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Mast cells and wound healing: Still an open question

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Summary. Mast cells, which originate from the bone marrow, possess the ability to secrete a diverse array of active molecules. These molecules include mediators (histamine, heparin), which have been identified for decades and are stored in specific granules, as well as small molecules generated instantaneously in response to stimulation (membrane lipid derivatives, nitric oxide), and a multitude of multifunctional cytokines that are secreted constitutively. Activated mast cells participate in the regulation of the local immune response and exert control over critical events of inflammation and healing with the assistance of a vast array of mediators. The involvement of these cell types in inflammatory states suggests that mast cells may function as sentinels that activate local immune processes in response to various types of stimuli and the entry of antigens. Moreover, due to their proximity to nerve fibers and reactivity to a variety of neurotransmitters, mast cells are among the cells that may facilitate local neuroimmune interactions. With this in mind, it is necessary to consider their participation in the repair of injuries in both acute and chronic conditions.

Key words: Basophils, Evolution, Histochemistry, Mast cells, Receptors, Signal transduction, Wound healing

Mast cells and evolution

Mast cells (MC) are present in all vertebrates with various quantities of secretory granules storing many mediators. Teleost MC contain tryptase and histamine. Most evolutionary advanced fish species have a cell population that resembles higher vertebrate MC. Basophil/MC-like granular hemocytes and test cells in ascidians (urochordates from 500 million years ago) may represent MC progenitors. Histamine and heparin are contained in both. Similarly, arthropod granular hemocytes resemble modern MC. MC probably evolved from a leukocyte progenitor that participated in primitive local innate immunity and disease phagocytosis. The MC phylogenetic progenitor turned into a tissue-regulating and remodeling cell in the Cambrian era, 550 million years ago. Hagfish, lamprey, and sharks shared a common ancestor 450-500 million years ago, which likely had early MC (Crivellato et al., 2015; Noorby, 2022; St. John et al., 2023).

Structure of mast cells

Ehrlich was the first to detect MC in connective tissue in 1878 by coloring their cytoplasmic granules with metachromatic dye, which revealed MC that hematoxylin and eosin staining could not (Ehrlich, 1878) (Fig. 1). All connective tissues include these cells, although they are more prevalent around blood and lymphatic capillaries, nerves, and epithelial surfaces that come into contact with environmental antigens, like

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Abbreviations. 5-LO, 5–lipoxygenase; AP1, activator protein 1; ATP, adenosine triphosphate; AC, adenylate cyclase; AA, arachidonic acid; JNK, c-Jun N-terminal kinases; CD, cluster of differentiation; CCR, chemokine receptor; CTMC, connective tissue mast cells; CRH, corticotropin release hormone; CXCR, CXC motif chemokine receptor; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; PLA2, cytosolic phospholipase A2; DC, dendritic cells; ERK, extracellular signal-regulated kinases; FcεRI, high-affinity IgE receptor; IgE,immunoglobulin E; IL, interleukin; IkB, inhibitor kappa B; IP3, inositol 1,4,5-triphosphate; INS3P, inositol 3-phosphate; JAK, Janus kinase; LYN, Lck/yes-related tyrosine kinase; LAT, linker for activation of T cells; MC, mast cells; MCC, mast cells containing only chymase; MCT, mast cells containing only tryptase; MAPK, mitogen-activated protein kinase; MMC, mucosal mast cells; NGF, nerve growth factor; NTAL, non-T-cell activation linker; NFκB, nuclear factor kappa B; NFAT, nuclear factor of activated T cells; PIP3, phosphatidyl 3,4,5-triphosphate; P13K, phosphatidylinositol 3-kinase; PI4.5P2, phosphatidylinositol 4,5-biphosphate; PDK1, phosphoinositide-dependent kinase 1; PLC, phospholipase C; PG, prostaglandin; EP2, prostaglandin EP2 receptor; PKA, protein kinase A; AKT, protein kinase B; PKC, protein kinase C; STAT3, signal transducer and activator of transcription; SYK, spleen tyrosine kinase; SFK, SRC family kinase; SFK, Src-family kinase; SCF, stem cell factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor

those in the skin, digestive, and respiratory systems. MC possess an elliptical shape, characterized by a centrally located circular nucleus that contains aggregated chromatin. Chromotropic secretory granules exhibit a diameter varying between 0.3 and 1 microns (Figs. 2, 3). When examined using electron microscopy, these granules are easily distinguishable due to the presence of a membrane and include a paracrystalline matrix consisting of lamellar arrays, whorls, and scrolls (Fig. 4) (Bacci et al., 2009; Bacci and Romagnoli, 2010; Bacci, 2022; Zmorzynski et al., 2024).

Histological methods for the identification of mast cells

The detectability of MC is influenced by various factors, including the type of test tissue, the dye used, the pH of the solution, the type of fixation solution, the fixation time, and the final processing technique of stained preparations. However, if immunohistochemistry is the most sensitive and selective MC identification approach, the histochemical technique of metachromatic staining is extensively employed for the identification of mastocytes in histological samples due to its simplicity, cost-effectiveness, efficiency, and broad applicability to various human and animal tissues (Table 1) (Grigorev and Korzhevskii, 2021).

