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Review

Mast Cell: A Mysterious Character in Skin Cancer

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Abstract. *Cutaneous malignancies represent a real concern and burden for the healthcare system, not only due to their increased frequency, but also due to the significant number of deaths attributed to these types of cancer. The genesis of tumors, their progression and metastasis are highly complex and researched subjects; apparently, mast cells (MCs) constitute an important piece in the complicated jigsaw puzzle of cancer. This article reviews the current knowledge of the roles MCs might play in the development of cutaneous malignancies. Besides their well-known and studied role in allergic reactions, MCs are linked to multiple and various disorders, including cancer. MCs exhibit incredible heterogeneity, being able to secrete numerous mediators that influence the tumor microenvironment and tumor cells. They are involved in many physiological and pathological processes, such as inflammation and angiogenesis. In this context, it is paramount to explore the advancements made so far in elucidating the roles that MCs have in skin cancer because they might provide valuable therapeutic targets in the future. Controversial and conflicting results were obtained across the studies examined.*

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The most frequent malignancy of Caucasians is skin cancer (1). The global incidence rates are increasing for both cutaneous melanoma and keratinocyte carcinoma [basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC)] (2). Melanoma is a rare (1-2% of all cutaneous malignancies) but deadly malignant tumor derived from melanocytes (3). It accounts for 90% of the deaths related to skin cancer (4). There are large variations in the incidence of melanoma between countries, namely due to the existence of different skin phenotypes and to distinctive patterns of sun exposure (5). Keratinocyte carcinomas, previously known as nonmelanoma skin cancers, account for most diagnosed skin cancers, BCC being responsible for 80% (6). Although BCC is associated with a low mortality rate, it can occasionally metastasize and lead to a fatal outcome (6). The second most common cutaneous malignancy, cSCC, represents less than a 6% risk of metastasis and less than a 2% risk of death (7).

Paul Ehrlich, the scientist who discovered and named mast cells (MCs) in 1878, was also the first to illustrate the presence of MCs in the tumor stroma, these observations being published in his doctoral thesis (8). In 1891, Westphal extended Ehrlich's work by describing the existence of MCs in the vicinity of tumors (9). In the past 140 years, the great advancements that have been achieved allowed a much better understanding of the complex relationship between MCs and cancer. However, there are still many unknown and debatable aspects concerning the biology of MCs, especially regarding tumorigenesis and the progression of different types of tumors. Acknowledged primarily for their role in allergic reactions, MCs are not only involved in regulating numerous physiological functions of the body (*e.g.*, vasodilatation, angiogenesis, and defense against parasites), but they have also been connected to a variety of pathophysiological phenomena present in many disorders, including autoimmune diseases (*e.g.*, rheumatoid arthritis and multiple sclerosis) and cancer (10, 11). MCs have been detected in the vicinity of cutaneous malignancies, frequently

around vessels (12, 13). Considering the great impact skin cancer has on public health, the aim of the present review article was to delve into the current knowledge of the roles MCs might play in the development of cutaneous malignancies.

An Overview of MCs

MC origin, subtypes and location in tissues. In 1977, Kitamura *et al*. demonstrated the hematopoietic origin of matured granule-containing MCs in adult mice (14). It was established that mature MCs derive from $CD34^+/CD117^+$ progenitor cells that migrate to target tissues, where they complete their differentiation in the presence of an array of local growth factors and cytokines (15, 16). Stem cell factor (SCF), the c-KIT ligand, besides acting as an MC growth factor, also serves as a chemotactic factor for MCs, inducing their migration into tissues (17).

Mature MCs are widely distributed in tissues, especially in the proximity of the external environment (skin, gastrointestinal tract, and respiratory mucosa), having a strategic location near the areas of invasion of potential antigens (18). They act as tissue-resident cells in the connective tissue, adjacent to blood and lymphatic vessels and nerve fibers, also near to other immune cells (19). In 1986, Irani *et al*. (20) described two subpopulations of human MCs, determined by their different composition in neutral serine proteases. Hence, traditionally, the classification of human MCs is based on their protease content, being divided into two subtypes: MCs that contain only tryptase, localized predominantly in the small intestine mucosa and the alveoli; and MCs that contain, in addition to tryptase, other proteases (*e.g*., chymase) and were identified as the major type of MCs resided in the small intestinal submucosa and the skin (20). Another type of MC is characterized by the expression of chymase, in the absence of tryptase (15).

