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THE IMPACT OF MAST CELLS IN NEUROIMMUNOLOGY AND CANCER

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ABSTRACT

The nervous system and immune system are connected by bidirectional pathways, and behavioral influences can have effects on immune functions. Immune system stress can have regulatory effects in neuroinflammation, allergic reactions, cancer growth, and other conditions. Additionally, pyschological stress can aggravate different conditions such as atopic dermatitis, rhinitis, and asthma. Mast cells (MCs) are immune cells derived from the myeloid lineage which migrate to peripheral tissues to differentiate and mature. They play an important role in the innate and adaptive immune responses, where the physiological and pathological aspects are regulated by the activation and degranulation of MCs. This includes immune responses such as those involved in infection, allergic disease, stress, and tumor growth. MCs cells are ubiquitous in the body, and have a close anatomical and functional relationship with neurons and neuronal processes in the central and peripheral nervous systems. MCs are rich sources of biologically active preformed mediators, which are contained in secretory granules. These cells can differentially and selectively release their mediators, and utilizing this selective release process in treatment could offer therapeutic opportunities for cancer, hypersensitivity reactions, and neuroinflammation.

KEYWORDS: *mast cells*, *neuroimmunology*, *neuroinflammation*, *immune*, *cancer*

INTRODUCTION

There is evidence indicating that the nervous system, which communicates with the whole organism, can regulate cancer growth directly or through the immune system. Published studies have indicated that stress may have a permissive effect on cancer growth (1-4), neuroinflammation, and other conditions, and it has now been established that stress can produce definitive changes in the make-up and function of the immune system (5, 6). Moreover, there is much discussion concerning psychoneuroimmunoendocrinology that studies the interplay between the psyche, neural, and endocrine functions and immune responses, and the applications of these effects on the immune response and cell proliferation (7-10).

Allergic reactions have been shown to have neuropsychologic elements that comprise a close association between the immune system and the nervous system (11). These cases involve a disease pathophysiology that cannot be accounted for solely by elevated levels of immunoglobulin E (IgE) and antigen (Ag). Different studies have shown the psychoneuroimmunoendocrinologic association in allergic reactions such as atopic dermatitis (AD), rhinitis, and asthma, which can be induced or aggravated by compounds of the nervous and endocrine systems and are linked to psychological stress (12-16).

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Mast cells (MCs) are immune and inflammatory cells that play an important role in the innate and adaptive immune systems. Additionally, they are the main effector cells implicated in allergic or anaphylactic reactions. Paul Ehrlich first identified these cells in 1878 using a staining process to show the multitude of granules they contained (17). MCs are derived from immature pluripotent hematopoietic progenitors in the bone marrow, and then migrate through the vasculature system to reach peripheral tissues where they differentiate and mature in a tissue-specific manner (18-21). The activation and degranulation of MCs regulates many physiological and pathological aspects, including the initiation and the continuation of inflammatory responses, including those in the central nervous system (CNS).

These cells are ubiquitous in the body and their membrane-bound secretory granules contain biologically active preformed mediators (22). During allergic immune reactions, MCs are triggered by IgE and Ag, as well as diverse neuropeptides. MCs are localized in association with the CNS and the peripheral nervous system, where they are directly innervated and have a close anatomical and functional relationship with neurons and neuronal processes (23). For this, it is suggested that MCs also have a close association with neurotransmitters and neuropeptides where there is likely bidirectional regulation.

MCs are located around the vasculature and are present in brain tissue, particularly in the hippocampus, thalamus, and hypothalamus (24). MC mediators may influence the physiopathology of the body, including the response to stress by regulating the levels of peptide hormones available in the hypothalamic-pituitary axis and the production of proinflammatory and antinflammatory molecules.

MCs are involved in the induction and development of immune responses in response to infection, allergic disease, and, although the mechanisms are still unclear, stress and tumor growth. The tumor microenvironment is made up of fibroblasts, adipose cells, immune-inflammatory cells, the extracellular matrix, and blood and vascular networks (25). It has been shown independently both *in vitro* and *in vivo* that MCs undergo differential or selective release of their mediators, a process that occurs without degranulation that might operate using vesicular shuttles utilizing specific mediator binding proteins (26-28). Inducing the selective release of MC mediators or selectively inhibiting MC degranulation after appropriate stimulation could result in either enhancement or suppression of tumor growth. Such a process could enhance science's understanding of the pathophysiology of cancer, type I and VI hypersensitivity reactions, and neuroinflammation, and could provide new therapeutic opportunities.

