Review paper

Mast cells as the strength of the inflammatory process

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The inflammatory process is a complex host defence mechanism aimed at the elimination of deleterious factors disturbing homeostasis. Inflammation consists of several interdependent stages controlled by a wide range of mediators. Those include acute phase proteins, heat shock proteins, complement components, biogenic amines, cytokines, lipid-derived mediators, reactive oxygen species, nitric oxide, proteolytic enzymes, and kinins. Due to the strategic location in the body, mast cells play a protective role in the inflammatory process, through its initiation, amplification, and resolution. Mast cells degranulate and/or newly produce, and release various mediators classified into three groups: preformed mediators, de novo synthesised lipid mediators, and newly synthesised cytokines. Those mediators have an impact on different processes occurring during inflammation, inter alia, they influence blood vessels leading to dilation, enhanced adhesion molecule expression, and increased permeability. Furthermore, mast cell mediators play a pivotal role in inflammatory cell chemotaxis, degradation of extracellular matrix proteins, impact on stationery cells and resolution of inflammation. The release of mast cell mediators and their actions constitute a highly complex and still not fully understood mechanism, which warrants further studies of the action of mast cells in inflammation. This review will focus on the current knowledge concerning the broad role of mast cells in the inflammatory process.

Key words: mast cells, inflammation, mediators, cytokines.

Inflammation

Inflammation is a complex biological process, occurring in higher organisms as a result of any tissue malfunction, caused by diverse conditions including pathogen infection or stress factors, e.g. ionising radiation, cold, hot, toxins, and exogenous or endogenous agents. This first-line defence strategy can be characterised by physical symptoms such as swelling, pain, redness and heat triggered by vasodilation, extravasation of fluids, or growing mediator concentrations. The purpose of inflammation is not merely the elimination of injurious agents, but also the removal and healing of damaged cells in order to restore homeostasis [1, 2].

In a properly functioning organism "physiological inflammation", known as acute phase response (APR), occurs quickly in the presence of detrimental conditions and subsides after its removal [3]. At this stage, a rapid infiltration of leucocytes, namely neutrophils, monocytes, and different subsets of lymphocytes, can be observed. Any disruption in the resolution process extends the duration of the inflammation, leading to undesirable consequences for healthy tissues and as a result to loss of organ function. This "non-physiological" state is defined as a chronic stage [1, 2, 3, 4]. Moreover, most inflammatory diseases originate from the continuous inflammatory response, not directly from deleterious factors. These medical conditions include atherosclerosis, type 2 diabetes, rheumatoid

arthritis, asthma, obesity, cardiovascular disease, Alzheimer's disease, and to a certain extent even cancer [1, 4].

Stimuli triggering the inflammatory response are first recognised by host cells, which are present in the site of harmful factor penetration [1, 2]. These agents are very diverse and comprise a variety of foreign factors such as pathogens, physicochemical agents, and certain endogenous stimuli, arising in response to cell damage and disruption of homeostasis occurring under pathological conditions [4, 5]. Recognition can be achieved mainly due to the presence of pattern-recognition receptors (PRRs), specific transmembrane receptors detecting microbial structures known as pathogen-associated molecular patterns (PAMPs), and cellular injuries known as damage-associated molecular patterns (DAMPs). Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and RIG-1-like receptors (RLRs) are distinguished among PRRs, and they play a crucial role in tissue damage recognition with subsequent activation of various signalling pathways [6]. Leukocyte recruitment is a significant process in the whole defence mechanism and involves many steps of cell adhesion and activation, occurring in a precise manner and period of time, in order to eliminate thoroughly hazardous factors and simultaneously causing less damage to healthy cells [7]. Although infiltration of inflammatory cells, such as monocytes/macrophages, neutrophils, lymphocytes, or dendritic cells, is of prime importance, the role of fibroblasts, epithelial cells, endothelial cells, or hepatocytes is no less significant [1, 2]. In order to restore homeostasis efficiently, every biological structure in an organism must cooperate and influence each other, thus released mediators from one cell trigger specific defensive reactions from different cells.

Prolonged duration of inflammation may lead to various pathological conditions; therefore, the mechanism of inflammation resolution is of critical importance for the organism. This process depends on the release of anti-inflammatory and pro-resolving mediators. Although both are responsible for stopping the inflammation, the former one inhibits or blocks a specific action, e.g. inhibition of pro-inflammatory cytokine secretion, while the latter one triggers stimulation and activation of certain mechanisms, like induction of leukocyte apoptosis [4].