The combination of certain stimuli present in their microenvironment controls the development of MCs and partly explains not only the remarkably heterogeneity of their phenotypic profile and functions, but also the plasticity by which they change their subtype (16, 21). Eventually, the microenvironment encountered by MCs in the periphery induces their mature phenotype (22).

MCs mediators, methods of identification and MC degranulation. MCs can secrete a wide array of substances (biogenic amines, proteoglycans, mucopolysaccharides, enzymes, cytokines, growth factors, hormones), which are largely divided into two main classes: Preformed and *de novo* (15, 23). The first class of substances is stored in electron-dense cytoplasmatic granules and consists of a variety of significant bioactive compounds, including proteases produced exclusively by MCs: serine proteases (tryptases, chymases) and carboxypeptidase A, a metalloprotease (24, 25). Other notable stored mediators are histamine, serotonin, lysosomal enzymes, several cytokines [interleukin 4 (IL4), SCF, basic fibroblast growth factor (bFGF)] and proteoglycans (heparin, chondroitin sulfates) (26). The latter class of bioactive compounds is composed of mediators that are synthesized after the activation of MCs and can be released immediately, such as the metabolites of arachidonic acid, leukotrienes and prostaglandins, or are substances released less promptly, like cytokines, chemokines and growth factors [*e.g*., vascular endothelial growth factor (VEGF), platelet-derived growth factor, FGF, tumor necrosis factor α (TNFα), transforming growth factor-β, IL1, IL3, IL4, IL5, IL8 and IL10] (15).

Due to their high content in anionic residues of sulfated glycosaminoglycans, histochemical identification of MCs with cationic dyes (*e.g*., toluidine blue, methylene blue) stains them metachromatically (23, 27). Metachromatic staining is advised for routine used in MCs detection (28). Although more expensive and laborious, immunohistochemistry represents the most sensitive and selective method for the identification of MCs, by targeting different compounds, including proteases, such as tryptase and chymase, biogenic amines (*e.g*., histamine, serotonin) or surface receptors [*e.g*., Fc epsilon receptor 1 alpha (FcεRI), the antigen-specific high-affinity receptor for IgE immunoglobulins; c-KIT/CD117] (23). Even if these methods are efficient for identifying mature MCs, immature MCs, in which secretory granules are scarce, are problematic in this regard (29).

There is a variety of receptors at the surface of MCs, the antigen-specific high-affinity receptor for IgE immunoglobulins (FcεRI) being well-known for its classical role in triggering the IgE-mediated hypersensitivity reactions (allergic disorders) (30). When encountering a specific allergen, the multiple FcεRI receptors become crosslinked, leading to degranulation (exocytosis of granules) and to the synthesis of *de novo* mediators. However, the activation of MCs can also take place *via* multiple non-IgE-dependent mechanisms, which include the IL33–T1/ST2 receptor interaction, the participation of Mas-related G protein-coupled receptor-X2 (MRGPRX2)/MRGPRB2 receptor, the engagement of extracellular toll-like receptors (TLRs), intracellular nucleotide-binding domain-like receptors, CD48 and other receptors (24, 25, 31-33).

