DOI:10.1111/j.1600-0625.2009.00860.x
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Mast cells: novel clinical perspectives from recent insights

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Accepted for publication 19 January 2009

Abstract: Mast cells are still generally viewed as mediators of type I allergic or pseudoallergic reactions. Research over the past 10 years revealed that our view was too small and that mast cells are of key importance in innate immunity and also types II, III and IV adaptive immune reactions. Understanding their role in modulating and amplifying of inflammatory responses provides important insights into the pathogenesis of skin diseases such as psoriasis, atopic dermatitis, bullous pemphigoid or the control of infections. This helps us to understand the course of these diseases, their trigger mechanisms, and, the new role of agents, which can modulate the function of mast cells. These insights will help to develop new therapeutic approaches.

Key words: adaptive immunity – antigen presenting cells – innate immunity – mast cells – skin infection – skin inflammation – skin tumor – T cells

Please cite this paper as: Mast cells: novel clinical perspectives from recent insights. Experimental Dermatology 2009; 18: 488–496.

Classical role of mast cells

Mast cells were widely viewed in the context of immediate type immune reactions. This is surprising, as mast cells store not only histamine, prostaglandins and leucotrienes, but also a large array of cytokines, chemokines, including immediate type cytokines, such as IL-4 that modulates antigen presenting cell (APC) functions or TNF. In consequence, mast cells also affect more complex immune responses including T-cell or B-cell-mediated immunity. Importantly, mast cells affect both the priming during innate and the effector phase during adaptive immune responses (1–6). Thus, mast cells influence all four types of the 'Coombs and Gell' immune reactions (Table 1). Mast cells may be activated either immunologically or through 'none immune' mechanisms, for example, by drugs, haptens and physically modulated stimuli such as pressure, cold or heat (6,7). Mast cells were first described in 1877 by Paul Ehrlich based on the unique staining characteristics of there cytoplasmic granules (8). Mast cells are established as central effector cells of IgE-mediated immediate-type immune responses, such as anaphylaxis, allergic rhinitis, asthma or urticaria (9). Anaphylaxis and acute urticaria are common disorders that often prompt patients to seek emergency treatment. Mast cells express the high affinity FcεRI receptor and become activated through cross-linking of these receptors, when occupied by the Fc part of IgE molecules. This initiates a well-defined signalling cascade, including calcium ion influx, phospholipid methylation and cyclic nucleotide metabolism that ultimately results in the release of mediators responsible for vasodilatation and serum extravasation as they occur during allergic rhinitis, type I allergic reactions to bee venom or anaphylactic shock. Depending on the mode of mast cell activation, a broad but selective spectrum of preformed vasoactive, chemotactic, pro-inflammatory and immunoregulatory mediators is released within minutes (Fig. 1). In contrast to other cells, mast cells are capable to store preformed mediators in large quantities. These mediators can be released within minutes including TNF, histamines, proteases, leucotriene C_4 (LTC_4) and prostaglandin D_2 (PGD_2) (2,5,6,9–12) (Fig. 1).

It is now clear that mast cells are not only critical for effector functions of classic IgE-associated allergic disorders and pseudoallergies but also play an essential role in the host defense against parasites, bacteria and viruses, in contact hypersensitivity reactions (CHSR), and even influence the manifestation of autoimmune diseases, including multiple sclerosis, rheumatoid arthritis (RA), psoriasis or bullous pemphigoid (BP) (2,5,6,9,10,12–14). Especially disease models of severe inflammatory autoimmune diseases reveal that neutrophil infiltration into sites of local inflammation and tissue destruction are critically influenced by mast cells (15–19).

