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REVIEW ARTICLE

Mast Cells as Regulators of Skin Inflammation and Immunity

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Mast cells are known to be the effector cells of immediate-type allergy, but experimental evidence obtained during the last decade has revealed their role in innate and acquired immunity. Upon activation mast cells can undergo an anaphylactic or piecemeal degranulation or degranulation-independent mediator secretion, resulting in rapid or slow release of soluble mediators, such as serine proteinases, histamine, lipid-derived mediators, cytokines, chemokines and growth factors. Mast cells can express different receptors and ligands on the cell surface, molecules that can activate the cells of the immune system, such as different subsets of T cells. All these mediators and cell surface molecules can promote inflammation in the skin. During the last years, a new role for mast cells has emerged; induction of tolerance or immunosuppression and interaction with regulatory T cells. However, the mechanisms that switch the pro-inflammatory function of mast cells to an immunosuppressive one are unknown. In this review, the immunoregulatory function of mast cells and its relation to skin inflammation are discussed. ***Key words: mast cell; mediator; skin; inflammation; immunosuppression.***

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Mast cells have traditionally been known as "allergy" cells that cause the symptoms of immediate-type allergy and are typically located at sites where the host tissue can encounter external antigens, allergens, toxins and microbes, e.g. the upper dermal skin, respiratory tract and bowel mucosa (1). Even though the physiological role of mast cells is not clear, evidence obtained from mouse models suggests that mast cells are essentially involved in protecting the skin from severe bacterial and parasitic infections (2–4) and from severe venom reactions after insect stings and snake bites (5). In addition, mast cells regulate cutaneous wound healing after trauma (6, 7).

Mast cells in the human tissues can be classified into MC_{TC}, MC_T and MC_C subtypes based on their proteinase content: MC_{TC} cells contain tryptase, chymase, carboxypeptidase and a cathepsin G-like proteinase, MC_T cells contain only tryptase (8–10), and MC_C cells show chymase and carboxypeptidase, but not tryptase (10). They all contain histamine. Almost all mast cells in the human skin belong to the MC_{TC} type, whereas MC_T cells predominate in the lung and bowel mucosa (8, 10). This suggests that the "C" type enzymes, chymase, carboxypeptidase and a cathepsin G-like proteinase, have a specific function in the skin after release from mast cells through degrading different proteins and peptides.

In a traditional model, mast cells are activated to degranulation and mediator release by an allergen that cross-links IgE molecules and their FcεRI receptors on the cell membrane. However, this is a highly simplified picture of the mast cell. Skin mast cells can express the FcγRI- and FcγRIIa-receptors and thereby be activated by IgG-dependent mechanisms (11, 12). In addition to the binding to cell surface immunoglobulin, foreign antigens, such as microbial products, can bind to a variety of toll-like receptors expressed on mast cells (13). Endogeneous peptides and proteins can activate mast cells for mediator release, such as complement products C3a and C5a (14), neuropeptides including substance P and vasoactive intestinal peptide (VIP) (15), stem cell factor (SCF) (16), tumour necrosis factor (TNF) (17), tryptase (18), cathelicidin LL-37 (19), α-melanocyte-stimulating hormone (20) and corticotrophin-releasing hormone (21). Furthermore, human mast cells can express CD30 ligand, a member of the TNF superfamily, and the cells can be activated via the CD30 receptor to chemokine secretion by means of reverse signalling (22). It is noteworthy that mast cells can not only be activated to mediator release by a simple on–off mechanism, i.e. resting cell or rapid and extensive anaphylactic degranulation. It has long been known that mast cells can undergo slow and partial piecemeal degranulation (23). In addition, other secretion mechanisms have been described, such as exosome secretion (24), and selective degranulation-independent mediator secretion (21, 22). For example, the increased interstitial histamine concentration in the psoriatic plaque suggests elevated mast cell activity and degranulation in a chronic inflammation without anaphylactic activation and urticarial whealing (25, 26).

