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Mast cells and cutaneous malignancies

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This paper reviews the role of mast cells in the development and progression of basal cell carcinoma, squamous cell carcinoma and malignant melanoma. Mast cells accumulate around cutaneous malignancies. Current evidence suggests that mast cells contribute to the tumorigenesis of cutaneous malignancies through four mechanisms. (1) *Immunosuppression*: Ultraviolet-B radiation, the most important initiator of cutaneous malignancies, activates mast cells. Upon irradiation of the skin, *trans*-urocanic acid in the epidermis isomerizes to *cis*-urocanic acid, which stimulates neuropeptide release from neural c-fibers. These neuropeptides in turn trigger histamine secretion from mast cells, leading to suppression of the cellular immune system. (2) *Angiogenesis*: Mast cells are the major source of vascular endothelial growth factor in basal cell carcinoma and malignant melanoma. Vascular endothelial growth factor is one of the most potent angiogenic factors, which also induces leakage of other angiogenic factors across the endothelial cell wall into the matrix. Mast cell proteases reorganize the stroma to facilitate endothelial cell migration. As well, heparin, the dominant mast cell proteoglycan, assists in blood-borne metastasis. (3) *Degradation of extracellular matrix*: Through its own proteases, and indirectly via interaction with other cells, mast cells participate in degradation of the matrix, which is required for tumor spread. (4) *Mitogenesis*: Mast cell mediators including fibroblast growth factor-2 and interleukin-8 are mitogenic to melanoma cells. Current evidence supports an accessory role for mast cells in the development and progression of cutaneous malignancies. Emerging data, however, also suggest that mast cells might, in fact, have opposing roles in tumor biology, and the microenvironment could polarize mast cells to possess either promoting or inhibitory effects on tumors.
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Cutaneous malignancies are the most common cancers. They account for nearly half of all cancers in the United States according to statistics from the American Cancer Society.[1] In Australia and New Zealand, where the incidence of skin cancer is the highest in the world, the total number of cutaneous malignancies exceeds that of all other cancers combined by several folds.[2,3] Approximately 77% of cutaneous malignancies are basal cell carcinomas, 20% are squamous cell carcinomas and the remainder consist of malignant melanoma and rarer tumors.[4] Basal cell carcinomas arise from mitotic epidermal cells, squamous cell carcinomas from differentiated epithelial keratinocytes and malignant melanomas from epidermal melanocytes.[5,6] Basal cell carcinomas are locally invasive but very rarely (less than 0.1%) metastasize. They tend to spread along the plane of least resistance such as periosteum, perichondrium, fascia and tarsal plate.[7] Squamous cell carcinoma has a 2–6% incidence of metastasis.[8] Melanoma, however, accounts for most of the mortality from cutaneous malignancies. Many factors affect the prognosis of melanoma, including tumor thickness, ulceration, location and gender. In all, 20% of patients with melanoma will develop metastatic disease and die within 5 years of diagnosis.[6]

Studies have shown that mast cells accumulate around the margin of these cutaneous malignancies.[9–14] There is compelling evidence that mast cell accumulation among the peritumoral inflammatory infiltrates contributes to a permissive microenvironment for carcinogenesis and metastasis.[15–17]

Mast cells originate from the bone marrow and the immature progenitor cells migrate to peripheral tissues and mature *in situ*.[18–20] Mast cells are not identified in the circulation.[21]

Mast cells possess many properties that enable them to participate in a diverse range of biological

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activities. They phagocytoze, process antigens, produce cytokines and release a variety of preformed (eg, histamine, proteoglycans and proteases) and newly formed (eg, leukotrienes and prostaglandins) physiological mediators.[20] Mast cells carry an array of adhesion molecules, immune response receptors and other surface molecules which permit them to react to multiple specific and nonspecific stimuli.[22] These wide-ranging biological characteristics, their ubiquitous distribution and strategic locations near blood vessels, nerves, inflamed tissues and neoplastic foci enable them to play a central role in a multitude of physiologic, immunologic and pathologic processes.[20,23–25] We have recently reviewed the biology of mast cells.[25]

The effects of mast cell mediators on the development and spread of cutaneous malignancies are likely to be mediated through multiple pathways, including immunosuppression, enhancement of angiogenesis, disruption of the extracellular matrix and promotion of tumor cell mitosis (Figure 1).

Mast cell density around cutaneous malignancies

Mast cells have been observed to accumulate around the margin of cutaneous malignancies.[9–14] The increased density of mast cells around many types of tumors is independent of the presence of an inflammatory infiltrate.[26] Cohen *et al*[27] find that the degree of peribasal cell carcinoma inflammation does not correlate with the relative density of mast cells. This suggests that mast cells are preferentially recruited to the vicinity of basal cell carcinoma (Figure 2).

Flynn *et al*,[28] in an experiment in which epidermoid carcinoma is induced in the hamster buccal pouches by repeated topical application of dimethylbenzanthracene, demonstrate sequential mast cell migration towards progressive mucosal dysplasia and subsequent development of squamous cell carcinoma. As they migrate from the deep connective tissue to the dysplastic epithelium, mast cell membrane-bound granules fuse to form multichambered sacs. This ultrastructural change takes place when a mast cell is stimulated.[29] This observation suggests that as mast cells are attracted to the carcinomatous lesion, they are stimulated to degranulate as well.

