complicates both diagnosis and the development of effective intervention strategies [34]. Anaphylaxis is an ever-evolving field, and desensitization treatments have shown some promise: they

Table. Main Associations Between Triggers and Molecular Mechanisms.

Type	Cells	Processes	Main Triggers	Reference
IgE-dependent	APCs B cells Helper T cells MCs Basophils ECs	– IgE-FcεRI binding – Effector cell activation – Production of inflammatory and vasoactive mediators. – Imbalance of resident tissue cells	– Food allergy – Drug allergy (pyrazolones, ß-lactams, chemotherapeutics) – Hymenoptera venom	[9] [10] [11] [12]
IgE-independent	B cells, Neutrophils Monocytes Macrophages MCs Eosinophils Platelets ECs	– IgG- FcγR binding. – Effector cell activation – Production of inflammatory lipids and oxidative mediators – Imbalance of resident tissue cells	– Drug allergy (NMBAs, chemotherapeutics)	[13] [14] [15] [16]
		– MC activation through MRGPRX2. – Production of mediators – Imbalance of resident tissue cells	– Drug allergy (NMBAs, fluoroquinolones, opioids, icatibant, vancomycin, octreotide, leuprolide, radio-contrast media)	[17] [18] [19] [20] [21] [22] [23]
		– Cox inhibition – Production of CysLTs – Imbalance of resident tissue cells	– NSAIDs	[18] [23]
Plasma components and systems	Soluble blood molecules MCs Basophils Macrophages ECs	– Complement activation – Production of inflammatory and vasoactive mediators – Consumption of contact coagulation system – Activation of fibrinolysis – Imbalance of resident tissue cells	– Food allergy – Drug allergy (ß-lactams) – Diverse substances (iodinated contrasts, liposomal drugs, polyethylene glycol, cellulose membranes, nanoparticles, solvents)	[11] [24] [25] [26] [27]

Abbreviations: APC, antigen-presenting cell; CysLT, cysteinyl leukotriene; EC, endothelial cell; FcγR, immunoglobulin G receptor; FcεRI, immunoglobulin E high-affinity receptor; IgE, immunoglobulin E; IgG, immunoglobulin G; MC, mast cell; MRGPRX2, mas-related G-protein coupled receptor member X2; NMBA, neuromuscular blocking agent; NSAID, nonsteroidal anti-inflammatory drug.

are effective in specific cases, such as IgE-mediated reactions, and may also be applicable in other instances, such as rapid drug desensitization. Furthermore, the unpredictability of anaphylaxis and the variation in individual responses make it difficult to establish consistent approaches for prevention and treatment. Although some indicators increase the likelihood of a severe allergic response, they are supported by limited scientific evidence [35]. Reactions are unpredictable, have an unforeseeable outcome, and present significant technical and ethical challenges for human studies [36].

In this article, we aim to summarize the variety of mechanisms involved in anaphylactic reactions and outline the intricate pathways altered in this syndrome. Moreover, we highlight that the allergen does not appear to be the sole trigger of the reaction, whose severity may be determined by either immunological predisposition or patient phenotype, making some individuals more susceptible to anaphylaxis than others. We hope to provide a useful tool that enables us to better understand the mechanisms involved in specific anaphylactic reactions and to identify potential phenotypic risk factors for severe reactions.

