Title

Mast cells and immunological skin diseases.

Journal

Clinical reviews in allergy & immunology, 33(1-2)

ISSN

1080-0549

Authors

Navi, Daniel
Saegusa, Jun
Liu, Fu-Tong

Publication Date

2007-10-01

Peer reviewed

Mast Cells and Immunological Skin Diseases

Daniel Navi, Jun Saegusa, and Fu-Tong Liu

Department of Dermatology, School of Medicine, University of California, Davis,

Sacramento, CA 95817

Corresponding author:

Fu-Tong Liu, MD, PhD
Department of Dermatology
School of Medicine
University of California, Davis
3301 C Street, Suite 1400
Sacramento, CA 95816

Key words: mast cells, IgE, contact dermatitis, atopic dermatitis, bullous pemphigoid, scleroderma, graft-versus host-disease

Abstract

Mast cells play an important role in both adaptive and innate immunity and a large body of literature demonstrates their functions in skin immunity. This article reviews the literature on the role of this cell type in the pathogenesis of a number of immunological skin diseases, including contact dermatitis, atopic dermatitis, immunobullous disease, scleroderma, and chronic graft-versus-host disease. In all these diseases, mast cells are noted to increase in number and undergo degranulation in the affected skin and in some cases their specific mediators are detected. Elucidation of the contribution of mast cells to the pathogenesis of these diseases has been aided significantly by the use of animal models, especially mouse models. The studies of mast cell-deficient mice in conjunction with normal congenic mice have been particularly fruitful, although in some cases, such as contact dermatitis, a definitive conclusion has not been achieved despite extensive efforts. The role of mast cells in atopic dermatitis has also been suggested by studies of gene polymorphism, which have linked some of the mast cell-related genes to the disease. In the case of scleroderma and chronic graft-versus-host disease, the function of mast cells in fibrosis is further supported by the ability of these cells and their mediators to induce activation and proliferation of fibroblasts. Therapies targeting mast cells may prove beneficial for treatment of these inflammatory and autoimmune diseases.

1. Introduction

Mast cells in the skin are normally located adjacent to blood and lymphatic vessels, where they can encounter substances delivered through these two streams. In addition, some of the cells are in connection with nerve endings, and thus can also receive signals from the nervous system. Existing literature suggests that this cell type has important functions in the immune system (1-4). Among these the one associated with IgE is undoubtedly the most well documented. These cells can be sensitized by IgE via their cell surface high-affinity IgE receptor (FcεRI). When sensitized mast cells encounter the antigens to which the bound IgE antibodies are specific, they respond in a fashion that culminates in the manifestation of immediate-type hypersensitivity. Mast cells can also serve as effector cells in the immune system in an IgE-independent fashion, as they can be activated by products of the complement cascae and various cytokines. A very interesting recent development is that mast cells may mediate in part the immune suppressive function of regulatory T cells (T_{reg}) (5).

Mast cells produce an array of cytokines, chemokines, and growth factors that regulate the recruitment, trafficking, and function of other immune cells and cells involved in the skin inflammatory response. First, mast cells have been shown to induce cell adhesion molecules on endothelium that are essential for leukocyte-endothelial cells interactions through their secreted tumor necrosis factor-alpha (TNF-α) (6). In addition, through IL-4 and IL-13 they can induce vascular cell adhesion molecule 1 on endothelial cells (7;8) that are also critically involved in inflammatory responses. These effects are likely to significantly contribute to the influx of leukocytes to the inflammatory skin sites. Mast cells can affect the differentiation of naïve T cells to Th1 and Th2 subsets and

enhance T cell activation (9;10). They can induce T-cell migration either directly through chemotactic factors or indirectly by inducing adhesion molecule expression on endothelial cells (11). They can also regulate primary B cell development and stimulate IgE synthesis in B cells (12-14).

Among the resident skin cells, mast cells can affect the functions of keratinocytes and dendritic cells. Histamine released by mast cells can act on keratinocytes and promote their production of adhesion molecules, proinflammatory cytokines and chemokines, as well as growth factors (15;16). This in turn results in augmented inflammation. An earlier study showed that specific activation of dermal mast cells in an organ culture led to the induction of $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins in Langerhans cells, through release of TNFα (17). A subsequent study demonstrated that when activated, skin mast cells can induce the migration of Langerhans cells to the local lymph nodes (18), also through the secretion of TNFα (19). They can thus promote antigen presentation by these dendritic cells to T cells.

Mast cell can also influence the antigen-specific T cell response by modulating the dendritic cell function. A recent study showed that through modulation of dendritic cells, mast cells affects Th1/Th2 polarization in response to an antigen (20). Another study suggests that through a mdiator they produce, prostaglandin D2, mast cells lead to Th2 polarized responses by suppressing IL-12 production by dendritic cells (21). Finally and importantly, mast cells appear to be capable of substituting for the function of dendritic cells by presenting antigens to T cells directly (22-26).

Therefore, mast cells can be considered as sentinel cells in the skin and they function both as effector and regulatory cells. Consistent with having these attributes, these cells

have been shown to be critically involved in the pathogenesis of various immunological skin diseases. The role of mast cells in urticaria is discussed in the review by Greaves and Tan. In this review, we summarize their roles in contact and atopic dermatitis, immunobullous diseases, scleroderma, and graft-versus-host disease.

2. Allergic contact dermatitis

Allergic contact dermatitis is a common inflammatory dermatosis caused by exposure to a variety of haptenic antigens in sensitive individuals. In the sensitization phase the inflammation is initiated by the antigen being taken up by the skin antigen-presenting Langerhans cells, which then migrate to lymph nodes and present the antigen to naïve T cells and activate these cells. During the elicitation phase T cells subsequently migrate to the affected skin site and are re-activated by the antigen-presenting cells. This leads to a cascade of inflammatory responses, representing a type IV allergic reaction. There are only a few studies addressing the function of mast cells in allergic contact dermatitis in humans. An early work examined allergic contact dermatitis reactions to dinitrochlorobenzene and urushiol (the antigen responsible for poison ivy contact dermatitis) and noted the presence of mitotic mast cells three days after the application of the allergens, as well as an increase in the number of these cells. In addition, they were noted to have undergone degranulation (27).

Most of our knowledge on the role of mast cells in allergic contact dermatitis is derived from studies of mouse models, in which skin reactions are induced by topical application of haptens. A number of studies demonstrated an increase in the mast cell density at the reaction sites. For example, in one study the investigators topically applied

picryl chloride on days 4, 11, 18, and 25, and after the 4th application noted a significant increase in the number of mast cells (28). These additional cells could originate from the bone marrow or from division of cells originally residing in the skin. In addition, it has been shown that cells with characteristics of mast cells could be derived from culturing hair follicles of adult mice (29), suggesting that the skin hair follicles may be a source.

Degranulation of mast cells is also a regular finding in the lesional skin in the mouse models. This is observed at the sites of allergic contact sensitivity induced by a variety of haptens, including oxazolone, picryl chloride, trinitrochlorobenzene (28;30;31). In a time course study, Kerdel *et al*. (31) noted there was modest degranulation of mast cells between 1 and 6 h and extensive degranulation at 12 h, after antigen challenge, in mice sensitized with 0.1% tinitrochlorobenzene (TNCB) and then challenged with 1% TNCB. Another study utilized ultrastructural features of mast cells to confirm their degranulation in picryl chloride-induced contact dermatitis (28). The relevance of mast cell degranulation is suggested by the finding that the extent of this process is lower in mice having a suppressed inflammatory response, for example in those deficient in certain proteins critical for the development of contact sensitivity (30;32).

In mouse models, IgE production often parallels the development of contact sensitivity (28;33). Thus, it is conceivable that mast cells are sensitized by antigen-specific IgE under the condition of contact sensitivity and are triggered to degranulate upon subsequent exposure to the antigens. In one study, mast cells isolated from the peritoneal cavity of mice treated topically with picryl chloride were noted to degranulate when exposed to the antigen in culture. Additional studies suggest that these cells were indeed sensitized by antigen-specific IgE (34). Contact dermatitis in humans is not

generally considered to be associated with antigen-specific IgE. It is possible such IgE does exist but in amounts that are below the detection limit.

In mouse models, repeated antigen exposure results in a change of the response from a typical delayed-type to an immediate-type in terms of the time course. For example, when repeatedly sensitized with oxazolone for 24 days at 2-day intervals, mice developed an immediate-type response at 30 min after the antigen application (33). Natsuaki *et al*. (35) confirmed these findings and further demonstrated the involvement of mast cells in the immediate-type response. They found that mast cell-deficient mice did not exhibit detectable immediate reaction, while congenic normal mice showed both immediate and delayed-type reactions. In addition, one study showed that repeated sensitization also resulted in accumulation of a large number of mast cells at the sensitized sites and elevation of serum levels of antigen-specific IgE (36). Thus, the development of an immediate-type response is most likely due to the sensitization of mast cells by antigen-specific IgE. These cells can then be triggered to release mediators when encountering the hapten again, which can become associated with certain proteins and form multivalent antigens. Whether in human contact dermatitis, repeated antigen exposure results in an immediate-type response awaits investigation.

