Role of TNF Alpha, IL-33 and CCL2/MCP-1 in Mast Cell Activity

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Abstract: Mast cells are the derivatives of hematopoietic progenitor cells and play an important role in immediate Type I hypersensitivity and late phase reactions but also in innate immunity (3), allergy and inflammation (4) by secreting a large variety of chemical mediators either from storage sites in their granules, or producing immuno-regulatory proteins upon stimulation (5-14). They directly interact with bacteria and appear to play a vital role in host defense against pathogens. The addition of certain cytokines to human umbilical cord blood-derived cultured mast cells shown to augment IgE-induced production of distinct cytokines, without histamine secretion. Mast cells could be recruited in the inflammatory site, by MCP-1, RANTES and SCF, and selectively secrete proinflammatory molecules; these could include growth factors, histamine, which is mitogenic (H1) and an immunosuppressant (H2), neovascularization agents, such as heparin, IL-8, and VEGF as well as proteases that could permit new blood vessel formation.

IL-33 belongs to the IL-1 family and binds to the ST2 receptor which has high homology to IL-1 receptor and has biological activities. IL-33, causes allergic inflammation and exerts significant biological effects both in vivo and in vitro. IL-33 induces expression of several cytokine and chemokine, resulting in severe inflammatory and allergic diseases. Using human umbilical cord blood mast cells (HUCBMCs), as a valid model, we found that IL-33 induces CCL2/MCP-1 release in HUCBMCs. This study documents the ability of IL-33 to directly stimulate HUCBMCs to produce CCL2/MCP-1. We reported that IL-33 is a strong activator of human mast cell capable to induce CCL2/MCP-1 released at translational level. The data described an additional biological activity of IL-33, suggesting that this cytokine may have an important effect on the recruitment of inflammatory cells in allergic diseases. IL-33 may be also critically involved in regulation of cyclooxygenase production in vitro and probably in vivo, providing a potential therapeutic target for inflammatory diseases. CCL2 monocytes chemotactic protein 1 (MCP-1) is a potent chemotactic molecule that attracts lymphocytes, monocytes, mast cells, and memory T cells, but not neutrophils. In this review we highlighted, for the first time, the importance of TNF alpha, IL-33, and MCP-1 in mast cell activity.

Keywords: Mast cell, Chemokine, Cytokine, Inflammation, Immunity.

Mast cells (MCs) derive from a bone marrow progenitor play an essential role in diverse physiological and pathological processes, such as atherosclerosis, malignancy, asthma, pulmonary fibrosis and arthritis [1]. Mast cells reside in connective tissues and are wildly recognized as effector cells important in innate and acquired immunity. They are important for allergic reactions, but also in inflammation, autoimmunity, and T-cell mediated immune responses [2-3]. Therefore, mast cells play a role in various physiological functions: innate and acquired immunity, epithelium remodeling and proliferation, angiogenesis, cancer, inflammation and infections [4]. They are activated by cross-linking of FcεRI molecules, which are involved in the binding of multivalent antigens to the attached IgE molecules, resulting in a variety of responses including the immediate release of potent inflammatory mediators [5]. Mast cells play a key role in the induction of inflammatory disorders and when they are activated by diverse stimuli, release mediators including histamine, proteases, several cytokines (which are found in relatively high quantities in these cells) [6] and mobilize arachidonic acid through cytosolic phospholipase A2, and rapidly generate prostaglandin D2 [7]. Prostaglandin D2 (PGD2) is a major cyclooxygenase metabolite of arachidonic acid produced by mast cells and it is released following allergen challenge in diseases, such as allergic diseases. Mast cells are known to be primary responders in allergic reactions, orchestrating strong responses to minute amounts of allergens. In IgE-associated biological responses, the cross-linking of FcεRI-bound IgE with multivalent antigens initiates the activation of mast cells by promoting aggregation of FcεRI. This cross-linking receptor-bound IgE by multivalent Ag initiates a cascade of intracellular reactions leading to mediator release such as proinflammatory mediators, chemokines and cytokines [8, 9]. It is likely that mature mast cells vary considerably in the cytokine/chemokine content and the phenotypic expression of mast cells does not appear to be fixed. Therefore, mast cells secrete a number inflammatory mediators. A number of these are known to be involved in neuroinflammation, such as prostanooids, tryptase, cytokines (IL-6 and/or IL-8) VEGF and SP [10]. Mast cells can also uniquely release several cytokines/chemokines selectively without degranulation [11]. The synthesis and expression of a plethora of cytokines and chemokines (such as GM-CSF, IL-1, IL-3, IL-5, TNF-alpha, and the chemokines IL-8, RANTES, MCP-1, and eotaxin) by mast cells can play an important role in allergic and inflammatory diseases [12, 13].
It has been found that mast cells are recruited in the inflammatory site, by MCP-1, RANTES (Conti et al., Blood) and SCF, and selectively secrete proinflammatory molecules [14].