Even though mast cells are important in immediate-type allergy and are involved in physiological skin reactions to trauma and infection, they can affect the immune system, promote inflammation or even suppress it. Pre-formed mediators stored in the secretory granules

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include different proteases, histamine, heparin proteoglycan, chondroitin sulphate E, acidic hydrolases, and various cytokines and growth factors. After activation, mast cells can secrete newly-synthesized mediators, including prostaglandin D_2, leukotriene C_4, and a range of cytokines, chemokines and growth factors. In addition, they can express cell membrane receptors and ligands. These molecules can modulate the immune system in the skin, e.g. in psoriasis, atopic dermatitis and epithelial cancers (1, 13, 27, 28). Therefore, the purpose of this review is to discuss the recent findings on the role of mast cells in skin inflammation and immunity. However, the anaphylactic aspects, urticaria or mastocytosis are not dealt with in the review.

ACCUMULATION OF MAST CELLS IN SKIN INFLAMMATION

The number of mast cells is increased in chronic skin inflammation, e.g. psoriasis, basal cell carcinoma and chronic ulcers. Furthermore, it is the MC_{TC} type of mast cell that is typically encountered just beneath the epidermis/epithelium, and sometimes even inside the epidermis (29–32). Intraepidermal mast cells have been found in other chronic inflammatory skin diseases showing epidermal proliferation (33, 34).

There are different possibilities for the activation and accumulation of mast cells during inflammation. The SCF, the ligand for the Kit receptor, is essential for the growth, migration, activation and survival of mast cells in different experimental models (35–41). In support of this, numerous SCF-positive cells have been detected in the psoriatic lesion, chronic ulcers and basal cell carcinoma (42–44), and even mast cells themselves can produce SCF (43, 45). Kit receptor is expressed by mast cells in the dermis and by melanocytes in the epidermis (42, 46). Furthermore, mast cells show increased Kit immunopositivity in the psoriatic lesion, chronic leg ulcers, and during skin wound healing (42). In addition, it is possible that the accumulation of mast cells is a result of the action of prosurvival proteins (47). Indeed, we have recently found that mast cells show increased levels of Bfl-1 immunoreactivity, an activation-induced prosurvival protein, in the lesional skin of psoriasis, atopic dermatitis and basal cell carcinoma (Ekoff et al., unpublished results).

The recruitment of mast cells and their haematopoietic progenitors from the blood circulation can be increased. This mechanism can be highlighted by the expression of several chemokine receptors on mast cells (27). Furthermore, SCF, TGF-β, RANTES and stromal cell-derived factor-1α (CXCL-12) can efficiently induce migration of human mast cells *in vitro* (48–50). Hence, chemoattractants produced in the inflamed skin tissue and chemokine receptors produced by mast cells could explain mast cell accumulation, though it is not known to what extent mast cells express these receptors in the inflamed skin. In addition to the essential role of SCF, there are several other relevant factors that can modulate the development or survival of mast cells, including IL-3, IL-4, IL-5, IL-6 (35), IL-9 (51), thrombopoietin (52), nerve growth factor (53), and endothelial cells (54).

MAST CELL TRYPTASE AND CHYMASE AS REGULATORS OF SKIN INFLAMMATION

The major protein in mast cell granules, β-tryptase, is a trypsin-like serine proteinase, which has a ring-like tetrameric structure with four active centres facing towards the central oval pore. Based on this structure, tetrameric β-tryptase is resistant to the action of large endogenous protease inhibitors, and heparin is needed to stabilize the enzyme (55–58). In agreement with this resistance to protease inhibitors, tryptase has histochemically been detected as catalytically active on skin cryosections from inflamed skin (30, 31, 59).