Inflammation is a sophisticated mechanism based on many interconnected steps and requires concerted action of various inflammatory cells. Mast cells are considered among the most important cells taking part in the development of acute, as well as chronic, inflammation. Their specific localisation in an organism, in areas exposed to a pathogen or endogenous factor penetration on the one hand, and a wide spectrum of pro- and anti-inflammatory mediators secreted, on the other hand, are both highly relevant features in the process of inflammation.

Mediators of inflammation

As discussed earlier, infiltration of inflammatory cells and activity of cells already existing at the site of inflammation are crucial for this process, and cell migration, as well as activation, is regulated by a wide range of mediators, which are necessary for the initiation, amplification, and resolution of inflammation. Cells capable of mediator secretion may be present in tissues (mast cells, macrophages, dendritic cells), create tissue (endothelial cells, epithelial cells, smooth muscle cells, fibroblasts, hepatocytes), or circulate in the bloodstream with a subsequent tissue infiltration after occurrence of detrimental agent (neutrophils, eosinophils, basophils, T cells, monocytes). Keeping in mind that the inflammatory process is controlled by a vast number of mediators making it very difficult to present a comprehensive list of them, there are some classes of mediators of a well-recognised role in controlling the inflammation. Some sources also categorise mediators into two main classes: plasma protein-derived mediators that are released from distant organs, e.g. acute phase proteins (APPs), heat shock proteins (HSPs), complement proteins, and kinins; and cell-derived mediators, e.g. biogenic amines, cytokines, lipid-derived mediators, and neuropeptides.

Acute phase proteins are classical examples of inflammatory mediators, which are synthesised by hepatocytes during APR. They are divided into two groups: negative APPs, e.g. albumin, transferrin, and retinol binding protein (RBP); and positive APPs, e.g. C-reactive protein (CRP), serum amyloid A (SAA), α2-macroglobulin (A2M), haptoglobin (Hp), ceruloplasmin, fibrinogen [8], and mannose-binding lectin (MBL) [9]. Heat shock proteins are the second classical representatives of inflammatory mediators, which are synthesised due to the action of stress factors, leading to denaturation of proteins. They are also known as chaperone proteins in view of their activities preventing denaturation and supporting proper folding and aggregation of proteins [10]. Common examples of HSPs include HSP60, HSP70, and HSP90 [11]. The complement system serves as a crucial mechanism initiating the inflammatory process upon pathogen infection. It consists of a set of proteins, which activate each other in a strictly defined order through classical, lectin, or alternative pathway, depending on the surface pattern recognition. Components C3a and C5a are mostly mentioned as those playing role in inflammation [12]. Inflammatory mediators comprise many other compounds taking part in the process of inflammation. Some of them may be classified into certain groups according to their structure, origin, or function. Biogenic amine

mediators constitute another class of mediators, with histamine as the model representative [13].

Cytokines are among the most commonly mentioned and the largest group of inflammatory mediators. Different cytokines may act agonistically or antagonistically on the same mechanism or cell; hence, they are divided into two major groups: pro-inflammatory and anti-inflammatory cytokines. This division is based on the general functions of certain cytokines because barely any of them may be considered as the only pro- or anti-inflammatory [14]. Interleukin (IL)-1β, IL-6, IL-17 and tumour necrosis factor (TNF) are basic representatives of pro-inflammatory cytokines, which can act singly or in co-operation to stimulate the release of other pro-inflammatory cytokines [1, 2, 3, 14]. However, some of them may also trigger the secretion of anti-inflammatory and pro-resolving mediators, e.g. IL-1β and TNF induce the production of IL-10 [4, 14], while IL-1β, interferon (IFN)-γ, and IL-4 contribute to lipoxin release [14, 15]. Transforming growth factor (TGF)-β and IL-10 are common examples of cytokines suppressing the inflammatory response [1, 2, 5, 14]. Interleukin 4 and IL-13 are also considered to act mainly as anti-inflammatory cytokines [2, 5, 14].

Certain growth factors are likewise classified as cytokines taking part in the inflammatory process, with central representatives of this group as follows: platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), anti-inflammatory TGF-β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and stem cell factor (SCF). The last frequently mentioned group of cytokines are low molecular weight proteins called chemotactic cytokines or chemokines. Common, and simultaneously very important, examples of chemokines taking part in the inflammatory process include: CXCL8, CCL2, CCL3, CCL4, and CCL5 [14].