Histopathology studies on human basal cell carcinoma and squamous cell carcinoma have shown that mast cell density is especially high in the more aggressive variants.[13,14,27,30,31] As well, the density of mast cell and microvessels is increased in

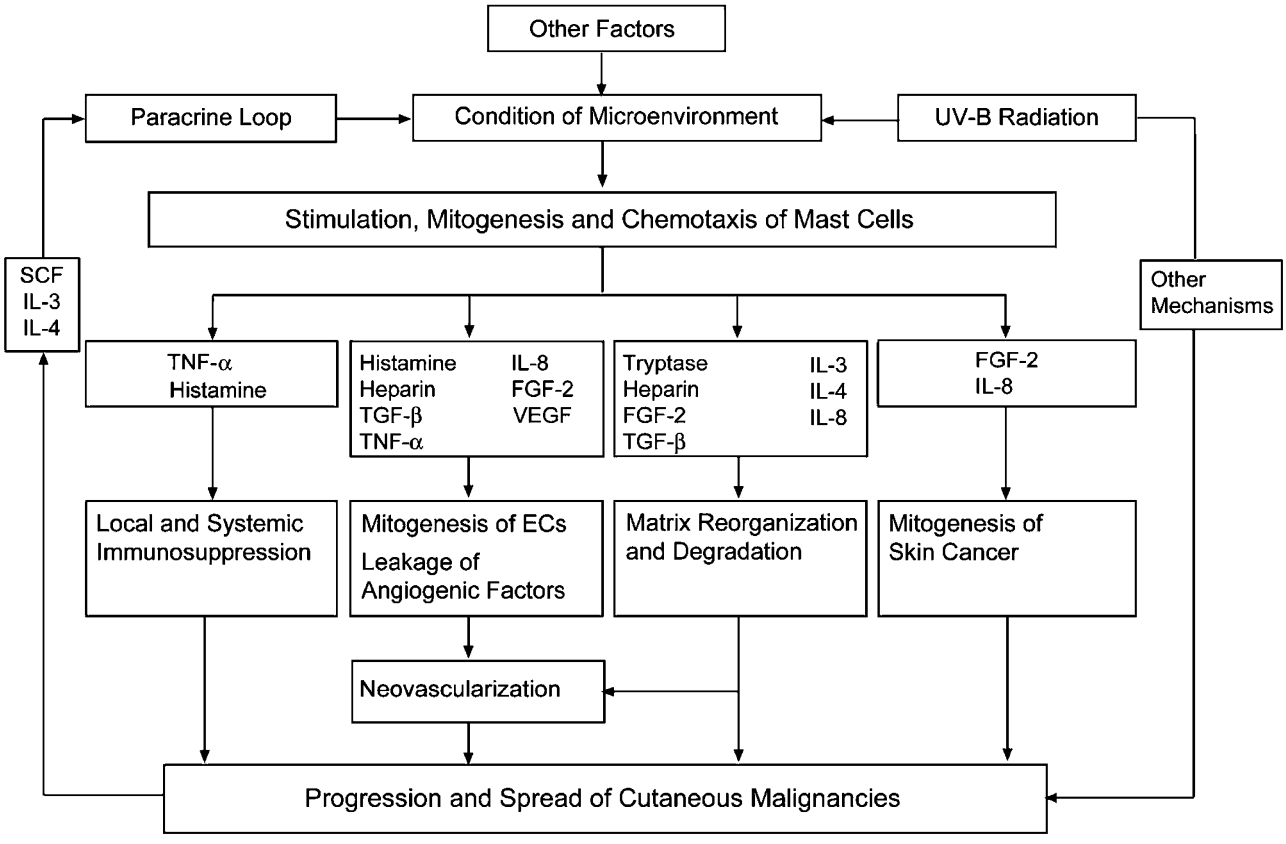

Figure 1 The accessory roles of mast cells in the progression and spread of cutaneous malignancies. UV-B, ultraviolet-B; SCF, stem cell factor; IL, interleukin; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; ECs, endothelial cells; TGF-β, transforming growth factor-β; FGF-2, fibroblast growth factor-2.

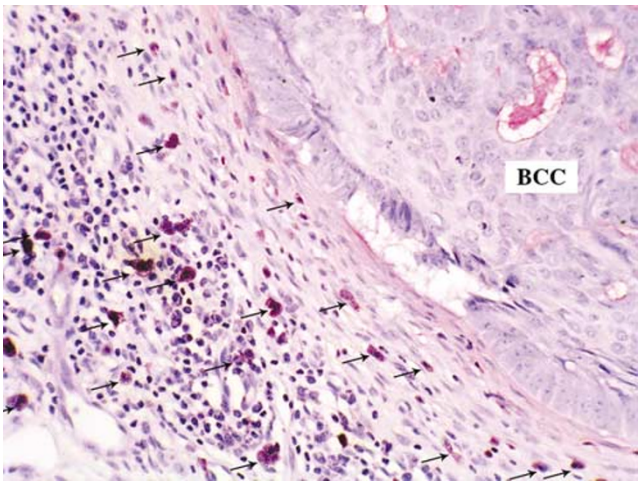

Figure 2 Toluidine blue stain showing accumulation of mast cells with dark blue granules (arrows) at the periphery of the of a basal cell carcinoma (right upper quadrant) (original magnification $\times 400$).

melanoma compared to benign naevus and melanoma *in situ*[10,11] (Figure 3).