The pathophysiological significance of β-tryptase is not clear. However, there are several experimental findings suggesting its role in the activation and recruitment of different cell types, including endothelial cells (60–63), peripheral blood mononuclear cells, T cells and neutrophils (64–66) (Table I). In animal models, tryptase injections induce accumulation of neutrophils, eosinophils and other cells of the immune system in the skin of guinea pigs (67). Interestingly, the PAR-2 receptor is expressed by human skin mast cells (18), and the percentage of mast cells showing PAR-2 is increased in the psoriatic lesion (68) suggesting a possibility for paracrine potentiation of inflammation. Furthermore, tryptase may promote neurogenic inflammation by activating PAR-2 on nerves leading to the release of neuropeptides substance P and calcitonin gene-related peptide (69, 70) (Table I).

Table I. *Mast cell tryptase can have both stimulatory and inhibitory functions in skin inflammation*

Stimulatory function	Inhibitory function
Stimulation of angiogenesis and MCP-1 and IL-8 in endothelial cells (60–63)	Cleavage of eotaxin and RANTES (81)
Activation of peripheral blood mononuclear cells and neutrophils for cytokine production (64–66)	Cleavage of neuropeptides VIP and CGRP (82–84)
Paracrine or autocrine activation of mast cells through PAR-2 (18, 68)	Cleavage of cathelicidin LL-37 (19)
Activation of nerves (69, 70) and keratinocytes (72–75) through PAR-2	
Activation of metalloproteinases MMP-3 and -9 (76–78) and pro-urokinase (79)	

MCP-1: Monocyte chemoattractant protein-1; IL-8: interleukin-8; VIP: vasoactive intestinal peptide; CGRP: calcitonin gene-related peptide; PAR-2: protease-activated receptor-2.

Tryptase can interact with the epidermis, since tryptase-positive mast cells are typically situated close to the psoriatic epidermis and tryptase degrades fibronectin in the basement membrane zone *ex vivo* (29, 30, 71). The enzyme may activate keratinocytes directly through activation of PAR-2 on their surface (72–75). Tryptase is able to activate metalloproteinases (76–78) and pro-urokinase (79), or it can function as a gelatinase (80). Thus, tryptase may make space for T cells and neutrophils in the extracellular matrix and basement membrane zone allowing their migration into the epidermis. In contrast to the stimulatory function, tryptase may also have inhibitory functions, since it can degrade chemokines, neuropeptides and cathelicidin LL-37 (19, 81–84) (Table I).

Human α-chymase is a chymotryptic serine proteinase that is stored in high quantities in mast cell secretory granules. Like tryptase, chymase also binds efficiently to heparin, but chymase-heparin proteoglycan complexes are larger in size and are situated in a different subregion of the granule from tryptase-heparin proteoglycan complexes (85, 86). Thus, tryptase can diffuse through the extracellular matrix, whereas chymase tends to remain at the activation site (87, 88). In contrast to tryptase, chymase is active in the absence of heparin, though heparin can regulate the interaction between the enzyme and its substrates/inhibitors (32, 89, 90). Another distinct difference is that endogenous protease inhibitors, such as α_1-proteinase inhibitor (α_1-PI), α_1-antichymotrypsin (α_1-AC) (91), α_2-macroglobulin (92), secretory leukocyte proteinase inhibitor (90) and squamous cell carcinoma antigen-2 (93) can inactivate chymase. However, this may be a more complex interaction, since chymase can effectively degrade α_1-PI and α_1-AC (91). Thus, chymase activity is regulated by the plasma protease inhibitors α_1-PI and α_1-AC, which are even present in increased levels in mast cells in the inflamed skin, as shown histochemically, e.g. in psoriasis, atopic dermatitis (94), basal cell carcinoma (31) and cutaneous herpes zoster (59). It is probable that they also partially inactivate chymase in allergic skin wheal reaction (95).