While considering various types of mediators, an additional concept, namely inflammasome, should be emphasised. Inflammasome is an intracellular inflammatory protein complex taking part in the maturation of cytokines, specifically IL-1β and IL-18. This complex consists of the following proteins: inflammasome sensor molecule, the adaptor protein apoptosis-associated speck-like protein containing caspase activation and recruitment domain (CARD) (ASC), and caspase 1. Inflammasome possesses the ability to detect PAMPs and DAMPs through TLR activation, leading to the production of inactive cytokine precursors, pro-IL-1β and pro-IL-18. CARD strongly binds caspase-1 and activates it through its self-cleavage. This, in consequence, contributes to the cleavage of cytokine precursors and the release of fully functional mediators IL-1β and IL-18, which significantly influence the inflammatory process [16].

Lipid-derived mediators include a class called eicosanoids, which are divided into prostanoids, leukotrienes, and pro-resolving mediators. Prostanoids comprise compounds known as prostaglandins (PGs), e.g. PGD_2, PGE_2, PGI_2, and PGH_2, and thromboxane (TX), e.g. TXA_2. Leukotrienes (LTs) include LTA_4 and LTB_4, while LTC_4, LTD_4, and LTE_4 represent a group known as cysteinyl leukotrienes (cys-LTs) [17, 18]. A relatively new addition to this list is a new class of eicosanoids, which includes pro-resolving mediators such as lipoxins (LX), e.g. LXA_4, LXB_4; resolvins (Rv), e.g. RvD_1, RvE_1, RvE_2; protectins (PD), e.g. PD_1, (also called neuroprotectins (NP), e.g. NPD_1); and maresins (Ma), e.g. MaR_1 [19]. Together with anti-inflammatory cytokines, they play a crucial role in the resolution of inflammation [4, 5, 15].

Certain enzymes also play a significant role in inflammation development. This includes proteolytic enzymes, which comprise, inter alia: tryptase, chymase, carboxypeptidase A, cathepsin G, and granzymes [20]. Matrix metalloproteinases (MMPs) with the prime function of extracellular matrix (ECM) remodelling, such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-14, MMP-15, and MMP-17, are also representatives of proteolytic enzymes important for the inflammatory process [21]. Proinflammatory activity of MMPs is directly controlled by the tissue inhibitors of metalloproteinases (TIMPs), namely TIMP1, TIMP2, TIMP3, and TIMP4 [22].

Inflammatory mediators comprise many other classes and unclassified compounds, and although not all of them could be listed here, there are two groups that should be mentioned, namely reactive oxygen species (ROS) with nitric oxide (NO) and kinins. ROS and NO also function as inflammatory mediators. They are released from neutrophils during degranulation, in order to create destructive conditions for foreign microorganisms, but may likewise affect the survival of host cells [2]. Kinins are inflammatory mediators, the functions of which are considered crucial for the first-line defence strategy, with bradykinin as a common example [23].

Mast cells

Mast cells are crucial elements of different organism physiological and defence strategies, such as maintenance of homeostasis, protection against pathogens, and inflammatory process. They are formed initially in the bone marrow as CD13+/CD34+/CD117+ multipotent haematopoietic progenitors, which subsequently are released to blood vessels in order to settle at the target tissue, where they may dwell for several months. Mast cells are localised in the organism in strategic places in the connective tissue, mainly the surfaces of the mucosa, enabling an efficient carriage

of their functions. Therefore, they are commonly localised close to the blood and lymphatic vessels, below the epithelium, lining the respiratory, digestive, or genitourinary systems and in the skin [24, 25, 26].

Mast cells are characterised by the expression of different receptors, activation of which leads to secretion of various inflammatory mediators. These signalling molecules may be expressed in different cellular compartments including cytoplasm, cell membrane, nuclear membrane, and endosome membrane [24, 25, 26]. Not all receptors are directly associated with inflammation; however, some of them should be mentioned due to their essential properties in determining mast cell functions. These specific molecules include a high-affinity receptor for IgE, e.g. FcεRI, and receptors for IgG, such as FcγRI, FcγRIIA, and FcγRIII. Moreover, mast cells possess hormone receptors, e.g. Mas-related gene X2 (MrgX2) for somatostatin, oestrogen receptor α (ERα), ERβ, progesterone receptor (PR), and multiple G protein-coupled receptors (GPCRs) including receptors for cannabinoids, e.g. cannabinoid receptor type 2 (CB2), and neurotransmitters such as adenosine, e.g. adenosine A2a receptor (ADORA2A), ADORA2B, ADORA3, for substance P, e.g. neurokinin 1 receptor (NK1R), or acetylcholine, e.g. nicotinic acetylcholine receptors (nAChRs) [24, 25, 26, 27].