Ultrastructural study of mast cells around cutaneous malignancies

Reports on the ultrastructure of mast cells surrounding basal cell carcinoma are contradictory. Janowski *et al*[32] observe that mast cells around basal cell carcinoma have a greater surface area, diameter and perimeter than normal mast cells. Conversely, Tharp *et al*[33] report that mast cells that infiltrate around basal cell carcinoma have no discernible difference in the cell surface area, nuclear size, number and size of cytoplasmic granules. There has been no published report on the ultrastructure of mast cells in squamous cell carcinoma and melanoma.

Ultraviolet-B-induced immunosuppression in photocarcinogenesis

Cutaneous malignancies are highly immunogenic, and a competent immune system should be capable of destroying the cancer cells.[34] Therefore, the development of cutaneous malignancies requires firstly, a malignant transformation of skin cells, and secondly, a compromised immunity, especially an impaired cell-mediated immune response.[35,36] There is compelling evidence that ultraviolet-B (280–320 nm) radiation plays a central role in both these mechanisms.[36]

Exposure of humans and animals to ultraviolet radiation, particularly ultraviolet-B, impairs the function of the immune system, both locally at the site of exposure and systemically. The immunosuppressive effects of ultraviolet radiation have been implicated in the pathogenesis of melanoma and nonmelanoma skin cancers. The association between suppression of immune response by ultraviolet radiation and the development of skin cancers was first demonstrated in the pioneering work of Fisher and Kripke.[37,38] They showed that, unlike most other murine tumors, ultraviolet-induced skin cancers failed to develop when transplanted into syngeneic nonirradiated mice. Interestingly, if the recipient mice were preexposed to ultraviolet radiation, the cancers were able to grow.[37,38]

In humans, a suppressed immune function has been demonstrated to be a causative factor for the development of skin cancers. Renal transplant patients, who are therapeutically immunosuppressed, display exceptionally high incidence of squamous cell carcinoma and basal cell carcinoma on sun-exposed sites.[39,40] In the general population, certain individuals seem to be more susceptible than others to the immunosuppressive effects of solar radiation.[41] Following exposure of the skin to ultraviolet radiation, 40% of normal subjects exhibit suppressed contact hypersensitivity responses to the topically applied experimental sensitizer, dinitrochlorobenzene, at the site of exposure. However, when skin cancer patients are tested using the same protocol, 92% are susceptible to the inhibitory effects of ultraviolet radiation.[41] These results indicate that the ultraviolet-induced suppression of immune function may be a significant risk factor for the development of skin cancers.

It is well established that the skin actively initiates immune responses against foreign antigens. A number of epidermal and dermal cell types participate in skin immune processes. The epidermal Langerhans cells and keratinocytes are largely responsible for initiating immune activation while dermal fibroblasts, dendritic cells, mast cells and endothelial cells maintain and mediate immune responses. Exposure to ultraviolet radiation can directly alter the function of these cell types resulting in the suppression of the immune function.[42]

Role of mast cells in ultraviolet-B-induced immunosuppression and cutaneous malignancies

Emerging evidence suggests that mast cells may play a critical role in ultraviolet-B-induced immunosuppression[43–46] (Figure 1).

In a study involving South Australian and Danish subjects, patients with a history of basal cell carcinoma and melanoma are found to have a significantly higher, genetically predetermined density of dermal mast cells.[47,48] It is suggested that a higher density of dermal mast cell is a predisposing factor for the development of basal cell carcinoma and melanoma. It has been hypothesized that a higher dermal mast cell density predisposes an individual to ultraviolet-B-induced immunosuppression.[47,49]