Chymase can be a potent candidate in the recruitment of inflammatory cells, since human chymase injected into the skin of guinea pigs stimulates the accumulation of neutrophils and eosinophils (96), and it stimulates monocytes, neutrophils, lymphocytes and eosinophilic cells *in vitro* (97, 98). Chymase may promote inflammation indirectly as it has been shown to activate pro-IL-1β to IL-1β (99), pro-IL-18 to IL-18 (100), and to generate a potent chemoattractant, 31-amino acid endothelin-1, for neutrophils and monocytes (101). However, chymase may regulate inflammation by degrading IL-6 and IL-13, and to some extent IL-5 and TNF-α (102). Furthermore, chymase can degrade eotaxin (81) and neuropeptides substance P and VIP (82, 103). Chymase is a potent enzyme, but the effect is dependent on the levels of enzymatically active chymase in inflamed skin, where increased levels of protease inhibitors can be detected. Chymase can affect the epidermis and induce blister formation in some conditions, since it detaches keratinocytes from substratum and degrades fibronectin (32, 104).

MAST CELLS STIMULATE THE CELLS OF THE IMMUNE SYSTEM

The close interaction between mast cells and T cells is now well-known, and mast cells can express soluble factors, cell surface molecules and co-stimulatory molecules, which can activate different subsets of T cells (13, 28, 105, 106). This stimulatory effect of mast cells on T cells is markedly dependent on soluble TNF-α, as well as on direct cell–cell interactions between mast cell OX40 ligand (OX40L) and T-cell OX40 receptor (106–108). Even though there are no data on the level of OX40L in mast cells in inflamed skin, mast cells are the predominant source of preformed TNF-α in normal skin (109), and along with increased mast cell numbers TNF-α-positive mast cells are increased in number in the lesional skin of psoriasis, atopic dermatitis and basal cell carcinoma (110, 111). In a recent study on co-cultures with mouse mast cells, effector T cells and regulatory T cells, concomitant influence of mast cell OX40L together with IL-6 from effector T cells induced reversal of regulatory T-cell-mediated suppression resulting in Th17 cell differentiation (112). In other experiments in mice, mast cells and mast cell-derived TNF-α enhanced antigen- and Th17 cell-dependent development of a neutrophil-rich inflammatory response in the airways (113) giving further support to the assumption that mast cells can promote Th17 cell-dependent inflammation *in vivo*. Neutrophil recruitment by mast cell TNF-α and MIP-2 has also been shown in a T-cell-dependent delayed-type hypersensitivity reaction in the skin of mice (114). Hence, OX40L on mast cells, together with TNF-α and IL-6, appear to be essential molecules in promoting tissue inflammation.

Mast cells can secrete other soluble cytokines that are relevant in chronic skin inflammation. In the psoriatic lesion, mast cells show increased levels of interferon-γ immunoreactivity and the cytokine associates with the Psoriasis Area and Severity Index. In contrast to psoriasis, mast cells in the atopic dermatitis lesions show elevated amounts of IL-4 immunoreactivity but are only weakly immunopositive for interferon-γ (115, 116). In addition, mast cell IL-4 has been shown to associate with the size of allergic skin prick-test wheal reaction and serum total IgE level in atopic subjects (117).

In addition to OX40L, mast cells have been shown to express another member of the TNF superfamily on

the cell surface, CD30L, which can activate $CD30^+$ lymphoma cell lines *in vitro* (118). Activation of the CD30 receptor on T cells has previously been shown to lead to interferon-γ secretion in Th1 cell clones and IL-4 and IL-5 secretion in Th2 cell clones (119). In the lesional skin of psoriasis, atopic dermatitis and basal cell carcinoma, mast cells show increased levels of CD30L immunoreactivity. Furthermore, the number of cells with CD30 receptor is increased in the upper dermis of these lesions as well (22, 111). *In vitro* and *ex vivo* experiments demonstrated that mast cells can be induced by means of reverse signalling through CD30 ligand for chemokine expression, such as IL-8, MIP-1α and MIP-1β (22). Therefore, during the interaction between CD30 ligand on mast cells and CD30 receptor on T cells both cells are presumably activated in the inflamed skin lesion.