The ability of MCs to induce such diverse degranulation responses is not only determined by their broad types of surface receptors on which different stimuli act, but also by their phenotype and by their localization in tissues (34). The heterogeneity of MCs was thoroughly assessed by Dwyer *et al*. in the first comprehensive analysis of the transcriptome of different anatomically localized mouse MC populations (35). Due to their ability to selectively produce various responses to a broad repertoire of different combinations of

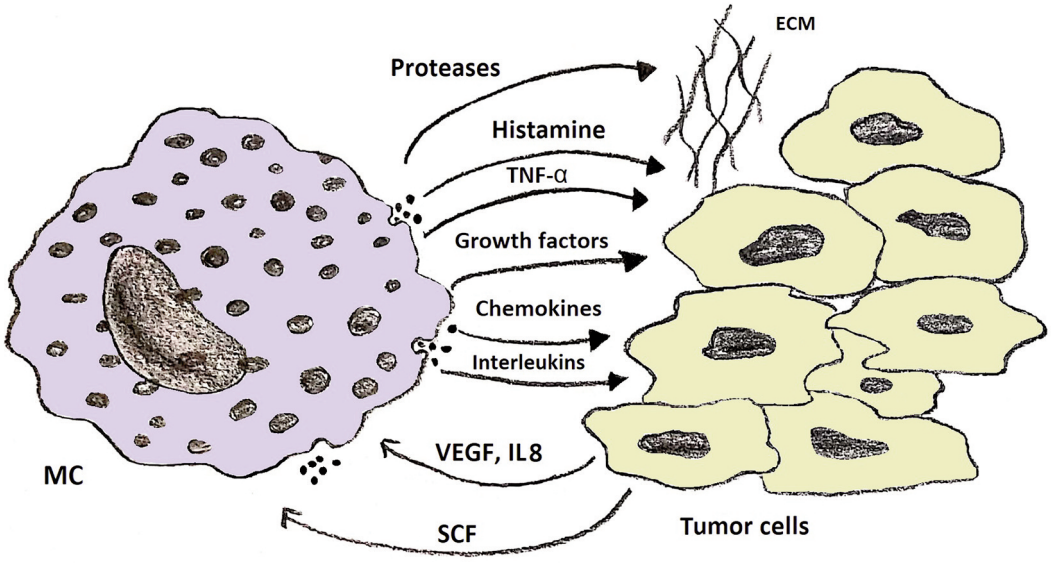

Figure 1. *Schematic illustration of the exchange of mediators between mast cells (MCs) and malignant cells in the tumor microenvironment. ECM: Extracellular matrix; IL8: interleukin 8; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.*

stimuli, the effects of MCs on the microenvironment are multifarious (16). Therefore, the impact that MCs might have on skin cancer carcinogenesis and progression is both complex and controversial and thus, gathering the results of different studies might draw a clearer picture of this enigma.

Cancer and tumor-associated mast cells (TAMCs). The tissue microenvironment can be either an ally or an enemy in the battle with cancer development. Although in a physiological state, the microenvironment maintains the normal architecture of tissues and prevents tumorigenesis by acting as a barrier, in certain circumstances, the signals produced in the microenvironment might actually disrupt the local homeostasis and thus promote the initiation of cancer (36, 37). Aside from interstitial extracellular matrix (ECM), the tumor microenvironment (TME) has a heterogenous cellular composition, encompassing, as well as tumor cells, a variety of non-malignant cells, such as immune cells (including MCs), fibroblasts and cells that configure the local network of supplying vessels (13, 37, 38). Tumor cells and TAMCs perform a mutual exchange of signals, in a dangerous correspondence that may have a tragic outcome (Figure 1). Cancerous cells emit multiple chemotactic factors that attract MCs to the site of tumorigenesis, such as the tumor-derived SCF that can activate TAMCs by acting on c-KIT receptor expressed on their surface (39). Other notable tumor-derived chemotactic factors for MCs are VEGF, angiopoietin 1 (ANG1), and IL8 (40). On the other hand, the mediators produced by MCs can drastically influence the growth of tumor cells and metastasis, the pro-tumoral responses being accomplished by supporting several events, such as immunosuppression, angiogenesis, lymphangiogenesis, ECM remodeling and promotion of cancerous mitosis (12, 13, 16, 41). Conversely, TAMCs secrete mediators that recruit other immune cells and thus can also exhibit anti-tumoral effects (41).

