Fine Regulation during Wound Healing by Mast Cells

Subjects: Immunology

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Mast cells (MCs) are bone marrow-derived cells capable of secreting many active molecules, ranging from the mediators stored in specific granules, some of which have been known about for several decades (histamine, heparin), to small molecules produced immediately upon stimulation (membrane lipid derivatives, nitric oxide), to a host of constitutively secreted, multifunctional cytokines. With the aid of a wide array of mediators, the activated MCs control the key events of inflammation and therefore participate in the regulation of local immune response. On the basis of the structure, origin, principal subtypes, localization and function of these cells, their involvement in injury repair is therefore to be considered in acute and chronic conditions, respectively.

acute wounds chronic wounds mast cells wound healing

1. Mast Cells

Mast cells (MCs) had long been elusive as to their functional role. The name itself tells us that they were first interpreted as nutrient storing cells, before being recognized as secretory cells. Later on and for a long time, emphasis on MCs secreting histamine and heparin and as effector cells of immediate type hypersensitivity had almost completely distracted from other possible roles of MCs in health and disease. The expanded knowledge on the structure, origin, and function of these cells has brought them to the front of stage of the injury response and repair processes through the release of histamine, glycosaminoglycans, enzymes, cytokines, arachidonic acid derivatives and nitric oxide and, perhaps, through direct, membrane molecule-mediated cell interactions.

The SCF and C-Kit signaling system is crucial for MC growth and development and the injection of SCF into the skin of humans results in local accumulation of MCs. MCs can quickly move within connective tissue and even transfer into epithelia and backwards. Histamine itself promotes MC migration [1][2].

MCs participate in the processes of natural immunity, as they degranulate in response to stimuli of various types, including among other things the activation of complement through the alternative pathway, possess killer activities under certain conditions and are cytotoxic to helminths [3][4][5][6].

MCs can participate in the processes of acquired immunity, and the effector role they play in allergic reactions has long been known. Their secretory products determine vasodilation and influence the recruitment, differentiation and function of lymphocytes, macrophages, fibroblasts and MCs themselves. Therefore, MCs may also be important in the triggering of delayed-type hypersensitivity reactions and in the late stages of inflammation including fibrosis.

The secretory products of MCs determine dilation and increase the permeability of capillary activation of coagulation, activation of fibrinolysis and a stimulus adhesion of leukocytes to the endothelium of blood vessels [3][4][5][6]. Furthermore, some MC secretory products stimulate the proliferation and secretory activity of fibroblasts and histamine can also affect other cell types involved in immune processes. The major effects of some mediators are summarized in **Table 1**.

Table 1. Involvement of some mediators secreted by mast cells in the response of the immune system.

Mediators	Functions
Histamine	Activation of a group of suppressor T cells
Prostaglandin D2	Inhibition of the activity of helper T cells, stimulation of the differentiation and function of suppressor T cells, inhibition of IgE production
Leukotrienes	Similar function of prostaglandin D2 and inhibition of the differentiation of plasma cells.
VIP	Inhibition of the secretory and proliferative responses of at least some of the subgroups of T and B cells.
Heparin (low concentration)	Activation of macrophages to produce IL-1, which in turn affects both the macrophages themselves and the surrounding cells and the whole organism

Modified by Bacci, S., Bonelli, A., Romagnoli P. Mast cells in injury response. In cell movement: New Research Trends. Abreu, T., Silva, G. Eds. Nova Science Publishers, Inc, Hauppage, NY, 2009, pp. 81–121. Bacci, S., Mastociti e cellule dendritiche della cute e delle mucose: analisi morfologiche e funzionali in condizioni normali e sperimentali. (Mast cells and dendritic cells of the skin and mucous membranes: morphological and functional analyses in normal and experimental conditions (Doctorate, PhD thesis, University of Florence, 1997).

2. The Wound Healing

The process takes place in distinct phases, but in some moments they overlap, preceded by a preliminary hemostatic phase. Below are the main events of the various phases that characterize this event.

Hemostatic phase: represents the local response to hemorrhage, caused by the rupture of blood vessels, through the action of thrombocytes and the activation of tissue coagulation factors. This phase is characterized by the formation of a clot, a structure consisting of a fibrin network in which the corpuscular elements of the blood which occupy the wound remain imprisoned.