Mast cells can express several immunologically active molecules on the cell surface, which are related to T-cell activation through antigen presentation. For example, mast cells can express MHC class I and MHC class II and therefore act as antigen-presenting cells to T cells *in vitro* (28, 105). Moreover, human mast cells have been shown to express MHC class II and to present staphylococcal superantigens to $CD4^+$ T-cell hybridomas, giving rise to T-cell activation (120). Interestingly, human cord blood-derived mast cells have been shown to bind and phagocytoze several bacteria strains *in vitro*, such as *Staphylococcus aureus*, leading to death of bacteria and TNF-α secretion from mast cells (121).

The presence of co-stimulatory molecules is important for effective T-cell activation upon antigen presentation. In line with this requirement, mouse and human mast cells cultured *in vitro* can express CD80 and CD86, molecules that are essential in such a co-stimulation (120, 122). Human mast cells have, in fact, been shown to express a range of other cell surface molecules as well, such as the CD antigens and adhesion molecules ICAM-1, VLA-4, Mac-1 and to some extent LFA-1 (123, 124). The adhesion molecules, especially ICAM-1, can stimulate T cells, but mast cells are activated upon interaction with activated T cells resulting in enhanced mast cell degranulation, migration and adhesion to extracellular matrix and endothelial cell ligands (125).

Like professional antigen presenting cells, mast cells can have the capability of migration to lymph nodes as evidenced by several experimental findings. For example, mouse experiments have shown that during dinitrofluorobenzene-induced contact hypersensitivity mast cells are activated and the cells migrate to draining lymph nodes where they can mediate T-cell recruitment (126). In addition to mast cells, mast cell mediators can diffuse to lymph nodes. For example, activation of mast cells in mouse footpad by injection of *Escherichia coli* or compound 48/80 resulted in rapid draining of mast cell-derived preformed TNF-α to lymph nodes where it induced hypertrophy and recruitment of circulating T cells (127). Further complexity provides the study by Jawdat et al. (128), who demonstrated that the lymph node activation in mice can be mast cell TNF-α-dependent in an allergic response or TNF-α-independent in a response to the injection of bacterial peptidoglycan.

Mast cells and their mediators can activate professional antigen presenting cells, Langerhans' cells and dendritic cells for migration. In a mouse model, mast cell activation in ear pinna induced by an IgE-dependent mechanism or by bacterial peptidoglycan was crucially involved in Langerhans' cell migration to draining lymph nodes (128). In another mouse model of FITC-induced contact hypersensitivity in ear pinna, mast cells and their TNF-α were essential for optimal migration of dendritic cells to local lymph nodes (129). Interestingly, mast cells can release exosomes that harbour exogenous antigens. These exosomes can stimulate maturation of mouse dendritic cells leading to enhanced antigen presentation to T cells (24). Furthermore, histamine can play a role in the activation of antigen presenting cells, as shown in co-cultures of *in vitro*-developed human mast cells and monocyte-derived dendritic cells. In this work, mast cells were activated by FcεRI cross-linking, which then induced maturation of dendritic cells. These cells in turn induced polarization of naïve T cells towards Th2 lineage, and the effect was largely dependent on histamine and mast cell-dendritic cell contacts (130). In fact, the stimulation of histamine receptor H1 on dendritic cells leads to the production of proinflammatory cytokines, Th1 priming and increased antigen presenting activity, but the stimulation of H2 receptor favours IL-10 induction and Th2 or tolerance priming (131).