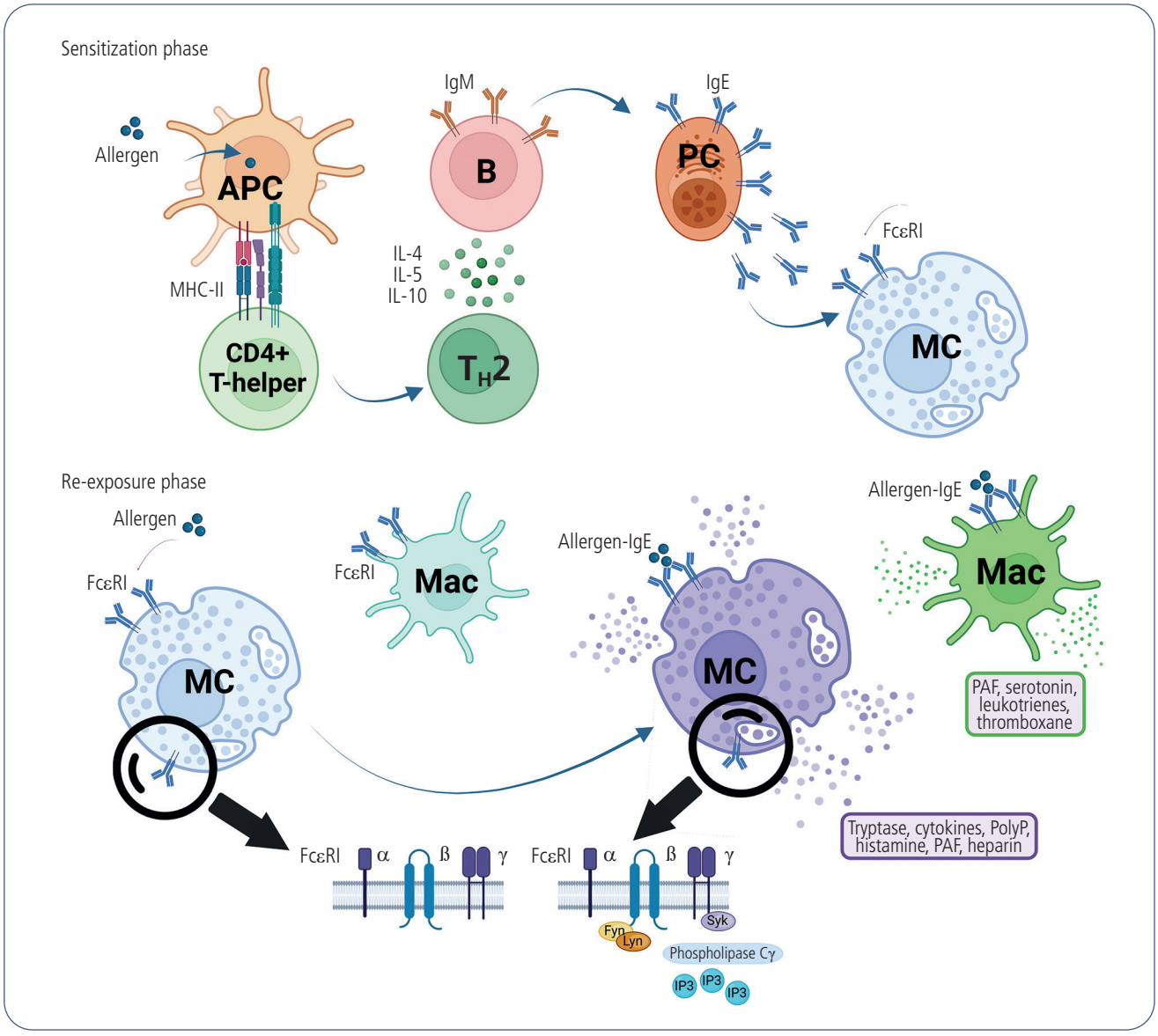

Figure 1. IgE-dependent mechanism. After internalizing the antigen, APCs travel to lymph nodes and present antigen fragments on their surface bound to the MHC class II molecules. Fragments are then recognized by naïve T_H cells, which differentiate into T_H2 cells in the presence of specific interleukins. This, in turn, prompts B cells to undergo class switching from IgM to IgE, specific to the antigen. These specific antibodies bind to FcεRI, which are present on MCs and basophils. In the elicitation phase, a multivalent allergen-IgE-FcεRI complex triggers cell activation through phosphorylation of the β chain by SRC kinase LYN and FYN, and the binding of Syk, to the cytoplasmic immunoreceptor tyrosine-based activation motifs of the γ subunit. As FcεRI lacks intrinsic kinase ability, this step is essential for signal transduction through activation of phospholipase Cγ and, therefore, generation of the secondary messenger IP3 that promotes intracellular calcium release, and, finally, degranulation of the cell. APC indicates antigen-presenting cells; B, B lymphocytes; FcεRI, high-affinity receptor for IgE; Fyn, SRC kinase FYN; IL, interleukin, inositol triphosphate; Lyn, SRC kinase LYN, Mac, macrophage, MC, mast cell; MHC-II, histocompatibility complex class II; PC, plasma cell; Syk, spleen tyrosine kinase; T_H, helper T cell.

Classical IgE-Dependent Mechanism

The classical and most extensively studied mechanism of anaphylaxis is the IgE-mediated reaction to allergens, with MCs and basophils being the primary effector cells in the case of type I hypersensitivity reactions. Since basophils were discovered along with MCs a century ago, the extent to which basophils contribute to anaphylaxis is a controversial issue, given their low abundance in blood and the concomitant activation of MCs during the reaction [29].

The IgE-dependent mechanism comprises 2 phases. During the sensitization phase, an antigen disrupts immune tolerance and is subsequently internalized by antigen-presenting cells, primarily dendritic cells (DCs), but also macrophages and B lymphocytes (B cells). Through involvement of naïve helper T cells (T_H) and interleukin (IL) 4, IL-5, and IL-10, B cells undergo class switching from IgM to IgE, which is specific to the antigen [37]. These specific antibodies circulate in the blood and bind to FcεRI, the high-affinity receptor for IgE present on human MCs and basophils, prompting them to express it further, thus ending the first phase of the process and preparing for initiation of the second stage, known as the elicitation phase. FcεRI exists in humans in 2 forms: a tetrameric form, αβ2γ, composed of an α subunit, a β subunit, and 2 disulfide-linked γ chains, and a trimeric form, α2γ, which lacks the β subunit. The first form is expressed mainly on MCs and basophils, while the other is expressed on DCs, Langerhans cells, and monocytes. It has been demonstrated that the tetrameric form is crucial for cell activation, as transgenic mice expressing only trimeric FcεRI did not elicit a significant response [38]. The α subunit of FcεRI comprises 2 extracellular Ig superfamily domains capable of binding the Cε3 region of the Fc fragment of IgE [39]. Binding of monomeric IgE to FcεRI in the absence of an allergen results in the formation of stable IgE-FcεRI complexes that diffuse freely on the surface of MCs, promoting cell survival without triggering degranulation. In contrast, when the allergen threshold is reached, a multivalent allergen-IgE-FcεRI complex forms, becomes immobilized, and is internalized, triggering cell activation [40,41] (Figure 1).

Consequent degranulation releases preformed mediators stored in intracellular granules (such as histamine, heparin, tryptase, and chymase) and generates de novo other mediators, such as tumor necrosis factor α, prostaglandin D2, leukotrienes (LTC4, LTD4, and LTE4), platelet activating factor (PAF), nitric oxide (NO), chemokines (CCL-2, CCL-3, CCL-5, CXCL-8), growth factors (stem cell factor, vascular endothelial growth factor, transforming growth factor ß [TGF-β]), and ILs (primarily IL-1, IL-3, IL-4, IL-5, IL-6, IL-10, and IL-13) [42]. The clinical outcome of this massive reaction includes vascular hyperpermeability with hemodynamic and cardiovascular changes, endothelial cell (EC) dysfunction, angioedema, urticaria, diarrhea, colic spasms, uterine contraction, nasal congestion, bronchospasm, hypotension, headache, and neurological symptoms [43]. However, these cellular and molecular players do not always correlate with observed clinical outcomes, suggesting that other signaling pathways are involved in anaphylaxis.

IgE-Independent Mechanisms

Anaphylaxis does not depend only on IgE, as indicated by preclinical murine studies [44,45]. IgE-independent mechanisms involve the participation of various cell types (basophils, neutrophils, monocytes, macrophages, platelets, ECs), IgG-dependent reactions, antigen-specific IgG binding forming immune complexes (ICs), cytotoxicity, cyclooxygenase (COX) inhibitors, Mas-related G protein–coupled receptor X2 (MRGPRX2), activation of complement, contact, and coagulation, neuropeptide release, and purinergic metabolism, as well as other, less explored or unknown signaling pathways [46].

IgG-Mediated Immunological Mechanisms

These reactions involve antigen crosslinking of ICs bound to IgG receptors, resulting in tissue damage [47]. In particular, identification of IgG antibodies forming ICs, mainly on cells from the innate immune system, is relevant in drug-mediated anaphylaxis [12,48]. One of the main features of IgG-mediated mechanisms is the need for higher antigen doses than in IgE-mediated reactions [11]. This fact is of relevance, as it implies that only high antigen exposures (drugs and some foods) trigger the IgG-driven reaction. Numerous studies support the existence of this alternative pathway, where IgG antibodies bind to Fc gamma receptors (FcγRs), which have different affinities and are expressed on a variety of cell types [11,49,50] (Figure 2).

