



Review

The two faces of mast cells in food allergy and allergic asthma: The possible concept of Yin Yang [☆]

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ABSTRACT

The purpose of this review is to discuss the role of mast cells in allergic inflammation. We have focused on inflammation associated with allergic asthma and food allergy. Mast cells are ‘first line of defense’ innate/adaptive immune cells and are widely distributed in tissues in surfaces exposed to the environment. Especially in allergic settings mast cells are extensively studied, as they can be activated to release a wide range of mediators by allergen-IgE specific triggers. In addition, in allergic inflammation mast cells can also be activated non-allergic triggers. Recent studies revealed that mast cells, besides the classical role of pro-inflammatory effector cell, have also emerged as modulators of allergic sensitization and down-regulators of allergic inflammation. Therefore, mast cells can be regarded as ‘Ying Yan’ modulators in allergic responses in intestinal tract and airways. This article is part of a Special Issue entitled: Mast Cells in Inflammation.

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1. Introduction

Over the past decades the prevalence of allergic diseases, such as asthma and food allergy, has increased dramatically. Allergic diseases arise as a result of unwanted and exaggerated immune responses to harmless proteins, also called allergens. A certain percentage of the population experiences adverse immunological reactions to these allergens that in non-allergic individuals only induce tolerance. This failure of tolerance is believed to result in the induction of an active immune response to allergens. One of the first events in the pathogenesis of allergy is capture and presentation of the allergen by antigen presenting cells at mucosal sites in the airways or intestinal tract and in draining lymph nodes, respectively. This will lead to the development of a large population of antigen-specific T helper 2 cells [1]. Activated allergen-specific T cells are found in the circulation of allergic patients. These T helper 2 cells, once encountering the allergen, will in turn activate B cells via the release of cytokines such as interleukin 4 (IL4) and IL13 critical for the development of plasma cells that will start the production of allergen specific immunoglobulin E (IgE) as well as IgG [1–3]. These IgEs will bind to their receptor FcεRI on basophils and extravascularly to mast cells. Allergen-induced cross linking of the IgE bound FcεRI results in the activation of mast cells. The release of mast cell derived pre-stored vasoactive amines,

such as histamine and serotonin, and cytokines, such as tumor necrosis factor α (TNFα), as well as produced cytokines and arachidonic acid metabolites, such as leukotrienes and prostaglandins. IL4, IL9 and IL13 will further enhance the propagation of the production of IgE and allergic inflammation in general. IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) are also produced and are important for growth and differentiation of eosinophils. Eosinophils are immune effector cells that can leave the circulation through the interactions of adhesion molecules due to chemo-attractants and migrate to the site of inflammation (For a review see Ref. [3]).

Mast cells play a critical role in allergy and this makes them attractive candidates for targeting allergic diseases. This review will focus on the central role of mast cells in inflammation associated with allergy, specifically in (allergic) asthma and food allergy.

2. Allergic asthma

Asthma represents a chronic inflammatory airway disease characterized by episodes of reversible airway narrowing, bronchial hyperresponsiveness and chronic pulmonary inflammation. Asthma can be classified either according to frequency of symptoms (clinical) or according to triggers causing the airway symptoms. Clinical classification of asthma severity consists of four types [4]. Intermittent: patients suffer less than once a week from symptoms having a forced expiratory volume in 1 s (FEV1) of more than 80% predicted. Mild: patients suffer more than once per week, but less than once per day from symptoms having a FEV1 of more than 80% predicted. Moderate persistent: patients suffer daily from symptoms having a FEV1 of 60–80% predicted. Severe persistent: patients suffer daily

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from symptoms associated with nighttime symptoms and having a FEV1 less than 60% predicted [5].