It was shown that the inflammatory microenvironment of a tumor has a significant contribution to tumorigenesis (42). The link between inflammation and cancer was first brought to light by Rudolf Virchow in 1863 due to the observation of a relatively increased occurrence of malignancies at the sites of chronic inflammation (40, 43, 44). Multiple studies have demonstrated a strong link between cancer and inflammation, since inflammatory cells and mediators are constantly present at the sites of tumors (45). Therefore, inflammation, a hallmark of cancer, might be both a causative agent and a repercussion of cancer (20, 46). MC infiltration might have a critical role in remodeling the TME by regulating immune and inflammatory reactions (39). The most notable mediators that are involved in local inflammatory responses and can also be produced by MCs are TNF-α, VEGF, IL6, matrix metallopeptidase 9, Inducible nitric oxide synthase and cyclo-oxygenase 2 (39). Tumoral cells whose microenvironment is shaped by MCs have an enhanced activity of nuclear factor kappa-light-chain-enhancer of activated B-cells and activator protein 1, while suppression of T cells and natural killer cells are also present (39). Individually, mediators might have either tumor-promoting effects or may inhibit the development of malignancies (40).

As the tumor mass of cells develops, new vessels need to be formed in order to maintain an adequate local supply of nutrients and oxygen, a process driven by the imbalance between different pro- and anti-angiogenic regulators (47, 48). Angiogenesis comprises proteolytic alteration of the ECM, along with the proliferation of endothelial cells (49). The abnormal tumor microvascular network favors an acidic and hypoxic TME and thus the growth of cancer cells by multiple mechanisms, including the inhibition of infiltrating effector T-cells and the enhancement of immunosuppressive events (48).

MC degranulation might be determined by tumor hypoxia and thus MCs can produce reactive oxygen species that are functionally correlated with their own activation (50, 51). MCs can release not only pro-angiogenic factors, such as bFGF, VEGF, transforming growth factor β, TNF-α and IL8, but also heparin and proteases that liberate pro-angiogenic factors bound to heparin (10). Tryptase and chymase showed similar pro-angiogenic proprieties to VEGF in the chorioallantoic membrane assay (52). Furthermore, histamine determines the hyperpermeabilization of vessels and certain lipid-derived mediators have angiogenic-promoting effects (53).

Puzzling Role of MCs in Skin Cancer

MCs represent controversial players in the development of various types of skin cancer due to the conflicting results obtained from human and animal model studies. Multiple studies whose aim was to establish the role of MCs in initiation, progression or even their impact on the clinical outcome for certain types of cutaneous malignancies came to different conclusions: MCs are favorable, damaging or they have no apparent influence on tumor behavior.

The studies used to unravel the mystery of the influence of MCs on skin cancers are multiple, encompassing both experimental and clinicopathological studies. There are articles in which the distribution of MCs in cutaneous malignancies (intratumoral or peritumoral locations) was assessed by histological or immunohistochemical analyses. Therefore, correlations between the density of MCs, the density of tumor vasculature and the progression of cutaneous malignancies were drawn. Although there are differences between MCs, based on their genetic background, even between MCs derived from BALB/c and C57BL/6 mice (54), MC-deficient mice were used in many studies. For example, one approach uses the inoculation of tumor cells or the induction of tumorigenesis in MC-deficient mice using different mutagens, followed by the inoculation of bone marrow-derived MCs (BMMCs) originating from wild-type mice in order to confirm the effects of MCs on tumor growth (41). 7,12 Diethyl benz(a)-anthracene–12-tetradecanoyl phorbol-13-acetate)-induced cutaneous carcinogenesis in CreMaster mice (depleted of MCs), revealed that MCs are not important regulators of tumorigenesis and neovascularization (55). However, other findings in this model of induced carcinogenesis in MC-deficient mice (KIT W/KIT W^v) revealed an enhancement of tumor development, while recapitulation with BMMCs reversed this effect (56).