In a study involving patients with food anaphylaxis induced by lipid transfer proteins (LTPs), an increase in specific anti-LTP IgG1 and IgG3 was observed, as was heightened expression of the 3 genes encoding the activating receptor FcγRI [51]. Previous studies have demonstrated that FcγRI-mediated activation of human MCs can occur via IgG [52]. Both IgG1 and IgG3 bind to FcγRI, which is expressed in monocytes and macrophages and can be induced in neutrophils and MCs [53]. FcγRI is unique among Fcγ receptors because of its ability to bind monomeric IgG (particularly IgG1 and IgG3) with high affinity. Muñoz-Cano et al [51] found that patients allergic to LTP exhibited both specific IgG and anti-LTP IgE, suggesting that the activation of both IgG and IgE pathways may significantly contribute to the anaphylactic response.

IgG-ICs bind to the FcγRIII on macrophages to activate synthesis of PAF [49]. This phospholipid is a noteworthy mediator associated with severe manifestations of anaphylaxis owing to its pleiotropic actions. Beyond its potential as a biomarker, PAF is an inflammatory factor involved in platelet aggregation and increased vascular permeability. Furthermore, it contributes to circulatory collapse, reduced cardiac output, and various other biological effects. It can activate platelet aggregation and induces the release of other mediators, such as leukotrienes, thromboxane, and serotonin [54]. In fact, the contribution of platelets and release of serotonin was demonstrated in transgenic murine models of IgG-dependent anaphylaxis. Nevertheless, the participation of platelets, monocytes, and macrophages in human anaphylaxis is not completely understood [11].

Preclinical studies in mice have shown that neutrophils can induce anaphylaxis, suggesting that they are also a relevant

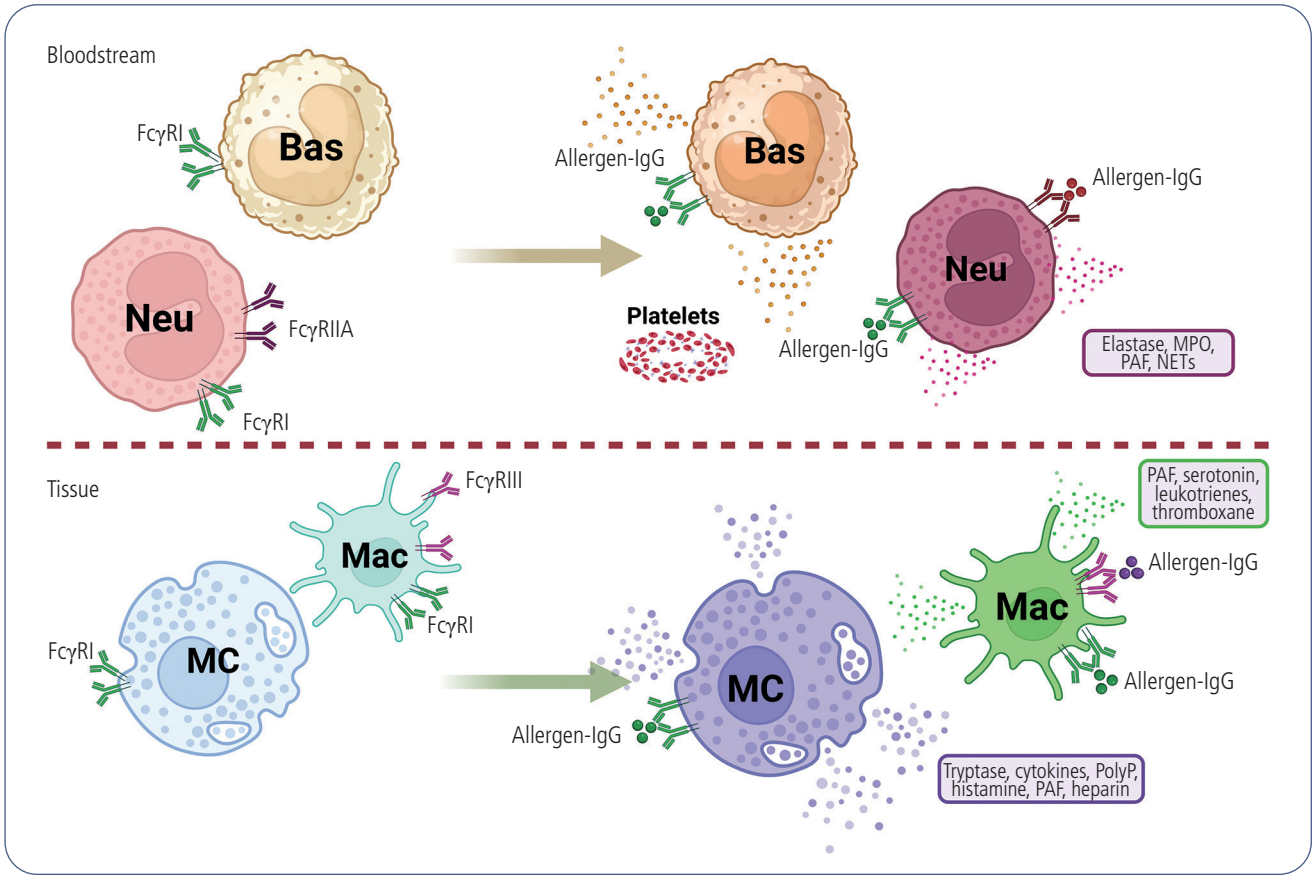

Figure 2. IgG-dependent mechanism in anaphylaxis. IgG molecules bind to FcγRs that are expressed in at least basophils, neutrophils, monocytes, macrophages, and the platelets activating them. These cells release mediators of a different nature into the bloodstream or the surrounding tissues. FcγRI, FcγRIIA, and FcγRIII induce activation. Bas indicates basophil; FcγRI, Fc gamma receptor type I; FcγRIIA, Fc gamma receptor type IIA; FcγRIII, Fc gamma receptor type III; Mac, macrophage; MC, mast cell; MPO, myeloperoxidase; Neu, neutrophil; NET, neutrophil extracellular trap; PAF, platelet-activating factor; PolyP, polyphosphates.

player in human anaphylaxis [55,56]. A study carried out in patients with suspected anaphylaxis to neuromuscular blocking agents (NMBAs) during general anesthesia reported that IgG markers of FcγR activation correlated with the severity of anaphylaxis. Specifically, markers of neutrophil activation, such as PAF, elastase, myeloperoxidase, and neutrophil extracellular traps, were associated with severity, thus establishing a role for neutrophils in drug-mediated anaphylaxis [14].