Several studies with mouse models have revealed a role for IgE in the elicitation phase of contact sensitivity. First, the intensity of contact sensitivity responses correlates with the level of hapten-specific IgE (37). Second, topical application of antigens can result in a contact sensitivity response in mice that receive antigen-specific IgE. In one study, Ray *et al*. (38) passively sensitized BALB/c mice with monoclonal anti-dinitrophenyl (DNP) IgE antibody and treated the mice on the ears 48 hr later with the

hapten 2,4-dinitrofluorobenzene (DNFB). A biphasic response gauged by the ear swelling was noted, which included an early, transient one occurring within 15 to 30 min of challenge and a second, more persistent one at 24 to 48 hr after challenge. Other investigators also employed passive transfer systems and found evidence for a function of antigen-specific IgE in contact sensitivity (39-41).

The contribution of IgE in contact sensitivity in mice has been definitively established by Bryce *et al*. with the use of IgE-deficient ($IgE^{-/-}$) mice (42). The delayed-type response to hapten sensitization was diminished in these mice, but was restored by administration of IgE before sensitization. Interestingly and remarkably, transferred IgE does not have to be specific for the relevant hapten. These investigators also noted that $IgE^{-/-}$ mice do not exhibit the reduction of dendritic cell numbers in the epidermis after hapten exposure that typically occurs during contact sensitivity. They thus suggested that IgE can promote sensitization by contact allergens through binding to and affecting the functions of mast cells, one of which could be the promotion of dendritic cell migration.

The function of mast cells in the development of contact sensitivity has been studied extensively with the use mast cell-deficient mice. In a number of studies, mice deficient in mast cells developed a significantly lower degree of contact sensitivity (43-46); however, some other studies did not reveal an essential role of this cell type (47-52). A large number of variables could contribute to these discrepancies, as discussed in detail by Bryce *et al*. (42). These include the nature and concentration of haptens used and genotype of mast cell-deficient mice employed. As mentioned above, repeated sensitization can result in an immediate-type response, which is undoubtedly mast cell-dependent. Thus, another confounding cause for the variable results could be the extent

of the immediate-type response that is elicited, which in turn could be related to the amount of hapten-specific IgE produced.

The contribution of mast cells has also been addressed by studying the effect of the mediators produced. One study examined the effect of histamine on development of contact dermatitis by using histamine-deficient mice. When mice were treated by repeated topical applications of the hapten diphenylcyclopropenone, development of dermatitic lesions was suppressed in histamine-deficient mice compared to wild-type mice. In addition, these authors found that development of dermatitic lesions in histamine-deficient mice was restored by treating mice with a type 1 histamine receptor agonist. In addition, a receptor antagonist suppressed development of such lesions in wild-type mice (53). As mentioned above, these findings could be related to the development of IgE- and mast cell-dependent immediate-type response in mice repeatedly treated with haptens, in which histamine likely plays a prominent part.

More recent studies continue to provide evidence for the role of mast cells in contact sensitivity as well as some mechanistic insights. In one, Biedermann *et al*. (46) demonstrated that, in trinitrochlorobenzne-induced contact sensitivity, this cell type is responsible for the recruitment of neutrophils into the site of skin reactions. They further concluded that a mast cell-derived cytokine, TNF, and a chemokine, MIP-2, contribute to the development of contact sensitivity. Suto *et al*. (54) subsequently showed that mast cells are responsible for migration of dendritic cells into the lymph nodes during contact sensitivity reactions and that TNF produced by these cells plays an important part.

In summary, allergic contact dermatitis in humans is associated with an increase in the number of mast cells and activation of these cells and these findings are noted also in

mouse models. The function of mast cells in the development of contact sensitivity in humans is currently unknown. While extensive studies of this subject in mouse models have not yielded conclusive information, they suggested intriguing possible future investigations in humans. In particular, it would be important to determine whether there is a component of immediate-type response in human contact dermatitis mediated by antigen-specific IgE and whether IgE plays a role in this dermatosis in an antigen-dependent as well as independent manner as observed in mice. In addition, it would be of interest to test whether mast cell inhibitors are useful for treatment of allergic contact dermatitis, in conjunction with other modes of therapies.

3. Atopic dermatitis

Atopic dermatitis (AD) is a relatively common chronic inflammatory skin disease characterized by intense pruritus and eczema, and is often associated with allergic asthma, rhinitis and food allergies. Various studies indicated that AD has a complex etiology, with involvement of multiple immunologic and inflammatory pathways. About 80% of AD patients show high levels of total and specific IgE antibodies to a variety of allergens, especially those in food and inhalant antigens, such as chicken egg, dust mites, pollens, and molds. Serum IgE levels in AD patients tend to be higher than those in other allergic diseases. Previous studies have shown a strong correlation between the serum IgE levels and severity of AD (55). IgE-dependent allergic reactions are therefore thought to contribute to the development of AD. However, the involvement of IgE in the pathogenesis of AD remains controversial. Mast cells have also been shown to represent key effector cells of acute AD lesions and contribute significantly to chronic AD. In acute

AD lesions, this cell population is normal in number but shows degranulation (56). In contrast, there is a significant increase in their number, especially in areas of lymphocytic infiltration in the papillary dermis, in chronic AD lesions (56;57).

Elevated concentrations of histamine have been detected in the skin and plasma of patients with AD (58). In AD skin, both IL-4 and IL-13, key cytokines for the development of the Th2 response, are increased. Mast cells have been shown to be the major source of these cytokines (59) and a recent report revealed that IL-4 and IL-13 are expressed by 66% and 20% of mast cells in AD skin, respectively (60). Mast cells can contribute to Th2 polarization in the skin of AD patients through these cytokines. Mast cells also produce IL-5, which is likely to contribute to eosinophil infiltration in the AD skin (61). More over, mast cells were found to be in close association with endothelial cells in the lesional skin and there is evidence suggesting that they stimulate vascular proliferation, probably via the release of proangiogenic factors (62). Thus, these cells can promote inflammation indirectly through increasing the vasculature at the inflammatory sites.

The current view is that AD, like other allergic disorders, results from complex interactions between a number of genetic and environmental factors. There have been several reports about a significant association between the polymorphism of mast cell-related genes and AD. One such report has demonstrated a strong association between gene polymorphism in the β chain of high-affinity IgE receptor (FcεRI) and AD (63). Such polymorphism can result in increased surface expression of this receptor as well as amplification of intracellular signaling, resulting in increased IgE-dependent mast cell activation. Chymase, which is a chymotrypsin-like serine protease stored in mast cell

granules that hydrolyzes a variety of substrates, such as angiotensin I, metalloproteases, lipoproteins, and procollagen, is increased in the AD skin (64). A significant association between genetic variants of mast cell chymase and AD has been reported (65).

The significant role of mast cells in AD has also been revealed by several animal experiments. Using mast cell-deficient mice (W/W^v), evidence has been provided to support mast cells' contribution to chronic AD through regulating IFN-γ expression in the skin and circulating IgE levels (66). A recent report revealed that Rab guanine nucleotide exchange factor I (RabGDF1) is a negative regulator of FcεRI-dependent mast cell activation and that RabGDF1-deficient mast cells exhibited enhanced degranulation and release of cytokine (67). Interestingly, mice lacking RabGDF1 displayed many of the features of human AD, such as elevated total IgE levels and skin inflammation characterized by epidermal hyperplasia and dense infiltrates of lymphocytes, eosinophils, monocytes/macrophages and mast cells in the dermis (67). The NC/Nga mouse strain is a popular model that spontaneously develops an inflammatory response in the skin resembling that seen in human AD. It has been reported that a mast cell chymase inhibitor improved dermatitis in NC/Nga mice (68).

An interesting recent development is that a drug targeting IgE, omalizumab, has shown promise in the treatment of AD. Omalizumab is a humanized monoclonal antibody that binds to IgE at the same location recognized by FcεRI and it is thus able to effectively inhibit IgE binding to mast cells. Administration of omalizumab results in a remarkable reduction in the level of free IgE in the serum. Recent studies have demonstrated the beneficial effect of omalizumab in AD patients (69). The results support a function of IgE in the manifestation of AD. In view of information supporting

mast cells as critical effector cells in both acute and chronic AD lesions, therapies targeting mast cells might prove useful for treatment of AD.

