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REVIEW ARTICLE

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Mast Cells as the Target of the Biological Effects of Molecular Hydrogen in the Specific Tissue Microenvironment

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Abstract

Mast cells (MCs) as key players in the development of both physiological and pathological processes in the organism can form a specific tissue microenvironment. Having a rich secretion of biologically active substances, MCs can secrete tryptase and/or chymase and thereby participate in the regulation of processes such as inflammation, neoangiogenesis, allergic reactions, and oncogenesis. Reactive oxygen intermediates (ROI) play an essential role in regulation of MC degranulation, shown in vitro and in vivo models. Application of molecular hydrogen as a substance with antioxidant characteristics pathogenically appears to be an important mechanism decreasing MC secretory activity, and, as a consequence, a novel option to reduce an inflammatory background in the specific tissue microenvironment.(**International Journal of Biomedicine. 2022;12(2):183-187.**)

Key Words: mast cell • tryptase • chymase • specific tissue microenvironment • molecular hydrogen

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Abbreviations

MC, mast cell; **ROI**, reactive oxygen intermediates; **UCP**, uncoupling protein; **Drp**, dynamin-related protein

The state of the specific tissue microenvironment represented by the vessels, cellular component, and extracellular matrix plays a key role in forming the abnormal focus. Each organ has specific cellular complexes of tissues that use proper regulatory mechanisms to support the local homeostasis. Mast cells (MCs) actively participate in the management of cellular cooperations, monitoring the majority of the key parameters of the cellular microenvironment.[1,2] The unique character of MCs involves an extraordinary combination of the sensor apparatus adapted to informationally significant signals of the integrative-buffer metabolic medium, on the one hand, and the polyfunctional effector apparatus represented by the secretome, on the other hand. The existent modifications of the tissue microenvironment are registered by MCs with the help of a wide range of receptors, including surface IgG receptors, toll-like receptors, C-type lectin receptors, retinoic acid-inducible gene-I (RIG-I)-like receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, siglecs, G-protein-coupled receptors, lipid mediator receptors, alarmin receptors, leukocyte immunoglobulin-like receptors, cytokine receptors, integrins, tetraspanins, nuclear receptors, and many others.[3,4]

Adequately responding to challenges of the tissue microenvironment, MCs with high selectiveness secrete a rich arsenal of biologically active substances. This arsenal may be divided into pre-formed mediators and mediators newly synthesized in the process of activating MCs. Previously

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accumulated products of secretome are represented by a wide range of biogenic substances: biogenic amines (histamine, serotonin, dopamine, polyamines), proteases (chymase, tryptase, carboxypeptidase A, cathepsin G, granzyme B, metalloproteinase), enzymes (kinogenase, heparanase, angiogenin, active caspase-3), including enzymes of lysosomes (β-hexosaminidase, β-glucuronidase, β-D-galactosidase, aryl sulfatase A, cathepsins), proteoglycans (heparin, chondroitin sulfate), cytokines (TNF, IL-4, IL-15)), chemokines (RANTES, eotaxin, IL-8, MCP-1 and others, growth factors (TGF-β, bFGF, VEGF, NGF, SCF), as well as numerous regulatory peptides (corticoliberin, endorphin, endothelin-1, P substance, vasoactive intestinal peptide, angiogenin, bradykinin, leptin, renin, somatostatin, etc.). Products of re-synthesis include cell-derived cytokines, growth factors, mitogens (TNF, interleukins; EGF, bFGF/FGF- 2, GM- CSF, IFN-γ, NGF, PDGF, SCF, TGF- β1, VEGF/VPF, and others), MC-derived chemokines, and various lipid metabolites, namely prostaglandins and leukotrienes.[5-7]

With the help of secretome components, MCs are closely integrated into the genesis of adaptive and pathological conditions, representing not only an informative marker of the disease progression, but also a prospective therapeutic target. Specific MC proteases (tryptase and chymase) are of great significance. Secretory pathways of proteases and other secretome components represent various options of the substance secretion, with high selectiveness, into the extracellular matrix.[2,8,9]

The accumulated experimental data on the biogenesis and effects of MC tryptase allow considering it a multi-functional mediator with specific molecular-cellular mechanisms. The tryptase attracts a special interest in the pathogenesis of an allergy and inflammation under pathologies of the various body systems, including cardiovascular, respiratory, digestive, nervous, musculoskeletal systems and the skin, in the realization of carcinogenesis, and in the study of the tissue adaptive mechanisms under various ambient conditions, including the microgravic environment.[10] The immune-morphological study of the tryptase biological effects offers novel potentials for diagnostics of pathological conditions and monitoring of the performed therapy, as well as in the search for new pharmacological solutions to the treatment.