Asthma may also be classified as atopic, where symptoms are induced by allergens or non-atopic where symptoms are induced by non-specific triggers. Workplace exposures are the world's most common cause of this so-called occupational asthma and 15–23% of new-onset asthma cases in adults are work-related [6]. During remission, patients suffer from symptoms such as nighttime coughing and shortness of breath when exercising [7,8]. Exacerbation of the disease consists of an acute asthma attack. During an asthma attack patients are short of breath, suffer from chest tightness and have a rapid heart rate (tachycardia) and wheezing can occur [7,8]. In the pathology of asthma, the inflammation in the airways is characterized by several inflammatory cells such as eosinophils, B lymphocytes and T-lymphocytes, however, the role of mast cells is undisputed (see Section 4).

More than 300 million people worldwide are diagnosed with asthma. Developed and westernized countries have higher asthma prevalence [9,10]. The prevalence of asthma has been increasing since the 1980s, particularly in children and young adults. To date, asthma is the most common chronic disease in children. Asthma is associated with a western-life style and this has been shown clearly for example by the rapid increase in the prevalence of asthma in children who have been migrated from developing countries to developed countries [11]. Four reasons could be involved in the increase of prevalence of asthma associated with life style [12]. First, exposure to house dust mite (major allergen in asthma) has increased due to modern housing and more time indoor. Secondly, exposure to a wide range of microorganisms has changed because of improved hygiene and wide spread antibiotic used. Thirdly, the prevalence of obesity has increased in children. Last but not least, changes of the western diet (decline of fresh vegetables, raw materials).

Classically, asthma has been regarded as a bronchoconstrictive disease and is predominantly treated with bronchodilators, such as β_2 agonists [13]. Currently, the chronic inflammatory process is the target of treatment with inhaled corticosteroids. For the management of asthma, patients take regularly inhaled corticosteroids with or without long acting β_2 agonists. However, 50% of the patients are poorly controlled and there is still a need for new therapies. Blocking the synthesis or receptor for a single mediator (such as lipid mediators) involved in asthma seems unlikely to be very effective. Anti-leukotrienes that block cysteinyl leukotriene receptor 1 (CysLT1), are currently used in therapy, but these drugs are less effective than inhaled corticosteroids [13]. In addition, leukotriene B4 (LTB4) receptor antagonists had shown no effect in mild asthma [14]. Compounds targeting another arachidonic metabolite and its receptor, prostaglandin D2, are now in clinical development for asthma. Since cytokines play a crucial role in orchestrating chronic inflammation, they have become important targets for asthma treatments. However, over 50 cytokines have been implicated in asthma and several cytokines and chemokines (IL4, IL5, IL13, TNF α , C-C chemokine receptor type 3(CCR3)) blocking antibodies are now in clinical development but clinical studies in asthmatic patients have been disappointing [13]. Antibodies blocking IgE are only used in the treatment of patients with severe asthma, due to high cost of treatment and the unclear mechanism of clinical efficacy (for a review see Ref. [15]). The most promising anti-inflammatory therapy is by the use of phosphodiesterase (PDE)4 inhibitors targeting T cells, eosinophils, smooth muscle cells and epithelial cells. Roflumilast, an oral PDE4 inhibitor, demonstrated inhibitory effects on allergen-induced responses in asthma similar to low doses of inhaled corticosteroids [16]. A different approach is specific immune therapy, whereby asthmatic patients are exposed in a controlled way to allergens or allergen-peptides, (either subcutaneously or sublingually) to induce tolerance and desensitization. Some efficacy by this approach has been demonstrated, however, longer studies and

comparison with inhaled corticosteroids are needed to determine efficacy [13].

Targeting mast cells in allergic asthma is directed toward mast cell sensitization, stabilization and their mediators released. Interestingly, besides acting as a smooth muscle relaxant, β_2 receptor antagonists have been shown to stabilize mast cells [17,18]. Other mast cell stabilizers, such as nedocromil and cromoglycate have only modest effects in allergic asthma [19,20, for a review see Ref. 18]. Today, mast cell stabilizers are not used in therapy.

To targeting mast cell sensitization the above mentioned anti-IgE-antibody therapy can be regarded. The humanized anti-IgE-antibody, omalizumab, did not show expected results and are only recommended to use in difficult-to-treat asthma [21–23, for a review see Ref. [24]].