Table 1. Mast cell involvement in immune reactions listed according to the 'Coombs and Gell' classification

Hypersensitivity reaction	
I	Allergic rhinitis
	Allergic asthma
	Anaphylaxis
	Urticaria
II	Bullous pemphipoid
III	Systemic lupus erythematodes
	Arthus reaction
	Rheumatoid arthritis
	Autoimmune vasculitis
IV	Contact hypersensitivity reaction
	Psoriasis
	Multiple sclerosis
	Graft-versus-host disease
	Insulin-dependent diabetes

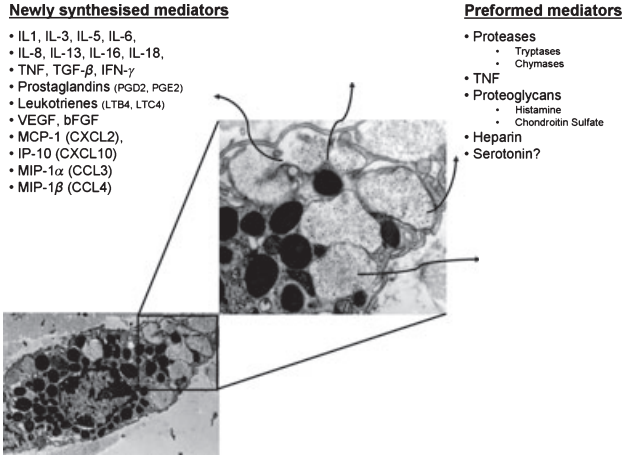

Figure 1. Activation of human mast cells results in the release of a wide array of preformed and newly synthesized cell mediators. Transmission electron micrograph of a skin mast cell with full cytoplasmatic granules. TNF, tumor necrosis factor; IFN, interferon; TGF, tissue growth factor; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; MCP, monocyte chemotactic protein; IP, interferon-inducible protein; MIP, macrophage inflammatory protein; IL, interleukin.

Mast cell distribution patterns

Mast cells are perfectly equipped with a wide range of receptors capable of recognizing danger signals from foreign structures. They are mainly located at the barrier between self and environment, the skin, gut and lung. In solid tissues, they localize close to capillaries and lymphatic vessels. Mast cells further accumulate near smooth muscle cells, hair follicles or are connected to the nervous system through nerve endings (2,6,20). Thus, in the upper dermis reside up to 10-fold more mast cells than in the subcutis. Analysis of human skin mast cell populations by total body surface mapping revealed no differences between males and females, young or adults. Yet, intra-individual mapping showed clear differences that correlate with the density of nerve endings. Mast cell numbers were highest at the extremities like fingers, chin and nose, and lowest at the trunk (20). Approximately 30–40 mast cell/mm^2 were found in the dermis of the trunk; at the head and the distal extremities, density was 1.5- to 2-fold higher (20).

Tissue-specific patterns of mast cell granules

Mast cells arise from haematopoietic progenitor cells and acquire their mature phenotype in the local tissue where they reside. Therefore, mature mast cells normally do not circulate in the blood. Inside tissues, mast cell-specific phenotypes are associated with a partly tissue-specific pattern of mediators in their granules. Based on patterns of proteinases, human mast cells can be divided into mainly tryptase and chymase (MC_{TC}), tryptase (MC_T) or chymase (MC_C) containing subtypes. In the dermis of the skin and submucosa, the MC_{TC} mast cell type predominates, whereas MC_T mast cells predominate in the lung and bowel submucosa (21–23). Moreover, mast cell numbers, tissue distribution and mast cell functions change inside tissues, organs and lymphoid structures during the course of immune responses. Thus, the number of mast cells in inflamed tissues can be regulated by mast cell proliferation, migration and survival. Chronic inflammation induces proliferation of resident tissue mast cells and additionally recruitment of mast cells from the periphery (2,24).

Classical mast cell-associated diseases

Immediate type reactions

Mast cells are long established as central mediators of whealing reactions. Through the release of histamine, heparin, tryptases, chymases, TNF, PGD_2 and leukotriene B_4 (LTB_4), they mediate whealing during allergic reactions, pseudo-allergic reactions (i.e. drug-induced mast cell activation) and in response to physical trauma (25–29). This function became evident by data showing that mast cells are the central source of histamine and leucotrienes released upon IgE-signalling through FcεRI (9,30–32). Immediate type hypersensitivity reactions (type I) are principally mediated by protein antigens binding to IgE antibodies attached to tissue mast cells trough the Fc-part. Mast cells are the major tissue population expressing the high affinity receptor for IgE, FcεR1. Exposure of IgE-binding mast cells to the corresponding antigen results in release of preformed histamine and lipid-derived mediators (PGD_2 and LTB_4) that cause the acute symptoms of early