4. Immunobullous diseases

The role of mast cells in autoimmune bullous diseases has been best documented in bullous pemphigoid (BP). This acquired disorder is characterized by subepidermal blisters resulting from autoantibodies directed at the hemidesmosomal antigens, primarily BP180 and BP230, which are detectable at the dermal-epidermal junction in skin lesions, along with complement proteins. Wintroub *et al.* (70) was first to report the presence of mast cells and their degranulation as prominent histological features of the affected skin in patients with BP. This finding was subsequently confirmed in other studies (71). Furthermore, the presence of high concentrations of histamine and mast cell-derived chemoattractants, including those acting on eosinophils, in blister fluid of BP patients, has been known for some time (72;73).

Additional support for the function of mast cells in immunopathogenesis of BP is provided through studies demonstrating elevated levels of tryptase, a serine protease produced by activated mast cells, in blister fluid of patients with BP (74;75). Furthermore, exposure of normal human skin explants to tryptase or compound 48/80, which can induce mast cell degranulation, resulted in focal dermal-epidermal junction separation (76).

Still another line of evidence comes from studies that investigate the function of IgE antibodies in this autoimmune disease. Elevated serum IgE levels have been reported in a majority of patients with BP (77). More recent studies have demonstrated that

circulating IgE antibodies in BP patients are directed against the NC16 ectodomain of BP180, the same antigenic region recognized by the IgG class autoantibodies (78-80). Furthermore, dermal mast cells in untreated BP patients were noted to contain IgE, as well as the BP180 antigen, on the cell surface as revealed by immunofluorescence labeling (79). The authors postulated that BP180-specific IgE can sensitize mast cells and lead to their degranulation when the cells are exposed to the BP180 antigen, thereby contributing to pathogenesis of BP.

The functional significance of mast cells in BP has been addressed through the use of animal models. In one model, skin lesions are created via injection of neonatal mice intradermally with IgG antibodies directed against mouse BP180. Mice develop subepidermal blisters and the lesions exhibit some of the key immunopathological features found in the human disease (81). It is now known that the pathogenesis of the antibody-induced disease in this model depends on the activation of the complement pathway (82) as well as neutrophil recruitment (83). Moreover, a series of intricate experiments have elucidated the critical role for mast cells in the pathogenesis of this experimental model (84). Wild-type mice injected intradermally with pathogenic anti-mouse BP180 IgG exhibited extensive mast cell degranulation in the skin, which occurred before neutrophil infiltration and development of skin lesions. In contrast, in mast cell-deficient mice, the accumulation of neutrophils and development of skin lesions were diminished. These responses were restored, however, in mast cell-deficient mice reconstituted with mast cells in the skin. Similarly, skin lesions developed in mast cell-deficient mice in which neutrophil accumulation was facilitated by administration of the neutrophil chemoattractant IL-8 at the site of injection of anti-BP180 antibodies. Finally,

neutrophil accumulation and skin blistering were blocked when mice were treated with a mast cell inhibitor, cromolyn. On the basis of these findings, the authors concluded that mast cell degranulation is crucial for pathogenesis in this experimental BP and accounts for approximately two-thirds of neutrophil recruitment into the developing lesions.

In summary, studies of human clinical samples have revealed the presence and activation of mast cells as consistent features of BP and studies of mouse models have supported a function of these cells in the autoantibody-mediated development of skin blisters. Future studies could address whether there is a subset of patients in whom IgE and mast cells play a more prominent part and whether medications targeting these molecules and cells would be beneficial in treatment of BP.

5. Scleroderma

Scleroderma is a multisystem disorder that is characterized by sclerotic changes of the skin as well as various internal organs and carries significant morbidity and mortality. The literature on the role of mast cells in scleroderma is rather extensive and provides several lines of evidence. Elevated density of this cell type in the affected skin of scleroderma patients constitutes one line of evidence. Earlier studies used conventional staining methods to demonstrate an increase in dermal mast cell density in early stages of the cutaneous lesions (85;86), but a decrease in more severely involved skin (86). Seibold *et al.* (87) utilized a double staining method with anti-FcεRI antibody for cell surface staining and avidin for cytoplasmic staining to demonstrate that the number of activated (i.e. degranulated) dermal mast cells was increased in the unaffected skin in the early phase of the disease, as well as in the affected skin in both early- and late-phase of

the disease. The authors concluded that mast cell proliferation and activation precede skin fibrosis in scleroderma.

More recent studies have utilized monoclonal antibodies against mast cell-specific proteases (i.e. chymase and tryptase) to stain these cells. The advantage of this approach is that degranulated mast cells are also stained, in contrast to conventional staining methods, which may not detect these cells. Using this approach, Irani *et al.* (88) found a decrease in mast cell density in half of the specimens from patients in the early stage (mildly sclerotic lesions) of the disorder, and variable density in specimens from patients in the later stages (severely sclerotic lesions) of the disorder. Furthermore, they noted an unusually high prevalence of the MCT (tryptase-positive, chymase-negative) phenotype in sclerodermatous skin, which is in contrast to the predominant MCTC (tryptase-and chymase-positive) phenotype seen in healthy adult skin (88). These findings were not fully confirmed by a later study that employed the same staining techniques but grouped patients according to the histological grade. That study found significantly increased mast cell density in grade 1 (sclerodermatous stage) skin, compared to normal skin, although there was individual variability between specimens. In contrast, mast cell density was significantly decreased in grade 2 (sclerotic stage) skin compared to normal skin. The study's finding with regard to changes in mast cell phenotype in scleordermatous skin was also inconclusive, since there was significant variability in MCTC to MCT ratio in both sclerodermatous and normal skin (89). These differing findings may be partly secondary to the different classification of patients each study employed. Nevertheless, both studies support involvement of this cell type in pathogenesis of cutaneous lesions in scleroderma. Furthermore, both group of

investigators suggested that localization of mast cells and phenotypic differentiation may be a function of the altered cytokine profiles in the microenvironment of sclerodermatous skin.

Another line of evidence supporting the important function of mast cells in scleroderma arises from studies of mouse models. Mast cell involvement in pathogenesis of scleroderma has been investigated in three such models: 1) tight-skin (Tsk) mouse, 2) bleomycin-induced scleroderma, and 3) chronic graft vs. host disease. The findings from the first two are discussed herein, whereas those from the third one are included in the next section. The Tsk mouse is a strain that displays a widespread disorder of connective tissues, including fibrosis of deep dermis and subcutaneous connective tissue (90;91) due to a gene mutation. Walker *et al.* (92) was the first to report that fibrotic lesions in Tsk mice were characterized by an increase in dermal mast cell density and a prominence of degranulated mast cells. In two other studies, the same investigative group reported a significant decrease in skin fibrosis of Tsk mice following treatment with inhibitors of mast cell degranulation, cromolyn (93) and ketotifen (94). Mast cell involvement in pathogenesis of the scleroderma-like phenotype in Tsk mice was further investigated in a study that utilized a mast cell-deficient strain. Mast cell-deficient mutants carrying the Tsk locus generated by interbreeding between the two strains were not different from Tsk mice in the early phase of the fibrotic disease. However, the former clearly had a significantly lower extent of fibrosis than the latter at advancing age (5-7 months), when the fibrosis is more pronounced. The results suggest mast cells contribute to the development of fibrosis (95).

Wang *et al.* (96) further investigated the mechanisms underlying mast cell accumulation in fibrotic cutaneous lesions of Tsk mice. A series of experiments were devised to quantitatively assess mast cell density and cytokine production in Tsk mice, their normal littermates, and skin heterografts between the two strains. The investigators reported that in comparison with normal mice, Tsk mice exhibited elevated dermal mast cell density as well as higher mRNA expression of transforming growth factor-β1 (TGF-β1), stem cell factor (SCF), and interleukin-15 (IL-15) --three cytokines known to be important in mast cell proliferation, differentiation, or recruitment. Interestingly, the authors found increases in both mast cell density and mRNA levels of the three cytokines in normal mouse skin grafted onto Tsk mice, but not in Tsk mouse skin grafted onto normal mice. The investigators concluded that mast cell accumulation in Tsk mice is mediated through cytokines, including TGF-β1, SCF, and IL-15, produced in the local environment. It is worth mentioning a study reported increased local SCF expression in dermis of patients with scleroderma, as seen in Tsk mice, supporting the contribution of this cytokine to mast cell hyperplasia seen in the human disease (97).

In the bleomycin-induced model, dermal sclerosis resembling scleroderma both histologically and biochemically is induced by repeated local injections of bleomycin (98). In bleomycin-treated mice, increased mast cell density as well as mast cell degranulation was noted in parallel with development of dermal sclerosis (98). However, in a later study, the investigators noted that bleomycin could induce dermal sclerosis even in genetically mast cell-deficient mice (99). Based on these findings, the investigators suggested that mast cells may be associated with, but are not required for the induction of dermal sclerosis (99;100).