Inhibition of Cyclooxygenase

The COX-1 and COX-2 pathways play a relevant role in hypersensitivity reactions and anaphylaxis. COX inhibition blocks PGE2 production by switching arachidonic acid metabolism to 5-lipoxygenase pathway activation, with the consequent production of proinflammatory cysteinyl leukotrienes (LTs), such as LTC4, LTD4, and LTE4 [57]. Despite the most classical clinical pictures being urticaria and respiratory symptoms (rhinitis or asthma), which frequently exacerbate the underlying condition, "blended reactions" involving multiple systems have been described. These reactions are indistinguishable from other anaphylactic reactions, and elevated tryptase has been reported [58]. Nonsteroidal anti-inflammatory drugs (NSAIDs), including acetyl salicylic acid and ibuprofen, are the most common triggers involved in these types of hypersensitivity reactions [59,60]. This pathway may also be relevant when NSAIDs act as cofactors in food-induced anaphylaxis [61].

Direct Mast Cell Activation (MRGPRX2)

The last decade has seen the identification of a mechanism in which certain drug-associated allergy-like events are not mediated by antibodies. Instead, these drugs can directly trigger mast cell degranulation through the activation of MRGPRX2, which belongs to the MRG family, consisting of over 50 members in various mammals [62]. MRGPRX2 is primarily expressed in MCs, although some evidence suggests that basophils and eosinophils may also express it [63,64]. Transcriptomic analysis has demonstrated that MRGPRX2 expression is abundant in skin MCs but scarce in lung and gut [65]; therefore, it is relevant in local skin reactions [19]. A variety of drugs, such as NMBAs, fluoroquinolones, opioids, and icatibant, are MRGPRX2 agonists, thus indicating their relevance in anaphylaxis without proven IgE-mediated sensitization [18,20].

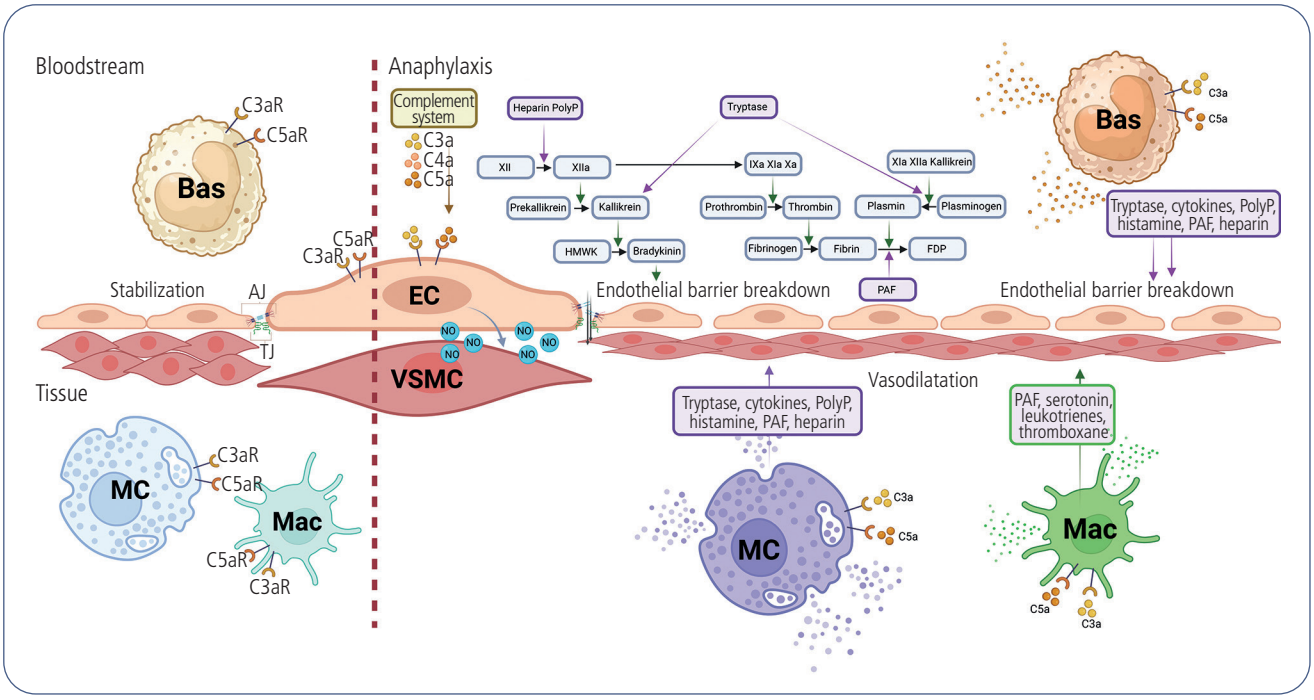

Figure 3. Plasma protein system activation in anaphylaxis. The activation of the complement system releases C3a and C5a, which bind to their C3aR and C5aR on the surface membrane of a variety of effector cells. The contact-coagulation and plasmin-fibrinolysis systems are also activated, thus disturbing vascular homeostasis. AJ indicates adherent junction; Bas, basophil; C3a, anaphylatoxin C3a; C5a, anaphylatoxin C5a; C3aR, C3a receptor; C5aR, C5a receptor; EC, endothelial cell; FDP, fibrin degradation products; HMWK, high-molecular-weight kininogen; MC, mast cell; Mac, macrophage; PolyP, polyphosphates; XII, factor XII; XIIa, activated factor XII; IXa, factor IXa; Xia activated factor Xi; Xa, factor Xa; PAF, platelet activator factor; NO, nitric oxide; TJ, tight junction; VSMC, vascular smooth muscle cell.

Plasma Components and Systems

Activation of the Complement, Contact, Coagulation, and Fibrinolytic Systems

The coagulation and contact systems, traditionally associated with hemostasis and inflammation, are now recognized as active participants in the complex cascade of events triggered during anaphylaxis (Figure 3). Such insights derive from published cases or small studies. MCs, the key effector cells in anaphylaxis, release a plethora of mediators upon activation, including heparin, which can activate these systems.

Induction of the coagulation cascade and hyperfibrinolysis have been described in cases of anaphylaxis [66-68]. Hypothetical mechanisms include heparin acting as an anticoagulant by binding to antithrombin, resulting in anti-factor Xa activity and prolonged activated partial thromboplastin time. In addition, tryptase tetramers directly impact the fibrinolytic pathway by activating urokinase, subsequently degrading fibrin polymers and increasing D-dimer levels.