Chemokines are cytokines with chemotactic properties on inflammatory cells and other cell and play an important role in the pathogenesis of allergic diseases and inflammation. Chemokines are inflammatory proteins acting via G-protein coupled chemokine receptors that trigger different signalling pathways [15]. An understanding of mechanisms which regulate production and function of cytokines is relevant and may result in the development of more effective methods of treatment of allergic and inflammatory diseases. In addition, it is interesting that mice lacking mast cells (W/Wv mice) exhibit 100% mortality [16].

**TNF ALPHA**

Mast cells are source of several cytokines including TNFα which is the only one stored as preformed cytokine in cytoplasmatic granules and allows for its quickly release upon stimulation [17]. Human mast cell-derived TNFα is involved in many physio-pathological events including host defense, angiogenesis, autoimmunity, chronic and acute inflammation. Mast cells are markedly increased at sites of inflammation and are fascinating, multifunctional, tissue cells that contain the preformed cytokine TNFα, which initiates the inflammatory cascade promoting the expression of interleukin-1 and interleukin-6 and other cytokines and chemokines [18].

Tumor Necrois Factor (TNF) is a 26 kDa membrane-bound protein and the prototype member of the TNF family of ligands, including lymphotoxins α and β, Fas ligand, CD40 ligand, and OX40 ligand. Mast cells are the only one capable to store pre-formed TNFα in their cytoplasmatic granules and release upon activation. It has been reported that vesicular-associated membrane protein-8 (VAMP-8) segregates secretory lysosomal granule exocytosis in mast cells from cytokine/chemokine molecular trafficking pathways. In fact, VAMP-8 is a fusion protein that segregates preformed mediator release from cytokine/chemokine molecular trafficking pathways in mast cells [19]. Therefore, glycosilation is not necessary for the release of TNFα by mast cells. In this respect, resting cells express low levels of TNF-converting enzyme.

TNFα is an important and powerful inflammatory cytokine, mainly produced by macrophages and involved in many patho-physiological conditions and autoimmune diseases mediated by different cells such as lymphocytes, mast cells (MCs), tissue cells, epithelial cells, fibroblasts and other cells [20]. However, the mechanism of action and generation of TNF remains poorly understood. To clarify how production and release of TNF are regulated, we focused on mast cells which are involved in allergic inflammation, cancer, and brain damage. TNF-alpha is a potent multifunctional cytokine that plays a central role in the pathogenesis of many inflammatory diseases such as inflammation, allergy, autoimmunity and cancer. This cytokine is found to be chemoattractant for neutrophils and monocytes. It has been reported that blocking TNF is effective in some autoimmune diseases; however, there has been concern over the possibility of increased susceptibility to infections after anti-TNF therapy, particularly tuberculosis [21].