As described above, several compounds have been developed to target mast cell mediators such as leukotrienes, prostaglandins and cytokines, however, none of these compounds can beat the corticosteroids.

3. Food allergy

Food allergy is a growing problem in Western Europe and the USA. Intolerance or hypersensitivity reactions toward food or food additives can result in adverse reactions after ingestion of a particular food (for a review see Ref. [25]). Food hypersensitivity reactions develop in genetically predisposed individuals associated with failure in the development or breaking down of tolerance. Clinical symptoms may involve dermatitis, respiratory distress and gastrointestinal symptoms such as nausea, diarrhea and stomachache and can even lead to a systemic anaphylactic reaction [26]. Food allergy, in contrast to food intolerance, is immunological hypersensitivity reaction mostly due to an inappropriate IgE- or non-IgE-mediated immune response. IgE-mediated food allergy accounts for the majority of food allergic reactions [26].

Typical foods accounting for food allergy are: cow milk, egg, peanut, tree nuts, soy, wheat, shell fish and fish proteins [27]. The prevalence of food allergy is the greatest during the first years of life where it affects around 8% of infants younger than 3 years of age [28]. Uncontrolled penetration of antigens through the not yet fully developed mucosal epithelial barrier of the intestinal tract might play a role in the increased prevalence during early life [27]. In this age group cow milk allergy is the most common type of food allergy. About 80% of these children develop clinical tolerance at the age of 5, however, this group is at risk to develop allergic asthma at a later age [27–29]. In adults, peanut hypersensitivity is the most common, severe and dangerous food allergy [30,31]. Peanut allergy remains for life and the prevalence rates exceed 1%.

Allergic reactions to food proteins can also occur independent of IgE. To date the mechanisms underlying these reactions are not clear. It has been suggested that T cells play a role in the immunopathogenesis as in cell-mediated or delayed type hypersensitivity reactions [32]. Studies performed in our group suggest the involvement of immunoglobulin free light chains (IgLC) in cow milk allergy [33,34].

The only remedy in food allergy is strict avoidance of allergic food components determined after a skin prick test. In several clinical trials treatments with humanized recombinant anti-IgE antibodies have shown to increase the threshold of sensitivity to peanut allergens [35]. However, in order to cure food allergy, re-education of the intestinal immune system is necessary to establish oral tolerance. This can be realized by performing allergen-specific immunotherapy. Recent reports have demonstrated partial success with oral immunotherapy in the treatment of food allergy [36–38]. Other strategies with immuno-modulating dietary interventions, such as pre- and probiotics, are currently under research in preclinical and clinical studies [39–41].

4. Mast cells in allergic inflammation

The role of mast cells in allergic inflammation has extensively been studied [42,43]. Triggering of mast cells and subsequent release of pre-stored mediators play an important role in the immediate phase of the allergic reaction resulting in vasodilatation, edema formation and/or bronchoconstriction. Through the production and release of chemotactic and other pro-inflammatory cytokines from mast cells, other non-specific (eosinophils) and allergen-specific (T cells) inflammatory cells infiltrate and get activated resulting in the late phase response.

Basophils share several characteristics with mast cells and represent less than 1% of peripheral blood leukocytes. They have been ignored for a long time and were often considered to play a minor role in allergic reactions. However, now it is widely acknowledged that basophils like mast cells respond to IgE-dependent stimuli and are involved in the onset, the effector phase and exacerbations of allergic (T helper 2 cell-mediated) responses. Basophils are often recruited to the site of allergic inflammation and release histamine, leukotrienes C4 and T helper 2 cytokines and play a role in T helper 2 cell differentiation. In addition, they contribute to immunoglobulin synthesis and can present antigens to T helper cells. [For reviews see Refs. [44,45]]. The role of basophils in allergy is beyond the scope of this review.