phase immune reactions including vasodlilation, increase in vascular permeability, contraction of bronchial smooth muscle, mucus secretion, sneezing, itching or coughing (9,33,34). The rapid systemic release of histamine, PGD_2 or LTB_4 also accounts for most of the pathology associated with anaphylaxis. In addition, mast cells rapidly release in response to IgE cross-linking a broad range of glycoproteins and newly synthesized mediators, starting within minutes. These mediators also initiate the so-called late-phase reactions that typically develop 2–6 h after allergen exposure and peak after 6–9 h (9).

As histamine causes vasodilatation and serum exudation, antihistamines were developed to impair histamine release. The goal for these compounds is to prevent whealing reactions, allergic rhinitis and often also urticaria. Antihistamines also may improve bronchial constriction or vasodilatation during immediate type allergic reactions (35–38).

Mastocytosis

Mastocytosis is another well-established mast cell-associated group of diseases. Mastocytosis is a benign proliferation of mast cells. It is frequently associated with intracellular mutations of the kit receptor (39,40). Mastocytosis most frequently affects the skin with dome-shaped brownish papules, sometimes macules that show whealing in response to physical trauma. Besides the skin, bone marrow, the intestine or spleen are most frequently involved.

In mastocytosis, mast cells aberrantly proliferate in a controlled, benign fashion leading to localized tumors, the mastocytomas (Fig. 2a,c) or disseminated mastocytosis (41–46) (Fig. 2b). Only very rarely this mast cell proliferation turns into malignant mastocytosis (47,48). In patients with systemic mastocytosis, serum levels of the mast cell-derived enzyme, mast cell tryptase, closely correlate with the degree of mast cell expansion *in vivo*. Today serum mast cell tryptase is the best-established parameter evaluating the clinical extend of systemic mast cell proliferation (49,50). Serum levels of mast cell tryptase >20 ng/ml are generally considered to demand further investigations, such as bone marrow biopsy and gastro-duodenoscopy. In the skin, the brown hyperpigmentation of mastocytomas is a direct consequence of melanocyte activation through c-kit/CD117 expressed by melanocytes and the mediator stem cell factor (SCF) released by dermal mast cells (39,51–53).

Mast cells in T-cell-mediated inflammation

Various disease models of severe inflammatory autoimmune diseases reveal that neutrophil-infiltration into sites of local inflammation and tissue destruction critically depend on mast cells. Thus, mast cells are involved in the initiation of experimental models of CHSR (16), psoriasis and RA (6,17,18) or bacterial infection (19,54–58). These observations seem to be of high relevance for human disease, as large numbers of activated mast cells infiltrate the tissues in the corresponding human diseases, such as allergic contact dermatitis, psoriasis or RA (59–63). Besides these diseases, mast cells are enrolled in multiple inflammatory and malignant diseases (Table 2). As mast cells modulate also other, T-cell-mediated diseases, such as experimental allergic encephalitis (EAE) (6) the model disease of multiple sclerosis, we review the potential role of mast cells in T-cell-mediated diseases. Most of the *in vivo* mast cell research was performed with mast cell-deficient

Table 2. Dermatological diseases with evidence for mast cell involvement

Anaphylaxis
Hay fever
Urticaria
Localized mastocytomas
Disseminated mastocytosis
Mast cell leukaemia
Contact dermatitis
Psoriasis and psoriasis arthritis
Atopic dermatitis
Bullous autoimmune diseases (bullous pemphigoid)
Autoimmune vasculitis
Systemic lupus erythematodes
Systemic sclerosis and morphea
Chronic graft-versus-host disease
Morbus Morbihan and rosazea
Skin infections
Bacteria, fungi
Parasites (Leishmania major)
Skin tumors (basal cell carcinoma, spinocellular carcinoma, angiosarcoma)