Various studies have supported the role of mast cells in promoting fibrosis. First, mast cell accumulation appears also in other fibrotic conditions, including normal reparative and pathologic wound healing (101), liver cirrhosis (102), pulmonary and myocardial fibrosis (101), and renal interstitial fibrosis (103;104), suggesting the key role of this cell type in promoting fibrosis. Second, the direct and indirect profibrotic effects of mast cell-derived mediators have been well-documented in the literature and reviewed by a number of authors (e.g., Claman (105) and Gruber (106)). Histamine, for example, has been reported to stimulate proliferation of fibroblasts from normal human adult lung (107) and to increase collagen synthesis in cultured fibroblasts derived from guinea pig skin (108). Tryptase has also been implicated as an activating and chemotactic factor for fibroblasts, and has been shown to induce cell proliferation and synthesis of type I collagen (109;110). Other potentially fibrogenic mast cell mediators include chymase, heparin, TGF-β, basic fibroblast growth factor (bFGF), tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4) and platelet-derived growth factor (PDGF) (106). Another clue to the profibrotic potential of mast cells comes from co-culture studies of these cells with fibroblasts. In particular, activated human mast cells induced proliferation and type I collagen production in co-cultured fibroblasts (109;111).

In conclusion, the involvement of mast cells in pathogenesis of scleroderma is suggested by several main lines of evidence: increased mast cell density in cutaneous lesions of both human patients and animal models of scleroderma; demonstration of amelioration or induction of the disease process in animal models using mast cell stabilizers or activators; and abundant experimental data supporting profibrotic potential of mast cells. Despite this body of evidence, however, the precise role of mast cells in

the pathogenesis of scleroderma remains to be elucidated. Claman presented an integrated schema for pathogenesis of scleroderma that emphasized the interactions among mast cells, fibroblasts, and endothelial cells mediated by a number of cytokines (112). Elucidation of the pathogenesis of scleroderma will require better understanding of the precise roles of these different cellular and molecular players.

6. Chronic graft versus host disease (cGVHD)

cGVHD is a serious complication of bone marrow transplantation caused by the reaction of human leukocyte antigen (HLA)-incompatible, immunocompetent donor cells against the tissues of an immunocompromised host. It occurs in up to 30% of long-term survivors (>100 days) of bone marrow transplantation (113) and is accompanied by the development of sclerodermatous skin. The role of mast cells in sclerodermatoid GVHD has been well-studied by using a particular mouse model generated by injection of spleen cells from immuncompetent donor mice into allogeneic recipient mice pretreated with a sublethal dose of total body irradiation (114). Within 2 weeks of induction, these mice were noted to have dermal fibrosis, atrophy of cutaneous fat and appendages, and mononuclear cell infiltrates resembling the histological features of both human cGVHD and scleroderma (114;115).

In a series of intriguing experiments, Claman and colleagues noted extensive degranulation of mast cells immediately prior to skin fibrosis in cGVHD mice. The authors noted a decrease in the detectable toluidine blue-stained cells over 2-4 weeks (115). Using double immunofluorescence and ultrastructural studies, they concluded that this was secondary to activation and degranulation of mast cells (116;117). Using the

same mouse model, Levi-Schaffer *et al.*(118) investigated the effects of treatment with a mast stabilizer (sodium nedocromil) and a mast cell activator (compound 48/80) on early skin changes of cGVHD. The authors reported that nedocromil ameliorated the skin manifestations of cGVHD and diminished skin fibrosis, while compound 48/80 induced skin changes resembling mild cGVHD in control mice (119). It should be noted that mast cell degranulation is also a feature of acute GVHD in mouse models (120).

Additional evidence for mast cell involvement in cGVHD pathogenesis arises from exposure of peritoneal mast cells cultured on fibroblast monolayers to splenocyte supernatants from cGVHD mice. In this *in-vitro* system, the cGVHD supernatant is believed to induce slow activation of mast cells, as indicated by both histamine release into the culture medium and morphological evidence using electron microscopy (121). Other experimental findings supporting mast cell-fibroblast interactions in co-culture systems and *in vitro* profibrotic effects of mast cells are reviewed in the section on scleroderma. These findings are relevant to understanding the role of mast cells in cGVHD and scleroderma, as fibrosis is the underlying pathogenic process in both conditions.

The putative role of mast cells in cGVHD has also been indirectly suggested by observations of elevated serum IgE levels in both human bone marrow transplantation patients (122;123) and mouse models of GVHD (124;125). In addition, Ushiyama *et al.* (126) reported a correlation between the level of IgE and liver disease as well as splenomegaly in a bone marrow transplantation mouse model of GVHD. They further noted that treatment with anti-IL-4 monoclonal antibodies that suppressed IgE production

by B-cells resulted in reduced liver disease and splenomegaly (126). The potential function of IgE in cGVHD pathogenesis was more directly assessed by Korngold *et al*. (127) using a lethal GVHD mouse model. The authors reported significant inhibition in development of lethal GVHD in mice treated with peptides that inhibit the interaction of IgE with FcεRI.

Conclusions

Mast cells are found to be increased in number in many of immunological skin diseases, including contact dermatitis, atopic dermatitis, immunobullous disease, scleroderma, and chronic graft versus host disease. In these diseases, mast cells are noted to undergo degranulation in the affected skin and in some cases mediators specific to this cell type are detected. The involvement of mast cells is also suggested by the presence of antigen-specific and disease-associated IgE in some of these diseases, which is known to be able to mediate mast cell activation. The function of mast cells in atopic dermatitis has been further suggested by the significant association between the polymorphism of mast cell-related genes and the disease. Based on the vast amount of literature on the functions of mast cells in adaptive and innate immunity, these cells are believed to contribute significantly to the pathogenesis of these immunological skin diseases. In particular, in addition to be able to mediate immediate hypersensitivity, mast cells are now known to have effects on T and B cells, keratinocytes, Langerhans cells and endothelial cells, through an array of cytokines, chemokines, and growth factors they produce. Through these effects, mast cells contribute to amplification of inflammatory responses.

Elucidation of the role of mast cells in these diseases has been aided significantly by the use of animal models, especially mouse models. The studies of mast cell-deficient mice in conjunction with normal congenic mice, as well as mast cell-deficient mice reconstituted with mast cells, has been particularly fruitful. In the case of contact dermatitis, extensive studies with these models have not resulted in a definitive conclusion, but suggested additional investigations to be conducted in humans. In the case of scleroderma and cGVHD, the function of mast cells in fibrosis is further supported by the ability of these cells and their mediators to induce activation and proliferation of fibroblasts. The key aspects of the functions of mast cells in immunological skin diseases are summarized in Figure 1.

The view of the involvement of mast cells in immunological skin diseases now needs to take into the consideration of the very recent development that mast cells appear to mediate the immune suppressive function of regulatory T cells (T_{reg}), as mentioned in Introduction (5). Thus, while mast cells may function in amplifying inflammatory responses, these actions may be offset by their part in dampening the responses through receiving signals from T_{reg}.

The identification of specific cell surface receptors on mast cells and elucidation of molecular mechanism underlying activation of these cells have led to development of mast cell-targeting therapeutic approaches and promised additional developments in the future (reviewed in (128)). These approaches may prove beneficial for treatment of the inflammatory and autoimmune diseases discussed in this review.

Acknowledgements

The authors thank Dr. Daniel Hsu for critical review of the manuscript and useful suggestions.

Reference List

1. Sharma, B.B., J.R. Apgar, and F.T. Liu. 2002. Mast cells. Receptors, secretagogues, and signaling. *Clin Rev Allergy Immunol* 22:119-148.

2. Galli, S.J., J. Kalesnikoff, M.A. Grimbaldeston, A.M. Piliponsky, C.M. Williams, and M. Tsai. 2005. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu Rev Immunol* 23:749-786.

3. Galli, S.J., S. Nakae, and M. Tsai. 2005. Mast cells in the development of adaptive immune responses. *Nat Immunol* 6:135-142.

4. Vliagoftis, H. and A.D. Befus. 2005. Mast cells at mucosal frontiers. *Curr Mol Med* 5:573-589.

5. Lu, L.F., E.F. Lind, D.C. Gondek, K.A. Bennett, M.W. Gleeson, K. Pino-Lagos, Z.A. Scott, A.J. Coyle, J.L. Reed, J. Van Snick, T.B. Strom, X.X. Zheng, and R.J. Noelle. 2006. Mast cells are essential intermediaries in regulatory T-cell tolerance. *Nature* 442:997-1002.

6. Walsh, L.J., G. Trinchieri, H.A. Waldorf, D. Whitaker, and G.F. Murphy. 1991. Human dermal mast cells contain and release tumor necrosis factor alpha, which induces endothelial leukocyte adhesion molecule 1. *Proc Natl Acad Sci U S A* 88:4220-4224.