Heterogeneity of mast cells

It has been documented that rodents possess connective tissue MC (CTMC), which are found in the peritoneal cavity and epidermis, in addition to mucosal MC (MMC), which are situated in the intestine and bronchial lamina propria. Similar to MMC in rodents, MC containing only tryptase (MCT) are normally present in the intestinal mucosa and lungs of humans (Figs. 5, 6). Conversely, MC that possess both tryptase and chymase (MCTC) resemble the connective tissue mast cells (CTMC) observed in rodents and are commonly located in the skin, synovial membrane, and surrounding blood vessels. In humans, a less prevalent group of MC, referred to as MC exclusively containing chymase (MCC), has been discovered, but their properties remain incompletely comprehended. Nevertheless, MC can transition between types, and their ultimate phenotype (either MCT or MCTC) is determined by the surrounding microenvironment (Bacci, 2022; West and Bulfone-Paus, 2022; St. John et al., 2023, Zmorzynski et al., 2024).

Mast cells relationships to basophils

MC and basophils are two distinct cell types that have identical characteristics, such as the production of histamine and heparin. They also originate from a common precursor and undergo similar stages of development. Basophils complete their maturation process only in the bone marrow, whereas cells of the MC lineage circulate in the bloodstream as immature forms and complete their growth in peripheral tissues.

Basophils typically have a lifespan of several days under normal physiological conditions. IL3 can enhance the generation and viability of human basophils and trigger an increase in basophil count in living organisms. In contrast, MC can exhibit significant longevity, and even mature MC can multiply under specific circumstances. Stem Cell Factor (SCF) plays a crucial

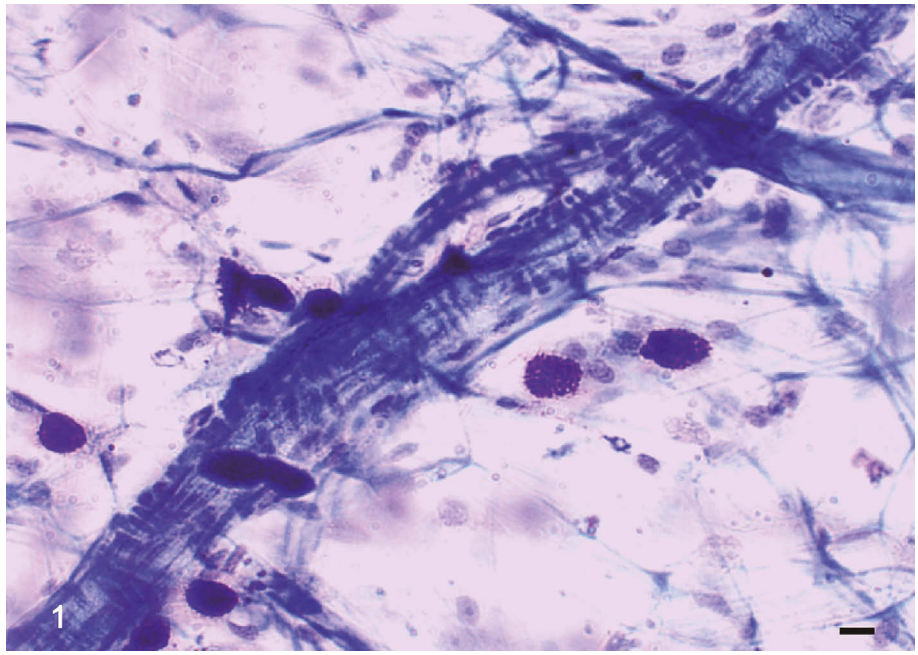
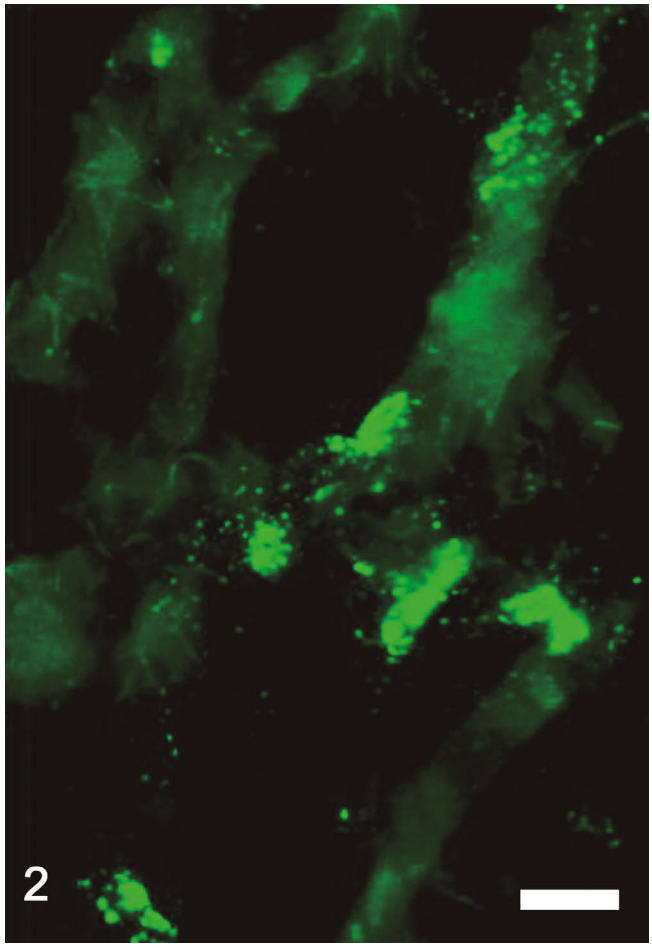
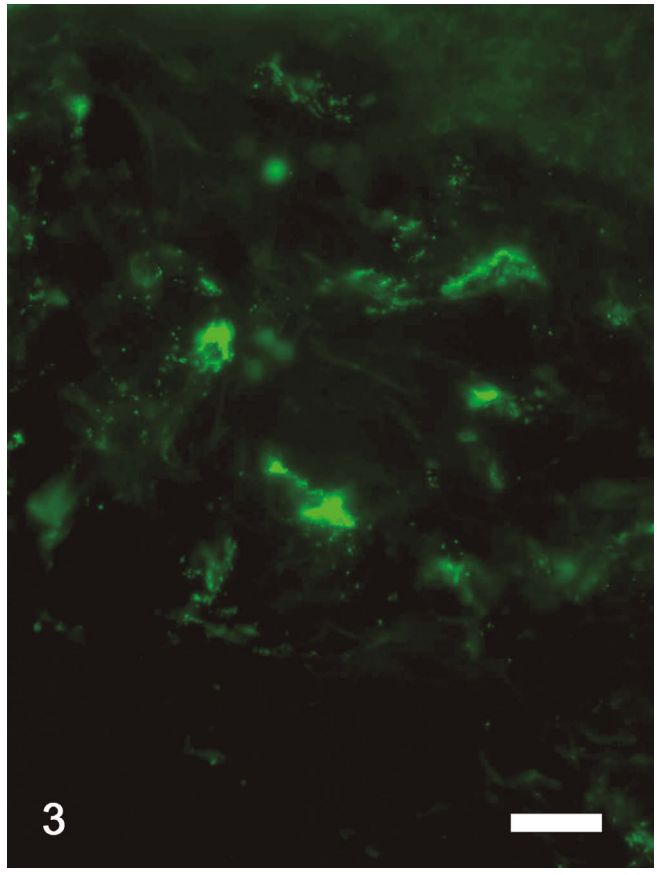