Exposure to UV radiation represents a major environmental risk factor for developing skin cancer by inducing immune suppressive reactions (57). The role of MCs in promoting immunosuppressive effects generated by UV radiation was investigated (58). MCs were found to play an important role in the development of suppressing secondary immune reactions generated by UVA radiation (59). The mechanisms by which MCs are involved in UV-induced immune suppression are complex and not fully understood, involving both cell-mediated and humoral immunity. However, MC-derived IL10 was shown to inhibit the production of antibodies and to suppress the function of follicular T-helper cells (60). In sun-unexposed skin (buttock), increased densities of MCs were associated with a higher risk of developing melanoma (61) or BCC (62), while for cSCC, a similar study revealed no such correlation (63).

In Table I and Table II the experimental findings of the effects that different mediators have on skin cancers are summarized.

Melanoma. Conflicting findings were reported regarding the correlation between the density of MCs in melanocytic lesions and the prognosis for the patient. Some studies associated a higher count of MCs with more severe melanocytic lesions (64, 65, 71) while others associated low numbers of MCs with a poorer prognosis (72, 73). The count of peritumoral MCs expressing VEGF was elevated in metastasizing melanomas, being correlated with increased density of microvessels (65). Moreover, monomeric IgE (in the absence of antigen) stimulated the secretion of VEGF by MCs and thus induced promotor effects on melanoma growth (74). Hypoxia-inducible factor 1α (HIF-1α) is notably present in human and mouse melanoma tissue, MCs being the cells that seem to express HIF-1α the most when stained for HIF-1α. Histamine released by MCs can lead to the expression of HIF-1α and VEGF and thus may promote neovascularization of tumors (50). Nevertheless, in mice lacking histamine due to knockout of the gene encoding for histidine decarboxylase, an enzyme that catalyzes the formation of histamine, skin carcinogenesis was found to be more frequent (75).

However, regarding MC-restricted proteases, studies revealed that in tryptase-deficient mice, the progression of melanoma was accelerated, indicating the antiproliferative effects tryptase might have on tumor cells (66). A similar conclusion was drawn from assessments in cell cultures (66,

Table I. *Significant experimental studies reported in the literature that suggest associations between different types of proteases produced by mast cells (MCs) and development of cutaneous malignancies.*

Study	Type of cancer/ tumor cell line	Type of experiment	Type of mouse model	MC protease	Role of protease(s)	Methods and results – Brief description
Grujic *et al.* 2020 (66)	Melanoma; B16F10 cell line	*In vivo*+ *in vitro*	Wild-type and tryptase deficient Mcpt6$^{-/-}$ mice	Tryptase (MCPT6)	Protective	After subcutaneously injecting melanoma cells into both types of mice (wild-type and tryptase-deficient), tumor proliferation was accelerated in Mcpt6–/– mice. Recombinant MCPT6 reduced the proliferation of melanoma cells in cultures.
Rabelo Melo *et al.* 2019 (67)	Melanoma; B16F10, MEL526, MM466, MM253, A375 cell lines.	*In vitro*		Tryptase (mMCP-6)	Protective	Co-culturing melanoma cells (B16F10) with wild-type BMMCs led to a significant reduction in the number of malignant cells, while co-culturing melanoma cells with tryptase-deficient BMMCs had no antiproliferative effects. The effects of tryptase were also evaluated for other melanoma cell lines, MEL526, MM466, MM253, A375, all except A375 line experiencing an inhibition of growth.
Grujic *et al.* 2017 (24)	Model of melanoma colonization of the lungs (B16F10 cell line)	*In vivo*	Wild-type, Mcpt4$^{-/-}$, Mcpt6$^{-/-}$, Cpa3$^{-/-}$ and Mcpt4/Mcpt6/Cpa3-deficient mice	Tryptase (MCPT6), chymase (MCPT4), CPA3	Protective when all three proteases were present, no influence when they were individually absent	Melanoma cells were injected intravenously. Colonization of the lungs was then assessed. The individual lack of MCPT6, MCPT4 and CPA3 showed no significant difference regarding the dissemination of melanoma cells to the lungs. However, simultaneous deficiency of all three types of proteases revealed significant enhancement of melanoma colonization of lungs compared to wild-type mice.
Coussens *et al.* 1999 (50)	Squamous cell carcinoma	*In vivo*	K14-HPV16 transgenic mice	Tryptase (MCP-6), chymase (MCP-4)	Tumor-promoting effects	Tryptase and chymase are involved in early neoplastic proliferation, MC infiltration was simultaneous with the angiogenic switch in premalignant lesions. In MC-deficient HPV16 transgenic mice (KITW/KITWWv) premalignant angiogenesis was diminished.
de Souza *et al.* 2012 (29)	DMBA-TPA-induced skin cancer	*In vivo+in vitro* (mouse epithelial cell line SVEC4-10)	BALB/c mice	Tryptase (mMCP-6, mMCP-7), chymase (mMCP-4, mMCP-5), carboxypeptidase A (mMC-CPA)	Tumor-promoting effects	Increased expression of tryptase, chymase and CPA is associated with angiogenesis. Tube formation in endothelial cells can be induced by some tryptase subtypes (mMCP-6, mMCP7).

