

REVIEW ARTICLE

The history of mast cell and basophil research – some lessons learnt from the last century

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Abstract

This year (2013) marks the 50th anniversary of death of Otto Carl Willy Prausnitz (1876–1963) and Heinz Küstner (1897–1963). The two physicians, when working at the Hygiene Institute at the University of Breslau, Germany (Prausnitz was the Head of the Institute), described in 1921 what is still called today the Prausnitz–Küstner or PK reaction showing that allergy could be transferred from the allergic person by transferring serum to a healthy person. Their discovery ended the belief that an anaphylactic/allergic reaction was caused by poisons, but to the contrary showed that the presence of the hypersensitivity factor could be transferred to other people. We know now that this factor is immunoglobulin E (IgE), sensitizing mast cells and basophils to respond to an allergic stimulus. We take this occasion to retrace some of the important discoveries and lessons learnt from the last century relating to the function of these two cell types as effectors of the IgE system and the mediators they produce.

Mast cells were first reported by Friedrich von Recklinghausen (1833–1910) when he described in 1863 the presence of granulated cells in unstained connective tissues from various species, including the tail of tadpoles (1). It was several years later that they were named by Paul Ehrlich (1854–1915). In his thesis on the theory and praxis of histological staining published in 1878, he described cells with granula in connective tissues that stained with basic aniline dyes (2). He initially thought that these cells derived from connective tissue cells that had ingested large amounts of nutrients, and therefore, he gave them the name 'Mastzellen', meaning well-fed cells. Paul Ehrlich also described for the first time basophil leukocytes during his studies on the staining properties of blood cells distinguishing neutrophilic, eosinophilic, and basophilic cells (3, 4). An apparent independent discovery was made by Paul Portier (1866–1962) and Charles Richet (1850–1935) publishing in 1902 the phenomenon of anaphylaxis (5). They investigated in the summer of 1901, aboard the yacht 'Princess Alice II' of Prince Albert 1^{er} of Monaco, the effects of toxins from the sea anemone *Physalia* when injected into dogs. Instead of achieving protection against these toxins by the dog's immune system (i.e., immunization),

they found that the dogs became hypersensitive to the toxins. Even small amounts of the toxins, which did not cause lethality after the first injection, led to the rapid death of the animal after the second injection. This discovery was in complete disagreement with the prevailing idea at the turn of the century that immunological mechanisms are protective (6). It is therefore the merit of Portier and Richet to have recognized the importance of anaphylaxis (from the Greek *ana* = against and *phylaxis* = protection) in the absence of any possibility – at the time – to explain this phenomenon. Subsequent work of other scholars expanded the field with the description of other hypersensitivities. This included the description in 1903 by Maurice Arthus (1862–1945) of a reaction caused by repeated subcutaneous injections of the same (horse) antiserum causing inflammation and necrosis of the tissue at the injection site, which was called Arthus phenomenon (7). Another such reaction was described by the physicians Clemens von Pirquet (1874–1929) and Béla Schick (1877–1967) who in 1905 (8) extended the Arthus reaction to the serum compartment as they observed that repeated intravenous injections with a protective antiserum caused serum sickness.

Somewhat later in 1919, Maximilian Ramirez reported a case of asthma after a blood transfusion. A patient with no history of hypersensitivity reactions was given a blood transfusion for anemia. A fortnight after the transfusion, the patient sat into a horse-drawn carriage in Central Park and shortly thereafter experienced an asthma attack. Dr Ramirez could trace back the blood to the donor who was hypersensitive to horses. He drew the conclusion that something had been transmitted from the donor to the recipient and pointed to the risk of transmitting what he called 'anaphylactic or reaction bodies' (9). A few years later in 1921, the German physicians Carl Prausnitz and Heinz Küstner (Fig. 1) performed experiments with themselves, which have become classical today: the injection of Küstner's serum, who was suffering from a severe fish allergy under the skin of Prausnitz followed by the local application of a fish extract 24 h later, produced an immediate state of anaphylaxis called cutaneous anaphylaxis (10). We now know that this latter phenomenon is based on the same mechanisms as the one found by Portier and Richet. Indeed, they depend on the IgE class of antibodies as well as on mast cells and basophils and can be observed within minutes following the injection, while the other two phenomena are dependent on IgG and require at least a few hours to develop, as had already been noted by the investigators. Nevertheless, although describing an IgG-dependent phenomenon, it was Clemens von Pirquet who coined the term 'allergy' (allergy from the Greek words *allos* = other and *ergon* = work) for the altered reactivity they had observed (11). In fact, his goal was to advance a unifying theory being convinced that immunity and hypersensitivity are opposite consequences of the same phenomenon.