Fig. 1. Mast cells containing metachromatically granules; Toluidine blue. Scale Bar: 20 μm.

role in regulating various aspects of MC development and survival. It acts as the ligand for the c-kit receptor, which belongs to the receptor tyrosine kinase III family of growth factor receptors. The c-kit receptor is expressed on the surface of MC, basophils do not have this receptor. Multiple cytokines promote the activation and release of granules from basophils, while they cause MC to move but not to release granules. The range of cytokines generated from basophils seems to be narrower compared with that of MC (Table 2) (Crivellato et al., 2004; Castells, 2006; Bacci et al., 2009; Bacci and Romagnoli, 2010; Varricchi et al., 2018; Shah et al., 2021; Bacci, 2022).





Figs. 2, 3. Mast cells stained with fluorescent avidin in the adventitia of human carotid artery or the dermis; scale bar: 20 *μ*m.

Table 1. Most effective markers for MC detection.

Markers	Staining technique
Sulfated glycosaminoglycans	Toluidine Blue, Methylene Blue, Safranin O
Heparin	Avidin, Berberine
Chondroitin sulfate E	Alcian Blue
Tryptase	Immunohistochemistry
Chymase	Immunohistochemistry
c-kit (CD117)	Immunohistochemistry
Immunoglobulin receptor E (Fc□RI)	Immunohistochemistry
Histamine	Immunohistochemistry
Serotonin	Immunohistochemistry
Vascular endothelial growth factor (VEGF)	Immunohistochemistry

Modified by Grigorev and Korzhevskii, 2021.

Origin and survival of mast cells

Multipotent hematopoietic stem cells in the bone marrow commit to the MC lineage and produce mature MC. Progenitors express CD13, C-Kit, and CD34 but lack FcεRI (Kirshenbaum et al., 1999). Other CD11b+ bone marrow cells secrete TNF-alpha to develop and expand the MC lineage, and in mice, bone marrow dendritic cells (DC) prime MC precursors for peripheral tissue homing (Wright et al., 2006; Alcaide et al., 2007). Committed progenitors mature in peripheral tissues by entering the circulation. α4 integrins, vascular cell adhesion molecule (VCAM)1, and E-selectin mediate endothelial cell adhesion (Gentek et al., 2018). SCF and eotaxin, which interacts with IL8R (CXCR2), chemokine receptor (CCR)3, CXC motif chemokine receptor CD184 (CXCR) 4, and CCR5, increase MC precursor migration into tissues. The availability of the local growth factors and cytokines SCF, IL3, IL4, IL6, IL9, and nerve growth factor (NGF) in tissues controls MC precursor proliferation and differentiation (Ochi et al., 1999; Nakahata and Toru, 2002).