Inflammatory mediators, which are released during the inflammatory process, may act in an autocrine or paracrine way through interaction with corresponding receptors leading to further activation or inhibition of different mediator synthesis, thus regulating inflammation. Mast cells express receptors for the following mast cell-derived mediators: LTs, specifically cys-LTs and LTB_4, e.g. CYSLTR1, CYSLTR2, G protein-coupled receptor 17 (GPR17), LTB4R, and LTB4R2; PGs, namely PGE_2, e.g. EP_2, EP_3, and EP_4; histamine, e.g. H_1, H_2, and H_4; and complement components, e.g. C3aR and C5aR [24, 25, 26, 27, 28]. Cytokine, e.g. interleukin 1 receptor like 1 (IL1RL1), IL-3R, IL-4R, IL-5R, IL-9R, IL-10R, GM-CSFR, and IFN-γR [28, 29], including chemokine receptors, e.g. CXCR1, CXCR2, CXCR3, CXCR4, CX3CR1, CCR1, CCR3, CCR4, and CCR5; neurotrophins like nerve growth factor (NGF), e.g. tropomyosin receptor kinase A (TrkA); and protease activated receptors (PAR), e.g. PAR1, PAR2, PAR3, and PAR4 for tryptase and chymase, are also expressed among mast cell receptors [14, 24, 25, 26, 27, 28].

Another group of mast cell receptors crucial in activation of mast cells during inflammatory processes is PRRs, known to be critical for defense against bacterial or viral infection. This include TLRs, e.g. TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10; NLRs, e.g. NOD1, NOD2; CLRs, e.g. dectin-1, macrophage-inducible Ca^{2+}-dependent lectin (mincle); and RLRs, e.g. RIG-1, melanoma differentiation-associated protein 5 (MDA5) [30, 31]. Activation of PRRs, particularly TLR2 and TLR4, usually leads to stimulation of inflammatory response through the increase of expression of inflammatory mediators [31]. However, the signalling pathway initiation through particular receptors, e.g. TLR3, may also downregulate this response due to inhibited degranulation and adhesion of mast cells [32]. Although PRRs seem to be specialised in recognition of structures specific for bacteria and viruses, there are many endogenous ligands that are also recognised by these receptors. These host-derived ligands include components normally present in physiological conditions, e.g. fibrinogen, fibronectin, and hyaluronan, as well as molecules synthesised during disturbed homeostasis or occurring after cell/tissue damage, like high-mobility group box 1 (HMGB1), cardiac myosin, and HSPs, e.g. HSP60, HSP70, and HSP72 [33].

Especially interesting are mast cell inhibitory receptors that upon activation mediate a decrease in production of certain pro-inflammatory mediators, e.g. histamine, tryptase, IL-1β, IL-6, IL-13, TNF, SCF, GM-CSF, CCL2, CCL3, and LTC_4, which may significantly reduce or even eliminate the severity of many pathological conditions associated with inflammation. Common examples of inhibitory receptors include FcγRIIB, paired Ig-like receptor B (PIR-B), cell surface glycoprotein OX2 receptor 1 (CD200R), CD300a (known also as inhibitory receptor protein 60 – IRp60), sialic acid-binding immunoglobulin-like lectin (Siglec), and mast cell function-associated antigen (MAFA) [34].

Mast cells also express integrins, which primarily serve as receptors for adhesion molecules, such as endothelial-leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), expressed by endothelial cells. Recognition of adhesion ligand is critical for the migratory abilities and localisation of mast cells during the inflammatory process [35]. Integrin receptors mediate the adhesion of mast cells to certain ECM glycoproteins such as fibronectin following activation via FcεRI [36]. Furthermore, these receptors also provide signal-enhancing release of mast cell mediators upon FcεRI stimulation [37] and play a role in the direct interaction of mast cells with other inflammatory cells [38].

Activated mast cells owe their fundamental role in inflammation to the production and release of a wide range of inflammatory as well as non-inflammatory mediators. These may be classified into three groups: preformed mediators, which are stored in the granules and secreted during degranulation almost instantaneously after mast cell activation; mediators de novo synthesised during membrane phospholipid metabo-