The dilemma of explaining anaphylaxis

The relationship between anaphylaxis and immunity was not clear from the onset. Different explanations prevailed

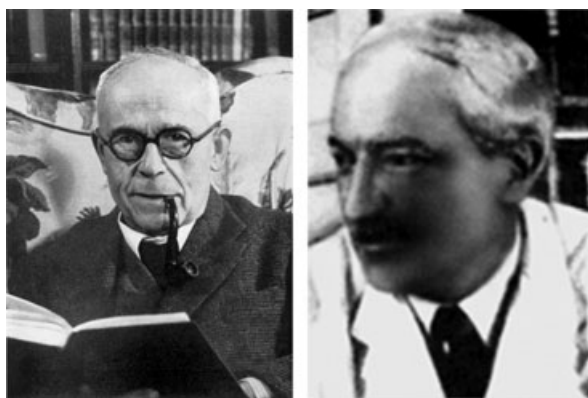


Figure 1 Otto Carl Willy Prausnitz (left, from Downie AW. Carl Prausnitz (Giles). 11 October 1876–21 April 1963. *J Pathol* 1966;92:241–252) and Heinz Küstner (right). Reprinted from *Journal of Allergy and Clinical Immunology*, Vol. 114, A. W. Frankland, Carl Prausnitz: A personal memoir, pages 700–705, Copyright 2004, with permission from Elsevier.

including the following: the existence of two active substances in *Physalia* extracts, one of weak potency but high immunogenicity (called 'thalassine') causing protection, the other of high toxicity but low immunogenicity (called 'congestine') causing anaphylaxis (12). E. Friedberger proposed in 1909 (13) that the serum contains a reactive substance called anaphylatoxin that results as a cleavage product after introducing the toxin. However, it was not until 1959 that Zoltán Ovary had identified such anaphylatoxins as cleavage products of complement proteins (14). These peptides can induce an anaphylactic reaction by mast cells and basophils, which bear receptors for these peptides on their surface. Nevertheless, it is a mechanism different from that observed by Portier and Richet as it does not involve IgE. While some researchers like Maurice Arthus persisted to say that there is no relationship between immunity and allergy (15), others like Pirquet defended the concept of protective and destructive antibodies (16), and it seems that Charles Richet had also accepted this hypothesis by proposing that anaphylaxis represents a rapid reaction of the immune system to low doses of toxins (17), coming close to defining the reaction we today know as type I immediate hypersensitivity.

Mast cells, basophils, and IgE in anaphylaxis

The serum factor

It took still many years to identify the mechanism behind anaphylaxis. One research axis concentrated on the serum factor. Maurice Nicolle (1862–1932) at the Pasteur Institute had demonstrated in 1907 (18) the possibility of a passive transfer of the anaphylactic factor in serum from a sensitized animal to another one. Prausnitz and Küstner, as already mentioned, described the local transfer in the skin. It is only much later on in 1966–1967 – likely because the serum factor is present in very small amounts in the serum – that Kimishige Ishizaka and his wife Teruko at the Children's Asthma Research Institute in Denver identified a biological activity in a gamma-globulin fraction that was not IgG or IgA. They called this serum factor γ E (for E = erythema) (19, 20). Their experiments were based on the Prausnitz–Küstner (PK) test to examine serum of patients allergic to ragweed pollen after biochemical fractionation. By injecting this fraction into rabbits, they were able to raise an antiserum capable to block the PK reaction. At the same time, S.G.O. Johansson and Hans Bennich at Uppsala University (Fig. 2), Sweden, isolated the first myeloma-derived IgE then called IgND (where ND are the initials of the patient's name) (21), which was also able to block the PK reaction (22). They could demonstrate increased serum levels of this new immunoglobulin in sera from subjects with asthma (23). Both teams concluded after a thorough study of their results and exchange of reagents that they had worked on the same immunoglobulin. During the WHO conference in 1968 (Lausanne), these researchers agreed to call this fifth class of serum immunoglobulin: the IgE (24).



Figure 2 Hans Bennich (left) and S.G.O. Johansson (right) (photograph copyright of and provided by S.G.O. Johansson, reproduced with permission).