In addition to its role in coagulation, heparin activates factor XII (FXII), a key component of the contact system, generating bradykinin, a potent vasodilator that contributes to the hypotension and angioedema observed in anaphylaxis [37,69]. Adding another layer of complexity, MC mediators can directly activate the contact system, independent of heparin. Significant consumption of contact system factors has been observed in IgE-mediated anaphylaxis models in mice [70] and in patients with anaphylaxis [68,71,72]. Deficiency or pharmacological inhibition of FXII, plasma kallikrein, high-molecular-weight kininogen, or the bradykinin B2 receptor significantly attenuated allergen-/IgE-mediated hyperreactivity of MCs in mice [68].

The complement system can trigger an anaphylactic reaction under certain conditions. It is activated rapidly by diverse substances and drugs, producing large amounts of C3a and C5a anaphylatoxins, which stimulate macrophages, basophils, and MCs, leading to anaphylaxis [73]. These potent inflammatory mediators cause vasodilation and smooth muscle contraction. Basophils and MCs respond by releasing histamine, while macrophages, neutrophils, and eosinophils undergo an oxidative burst [74-76].

Circulating Proteins

Beyond immune cells and activation of classic homeostatic pathways, assays performed with sera from patients with anaphylaxis demonstrate a reduction in the major molecular components of blood. Human serum albumin is a particularly abundant circulating protein, accounting for 55% of the total protein concentration [77]. A study involving 112 anaphylaxis patients found that both serum protein concentration and human

serum albumin levels decreased according to the severity of the reaction, thus providing indirect evidence of underlying fluid extravasation [78]. Furthermore, apolipoproteins (Apo) and lipoproteins have been analyzed in various cohorts of serum samples from individuals experiencing anaphylaxis. Pioneer studies showed a reduction in serum Apo A1 [79,80], and Apo B was found to be inversely related to severity in children with food-induced anaphylaxis [81]. Similarly, a study including 115 serum samples from patients experiencing anaphylaxis confirmed decreased levels of ApoA1, ApoB, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol in sera from patients with severe anaphylactic reactions. Specifically, in vitro experiments demonstrated that the HDL-C of anaphylactic patients lost its beneficial role in endothelial barrier stability and was barely able to induce macrophage cholesterol efflux [82]. These advances are likely to be a useful diagnostic tool, although, more importantly, they pave the way for new and underexplored mechanistic avenues for research in anaphylaxis.

The Functions of the Vascular System

As described above, multiple molecules are released from different sources or formed from activation of homeostatic cascades in anaphylaxis [30]. These immune and nonimmune signals impact on the vascular wall, producing a variety of pathophysiological events [33]. Primarily, those coming from MCs may act in a paracrine way in several organs (eg, skin, mucous membranes, blood vessels, lung, heart) [83]. Similarly, macrophages may interact with the surrounding tissues. Simultaneously, mediators are systematically distributed through the bloodstream, likely owing to the activation of other blood cells such as basophils and neutrophils or the activation of homeostatic cascades. Thus, the vascular niche receives a variety of signals that can in turn activate specific molecular mechanisms, contributing to the range of clinical events [37].

The main severe manifestations in anaphylaxis include cardiovascular effects such as increased vascular permeability, vasodilatation, hypotension, impaired venous return, and hemodynamic compromise [33,84,85]. Specifically, the large extension of the endothelium, which is the main signal receptor, plays an essential role beyond the immune reaction, controlling loss of fluids and participating in the homeostasis of the reactions [33,86,87] (Figure 4). In addition, smooth muscle cells (SMCs) and cardiomyocytes are key cellular components involved in most of the phenomena associated with severe anaphylactic reactions. Specifically, vascular SMCs and, indirectly, ECs contribute to vascular tone modulation via synthesis and release of vasoactive substances such as NO, the main relaxant released in anaphylaxis [88,89]. Adrenaline (epinephrine) is the first-line treatment for anaphylaxis because it restores the homeostasis of the cardiovascular system and reverses bronchial constriction [1,90]. Its administration prevents cardiovascular collapse and improves blood flow through its mechanism of action on α and β adrenergic receptors [33].

Heterotrimeric guanine-nucleotide-binding regulatory proteins/G protein coupled receptors (GPCRs) regulate physiological functions and participate in the pathophysiology of many diseases [91]. Specifically, anaphylactic shock depending on endothelial Gq/G11 has been characterized in mice models [92], and most of the mediators in anaphylaxis bind to GPCRs. However, downstream signaling pathways are