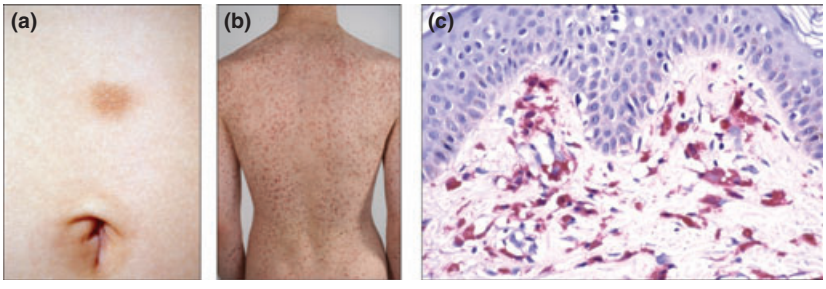

Figure 2. Clinical image of a (a) local mastocytoma and (b) disseminated mastcoytosis. (c) Mast cell tryptase staining confirmed a strongly increased number of mast cells.

$Kit^{W}/Kit^{W\text{-}v}$ mice, an experimental model with the limitation that $Kit^{W}/Kit^{W\text{-}v}$ mice have, in addition, macrocytic anaemia, neutropenia and a defect in mobilizing blood neutrophils (5,64) .

Delayed type hypersensitivity reactions and contact hypersensitivity reactions

Mast cells are increasingly recognized to be critical for the initiation and translation of T-cell-mediated delayed type hypersensitivity reactions (DTHR) and T-cell-mediated autoimmune diseases. Thus CHSR, are adaptive immune responses mediated by IFN-γ producing $CD4^{+}$ T cells (Th1) and interleukin (IL) 17 producing $CD4^{+}$ T cells (Th17) or IFN-γ producing $CD8^{+}$ T cells (Tc1) (65–68). In CHSR, the number of mast cells is increased and mast cells are activated (60). In 1983, it was first experimentally shown that mast cell-deficient mice have attenuated CHSR (69). Yet, the role of mast cells in CHSR was long under debate, as WBB6F1-$Kit^{W}/Kit^{W\text{-}v}$ mice also have several other abnormalities, such as macrocytic anaemia, decreased numbers of bone marrow and blood neutrophils (5). Furthermore, the dependence of mast cells on CHSR can be overcome if very strong stimuli are used for CHSR (16,70). This discrepancy was resolved, once mast cells could be cultured *in vitro* and selectively transplanted into sites of interest. This *knock-in* approach allows detailed analysis of mast cell functions and distinct mast cell mediators and receptors. Mast cell *knock-in* experiments clearly showed that the key function of mast cells is that of a powerful modulator and amplifier of innate and adaptive immune responses. Thus, mast cells exert a key function in inflammatory diseases, such as EAE, RA, inflammatory bowel disease or CHSR. For T-cell-mediated adaptive immune responses, this was first shown for hapten-induced DTHRs of the skin. There, mast cells determine T-cell-dependent neutrophil recruitment through TNF and the CXC chemokine macrophage inflammatory protein 2 (MIP-2), the mouse equivalent of IL-8. Both, tissue inflammation and neutrophil recruitment are severely impaired in mast cell-deficient $Kit^{W}/Kit^{W\text{-}v}$ mice. Mast cells derived from wild-type mice efficiently restore both clinical and histological manifestations of DTHR and IL-8-dependent neutrophil recruitment in $Kit^{W}/Kit^{W\text{-}v}$ mice. Importantly, mast cells from TNF.KO mice fail to restore this DTHR, showing that mast cell-derived TNF is essential for appropriate manifestation of tissue damage and neutrophil recruitment. Similar results were shown for IL-8. Both mast cell-derived mediators are critical for neutrophil recruitment, as TNF and IL-8 provide two qualitatively different but synergistic signals. One major biological significance of TNF is the induction of adhesion molecules required for neurgophil attachment to endothelial cells (Kneilling, M. et al., unpublished data), whereas IL-8 establishes the chemotactic gradient required for diapedesis and directed migration of neutrophils (Fig. 3). The knock-in approach showed that the deficiency in ear swelling responses and neutrophil recruitment in $Kit^{W}/Kit^{W\text{-}v}$ mice are directly caused by the missing mast cells. This was important to demonstrate, as Kit-deficient mice have multiple defects in their haematopoietic system (71). Analysis of CHSR revealed that mast-cell deficient mice normally develop IFN-γ-producing Th1 cells showing that the major role of mast cells is the translation of T-cell responses into an inflammatory response, but not T-cell priming or T-cell differentiation (16).

