Genitourinary mast cells and survival

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Abstract: Mast cells (MCs) are ubiquitous in the body, but they have historically been associated with allergies, and most recently with regulation of immunity and inflammation. However, it remains a puzzle why so many MCs are located in the diencephalon, which regulates emotions and in the genitourinary tract, including the bladder, prostate, penis, vagina and uterus that hardly ever get allergic reactions. A number of papers have reported that MCs have estrogen, gonadotropin and corticotropin-releasing hormone (CRH) receptors. Moreover, animal experiments have shown that diencephalic MCs increase in number during courting in doves. We had reported that allergic stimulation of nasal MCs leads to hypothalamic-pituitary adrenal (HPA) activation. Interestingly, anecdotal information indicates that female patients with mastocytosis or mast cell activation syndrome may have increased libido. Preliminary evidence also suggests that MCs may have olfactory receptors. MCs may, therefore, have been retained phylogenetically not only to "smell danger", but to promote survival and procreation.

Keywords: Arousal; cervix; contractions; mast cells (MCs); prostate; uterus

Introduction

Mast cells (MCs) develop from hematopoietic precursors in response to stem cell factor (SCF) the ligand of the CD117 (KIT) tyrosine kinase receptor. Precursors then migrate from the blood into all tissues where they acquire their tissue-specific phenotype, influenced by the local microenvironment (1).

MCs are best known for causing allergic reactions when activated through exposure to an antigen (allergen) that crosslinks allergen-specific immunoglobulin E (IgE), already bound to the high affinity Fc epsilon receptor 1 (FcεRI) (2). MCs can also be activated by anaphylatoxins (C3a, C5a), hormones, physical stimuli (pressure and temperature changes), as well as cytokines and neuropeptides (3) such as corticotropin-releasing hormone (CRH), neurotensin (4), and substance P (SP) (5). MCs express receptors for diverse ligands (6), including toll-like receptors (7) that can be activated by bacterial and viral products (8). MC stimulation can be enhanced by SCF and IL-33 (9), which together with SP, induce vascular endothelial growth factor (VEGF) release (5) and act as "sensors of cell injury" (10). Each MC contains about 500,000 secretory granules filled with numerous biologically active molecules (11).

MC stimulation leads to secretion of numerous vasoactive, muscle contracting, neurosenzitizing and proinflammatory mediators (3,12). In particular, histamine causes muscle concentration, exocrine gland secretion and vasodilation; it also activates the hypothalamic-pituitary adrenal (HPA) axis (13), as does MC-derived IL-6 (14) and CRH (15). In fact, MCs have been implicated in the regulation of HPA axis both in the brain (16), and its equivalent in the skin (17,18).

MCs can secrete the content of individual granules (19)

or individual mediators, such as serotonin, selectively without degranulation (20). MCs can also communicate with neurons by transgranulation (21) or undergo "polarized" exocytosis of proteolytic enzymes at surface sites called "antibody-dependent degranulation synapse" (22). MCs can also secrete nanovesicles (exosomes) (23) containing many different biologically active molecules (24), in a manner that may be guided by antigens embedded in their phsopholipid envelope (25). Such exosomes could participate in immune (26,27) and neuropsychiatric diseases (28,29).

The ability of MCs to secrete some mediators selectively (30), permits MCs to participate in diverse processes without causing allergic or inflammatory reactions (12). For instance, we showed that IL-1 can stimulate selective release of IL-6 (31) and so did SCF (32). We also showed that CRH stimulated selective release of VEGF (33) and so did prostaglandin D_2 (PGD$_2$) (34), all without any degranulation. Taken together, available data suggest that MCs are capable of releasing a panoply of molecules that may participate in many pathophysiological processes such as innate immunity (1,35), autoimmunity (36), and neuroinflammation (37), but may also have immunomodulatory (38) functions.

Effect of stress

Emotional stress is the most common trigger of symptoms in patients with systemic mastocytosis, characterized by increased number and degree of activation of MCs (39). In one case, symptoms worsened with stress and there was elevated serum CRH levels, with bone marrow MCs express CRHR-1 (40). MCs (15) and other immune cells (41) can produce CRH (42). Amazingly, even corticosterone has been localized inside MC secretory granules (43).

It is not well understood how animals "smell danger" or are attracted to their mates through odors since the olfactory nerve does not connect directly to the hypothalamus. We and others reported that stimulation of nasal MCs leads to activation of the HPA (44-46) driving the organism into a fight-or-flight mode. Recently olfactory and taste receptors were identified in subpopulations of human circulating leukocytes (47). MCs may turn out to also express such receptors since brain MCs were reported to be influenced by chemosensory cues associated with estrus induction (48).