It is reported by several authors that TNF releasing steps are regulated via the PKC alpha-dependent pathway [22]. ERK and JNK are also involved in ATP-induced TNF transcription, while p38 regulates the transport of TNF mRNA from the nucleus to the cytosol. A better understanding of the specific pathways that regulate TNF release for each effector cell may offer further possible therapeutic targets for inflammatory diseases [22]. As far as we know, TNFα is the only cytokine preformed immune-reactive observed within human mast cell granules, which can be prompt release after mast cell antigen activation.

Stressors provoke the activation of mast cells and neurons of the paraventricular nucleus (PVN) of the hypothalamus, resulting in the release of corticotropin releasing hormone (CRH) from the median eminence, which then stimulates ACTH secretion from the anterior pituitary, and hence adrenal glucocorticoids secretion [23-25]. Viral and bacterial are stimulators of TNFα and are products that increase circulating levels of stress-reactive hormones, including ACTH and corticosterone, and increase the activity of hypothalamic and extrahypothalamic monoamine activity [26]. It is thought that in addition to functioning as signaling molecules of the immune system, cytokines may also act to signal the CNS about the presence of an immunological challenge.

The production of TNFα by mast cells, occurred by antigen and immunoglobulin E (IgE) stimulation, via the
high-affinity receptor (FccRI) for IgE, can be enhanced by stem cell factor (SCF) (which is also required for IL-4 production) and probably other cytokines. This cooperation may be important in acute and chronic inflammation diseases. Two TNF receptors (TNFR) are describe: TNFR1 (p55) is expressed on a wide range of cell types, contains the cytoplasmic death domain found in several TNFR family members; and TNFR2 (p75) is expressed on a more limited range of cells, including leukocytes and epithelial cells [27]. Recently an anti-IgE monoclonal antibody and TNF-alpha antagonists have been approved for severe acute and chronic inflammatory diseases. These compounds inhibit TNFα and have demonstrated their ability to suppress inflammatory autoimmune diseases and chronic inflammation.

It has been reported that TNFα up-regulates adhesion molecules and is acts directly on migration of inflammatory cell playing an important role in inflammation and allergic diseases where mast cells are deeply involved. In fact, TNFα is a chemoattractant for neutrophils by inducing IL-8, a C-X-C chemokine, for monocytes by inducing C-C chemokines, and mast cells [28]. Deprivation of mast cell-derived pool of TNF leads to a great reduced influx of neutrophils. MCs undergo rolling on skin vessels in vivo and exhibit strong adhesion to skin endothelial cells in vitro under static and flow conditions [29]. This cell-to-cell contact requires the endothelial adhesion molecules E- and P-selectin, vascular cell adhesion molecule-1 (VCAM-1), and platelet endothelial cell adhesion molecule-1 (PECAM-1) and is followed by directed and dose-dependent trans-endothelial migration in response to TNF [29].

Syk an intracellular protein tyrosine kinase is a relevant mediator of immune-receptor signaling in a host of inflammatory cells including mast cells, and other immune cells. The inhibition of Syk during allergic inflammation blocks the release of histamine, arachidonic acid products and cytokine production, such as TNFα. This effect candidate Syk as a good approach for the therapy of autoimmunity and chronic inflammatory diseases.

Anti-TNF drug (Adalimumab) (a recombinant human IgG1 anti-TNF monoclonal antibody) therapy suggests that these treatments reduced the expression of VEGF (vascular endothelial growth factor), an angiogenic factor, increased in synovial membrane from patients within the rheumatoid arthritis [30].

Several authors suggest that mast cells play a role in host defense against pathogens by elaboration of tumor necrosis factor alpha. Various cellular anti-self responses are mediated by chronic over-expression of tumor necrosis factor, along with some other cytokines as key factors in autoimmune processes.