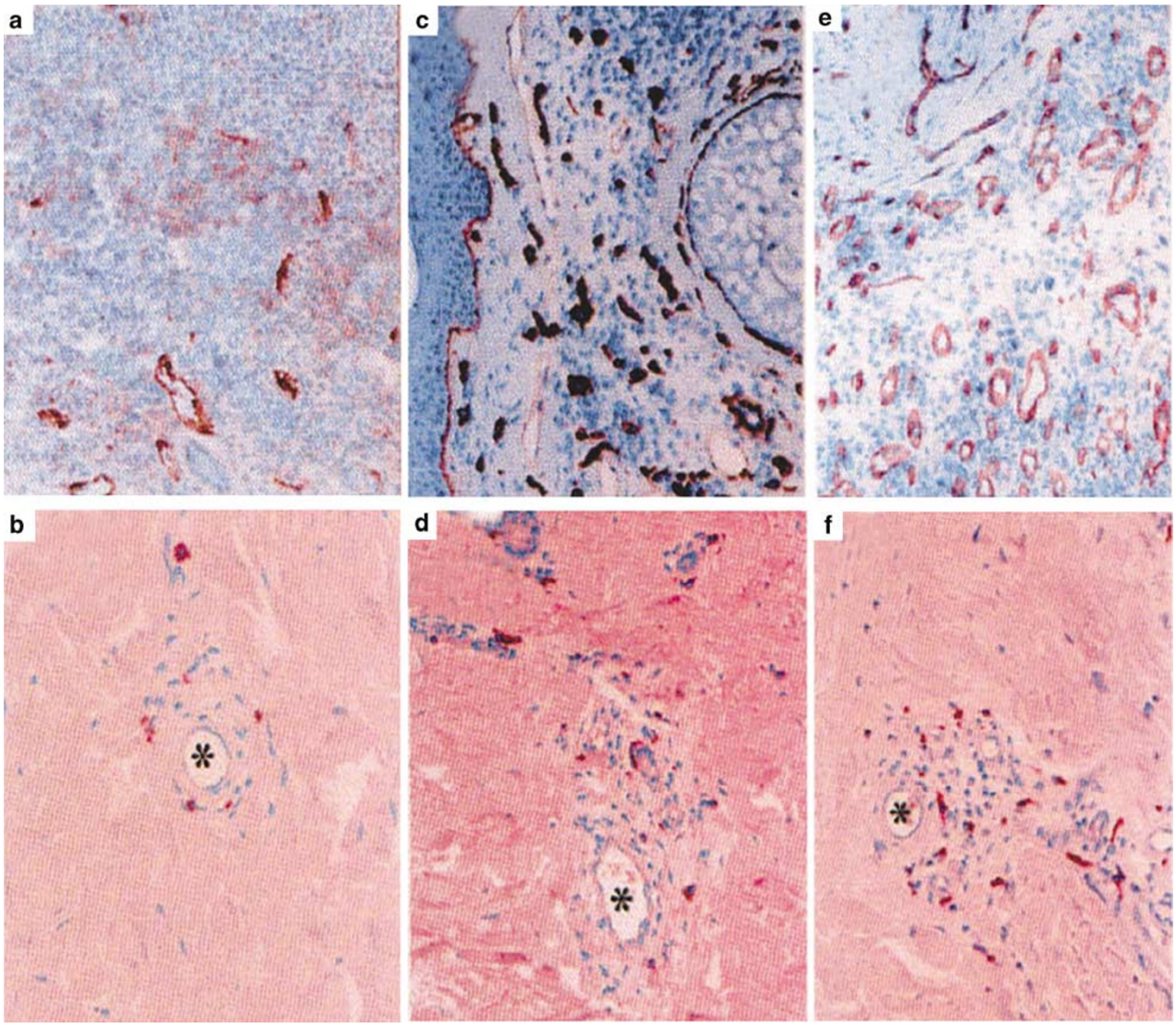

Figure 3 Adjacent sections of a common naevus (**a**, **b**), naevus with architectural disorder and melanocytic atypia (**c**, **d**), and metastatic malignant melanoma (**e**, **f**) stained with anti-CD31 (**a**, **c**, **e**) for microvessels and antitryptase for mast cells (**b**, **d**, **f**). Note the progressive increase of the number of microvessels (**a**, **c**, **e**) and mast cells located around these microvessels (*) (**b**, **d**, **f**) from common naevus, through naevus with atypia, to metastatic malignant melanoma. (Reproduced with permission from Ribatti *et al*.[68])

However, a similar correlation has not been found for patients with squamous cell carcinoma.[5] Epidemiological studies have shown that the relative incidence of 1:4 for basal cell carcinoma:squamous cell carcinoma in the general Caucasian population reverses to 3:1 in drug-induced systemic immunosuppression following renal transplant. This indicates a stronger correlation between immunosuppression and the development of squamous cell carcinoma.[49] The reason why patients with basal cell carcinoma and melanoma but not those with squamous cell carcinoma are found to have higher dermal mast cell densities is unclear. Grimbaldeston *et al*[5] suggest that the development of squamous cell carcinoma may be supported by other immunomodulatory mechanisms.

Using the W/W^v mice, Hart *et al*[50] demonstrate a direct correlation between mast cell density in the dermis and susceptibility to ultraviolet-B-induced systemic immunosuppression. These mice, which are homozygous for the *W* (white-spotting) mutation, and therefore severely mast cell deficient, are unresponsive to ultraviolet-induced immunosuppression unless first injected with mast cell precursors derived from the bone marrow at the irradiated site.[48,50] The *W* locus is on chromosome 5 and encodes the *c-kit* tyrosine kinase receptor that binds stem cell factor, which is the main growth factor for mast cells and vital for their development, maturation and migration.[20]

It has been proposed that ultraviolet-B indirectly activates mast cells through two mechanisms.

Firstly, the more immediate effect involves isomerization of photo-receptor *trans*-urocanic acid (UCA) to *cis*-UCA in the stratum corneum. *Cis*-UCA stimulates neuropeptide secretion, especially substance P and calcitonin gene-related peptide, from cutaneous sensory nerves.[47,51,52] These neuropeptides in turn stimulate release of mediators from mast cells. Secondly, irradiated keratinocytes secrete nerve growth factor, which sustains release of neuropeptides from the sensory nerves.[47]

The critical mast cell products involved in ultraviolet-induced immunosuppression are believed to be tumor necrosis factor-α (TNF-α) and histamine, which are important for the local and systemic effects, respectively[34] (Figure 1).