MAST CELLS AS SUPPRESSORS OF THE IMMUNE SYSTEM

Mast cells can be involved in the induction of tolerance or immunosuppression (105). For example, mast cells induce regulatory T-cell-dependent peripheral tolerance in a mouse model of skin allografts, and this reaction is related to the production of IL-9 from activated regulatory T cells (132). However, this tolerance to skin allografts in mice can be reversed by intragraft or systemic mast cell degranulation, giving rise to acute T-cell-dependent rejection and loss of the suppressive functions of regulatory T cells (133). The interesting role of IL-9, a mast cell growth and activation factor, has recently been shown in another mouse model, too. In this work on nephrotoxic serum nephritis model in mice, regulatory T cells, IL-9 secreted from them, and mast cells recruited by them into kidney-draining lymph nodes were crucial for nephroprotective and anti-inflammatory effects (134). In a recent study with

mouse cells *in vitro*, bone marrow-derived mast cells could induce increased percentage of $CD4^+$, $CD25^+$, $FoxP3^+$ regulatory T cells from isolated spleen T cells and this induction was partially inhibited by a neutralizing anti-TGF-β1 antibody in the co-culture system (135). On the other hand, FcεR-activated bone marrow-derived mouse mast cells can inhibit through H1 receptor the suppressive function of mouse $CD4^+$, $CD25^+$, $FoxP3^+$ regulatory T cells over responder T cells (136).

Previously, mast cells have been thought to be proinflammatory in models of contact hypersensitivity, but this is not always the case. Interestingly, in a mouse model of contact hypersensitivity and using prolonged monitoring for up to 15 days after challenge, mast cells were shown to limit the inflammatory skin reaction by producing the immunosuppressive cytokine IL-10. Furthermore, mast cells were able to attenuate the mouse skin reactions induced by multiple challenges with ultraviolet irradiation for up to 30 days (137). One possible mechanism for this UV-induced immunosuppression has recently been clarified in this mouse skin model: chronic low-dose UVB irradiations induce the production of 1α, 25-dihydroxyvitamin D_3, which, in turn, stimulates the corresponding vitamin D receptor on mast cells, resulting in IL-10 secretion and immunosuppression, but other mechanisms may also be involved (138). In addition, immunosuppression of mouse skin contact hypersensitivity reaction by UV-irradiation can be dependent on CXCR4-positive mast cells, which migrate from the skin to the B-cell area of draining lymph node caused by the action of the chemoattractant CXCL-12 (139). Interestingly, the interaction between mast cell CXCR4 and CXCL-12, are important in the suppression of contact hypersensitivity reaction in mouse skin, an immunosuppression, which was induced by the application of the organic chemical mixture, JP-8 jet propulsion fuel, onto the mouse skin (140). The role of IL-10 has been described in another mouse skin model, where mast cells and concomitant IL-10 expression in lymph nodes were critical intermediaries in the mosquito bite-induced suppression of delayed-type hypersensitivity reaction (141). Mast cell IL-10 induced by UV irradiation may not only inhibit cellular delayed-type hypersensitivity, but it can inhibit humoral immune responses. This possible mechanism was demonstrated recently by showing that UV irradiation of mouse skin blocks germinal centre formation in draining lymph nodes, antibody secretion, and T follicular helper cell function. IL-10 derived from mast cells was found to be an essential factor in these events and $IL\text{-}10^+$ mast cells were detected in the draining lymph nodes 24 h after UV irradiation (142). Human mast cells have been shown to express IL-10 (143) and TGF-β (144). Hence, these cytokines may act in human skin to modify immune responses, though it is not known to what extent they are expressed in mast cells in diseased human skin. In addition, IL-10 released from human mast cells can have the capability of inhibiting mast cell function in an autocrine or paracrine fashion (145).