Mast cells also express the Toll-like receptor and may play a protective role in host defense against bacteria through production of TNF-alpha, mainly as a result of Toll-like receptor 4 (TLR4)- or CD48-mediated activation [31]. TNF secreted by mast cells after antigen activation has a crucial role in the accumulation of lymphocytes in, and subsequent hyperplasia of, draining lymph nodes during an immune response. Although TNFα released by mast cells appear to be important in developing a protective response to infection. During infection, resident MCs contribute to the primary protective adaptive response through recruitment of dendritic cells from the circulation into infected sites.

c-Kit is the most important growth factor receptor of human mast cells. Inhibition of, c-Kit, by the selective tyrosine kinase inhibitor, induces apoptosis of mast cells and may have an anti-inflammatory activity in the treatment of patients with autoimmune diseases.

Recently it has been shown in several reports the link between MCs, TNFα and immune regulation. Injection of LPS into animal tissue causes hypertrophy and inflammation due to influx of inflammatory cells, including mast cells. These studies indicate that mast cell-derived TNFα has an important and early role in the pathogenesis of inflammatory diseases and in immune response [32].

**IL-33**

Schmitz et al. recently identified a new cytokine, IL-33 (IL-33/IL-1F11/NF-HEV), which induces Th2 responses and plays a role in adaptive immunity contributing to allergy by the release of cytokines [33, 34]. Th2 cells are critical effector cells and are required for the development of allergic inflammation. IL-33 is a novel endogenous “alarming” cytokine produced in response to inflammation and tissue damage [35]. This cytokine is one of the newest inflammatory interleukin identified as a novel member of IL-1 family and synthesized as a 31 kDa peptide precursor cleaved by caspase-1 to generate mature cytokine IL-33. IL-33 is found to be a potent inducer of T helper 2 (Th2) responses and Th2-associated cytokines IL-4, IL-5, and IL-13, but not Th1, in contrast to other closely
related family members [36, 37]. IL-33 induces biological effects on mast cells and T cells through its receptor IL-33 and may have pro-inflammatory potential effects similar to the cytokines from the same family. IL-33 is found to be highly expressed in high endothelial venules from tonsils, lymph nodes, and Peyer’s patches, in vessels from inflamed human tonsils, in the intestine of patients with Crohn’s disease, and in the synovium of patients with rheumatoid arthritis. IL-33 is known to enhance experimental allergic inflammation by directly stimulation mast cells to produce inflammatory cytokines [38, 39].

The addition of certain cytokines to human umbilical cord blood-derived cultured mast cells shown to augment IgE-induced production of distinct cytokines, without histamine secretion.

IL-33 is more similar to IL-1α than to IL-1β and is expressed in keratinocytes, mucosal cells and endothelial cells of human psoriatic plaques [40, 41]. IL-33 increases the levels of IgE, characteristic of an allergic response and also increases serum immunoglobulin (Ig) levels that are typical of Th2-driven hyperresponsiveness. IL-33 is capable to regulate several cytokines including IL-8, TNF-alpha, VEGF and possibly other cytokines (IL-37) (unpublished data), suggesting a possible role of this newly cytokine in the inflammatory response and recruitment of inflammatory cells. This effect, may involve this new protein in several autoimmune diseases where cytokines/chemokines play an important and active role.

IL-33 affects several arrays of basophil functions: this cytokine up-regulates CD11b expression on the cell surface of basophils, enhanced eotaxin-directed chemotaxis, induces Th2 cytokine IL-4 secretion, and augments the IgE-mediated histamine release reaction.

Mast cells can have important effector functions in both innate and adaptive immune responses [42].

It has been reported that MCs stimulated with IL-33 or IL-1/TNF or by FcεR1 cross-linkage release several cytokines and chemokines (IL-5, IL-6, IL-10, TNF, GM-CSF, CXCL8, and CCL1) [43]. IL-4, IL-10 and TGF beta have potential anti-inflammatory and immunosuppressive properties, helpful for immunotherapy on autoimmune diseases. However, nothing is know about the production of MCP-1 released by mast cells and in particular by HUCMC after IL-33 stimulation.

