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# The mastcell, director of chronic pelvic pain orchestra: implications for the gynaecologist

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**Background:** Acute and chronic inflammation are mediated by the mastcells (MCs). They are distributed in all organs and vascularised tissue, where they work as immune sentinels. They are recruited to the sites of inflammation, where they orchestrate the inflammatory response. MCs contain different angioactive, pro-inflammatory and neurotrophic factors, packed in vesicles which differentially release their content outside the cell into the tissue, according to the type and timing of damaging factors ("agonists" of the degranulation process). The majority of gynaecologists are not familiar with MC's role.

**Aim of the presentation:** to update the knowledge and understanding of MCs role in chronic pelvic pain (CPP), focusing on endometriosis, vulvar vestibulitis, irritable bowel syndrome and interstitial cystitis.

**Method:** review of the literature.

**Results:** Increasing evidence supports the prominent role of up-regulated mastcells in the maintenance of chronic inflammation and in the shifting from nociceptive to neuropathic pain in the affected tissues, contributing to CPP. New therapeutic lines consider reduction of agonists and/or using drugs ("antagonists") that can down-regulated the release of pro-inflammatory, angiogenic and neurotrophic factors from the mastcells.

**Conclusions:** MCs are the real conductor of the inflammatory process. In CPP, MCs are the maintaining contributors of chronic inflammation, leading to the shift between nociceptive and neuropathic pain. Gynaecologist' may improve CPP by understanding the pathophysiology of MCs in chronic inflammation and addressing it in a multimodal therapeutic process.

## **Introduction**

Mast cells (MCs) play a key role in inflammation [1-3]. They are ubiquitous, distributed in virtually all organs and vascularised tissue, where they work as immune sentinels. MCs are present in and recruited to the sites of inflammation, where they orchestrate all the steps of the inflammatory response [2-5]. They contain different angioactive, pro-inflammatory and neurotrophic factors, packed in vesicles which differentially release their content outside the cell into the tissue, according to the type of damaging factors. MCs are the real conductor of the complex defence process that may protect the body from a great range of threats [2-7]. If chronically up-regulated, MCs become the maintaining contributor of chronic inflammation, and contribute to the shift between nociceptive and neuropathic pain, mediated by the MCs' increased production and release of neurotrophins, such as the Nerve Growth factor (NGF) [7].

The chapter reviews the current evidence on mast cells and their critical role in shifting pain from nociceptive to neuropathic, focusing on vulvar vestibulitis/vulvodynia, leading cause of dyspareunia in fertile women, with a clinical perspective.

## **The biochemical identity of mast cells**

Although their discovery dates from over 100 years ago, [1] the mast cells still represent a "biological enigma". These cells possess a series of biochemical and functional resources which place them at the centre not only of protective inflammatory and immune responses, but of the homeostatic tissue regulation mechanisms in general [2]. Even taking account of the substantial differences in terms of morphological heterogeneity and reactivity to secretagogues found in the various tissues and/or the various species, all mast cells are activated by stimuli of various kinds ("agonists") , and release, by means of degranulation, a wide array of biologically active mediators which are not only synthesised at the time of the stimulus as in all the other cells, but can also be released with immediate and differential kinetics because they are stored in cytoplasmic granules. [3-5]

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Recognition of their ability to respond to a composite range of agonist stimuli, and the identification of an increasing number of biochemical mediators contained in and differentially released by the mast cells, [6, 7] has in time led to an extension of the functional role of these cells in an increasingly wide range of diseases, from inflammatory diseases to fibrotic involutions [8, 9]

Later, as a result of continual research into its functional characteristics, this cell has acquired increasing importance in all the processes that require delicate biological coordination between the cells of the skin area for their correct performance.

**Clinical meaning**

MCs contain and differentially release:

- 1) all the molecules that mediate the typical signs and symptoms of local inflammation: reddening of the tissue, oedema, increase of local temperature, pain, and functional impairment, well described by the ancient roman physicians in "rubor, tumor, calor, dolor, functio laesa";
- 2) molecules ("neurotrophins"), that activate the nerve endings of pain fibres, inducing proliferation and superficialization of the nerve terminals in the inflamed mucosa. These changes are the morphological correlates, respectively, of hyperalgesia, the increased perception of pain, and allodynia, when a tactile stimulus is perceived as a burning pain: a perceptive pain change typical, for example, of vulvar vestibulitis.