BMMCs: Bone marrow-derived MCs; CPA 3: carboxypeptidase A3; DMBPA: 7,12-dimethylbenz(a)anthracene; MC-deficient HPV16 transgenic mice (KITW/KITWWv); MCP-4: MC protease-4; MCP-6: MC protease-6; MCPT4: MC protease-4; MCPT6: MC protease-6; Mcpt6$^{-/-}$ mice: MC protease-6 (tryptase) gene-deficient mice; mMC-CPA: mouse MC carboxypeptidase A; mMCP 7: mouse MC protease 7, a tryptase of unknown function expressed by a subpopulation of MCs that reside in numerous connective tissues; mMCP-4: mouse MC protease 4; mMCP-5: mouse MC protease 5; mMCP-6: mouse MC protease-6, tryptase; SVEC 4-10: endothelial cells that were isolated from the vascular epithelium of an adult male mouse; TPA: 12-O-tetradecanoyl phorbol-13-acetate.

Table II. *Experimental studies reported in the literature that suggest associations between different mediators produced by mast cells (MCs) and cutaneous malignancies.*

Study	Type of cancer	Type of experiment	Mouse model	MC origin	MC mediators assessed	Methods – Brief description	Results – Brief description
Artuc *et al.* 2011 (68)	Melanoma (Mel-1, Mel-2, Mel-4) and SCC lines (SCL-1, SCC-12, SCC-13)	*In vitro*	-	Primary human skin-derived MCs	TNF-α, histamine	Co-cultivation of MCs and tumor cells (Transwell chamber system). Treatment of tumor cells with supernatants of MCs.	MC-derived TNF-α and/or histamine induced the up-regulation of IL6 and IL8 in SCC cell lines (SCL-1, SCC-12) and increased the expression of IL8 in melanoma cell lines (Mel-1, Mel-2). Histamine stimulation of Mel-4 cell line led to elevated expression of IL8.
Jeong *et al.* 2013 (47)	Melanoma (B16F10 cell line)	*In vitro*+ *in vivo*	C57BL/6	BMMCs (BALB/c and C57BL/6 mice)	HIF-1α, histamine	Tumor growth experiments – mice inoculated with B16F10 cells. Immunohistochemical analysis of melanoma lesions. Assessing the effects of the H1 receptor antagonists on HIF-1α expression.	HIF-1α promoted the growth of melanoma in mice while HIF-1α depletion significantly inhibited tumor development. Histamine induced HIF-1α expression in BMMCs. H1 receptor antagonists inhibited the tumor angiogenesis, thus it was also suggested that the release of histamine amplifies neovascularization.
Oldford *et al.* 2010 (69)	Melanoma (B16.F10), orthotopic and Matrigel -tumor model	*In vitro*+ *in vivo*	Wild-type C57BL/6 and MC-deficient mice ($Kit^{W\text{-}sh/W\text{-}sh}$)	BMMCs (C57BL/6 and TLR2 -deficient mice)	IL6	Orthotopic and *in vivo* Matrigel tumor growth experiments; (subcutaneous administration of B16.F10 cells).	A MC-derived IL6-dependent mechanism *via* TLR2 pathway activation seemed to inhibit tumor progression.
Chacón-Salinas *et al.* 2011 (60)	Sunlight-induced skin cancer	*In vivo*	Wild-type C57BL/6, MC- deficient, ($Kit^{W\text{-}sh/W\text{-}sh}$), IL10-deficient, PGE_2-deficient	BMMCs	IL10	Assessing the immune suppression induced by UV radiation.	Exposure to UV radiation did not suppress GC formation, follicular T-helper cells, and the production of antibodies in MC-deficient mice. When reconstructed with BMMCs from wild-type mice, immune suppression was established. Conversely, reconstituting MC-deficient mice with BMMCs derived from IL10-deficient mice did not restore the inhibition of GC formation when exposed to UV radiation.
Müller *et al.* 2012 (70)	Melanoma, (IPC-298)	*In vitro*		Human mast cells (HMC-1)	Serotonin	HMC-1 cells were irradiated (ionizing radiation) and the level of serotonin released was assayed using ELISA; IPC-298 human melanoma cells were then treated with serotonin. The expression of adhesion molecules on melanoma cells was assessed.	A dose-dependent decrease in proliferation of melanoma cells was observed starting from a specific concentration of serotonin, lower concentrations having no significant impact on IPC-298 cell growth. Melanoma cells presented higher expression of adhesion molecules when serotonin was added to the culture.