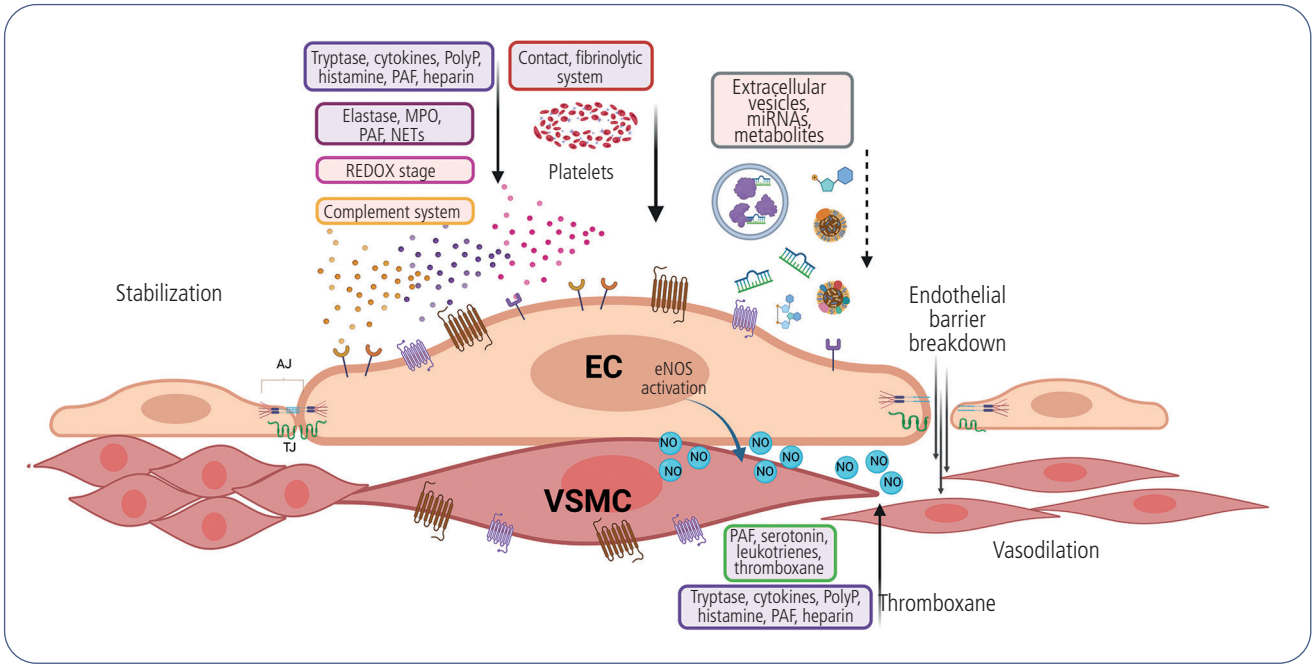

Figure 4. Activation of vessels during anaphylaxis. The diverse mediators and system activation impact on the vascular wall, inducing barrier breakdown, vasodilation, and disturbance of vascular hemostasis. AJ indicates adherent junction; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; TJ, tight junction; MPO, myeloperoxidase; NET, neutrophil extracellular tramps; NO, nitric oxide; PAF, platelet activator factor; PolyP, polyphosphates; REDOX, a chemical reaction between an oxidizing and a reducing substance; VSMC, vascular smooth muscle cell.

not well defined for either of them, even though their impact on the vascular wall is well established [30,33].

The main molecular process underlying the increased leakage of fluids is the destabilization of the connective proteins located in the endothelial barrier. Under physiological conditions, tight junctions (TJs) and adherent junctions (AJs) contribute to barrier stabilization by providing mechanical cohesive strength between ECs [93]. In anaphylaxis, key mediators such as tryptase, histamine, PAF, cysteinyl LTs, bradykinin, and C3a bind to Gq/G11, thus activating calcium-dependent mechanisms and leading to the disruption of the endothelium [94]. In addition to receptor-mediated molecular signaling, the endothelial glycocalyx and extracellular matrix components play crucial roles in anaphylaxis, forming an interface that interacts with blood components such as the complement and contact systems [95]. Furthermore, stabilizing endothelial barrier agents have been identified in these settings. Such is the case of HDL-C, which is reduced or perhaps loses its function, as demonstrated by the increased vascular permeability of human dermal microvascular ECs when exposed to purified HDL particles from serum samples from patients who experience anaphylaxis [82].

Other types of receptors have also been proposed as potential therapeutic targets, mainly in mouse models of anaphylaxis. These include nonreceptor tyrosine kinases, fibroblast growth factor-inducible 14 receptor, signal transducer and activator of transcription 3, peroxisome proliferator-activated receptor, and mucosa-associated lymphoid tissue lymphoma translocation gene 1 protease activity [30,96].

Genetics, Epigenetics, and Transcriptomics

Genetic factors play a significant role in anaphylaxis, with studies highlighting various genetic traits associated with an increased risk of severe anaphylactic reactions. Hereditary α-tryptasemia has been identified as a common autosomal dominant genetic trait linked to elevated baseline serum tryptase levels, potentially increasing the risk of anaphylaxis [97]. Additionally, the presence of the KIT p.D816V missense variant in patients with severe Hymenoptera venom–triggered anaphylaxis suggests a strong association between clonal MC-related disorders and anaphylaxis [98]. Furthermore, gene polymorphisms related to the renin angiotensin system (RAS) have been linked to anaphylaxis involving airway angioedema and cardiovascular collapse, thus indicating lower RAS activity in such cases. This decrease impacts angiotensin II levels and endothelial NO activity, potentially influencing susceptibility to anaphylaxis [99]. Finally, studies have identified various mutations in the lysyl-tRNA synthetase 1 (KARS) gene that lead to a constitutive activation of transcription factors involved in MC functions, ultimately increasing proinflammatory mediator release during antigen-/IgE-dependent responses [100,101].

Transcriptomic studies on human anaphylaxis have shown that reactions lead to extensive blood alterations involving the dysregulation of various genes, including up-regulation of cell movement, migration, and neuroinflammatory signaling, as well as down-regulation of lipid activating nuclear receptor signaling [102]. Moreover, studies on DCs during anaphylaxis have shown an overrepresentation of the TGF-β pathway among the genes that changed expression during anaphylaxis; this pathway is crucial in regulating immune responses and inflammation [103]. Lastly, validation studies confirm up-regulation of innate immune pathways and myeloid cells during anaphylaxis, indicating the activation of neutrophils as a crucial aspect of the allergic reaction [104]. However, patients who have experienced anaphylaxis, even outside an anaphylactic episode, also exhibit a distinct transcriptomic profile compared to healthy individuals. This is characterized by up-regulation of the expression of genes regulating gastrointestinal epithelial renewal, altered B-cell pathways, and increased neutrophil activation markers [51].

Studies have shown that environmental changes, such as increased exposure to tobacco smoke, contribute to the rising incidence of allergic diseases, including anaphylaxis, by influencing epigenetic processes [105]. These modifications may affect immune regulation, particularly T_H-cell polarization and regulatory T-cell differentiation. Methylation changes have been observed on the promoter regions of critical transcription factors for regulatory T cells after sublingual immunotherapy with synthetic glycodendropeptides in a murine model of food anaphylaxis, in which forkhead box protein P3, was seen to be hypomethylated exclusively in tolerant mice, whereas GATA3 was only hypomethylated in desensitized mice [106]. Research has also focused on identifying specific epigenetic markers associated with anaphylaxis, with DNA methylation patterns being of particular interest [107]. Eighteen methylation signatures and 1459 differential DNA methylation patterns regulating mitogen-activated protein kinase and other signaling pathways have been identified in β-lactam–induced fatal anaphylaxis [108].

Other Molecular Components and Biological Systems

Evidence From Omics Studies (Proteomics and Metabolomics)

Recent technological and biomedical advances have led to the development of omics, which uses high-throughput techniques to integrate multiple levels of systems biology, thereby transforming research strategies and deepening our understanding of molecular biology [32]. However, a limited number of studies have explored anaphylaxis from this perspective. The results of a recent meta-analysis support the relevance of neutrophils and platelets in the pathophysiology of anaphylaxis through evaluation of 4 proteomic studies carried out in humans and 3 in animal models [109]. Metabolomics specifically examines the end products of changes occurring at higher biological levels, such as genes, transcripts, and proteins, as well as the influence of external factors on these products [110,111]. Specifically, its central aim is to investigate metabolic profiles in various biological contexts [112]. By analyzing and comparing these molecular fingerprints, it is possible to identify biomarkers with the potential to improve the diagnosis, prognosis, and treatment of the conditions

studied while deepening our understanding of the underlying mechanisms [111].