Table I. Human mast cell mediators

Preformed mediators	*De novo* synthesised mediators
Biogenic amines	Lipid mediators
Histamine, serotonin	Arachidonic acid derivatives
Proteases	LTB4
Tryptase, chymase, carboxypeptidase A, cathepsin G, granzyme B, MMP-9, renin	LTC4, LTD4, LTE4
Lysosomal enzymes	PGD2, PGE2
Arylsulfatase A, β-hexosaminidase, β-glucuronidase, β -D-galactosidase	PAF
Other enzymes	Cytokines
Angiogenin, kinogenases, phospholipases	Interleukins
Peptides	IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-16, IL-17, IL-18, IL-22, IL-31, IL-33
Endothelin, CRH, kinins (bradykinin), leptin, LL-37, substance P, urocortin, VIP	Growth factors
Glycosaminoglycans	TGF-β, SCF, GM-CSF, bFGF, NGF, NT-3, PDGF, VEGF
Heparin, chondroitin sulphate, hyaluronic acid	TNF
Proteoglycans	MIF
Serglycin	IFN-α, IFN-β, IFN-γ
Cytokines	Chemokines
Interleukins	CXCL1, CXCL2, CXCL8, CCL2, CCL3, CCL4, CCL5, CCL8, CCL13, CCL20, XCL1
IL-4, IL-5, IL-6, IL-15	Others
Growth factors	NO
TGF-β, SCF, bFGF, NGF, VEGF	ROS
TNF	
Chemokines	
CXCL1, CXCL2, CXCL8	

CRH – corticotropin-releasing hormone; LL-37 – leucine, leucine-37; VIP – vasoactive intestinal peptide; VEGF – vascular endothelial growth factor; PAF – platelet-activating factor; NT-3 – neurotrophin-3; MIF – macrophage migration inhibitory factor; XCL1 – X-C motif chemokine ligand 1

lism, which are produced and released in tens of minutes after activation; and newly synthesised cytokines and other mediators, which are formed and secreted several hours after mast cell activation (Table I) [24, 25, 26, 27, 39, 40, 41, 42].

Mast cells in inflammation

When mast cells are activated, they degranulate releasing a wide range of already stored mediators and/or secrete newly synthesised lipid derivatives and cytokines because the release of mediators is highly dependent on the stimulus and does not always occur with the secretion of all three classes of mediators [24, 25, 27]. Various, mainly pro-inflammatory, functions of released substances mean that mast cells affect different stages of inflammation, including its initiation and maintenance, but also its resolution, suggesting a pivotal role of mast cells in the inflammatory process. The involvement of mast cell mediators in inflammation is presented in Fig. 1. The essential role of mast cells in the process of inflammation could be observed both in APR and chronic stage, where the latter could lead to many pathological conditions. While this review focuses on "physiological inflammation", it is worth noting that pro-inflammatory functions of mast cells may initiate and/or amplify multiple pathological inflammatory conditions including rheumatoid arthritis [43], periodontal disease [44], Hodgkin lymphoma [45], and cancer, where they also play an important role in the process of tumour angiogenesis [46].

It is well known that inflammatory cells incessantly circulate in the bloodstream; however, only some of them will infiltrate the inflammatory site due to precisely defined mechanisms, and mast cells significantly contribute to this movement. It should be kept in mind that the mechanism of cell extravasation to the tissue consists of many stages including margination, rolling, activation, tight adhesion, diapedesis, and