The cellular players

Already in 1910, it became clear that the serum factor had a particular property to bind strongly to tissues without being able to be subsequently removed by washing. William Schultz showed in 1910 that small pieces of intestine from sensitized guinea pigs contracted after addition of a specific antigen (25). One year later, Henry Dale (1875–1968) and Patrick Laidlaw (1881–1940) discovered that it was tissue histamine, which was responsible for inducing intestinal smooth muscle contraction analogous to an anaphylactic reaction (26). Histamine had initially been isolated by Dale from *Claviceps purpurea*, a fungal parasite of rye and other related cereals responsible for ergotism, a ravaging disease in medieval times. However, it was not until 1953 that James F. Riley (1912–1985) and Geoffrey B. West (1916–1990) showed that histamine is stored predominantly in mast cell granules (27). Because mast cells are found in almost all tissues except blood, where they seemed to be replaced by basophils, Riley and West suggested that these cells may be involved in anaphylaxis. Somewhat later, the Hopkins's school in Baltimore led by Philip Norman and Lawrence Lichtenstein showed in a comparative study of PK-sensitizing antibody titers and leukocyte sensitivity measurements that the latter represented a valuable index of the severity of ragweed hay fever (28). After the discovery of IgE, the Ishizakas also found IgE binding sites present on basophils and monkey mast cells and that their aggregation by anti-IgE on basophils caused them to release histamine (29, 30). It was in 1974 that Henry Metzger provided a first biochemical analysis on a mast cell line showing that IgE is bound in a saturable manner and with very high affinity (31). The molecular cloning and expression of the receptor detected initially by a rosetting assay (Fig. 3) led to elucidation of its molecular structure as a multimolecular complex composed of one α -chain responsible for IgE binding, one β - and two γ -chains responsible for signal transduction in the late 1980s (32). This laid the ground for

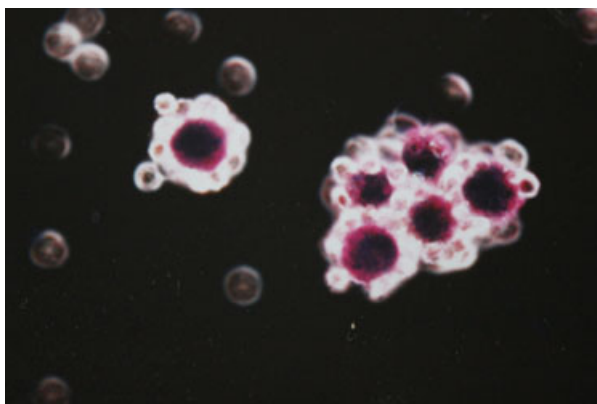


Figure 3 The picture shows the formation of IgE rosettes after transfection of cDNAs coding for the α -, β -, and γ subunits of the high-affinity IgE receptor into Cos7 cells and sensitization with mouse IgE antinitrophenyl before being exposed to red blood cells derivatized with trinitrophenol. Detection by rosetting was crucial in the initial experiments as the transfection efficiency was very low and allowed to detect a few rosetting cells among thousands of cells. The experiments provided definitive proof that the α -, β -, and γ -subunits constitute the functional unit to obtain expression of the receptor and IgE binding.

expressing the human receptor (33, 34) and to obtain an atomic view of the receptor with its bound IgE in 2000 by Jean-Pierre Kinet together with Theodore Jardetzky, a crystallographer (35). These studies also provided the basis for the development of the first biotechnology drug, a humanized antibody (omalizumab), which blocks IgE binding but is unable to cause aggregation (36) and which is now used for the treatment of severe asthma.

Mast cells and basophils as the source of many other mediators beyond histamine

In addition to the prompt release of preformed mediators stored in secretory granules including histamine, proteases, and proteoglycans, mast cells also rapidly upon activation form lipid mediators by enzymatic biosynthesis mainly from arachidonic acid, but also from several other fatty acids (37). The main products of arachidonic acid are the prostaglandins and the leukotrienes, the latter first described as slow-reacting substances (SRS). Both products, or their activity, were described in the 1930s, prostaglandins by Ulf von Euler (1905–1983), and the SRS by Fedelberg and Kellaway (38, 39). The initial work on SRS was performed using either cobra venom or antigen stimulation of sensitized rats or guinea pigs where the effect of histamine could be distinguished from that of SRS. It was discovered that in contrast to histamine that gives a rapid response, there was also a product that caused a contraction that was slow in onset but gave a sustained reaction. Hence, this product was named slow-reacting substance (39). Work by Uvnäs in Sweden and Brocklehurst in the UK confirmed the release of SRS activity following anaphylactic challenge, and Brocklehurst named