In anaphylaxis, most studies are conducted using animal models for ethical reasons. This approach enables safer experimental control and a more detailed exploration of pathophysiological mechanisms [113].

Nevertheless, despite all the technical challenges involved, one study found changes in the metabolome of 19 patients with moderate or severe anaphylaxis according to the classification of Brown [114], focusing on reactions triggered by foods or drugs [115]. Metabolomic analysis was conducted at 3 time points: baseline (T0), onset (T1), and 2-4 hours later (T2). The study found significant metabolic alterations, particularly in food-induced anaphylaxis, with 73 metabolites affected, primarily in phospholipid-related pathways. An increase in choline and a decrease in phospholipids at T1 indicated that these were key regulators of the acute phase. Additionally, higher levels of glutamine and phenylalanine were linked to catabolism and vascular dysfunction. Patients with moderate reactions showed elevated amino acids at T1, contributing to inflammation. Fewer changes were observed in severe cases, suggesting a more sustained latent inflammation. The study also identified metabolites that could signal a predisposition to severe reactions—even at baseline—characterized by elevated glucose and lipid levels, along with reduced cortisol levels in the most affected cases. These findings suggest that certain metabolic profiles may serve as risk markers for severe anaphylaxis, even in serum samples at baseline.

Extracellular Vesicles and miRNAs

Extracellular vesicles (EVs) are particles released by cells that are bound by a lipid bilayer and unable to replicate on their own [116]. In recent years, interest these particles has increased owing to their application as biomarkers and their involvement in intercellular communication, under both physiological and pathological conditions. EVs have been proposed as biomarkers for the diagnosis of several diseases, as they are present in easily accessible biological fluids such as blood, urine, sperm, and saliva [117]. In addition, they reflect the state of the cell that releases them, enabling differentiation between health and disease [118]. EVs can exert their action in an autocrine or paracrine manner and interact with cells at great distances from their site of origin [119].

EVs regulate processes such as coagulation, inflammation, and stem cell proliferation and participate in the development of allergic diseases [120,121]. They can carry and present antigens and may participate in the switch between lymphocyte phenotypes [122,123]. Moreover, MC-derived EVs have emerged as major players in the allergic response [124,125]. Specifically, a study carried out in patients with anaphylaxis identified a differential protein composition between EVs circulating during the reaction and those present at least 14 days later in the basal state. Mass spectrometry analysis revealed 99 proteins whose levels varied between the 2 conditions (increased in 83 and decreased in 16) during the anaphylactic reaction. In turn, changes in 3 of these proteins (CDC42, Ficolin 2, and S100A9) were validated in a larger cohort of patients with anaphylaxis [126].

EVs may contain various molecules including proteins, lipids, metabolites, and nucleic acids (eg, RNA, DNA, small noncoding RNAs [sncRNAs, including microRNAs]) [116]. However, their cargo and/or composition vary with different inflammatory and allergic diseases [127,128].

Changes have also been reported in the levels of microRNA, whether free in blood or carried by EVs during anaphylaxis [30]. Specifically, miR-21-3p and miR-487b-3p levels increased in a pediatric population with food-induced anaphylaxis [129], as did miR-451 in adult patient blood samples [80]. Of special interest, specific sncRNA profiles were observed in a comparative study carried out in samples of children with food-mediated anaphylaxis and adults with drug-mediated anaphylaxis [130]. Moreover, when microRNAs are encapsulated within EVs, they are protected from degradation by circulating nucleases, thus making them promising agents for the study of multifactorial and complex events, such as anaphylaxis [131]. Indeed, increased miR-21-3p and decreased miR-375-3p levels have been reported in EVs from patients with anaphylaxis [132]. Overall, these data suggest the specificity of novel molecular agents as players in anaphylaxis and point to their potential usefulness in clinical settings [133]. Further exploration in this direction is warranted.

Implications for Future Therapeutic Interventions

Current insights into the underlying triggers of anaphylaxis and subsequent signaling pathways have enabled the development of targeted therapeutic strategies to prevent and/or treat anaphylaxis. As the IgE-FcεRI pathway is the best-understood underlying mechanism, it has become a prime target for therapy. Anti-IgE biologics block free IgE, reducing its capacity to bind to allergens and activate both FcεRI and FcεRII. The first biologic to demonstrate the effectiveness of this approach by raising the peanut threshold in peanut-allergic patients was talizumab, which paved the way for omalizumab and ligelizumab. Humanized IgG1k monoclonal antibodies bind the IgE Cε3 domain of free IgE, with ligelizumab proving much more effective at inhibiting the activation of circulating basophils and decreasing IgE production owing to its 88-fold higher affinity for IgE [134]. These drugs have shown high tolerability and safety, with minimal impact on antihelminth defense in developed countries. Omalizumab has proven efficacious not only in allergic respiratory diseases and chronic spontaneous urticaria, but also in food allergy, as it lowers the frequency of food-dependent reactions and, as an adjuvant therapy, during the build-up phase of oral immunotherapy. Moreover, this biologic has also proven useful in drug desensitization procedures.

A novel class of anti-IgE designed ankyrin repeat proteins has proven effective in mouse models by binding free IgE, breaking IgE-FcεRI complexes, and halting preinitiated anaphylaxis [135]. Another therapeutic target involves tyrosine kinases, particularly Bruton tyrosine kinase, drawing on experience from treating B-cell lymphoma. Four such inhibitors are currently available, and their oral administration, rapid onset, and quick cessation of action make them attractive therapeutic options. Ibrutinib and acalabrutinib