As mentioned before, there is a prominent role for mast cells in allergic asthma. In the healthy human lung the major mast cell type is tryptase positive, whereas 20% is double tryptase and chymase positive [46]. Tryptase positive mast cells are predominantly found at mucosal sites. In contrast, tryptase and chymase positive mast cells are located in the skin and submucosa, protected from external triggers [47]. It is generally believed that the microenvironment is important for the phenotype of mast cells and changes in this microenvironment (for example during allergic inflammation) can induce changes in mast cell type. The two mast cell phenotypes functionally differ: tryptase and chymase positive mast cells seem to be more responsive to allergic triggers when compared to only tryptase positive mast cells. Recently it was demonstrated that increasing asthma severity is associated with an enhanced shift toward tryptase and chymase positive mast cells in airway mucosa [48]. In addition, it was suggested that these mast cells contribute to the increased level of PGD2 in bronchoalveolar lavage fluid of severe asthmatics.

The role of mast cells in food allergy is indicated by high levels of histamine, TNF α , IL5 and tryptase in serum, intestinal lavage fluid and stool samples of patients suffering from food allergy [49,50]. Impairment of intestinal barrier function is of importance in food allergy and it has been shown that inflammation enhances intestinal mucosal permeability by mast cell-dependent mechanisms [51,52]. As a result intestinal mast cells can contribute to an ongoing inflammation due to enhanced influx of potential allergens and harmful microbes into the intestinal tissue [50]. Indeed, *in vitro* studies using epithelial cells, have shown that human chymase can induce increased intestinal permeability [53]. Mast cell degranulation in the intestinal mucosa has been demonstrated in food allergic individuals [54]. Furthermore, it has been shown that IgE-stimulated mast cells trigger enteric nerves resulting in pain and diarrhea [52,55]. The development of oral antigen-induced diarrhea in mice is associated with a marked intestinal mucosal mast cell degranulation.

As described for the human lung, tryptase and chymase positive mast cells are found in the submucosa of the intestinal tract, whereas tryptase positive mast cells are located in the mucosa [56]. To our knowledge, not much is known about the mast cell phenotype involved in food allergic patients. Based on the direct effects of human chymase on epithelial integrity, however, it is tempting to speculate that the tryptase and chymase positive mast cell population is responsible for the food allergy symptoms such as decreased barrier function and diarrhea.

The role of mast cells in the pathogenesis of allergic asthma and food allergy has been studied in different animal models, especially using genetic mast cell deficient mice (WBB6F1-Kit^{W/W^v} or C57BL/6-Kit^{W-sh/W-sh}) and mast cell-reconstituted mice [57–60]. In these studies, mast cells have been shown to either directly or indirectly enhance the magnitude of several features of allergic asthma: airway hyperresponsiveness, infiltration of leukocytes, mucus production and tissue remodeling. However, in experimental setting where high doses of antigen and adjuvants were used to induce allergic asthma no contribution of mast cells was detected.

Mice deficient in mast cell deficient or mast cell chymase show enhanced intestinal barrier function [53]. To our knowledge only one study in mast cell deficient and reconstituted mice is performed in a murine model for food allergy, where it was shown that mast cells are important in promoting the development of peanut-induced intestinal responses [57]. All studies in mast cell deficient mice do not exactly pinpoint where mast cells play a role in the pathogenesis of allergic inflammation. Therefore, below we will describe the current knowledge of the role of mast cells in the sensitization and effector phase of allergic inflammation as well as their possible role in suppression of the allergic inflammation.