Using knock-in experiments with selective reconstitution of either distinct T-cell populations (Th1, Tc1), or distinct mast cell populations into either control, TNFR1.KO, TNF.KO or $Kit^{W}/Kit^{W\text{-}v}$ mice, we found that Th1 or Tc1 cells can normally develop in TNFR1.KO and TNF.KO mice. Dissecting the single steps of DTHR, starting with *in vivo* T-cell priming through T-cell differentiation and T-cell effector functions, we localized the defect downstream of the T-cell–mast cell interaction. In TNFR1.KO mice, TNF-producing mast cells were exclusively unable to translate T-cell-mediated DTHR. Phenotypically, TNF.KO, TNFR1.KO and $Kit^{W}/Kit^{W\text{-}v}$ mice show the same defects during CHSR. Currently, it is reasonable to speculate that mast cells promote neutrophil recruitment through TNF-dependent induction of P-selectin, ICAM-1 and VCAM-1 on endothelia. This is deficient in TNFR1.KO mice (72) (Kneilling, M. et al., unpublished data; Fig. 3).

This pathway seems to be of critical relevance and provides a solid explanation for the mode of action of anti-TNF therapy in humans. In line with this, blocking TNF

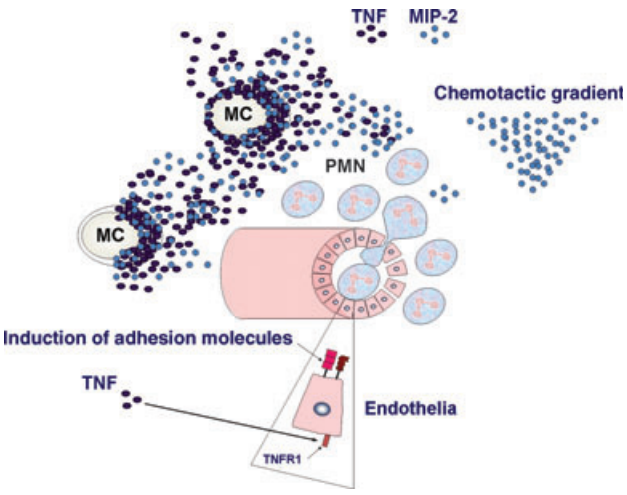

Figure 3. Mast cell-derived TNF and IL-8 are critical for neutrophil recruitment during CHSR. TNF and IL-8 provide two qualitatively different but synergistic signals. TNF induces adhesion molecules required for PMN attachment through TNFR1-expressing endothelial cells, whereas IL-8 establishes the chemotactic gradient required for diapedesis and directed migration of neutrophils.

action in humans is highly effective in diseases that involve neutrophil recruitment such psoriasis, psoriasis arthritis (73–77), RA (73,77–79) or inflammatory bowel disease (73,80).

Mast cells in psoriasis and psoriasis arthritis

Psoriasis, a T-cell-dependent autoimmune disease of the skin and joints, is orchestrated by IFN-γ-producing $CD4^+$ T cells (Th1) and IL-17-producing $CD4^+$ T cells (Th17) interacting with dermal dendritic cells, macrophages, neutrophils, papillary mast cells and keratinocytes (81,82). In line with this, increased numbers of mast cells (MC_{TC}) are present in the papillary dermis (Fig. 4) (22,83). In early psoriasis lesions, mast cells are frequently activated and degranulated, appearing as 'ghost cells'. In psoriasis plaques, approximately 70% of mast cells are positive for IFN-γ, while in contrast only 10% are positive for IFN-γ in atopic dermatitis (AD) (83). As suggested by the experimental data from mice, mast cells seem to play an important role in triggering psoriasis in response to innate or adaptive immune stimuli (84,85).