Importantly, MCP-1 is potently enhanced by IL-33 in HUCMC cultures. Our data confirm the observation, that MCP-1 protein is not seen in non inflamed tissue. In vivo local administration of IL-33 was reported to attract inflammatory cells to inflammatory sites. Therefore, we investigated whether IL-33 stimulates the release of MCP-1 in MCs. IL-33 was added to the in vitro HUCMC cultures. When added to the cell cultures, IL-33 at 50 ng/ml enhanced MCP-1 release from HUCBMC suggesting that IL-33 affects MCs chemokine release. Freshly isolated HUCBMC did not de-granulate in response to IL-33 (data not shown). We next assessed whether IL-33 affects the viability of IL-3-cultured HUCBMC, but it did not show any effect (data not shown). In this study, we investigated the production of MCP-1 in a HUCBMC model. This study provides the first evidence that IL-33 alone play a significant role in MC-released MCP-1 by directly acting upon mature human MCs [6].

IL-33 has been previously demonstrated to induce the activation of Th2 cells and mast cells, via effects mediated by the IL-33 receptor. Recently, likura et al. [44] demonstrated that IL-33 enhanced the survival of human umbilical cord blood-derived mast cells and promoted their adhesion as well as their production of the chemokine IL-8 and the cytokine IL-13.

The novel discovered cytokine IL-33 is the natural ligand of ST2L, a long known orphan member of the IL-1 receptor superfamily; this receptor along with the induction of activation NF-kB and MAPKs is functional in IL-33-stimulation of mast cell production of some cytokines. Several evidences support the hypothesis that the IL-1 family member IL-33 and its receptor may contribute to pathology in allergic disorders at least in part via effects on mast cells. It has been reported that IL-1beta, IL-18 or IL-33 induced phosphorylation of Erk, p38 and JNK in naïve human MCs, and IL-33 or IL-1beta, but not IL-18, enhanced the survival of naive MCs [45].

Axel J. Hueber et al. show that IL-33 can induce inflammatory skin lesions an inflammatory effect mediated by mast cell activation and neutrophil recruitment [40]. In addition, IL-33 can reduce the development of atherosclerosis and it may promote the development of asthma and arthritis.

However, the effects of members of the IL-1 family of cytokines on human mast cells remain poorly understood.

In conclusion, we found that IL-33 is a strong activator of human mast cell capable to induce MCP-1
(a C-C chemokine family member) released at translational level. Moreover, the present data describes an additional biological activity of IL-33, suggesting that this cytokine may have an important effect on the recruitment of inflammatory cells and allergic diseases mediated by immune-activated mast cells.

CHEMOKINE CCL2/MCP-1

The chemokine supergene family are 8- to 10-kD proteins inducible in a number of pathophysiologic processes. Members of the C-C subfamily include monocyte chemotactic proteins (MCP-1, MCP-2, MCP-3), macrophage inflammatory proteins (MIP-1α, MIP-1β), and regulated on activation, normal T-cell expressed and presumably secreted (RANTES), which generally mediate monocyte/macrophage activation and recruitment. CCL2/MCP-1 is a beta chemokine capable to attract and activate lymphocytes, macrophages, memory T cells and basophilic cells, but not neutrophils. CCL2/MCP-1 regulates the recruitment of inflammatory cells into tissue during inflammation and allergy. Monocyte chemoattractant protein-1 (CCL2/MCP-1) is a C-C chemokine in which the cysteines are adjacent and therefore is a prototype member of the C-C chemokine subfamily, purified from different sources and with chemoattractant and activator properties. CCL2/MCP-1 is a small (8000-10000 MW) protein and is one of the major and most studied members of the CC chemokine beta subfamily. The roles of CCL2/MCP-1 is emerging in regulating the recruitment of inflammatory cells into tissue during inflammation and allergy [46, 47]. CCL2/MCP-1 is one of the major and most studied members of the CC chemokine beta subfamily. The roles of MCP-1 is emerging in regulating the recruitment of inflammatory cells into tissue during inflammation. The inhibition of MCP-1 with the corresponding antibody or other inhibitors may provide benefits in different clinical scenarios including inflammation, CNS disorders, cancer, parasitic diseases, autoimmune and heart diseases. MCP-1 may represent targets for diagnostic procedures and therapeutic intervention, and may be useful as a prognostic factor in many diseases. Substance P (SP) is also an inflammatory protein intimately linked to the pathophysiology of several relevant neurological and psychiatric disorders, such as migraine, nausea, anxiety, depression and stress. It has been reported that chronic diseases characterized by disregulation of inflammation are particularly susceptible to exacerbation by stress and emotion. SP involved in neurogenic inflammation and pathogenesis of several inflammatory diseases enhances cytokine production including TNFα and IL-8 (a C-X-C chemokine capable to attract neutrophils in several inflammatory diseases). Regulation of leukocyte migration and activation by cytokines/chemokines are