7. Schleimer, R.P., S.A. Sterbinsky, J. Kaiser, C.A. Bickel, D.A. Klunk, K. Tomioka, W. Newman, F.W. Luscinskas, M.A. Gimbrone Jr, B.W. McIntyre, and a.l. et. 1992. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium. Association with expression of VCAM-1. *J Immunol* 148:1086-1092.

8. Sironi, M., F.L. Sciacca, C. Matteucci, M. Conni, A. Vecchi, S. Bernasconi, A. Minty, D. Caput, P. Ferrara, F. Colotta, and a.l. et. 1994. Regulation of endothelial and

mesothelial cell function by interleukin-13: selective induction of vascular cell adhesion molecule-1 and amplification of interleukin-6 production. *Blood* 84:1913-1921.

9. Nakae, S., H. Suto, M. Iikura, M. Kakurai, J.D. Sedgwick, M. Tsai, and S.J. Galli. 2006. Mast cells enhance T cell activation: importance of mast cell costimulatory molecules and secreted TNF. *J Immunol* 176:2238-2248.

10. Nakae, S., H. Suto, M. Kakurai, J.D. Sedgwick, M. Tsai, and S.J. Galli. 2005. Mast cells enhance T cell activation: Importance of mast cell-derived TNF. *Proc Natl Acad Sci U S A* 102:6467-6472.

11. Mekori, Y.A. and D.D. Metcalfe. 1999. Mast cell-T cell interactions. *J Allergy Clin Immunol* 104:517-523.

12. Tkaczyk, C., P. Frandji, H.-G. Botros, P. Poncet, J. Lapeyre, R. Peronet, B. David, and S. Mecheri. 1996. Mouse Bone Marrow-Derived Mast Cells and Mast Cell Lines Constitutively Produce B Cell Growth and Differentiation Activities. *J Immunol* 157:1720-1728.

13. Pawankar, R., M. Okuda, H. Yssel, K. Okumura, and C.S. Ra. 1997. Nasal mast cells in perennial allergic rhinitics exhibit increased expression of the FcŒRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 99:1492-1499.

14. Gauchat, J.-F., S. Henchoz, G. Mazzel, J.-P. Aubry, T. Brunner, H. Blasey, P. Life, D. Talabot, L. Flores-Romo, J. Thompson, K. Kishi, J. Butterfield, C. Dahinden, and J.-Y. Bonnefoy. 1993. Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* 365:340-343.

15. Kohda, F., T. Koga, H. Uchi, K. Urabe, and M. Furue. 2002. Histamine-induced IL-6 and IL-8 production are differentially modulated by IFN-gamma and IL-4 in human

keratinocytes. *J Dermatol Sci* 28:34-41.

16. Kanda, N. and S. Watanabe. 2004. Histamine enhances the production of granulocyte-macrophage colony-stimulating factor via protein kinase Calpha and extracellular signal-regulated kinase in human keratinocytes. *J Invest Dermatol* 122:863-872.

17. Ioffreda, M.D., D. Whitaker, and G.F. Murphy. 1993. Mast cell degranulation upregulates alpha 6 integrins on epidermal Langerhans cells. *J Invest Dermatol* 101:150-154.

18. Jawdat, D.M., E.J. Albert, G. Rowden, I.D. Haidl, and J.S. Marshall. 2004. IgE-mediated mast cell activation induces Langerhans cell migration in vivo. *J Immunol* 173:5275-5282.

19. Suto, H., S. Nakae, M. Kakurai, J.D. Sedgwick, M. Tsai, and S.J. Galli. 2006. Mast cell-associated TNF promotes dendritic cell migration. *J Immunol* 176:4102-4112.

20. Mazzoni, A., R.P. Siraganian, C.A. Leifer, and D.M. Segal. 2006. Dendritic cell modulation by mast cells controls the TH1/TH2 balance in responding T cells. *J Immunol* 177:3577-3581.

21. Theiner, G., A. Gessner, and M.B. Lutz. 2006. The mast cell mediator PGD(2) suppresses IL-12 release by dendritic cells leading to Th2 polarized immune responses in vivo. *Immunobiology* 211:463-472.

22. Frandji, P., C. Oskéritzian, F. Cacaraci, J. Lapeyre, R. Peronet, B. David, J.-G. Guillet, and S. Mécheri. 1993. Antigen-dependent stimulation by bone marrow-derived mast cells of MHC class II-restricted T cell hybridoma. *J Immunol* 151:6318-6328.

23. Fox, C.C., S.D. Jewell, and C.C. Whitacre. 1994. Rat peritoneal mast cells present

antigen to a PPD-specific T cell line. *Cell Immunol* 158:253-264.

24. Frandji, P., C. Tkaczyk, C. Oskéritzian, J. Lapeyre, R. Peronet, B. David, J.-G. Guillet, and S. Mécheri. 1995. Presentation of soluble antigens by mast cells: Upregulation by interleukin-4 and granulocyte/macrophage colony-stimulating factor and downregulation by interferon-gamma. *Cell Immunol* 163:37-46.

25. Frandji, P., C. Tkaczyk, C. Oskeritizian, B. David, C. Desaymard, and S. Mecheri. 1996. Exogenous and endogenous antigens are differentially presented by mast cells to $CD4^+$ T lymphocytes. *Eur J Immunol* 26:2517-2528.

26. Malaviya, R., N.J. Twesten, E.A. Ross, S.N. Abraham, and J.S. Pfeifer. 1996. Mast Cells Process Bacterial Ags Through a Phagocytic Route for Class I MHC Presentation to T Cells. *J Immunol* 156:1490-1496.

27. Dvorak, A.M., M.C. Mihm Jr, and H.F. Dvorak. 1976. Morphology of delayed-type hypersensitivity reactions in man. II. Ultrastructural alterations affecting the microvasculature and the tissue mast cells. *Lab Invest* 34:179-191.

28. Jung, J.Y., A. Yasoshima, J. Saegusa, H. Nakayama, and K. Doi. 2003. Ultrastructural features of mast cells in picryl chloride (PCL)-induced contact dermatitis in IQI/Jic mice. *Exp Toxicol Pathol* 54:265-271.

29. Kumamoto, T., D. Shalhevet, H. Matsue, M.E. Mummert, B.R. Ward, J.V. Jester, and A. Takashima. 2003. Hair follicles serve as local reservoirs of skin mast cell precursors. *Blood* 102:1654-1660.

30. Subramaniam, M., S. Saffaripour, S.R. Watson, T.N. Mayadas, R.O. Hynes, and D.D. Wagner. 1995. Reduced recruitment of inflammatory cells in a contact hypersensitivity response in P-selectin-deficient mice. *J Exp Med* 181:2277-2282.

31. Kerdel, F.A., D.V. Belsito, R. Scotto-Chinnici, and N.A. Soter. 1987. Mast cell participation during the elicitation of murine allergic contact hypersensitivity. *J Invest Dermatol* 88:686-690.

32. Jung, J.Y., J. Saegusa, H. Nakayama, and K. Doi. 2004. Comparative study on picryl chloride (PCL)-induced contact dermatitis in female IQI/Jic and BALB/c mice. *Exp Anim* 53:89-96.

33. Shimada, Y., M. Hasegawa, Y. Kaburagi, Y. Hamaguchi, K. Komura, E. Saito, K. Takehara, D.A. Steeber, T.F. Tedder, and S. Sato. 2003. L-selectin or ICAM-1 deficiency reduces an immediate-type hypersensitivity response by preventing mast cell recruitment in repeated elicitation of contact hypersensitivity. *J Immunol* 170:4325-4334.

34. Thomas, W.R., N. Vardinon, M.C. Watkins, and G.L. Asherson. 1980. Antigen-specific mast cell degranulation in contact sensitivity to picryl chloride. An early event. *Immunology* 39:331-336.

35. Natsuaki, M., N. Yano, K. Yamaya, and Y. Kitano. 2000. Immediate contact hypersensitivity induced by repeated hapten challenge in mice. *Contact Dermatitis* 43:267-272.

36. Kitagaki, H., S. Fujisawa, K. Watanabe, K. Hayakawa, and T. Shiohara. 1995. Immediate-type hypersensitivity response followed by a late reaction is induced by repeated epicutaneous application of contact sensitizing agents in mice. *J Invest Dermatol* 105:749-755.

37. Nagai, H., N. Inagaki, and H. Tanaka. 1999. Role of IgE for the onset of allergic cutaneous response caused by simple chemical hapten in mice. *Int Arch Allergy Immunol* 118:285-286.

38. Ray, M.C., M.D. Tharp, T.J. Sullivan, and R.E. Tigelaar. 1983. Contact hypersensitivity reactions to dinitrofluorobenzene mediated by monoclonal IgE anti-DNP antibodies. *J Immunol* 131:1096-1102.

39. Graziano, F.M., L. Gunderson, L. Larson, and P.W. Askenase. 1983. IgE antibody-mediated cutaneous basophil hypersensitivity reactions in guinea pigs. *J Immunol* 131:2675-2681.