The SCF and C-Kit signaling system are essential for MC growth and development, and injecting SCF into human skin causes local MC accumulation. MC can quickly travel through connective tissue and epithelia. Histamine stimulates MC migration (Ochi et al., 1999; Nakahata and Toru, 2002).

In the presence of SCF, NGF helps rat peritoneal MC and human cord blood-derived MC to survive. IL3 stimulates murine MC proliferation and improves their development in response to SCF *in vitro*. Human MC progenitors and intestinal MC express IL3 receptors, while lung, uterus, kidney, tonsils, and skin MC do not (Kanbe et al., 2000). IL33 stimulates human umbilical cord blood-derived MC survival, adherence to fibronectin, and cytokine production; adherence receptors may also play a role. The survival of mature human MC in tissues depends on local SCF synthesis as its withdrawal causes apoptosis (Crivellato et al., 2004; Berent-Maoz et al., 2006; Okayama and Kawakami, 2006; Bacci et al., 2009; Bacci and Romagnoli, 2010; Da Silva et al., 2014; Bacci, 2022; Zmorzynski et al., 2024)

Table 2. Differential features of Basophils and Mast cells in human.

	Basophils	Mast cells
Size	9 microns	14 microns
Nucleus	Segmented	Non-Segmented
Granules	Few, large	Small, numerous
Glycogen	Included	Not included
Compound exocytosis	No	Yes
Tryptase	Included	Included
Precursor differentiation in response to fibroblast activation	No	Yes
Expression of c-kit	No	Yes

Modified from Bacci et al., 2009 and Bacci, 2022.

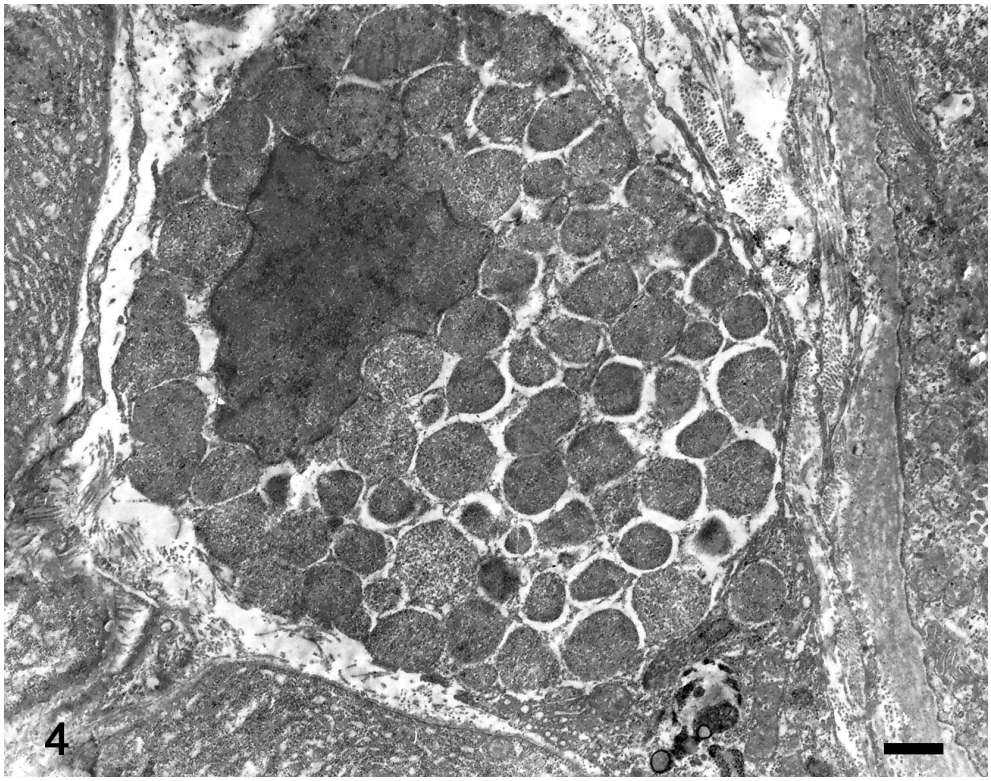


Fig. 4. Human TC mast cell in the stroma of the exocrine pancreas showing numerous secretion granules with a granular matrix. Scale bar: 1 μm.

Secretory products of mast cells

Through morphologically distinct secretion types, preformed mediators contained in specific secretory granules can be released via compound exocytosis, piecemeal degranulation, and focal exocytosis, which involves the exocytosis of individual granules. Compound exocytosis, which is characterized by the fusion of cytoplasmic granules and, in the case of Immunoglobulin (Ig)E-stimulated anaphylactic degranulation, the most superficial granules to the plasma membrane, generates open channels through which the granule content is rapidly and massively released. A progressive loss of granule contents occurs during fragmentary degranulation via exocytosis of shuttle vesicles between individual granules and the cell surface. This mechanism enables the secretion of distinct molecules contained within a single granule in an independently regulated manner. Assuming they are transported to the cell surface via small vesicles, numerous molecules secreted by MC do so via constitutive secretion. Constitutively secreted by MC, the release of cytokines, chemokines, growth factors, neuroendocrine and antimicrobial peptides is governed by fluctuations in their synthesis rate; there is a delay of minutes to hours between cell stimulation and an increase in secretion. It is possible that each cytokine could be unilaterally impacted by this regulation (See Table 3 for specifics regarding the secretory products of MC and their receptors) (Theoharides et al., 2007, 2019; Bacci, 2022; Dilepaan et al., 2023, Zmorzynski et al., 2024).