As valid for many inflammatory diseases, psoriasis may be triggered and exacerbated by mechanical stress that also causes mast cell activation (Koebner phenomenon) (84–88). During early phases of psoriasis triggered by the Koebner phenomenon, mast cell numbers start to significantly increase on day 4 after induction. This increase peaks on day 14 together with the manifestation of psoriasis. In line with this mast cell activation, interstitial histamine concentration are increased (89). Inversely, efficient psoriasis therapy, such as anthralin, reduces mast cell numbers in the skin (22,89,90). Interestingly, topical corticosteroid treatment with 0.05% clobetasol-17-proprionate cream over 4 weeks, a therapy that is normally followed by relapses of pustular psoriasis, reduces the number of mast cells only in unaffected skin (91) but not in psoriatic plaques (22,92,93). Cyclosporine A and bath-PUVA therapy also decrease the number of mast cells and inhibit mast cell activity in psoriatic skin (22,92,94–97). Moreover, in a double-blind, controlled study using 10 mg cetirizine three times per day for 15 days, cetirizine improved the psoriasis area and severity index and significantly decreased the number of tryptase positive mast cells and the expression of adhesion molecules in psoriasis lesions (98,99), further strengthening the impact of mast cells on the manifestation of psoriasis (Fig. 4).

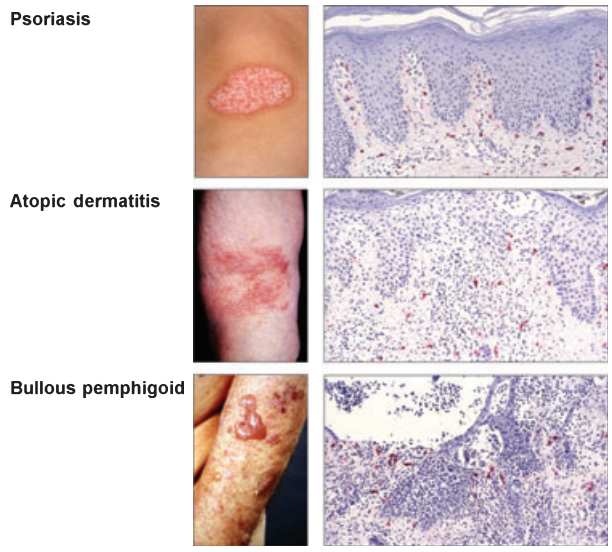

Figure 4. Increased numbers of tryptase positive mast cells in the skin of psoriasis, atopic dermatitis or bullous pemphigoid.

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Psoriasis affects approximately 2–3% of the population and the prevalence of PsA in psoriasis patients is between 6 and 39% (100,101). The relative risk for psoriasis and PsA among first-degree relatives indicates a strong genetic association. PsA (asymmetric oligoarthritis) is negative for rheumatoid factor and can be distinguished from RA (symmetric polyarthritis), which affect 1% of the worlds' population (102) based on demographic data, genetic predisposition, histopathology, radiographic appearance and clinical course (103–105). No differences are found in the expression of either ICAM-1 or VCAM-1, or the numbers of infiltrating T and B cells (106). Synovial fluid, serum and synovial tissue of patients with PsA all show strongly enhanced TNF levels. PsA or RA ultimately results in pathologic proliferation of synovial cells and severe damage of the synovial architecture with pannus formation and destruction of cartilage and bone (102,107–110).

Several experimental animal models allow investigating the mechanisms underlying the cartilage and joint destruction of arthritis. K/BxN mice spontaneously develop a progressive joint-specific autoimmune disease that shares striking similarities with human RA, including spontaneous development, primarily in the distal joints. Adoptive transfer of serum from diseased K/BxN mice induces autoantibody-mediated arthritis in healthy mice that critically depends on mast cells. In this model, we showed that mast cells provide the $\alpha_V\beta 3$ integrin activation associated with PsA (88). Mast cell activation and neo-angiogenesis can all be inhibited by selective mast cell silencing with either salbutamol or cromolyn (18). The critical relevance is underlined by the above-mentioned study, showing that psoriasis improves with continuous application of antihistamines (98,99).