40. Matsuda, H., W. Ptak, and P.W. Askenase. 1995. Role of mast cells versus basophils in IgE-dependent local ear skin release of the serotonin required to initiate contact sensitivity in mice. *Int Arch Allergy Immunol* 107:364.

41. Ptak, W., G.P. Geba, and P.W. Askenase. 1991. Initiation of delayed-type hypersensitivity by low doses of monoclonal IgE antibody. Mediation by serotonin and inhibition by histamine. *J Immunol* 146:3929-3936.

42. Bryce, P.J., M.L. Miller, I. Miyajima, M. Tsai, S.J. Galli, and H.C. Oettgen. 2004. Immune sensitization in the skin is enhanced by antigen-independent effects of IgE. *Immunity* 20:381-392.

43. Yokozeki, H., M.H. Wu, K. Sumi, K. Igawa, Y. Miyazaki, I. Katayama, K. Takeda, S. Akira, and K. Nishioka. 2003. Th2 cytokines, IgE and mast cells play a crucial role in the induction of para-phenylenediamine-induced contact hypersensitivity in mice. *Clin Exp Immunol* 132:385-392.

44. Askenase, P.W., H. Van Loveren, S. Kraeuter-Kops, Y. Ron, R. Meade, T.C. Theoharides, J.J. Nordlund, H. Scovern, M.D. Gerhson, and W. Ptak. 1983. Defective elicitation of delayed-type hypersensitivity in W/Wv and SI/SId mast cell-deficient mice. *J Immunol* 131:2687-2694.

45. Geba, G.P., W. Ptak, G.M. Anderson, V. Paliwal, R.E. Ratzlaff, J. Levin, and P.W. Askenase. 1996. Delayed-type hypersensitivity in mast cell-deficient mice: dependence on platelets for expression of contact sensitivity. *J Immunol* 157:557-565.

46. Biedermann, T., M. Kneilling, R. Mailhammer, K. Maier, C.A. Sander, G. Kollias, S.L. Kunkel, L. Hultner, and M. Rocken. 2000. Mast cells control neutrophil recruitment during T cell-mediated delayed-type hypersensitivity reactions through tumor necrosis factor and macrophage inflammatory protein 2. *J Exp Med* 192:1441-1452.

47. Galli, S.J., B.K. Wershil, and Y.A. Mekori. 1987. Analysis of mast cell function in biological responses not involving IgE. *Int Arch Allergy Appl Immunol* 82:269-271.

48. Thomas, W.R. and J.W. Schrader. 1983. Delayed hypersensitivity in mast-cell-deficient mice. *J Immunol* 130:2565-2567.

49. Galli, S.J. and I. Hammel. 1984. Unequivocal delayed hypersensitivity in mast cell-deficient and beige mice. *Science* 226:710-713.

50. Mekori, Y.A. and S.J. Galli. 1985. Undiminished immunologic tolerance to contact sensitivity in mast cell-deficient W/Wv and Sl/Sld mice. *J Immunol* 135:879-885.

51. Ha, T.Y., N.D. Reed, and P.K. Crowle. 1986. Immune response potential of mast cell-deficient W/Wv mice. *Int Arch Allergy Appl Immunol* 80:85-94.

52. Mekori, Y.A., J.C. Chang, B.K. Wershil, and S.J. Galli. 1987. Studies of the role of mast cells in contact sensitivity responses. Passive transfer of the reaction into mast cell-deficient mice locally reconstituted with cultured mast cells: effect of reserpine on transfer of the reaction with DNP-specific cloned T cells. *Cell Immunol* 109:39-52.

53. Seike, M., T. Takata, M. Ikeda, H. Kodama, T. Terui, and H. Ohtsu. 2005. Histamine helps development of eczematous lesions in experimental contact dermatitis in mice.

Arch Dermatol Res 297:68-74.

54. Suto, H., S. Nakae, M. Kakurai, J.D. Sedgwick, M. Tsai, and S.J. Galli. 2006. Mast cell-associated TNF promotes dendritic cell migration. *J Immunol* 176:4102-4112.

55. Johnson, E.E., J.S. Irons, R. Patterson, and M. Roberts. 1974. Serum IgE concentration in atopic dermatitis. Relationship to severity of disease and presence of atopic respiratory disease. *J Allergy Clin Immunol* 54:94-99.

56. Soter, N.A. 1989. Morphology of atopic eczema. *Allergy* 44 Suppl 9:16-19.

57. Irani, A.M., H.A. Sampson, and L.B. Schwartz. 1989. Mast cells in atopic dermatitis. *Allergy* 44 Suppl 9:31-34.

58. Ring, J. and P. Thomas. 1989. Histamine and atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 144:70-77.

59. Obara, W., Y. Kawa, C. Ra, K. Nishioka, Y. Soma, and M. Mizoguchi. 2002. T cells and mast cells as a major source of interleukin-13 in atopic dermatitis. *Dermatology* 205:11-17.

60. Horsmanheimo, L., I.T. Harvima, A. Jarvikallio, R.J. Harvima, A. Naukkarinen, and M. Horsmanheimo. 1994. Mast cells are one major source of interleukin-4 in atopic dermatitis. *Br J Dermatol* 131:348-353.

61. Spergel, J.M., E. Mizoguchi, H. Oettgen, A.K. Bhan, and R.S. Geha. 1999. Roles of TH1 and TH2 cytokines in a murine model of allergic dermatitis. *J Clin Invest* 103:1103-1111.

62. Groneberg, D.A., C. Bester, A. Grutzkau, F. Serowka, A. Fischer, B.M. Henz, and P. Welker. 2005. Mast cells and vasculature in atopic dermatitis--potential stimulus of neoangiogenesis. *Allergy* 60:90-97.

63. Cox, H.E., M.F. Moffatt, J.A. Faux, A.J. Walley, R. Coleman, R.C. Trembath, W.O. Cookson, and J.I. Harper. 1998. Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 138:182-187.

64. Badertscher, K., M. Bronnimann, S. Karlen, L.R. Braathen, and N. Yawalkar. 2005. Mast cell chymase is increased in chronic atopic dermatitis but not in psoriasis. *Arch Dermatol Res* 296:503-506.

65. Mao, X.Q., T. Shirakawa, T. Yoshikawa, K. Yoshikawa, M. Kawai, S. Sasaki, T. Enomoto, T. Hashimoto, J. Furuyama, J.M. Hopkin, and K. Morimoto. 1996. Association between genetic variants of mast-cell chymase and eczema. *Lancet* 348:581-583.

66. Alenius, H., D. Laouini, A. Woodward, E. Mizoguchi, A.K. Bhan, E. Castigli, H.C. Oettgen, and R.S. Geha. 2002. Mast cells regulate IFN-gamma expression in the skin and circulating IgE levels in allergen-induced skin inflammation. *J Allergy Clin Immunol* 109:106-113.

67. Tam, S.Y., M. Tsai, J.N. Snouwaert, J. Kalesnikoff, D. Scherrer, S. Nakae, D. Chatterjea, D.M. Bouley, and S.J. Galli. 2004. RabGEF1 is a negative regulator of mast cell activation and skin inflammation. *Nat Immunol* 5:844-852.

68. Watanabe, N., Y. Tomimori, K. Saito, K. Miura, A. Wada, M. Tsudzuki, and Y. Fukuda. 2002. Chymase inhibitor improves dermatitis in NC/Nga mice. *Int Arch Allergy Immunol* 128:229-234.

69. Vigo, P.G., K.R. Girgis, B.L. Pfuetze, M.E. Critchlow, J. Fisher, and I. Hussain. 2006. Efficacy of anti-IgE therapy in patients with atopic dermatitis. *J Am Acad Dermatol* 55:168-170.

70. Wintroub, B.U., M.C. Mihm Jr, E.J. Goetzl, N.A. Soter, and K.F. Austen. 1978.

Morphologic and functional evidence for release of mast-cell products in bullous pemphigoid. *N Engl J Med* 298:417-421.

71. Dvorak, A.M., M.C. Mihm Jr, J.E. Osage, T.H. Kwan, K.F. Austen, and B.U. Wintroub. 1982. Bullous pemphigoid, an ultrastructural study of the inflammatory response: eosinophil, basophil and mast cell granule changes in multiple biopsies from one patient. *J Invest Dermatol* 78:91-101.

72. Baba, T., H. Sonozaki, K. Seki, M. Uchiyama, Y. Ikesawa, and M. Toriisu. 1976. An eosinophil chemotactic factor present in blister fluids of bullous pemphigoid patients. *J Immunol* 116:112-116.

73. Katayama, I., T. Doi, and K. Nishioka. 1984. High histamine level in the blister fluid of bullous pemphigoid. *Arch Dermatol Res* 276:126-127.