Surprisingly, MC numbers and reactivity have been reported to undergo daily rhythmic variations (49) and the reactivity of individual MCs was further shown to follow a "circadian clock" (50,51). In this context, it is of interest

that mast cell behavior is affected by the pineal through the expression of melatonin receptors and MCs release melatonin, themselves (52).

Excessive stress can lead to pathological outcomes in various tissues (53). Stress has been reported to induce inflammatory change in rat bladders (54), as well as selective release of VEGF (55), effects that are absent in MC deficient mice (56). Acute stress (57,58) and locally secreted CRH (59) activated MCs (53,59) leading to neurogenic inflammation with subsequent chronic nerve sensitization (60).

MCs (15), immune cells (41), human endometrium, intrauterine pregnancy tissues (61,62), and local nerve endings (42) can produce CRH (42). We reported high levels of CRH and tryptase in products of conception from women with habitual spontaneous abortions (63). Maternal stress has been also linked to preterm delivery (64) and high levels of CRH expression has been reported for placenta, decidua and fetal membranes, where it induces prostaglandin production and promotes labor (65). The decidua of women with high levels of stress have also been reported to have high number of tryptase-positive MC (66), as also reported in aborted deciduas (67). Endometriosis tissue has also been associated with high number of activated MCs (68), which were shown to be increased in response to stress which exacerbated endometriosis in a rat model (69).

Genitourinary MCs

MCs are present in animal and human bladder (70,71), prostate (72-75), uterus (76-79), penis (80,81), vagina (76,82) and placenta (83). However, their role in these tissues is unknown especially since they are not known to undergo allergic reactions. Uterine MCs are increased during pregnancy and may be important for reproductive processes (84,85). MCs can release muscle contracting and vasodilatory substances that could contribute to clitoral enlargement and uterine contractions (78,86,87). IgE-independent MC activation has been reported to augment contractility of guinea pig (88), mouse (89) and human (86) myometrium. Activation of MCs also leads to angiogenesis in the rat uterine cervix during pregnancy (90). MC degranulation also modulates cervical contractility as shown in the guinea pig (91).

Current evidence from clinical and laboratory studies confirms that MC play a central role in the pathophysiology of bladder pain syndrome/interstitial cystitis (BPS/IC) (92,93) and possibly prostate hyperplasia (74) and sterile prostate inflammation (73). Damaged or dysfunctional

urothelial cells produce cytokines, such as SCF, that can stimulate proliferation and/or activation of MCs (71). In fact, MCs are increased in the detrusor of BPS/IC (71,94-97), and are maximally activated by SCF (98,99) and nerve growth factor (NGF), which is increased in patients with BPS/IC (100). We have shown that CRH activates rat bladder MCs (101) and CRH is involved in signaling in feline bladder urothelial cells (102). In fact, CRH has been considered a mediator of emotional influences on bladder function (103).

Effect of sex hormones

Human MCs express estrogen receptors (104) activation of which increase MC stimulation (105,106). Estradiol also induced MC migration into the uterus and their degranulation (107). Treatment of mice with leutinizing hormone (LH), follicle stimulating hormone (FSH) or estradiol increased the number and extent of MC degranulation in the ovaries (108). Estrogen receptors are also expressed on bladder (109-111), and lung (112,113) MCs. Human MCs also express progesterone (114,115) and testosterone (116) receptors, but their activation appears to have an inhibitory effect.

One laboratory has reported gonadotropin-releasing hormone-like immunoreactive MCs in the habenula of doves (equivalent to the hypothalamic infundibulum in humans) (117), which increased during courting (118). MCs in ovarian, uterine and brain tissues change their histamine content throughout the rat estrus cycle; moreover, MCs are absent from the thalamus during pro-estrus but are present in the hypothalamus only during the estrus phase (119).

MC-derived mediators, especially histamine, are considered to be important in sexual arousal and coitus (120). Anecdotal information suggests that patients with mastocytosis or MC activation (3) may have increased libido. Uterine MCs were shown to have oxytocin receptors, activation of which prevented serotonin uptake and increased serotonin availability (121) that may positively affect sexual behavior. Circulating levels of oxytocin are known to increase during sexual arousal and orgasm in both men and women (122). It is interesting that intranasal oxytocin was reported to increase libido and related sexual behavior in a male subject (123).

Conclusions

MCs have been retained throughout the phylogenetic tree (124). Moreover, MC ability to produce numerous hormonal, immune and neural substances resemble that of the unicellular organism Tetrahymena dating from some 500 million years ago (125,126). MCs are present in all mammals and may be necessary for survival of the species by regulating immunity (127), protecting the organism against external triggers (53), supporting pregnancy (128), augmenting delivery and also ensuring optimal conditions for procreation.

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