News in Cellular Allergology: A Review of the Human Mast Cell and Basophil Granulocyte Literature from January 2013 to May 2015

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Key Words

Allergy · Basophils · Mast cell degranulation · Mast cell protease · Mast cells · Maturation

Abstract

Mast cell activation releases the mediators associated with type I allergy. As such, the study of mast cell activation is critical for understanding the allergic reaction, and for developing methods to control it. Importantly, another ligand receptor pair (compound 48/80 and MRGPRX2) that activates mast cells in addition to allergen-IgE-FcεRI has been identified. As mast cells mature in tissue from hematopoietic stem cells, their physiology and pathophysiology is difficult to study. Mast cell lines and mast cells cultured from stem cells are often studied instead of tissue mast cells. There has been some progress in the description of the mechanism of the activation of mast cells, substances limiting mast cell activation and in the catalogue of proteases that mast cells express. Basophil granulocytes express FcεRI, bind IgE and respond to allergen crosslinking in a very similar fashion to mast cells. In the recent literature, basophils were mistakenly described as antigen-presenting cells; this has convincingly been disputed in a number of subsequent publications. Their function in physiology and pathophysiology is not known, but they are frequently used to docu-

ment allergic sensitisation in the basophil activation test. Significant progress has been made in documenting the relevance of basophil activation as a second-line test in allergy diagnosis. Basophil reactivity and sensitivity may reflect symptom severity and allergen threshold, and are used to document and monitor allergy. The physiology and pathophysiology of allergic effector cells remain an important area of research.

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An Update on the Role of Mast Cells in Allergic Response

Mast cells may have developed 500 million years ago, as man shares cells secreting heparin and histamine in response to compound 48/80 with the urochordate sea squid *Styela plicata* [1]. In a recent transcriptome analysis mast cells were shown to share many features with non-leukocyte cells [2], which makes them rather unique. MRGPRX2, the receptor for compound 48/80, was among the novel markers of mast cells not expressed by blood basophils [3]. Mast cells derive from hematopoietic stem cells that mature in tissue. For this reason they are difficult to study; both immortalised mast cell lines and primary cultures of mast cells derived from stem cells are

used for the study of the function of mast cells *in vitro*. In a comparison of primary human mast cell culture protocols [4], mast cells derived from CD133+ stem cells from peripheral blood [5] were more versatile in secreting both histamine and cytokines, and hence the most mature. The generation of arachidonic acid metabolites is a major cause of asthma symptoms [6] and mast cells cultured with low-density lipoprotein as a lipid source depend on both adipose triglyceride lipase or cytosolic phospholipase A2 for generation of these fatty acids [7]. The distribution of long- and short-chain polyunsaturated fatty acids in culture medium modified the inflammatory profile (reactive oxygen species, IL4 and IL13 generation) of mast cell lines LAD2 and HMC.1 [8]. As an alternative to primary mast cells, the human mast cell line LAD2 has been available since 2003; it has been used extensively to study receptor expression, cell signalling and degranulation [9].

Mast Cell Priming and Activation by Exogenous Substances

IL33 is a survival factor for mast cells [10] that does not induce degranulation of mast cells or basophils, but is released during activation of these cells [11]. TSLP (thymic stromal lymphopoietin) and IL33 synergise with IgE to enhance Cys-LT, but not PGD2 synthesis in human cord blood-derived mast cells [12]. Mast cell tryptase and chymase mature IL33 to a more potent form lacking the first 95–108 amino acids, which activates ILC2 30-fold more than the native IL33 does [13]. An acute response to IL33 results in neutrophil recruitment by human mast cells [14], but after 72 h IL33 induces a hyporesponsive phenotype in murine and human mast cells through MyD88-mediated downregulation of phospholipase C1 and Hck [15].

Mast cells recognise an invading virus through intracellular virus sensors [16, 17]. Human influenza A virus and respiratory syncytial virus infect and activate mast cells, but do not amplify well in them [18, 19]. Pre-treatment with TLR2 agonists inhibits IgE-mediated activation of LAD2, whereas simultaneous activation through TLR2 and IgE synergises IL8 release [20]. Co-stimulation of peripheral blood-derived mast cells through IgE and TLR4 or TLR6 induces the production of IL13 [21].