Mast cell activation

The most extensively researched signal transduction pathways are those initiated by the activation of FcεRI; however, MC also express other receptors, some of which can be stimulated by secretory products of MC themselves.

During the initial stages of stimulation via FcεRI, the receptors are linked together and clustered in specific areas of the cell membrane called lipid rafts. These lipid rafts also contain other kinases, such as Lck/yes-related tyrosine kinase (LYN), which belongs to the Src-family kinase (SFK) group. Activation of LYN may also be facilitated by a protein kinase C (PKC) isoform that is triggered by FcεRI. LYN activation results in the phosphorylation of tyrosine residues in FcεRI; this process enhances the activity of LYN and triggers the activation of spleen tyrosine kinase (SYK) and the linker for activation of T cells (LAT). Other than LAT, another transmembrane adaptor protein is a non-T-cell activation linker (NTAL) located in lipid rafts with interactions with LYN and SYK. When LAT and NTAL signals are simultaneously blocked, there is a complete elimination of calcium mobilization and degranulation in response to FcεRI stimulation. Adaptor activation leads to the recruitment of other molecules, such as different kinases and phospholipase C (PLC), resulting in many downstream signaling pathways that ultimately lead to the secretion of different proinflammatory substances (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli, 2010; Agier et al., 2018; Bacci, 2022; Dilepaan et al., 2023; Zmorzynski et al., 2024).

MC express the γ1 and γ2 isoforms of PLC, with PLCγ1 being the primary isoform responsible for the function of these cells. The production of inositol 1, 4, 5-triphosphate (IP3) by PLCγ1 subsequently leads to an elevation in cytosolic Ca^{2+} levels, which in turn initiates the exocytosis of prepared granules. This elucidates the process of degranulation induced by calcium ionophores. The process of cytokine secretion is initiated by LAT, which leads to the activation of VAV56 (a tyrosine phosphorylation-regulated signal transduction molecule) and SOS (a distress signal used to sense DNA damage or replication fork blockages) 57 that triggers the RAS- and RAF-dependent pathway, resulting in the phosphorylation of mitogen-activated protein kinase (MAPK)s including extracellular signal-regulated kinases (ERK)1, 2, p38, and c-Jun N-terminal kinases (JNK). Subsequently, these substances stimulate the activation of transcription factors, including FOS and JUN, which are part of activator protein 1 (AP1), along with some components of the nuclear factor of activated T cells (NFAT), ultimately resulting in the activation of cytokine genes. PLCγ may also be involved in this pathway, as it can lead to the activation of FOS and JUN by PKC64, as well as the activation of NFAT through calcium, according to studies. ERK1 and ERK2 facilitate the activation of cytosolic phospholipase A2 (PLA2) in the release of arachidonic acid (AA). This AA is then oxidized by cyclooxygenase (COX) and 5-lipoxygenase (5-LO) to produce eicosanoids and reactive oxygen species. MC express the COX2 isoform with the constitutive COX1 enzyme. The synthesis of prostaglandin (PG) occurring during the early MC response appears to be attributed to COX1, while the formation of PG during the late phase is a result of the stimulation of COX2. (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli, 2010; Agier et al., 2018; Dilepaan et al., 2023; Zmorzynski et al., 2024).

Another pathway that originates from activated FcεRI involves the participation of FYN, a member of the SRC family kinase (SFK). This pathway also includes the cytosolic adaptor molecule GAB2 and phosphatidylinositol 3-kinase (PI3K). PI3K transforms phosphatidylinositol 4,5-biphosphate (P14.5P2) into phosphatidyl 3,4,5-triphosphate (PIP3). The second molecule selectively binds to Pleckstrin homology domain-containing proteins, including phosphoinositide-dependent kinase 1 (PDK1) and protein kinase B (AKT), and localizes them to the plasma membrane. Phosphoinositide-dependent kinase 1 (PDK1) promotes MC degranulation and phosphorylates and activates

AKT, which enhances cytokine production in MC. This mechanism is likely accountable for a delayed yet prolonged response in comparison with the PLCγ-dependent pathway that expresses the COX2 isoform. The synthesis of PG occurring during the early MC response is attributed to COX1, while the formation of PG during the late phase is a result of the stimulation of COX2 (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli , 2010; Agier et al., 2018; Dilepaan et al., 2023; Zmorzynski et al., 2024). The transcriptional factor nuclear factor kappa B (NFκB) has a crucial role in regulating cytokine production by MC, particularly TNF-alpha and IL6. AKT and current treatment with a phorbol ester and calcium can activate this factor,

Table 3. Mast cell-released mediators affect physiological processes through their receptors on target cells.