74. Brockow, K., D. Abeck, K. Hermann, and J. Ring. 1996. Tryptase concentration in skin blister fluid from patients with bullous skin conditions. *Arch Dermatol Res* 288:771-773.

75. D'Auria, L., M. Pietravalle, P. Cordiali-Fei, and F. Ameglio. 2000. Increased tryptase and myeloperoxidase levels in blister fluids of patients with bullous pemphigoid: correlations with cytokines, adhesion molecules and anti-basement membrane zone antibodies. *Exp Dermatol* 9:131-137.

76. Kaminska, R., P. Helisalmi, R.J. Harvima, A. Naukkarinen, M. Horsmanheimo, and I.T. Harvima. 1999. Focal dermal-epidermal separation and fibronectin cleavage in basement membrane by human mast cell tryptase. *J Invest Dermatol* 113:567-573.

77. Arbesman, C.E., J.I. Wypych, R.E. Reisman, and E.H. Beutner. 1974. IgE levels in sera of patients with pemphigus or bullous pemphigoid. *Arch Dermatol* 110:378-381.

78. Dopp, R., E. Schmidt, I. Chimanovitch, M. Leverkus, E.B. Brocker, and D. Zillikens. 2000. IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in Bullous pemphigoid: serum levels of these immunoglobulins reflect disease activity. *J Am Acad Dermatol* 42:577-583.

79. Dimson, O.G., G.J. Giudice, C.L. Fu, F. Van den Bergh, S.J. Warren, M.M. Janson, and J.A. Fairley. 2003. Identification of a potential effector function for IgE autoantibodies in the organ-specific autoimmune disease bullous pemphigoid. *J Invest Dermatol* 120:784-788.

80. Fairley, J.A., C.L. Fu, and G.J. Giudice. 2005. Mapping the binding sites of anti-BP180 immunoglobulin E autoantibodies in bullous pemphigoid. *J Invest Dermatol* 125:467-472.

81. Liu, Z., L.A. Diaz, J.L. Troy, A.F. Taylor, D.J. Emery, J.A. Fairley, and G.J. Giudice. 1993. A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. *J Clin Invest* 92:2480-2488.

82. Liu, Z., G.J. Giudice, S.J. Swartz, J.A. Fairley, G.O. Till, J.L. Troy, and L.A. Diaz. 1995. The role of complement in experimental bullous pemphigoid. *J Clin Invest* 95:1539-1544.

83. Liu, Z., G.J. Giudice, X. Zhou, S.J. Swartz, J.L. Troy, J.A. Fairley, G.O. Till, and L.A. Diaz. 1997. A major role for neutrophils in experimental bullous pemphigoid. *J Clin Invest* 100:1256-1263.

84. Chen, R., G. Ning, M.L. Zhao, M.G. Fleming, L.A. Diaz, Z. Werb, and Z. Liu. 2001. Mast cells play a key role in neutrophil recruitment in experimental bullous pemphigoid.

J Clin Invest 108:1151-1158.

85. Hawkins, R.A., H.N. Claman, R.A. Clark, and J.C. Steigerwald. 1985. Increased dermal mast cell populations in progressive systemic sclerosis: a link in chronic fibrosis? *Ann Intern Med* 102:182-186.

86. Nishioka, K., Y. Kobayashi, I. Katayama, and C. Takijiri. 1987. Mast cell numbers in diffuse scleroderma. *Arch Dermatol* 123:205-208.

87. Seibold, J.R., R.C. Giorno, and H.N. Claman. 1990. Dermal mast cell degranulation in systemic sclerosis. *Arthritis Rheum* 33:1702-1709.

88. Irani, A.M., B.L. Gruber, L.D. Kaufman, M.B. Kahaleh, and L.B. Schwartz. 1992. Mast cell changes in scleroderma. Presence of MCT cells in the skin and evidence of mast cell activation. *Arthritis Rheum* 35:933-939.

89. Akimoto, S., O. Ishikawa, Y. Igarashi, M. Kurosawa, and Y. Miyachi. 1998. Dermal mast cells in scleroderma: their skin density, tryptase/chymase phenotypes and degranulation. *Br J Dermatol* 138:399-406.

90. Green, M.C., H.O. Sweet, and L.E. Bunker. 1976. Tight-skin, a new mutation of the mouse causing excessive growth of connective tissue and skeleton. *Am J Pathol* 82:493-512.

91. Menton, D.N. and R.A. Hess. 1980. The ultrastructure of collagen in the dermis of tight-skin (Tsk) mutant mice. *J Invest Dermatol* 74:139-147.

92. Walker, M., R. Harley, J. Maize, F. DeLustro, and E.C. LeRoy. 1985. Mast cells and their degranulation in the Tsk mouse model of scleroderma. *Proc Soc Exp Biol Med* 180:323-328.

93. Walker, M.A., R.A. Harley, and E.C. LeRoy. 1987. Inhibition of fibrosis in TSK mice

by blocking mast cell degranulation. *J Rheumatol* 14:299-301.

94. Walker, M., R. Harley, and E.C. LeRoy. 1990. Ketotifen prevents skin fibrosis in the tight skin mouse. *J Rheumatol* 17:57-59.

95. Everett, E.T., J.L. Pablos, R.A. Harley, E.C. LeRoy, and J.S. Norris. 1995. The role of mast cells in the development of skin fibrosis in tight-skin mutant mice. *Comp Biochem Physiol A Physiol* 110:159-165.

96. Wang, H.W., N. Tedla, J.E. Hunt, D. Wakefield, and H.P. McNeil. 2005. Mast cell accumulation and cytokine expression in the tight skin mouse model of scleroderma. *Exp Dermatol* 14:295-302.

97. Kihira, C., H. Mizutani, K. Asahi, H. Hamanaka, and M. Shimizu. 1998. Increased cutaneous immunoreactive stem cell factor expression and serum stem cell factor level in systemic scleroderma. *J Dermatol Sci* 20:72-78.

98. Yamamoto, T., S. Takagawa, I. Katayama, K. Yamazaki, Y. Hamazaki, H. Shinkai, and K. Nishioka. 1999. Animal model of sclerotic skin. I: Local injections of bleomycin induce sclerotic skin mimicking scleroderma. *J Invest Dermatol* 112:456-462.

99. Yamamoto, T., Y. Takahashi, S. Takagawa, I. Katayama, and K. Nishioka. 1999. Animal model of sclerotic skin. II. Bleomycin induced scleroderma in genetically mast cell deficient WBB6F1-W/W(V) mice. *J Rheumatol* 26:2628-2634.

100. Yamamoto, T. 2006. The bleomycin-induced scleroderma model: what have we learned for scleroderma pathogenesis? *Arch Dermatol Res* 297:333-344.

101. Gruber, B.L. 1995. Mast cells: accessory cells which potentiate fibrosis. *Int Rev Immunol* 12:259-279.

102. Jeong, W.I., C.S. Lee, S.J. Park, J.Y. Chung, and K.S. Jeong. 2002. Kinetics of

macrophages, myofibroblasts and mast cells in carbon tetrachloride-induced rat liver cirrhosis. *Anticancer Res* 22:869-877.

103. Toth, T., R. Toth-Jakatics, S. Jimi, M. Ihara, H. Urata, and S. Takebayashi. 1999. Mast cells in rapidly progressive glomerulonephritis. *J Am Soc Nephrol* 10:1498-1505.

104. Kondo, S., S. Kagami, H. Kido, F. Strutz, G.A. Muller, and Y. Kuroda. 2001. Role of mast cell tryptase in renal interstitial fibrosis. *J Am Soc Nephrol* 12:1668-1676.

105. Claman, H.N. 1989. On scleroderma. Mast cells, endothelial cells, and fibroblasts. *JAMA* 262:1206-1209.

106. Gruber, B.L. 2003. Mast cells in the pathogenesis of fibrosis. *Curr Rheumatol Rep* 5:147-153.

107. Jordana, M., A.D. Befus, M.T. Newhouse, J. Bienenstock, and J. Gauldie. 1988. Effect of histamine on proliferation of normal human adult lung fibroblasts. *Thorax* 43:552-558.

108. Hatamochi, A., K. Fujiwara, and H. Ueki. 1985. Effects of histamine on collagen synthesis by cultured fibroblasts derived from guinea pig skin. *Arch Dermatol Res* 277:60-64.

109. Gruber, B.L., R.R. Kew, A. Jelaska, M.J. Marchese, J. Garlick, S. Ren, L.B. Schwartz, and J.H. Korn. 1997. Human mast cells activate fibroblasts: tryptase is a fibrogenic factor stimulating collagen messenger ribonucleic acid synthesis and fibroblast chemotaxis. *J Immunol* 158:2310-2317.

110. Cairns, J.A. and A.F. Walls. 1997. Mast cell tryptase stimulates the synthesis of type I collagen in human lung fibroblasts. *J Clin Invest* 99:1313-1321.