Mast cells are typically increased in number in different cutaneous malignancies and they are assumed to participate in skin carcinogenesis by different mechanisms, such as immunomodulation, induction of angiogenesis, degradation of the extracellular matrix components, and promotion of tumour cell mitosis. The development of skin carcinomas requires malignant transformation and compromised immune system (146). UV irradiation is the major causative factor for skin carcinogenesis and mast cells evidently have a role in UV-induced immunosuppression using different mechanisms (137–139, 142, 146). The recruitment of immunomodulatory or immunosuppressive mast cells to the skin tumour may be due to carcinoma cell-derived SCF and Kit receptor on mast cells (42, 43, 111). There is recent experimental evidence to support this mechanism. First, in a mouse model of hepatocarcinoma SCF from tumour cells promoted the recruitment of injected bone marrow-derived mast cells to the tumour. On the other hand, activated mast cells were shown to release adenosine, which inhibited effector T cells and natural killer cells, and immunosuppression was enhanced by the increased presence of $FoxP3^+$ regulatory T cells in the tumour (147). Secondly, in this same mouse hepatocarcinoma model, injected mast cells induced the SCF/Kit-dependent appearance of $GR\text{-}1^+$, $CD11b^+$ myeloid-derived suppressor cells. In addition, regulatory T cells increased in the tumour and showed increased expression of ectoenzymes CD39 and CD73, molecules, which in turn can produce inhibitory adenosine from ATP. Furthermore, regulatory T cells produced IL-9, which was essential for the tumour-promoting effects and survival time of mast cells (148). Nevertheless, the interaction between mast cells and regulatory T cells in cancer may be complex. Recently, in human colorectal cancer and murine polyposis it was demonstrated that

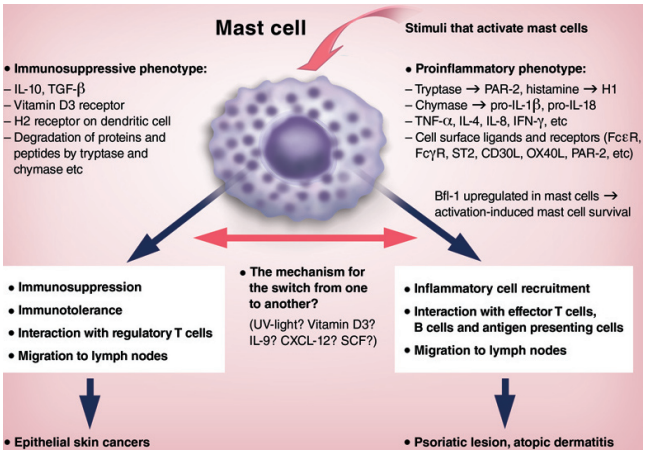

Fig. 1. A hypothetical model for the function of mast cells as proinflammatory or immunosuppressive cells in skin inflammatory diseases.

this interaction can lead to mast cell-induced generation of proinflammatory regulatory T cells without losing their T-cell-suppressive properties (149). This finding may support the concept that a cancer is often characterized by inflammation and peritumoural inflammatory cells, but sufficient immunosuppression is required to prevent excessive inflammation and harmful damage to the tumour.

CONCLUSION

Current knowledge indicates that mast cells are involved in chronic skin inflammatory diseases. A range of different factors is known to activate mast cells, and subsequently these cells can release rapidly or slowly effective preformed and newly-synthesized soluble mediators. Furthermore, mast cells can express cell surface ligands and receptors, and all these different mediators and cell surface molecules can be either proinflammatory or immunosuppressive (Fig. 1). Mast cells can potently recruit the cells of the immune system, e.g. T cells, neutrophils and eosinophils, to the site of skin inflammation, and mast cells can stimulate the maturation of Langerhans' cells and dendritic cells and their migration to lymph nodes. Moreover, mast cells are capable of migrating to draining lymph nodes and activating the immune cells within them. Mast cells show plasticity in the expression of cytokines and TNF family ligands in skin inflammatory diseases, such as psoriasis, atopic dermatitis and basal cell carcinoma. New exciting functions for mast cells have emerged during recent years – induction of tolerance or immunosuppression, and protection from infections and toxins. However, the current evidence comes mostly from cell culture and animal models and further studies are required to verify the situation in humans. Further research is required into the mechanisms that switch proinflammation to immunosuppression or vice versa (Fig. 1).

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