Ligands	Receptors	Functions
Immunoglobulins	FcεRI	Secretion of mediators
	FcγRI	
Cytokines and chemokines	IL1R	Activation of T and B lymphocytes, promotion of vascular permeability
	IL2R	Stimulation of T cell proliferation and differentiation
	IL3R	Secretion of mediators.
	IL4R	Increased expression of FcεRI, LT4 synthase, and cysteinyl-LT receptors
	IL5R	Eosinophil activation, maturation, and migration
	IL6R	Inhibition of SCF-dependent proliferation and differentiation
	IL8R, IL8RA/B	Chemotaxis of neutrophils and lymphocytes, cell adhesion activation of neutrophils
	IL13R	Enhancement of Th1 response
	IL18R	Secretion of cytokines
	IL31R	Proliferation of epidermal cells
	MCP1	Chemotaxis and activation of monocytes
	CC3R	Migration
	TNFR1, TNFR2	Activation of macrophages, enhancement of vascular permeability
Growth factors	GMCSFR	Proliferation and differentiation
	NGFR	Proliferation and differentiation
	TGFbR	Migration
	cKIT	Proliferation and differentiation
Lipid mediators	EP2R	Inhibition of degranulation
	EP3R	Secretion of peptide mediators potentiation of histamine secretion
	LTR	Secretion of peptide mediators upon IL4 priming
	PPARγ	Growth PGD2 secretion
	PAFR	Secretion of histamine, migration
Hormones and Neurotransmitters	MC1R	Secretion of histamine
	MC5R	Secretion of histamine
	CRF2	Secretion of VEGF
	GCR	Inhibition of degranulation
	β2 adrenoceptor (ADR-B2)	Secretion of LT and cytokines, inhibition of histamine secretion
	α1 adrenoceptor (ADR-AI)	Degranulation
	NK1R	Degranulation
	NK2R	
	NK3R	Secretion of mediators
	VPAC2R	
Microbial and antimicrobial molecules	TLR	Endocytosis of bacteria
	CD48R	Secretion of peptide mediators and leukotrienes
	LL37R	Migration, degranulation, secretion of PGD2
Extracellular matrix and cell surface molecules	VLA3R	Adhesion, secretion of cytokines, survival
	VLA4R	
	VLA5R	
	αVβ3R	
	CD44R	
Proteases	Chymase (PAR2)	Different action on blood vessels, smooth muscle, gastrointestinal tract, and skin nerves.
	Tryptase (PAR2)	Different action on blood vessels, smooth muscle, gastrointestinal tract, and skin nerves.
	Carboxypeptidase A3	Degradation of peptides
	Heparin	Anticoagulant, anti-inflammatory, and immunomodulatory properties

Modified from Bacci and Romagnoli, 2010 and Dilepaan et al., 2023.

implying a physiological role for PLC-mediated signaling involving Inositol 3 phosphate (Ins3P), diacylglycerol, calcium, and calcium-dependent PKC. Degradation of Inhibitor Kappa B (IkB)-alpha, an inhibitory protein, is necessary for NF②B activation (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli, 2010; Agier et al., 2018; Dilepaan et al., 2023; Zmorzynski et al., 2024).

Another process includes Janus Kinase (JAK) 3, which occurs when FcεRI cross-links with other receptors. This kinase enhances signal transducer and activator of transcription (STAT)3, which controls protein synthesis. Additionally, it increases the movement of 5LO to the nuclear membrane, where it becomes active and produces eicosanoids (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli, 2010; Agier et al., 2018; Dilepaan et al., 2023; Zmorzynski et al., 2024).

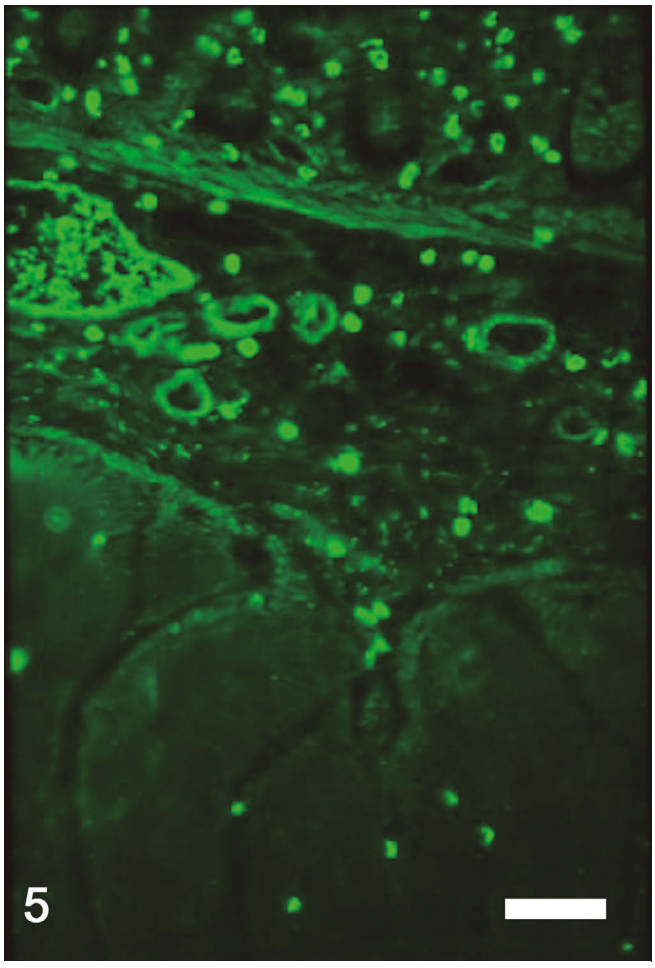


Fig. 5. Localization of tryptase in mast cells of human intestinal mucosa. Scale bar: 20 *μ*m.