Mast cells and neuroinflammation

Neuroinflammation is a hallmark of neurodegenerative diseases, with MCs playing an important role in this process. The immune system initiates the protective response of inflammation to repair and heal damage inflicted by injury, bacteria, or other harmful insults. Neuroinflammation is the inflammatory response that occurs in the CNS which can be detrimental if it is prolonged. Chronic neuroinflammation can inhibit regeneration and lead to brain injury (29), and it is a characteristic feature of diseases such as Alzheimer's disease (AD) (30, 31), Parkinson's disease (PD) (32), and amyotrophic lateral sclerosis (ALS) (33). Interactions between glial cells, immune cells, and neurons can produce and sustain neuroinflammation. Microglia and astrocytes mediate innate immune responses in the brain that can be activated by proinflammatory stimuli that are released from immune cells such as MCs. MCs produce various inflammatory mediators including histamine, proteases, growth factors, chemokines, and cytokines. MCs are normally found in low numbers in the brain (34), but increased numbers of these cells have been observed during trauma, stress, infection, and in some CNS diseases such as stroke (35) and multiple sclerosis (36, 37). MCs participate in neuroinflammation by interacting with glial cells and neurons, and effecting blood-brain barrier (BBB) permeability and neurodegenerative processes such as neuronal death, excitotoxicity, and synaptic dysfunction (38).

Microglia and MCs can interact by complex unidirectional or bidirectional cross-communication. For example, tryptase released from MCs activates microglia (through PAR2 receptors) to release reactive oxygen species (ROS), tumor necrosis factor (TNF), and IL-6 (36, 39). However, due to their prestored granule supply of mediatory substances such as immunomodulators, neuromodulators, proteases, growth factors, and amines, MCs can act quickly to injury and insult and are increasingly being considered as first-responders in the immune response in the CNS (40). MC degranulation releases gonadotropin hormone-releasing hormone (GnRH), monoamines, proteases including chymases, tryptases, carboxypeptidase, cytokines, and histamine (41, 42), which exert effects on nearby cells (e.g. T cells) that enter the brain through the compromised BBB in states of infection and inflammation. Additionally, these MC-released compounds activate microglia, which go on to release pro-inflammatory cytokines that exacerbate the inflammatory state. Due to their close proximity, microglia and MCs interact and affect each other through paracrine mechanisms (38).

Finally, MCs may be involved in stress-related neuroinflammation and neurodegeneration. Chronic stress has been linked to neuroinflammation, which it seems to exacerbate, and increases the risk of neurodegenerative diseases such as AD (43, 44). During stress and inflammation, molecules such as corticotropin-releasing hormone (CRH) are released by

MCs, which activate microglia cells and pro-inflammatory processes, suggesting that MCs are involved in stress-related neuroinflammation and neurodegeneration (45).

Mast cells in hypersensitivity reactions

MCs derive from the bone marrow and then migrate into peripheral tissues to mature. The maturation of MCs is dependent on microenvironmental conditions such as the presence of IL-3, IL-6, stem cell factor (SCF), and other growth factors released from activated T-cells (46, 47). Activated mucosal MCs and those from bone marrow can secrete inflammatory proteins without degranulation. MCs which mature in the presence of IL-3 also express IL-2 receptors (48), and IL-2 additionally promotes the generation of lymphocyte-activated killer (LAK) cells, as well as CD8+ T cells and natural killer (NK) cell cytolytic activity (49).

Cytotoxic T cells that express CD8+ are the strongest effectors in the immune response against cancer (50), and the interaction between MCs and Tregs can influence the intensity of tumor-induced inflammation, resulting in the inhibition or promotion of the growth of tumors (51). Therefore, the MC-Treg relationship may offer useful therapeutic options for tumor immunotherapy.

Lymphocyte products, such as IL-1, can trigger or increase MC secretion (52, 53), and the early release of MCs could be related to the delayed response of T-cells (54), a process that may be linked to allergic reactions which include a late phase component (55).

Studying the relationship between MCs and T-cells, and their possible regulation by neuroendocrine or tumor-generated substances, could provide the basis for new therapies.

The role of mast cells in tumor growth

As early as 1877, MCs were seen at tumor sites (56) and as time progressed, were subsequently suspected to be involved in the growth of tumors (57). It is now clear that these immune cells proliferate around tumors and in the tumor microenvironment during disease progression. The accumulation of MCs has been seen in a variety of tumors including epidermoid carcinoma (58), adenomatous polyps (59), rat mammary adenocarcinoma (60), pancreatic β-cell tumour (61), cervical carcinoma (62), and melanoma (63).

Tumor-secreted factors recruit and activate MCs, with the primary one being SCF (64). However, fibroblast growth factor (FGF)-2, vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), RANTES, monocyte chemotactic protein (MCP)-1, adenosine, and adrenomedullin have also been seen to recruit and/or activate MCs to the tumor site (65-67).