The biological significance of the chymase depends on the mechanisms of degranulation and is characterized by selective effects and the cellular and non-cellular components of the specific tissue microenvironment. The chymase is known to be involved in the mechanisms of allergy and inflammation, angiogenesis and oncogenesis, remodeling of the extracellular matrix of the connective tissue, and modifications of the organ histoarchitectonics. The number of chymase-positive MCs in the intra-organ population, mechanisms of secretome biogenesis, and degranulation represent the informative criteria for interpreting the internal organ status. The chymase takes an active part in the signaling molecular-cellular integrative mechanisms of the specific tissue microenvironment. The analysis of chymase-positive MCs gives new opportunities for understanding physiological and pathological reactions in various body systems, including cardiovascular, respiratory, digestive, musculoskeletal systems, the skin, and others.

The chymase is now of special importance relating to the fundamental oncological problems. This circumstance determines the need to further study specific MC proteases in basic and clinical research. Direct or indirect chymase effects in relation to the smooth muscle tonus of the cardiovascular and respiratory organs; penetration of vessels of the microcirculation; immunocompetent cells; cells of the fibroblastic programmed differentiation; the secretory epithelium; regulation of the cell division, growth, differentiation and apoptosis; modulation of cytokine, chemokine and growth factor activity; and remodeling of the extracellular matrix of the specific tissue microenvironment allow significantly expanding the informative value of the histologic study relating to a specific internal organ/tissue.

Therefore, further study of the role of MC proteases in the biology of the specific tissue microenvironment will significantly expand current views about the functional potentials of their organ-specific populations, giving unique opportunities to diagnose and evaluate the efficiency of the therapeutic protocols and to find breakthrough pharmacological solutions in the targeted therapy. Nowadays, there is a great deal of experimental data about the essential role of the reactive oxygen intermediates (ROI) in the regulation of MC degranulation on models in vitro and in vivo. ROI, which participate in intracellular signaling, stimulate certain anti-inflammatory MC mediators. There are several sources of ROI in MCs, including the electron transport chain of mitochondria, dehydrogenases in the matrix, p66shc protein in the intermembrane space and monoamine oxidases in the outer mitochondrial membrane, xanthine oxidase, cyclooxygenases, myeloperoxidase. NADPH-oxidases (NOX-enzymes) and lipoxygenases generate ROI in response to the hormone, growth factor, and cytokine effects. Most of these enzymes form superoxide ($O_2^{\bullet-}$), which later reacts to form peroxide (H_2O_2), giving a hydroxyl-radical (•OH).

High concentrations of ROI are known to impair DNA, RNA, lipids, and proteins; their low concentrations act as significant mediators participating in cell growth regulation, adhesion, differentiation, apoptosis, and other functions.[11,12] Results of numerous studies confirm that MC degranulation is caused by the chemical agents (salts of mercury and gold, substance 48/80, Ca^{2+} ionophores, etc.), as well as physiological stimuli (antigens, neurotrophic growth factor, P substance, and others), and is accompanied by the increased content of ROI in the cytosol.[13]

ROIs participate in the formation and further support activity of the intracellular complex regulating the level of Ca^{2+} in the cytoplasm.[13] The model of ovalbumin-induced food allergy demonstrated the participation of ROI formed on the basis of the PI3K-dependent path in the intensification of Ca^{2+} mobilization.[14] MC activation by the factors inducing phagocytosis may be also accompanied by ROI production.

Application of molecular hydrogen as a substance with antioxidant characteristics pathogenically appears to be an important mechanism for decreasing MC secretory activity, and, as a consequence, a novel option to reduce an inflammatory

background in the specific tissue microenvironment. In particular, it has been demonstrated that inhibition of ROI accumulation in the murine MCs prevented FcεRI-dependent degranulation and secretion of leukotrienes and cytokines.[13,15]

The protein of the mitochondria inner membrane UCP2 regulating ROI production was found to be able to inhibit the MC activation.[16] UCP2 is included in the family of uncoupling proteins; its title member, UCP1, results in the thermoregulatory uncoupling of oxidative phosphorylation in the mitochondria of brown adipose tissues. Recent studies have demonstrated that UCP2 catalyzes the transport of malate, oxaloacetate, and aspartate in exchange for phosphate through the inner mitochondrial membrane.[17] Export of C4 leukotrienes from mitochondria results in inhibition of oxidation of the Krebs cycle substrates; this significantly modifies the metabolism in mitochondria and, as a result, essentially decreases ROI production. Moreover, UCP2 not only neutralizes ROI but prevents its formation. As demonstrated, it may also have an impact on the dynamics of the increased concentration of calcium ions necessary for MC degranulation.[18]