Stimulation of G-protein-coupled β-adrenoceptors and prostaglandin EP2 receptors (EP2) increase cAMP, a second messenger synthesized from adenosine triphosphate ATP by adenylate cyclase (AC), which activates PKA. Increased cAMP in MC, caused by receptor activation or phosphodiesterase inhibition, hinders FcεRI-mediated MC secretion. The corticotropin release hormone (CRH) receptor activates AC, however, it only secretes vascular endothelial growth factor (VEGF) without mediators or cytokines (Crivellato et al., 2004; Gilfillan and Tkaczyk, 2006; Kambayashi and Koretzky, 2007; Yamasaki and Saito, 2008; Grochowy et al., 2009; Bacci and Romagnoli, 2010; Agier et al., 2018; Dilepaan et al., 2023; Zmorzynski et al., 2024).

Mast cells and wound repair

Substantial evidence indicates that MC, along with other cells, act as regulators of acute skin wounds. Egozi et al. (2003) showed that MC can regulate the crucial stages of wound healing by modulating the inflammatory response. Weller et al. (2006), conducted a study on artificially created skin wounds in mice that lacked MC (MC-deficient KitW/KitW-v mice), mice with normal MC (Kit+/+ mice), and mice with MC reintroduced (MC-reconstituted KitW/KitW-v mice). Significantly, the process of wound healing, extravasation, and neutrophil recruitment were seen to be normal in mice that had been reconstituted with MC. These data unequivocally demonstrate the involvement of MC in the process of wound healing.

During the inflammatory phase of wound healing, the numbers of MC and the degranulation index increase along the edge of a wound within 1-3 hours after injury and then fall. After 6 hours, they fall below initial levels. The rapid fluctuation in MC number and their distribution within connective tissue (15 minutes for trauma, namely in the skin) suggests that the recruitment of precursor cells and the differentiation of new MC are not significant mechanisms during this phase of the injury response (Bonelli et al., 2003). Oehmichen et al. (2009) discovered that MC degranulate close to the edge of skin wounds within sixty minutes, as shown by enzyme histochemistry for a granule-bound esterase. Endothelial adhesion molecules are upregulated by molecules from MC, like TNF-alpha and histamine, which are released shortly after damage. These substances enhance the expression of adhesion molecules, which facilitate the attachment of leukocytes to blood arteries (Bacci et al., 2006). Leukotrienes, proteases, and cytokines are all examples of chemotactic signals that are released by MC. These signals are conveyed to neutrophils, basophils, and eosinophils. The connections between endothelial cells and leukocytes, as well as the behavior of leukocytes at sites of inflammation, are likewise regulated by tryptase and cathepsin G. Inducing eosinophils to express chemokines for neutrophils is something that chymase can do (Terakawa et al., 2006; Bacci et al., 2009; Komi

et al., 2020; Bacci, 2022). It has been suggested that TGF-beta, TNF-alpha, and proteases can modulate the responses of fibroblasts (Gailit et al., 2001). During the proliferative phase, the number of MC increases once again later on, reaching a maximum at ten days, and then begins to drop after that, eventually returning to control values twenty-one days after the wounding. There is a correlation between the late rise and upregulation of MCP1, as well as the generation of TGF-beta, which is also a powerful chemoattractant for MC (Trautmann et al., 2000). In addition to chymase and tryptase, TGF-beta and VEGF are also known to induce angiogenesis. Heparin, on the other hand, has the potential to limit angiogenesis by interacting with pro-angiogenetic factors and thus decreasing their activity (Muramatsu et al., 2000; Presta et al., 2003; Abdel-Majid et al., 2004; Doggrell and Wanstall, 2004; Somasundaram et al., 2005). Growth factors and cytokines that are derived from MC have the potential to impact the phenotype of activated fibroblasts during the later stages of the repair process. This can result in the formation of myofibroblasts, which ensure the transition from fibroplasia to contraction and the ultimate healing of the wound (Gailit et al., 2001; Bacci et al, 2009).

In terms of tissue remodeling, MC can activate fibroblasts, which in turn promotes the production of collagen. This effect may be partially attributed to tryptase, which has been demonstrated to stimulate the production of type I collagen in human dermal fibroblasts (Abe et al., 1998; Komi et al., 2020).