the activity slow-reacting substance of anaphylaxis (SRS-A) (40). He also drew the conclusion that antigen-antibody activation of mast cells induced a series of enzymatic steps that resulted in the specific release pattern of SRS-A. In 1971, Uvnäs showed that SRS-A was not a prostaglandin (41). More detailed studies of SRS-A as a mediator of immediate hypersensitivity reactions were performed by Priscilla Piper in the United Kingdom (42) and Frank Austen and colleagues in the USA (43). The birth of the leukotriene family came from the work of Bengt Samuelsson and his coworkers at the Karolinska Institutet, Stockholm, who discovered LTB_4 as a new lipoxygenase-catalyzed metabolite in leukocytes. The properties of LTB_4 resembled those of SRS-A, and SRS-A from a mouse mastocytoma was subsequently identified as a glutathione-conjugated metabolite named LTC_4 (44). Both mast cells and basophils synthesize leukotrienes, but in contrast to basophils, mast cells also have the capacity to synthesize PGD_2 (45).

In addition to the release of preformed mediators, it was recognized at the end of the 1980s that mast cells and basophils are potent sources of cytokines and growth factors with multifunctional capacities. These discoveries put mast cells and basophils into a new context as multifunctional inflammatory cells acting not only as effector cells in allergy, but also as regulators affecting a diverse set of immunological and physiological functions. The first study that demonstrated mast cells to be a source of cytokines was published in 1987 by Brown et al. (46) who described mRNA expression and release of IL-4 in mouse mast cells. This study was followed by others that showed the capacity of mast cells to *de novo* synthesize and release other cyto-

kines upon immunological stimuli, including IL-3, IL-5, and IL-6, chemokines, interferon γ , and GM-CSF (47, 48). During this time, basophils were also identified as a source of IL-4 (49) and, as shown by three laboratories a few years later, of large amounts of IL-13 (50–52). Mast cells and basophils not only produce cytokines upon stimulation, but also preform and store cytokines, for example, TNF in their granules (53). Small amounts of IL-4 can also be detected in granules of human basophils (50). This capacity to store preformed cytokines in granules from which they are released rapidly upon stimulation is in contrast to most other cells where a *de novo* protein synthesis of the cytokine is induced leading to cytokine secretion in a delayed fashion.

The first studies of cytokine expression and release from mast cells were performed on transformed mouse mast cell lines or bone marrow-derived cultured mast cells, but they were soon followed by studies on human mast cells as well. Over the last 20 years since the first paper was published on IL-4 released from mast cells, more than 30 different types of cytokines, chemokines, growth factors, and interferons have been shown to be released from mast cells (54). The cytokine spectrum appears to be more restricted to a Th2-like phenotype for basophils (55). For mast cells, the expression very much depends on the context, for example, species, source, type of stimulation, and pretreatment. It is noteworthy to point out that in human diseases, that is, asthma or atopic dermatitis, the percentage of mast cells expressing a specific set of cytokines is often increased and they express different type of cytokines depending on the type of inflammation (56–58).