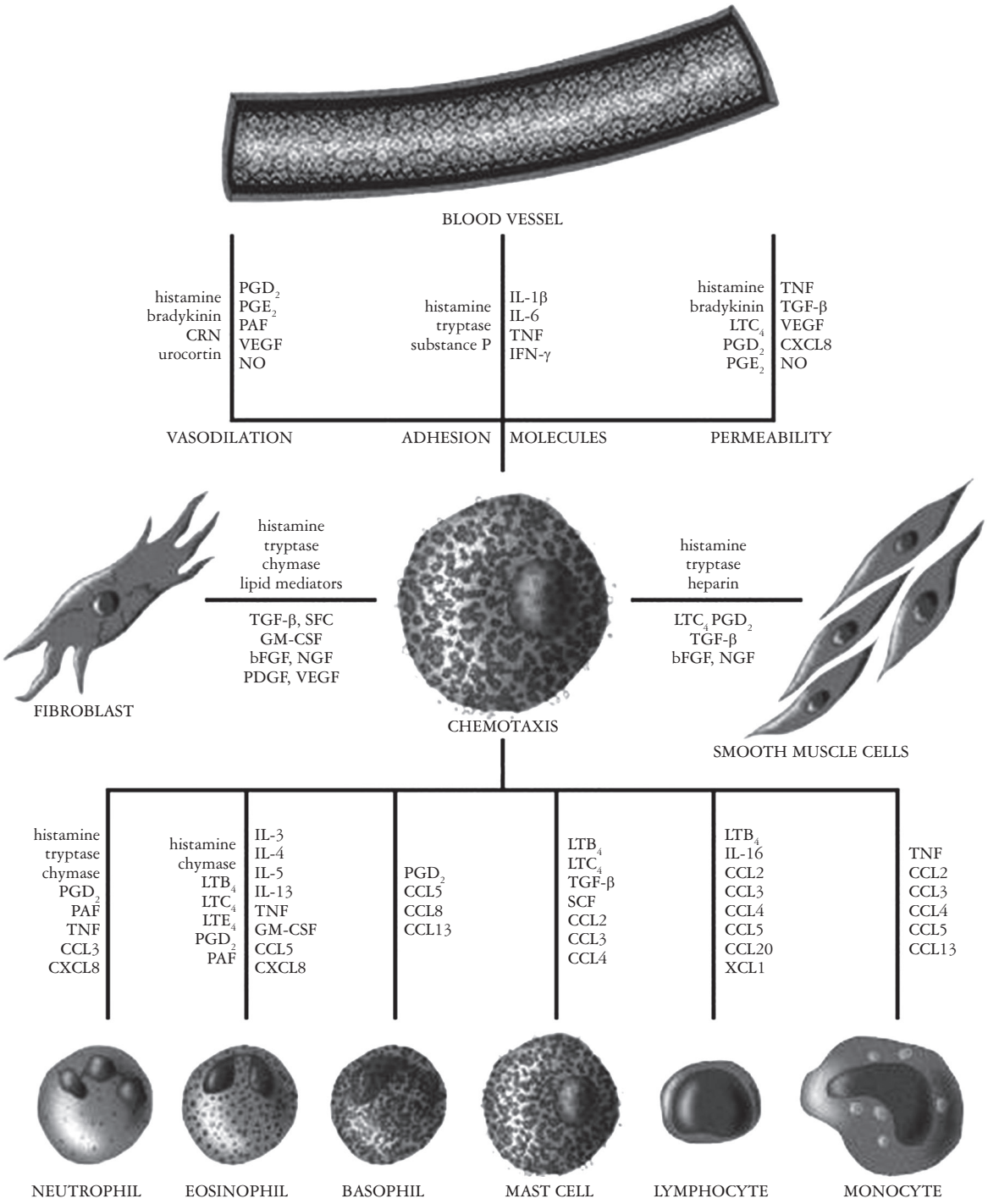

Fig. 1. Mast cell mediators acting on selected cells/structures

chemotaxis [7]. These processes are firmly regulated through various mediators. Firstly, all recruited cells should have the possibility to attach to the vascular endothelium. This may be accomplished due to the activity of histamine, bradykinin, corticotrophin-releasing hormone (CRH), urocortin, PGD_2, PGE_2, platelet activating factor (PAF), vascular endothelial growth factor (VEGF), and NO, which lead to a violent dilation of blood vessels, resulting in blood flow slowdown. Although NO may seem to be unimportant in the early stage of inflammation due to its release only a few hours after mast cell activation, it may fulfil its functions in prolonged inflammatory process. However, mediators arising from membrane phospholipid metabolism may provoke vasodilation after tens of minutes from mast cell activation, while histamine, bradykinin, CRH, and urocortin act even more rapidly, in the first moments after the activa-

tion. VEGF also affect vasodilation almost instantaneously, when secreted as a preformed mediator or after several hours, when it is newly synthesised [27, 35, 47].

Another step facilitating the attachment between endothelial and inflammatory cells is increased expression of adhesion molecules, which, due to the molecule type, selectively bind certain cells that will take part in the inflammation [7, 25]. This process is also controlled by a set of mast cell mediators, which influence adhesion molecule expression, inter alia, by increasing it. Histamine may trigger this reaction, but also tryptase, substance P, IL-1β, IL-6, TNF, and IFN-γ [25, 48, 49]. Interferon γ, as well as IL-1β, affect adhesion molecule expression several hours after mast cell activation, while tryptase and substance P act immediately as histamine. Due to the fact that IL-6 and TNF may be stored in mast cell granules or de novo synthesised, they may function in two ways: instantly and/or after a few hours. Zhang *et al*. [49] studied the effect of mast cell-derived IL-6, TNF, and IFN-γ on the expression of VCAM-1, ICAM-1, P-selectin, and E-selectin and observed increased expression of adhesion molecules, with the activity of IFN-γ being the weakest, and TNF the strongest. Moreover, IL-6 and TNF influence adhesion of neutrophils to endothelial cells.