Disruption of the function of Langerhans cell, the principal antigen presenting cell of the skin by ultraviolet radiation has been shown to be an important component of ultraviolet-induced local immunosuppression. Langerhans cells are especially sensitive to the effects of ultraviolet radiation and they undergo morphological and ultrastructural changes upon exposure that may result in altered or diminished antigen presentation. TNF-α has been identified as a key mediator in ultraviolet-induced local immunosuppression. Its level is raised in ultraviolet-exposed skin and it may act by altering Langerhans cell morphology and function.[53] Mast cells store large amounts of TNF-α, which are released on activation.[50] A murine study suggests that the degree of susceptibility to ultraviolet-B-induced local immunosuppression depends on TNF-α levels within the epidermis after ultraviolet-B irradiation. Intracutaneous administration of TNF-α has been shown to evoke morphological changes in Langerhans cells similar to those observed upon ultraviolet irradiation while antibodies to TNF-α protect Langerhans cells from the effects of ultraviolet radiation.[54]

Mast cell-derived histamine stimulates prostaglanidin E_2 (PGE_2) production from keratinocytes. PGE_2 alters the cytokine balance in favor of the immunosuppressive interleukin-10 (IL-10) against the immunostimulatory IL-12.[55] IL-12 is central to the orchestration of both innate and acquired cell-mediated immune responses.[56] IL-12 is able to abort T suppressor cell-induced apoptosis in Langerhans cells. IL-12 has also been shown to cause a remarkable reduction in ultraviolet-specific DNA lesions through the induction of DNA repair.[57] Indomethacin, a cyclooxygenase inhibitor, which blocks prostaglandin synthesis, has been shown to cause significant reversal of ultraviolet-B and *cis*-UCA-induced systemic immunosuppression.[50] This finding further affirms the role of prostaglandins in ultraviolet-B-induced systemic immunosuppression.

Histamine also increases suppressor T-cell function by binding to the H2 receptors. These suppressor T cells in turn release higher levels of immune suppressive cytokines including IL-10, and induce apoptosis of antigen-presenting cells.[31,43,58] Suppression of immune responses to melanoma antigens and functional inactivation of tumor-reactive T cells are important for the development of melanoma in humans. Treatment of mice with cimetidine, an H2 receptor antagonist, has been reported to retard the growth of melanoma.[58]

Mast cells and angiogenesis

Mast cells stimulate neovascularization at the tumor–host interface[12] (Figures 1, 2 and 4). The growth and metastasis of a tumor depends on its ability to elicit new blood supply.[59,60] Acquisition of the angiogenic phenotype, which enables the tumor to establish its independent blood supply, represents an increase in malignancy potential.

Tumor angiogenesis requires a combination of angiogenic factors and stromal remodeling by proteolytic enzymes. Proteolysis of the extracellular matrix not only facilitates endothelial-cell migration, but also releases sequestered latent stores of

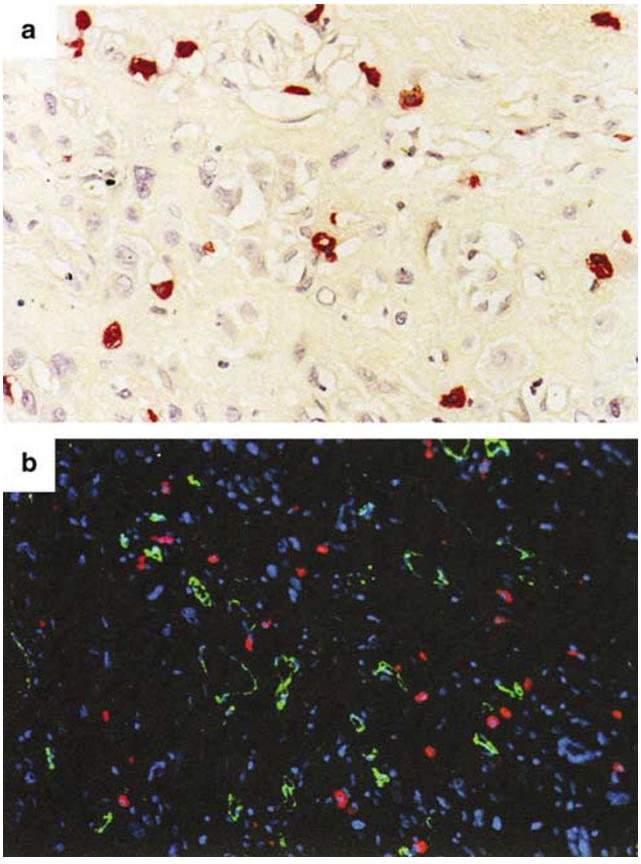

Figure 4 (**a**) Antitryptase monoclonal antibody stain of a melanoma. Note the close relationship between tumor cells, capillaries and mast cells (original magnification ×400). (**b**) Double immunostaining showing mast cells (stained red with antitryptase rhodamine) accumulation in microvessel-rich (stained green with anti-CD34, FITC) area (original magnification ×200). (Reproduced with permission from Toth *et al*.[12])

angiogenic factors.[61–64] The evidence that the intensity of angiogenesis in a human tumor could predict the likelihood of metastasis was first reported in cutaneous melanoma.[65] Patients with intermediate thickness (0.76–3.99 mm) melanomas were divided into two groups that were matched for age, sex, Breslow thickness and Clark's level. The group that developed metastasis was found to have a more than two-fold increase in vascular area at the base of their melanoma lesions compared with the metastasis-free group.[65] Mast cell accumulation around the margin of tumors has been observed to peak just as the tumors acquire the angiogenic phenotype, preceding growth of new capillaries towards the tumors.[26,66] Peritumoral mast cell count correlates strongly with microvascular density, melanoma progression and prognosis.[11,12]