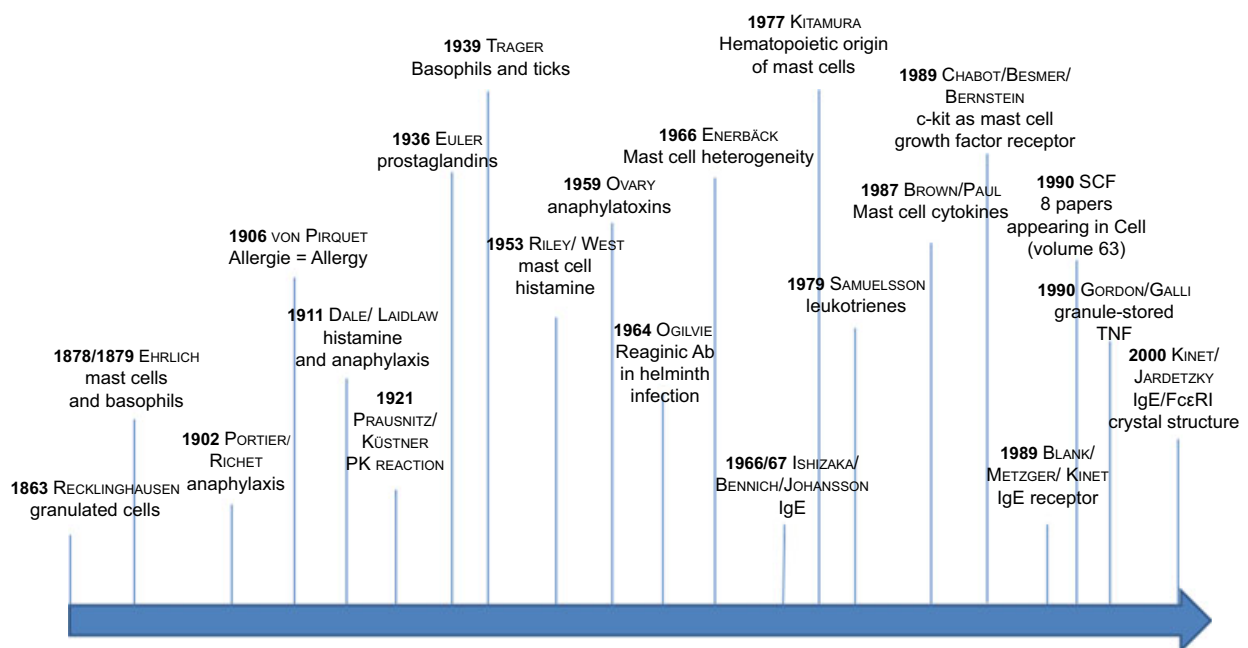


Figure 4 Some milestones in mast cell and basophil research (1863–2000).

Development of mast cells and basophils

Although mast cells and basophils both were discovered in the end of the 19th century, it took a long time until their hematopoietic origin and relationship were deciphered. As other granulocytes, basophils mature in the bone marrow and circulate in the blood as terminally differentiated cells that enter the tissue. Because mature mast cells do not circulate in the blood, their origin was for long uncertain. Paul Ehrlich even suggested that they were a type of fibroblast in the connective tissue. During the 1970s, Yukihiko Kitamura (Osaka, Japan) performed a number of crucial experiments and could demonstrate that hematopoietic stem cells are the origin of tissue mast cells, by transplanting mouse bone marrow cells to irradiated recipients (59). About the same time, Kitamura and his colleagues also discovered two different mouse strains that are mast cell deficient, that is, the *Sl/Sl^d* and *W/W^v* strains (60, 61), where especially the latter has been widely used in animal models to investigate mast cell functions in health and disease (62). The *W/W^v* mouse has a mutation in the *c-kit* gene coding for a tyrosine kinase receptor, Kit (63), pointing to a crucial role for Kit in mast cell biology. The search for the Kit-ligand was intensive for several years, which finally resulted in a unique occasion where eight papers were published in the same issue of *Cell*, demonstrating the cloning and characterization of Kit-ligand, a product of the steel locus mutated in the *Sl/Sl^d* mouse, today commonly referred to as stem cell factor (SCF) (64). The identification of SCF gave a boost to mast cell research, especially investigations on human mast cells, as it now provided a possibility to differentiate and grow human mast cells *in vitro*. In contrast to mouse where IL-3 induces the differentiation of mast cells (65), in humans, IL-3 gives rise to basophils and not mast cells (66). In 1992, four groups published on SCF as a major human mast cell growth and differentiation factor that paved the way for more insights on mast cell biology and regulation of its function (67–70). The ontogeny of human basophils is not fully solved. Work from the mid-1980s suggested a common eosinophil–basophil progenitor (71, 72), while other work pointed to a closer relationship with mast cells (73, 74).

Mast cell heterogeneity

Mast cells were first recognized by their metachromasia when stained with toluidine blue, a staining property that Holmgren and Wilander in 1937 could relate to a high content of heparin in the cells (75). Variation in staining properties provided the first experimental evidence of the existence of subpopulations of mast cells, suggesting heterogeneity. Lennart Enerbäck used different fixation methods to describe different types of mast cells in the rat gastrointestinal mucosa (76, 77). In rodents, mast cells are referred to as connective tissue mast cells and mucosal mast cells. In humans, two distinct types of mast cells were described by Irani and Schwartz based on the expression of neutral proteases (78). One type contains only tryptase and is referred to as MC_T and corresponds in part to the mucosal type. The other type