The promotion of acute inflammation, proliferation/re-epithelialization, and angiogenesis, as well as scar contraction and collagen cross-linking, are all processes that MC influence in the process of wound healing (Komi et al., 2020; Bacci, 2022)

Mast cells and chronic wounds

Clinically, wounds that deviate from the typical healing process and experience a substantial delay in healing are considered chronic wounds (Grandi et al., 2022). In these kinds of wounds, studies have shown that MC not only increase in quantity and degranulation index, but also express TNF-alpha, SCF, and the receptor C-Kit. Activation of C-Kit triggers the release of granules, facilitates the movement and specialization of new precursor cells, and inhibits programmed cell death, potentially playing a role in the development of a persistent inflammatory milieu (Huttunen et al., 2000, 2002; Corsi et al., 2016).

Experimental observations in chronic wounds indicate that the interaction between nerves and MC plays a crucial role in the healing process. The presence of NGF, vasoactive intestinal peptide (VIP), and inducible Nitric Oxide (iNOs) in the cytoplasm of MC supports this hypothesis. These mediators can interact

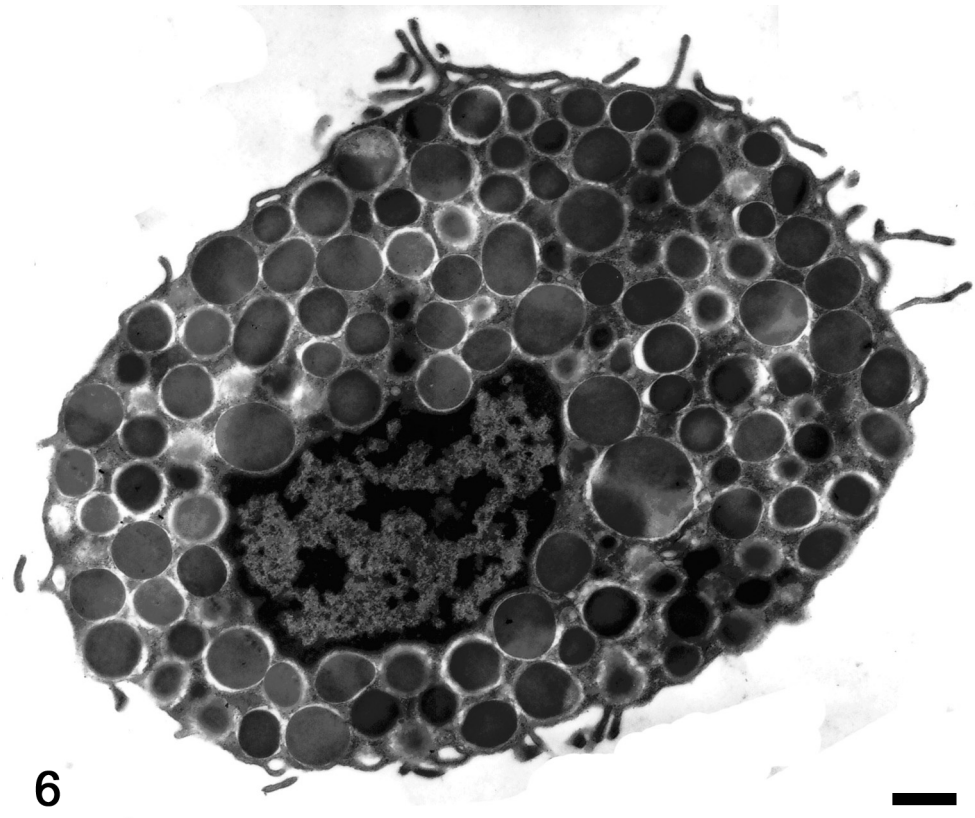


Fig. 6. Guinea pig mast cell isolated from the peritoneal serosa showing similar features to human TC mast cells, namely numerous secretion granules with a homogeneous electron-dense matrix. Scale bar: 1 μm.

with neurons and nerve fibers in the dermis, leading to improved healing. The stimulation of nerve fibers may be associated with other occurrences in chronic wounds, such as the heightened release of extracellular matrix by fibroblasts, as previously noted in the elevation of TGF-beta and the reaction of cellular infiltrates (Corsi et al., 2016; Grandi et al., 2018, 2021, 2022; Notari et al., 2023).

Conclusion

Based on the main discoveries from this investigation, it seems justifiable to suggest that MC are essential in wound healing. During acute wound situations, MC are activated by various cell types or environmental stimuli, leading to the release of TNF-alpha, which facilitates the development of DC. MC emit substances that promote angiogenesis, while fibroblasts secrete extracellular matrix. Therefore, these activities contribute to the cellular response to the injury. Various cells in the environment generate TGF-beta, leading to the differentiation of macrophages into the M1 and M2 phenotypes. These cells likely collaborate with keratinocytes to induce fibroblasts to develop into myofibroblasts. TGF-beta's function is associated with the development of plasmacytoid DC, which interact with Treg cells to improve tolerance by expressing CD45 in these cell types during wound-healing processes.

Further data reinforces the crucial importance of these cells in chronic wounds. Several studies have shown an increased degranulation index in MC present in chronic wounds. This event causes changes in the inflammatory cells, triggering various reactions from the different cell types present. TGF-beta, a cytokine produced in this environment, is crucial in many stages to aid in the healing process of chronic wounds. This wound type entails a documented interaction between MC and neural cells. The release of nerve mediators involved in wound healing is connected to the interaction between these specific cell types (Fernandez-Guarino et al., 2023).

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