4.1. Involvement of mast cells in sensitization to allergens

It has been hypothesized that mast cells can be involved in the process of sensitization to allergens because of their role as regulators of epithelial barrier integrity. In the gastrointestinal tract, it has been demonstrated that non-specific mast cell activation (for example chronic stress) can lead to an increase epithelial permeability leading to a higher exposure to allergens and thus induction of sensitization to food allergens [61,62]. In addition, studies in mast cell deficient mice have shown that mast cells are important in the recruitment of dendritic cells, in the induction of major histocompatibility complex-I (MHC-I) dependent T cell priming and proliferation of CD4+ and CD8+ T cells [63]. Mast cell-derived TNF α induces the migration of T cells to draining lymph nodes at sites of inflammation demonstrating a role for mast cells in the processing of environmental allergens [64]. Furthermore, mast cells are proposed to become antigen-presenting cells for T cells due to factors from the micro-environment that induce the expression of MHC class II on mast cells [65]. For instance the TLR4 ligand, lipopolysaccharide, induces an increased number of MCHII-expressing mast cells in lymph nodes of mice [65]. Mast cells are able to produce and release IL4 and IL13. These cytokines promote Ig class switching and IgE production. Finally, it is shown that allergens can be stored in lysosomes of mast cells after first being internalized by IgE-Fc ϵ R1-mediated phagocytosis [66]. Noted should be that these antigen-containing mast cells can activate antigen-specific T cells responses *in vitro* only when they undergo apoptosis and are then ingested by antigen-presenting cells [58]. Thus mast cells can drive further IgE production and epitope spreading in allergic diseases.

4.2. The role of mast cells in the onset of allergic inflammation

Allergen-IgE dependent mast cell activation is widely regarded to be the major initiator of the clinical signs and symptoms that are demonstrated rapidly after exposure of small amounts of allergen to an allergic individual. However, mast cells express many stimulatory and inhibitory receptors. Allergen-specific mast cell activation can occur via IgE, IgG1, IgG2a and IgG2b through the cross-linking of their high affinity IgE receptor, Fc ϵ R1, Fc γ R1 (human), Fc γ R1 α (human/mouse) or Fc γ R1 β (mouse) receptors [67,68]. In addition, antigen-specific mast cell degranulation can also be induced by cross-linking of immunoglobulin free light chains IgLC [32]. This mechanism might also be involved in asthma or food allergy, since blockage of IgLC was effective in down regulating airway and skin hypersensitivity reactions in murine models of asthma and cow milk allergy [33,69].

Allergen-independent mast cell activation may also occur in an allergic setting. Activation of neuropeptide receptors, c-Kit, toll-like receptors (TLRs), complement receptors or direct interaction with G-proteins can also be involved in mast cell activation [67,70–74]. Of interest are TLRs, since mast cells found in the submucosa and serosa express greater levels of TLR2, TLR3, TLR4, TLR7 and TLR9 compared to mucosal mast cells [75]. TLR2 and TLR4 ligands directly induce the generation and release of inflammatory mediators from mast cells [76,77]. In addition, in the context of allergic asthma, TLR ligands such as lipopolysaccharide (TLR4 ligand) are suggested to synergize with the crosslinking of allergen-IgE-FcεRI to enhance allergic inflammation [78]. Furthermore, it has been demonstrated that commensal bacteria in the intestinal tract via TLR signaling promote the migration of mast cells to the intestine [79]. Similar functions have been reported for chemokine receptors: CCR1 and CCR3 are involved in IgE-induced mast cell activation and epithelial derived CXCR2 ligands are important in the TLR-mediated mast cell recruitment to the intestinal tract [17,79].

Activated mast cells release their pre-stored mediators (vasoactive amines, cytokines such as TNFα, proteases, peptides such as bradykinin) via exocytosis of their granules or via differential release of mediators without degranulation, so-called piecemeal degranulation [80]. The pre-stored vasoactive amines, such as histamine and serotonin, mediate mainly vascular effects associated with the inflammatory response such as vasodilatation/constriction and changes in vascular permeability as well as acute bronchoconstriction [80]. The acutely released proteases, such as tryptase and chymase are involved in tissue damage and the peptides (bradykinin, substance P, vasoactive intestinal peptide and vascular endothelial growth factor (VEGF) are also involved in the acute inflammation and pain perception [80].

Mast cell activation also leads to the 'de novo' synthesis and release of lipid mediators and chemokines and cytokines. The newly synthesized arachidonic acid metabolites such as LTB4 and LTC4, platelet activating factor (PAF) and prostaglandin D2, cytokines, among which IL1, IL4, IL5, IL6, IL9, IL13, interferon γ (IFNγ) and TNFα, and chemokines are responsible for the late phase event during an allergic inflammatory response: leukocyte migration, infiltration and activation [73,74,80,81].