In addition to IgE, basic secretagogues including compound 48/80, which also activates test cells in invertebrates [1], can activate mast cells through the receptor

MRGPRX2 [3]. This receptor is the target of a number of small molecules like the neuromuscular blocking agents atracurium and rocuronium, associated with anaphylactoid and pseudo-allergic reactions, and may be the receptor-mediating response in some drug allergies where it can be difficult to document drug-specific IgE.

The antimicrobial peptide Api88 from honeybee hemolymph induced mast cell activation [22]. Pleurocidin, a fish cationic antimicrobial peptide, activates mast cells to secrete CCL2 and CCL4 [23]. The human cathelithicin LL-37 activates degranulation and cytokine secretion, but not the synthesis of arachidonic acid metabolites [24].

The tryptophan metabolite kynurenine binds the aryl hydrocarbon receptor on mast cells to enhance degranulation [25]. Similarly, the β -blocker metoprolol in combination with either the ACE inhibitor ramipril or bradykinin increased the sensitivity of mast cells [26]. This mast cell priming was particularly effective when the Fc ϵ RI engagement was suboptimal, as is often the case *in vivo*. Release of zinc from LAD2 cells was induced by Fc ϵ RI crosslinking but partially independent of degranulation [27].

The anti-allergic mast cell stabilisers lodoxamide and bufrolin target GPR35, similar to cromolyn and nedocromil sodium, are more promising drug candidates as they are several orders of magnitude more potent [28]. A number of other factors inhibiting mast cell activation are listed in table 1.

Signalling in Mast Cells through Fc ϵ RI and Factors Mediating This Process

The best-studied process mast cells are involved in is degranulation in response to IgE crosslinking by allergens. A number of other functions have been ascribed to mast cells on the basis of research done in mast cell-deficient mice with spontaneous mutation-deleting kit, which also affect a range of other genes and hence are not as specific as proposed [29]. The transcription factors PU.1 and GATA1 are involved in Fc ϵ RIa transcription, and GATA2 modulates Fc ϵ RIb transcription. Suppression of these transcription factors leads to decreased expression of Fc ϵ RI and IgE-mediated degranulation [30]. The microRNA miR-142-3p enhances Fc ϵ RI-mediated activation, and can be inhibited by overexpression of Dicer, an enzyme in the miRNA pathway [31].

Mast cells can form an antibody-dependent secretory synapse based on either IgG or IgE, in which degranulat-

Table 1. Mast cell inhibitors

Substance	Effect	Reference No.
Prostaglandin E	Binds the EP2 receptor	109
Vitamin D3		110
Allergen-1	Inhibits IgE-mediated activation	111
Artesunate	Inhibits Syk phosphorylation	112
Cinnamon extract		113
Benzodiazepine	Binds the adenosine A(2B) receptor	114
Piceatannol		115
Homoisoflavone	Inhibits the Syk pathway	116
Tetramethyl-luteolin		117
Caffeic acid phenethyl ester	Limiting phosphorylation of MAPK, c-Jun and NF- κ B	118
Clostridium difficile toxin B (TcdB)	Inactivating Rho-family GTPases by glycosylation	119
Single-walled carbon nanotubes		120
Water-soluble C70 fullerenes conjugated to inositol		121

ing substances are present at a high concentration [32]. IgE stabilises Fc ϵ RI on mast cells, with varying Fc ϵ RI concentration at a very high and varying sensitivity at a very low concentration of IgE [33]. Mast cell expression of Fc ϵ RI and histamine release was optimal at 250 ng/ml of IgE in the medium. Synthesis of prostaglandin D2 was less affected by the IgE concentration [34]. Once the signal of allergen crosslinking Fc ϵ RI reaches inside the cell, Syk stimulation has to override the phosphatase activity of SHP-1 and SHIP [35]. Cytoplasmic free Fc ϵ RIb may function as a negative regulator of Fc ϵ RI activation by sequestering lyn kinase [36]. A truncated form of Fc ϵ RIb containing a calmodulin-binding domain may be involved in intracellular poisoning of mast cells for degranulation [37]. Mitochondrial STAT3 is induced by ERK1/2 to induce oxidative phosphorylation that precedes degranulation [38]. Inhibition of STAT3 signalling in mast cells leads to impaired Fc ϵ RI-mediated proximal and distal signalling, as well as reduced degranulation [39].