**The mast cell's morphology**

Selye was the first to describe human mast cell as rounded element with an oval nucleus and cytoplasm filled with spherical metachromatic granules, typically situated in the dermis, near the blood vessels, glandular ducts and hair follicles. Toluidine blue and Giemsa were the usual staining techniques used until recently [10, 11]. Unfortunately these staining techniques were not adequate to prove the presence of MCs in the inflamed tissue, in different degranulation conditions. This limit contributed to the controversies on the non inflammatory condition of many painful syndrome, when an increased number of MCs could not be proved in the examined tissue. Thanks to the immunostaining techniques, such as the immunotryptase, MC are now proved to be significantly increased in the initial stages of different conditions such as vulvar vestibulitis, interstitial cystitis, irritable bowel syndrome, and endometriosis, just to mention the main contributors of Chronic Pelvic Pain (CPP) in women. In later stages of the diseases, when the chronic inflammation has led to fibrotic tissue, MCs may indeed almost disappear from the functionally deserted tissue.

In lab animals, the mast cells are currently divided into two main types (connective and mucosal) [10, 11], while in man they are now classified in three groups, based on their immunocytochemical characterisation [12, 13]. Specifically, there are mast cells containing tryptase only (MC<sub>T</sub>), which correspond to the mucosal mast cells; mast cells containing tryptase, chymase, carboxypeptidase and cathepsin G (MC<sub>TC</sub>), which correspond to the connective mast cells, and mast cells with differing tissue locations containing chymase and carboxypeptidase (MC<sub>C</sub>).

This heterogeneity is typical of the human mast cells. These cells are preferentially located in the dermis and, as in the other tissues, are anatomically adjacent to nerve endings and microvascular networks [3, 14, 15]. Though traditionally considered to be resident in the dermis, the skin mast cells have migratory capacity and also demonstrate extraordinary functional adaptation in response to disturbance of tissue homeostasis [3, 16, 17].

**Clinical meaning**

The lag time between the beginning of the inflammatory status, and the moment when the biopsy is performed, may explain different histological data when considering the number of MCs per high power field. These differences simply mirror different evolutive steps and moments in the natural history of a chronic inflammatory disease, like different shots in a movie. Coherently with these changes, whilst at the beginning MCs may be prominent with minor nerve proliferation, with the ongoing disease, MCs may return to normal concentration and even tend to disappear in the late fibrotic evolution, whilst nerve proliferation and nerve-related symptoms, such as spontaneous hyperalgesia, become prominent.

**Functional role of mast-cells**

As regards the functional activation, the skin mast cell, which is strategically located between vessels and nerves, is directly stimulated by immunological signals (cytokines, IgE and complement fractions) [3, 18] and by stimuli of nerve origin [14, 15].

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**A) The neurogenic inflammation**

The neuropeptides (NGF; Calcitonin Gene Related Peptide, CGRP; and Somatostatin, SOM) released by stimulated or damaged dermo-epidermal nerve endings not only initiate the vessel's response to neurogenic inflammation [19], but also act as factors which directly activate the local mast cells, causing their degranulation [15]. In addition, numerous stimuli of a physical, chemical and/or mechanical nature act as agonistic stimuli [20-22]. In other words, by directly disturbing the mast cell membrane or indirectly acting by stimulating local sensory endings, they can trigger the release by degranulation of mediators with biological activity which the mast cell synthesises and stores in the cytoplasmic granules. Once released, cytokines, growth factors, vasoactive amines and proteolytic enzymes influence all the surrounding cell elements, coordinating the biological response to aggressive events of various kinds within a "threshold" degranulation value, with defensive and reparatory purposes. Once activated by direct tissue injury [20], the mast cell located at the wound edges releases by means of degranulation the mediators essential to trigger the inflammatory reaction of the injured tissue, which mainly influence the local endothelial cells [23].

**B) The mast cell mediated vascular response**

The mast cells, which adhere to the outer wall of the vessels and are even distributed in the intimal layers, are part of a vascular control system which is responsible for constant monitoring of microcirculatory homeostasis [24]. In particular, through the release of vasoactive mediators like histamine, protease, Tumor Necrosis Factor (TNF) and metabolites of arachidonic acid, they induce vasodilatation and increase vascular permeability, with tissue oedema, reddening and swelling [25, 26].

**C) The mast cell' directed inflammatory response**

As the inflammatory process develops, a crucial event is represented by the recruitment in the injured area of circulating leucocytes which, together with the resident macrophage populations, perform specific defence functions (phagocytosis) and a kind of debridement. This leukocyte recruitment is a complex phenomenon, in which the mast cells play a direct part [27]. It has now been clearly demonstrated that these cells are involved, through the release of specific mediators, in a whole series of events ranging from initial contact between the leukocyte and the vessel wall (rolling) to marginalisation, transendothelial migration by diapedesis, and hyperafflux to the tissues by chemotactic signals. In fact, while molecules of mast cell origin like TNF and histamine favour the adhesion of the leukocytes to the vessel, increasing the expression of endothelial adhesion molecules (selectin, integrin) [28, 29] other mediators, also released by the mast cell (leucotrienes, proteases and cytokines, especially interleukin-8 (IL-8)), represent chemotactic signals for neutrophils, basophils and eosinophils [30].