111. Abe, M., M. Kurosawa, Y. Igarashi, O. Ishikawa, and Y. Miyachi. 2000. Influence

of IgE-mediated activation of cultured human mast cells on proliferation and type I collagen production by human dermal fibroblasts. *J Allergy Clin Immunol* 106:S72-77.

112. Claman, H.N. 1990. Mast cells and fibrosis. The relevance to scleroderma. *Rheum Dis Clin North Am* 16:141-151.

113. Sullivan, K.M., H.M. Shulman, R. Storb, P.L. Weiden, R.P. Witherspoon, G.B. McDonald, M.M. Schubert, K. Atkinson, and E.D. Thomas. 1981. Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood* 57:267-276.

114. Jaffee, B.D. and H.N. Claman. 1983. Chronic graft-versus-host disease (GVHD) as a model for scleroderma. I. Description of model systems. *Cell Immunol* 77:1-12.

115. Claman, H.N., B.D. Jaffee, J.C. Huff, and R.A. Clark. 1985. Chronic graft-versus-host disease as a model for scleroderma. II. Mast cell depletion with deposition of immunoglobulins in the skin and fibrosis. *Cell Immunol* 94:73-84.

116. Claman, H.N., K.L. Choi, W. Sujansky, and A.E. Vatter. 1986. Mast cell "disappearance" in chronic murine graft-vs-host disease (GVHD)-ultrastructural demonstration of "phantom mast cells". *J Immunol* 137:2009-2013.

117. Choi, K.L., R. Giorno, and H.N. Claman. 1987. Cutaneous mast cell depletion and recovery in murine graft-vs-host disease. *J Immunol* 138:4093-4101.

118. Levi-Schaffer, F., Y.A. Mekori, V. Segal, and H.N. Claman. 1990. Histamine release from mouse and rat mast cells cultured with supernatants from chronic murine graft-vs-host splenocytes. *Cell Immunol* 127:146-158.

119. Levi-Schaffer, F., M.A. Goldenhersh, V. Segal, and A. Nagler. 1997. Nedocromil sodium ameliorates skin manifestations in a murine model of chronic graft-versus-host

disease. *Bone Marrow Transplant* 19:823-828.

120. Murphy, G.F., H. Sueki, C. Teuscher, D. Whitaker, and R. Korngold. 1994. Role of mast cells in early epithelial target cell injury in experimental acute graft-versus-host disease. *J Invest Dermatol* 102:451-461.

121. Levi-Schaffer, F., V. Segal, Y.A. Mekori, H.N. Claman, and I. Hammel. 1991. Morphological evidence for chronic mast cell activation after prolonged exposure with supernatants from chronic graft-versus-host splenocytes. *Immunol Lett* 27:13-18.

122. Geha, R.S., J.M. Rappaport, F.J. Twarog, R. Parkman, and F.S. Rosen. 1980. Increased serum immunoglobulin E levels following allogeneic bone marrow transplantation. *J Allergy Clin Immunol* 66:78-81.

123. Heyd, J., A.D. Donnenberg, W.H. Burns, R. Saral, and G.W. Santos. 1988. Immunoglobulin E levels following allogeneic, autologous, and syngeneic bone marrow transplantation: an indirect association between hyperproduction and acute graft-v-host disease in allogeneic BMT. *Blood* 72:442-446.

124. Claman, H.N. and H.L. Spiegelberg. 1990. Immunoglobulin dysregulation in murine graft-vs-host disease: a hyper-IgE syndrome. *Clin Immunol Immunopathol* 56:46-53.

125. Doutrelepont, J.M., M. Moser, O. Leo, D. Abramowicz, M.L. Vanderhaegen, J. Urbain, and M. Goldman. 1991. Hyper IgE in stimulatory graft-versus-host disease: role of interleukin-4. *Clin Exp Immunol* 83:133-136.

126. Ushiyama, C., T. Hirano, H. Miyajima, K. Okumura, Z. Ovary, and H. Hashimoto. 1995. Anti-IL-4 antibody prevents graft-versus-host disease in mice after bone marrow transplantation. The IgE allotype is an important marker of graft-versus-host disease. *J Immunol* 154:2687-2696.

127. Korngold, R., B.A. Jameson, J.M. McDonnell, C. Leighton, B.J. Sutton, H.J. Gould, and G.F. Murphy. 1997. Peptide analogs that inhibit IgE-Fc epsilon RI alpha interactions ameliorate the development of lethal graft-versus-host disease. *Biol Blood Marrow Transplant* 3:187-193.

128. Kovarova, M. and J. Rivera. 2004. A molecular understanding of mast cell activation and the promise of anti-allergic therapeutics. *Curr Med Chem* 11:2083-2091.

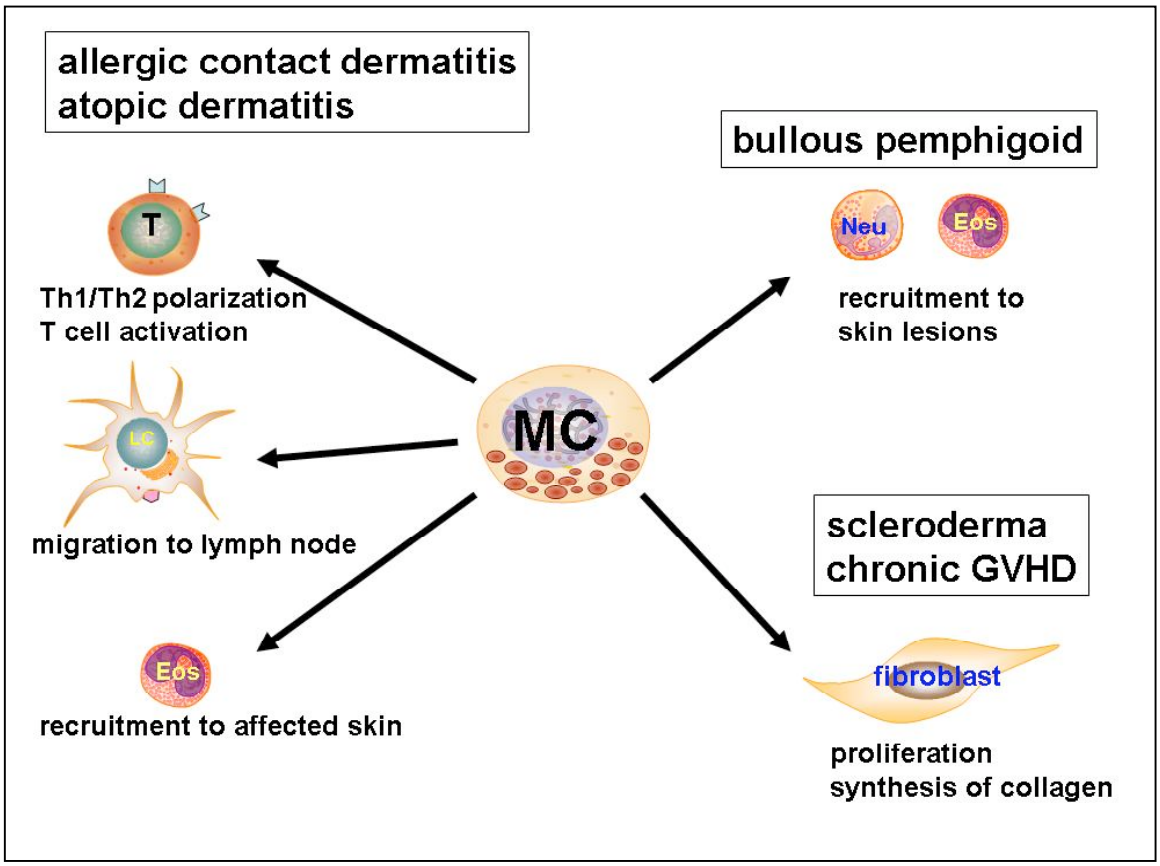

Figure 1. Role of mast cells in immunological skin diseases. Mast cells are found to be increased in number and undergo degranulation in contact dermatitis, atopic dermatitis, immunobullous disease, scleroderma, and cGVHD. The roles of mast cells in these diseases are suggested by the known effects of these cells on the immune and inflammatory cells, through mediators, cytokines and chemokines they produce. Studies of mouse models of these diseases have further supported the contributions of this cell type to their pathogenesis. In the case of contact and atopic dermatitis, mast cells are likely to contribute to Th1/Th2 polarization, migration of Langerhans cells to lymph nodes, and recruitment of eosinophils to the lesional skin. In the case of immunobullous disease, recruitment of neutrophils and eosinophils by mast cells may contribute to blister formation. In the case of scleroderma and cGVHD, the activation of fibroblasts by mast cells may be one of the primary underlying causes of fibrosis.