The Protease Expression Palette of Mast Cells

Mast cell chymase has been proposed as a differentiation marker for connective tissue mast cells [40, 41]. However, given enough time, the gene for chymase is expressed by 100% of cultured mast cells [42, 43]. Chymase may thus be a marker of mast cell age, rather than a differentiation marker. If this is true, the fraction of mast

cells expressing chymase could be used as an indicator of the turnover of mast cells in that particular tissue.

The mucosa of patients with food allergy and gastrointestinal symptoms contains elevated levels of tryptase [44]. In addition to the lineage-specific expression of tryptase, human mast cells express granzyme H [45]. HMC-1 expresses metalloproteases of the A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family members 5, 6 and 9 [46].

Progress in Research on the Function and Diagnostic Application of Human Blood Basophil Granulocytes

Evidence for a role of basophils in allergic or other diseases has been scant – in part hampered by the large difference in immune biology and basophil function between man and mouse. Basophils share a number of features with mast cells, in particular they are circulating cells expressing functional Fc ϵ RI that degranulate upon allergen crosslinking. A recent gene expression study found little relation between basophils and mast cells beyond this observation [2]. Whereas mast cells express genes shared with cells not primarily dedicated to immune function, blood basophils were typical myeloid immune cells. The ready availability of blood basophils has made them a choice *ex vivo* tool for elucidating the response to IgE crosslinking in the basophil activation test (BAT), which was the subject of a recent EAACI position paper [47].

Factors Affecting Basophil Activation

Both the nature of the allergen and the condition of blood basophils contribute to basophil activation. The heavily glycosylated allergen Hev b 2 may activate basophils through the carbohydrate moiety [48]. Ammonium persulfate oxidises human albumin to create an allergen that sensitised hairdressers' basophils responded to specifically in BAT [49]. Additional allergens identifiable by BAT are listed in table 2.

A major advantage of BAT is that recombinant allergens (that have to undergo expensive and extensive GMP for use in man) can be used as it occurs *ex vivo*. A recurrent concern is the presence of LPS in such preparations. Only an unnaturally high LPS concentration (>200 ng/ml) elevated CD63 upregulation and histamine release from allergen-stimulated basophils [50]. An LPS contamination <50 ng/ml of allergen preparations may thus not influence the outcome of a BAT.

Aspirin enhances the phosphorylation of Syk to intensify the degranulation of basophils [51]. Escalating doses of sub-threshold allergen, however, induce anergy to FcεRI-mediated activation in blood basophils [52]. Ingestion of the common dietary isoform of vitamin E, γ-tocopherol, significantly decreased the CD63 and CD203c reactivity of basophils *ex vivo* of mite-allergic patients [53]. The ingestion of ligands of nicotinic acetylcholine receptors on basophils inhibited FcεRI-mediated upregulation of CD203c [54].

Progress in the Diagnosis and Monitoring of Allergy by Basophil Activation

The provocation outcome of wheat-sensitised patients could be predicted with a combination of basophil sensitivity and s-IgE to wheat allergen [55]. Spontaneous CD203c expression on blood basophils and basophil reactivity correlate with the degree of tolerance among patients with cow's milk allergy [56]. Food-allergic patients sensitised to lipid transfer proteins could be sensitised to *Cannabis sativa* or *Humulus*, and were more than 10-fold more sensitised to cannabis extract [57]. The discovery of novel strong sensitising allergens suggests that the strongest primary sensitising allergens may yet to be discovered.