The local innervation is influenced by the functional state of the mast cell, also involved in the electrophysiological alterations found in the injured area [31]. In particular, NGF, released by the mast cells by means of degranulation [32], causes a reduction in the nociceptive threshold, the key mechanism responsible for the hyperalgesia which generally affects the injured area [33-35].

The mast cell coordinates neovascularisation in the injured area, influencing the regrowth potential of the endothelial cells. Vasoactive amines (histamine), heparin, cytokines (TNF, IL-6 and IL-8) and growth factors, [Platelet Derived Growth Factor (PDGF); Vascular Endothelial Derived Growth Factor (VEDGF); Transforming Growth Factor-beta (TGF-beta); and Fibroblast Growth Factor (FGF)] represent the "angiogenic pool" which the activated mast cell rapidly releases by means of degranulation, and which modulates the various stages leading directly or indirectly to new vessel formation, aiding the formation of a temporary substrate of connective tissue to ensure correct migration of the endothelial cells [23, 37-39].

**D) MCs and the evolution from inflammation to scarring**

The mast cells play as well an essential role on connective matrix through a dense two-way interplay with the cells most involved in the process, namely the fibroblasts. The mast cells, which are anatomically adjacent and functionally able to release substances with specific fibroproliferative activity like histamine [40, 41], fibrogenic cytokines (Interleukin-1, IL-1; Interleukin-4, IL-4; and TNF) [42], tryptase [43] and growth factors (TGF and FGF) [44, 45], possess the biological weapons needed to stimulate chemotaxis, migration, phenotype differentiation and biosynthesis activity by the fibroblasts. Basically, there is a profound functional synergy between mast cells and fibroblasts, boosted by the recent discovery that a veritable membrane apparatus (gap junctions) exists between these two cell types, allowing direct physical interconnection and close intercommunication [23, 46].

**E) MCs and the evolution to re-epithelisation**

The mast cell mediators also influence the re-epithelialisation process which, by means of sophisticated processes of keratinocyte migration and proliferation from the wound edges, leads to the formation of new epithelium [47, 48]. In fact, while the activated keratinocyte is able to influence the skin mast cell, causing its degranulation [49], the mast cell directly influences the functionality of the keratinocyte, modulating its proliferation and locomotion processes by releasing growth factors [Epidermal Growth Factor (EGF); TGF and NGF] and specific cytokines (IL-1 and TNF) [38, 50, 51]. Basically, although the mast cell acts as "homeostatic orchestrator" of the tissue once the "degranulation threshold" has been exceeded it turns into a "damage effector". [52]

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### **Clinical meaning**

MCs show an extraordinary complexity and heterogeneity in their vesicles' content. Even more important, they show a great selectivity in the differential release of the vesicles, according to the stage of the inflammation, the site of the damage, the response of the other cells participating to the inflammatory process, the presence or not of adequate treatments reducing the agonist predisposing precipitating, and maintaining factors. Disregulation of the inflammatory process, and/or persistence of the inflammatory stimuli (agonist factors), in underdiagnosed and unaddressed conditions, may alter the healing process, maintaining the up-regulation of the MCs response. This worsens the neurogenic inflammation and the tissue damage, with two leading consequences. First, the progressive functional and anatomic damage, associated with a prominent tissue scarring, well exemplified in the natural history of Interstitial cystitis. Second, the up-regulation of the nerve pain system, with morphological and functional changes. In vulvar vestibulitis, this may contribute to the shift from the typically inflammatory condition of the early phases, which may last from a few months, to one or two years, when MCs are significantly increased in the vestibular tissue, to the late phases when only the increased proliferation of pain fibers can be histologically proved. At this stage, pain definitely shifts from the nociceptive nature typical of (chronic) inflammation, when the term of vulvar vestibulitis is appropriate, to the neuropathic, spontaneous or provoked pain in a tissue where no more overt signs of inflammations can be detected and the term vulvodynia is definitely the most adequate.

### **Conclusions**

Understanding pathophysiology of local inflammation is critical if physicians want to move from symptomatic, late interventions in inflammatory and painful conditions such as vulvar vestibulitis/vulvodynia, to etiologically based multimodal treatments. In this reading, MCs play a substantial role as sophisticated directors of the immune and inflammatory response, which can have a positive or negative outcome, according to genetic, local and contextual factors. Physicians can definitely change the natural history of many persisting inflammatory conditions leading to chronic and aggressive pain if they go back to a better understanding of MCs critical role and test two major groups of intervention. On one side, those which reduce the *agonist* stimuli, either predisposing, precipitating or maintaining factors, leading to MC up-regulation and damaging degranulation. On the other, testing and using drugs that may act as *antagonist* modulators of MCs, reducing the up-regulation and the hyper release of inflammatory and neurotrophic substances.

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