Finally, mast cells may influence blood vessels through modification of vascular permeability. This is a key phenomenon of the inflammatory process because it facilitates the exudation in the tissue, thus enabling the infiltration of leukocytes to the site of inflammation, as well as extravasation of various proteins including complement components, e.g. C3a, C5a, fibrinogen, and other humoral factors. Multiple mast cell mediators cause an increase in vascular permeability. Those include a similar set of substances playing a role in vasodilation: histamine, bradykinin, LTC_4, PGD_2, PGE_2, TNF, TGF-β, VEGF, CXCL8, and NO [25, 39, 48, 50]. LTC_4, similarly to other arachidonic acid derivatives, increase vascular permeability after tens of minutes due to de novo synthesis. Because TGF-β and CXCL8 may be newly synthesised, they may also act after a long period of time; however, when released through degranulation, the increase in permeability is very rapid. Similarly, heparin also affects vascular permeability almost instantaneously when secreted as a preformed mediator [25].

Selected inflammatory cells, attached to certain adhesion molecules on endothelial cells, are subsequently attracted by particular chemokines and other mediators, which force cells to migrate in the designated direction indicating the inflammatory site. Some substances may be specific to certain cell populations, mainly leukocyte; however, they may also have an impact on the infiltration of different cells [25]. Mast cells are able to induce chemotactic moves of lymphocytes, which in turn release other mediators that cooperate in the initiation and maintenance of inflammation, e.g. Th1 cells secreting IL-2, IL-3, TNF, and IFN-γ; Th2 cells that are able to release IL-4, IL-5, IL-6, IL-10, IL-13, and TGF-β; or in the resolution, e.g. regulatory T cells secreting IL-10 and TGF-β. Lymphocytes may be attracted through multiple mediators that may be released a few hours after mast cell activation [48, 51, 52, 53]. Monocytes, with phagocytic abilities and their own set of cytokines, e.g. IL-1, IL-6, IL-12, and TNF [54], are another cell population attracted by mast cell-derived monocyte chemoattractants [25, 39, 55, 56].

Granulocytes are also relevant in the process of inflammation due to their ability to carry on phagocytosis and release of a wide range of mediators, and all granulocytes may also be attracted by mast cell cytokines and other substances. Firstly, mast cells may affect chemotactic movements of neutrophils [25, 27, 39, 41] that secrete mediators such as cathepsin G, MMP-9, defensins, and various enzymes [57]. Mast cell-derived preformed and de novo synthesised mediators induce the infiltration of eosinophils [27, 28, 51, 52, 56] that not only possess the ability to phagocytose but are also a source of many mediators, e.g. LTC_4, PGE_2, PAF, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, and TGF-β [58]. Finally, mast cells act as chemoattractants for basophils [56] that are known to release histamine, heparin, LTC_4, LTD_4, LTE_4, IL-4, IL-13, and GM-CSF as well as various enzymes [28]. It is worth emphasising that mast cells are able to attract different inflammatory cells through various mediators; however, they may also increase the infiltration of the inflammatory site by other mast cells through the release of preformed and newly synthesised mediators [27, 35, 59, 60].

Despite the ability of mast cells to release chemoattractants for various cell migration, their effective infiltration would not be possible without the loosening of extracellular molecules secreted by different cells in order to maintain their function. Therefore, there are a set of mediators that enable the remodelling of ECM, and thus the destruction of physical barriers preventing inflammatory cells from entering the inflammatory site, and mast cells are able to secrete some of those enzymes [25]. These mediators comprise a group of protease enzymes involving tryptase, chymase, cathepsin G, which can activate metalloproteases, and MMP-9 [20, 25, 41]. Since all of those mediators are stored in mast cell granules, they may be quickly released after mast cell activation, enabling a smooth migration of recruited cells from the beginning of the inflammation process. Mechanisms concerning ECM degradation by mast cell-derived enzymes include collagen type VI cleavage (tryptase), proteoglycan degradation (MMP-9), collagenase activation (tryptase, chymase), collagen

type IV, type V, and fibronectin cleavage (cathepsin G, chymase and MMP-9) or vitronectin degradation (chymase) [20, 25, 41, 48, 56]. However, tryptase and chymase may also take part in the synthesis of ECM structures; specifically, they stimulate collagen production through the activation of lung fibroblasts (tryptase) or by the cleavage of procollagen (chymase) [48].