Inflammatory phase: in the case of the wound, inflammation provides for the elimination of the microbial agent, any foreign bodies and necrotic cells, but also the activation of those factors that are at the basis of the subsequent proliferative processes and, therefore, of the repair or replacement of damaged tissue. It involves vasodilation and plasma exudation and the proliferation of macrophages, mononuclear cells with phagocytic capacity, which together with neutrophil granulocytes during the inflammatory reaction begins immediately after the

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trauma and lasts a few days, also persisting during the next phase. In this period the wound is edematous and strongly red.

Proliferative phase: this begins a few hours after the injurious event and has the purpose of replacing the clot with a solid, definitive structure. In fact, 24–72 h after the trauma, an important proliferation of fibroblasts guarantees the secretion of hyaluronic acid, an active component in the formation of collagen fibers. Fibroblasts already at the end of the first week represent almost all the cells present in the wound; their activity will continue for the time necessary for the collagen produced to fill the wound. At this point, having completed their task, around the third week, the fibroblasts are activated and acquire α-SM actin expression and become myofibroblasts. These myofibroblastic cells synthesize and deposit the ECM components that eventually replace the provisional matrix. Simultaneously with the others, the proliferation of cells of the basal layer of the epithelium also begins.

Maturation phase: corresponds to that phase in which the wound, initially edematous and reddened, is permanently closed by a scar with very different characteristics: pale, smooth, inelastic, without skin appendages with reduced spraying and innervation. This phase lasts at least three weeks, but sometimes it also continues for months or years [7][8][9][10][11][12][13][14][15].

3. Mast Cells and Wound Repair

Weller et al., 2006 [16], studied experimentally induced skin wounds in MC-deficient KitW/KitW-v mice, normal Kit+/+ mice, and MC-reconstituted KitW/KitW-v mice. Wound closure was significantly impaired in the absence of MCs during the first 6 days of wound healing and histomorphometric analyses of MC degranulation at the wound edge revealed distance-dependent MC activation. In addition, KitW/KitW-v mice showed impaired extravasation and recruitment of neutrophils to the wound area. Notably, wound closure, extravasation, and neutrophil recruitment were found to be normal in MC-reconstituted KitW/KitW-v mice. Besides, wound closure was reduced in mice treated with an H1-receptor antagonist but not after treatment with an H2-receptor antagonist or in the absence of TNF-alpha. Other scholars have shown that the MC products histamine and serotonin exert mitogenic effects on murine epidermal keratinocytes in situ [17]. In vitro studies have demonstrated that MC can promote the conversion of fibroblasts to a myofibroblast phenotype [18], as well as stimulate fibroblast proliferation and migration [19] and that MCs, which accumulate at sites of neovascularization, can induce neoangiogenesis [20]. These findings undoubtedly indicate that MCs are involved in wound healing. In particular, Egozi et al. [21] demonstrated that MCs are able to control the key events of wound healing as an inflammatory response. However other scholars evoked for MCs a role in the revascularization of damaged tissue, re-epithelialization, and deposition and subsequent remodeling of connective tissue [22][23]. Once activated by tissue injury, MCs release mediators which induce vasodilation and increase vascular permeability [16]. The endothelial cells, in turn, influence the functional state of MCs by releasing SCF, IL3 and thrombin which enhance migration, proliferation and local differentiation of the MCs. At the edge of wound, keratinocytes can secrete several cytokines and IL-33, which influence MC recruitment and function [4].

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MC numbers and their degranulation index increase at the border of the wound with a maximum of 1–3 h from trauma and decrease thereafter, becoming less than baseline values after 6 h from trauma. The quick variation in MC numbers and location within connective tissue (15 min for trauma, in the skin) speaks against the recruitment of precursors and differentiation of new MCs as a relevant mechanism in this phase of the response to injury [24]. These cells increase again in number later on, to a maximum of 10 days, and decrease thereafter returning to control values after 21 days from wounding. The late increase correlates with the upregulation of MCP1 and with the production of TGF-beta, which is also a potent chemoattractant for MCs [25].

Angiogenesis is stimulated by TGF-beta, VEGF, chymase and tryptase. In contrast, heparin may inhibit angiogenesis by interacting with, and inhibiting pro-angiogenetic factors [26][27][28][29][30]. In the late phases of repair, MC-derived growth factors and cytokines may influence the phenotype of the activated fibroblasts inducing the appearance of myofibroblasts which ensure the changeover from fibroplasia to contraction and final healing of the wound [4][18]. Concerning tissue remodeling, MCs can activate fibroblasts, promoting collagen synthesis: this effect may be partly due to tryptase, which has been shown to stimulate the synthesis of type I collagen in human dermal fibroblasts [31][32].