Purified natural and recombinant Pan b 1 at 0.5 µg/ml (15 µM) activated basophils to a similar degree as 1 µg/ml of shrimp extract [58]. BAT with molecular allergen Ara h 2 is good at identifying true peanut-allergic Mediterranean

Table 2. Allergens characterised by BAT reactivity

Allergen	Reference No.
Pholcodine	122
Iomeprol	123
Carboplatin	124
Piperacillin	125
L-asparaginase, treatment of paediatric leukaemia	126
Atracurium	127
Tick bite	128
α-Gal, cetuximab	129
Carminic acid	130
Iroko wood	131
Sesame (tahini sauce)	132
Pristinamycin	133
Formaldehyde	134

nean patients and distinguishing them from peach-allergic patients [59]. Ara h 2 and Ara h 6 may be allergologically redundant, and the native, purified allergens independently account for most peanut sensitisation of patients in Colorado [60].

The basophil sensitivity of peanut-allergic children was more reproducible than a double-blind, placebo-controlled food challenge [61], and severe peanut allergy was associated with a higher basophil sensitivity [62]. Change in basophil sensitivity can be assessed by measuring only a single allergen concentration [47]. In a two-step approach for diagnosing peanut allergy in the LEAP study, if only cases without clear first-line test results were investigated by BAT, the number of food challenges was reduced by 97% [63]. In the same study the reactivity of basophils correlated with symptom severity, whereas basophil sensitivity was associated with the allergen threshold at which allergic subjects responded [64]. Supporting this, symptom severity during failed oral food challenges correlated with basophil reactivity [65]. Basophil and mast cell activity *in vivo* depends on both the IgE affinity and concentration, and also on competing IgG4 to the same allergen [66]. Although hydrolysates of peanut flower appeared to reduce the molecular weight of allergens, the basophil reactivity of peanut-allergic patients was not reduced by this treatment, suggesting that IgE epitopes were predominantly linear, and peptides containing IgE epitopes were resistant to degradation [67].

Light-sensitive allergens like fluoroquinolones should be prepared and tested under low light conditions as light

reduces their allergenicity [68]. The predictive value, especially the negative predictive value of BAT, in the diagnosis of anaphylaxis to neuromuscular blocking agents is very good [69]. BAT should always only be considered after skin testing and s-IgE determination have been explored, unless there is evidence of the superiority of BAT. BAT is the only useful test during the diagnosis of rocuronium-related responses [69].

The identity of sensitising insects in patients with hymenoptera venom allergy but without s-IgE to venoms could be determined with BAT [70]. In a head-to-head comparison, CRD (component-resolved diagnosis) could not completely replace BAT in the diagnosis of *Vesputula vulgaris* venom allergy in patients negative for other first-line tests [71]. Four of 149 patients could only be diagnosed by BAT. BAT with recombinant insect venom allergens improved specificity compared with s-IgE detection [72].

There was good concordance ($k = 0.593$) between ASST (autologous serum skin test) and BAT in the diagnosis of chronic urticaria [73]. The level of spontaneous CD203c expression on basophils of patients with chronic urticaria associates with disease intensity [74]. Naturally occurring auto-anti-IgE binding of both free and FcεRI-complexed IgE is found independently of the allergic status (and of the diagnosis of chronic urticaria?), and can both inhibit and accentuate basophil reactivity [75]. Patients with chronic urticaria may be sensitised to double-stranded DNA [76].

Exploring the Mechanism of AIT with Basophil Activation

Basophil sensitivity is reduced unspecifically during rush immunotherapy [77], in a process that can be reproduced ex vivo [52]. Basophil sensitivity reflected an increase in the protection afforded by subcutaneous immunotherapy (SCIT) with insect venom after 6 weeks and 1 year of treatment [78]. In grass pollen-allergic patients, basophil sensitivity to allergen decreases up to 500-fold during up dosing of subcutaneous allergen immunotherapy [79] and predicts the efficacy of SCIT. Similarly, basophil reactivity through CD203c at a submaximal allergen concentration was reduced by allergen immunotherapy [80]. Basophil sensitivity was significantly decreased by SCIT of grass pollen-allergic patients [81]. The effect of SLIT (sublingual immunotherapy) was markedly less than that of SCIT. Surprisingly, BAT reactivity increased during a course of SLIT [82].