4.3. Mast cells as suppressors of allergic inflammation

Recently, attention has been drawn to the potential role of mast cells in suppressing or breaking of allergic inflammation.

First, it was demonstrated that mast cell-derived proteases (such as β-tryptase) can cleave IgE. Treatment with protamine (an inhibitor of proteases) enhanced IgE-mediated allergic skin inflammation in man [82]. Although not yet demonstrated in an allergic setting, it has been shown that endogenous and exogenous peptides (endothelin-1, neurotensin and snake venom) that induce mast cell activation are also cleaved by mast cell proteases and thereby down-regulating the peptide damaging effects [83–85]. In addition, mast cells have been shown to have immunosuppressive functions following UVB radiation, mosquito bites or in peripheral tolerance to skin allografts [86–88]. How mast cells mediate these immunosuppressive effects remain to be elucidated, but naturally arising regulatory T cells seem to be involved [88]. IL9 derived from these regulatory T cells induces the recruitment and activation of mast cells. In turn, mast cells can mediate this immunomodulatory function *in vivo* by the production of IL10. Recently, the role of naturally arising regulatory T cells in the induction of oral tolerance to peanut allergens was challenged. Rezende and coworkers [89] have demonstrated that adoptive transfer of naturally arising regulatory T cells from peanut tolerant mice did not induced tolerance in recipient mice that were sensitized to peanut. They found evidence that TGFβ-secreting regulatory T cells may play an important role instead. However, in several clinical trials of allergen specific immunotherapy in allergic subjects, the induction of tolerance seems

to be related to naturally arising regulatory T cells and IL10 producing type 1 regulatory T cells [For a review see Ref. [90]].

IL10 derived from mast cells is important for the limitation of chronic skin inflammation following contact hypersensitivity responses to the allergen-containing components of poison ivy [91]. The pathways that link mast cells-IL10 to the observed changes remain to be defined and to be shown in an allergic setting.

Lastly, mast cells are equipped to sense the environment to decide to become potentially suppressive in allergic inflammation. It has been suggested that such action could be realized via sialic acid-binding immunoglobulin-like lectin 8 (siglec-8) [92]. Siglecs are cell surface receptors and member of immunoglobulin super family (I-type lectins) that recognize sugars [93]. Siglec-8 is highly similar in structure to CD33 and has two conserved immunoreceptor tyrosine-based inhibitory motif (ITIMs)-like motifs in their cytoplasmic tails [94]. This suggests that siglec-8 function as inhibitory molecules. *In vitro*, siglec-8 promotes the apoptosis of eosinophils and inhibits IgE-FcεRI-induced mast cell mediator release [95,96]. Recently, Gao and coworkers have described that polymorphisms of the siglec-8 gene are associated with the susceptibility to asthma [97]. Further studies are required to validate siglec-8 as useful target to induce mast cell-dependent down regulation of allergic inflammation.

5. The two faces of mast cells in allergic inflammation: Ying Yan concept

Mast cells are typically regarded as troublesome cells due to their prominent role in IgE-dependent allergic hypersensitivity reactions such as allergic asthma and food allergy. Further, it seems that mast cells are also able to play an additional role in the 'allergic' sensitization-processes. Recent findings show that mast cell functionality is not only pro-inflammatory, but can on the contrary have suppressive or immunomodulatory effects in allergic inflammation (Fig. 1). The latter is mainly based on *in vitro*-studies and one should keep in mind that these circumstances do not reflect the true nature of mast cells in their micro-environment in intestinal wall or airways. More evidence needs to be obtained from *in vivo* and human studies to prove the immunomodulatory role of mast cells in allergic inflammation. In Chinese philosophy, the concept of yin yang is used to describe