In addition to inhibition of ROI production, uncouplers may modulate the Ca^{2+}-dependent signaling inhibiting Ca^{2+} accumulation in mitochondria, and decrease the excessive ROI generation by the mitochondria respiratory chain.[19-21]

The process of MC degranulation is known to be accompanied by the transfer of mitochondria towards the plasma membrane and their Drp1 mediated fragmentation.[22] Inhibition of Drp1 activity or its expression suppresses fragmentation of mitochondria and their transfer towards the plasma membrane, decreasing MC degranulation and TNF secretion.[22] As it is known, fragmentation of mitochondria in cells is able to be induced by the mitochondrial ROI effect;[23,24] this, in turn, may contribute to the regulation of MC activation.

ROI may cause reverse post-translational modifications of proteins participating in the intracellular signaling. For instance, some of the proteins are composed of functionally significant cysteine residues that may be exposed to oxidation. Thus, H_2O_2 can oxidize sulfhydryl groups (–SH) by forming sulfenic acid (–SOH); the latter may react with glutathione by forming the disulfide linkage (protein-SSG), with neighboring thiol groups with the formation the disulfide linkage (–SS–), or with amides with the formation of sulfanilamides. Sulfenic acid (–SOH) may be modified by exposure to further oxidation to sulfinic ($–SO_2H$) and then sulfonic ($Cys–SO_3H$) acids. Each of these modifications is able to change protein activity, thereby affecting its function in the signal transmission path.[25]

The increase of cytoplasmic concentration of calcium ions that are the key elements in mechanisms of degranulation appears to be one of the major events mediated by ROI impact and modification of the cellular redox status.[26,27] In particular, mitochondrial ROI may play an important role in Ca^{2+} mobilization.[28,29] It should be noted that modification of the Ca^{2+} intracellular concentration, in turn, impacts ROI generation.[29]

Phosphatases SHP-1, SHP-2, and PTEN participating in MC activation contain cysteine residues in their catalytic center and serve as one of the possible targets for ROI.[29,30] As shown, phosphatase inhibition under the H_2O_2 effect and/or with the help of pervanadate causes phosphorylation of tyrosine residues of β- and γ-subunits of FcεRI, calcium influx, and MC degranulation.[31]

All isoforms contain zinc finger domains and a high concentration of cysteine residues located in the regulatory region, as well as free sulfhydryl groups in the catalytic site. Moreover, redox-dependence of protein kinase C may be related to oxidative activation of phospholipase C[32,33] and mobilization of Ca^{2+}, and to phosphorylation of tyrosine residues by the redox-sensitive kinases of the Src family.[33] Therefore, ROI-dependent activation of protein kinase C is considered to be one of the mechanisms regulating MC activation.

In addition, linker for activation of T cells (LAT) (tansmembrane adapter protein associated with T cell activation) may also be the target for ROI; interaction with it enables induction of the FcεRI-dependent path of MC activation.

It is known that MARK-signaling with mitogen-activated protein kinases also depends on ROI.[34] As reported, transcriptional factors activated by the FcεRI-dependent path are redox-sensitive, including NF-κB and AP-1.[35] Thus, ROI may be of great significance in the regulation of the FcεRI-signaling cascade for MC degranulation. There is also a range of other potential targets sensitive to ROI impact. Research studies relating to the impact of ROI on various paths of MC activation, especially the FcεRI-dependent way, give striking perspectives for developing medical preparations based on antioxidants and inhibitors of ROI production and introducing them into clinical practice.

Molecular hydrogen, with its antioxidant characteristics being widely discussed nowadays, may serve as such an agent.[36-38] Molecular hydrogen may be applied for the effective treatment of pathological conditions associated with MCs, first of all, allergic conditions. Molecular hydrogen may be applied in various ways and acts as a blocker of the secretory MC activity, restricting their potential to the formation of the anti-inflammatory background in the specific tissue microenvironment; it may also be beneficial in the therapy of the diseases of various inflammatory and allergic geneses.

Therefore, MCs are closely involved in the effects of molecular hydrogen at the level of the specific tissue microenvironment, providing its anti-allergic, anti-inflammatory, anti-apoptotic, immuno-modulating, and vasotropic effects, as well as effects remodeling the extracellular matrix.

Competing Interests

The authors declare that they have no competing interests.

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