Basophil Function during Treatment Modulating IgE or FcεRI

Therapy with anti-IgE reduces the activating signal and does not per se inhibit mast cell or basophil activation [83]. BAT reactivity was reduced by treatment with omalizumab [84]. Anti-IgE treatment disposes patients to be more sensitive to anti-IgE antibody, with more reactivity as well as greater sensitivity [85]. CD203c is a dynamic marker of basophil reactivity that is elevated in allergic patients before allergen stimulation, and is depressed during anti-IgE treatment in patients [86].

In addition to treating severe allergic asthma, anti-IgE is useful in the treatment of chronic urticaria [87, 88]. There are conflicting results regarding the effect of anti-IgE on the concentration of blood basophils during treatment; it appears to increase (normalise) in adults suffering from chronic urticaria who present with a reduced number of blood basophils [83], but may be reduced in children treated for severe asthma [89].

DARPin selected to disrupt the IgE-FcεRI interaction are more efficient at limiting IgE-mediated type I hypersensitivity response, and can prevent anaphylaxis in a humanised mouse model expressing human FcεRI [90]. DARPins were 10^2 - to 10^4 -fold more effective at disrupting the FcεRI-IgE complex than omalizumab. The efficacy of IgE removal is not dependent on the affinity of the inhibitor but rather on its epitope specificity. A DARPin construct crosslinking FcεRI and FcγRII inhibited basophil activation [91]. This effect was increased by increasing the affinity of DARPin for FcγRII [92].

Progress in Elucidating the Biological Relevance of Basophils in Man

TSLP activates basophils in bone marrow, blood and allergen-challenged lung [93]. Basophils are recruited to the site of allergic inflammation. This was confirmed by the detailed study of lung and blood basophils after allergen challenge in allergic patients, where accumulation of CD123+CD203c+ basophils in bronchoalveolar lavage corresponded with a decrease in the number of blood basophils [94]. The basophil sensitivity of patients with allergic rhinitis was more reproducible than the total nasal symptom score or nasal peak flow in challenge tests [95]. Local allergic rhinitis is a condition predominating in southern Europe. It can be diagnosed by BAT [96], which is both less time consuming and a more reproducible procedure than nasal provocation [95]. Blood basophils of

α -gal-sensitised individuals upregulated CD63 in vivo concomitant with the appearance of allergic symptoms after the ingestion of red meat [97].

Long-term (60 min) exposure to sub-threshold doses of anti-Fc ϵ RI antibody or allergen enhances basophil mediator release to the non-Fc ϵ RI stimuli MCP-1, FMLP and leukotriene B4 [98]. Basophils express all TLRs, and TLR4 and TLR9 activation synergises with Fc ϵ RI-activation to enhance IL4 and IL8 production, respectively [99]. Blood basophils constitutively express B cell activating factor BAFF, which is upregulated by TLR2 ligands and fMLP, but not by the TLR4 ligand LPS and not by allergens [100]. Purified basophils secrete TNF- α upon anti-IgE stimulation [101].

Basophils Do Not Present Antigen to T Cells

A major stir was caused by three reports in *Nature* about the antigen-presenting capacity of basophils. This has been refuted elegantly [102] and shown to be due to the confusion of basophils with plasmacytoid dendritic cells [103, 104]. It is further refuted as basophils did not express the functional HLA class II molecules CD80 or CD86 [105, 106]. Basophils, in contrast to human mast cells [107], do not drive CD4 T cells toward an IL22-pro-

ducing phenotype [105]. Basophils do not support Th17 T cell growth as they do not express costimulatory molecules required for interaction with T cells [108].

Concluding Remarks

Allergic effector cells are activated by allergen through Fc ϵ RI – and respond in a remarkably similar way by releasing substances associated with the type I allergic response. Mast cells can also be activated through MRGPRX2, and the study of mast cell response in culture remains an important tool for understanding processes in allergy. Blood BAT is a useful second-line test for allergic sensitisation, and for assessing the effect of treatment that changes IgE to modulate allergy. During the diagnosis of allergy, blood basophils should be used in conditions that make them as sensitive a tool as possible. For the monitoring of allergic disease, blood basophils should reflect the in vivo situation as closely as possible. A number of factors that strengthen and limit basophil activity, and hence may affect basophil performance, have recently been described. Further research into allergic effector cells may result in drugs that interfere with the acute response, and in improved tools for diagnosing and monitoring allergy.

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