contains both tryptase and chymase and is referred to as MC_{TC} and corresponds to the connective tissue type. The heterogeneity among mast cells goes beyond their localization and protease content and includes as well differences in expression of other mediators and response to immunological and nonimmunological stimuli (79–81). However, mast cell heterogeneity is not only a matter based on mediator content and release upon stimulation, but might also include heterogeneity in functionality. Mast cells can either be pro-inflammatory, anti-inflammatory, or immunosuppressive (82). Whether this is a reflection of mast cell plasticity or points to the existence of even more mast cell heterogeneity than previously recognized, only future will tell. Whether basophils display a similar degree of heterogeneity, for example, after migration into different tissues during inflammation, is also still an open question.

Mast cells and basophils and their role in parasite infections

While basophils were first described in 1879, for a long time their role remained a mystery. First hints regarding potential roles of basophils were obtained in the 1930s. Thomas Duckett Jones (1899–1954) and John R. Mote described a delayed, transient reaction in patients after repeated injection of a foreign protein in 1934 (83). This reaction was later renamed cutaneous basophil hypersensitivity (CBH), as it became increasingly clear that it involved an accumulation of basophils in the skin. Five years later in 1939 (84), a similar accumulation of basophils was described in the context of parasitic infestation by William Trager (1911–2005). Trager was the first to observe that basophils were involved in acquired immunity against the tick *Dermacentor variabilis*. In his classic 1939 paper, he was able to show that upon repeated exposure of animals to hard ticks, which remain attached to their hosts for several days to weeks, large numbers of basophils are recruited to the attachment site and result in lower engorgement size. William Trager's, as well as subsequent work by others, also points to an important role of (mast cell or basophil-derived) histamine in antitick immunity, as the release of histamine results in itching, followed by identification and removal of the parasite by the host. Subsequent work showed that basophils were not the only cell types involved in antitick acquired immunity, and the relative contributions of mast cells, basophils, and eosinophils became the subject of controversies. Nevertheless, Trager's classical work showed the importance of basophils as a major component of acquired resistance to ticks in cutaneous basophil hypersensitivity. More recently, elegant work from Hajime Karasuyama's laboratory was able to reconcile the apparent contradictory findings by showing that while mast cells and basophils are both required for the manifestation of resistance, only basophils require the presence of receptors for the Fc part of immunoglobulins (FcR) (85). His work showed that in the context of tick infection, mast cells and basophils act independently, are both required for immunity, and cannot compensate for each other. To date, this is one of few examples illustrating an essential, nonredundant function of basophils in immunity.

In the following, it became clear that the role of mast cells and basophils was not limited to ectoparasites, but also played a role in immunity against endoparasites, in particular intestinal helminths. The earliest suggestion that hypersensitivity reactions may play a role in expulsion of helminth parasites from the gut (of sheep) came from D. F. Stewart in 1953 (86). About 10 years later, a few years before the discovery of IgE, Bridget Ogilvie was the first to show the existence of reaginic antibodies in animals infected with helminthic parasites (87). Ogilvie also found that they were 'permanently attached to the skin of the species in which they are stimulated', but were 'incapable of sensitizing guinea pig skin in passive cutaneous anaphylaxis' (see PK reaction and serum factor). As neither IgE nor the high-affinity IgE receptor was known at the time, a link with mast cells and basophils could not be made. Ten years later, however, it had become clear that parasitic helminths were the most powerful and reliable inducers of IgE (88). Jarrett and Miller showed that during infection with *Nippostrongylus brasiliensis*, mast cell numbers increased exponentially during the first 2 weeks after infection, peaking at the time of parasite expulsion (self-cure) (89). It was also clear by then that such mechanisms were dependent on degranulation and histamine release by mast cells, as treatment with antihistamine drugs interfered with parasite expulsion (90). It was not long however, before this exclusive role of mast cells was questioned by work published in 1980, showing that mast cell-deficient mice were able to expel intestinal worms, ascribing instead a key role to intestinal goblet cells producing mucus (91). Since then, the body of evidence describing the roles of mast cells in helminth expulsion has grown considerably in the past decades; most recently, work by David Voehringer, Karasuyama and several other authors has highlighted the additional, nonredundant roles of basophils in antihelminth immunity (55, 92, 93).