ELISA: Enzyme-linked immunosorbent assay; GC: germinal center; HIF-1α: hypoxia-inducible factor 1α; IL6: interleukin 6; IL8: interleukin 8; IL10: interleukin 10; BMMCs: mouse bone marrow-derived mast cells; PGE2: prostaglandin E2; SCC: squamous cell carcinoma; TLR2: toll-like receptor 2; TNF-α: tumor necrosis factor; UV: ultraviolet.

Table III. *Clinicopathological studies reported in the literature that suggest associations between serum tryptase levels and development of cutaneous malignancies.*

Study	Type of study	Type of cancer	Participants	Results
Paolino *et al*., 2016 (77)	Cross-sectional	Melanoma	Total: 38 (25 Males, 13 females; median age=60 years)	Serum tryptase levels were significantly decreased in deeper melanomas, as well as in melanomas with ulcerations.
Paolino *et al*., 2019 (78)	Case-control	Melanoma	Total: 85 (37 Females, 48 males) 40 Patients with melanoma 45 Controls	Serum tryptase levels were lower in thicker, ulcerated and metastatic melanoma.
Crincoli *et al*. 2019 (79)	Cross-sectional	Melanoma	35 (21 Males, 14 females)	Serum tryptase level was greater in patients that had a higher total number of nevi, while lower levels were reported for patients with ulcerated lesions or with lesions having a higher mitotic index.
Komulainen *et al*., 2021 (80)	Cross-sectional	Skin cancer (melanoma, cSCC or BCC)	399 Adults (aged 21-79 years)	Elevated serum tryptase levels were associated with skin cancer.

BCC: Basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma.

67). Additionally, an axis regulating tumor proliferation was proposed, in which tryptase binds to the exosomes derived from tumor cells. This process is followed by the uptake of the exosomes into the nuclei of tumor cells, where tryptase influences the expression of certain genes (66, 67). Furthermore, the simultaneous deficiency of tryptase, chymase and carboxypeptidase was associated with intensified colonization of lungs in a mouse model of melanoma dissemination, in which melanoma cells were injected intravenously. Interestingly, in mice with a deficiency of only one of these proteases, dissemination of tumor cells was not affected compared to wild-type mice (24). An approach employing MC deficiency obtained by using Cre recombinase controlled by mast cell protease 5 promoter in a mouse model provided more evidence to support the hypothesis that MCs promote the metastasis of melanoma to the lungs (76).