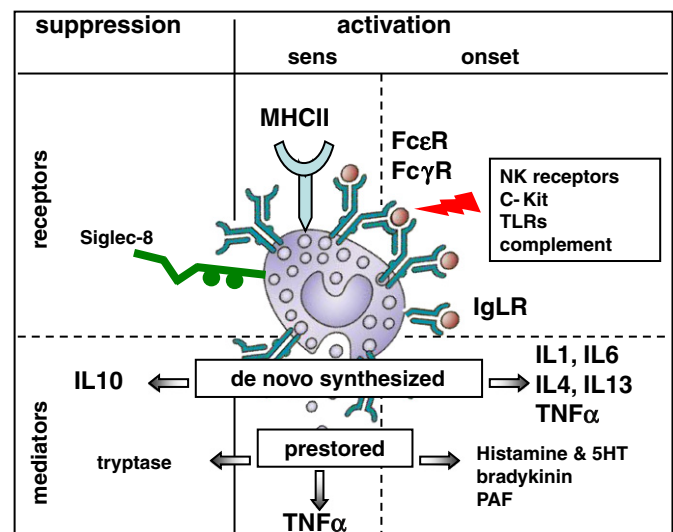


Fig. 1. The two faces of mast cells in allergic inflammation: inducer/activator and suppressor. MHC: major histocompatibility complex; IL: interleukin; PAF: platelet activating factor; FcεR: IgE receptor; FcγR: IgG receptor; IgLR: Ig light chain receptor; TNFα: tumor necrosis factor α; NK receptor: neurokinin receptor; 5HT: serotonin; TLR: toll like receptor; sens: sensitization phase. Adapted from Ref. [98].

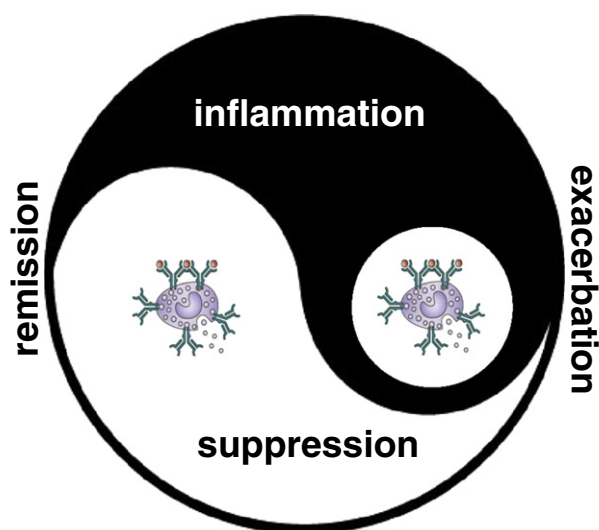


Fig. 2. Yin Yang concept for mast cells. The suppressor and activator roles of mast cells in allergic inflammation are seemingly contrary. While mast cells play an important activator role in allergic inflammation, Mother Nature has created a down regulating role for mast cells as well. Only during allergic exacerbations there is an imbalance of these mast cell functions resulting in the symptoms related to allergic asthma and food allergy. During remission the balance is restored. Opposite roles for mast cells in allergic inflammation thus only exist in relation to each other. Thus mast cells follow the Yin Yang concept in allergy.

how seemingly contrary forces are interconnected and interdependent in the natural world, and how they give rise to each other in turn. May be we should regard the suppressor and activator roles of mast cells in allergic inflammation as such. While inducing inflammation, Mother Nature has created a down regulating role for mast cells as well. Only during allergic exacerbations there is an imbalance of these mast cell functions resulting in the symptoms related to allergic asthma and food allergy. Opposite roles for mast cells in allergic inflammation thus only exist in relation to each other (Fig. 2).

Still, the possible suppressor role of mast cell in allergic inflammation and/or the possible role of mast cells in the development of immunological tolerance, leads to the following questions:

1. How careful should we be in targeting mast cells in allergic inflammation?
2. How can we manipulate specific mast cell suppressor functions therapeutically?

A better understanding of mast cell biology will give us new insights for improving strategies to treat allergic inflammation associated with asthma and food allergy.

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