Figure 1: Involvement of TNFa, IL-33 and MCP-1 in mast cell activation.
recognized as potentially important functions in the induction of acute and chronic inflammatory reactions. CCL2/MCP-1, and related molecules constitute the C-C class of the beta chemokine supergene family with inflammatory properties.

Table 1:

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<th>Mast Cell Mediators:</th>
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<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
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<td>Interleukin 8</td>
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<td>Histamine</td>
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<td>Substance P</td>
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<td>Tryptase</td>
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<td>Tumor necrosis factor</td>
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<td>Vasodilatory</td>
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<td>Bradykinin</td>
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<td>Histamine</td>
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<td>Nitric oxide</td>
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<td>Tumor necrosis factor</td>
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<td>Tryptase</td>
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<td>Vascular endothelial growth factor</td>
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<td>Vasoactive intestinal peptide</td>
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<td>Vascular endothelial growth factor (VEGF)</td>
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<td>Tumor necrosis factor (TNF)</td>
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<td>Prostaglandin D2 (PGD2)</td>
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The induction of inflammatory cells by SP in the site of inflammation may be due to its capacity of stimulating not only prostaglandin and 5-lipoxygenase products, such as LTB4 (which is chemoattractant for macrophages and neutrophils), but also specific chemokine such as CCL2/MCP-1 capable to recruit mast cells in the inflammatory sites [48, 49]. Using LAD 2 “Laboratory of Allergic Diseases”) mast cell line for the eventually release of CCL2/MCP-1, under stimulation with Substance P (SP), it has been found that CCL2 expression (CCL2 mRNA) and production increases in LAD2 mast cell line activation increasing in a dose-dependent manner [50]. These data demonstrate that SP produce inflammation by recruitment of mast cells through the stimulation of CCL2/MCP-1 and may offer promising therapeutic options to be integrated within classic anti-inflammatory compounds.

The migration of mast cells is regulated by some chemokines such as RANTES, eotaxin, IL-8 and MCP-1. In addition, many cytokines induce the migration of mast cells, such as IL-1, TNF, IL-15, some directly and others through the induction of chemokines(s). This migration is also due to many other humoral factors, including LTB4, C3a, C5a and neuropeptides such as SP and neurotensin. We found that SP stimulates CCL2/MCP-1 chemokine transcription and translation protein in LAD2 cells in vitro (unpublished data).