During the course of inflammation, mast cell mediators affect infiltrated cells by activating them to release their sets of mediators, involving them in the amplification of the inflammatory process, but they also influence stationery cell populations including fibroblasts or those creating tissues: epithelial and smooth muscle cells [25]. Fibroblasts are mainly responsible for the remodelling of ECM, inter alia, through the production of MMPs and TIMPs. Tryptase and chymase released from mast cell granules stimulate fibroblasts in the process of ECM synthesis, but so do histamine, lipid mediators, TGF-β, and VEGF. Furthermore, stimulation of fibroblast may occur due to the activity of preformed or newly synthesised mediators such as SCF, bFGF, and NGF, while GM-CSF and PDGF are synthesised de novo after mast cell activation [52]. The prime function of epithelium is to protect blood vessels and organs against physical injuries by lining their surfaces. Moreover, epithelial cells are a source of various mediators, e.g. defensins, LL-37, IL-1β, CCL2, and CXCL8 [61]. Mast cells may activate epithelial cells, leading to a release of cytokines, through secretion of bFGF, NGF, PDGF, and VEGF [26], which also induce epithelial cell proliferation. Other mast cell mediators such as chymase, LTC_4, PGD_2, TNF, IL-6, and IL-13 that is newly synthesised after several hours [25, 27, 56] increase the secretion of mucus from mucous glands, which are present in the epithelium. Numerous activities of tryptase comprise also the ability to sensitise muscle cells to histamine [62], leading to their constriction. The activity of TGF-β, bFGF, and NGF [56] leads also to increased smooth muscle cell proliferation, while histamine, heparin, LTC_4, and PGD_2 [25, 63] induce the constriction of smooth muscle cells.

Although mast cells play a key role in initiation and maintenance of the inflammatory process, they may also take an active part in its resolution, thus preventing the adverse effects of prolonged inflammation. Thus, mast cells secrete known anti-inflammatory mediators, such as IL-10, which may lower the migration of T cells, granulocytes and macrophages [53], and TGF-β [51]. Furthermore, mast cell proteases, apart from their role in the degradation of ECM, are able to degrade inflammatory mediators. The list of known proinflammatory cytokines inactivated by mast cell proteases includes IL-5, IL-6, IL-13, IL-33, TNF, and endothelin [64, 65, 66]. Moreover, these proteases are also able to degrade certain danger signals released from damaged tissues, e.g. HSP70 [65].

Conclusions

The review of available data clearly indicates that mast cells are critical players in the inflammatory processes; however, it should be remembered that the degree of involvement of these cells largely depends on the site of inflammation and inducing stimulus. Various factors may activate mast cells through different receptors, thus initiating alternative signalling pathways. Due to this, secretory response of mast cells may be varied, e.g. activation via FcεRI triggers a rapid degranulation of preformed mediators, as well as *de novo* synthesis of arachidonic acid and lipid derivatives, cytokines, and other mediators; while in the case of activation via PRRs, mainly TLR4, no degranulation is observed despite the increased synthesis of cytokines. On the other hand, activation of mast cells by neuropeptides, e.g. substance P and VIP, initiates exclusively degranulation. Because of such differential mast cell response to an inflammatory stimulus, the effect of mast cell activation on the course and intensity of inflammatory process may be greatly different. Therefore, the result of mast cell involvement in allergic inflammation triggered via FcεRI-specific antigen, and in neurogenic inflammation, initiated via neuropeptide receptors, vary from their role in an inflammatory process initiated as a defence mechanism against pathogens.

Furthermore, the role of mast cells in the process of inflammation is directly dependent on their subpopulations. Human mast cells are categorised according to proteolytic enzyme content in the granules. Thus, MC_T (which corresponds to rodent mucosal mast cells [MMCs]) represents a mast cell population that stores tryptases, while MC_{TC} (rodent connective tissue mast cells [CTMCs]) is characterised by the presence of tryptases, chymases, and carboxypeptidases. The former subpopulation can be found predominantly in a close neighbourhood to T cells or in the mucosa of lungs and intestine, while the latter is present in the skin, lymph nodes, as well as in the lung and intestine submucosa. Besides different localisation, those mast cell subpopulations differ in the content of various mediators, expression of certain receptors, and sensitivity to stimulation; therefore, those features affect mast cell response to particular factors [24].

It should also be noted that mast cells, through their wide range of mediators, may not only constitute the first cell population initiating inflammation, but may also amplify the inflammatory process, particularly in cooperation with neutrophils, eosinophils, and fibroblasts. Finally, it should be stressed that mast cells are able to play a significant role in the

resolution of the inflammatory process, by different mechanisms involving mast cell-derived cytokines and proteases. Therefore, it is of prime importance to understand mast cells in order to enhance their beneficial activity, while impeding deleterious actions.

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