4. Mast Cells and Scars

MCs are likely candidates to play a role in the etiology of hypertrophic scar formation [33]. It has been reported that early cutaneous wounds express low levels of inflammation and can heal without a scar and can regenerate hair follicles. In contrast, wounds in the late fetal developmental stages have high levels of inflammation and heal with a fibrotic scar. In a mouse fetal repair model study, embryonic day E15 wounds healed without a scar and E18 wounds healed with a scar; it has been demonstrated that there were fewer MCs, which were less mature, and there was no degranulation upon wounding in the scarless E15 wounds compared to the fibrotic wounds produced at E18 [34][35][36][37].

In man, the greatest increase in numbers of MCs at week 1 compared to uninjured skin with a gradual decrease from week 1 to week 8 has been demonstrated. These findings were similar to those of markers of angiogenesis as well as of CD8+ cells; furthermore, macrophages slowly increased from uninjured skin and showed greatest levels at week 5 where levels reduced thereafter [36][37][38]. It has been demonstrated that MCs, after stimulation with substance P, activate fibroblasts through the release of histamine that is significantly elevated in the plasma of patients developing hypertrophic scars compared with age-matched normal volunteers. Since MCs are able to promote the proliferation of fibroblasts also by the release of TGF-beta1, TNF-alpha and IL-4, this indicates that MCs may play a role in hypertrophic scar formation via different mediators [36][37][38].

5. Mast Cells and Chronic Wounds

Various pathophysiologies of wounds that do not follow the normal healing process and have a significant delay in healing receive the clinical designation of a chronic wound [39]. The incidence of chronic wounds is estimated to be

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about 1–2% in developed countries [40]. In particular in chronic wounds, MCs have a significantly different functional repertoire and location than in acute healing. It has been observed that MCs increase their number and degranulation index in chronic wounds other than expressing TNFα, as well as SCF and the receptor C-Kit [41][42][43]. Signaling through C-Kit induces degranulation, promotes migration differentiation of new precursors, and prevents apoptosis, thereby potentially contributing to the chronic inflammatory microenvironment [41][42][43].

6. Neurogenic Stimuli and Mast Cells in Chronic Would Healing

Immune system activity can be modulated by the nervous system; this close correlation is also documented in healing wounds. Interactions between the nerves and MCs are crucial in the healing process and the expression in their cytoplasm of NGF and VIP clearly demonstrate this hypothesis and these mediators are able to interact with neurons and nerve fibers of the dermis, thus obtaining an improvement [44]. The activation of nerve fibers could in turn be related to other phenomena in chronic wounds, such as the increased secretion of extracellular matrix by fibroblasts as has been observed previously in the increase of TGF-beta and the response of cellular infiltrates [44][45][46].

7. Conclusions

MCs can be proposed for a double role in injury response. Very early, they release different types of mediators activating the vascular phase of inflammation and the recruitment of leukocytes which provide for the cellular phase of inflammation itself. To these aims, MCs most probably concur with other ready-to-fire local control systems, i.e., platelets (which are activated immediately upon endothelial damage) and peripheral nerve fibers, in particular sensitive fibers which are involved in axo-axonal reflexes and secrete peptide mediators. In the skin, but not necessarily in other organs, MCs gather near the site of injury to perform their roles. In the intermediate phase of the response, MCs decrease in number, probably in part because they degranulate and so become undetectable by the usual histochemical methods, in part because they die in response to hyperstimulation and toxic substances (e.g., high concentrations of NO and other oxidants). The new, late increase in numbers and the late activity of MCs can concur to drive definitive tissue repair by stimulating angiogenesis and inducing fibroblasts to secrete extracellular matrix and to differentiate into myofibroblasts to contract the collagen matrix. MCs promote the proliferation of fibroblasts, endothelial cells and keratinocytes during the proliferative phase of wound healing. In the mouse, histamine and serotonin (which is also secreted by rodent MCs) exert mitogenic effects on murine epidermal keratinocytes in situ and therefore influence re-epithelialization. In conclusion, if the news regarding the role of MCs in acute wounds begins to flow and, therefore, authorizes the reader to have ideas about the possible role of these cell types, the picture, however, turns out to be extremely confused and contradictory for the role assumed by these cells in chronic wounds [47].

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