The angiogenic response to implanted melanoma in mast cell-deficient W/W^v mice is delayed and less intense initially. These mice are also less likely to develop lung metastasis. Their angiogenic response and propensity for hematogenous metastasis approach that of their mast cell-proficient counterparts upon mast cell restoration with bone marrow cell injection.[67]

Mast cells contain various angiogenic factors such as histamine, heparin, transforming growth factor-β (TGF-β), TNF-α, IL-8, fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF).[68–70] Ugurel *et al*[71] show significantly elevated serum levels of FGF-2, VEGF and IL-8 in melanoma patients when compared with healthy subjects. Furthermore, elevated serum levels of these factors correlate positively with the stage of disease and tumor burden, and confers a poor overall survival and high probability of progression [71] (Figure 5).

Mast cells around cutaneous melanoma (50–90% of mast cells) and basal cell carcinoma (90.2% of mast cells) are the major source of VEGF (Figures 6 and 7a and b).[12,14] VEGF is one of the most potent angiogenic factors which contributes to neovascularization by promoting mitosis of endothelial cells and inducing hyperpermeability in microvessels, leading to extravasation of other proangiogenic factors into the extracellular matrix.[72,73] Tumor cells and stromal cells in turn secrete cytokines such as TGF-α and platelet-derived growth factor, which perpetuate mast cell expression of VEGF.[72]

In an elegant study, Coussens *et al*[74] show that mast cell-deficient human papillomavirus-infected transgenic mice have severely attenuated tumor angiogenesis and growth when compared with their wild-type littermates. This study shows that tryptase and chymase, the two mast cell-specific proteases, contribute to neovascularization during squamous cell carcinogenesis.[74] Tryptase is a fibroblast mitogen and chemoattractant, and it stimulates type α1(I) procollagen mRNA synthesis in human fibroblasts *in vitro*.[75,76] Preceding malignant transformation in angiogenic dysplasia, high levels of tryptase has been observed, with increased dermal fibroblasts and type α1(I) procollagen mRNA widely expressed in the stroma. This observation supports the role for tryptase in matrix reorganization associated with neovascularization.[74] Blair *et al*[77] demonstrate that addition of tryptase to microvascular endothelial cell cultures causes a pronounced increase of capillary growth by more than 20-folds, and this can be suppressed by specific tryptase inhibitors. Chymase can directly and indirectly, through its ability to activate progelatinase B, trigger

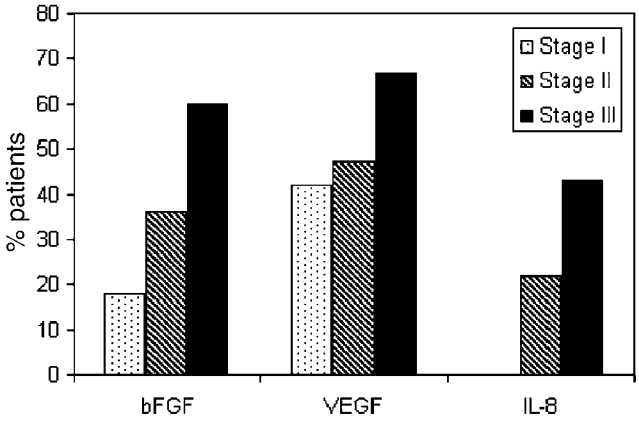

Figure 5 Stage-dependent increase of serum levels of angiogenic factors in 125 malignant melanoma patients. The bars represent the percentage of patients with a serum level above a threshold (bFGF >3.19 pg/ml, VEGF >363.8 pg/ml, IL-8 >226.8 pg/ml), calculated using the receiver operating characteristic curve analysis. Stage I, primary melanoma; stage II, regional lymph node and/or intransit metastasis; stage III, distant metastasis. (Adapted with permission from Ugurel *et al*.[71])

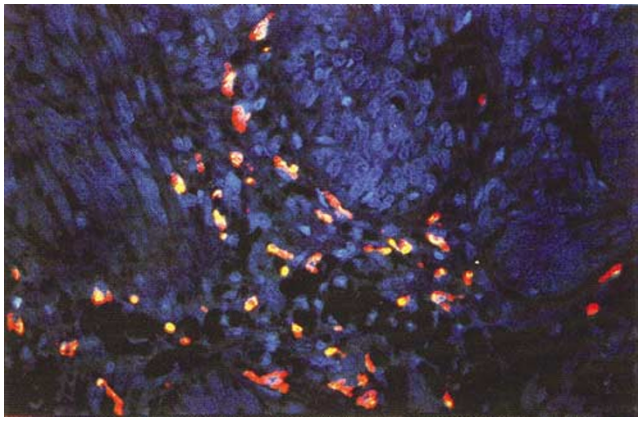

Figure 6 Double immunofluorescence stain of a malignant melanoma showing peritumoral zone rich in mast cells close to tumour. Most of the MCs show immunoreaction for both antitryptase (red) and anti-VEGF (yellow). Note the absence of VEGF expression in the MCs, microvessels, inflammatory cells and tumor cells within the tumor. Far from the tumor margin, MC react mostly with antitryptase antibody but not VEGF (original magnification $\times 200$). (Reproduced with permission from Toth *et al*.[12])