Mast cells and basophils as mediators of innate immunity

Since the early discoveries on immunity at the turn of the 20th century, the study of adaptive immunity mechanisms mediated by antibodies and T cells was at the center stage. It took almost another century during which research tried to integrate the fact that cells were also naturally responding to microbial compounds such as LPS, BCG, and zymosan, now also called pathogen-associated molecular patterns or PAMPs, through nonclonal pattern-recognition receptors (PRRs; reviewed in (94)). Following this general trend, research on mast cells and basophils, since the exciting discoveries of IgE and its receptors, had also focussed on the adaptive effector arm studying allergy and to a lesser extent parasite immunology. Yet, as mentioned above, mast cell tissue passive cutaneous anaphylaxis responses could be induced by IgG but also anaphylatoxins, providing early hints regarding mast cells' ability to respond to signals other than immunoglobulins (14). Furthermore, it became clear that mast cells express numerous receptors and produce many inflammatory products with potential effects in tissue responses, host defense mechanisms, and immunoregulation advocating a role of

these cells well beyond allergy. The same can be said about basophils, which can be activated by non-IgE-dependent pathways such as complement (95, 96), bacterial peptides (97), viral (gp-120) (98), and parasitic molecules (e.g., IPSE/alpha-1 from *Schistosoma mansoni*) (99).

Based on this and helped by the availability of deficient mouse models and depletion strategies, an important aspect of mast cell and basophil function worked out in the last 20 years is their role as integral actors of the innate immune system (55, 100). It became evident that mast cells act as sentinels able to rapidly produce mediators with specific tasks in immunity to combat bacterial, parasitic, fungal, and viral infection [reviewed in (101, 102)]. They also play important role in tissue remodeling and repair responses (103).

Mast cells are producers of specific proteases and cytokines involved in innate immunity. For example, several publications have now clearly established that mast cell-derived proteases protect the organism from exogenous (venoms) or endogenous toxins (endothelin-1 and VIP). It also appeared that *via* the production of multiple cytokines and chemokines, mast cells can participate in the inflammatory process and regulate the activity or mobilization of other immune cell populations, thereby directly impacting on additional effector arms of the innate and/or the adaptive immune system (102, 104, 105). For some of these functions, mast cells may also represent a sort of relay station responding to signals emanating from nonimmune effector cells including IL-25, IL-33, or thymic stromal lymphopoietin (TSLP) to drive, for example, Th2 immunity (106, 107). One of the striking features of human basophils is their apparent restriction to pro-Th2 cytokines such as IL-4, IL-13, IL-25 and, in murine basophils, TSLP, which together with the ability to be activated by nonantigen-specific stimulations, has led to consider basophils as a cell type not only important in amplification, but also as initiator of Th2 responses (55, 108). On the other hand, basophil-derived cytokines such as IL-6, VEGF, GM-CSF, and IL-3, similarly to mast cells, point to yet-to-be-explored roles in angiogenesis, tumor immunity, autoimmunity, and hematopoiesis (109).

Concluding remarks

In this review, we retrace some of the important discoveries that have accompanied the description of the Prausnitz and Küstner reaction (Fig. 4), which showed that the factor responsible for anaphylaxis could be transferred from one individual to the other. In particular, we describe the discovery of IgE and the IgE receptors as well as the cell types and mediators responsible for the anaphylactic type of activity. Mast cells and basophils in addition to their role in adaptive immunity via the IgE effector arm are now getting increased attention as essential effectors in innate immune responses with a growing list of mechanisms. This is made possible by the expression of numerous surface receptors enabling them to sense pathogens or danger signals as well as the extraordinary wealth of mediators they produce that has been covered in many recent reviews only some of which can be cited (55, 82, 102, 105, 110–112). Thus, while researchers like Prausnitz and

Küstner had in mind to uncover the mechanisms of anaphylaxis and allergy, it is well beyond these mechanisms that a century of research has led us. In fact, it has become clear that these cells are not only culprits, but also versatile effectors able to exert protective functions for the organism either directly by flooding the organism or tissues with a variety of specific mediators, but also by functioning as cellular relays to regulate immune functions in close collaboration with other immune effector cells. Given that they can produce a variety of products potentially dangerous for the organism, it is also clear that their inappropriate activation will promote pathology. It will now be the researchers' task for the upcoming century to translate the acquired knowledge into novel therapeutic strategies aiming to prevent or to the contrary support their action.

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Author contributions

All authors have contributed equally to this review.

Conflict of interest

All authors declare that they do not have any conflict of interest.

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