MC accumulation is also correlated with vascularization, with increased numbers of MCs seen in highly vascularized areas of certain tumors (62,68,69). An association has also been reported between MC migration and new vessel formation in breast, colorectal, and uterine tumors (68,70,71). The perivascular location of MCs, and the fact that they can release vasoactive agents, links these immune cells to the support and maintenance of the vasculature and angiogenesis (72,73). Interestingly, MCs accumulate at tumor sites before new capillaries are formed (73). In fact, MCs contain and secrete mucopolysaccharide heparin, which causes capillary endothelial cell migration *in vitro* (74).

Numerous normal tissues produce a small amount of VEGF, but this process is tightly regulated, and the endothelial growth factors are minimally expressed in normal conditions (75), contrasting the high rate of expression that occurs in tumors where angiogenic factors appear to be continuously expressed (76). Tumor-derived peptides attract MCs to the tumor site where they can secrete heparin within the collagenous stroma (77). A track, or path, is formed behind the migrating MCs as they partially release this heparin, which could direct the movement of sprouting capillaries towards the direction of the tumor (74). Growth factors such as nerve growth factor (NGF) (78), as well as IL-1 produced by macrophages, which are abundant in proliferating tissues, induce MC degranulation.

Histamine from MCs can stimulate local cell proliferation, which has been seen by the rapid growth of cells neighboring to activated degranulated MCs (79). MC-derived histamine also activates T-suppressor cells, which can inhibit the immune system (80,81).

The antitumorigenic functions of mast cells

While MCs have effects that favor tumor growth and are associated with unfavorable prognosis, they also show inhibitive effects as well. In fact, MC infiltration at tumor sites has sometimes been associated with favorable prognosis. Studies have shown that the presence of MCs in some colon cancers such as colorectal cancer has positive effects and increases survival (82-84). Additionally, MC infiltration has also been correlated with improved prognosis in prostate carcinoma (85) and breast carcinoma (86). Whether MCs have pro- or anti-tumorigenic effects against cancer could depend on the nature of local MC subsets and the particular stimuli within the tumor microenvironment (87).

MCs can have cytotoxic activity and recruit and activate immune cells at the tumor microenvironment. They can directly interact with tumor cells, release different mediators that modulate the immune response at the tumor microenvironment, and by producing cytokines and chemokines, recruit other immune cells to the tumor site (87). MCs have been seen to have a selective action against tumor cells, showing cytotoxic activity to tumor cells in a preferential manner that does not harm other cells, such as fibroblasts (88).

Serine proteases from basophils have cytotoxic actions against tumor cells, and MCs are a rich source of these proteases which are stored in large amounts in the cytoplasmic granules of MCs and are also released in the process of degranulation (89).

Further evidence with MC-deficient W/Wv mice has shown that tumor growth incidence is lower after subcutaneous treatment with 3-methylcholanthrene, when compared with normal congenital mice following the same treatment (88,90). When the carcinogen was given after the MC deficiency had been overcome by bone marrow transplantation, this increased tumor incidence was seen at normal levels (88,90).

Vasoactive amines that are released by MCs could also contribute to the modulation of the tumor microenvironment. Studies have shown that late hypersensitivity reactions involving killer T-cells are dependent on the early MC secretion of certain vasoactive mediators (54), a process which could be vital for the immune system to launch an effective defense against cancer cells. T-cells that are recruited by MCs may then proceed to secrete cytokines, which further stimulate the secretion of MCs (91). Considering this, tumor cells may play a selective role in inhibiting or promoting the secretion of specific MC mediators. It has been reported that MCs located very close to growing tumor cells had been inhibited and were unresponsive to the regular secretagogues (92), and that certain polyamines found in growing tumor cells impede MC degranulation (93-95).

CONCLUSIONS

MCs are well known for their involvement in allergic reactions, but they are increasingly being implicated in other physiological and pathological conditions. In the brain, MCs partake in complex interactions with microglia and participate in neuroinflammation, effecting the permeability of the BBB and neurodegenerative processes such as neuronal death, excitotoxicity, and synaptic dysfunction. It is known that the nervous system, with the production of neuropeptides, can influence both tumor onset and growth. MCs, the immune elements that mediate both inflammation and the body's defense, play an important role in this stage. Neuropeptide-activated MCs can release proinflammatory molecules such as cytokines that aggravate the tumor state, while they can also produce molecules that oppose tumor growth. Further definition of the role of MCs is needed to uncover their actions in neuroimmunology and tumor growth, and to identify MC-targeted treatments.

Conflict of interest

The author declares that they have no conflict of interest.

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