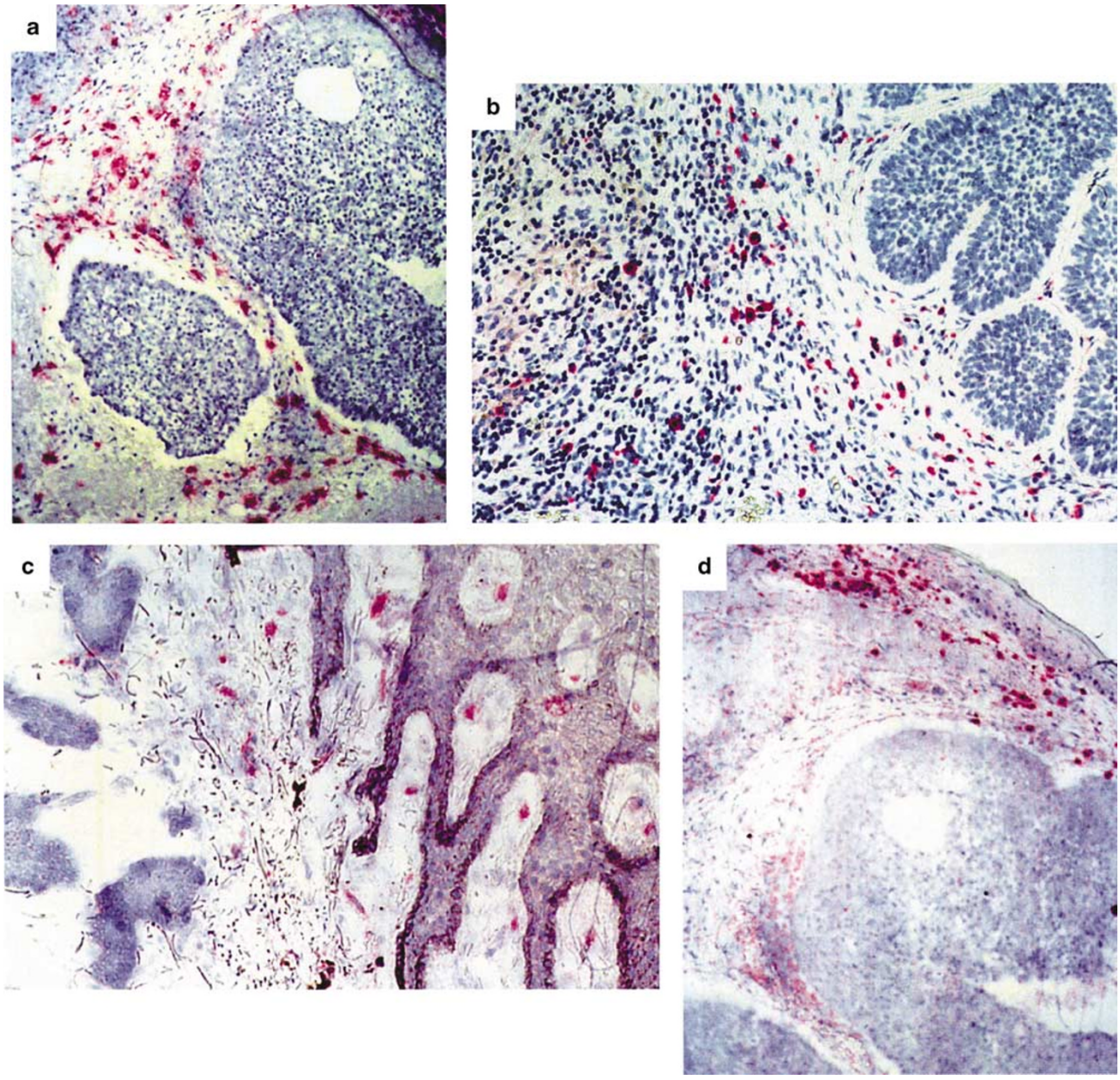

Figure 7 Frozen sections of a basal cell carcinoma with positive staining for anti-tryptase (highlighting mast cells) (**a**), VEGF (**b**), IL-8 (**c**), and RANTES (**d**) monoclonal antibodies. (Reproduced with permission from Aoki *et al*.[14])

proteolysis of the extracellular matrix thereby releasing sequestered angiogenic factors including VEGF and FGF.[74]

Heparin, the dominant proteoglycan in mast cells, has many properties including being mitogenic for endothelial cells.[78,79] It also stimulates migration of cultured capillary endothelial cells.[66] Its anticoagulant effect prevents microthrombi in the new vessels, which helps propagation of metastases.

Mast cell also produces IL-8, which exhibits potent angiogenic activities both *in vitro* and *in vivo*.[80] In all, 50% of melanoma in the vertical growth phase, 100% of melanoma metastatic lesions, and none of the radial growth phase melanoma express IL-8.[81] It is believed that IL-8 exerts its angiogenic activity through the induction of matrix metalloproteinase 2, thereby facilitating endothelial cell migration through the stroma and consequently, assisting tumor metastasis.[80] IL-8 has also been implicated in tumor angiogenesis in basal-cell carcinoma[14] (Figure 7c).