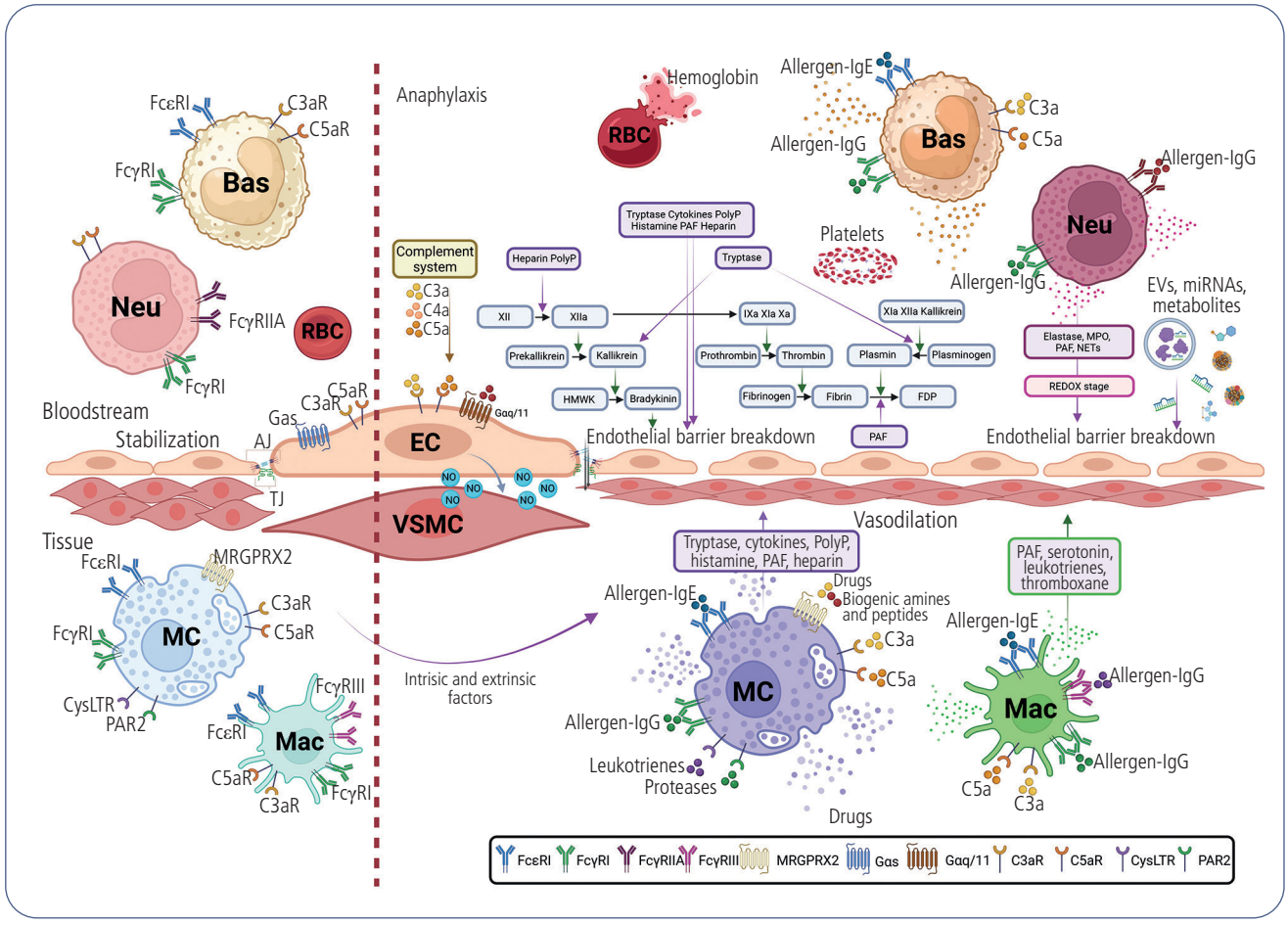

Figure 5. Overview of the molecular and cellular mechanisms underlying anaphylaxis. Left, main cells in the physiological state. Right, the activation of cells, molecules, and systems involved in anaphylaxis. AJ indicates adherent junction; Bas, basophil; CysLTR: cysteinyl leukotriene receptor; C3a, anaphylatoxin C3a; C5a, anaphylatoxin C5a; C3aR, C3a receptor; C5aR, C5a receptor; EC, endothelial cell; EVs, extracellular vesicles; FcεRI, high-affinity receptor for IgE; FcγRI, Fc gamma receptor type I; FcγRIIA, Fc gamma receptor type IIA; FcγRIIB, Fc gamma receptor type IIB; FcγRIIC, Fc gamma receptor type IIC; FcγRIIIA, Fc gamma receptor type IIIA; FcγRIIIB, Fc gamma receptor type IIIB; FDP, fibrin degradation products; Gαq/11, G protein coupled receptor Gαq/11; Gαs, G protein coupled receptor Gαs; IgE, immunoglobulin E; IgG, Immunoglobulin G; HMWK, high molecular weight kininogen; IXa, factor IXa; MC, mast cell; Mac, macrophage; miRNAs, microRNAs; MPO, myeloperoxidase; MRGPRX2, Mas-related G protein-coupled receptor X2; NET, neutrophil extracellular traps; Neu, neutrophil; NO, nitric oxide; PAF, platelet-activating factor; PolyP, polyphosphates; PAR2, protease-activated receptor 2; RBC, red blood cells; TJ, tight junction; VSMC, vascular smooth muscle cell; Xa, factor Xa; XIa, activated factor XI; XII, factor XII; XIIa, activated factor XII.

have already proven effective by enabling the administration of chemotherapy in 2 patients with severe IgE-mediated reactions who could not tolerate the drug in a desensitization protocol [136,137]. Furthermore, a phase 2 trial has shown the efficacy of acalabrutinib in preventing peanut-induced anaphylaxis. Lastly, the least advanced therapeutic targets are the inhibitory receptors, which dephosphorylate the aforementioned kinases and down-regulate the IgE-FcεRI pathway. Lirentelimab targets sialic acid–binding Ig-like lectin 8 (Siglec-8) and has shown promise in a phase 2 trial in indolent systemic mastocytosis by halting MC activation [138].

Other therapeutic targets have been less explored but may continue to provide opportunities for further research. For example, synergistic activation of IgE and MRGPRX2 molecular pathway 39 favors development of MRGPRX2 antagonists for potential treatment of mast cell–mediated disease and is being studied to block allergic reactions [139].

Some of the abovementioned pathways and related molecules may prove useful in further endotyping anaphylactic reactions. Diagnostic panels could be developed to measure specific levels of proteins, microRNAs, metabolites, and other molecules, supporting clinical phenotyping or predicting the risk of a severe reaction. These panels would enhance diagnostic confirmation and help identify potential treatment targets.

Concluding Remarks

The existence of a wide variety of IgE-independent mechanisms participating in anaphylaxis is supported by abundant scientific and theoretical evidence (Figure 5). However, before they can be applied in clinical practice, it is necessary to fully understand their complexity. New

perspectives in genetic, epigenetic, metabolic, and molecular biology not only enhance our understanding of the underlying mechanisms of anaphylaxis, but also pave the way for potential advancements in personalized management, risk stratification, and treatment strategies for individuals at risk of anaphylaxis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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