The enhanced response of SP treated LAD2 followed time and dose-dependent curves for CCL2/MCP-1. We demonstrate that the steady state levels of LAD2 CCL2 mRNA and secreted CCL2 are increased by SP in a dose-dependent manner. It has been reported that mast cells in vitro release significant amounts of preformed C-C subfamily chemokines, such as MCP-1 after stimulation with biological pro-inflammatory stimuli (anti-IgE). Mast cells express receptors for and can be stimulated by SP secreted under stress increasing neuroinflammation. In addition, SP could be released in response to immunological stimulation and lead to mast cell activation and vascular permeability. Therefore mast cells not only respond to, but also synthesize and secrete SP. It is well known that chronic stress is related to inflammatory response and suppresses the immune system and could further exacerbate tumor growth and neuroinflammation. Moreover, it has been reported that local inflammation can be conducive for immunosuppression and cancer growth. Mast cells are considered to be the chief cell types in inflammation including neuroinflammation. Stress appears to increase the inflammatory response, but the mechanism is not understood. Recent evidence suggests that MC play an essential role in the pathophysiology of brain and their migration is due to many humoral factors such as neuropeptide SP, which can trigger mast cell-activation leading to selective secretion of numerous mediators such as cytokines/chemokines in the inflammatory site. We previously reported that mast cells could be recruited in the inflammatory site by MCP-1 and RANTES and secrete proinflammatory molecules inducing growth factors, histamine, heparin, VEGF and IL-8. Activation of MC with SP causes the release of MCP-1 and other inflammatory mediators that either directly mediate inflammation or further enhance the recruitment of
mast cells. Understanding the pathophysiology of inflammation and the role of chemical mediators such as SP may improve inflammation management. Stress contributes to inflammation, an effect mediated by SP through the stimulation of mast cells and releasing chemokines. It is now clear that mast cell functions are altered in stress and it is involved in the mast cell stress response. SP has various inflammatory and immunomodulating effects, including in vitro modification of mast cell secretion and cytokine/chemokine release. In addition, SP on mast cells appears to be a stimulating one in vivo and in vitro and since it is released by sensory nerves, participates in inflammation by interacting directly or indirectly with NK-IR expressed on nerves and immune and inflammatory cells, such as mast cells and macrophages.

We previously reported that mast cells can accumulate in the tissue in response to exogenous injections of CCL2/MCP-1, or RANTES. Mast cells could promote inflammatory response through many different ways, including the production of VEGF, which is secreted by mast cells in response to allergic stimulation; CXCL8 (IL-8) which can act as a chemotactic factor; and SP, which was recently considered as a possible link between stress and neuroinflammation.

SP elaborated by LAD2 cells could initiate and promote the inflammatory process producing CCL2/MCP-1 and recruiting to the focal area inflammatory cells including mast cells and monocytes. Locally produced CCL2/MCP-1 could further the progression of the inflamed site by recruiting more immune cells. SP stimulates CCL2/MCP-1 expression inLAD2 cells. This phenomenon may prove to be a general mechanism which amplifies the local pathological effects of this mediator, although it remains to be seen whether other CCL2/MCP-1 producing cell types respond similarly to SP.

The mast cell inflammatory response is characterized by an early phase with massive discharge of mediators stored in cytoplasmic secretory granules. Through multigranular/compound exocytosis and a late phase that involves generation of arachidonic acid metabolites and de novo synthesis of cytokines/chemokines and growth factors. Vitamins have been shown to have a protective effect on the body's immune cells. Vitamin C and E are necessary in allergic disease treatment where mast cells are involved [51]. There are few inflammatory chemotactic factor that is directly active on phagocytic cells involved in inflammatory diseases which mediate in particular psoriasis. These compounds, probably participate in the early phases of psoriasis development [52].

The amounts of hyaluronan increase during inflammation and tumorigenesis through the action of chemokines and growth factors [53, 54]. In several inflammatory states infiltration of lymphocytes and mast cells and connective tissue activation leading to a disordered accumulation of hyaluronan and intense inflammation [55, 56]. Activated human mast cell line in vitro, can activate human fibroblasts to produce increased levels of prostaglandin E2 and hyaluronan, as it is evidenced by a 2-fold increase in [3H]glucosamine incorporation into the macromolecule. These findings demonstrating the ability of mast cells to activate fibroblasts, and the findings suggest a potential role for these cell-cell interactions in the pathogenesis of certain inflammatory diseases [57-59].

These studies indicate that cytokines/chemokines may be critically involved in regulation of mast cells pathophysiology in vitro and in vivo, providing a potential therapeutic target for inflammatory disorders.

However, the exact mechanisms of regulation, production and release of cytokine by mast cells remain unclear.

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