Other mast cell mediators known for their roles in tumor angiogenesis include histamine, FGF and TNF-α.[62] However, their angiogenic role has not been studied specifically for cutaneous malignancies.

Mast cells and the degradation of extracellular matrix

Mast cell plays an accessory role in the degradation of extracellular matrix, the first of a series of linked sequential steps for a tumor to establish successful metastasis[74,82,83] (Figure 1).

Dabbous *et al*[84] show that mast cell degranulation is commonly associated with disruption and lysis of the connective tissue matrix occurring in tumor infiltration. Mast cells have been implicated in this process either directly through the action of their enzymes, or indirectly through modulation of the collagenolytic activity of fibroblasts, macrophages and tumor cells.[85,86] Tryptase activates latent metalloproteinases and plasminogan activator, which degrade the extracellular matrix.[86] Heparin enhances both the activity and production of collagenase *in vitro*.[87] Heparin also releases plasminogen activator from endothelial cells.[88] Other mast cell mediators such as FGF-2, TGF-β, IL-3 and IL-4 can stimulate collagenase and β-hexosaminidase production by fibroblasts, and IL-1 by macrophages. These factors work in concert to loosen up the stromal *milieu* to facilitate tumor invasion.[68,86,89,90]

Mitogenic effect of mast cells

There is increasing evidence that mast cells support tumor progression by providing direct mitogenic stimulation of cancer cells[89] (Figure 1). Among the mediators released by mast cells, FGF-2 and IL-8 are directly mitogenic to melanocytes and melanoma cells.[91,92]

Several studies have shown a close correlation between melanoma progression and the degree to which the tumor cells react to FGF-2.[11,89] The most important gene of the FGF receptor family, *fgfr-1* gene is expressed throughout the human melanocytic system, albeit at higher levels in melanoma than in naevi and normal melanocytes. Antisense targeting of *fgfr-1* in melanoma cells completely blocks tumor growth, inhibits intratumoral angiogenesis causing extensive tumor necrosis, and can even lead to regression in melanoma *in vivo*.[93,94]

Tumor–host paracrine loop

As mast cells' recruitment to the vicinity of cutaneous malignancies is independent of an inflammatory infiltrate, these tumors must secrete mast cell chemoattractants, thus forming a paracrine loop (Figure 1).

Reed *et al*[89] demonstrate that melanoma cells recruit mast cells *in vivo* by producing mast cell chemotactic and mitogenic factors such as IL-3, and the level of IL-3 in the stroma correlates with melanoma progression. This result, however, contradicts another report that shows the absence of IL-3 receptor on human mast cells.[95] Poole *et al*[66], using agarose migration assay, demonstrate that mast cells migrate towards undefined factors released from a variety of tumors including melanoma.

Basal cell carcinoma cells secrete stem cell factor and IL-1, which can stimulate mast cell proliferation and degranulation, thus forming a paracrine loop.[10,28,31]

Opposing roles for mast cells?

The body of evidence presented thus far supports a tumorigenic role for mast cells in the development and progression of cutaneous malignancies. Could this be an incomplete portrayal of the mast cells? Could mast cells in fact fulfil opposing roles depending on the microenvironment in which they reside, playing the Jekyll and Hyde of tumor growth?[17]

This dual role for mast cells certainly seems probable. Firstly, mast cells have a vast array of mediators, some of which have promoting, and others, inhibitory effects on malignancies.[17] Secondly, the phenotypic expression of mast cell is not static and its secretory pattern alters according to the microenvironment. Mast cells have the ability to secrete individual granules (in contrast to indiscriminate degranulation in an anaphylactic reaction) or distinct mediators selectively.[96,97] For instance, acidity inhibits allergic degranulation but promotes IL-4 production. IL-6 can be secreted without histamine *in vitro*; and murine mast cells can secrete VEGF without parallel release of serotonin.[98–100]

Several studies have shown a tumor cytotoxic role for mast cells in cutaneous malignancies.[14,101–103]

Schittek *et al* demonstrate that mast cell-deficient W/W^v mice develop melanoma metastasis more readily than their $+/+$ littermates. It has been hypothesized that histamine increases prostacyclin synthesis by endothelial cells, and that prostacyclin has a potent antimetastatic action.[101]

Certain mast cell mediators including TNF-α, IL-1, IL-6 and interferon-γ have been reported to suppress melanoma cell growth.[102,103]

Aoki *et al*[84] show that mast cells in basal cell carcinoma express mRNA of RANTES, which is a potent chemoattractant for many types of inflammatory cells including neutrophils, eosinophils and monocytes (Figure 7d). RANTES is also known to have the ability to selectively attract T cells of the CD4+/CD45RO+ phenotype, which may contribute to antitumor immunity.

Conclusion

Mast cell attracts as much interest as controversy today in a variety of physiological and pathological processes, including cutaneous malignancies. The divergence in opinion on the functional role of mast cell in these tumors is not surprising given its

versatility and the plethora of mediators it secretes, which have wide-ranging and sometimes opposing effects. However, the great majority of studies to date support an accessory role for mast cells in the development and progression of cutaneous malignancies.

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