Mast cells in atopic dermatitis

AD results from multiple factors, including changes in the epidermal barrier, innate and adaptive immune system.

The immunological findings include altered Th2 cell regulation, increased IgE production, enhanced dendritic cell signalling and mast cell hyperactivity. The number of mast cells is markedly increased in AD (Fig. 4). Mast cells may exert multiple functions in AD. They release mediators capable of inducing severe pruritus, such as histamine, nerve growth factor (111), IL-6, IL-8 and granulocyte-macrophage colony stimulating factor (112). In line with this, mast cell tryptase mediates itch sensation and release of neuropeptides, such as substance P and neurokinin A that subsequently activate proteinase activated receptor 2 (PAR-2). Expression of tryptase and PAR-2 is increased in AD. It is interesting that chymase-positive mast cells are increased in both lesional and non-lesional skin of AD patients when compared with psoriasis and controls (113). The aggravation of AD in response to stress might result from the direct connection of mast cells with sensory nerve endings. These nerves may be activated through neuropeptides present in mast cells. Therefore, stress may promote development of eczema and itching through the amplification of T-cell-mediated inflammation (87,114). In line with this, it is interesting that topical calcineurin inhibitors may attenuate activated mast cells during treatment of AD (115). Important information comes from treatment of AD with antihistamines. While short periods of therapy with antihistamines rarely influence the course of AD, long-term treatment over several weeks improves AD and reduces consumption of topical steroids in a placebo-controlled trial (116). This is of special interest in view of the animal data showing that mast cells are important amplifiers of immune responses. Thus, it is unlikely that mast cell inhibitors directly improve local inflammation, as do glucocorticosteroids. Animal data propose that mast cell inhibitors rather attenuate the capacity of mast cells to amplify cutaneous inflammation and should improve the long-term outcome as demonstrated by these studies.

Bullous pemphigoid

BP is a blistering autoimmune disease, characterized by an immune response against two hemidesmosomal proteins within the dermal–epidermal junction, BP180 and BP230. The antibodies bind to the dermo-epidermal junctions, where they attract a strong infiltrate of inflammatory cells that seems to cause the separation of the epidermis from the dermis. The inflammatory infiltrate contains multiple activated mast cells and increased levels of histamine, leucotrienes and TNF (117). Hypogranulated mast cells are in the papillary dermis in the vicinity of damaged endothelial cells (Fig. 4) (118). Passive transfer of antibodies to the murine BP180 antigen induces in mice a skin disease that closely resembles human BP. Lesion formation in this model disease depends on complement activation, mast cell degranulation and accumulation of neutrophils and eosinophils (Fig. 4). Mast cell-deficient mice do not develop experimental BP. Disease susceptibility is restored by engraftment of mast cells (119). These data underline clearly the potential of mast cells to amplify adaptive and innate immune responses.

Mast cells and pathogens

TNF promotes symptoms of septic shock including fever, tachycardia, hypotonia and ultimately lethal shock in response to bacterial toxins such as LPS (120,121). Based on these findings, a placebo-controlled trial was initiated for patients with bacterial sepsis. Unexpectedly, treatment of septic patients in these studies revealed that TNF inhibition (TNF receptor fusion protein, 1.5 mg/kg body weight) increased mortality of septic shock 1.75-fold when compared with controls (122), even though earlier studies failed to predict this outcome (123). These data showed that, surprisingly, TNF has a protective role in the control of bacterial infections (124). Simultaneous and subsequently published manuscripts show in experimental models of bacterial pneumonia or bacterial sepsis that mast cells are critically involved in the establishment of protective responses against bacteria. Again this protection relies on mast cell-derived TNF that is needed for neutrophil recruitment (19,54). Thus, mast cell TNF promotes the defense against bacteria.