Measurement of serum tryptase concentrations indicated levels were lower in patients with deeper, ulcerated, or metastatic melanomas, suggesting a correlation between lower serum tryptase concentration and a poorer prognosis (77-79) (Table III). The serum tryptase levels were observed to gradually decrease from healthy individuals to patients with progressively more severe melanocytic lesions (78). Paolino *et al*. proposed two possible explanations for these results. Firstly, these observations might be in line with the hypothesis that tryptase has an antiproliferative effect on melanoma. The second hypothesis suggests that tryptase may be involved in the first stages of tumorigenesis, higher levels being present in serum until the tumor cells reach self-sustenance, when the serum level of tryptase drops (78).

TLR2 expression on MCs promotes inhibitory actions regarding tumor growth, by recruiting immune cells and by inhibiting angiogenesis. The TLR2 receptor agonist, Pam3CSK4, suppressed the evolution of melanoma tumors in wild-type mice, while in MC-deficient mice, this result was not noted (69). Furthermore, the stimulation of TLR4 in TAMCs by lipopolysaccharide induced the release of C-X-C motif chemokine ligand 10 by TAMCs and thus the recruitment of T-cells that infiltrated B16-OVA-induced melanoma tumors (81).

Keratinocyte carcinomas. Regarding BCC lesions, an increased count of MCs was observed in the tumoral stroma (82, 83). Immunohistochemistry showed that MCs secrete the pro-angiogenic factors VEGF and IL8, while the production of C-C motif chemokine ligand 5 (RANTES) and IL8 illustrate their role in regulating the recruitment of lymphocytes (82). Although the count of tryptase- and chymase-positive MCs was elevated in BCC lesions, chymase was shown to be partially inactivated (84).

There is evidence to support the pro-angiogenic effects of MCs during the tumorigenesis of SSC. When a transgenic K14-HPV16 mouse model was used, in MC-deficient animals, premalignant angiogenesis was reduced (49). Conversely, another study reported that MCs have no impact on growth, angiogenesis, or tumor micro-environment of human papillomavirus (HPV)-associated SCC, also using a transgenic mouse model (85). In another experiment, skin grafts expressing HPV16 E7 protein were transferred to C57BL/6 mice and the results obtained indicated that MCs play a significant role in immunosuppression established by the expression of E7 oncoprotein (86). The effects of inhibition of MCs have been evaluated for different types of cancer. For example, in one study that assessed the effects of masinitib, a

tyrosine kinase inhibitor acting selectively on KIT, the SCF receptor, tumor growth (Δ27-expressing Ba/F3 cells) was inhibited (87). Another study showed that phenotypic alterations of melanoma spheroids grown in the presence of mast cells and mast cell-conditioned media were, at least partly, due to nutrient starvation rather than to the action of factors secreted by MCs (88).

Conclusions and Future Perspectives

The findings discussed in this review have contributed to a better understanding of the importance of MCs in the genesis, growth, and metastasis of skin cancer. Obviously, there are many controversies in this field of research, due to the considerable variation of the results reported on this topic. One possible explanation for the discrepancies observed may be the different experimental approaches used, human or mouse models, distinct types of mouse models, and also the types of skin tumors and their mechanisms of induction in an experimental setting. The conclusions drawn in studies using mouse models need to be further explored in order to establish if they are applicable to human skin malignancies. On the other hand, the incredible heterogeneity and plasticity of MCs might explain, at least partially, the apparent conflicting results between different studies. In the future, the various functions of MCs might be exploited to develop antitumoral therapeutic strategies targeting MCs. Novel drug-delivery strategies, the improvement of pharmacokinetic behavior and therapy dosage and the use of MCs as a new cell type for adoptive cell transfer for cancers in which tumor-specific Ig Es are available may represent important future directions.

In conclusion, until the MC response can be influenced therapeutically so as to stop tumor growth and development, further investigations must be performed to clear up the mystery surrounding these cells, which are clearly important players on the scene of skin cancer.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

MR and RMC were responsible for conceptualization, methodology, formal analysis, and revision; SA, PNG and RAC were responsible for writing and original draft preparation.

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