Mast cells seem to be also required for control of bacterial or fungal infections in the skin (58,125) and peritoneum (19,55–57,126,127). A large body of data suggests that close interactions between mast cells and APC determine the outcome of innate and adaptive immune responses. During infection, mast cells are subject to the same microbial environment as APC and mast cells can affect key functions of APC, such as antigen presentation, migration into the lymph nodes or differentiation (6,128,129). Mast cells can be activated, through pattern recognition receptors and produce cytokines in response to bacterial peptidoglycans or LPS via Toll-like receptor pendent mechanisms (12). The mast cell mediators PGE_2 and TNF have the ability to alter APC migration and lymph node hypertrophy (128,129). This was shown in models of infections, such as *Escherichia coli* footpad infection. Draining lymph nodes from mast cell-deficient mice failed to respond to infection. Only mast cells derived from wild-type mice successfully reconstituted infection-induced lymph node hypertrophy (130). Other important antibacterial mechanisms of mast cells may rely on their capacity to express complement receptors (57) or endothelin-1 receptors (55) and to directly detect bacteria via CD48 (131).

In human skin, mast cell density differs between sites and is high at sites where the risk of bacterial, fungal or parasitic infection is enhanced (20). Several experimental studies have verified the need for mast cells in skin infections. *Pseudomonas aeruginosa* induces about twofold larger skin lesions in $Kit^{W}/Kit^{W\text{-}v}$ mice than in wild-type mice. Neutrophil recruitment and bacterial clearance from sites of infection are significantly impaired in $Kit^{W}/Kit^{W\text{-}v}$ mice and can be restored by mast cell engraftment of $Kit^{W}/Kit^{W\text{-}v}$ mice (58). Leishmaniasis is primarily controlled by the interplay between DCs and T cells (132). Mast cells also contribute to the control of parasitic skin infections of the skin such as *Leishmania major* infection. *Leishmania major*-infected $Kit^{W}/Kit^{W\text{-}v}$ mice develop markedly larger skin lesions than wild-type mice, and site-specific reconstitution with mast cells normalizes lesion development. $Kit^{W}/Kit^{W\text{-}v}$ mice contain significantly more parasites in the skin and parasites spread more rapidly to the spleens as compared with controls. Again, recruitment of pro-inflammatory neutrophils, macrophages and DCs was impaired in infected mast cell-deficient mice (133).

Effects of mast cells on tissue differentiation

Mast cell distribution pattern show that mast cells enrich at sites of tumor formation around basal cell carcinomas (BCC), squamous cell carcinomas or angiosarcomas (134–136). This is of interest as activated mast cells can produce growth factors, growth and differentiation modulating factors such as IFN-γ (83,137) or TNF (5,6,16), and angiogenic mediators, such as vascular endothelial growth factor (VEGF), epithelial growth factor, basic fibroblast growth factor (bFGF), heparin, histamine (6,138) and matrix metalloproteinase 9 (5,6,139). High numbers of skin mast cells are associated with a high prevalence of nodular BCC, suggesting that local mast cells in the skin may promote growth of developing premalignant tumors (140). It is possible that mast cells exert a similar bi-phasic action on tumor development as does TNF-signalling through TNFR1: at early phases, it may promote tumor development while at later phases mast cells may allow to raise immune responses that help to destroy tumors (72,141). The number of mast cells at sun-exposed skin sites do not correlate with an increased risk of developing BCC (142) but with BCC growth patterns, as at the head, 86% are nodular BBC (140).

Conclusion

Beyond the field of immediate type reactions, mast cell biology opens a broad spectrum of new fields. While macrophages may remain the most frequent antigen-presenting cell in tissues, mast cells evolve as key modulators in the functional vicinity of macrophages by releasing critical mediators mainly in the context of inflammation such as psoriasis, arthritis, eczema, BP or skin infection. Their main role is thought to be the amplification, turning a glimpse of action into a full-blown immune reaction. Future concentration on these 'immune amplifiers' will allow developing novel therapies, especially at the level of disease prevention.

Acknowledgements

The work was supported by SFB 685, Wilhelm Sander-Stiftung (97.041.3) and deutsche Krebshilfe (107128).

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