*Обзоры*

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# Thymic mast cells: From morphology to physiology

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***Abstract.*** This minireview summarizes some of our results on the structure, origin, and functions of thymic mast cells, as well as their role in stress-induced thymic atrophy. A comparison of the thymic mast cells with the connective tissue and mucosa mast cells is carried out. The morphological and cytochemical similarity of thymic and mucosa mast cells has been proven. The mechanisms of neuro-mast cell interaction, as well as the features of intercellular signaling are analyzed. Another aspect of the review is related to the assessment of thymic mast cell functions in stress-induced atrophy. It is hypothesized that the main function of these cells under stress is to regulate the T-cell emigration. The role of the thymus as an endocrine gland is also discussed. Probably, its endocrine function is mainly associated with the thymic mast cells which are regulated by the nervous system. Regardless of their localization and despite their hemopoietic origin, all mast cells are an important addition to the nervous system. They are a unique combination of both receptor and effector cells located in all organs and tissues. The mast cells supply the central nervous system with information about any local changes in tissue homeostasis and enhance local nervous influences. At the same time, mast cells are extremely important for neuro-immune communication as well as their mutual control on local defense reactions and mucosa conditions.

***Keywords:*** mast cells, thymus, neuroimmune interactions, mast cell-nerve contacts, stress, mediators.

## Introduction

The role of mast cells (MCs) in neuroimmune interactions has been the subject of intense research in recent years. By PubMed, about 1,700 publications on this topic are published in the world per year. Such interest in MCs is associated with their detection in almost all organs and tissues, including the brain (Grigorev, Korzhevskii 2021), their involvement in allergic reactions (Gushchin 2020), their ability to synthesize a broad spectrum of cytokines, chemokines, and growth factors, with potential autocrine, paracrine, local, and systemic effects (Da Silva et al. 2014; Mukai et al. 2018). These molecules play a critical role in the regulation of both immune reactions and a variety of brain and physiological functions (Forsythe 2019). The involvement of MCs in the regulation of the maturation and differentiation of immunocompetent cells and the immune response became an undoubted fact after the discovery of the intrathymic MC population (Bodey et al. 1987).

Interest in MCs physiology arose after the discovery of intercellular contacts between MCs and nerve terminals and experimental evidence of functional interactions between them (Pearce et al. 1989). Based on these results, it was suggested that MC are simultaneously cells of the nervous and immune systems, which provide bilateral translation and transformation of signals from peptides, cytokines, hormones, and other macromolecules as well as mutual regulation of functions (Forsythe 2019). This hypothesis is valid for all the described MC populations, their participation in neuroimmune interactions in connective tissue and mucosa. But the thymic MC population remains poorly studied.

Therefore, a brief analysis of the intrathymic mast cell population and mechanisms of its participation in neuroimmune interactions under stress will be carried out in this minireview.

## Morphology and physiology of thymic mast cells

MCs appear in the thymus already during embryogenesis. According to our data, they are detected in the mouse thymus from the 19$^{th}$ day of gestation. MCs are localized in the medulla and deep cortex during embryogenesis, and they are found mainly in the connective tissue of septa, trabeculae, and perivascular area in adult animals (Guselnikova et al. 2012). Thymic mast cells have a large, light, unsegmented nucleus (4–7 μm). The linear dimensions of rounded or oval thymic MCs are 8–12 μm in embryogenesis and they increase till 15–25 μm in adult mice. The cytoplasm of mature mast cell contains approximately 1,000 granules (Komi et al. 2020).

The composition of the granules of all MCs, including thymic ones, is rather similar. To characterize the functions of MCs, it turned out to be very convenient to divide the components of their granules into preformed ones, which provide MC immediate reactions and synthesize *de novo* in response to activation, which, in turn, are associated with long-term MC responses (Forsythe 2019). Preformed components of thymic MC granules are proteases (cathepsins C, G, B, L, D, E, caspases-1, -3, serine proteases tryptase and chymase, metalloproteinases), biogenic amines (histamine, serotonin, dopamine, polyamines), proteoglycans (chondroitin-4- and -6-sulfates, but not heparin) as well as numerous cytokines and growth factors (TNFα, IL-4, GM-CSF, FGFβ, VEGF, NGF). Upon activation, MCs synthesize a wide range of regulatory cytokines (IL-1, -3, -4, -5, -6, -9, -10, -12, -13, -14, -16, -18, -25, -37, TNFα), chemokines (IL-8, MCP-1, MIP-1α, -1β, RANTES, TARC (CCL-17), eotaxin), growth factors (TGFβ, SCF, GM-CSF, MCSF , FGFβ, PDGF, VEGF, NGF), as well as neuropeptides (CRF, VIP, SP) and eicosanoids (LT-B4, -C4, PAF, PGD2) (Da Silva et al. 2014; Forsythe 2019; Komi et al. 2020; Mukai et al. 2018).

In humans, MCs are traditionally classified based on the composition of produced serine proteases, tryptase and chymase. There are two main phenotypes of human MCs: MCs containing only tryptase (predominantly reside in the mucosa of the small intestine and alveolar septa) and MCs containing tryptase, chymase, and carboxypeptidases (generally found in the skin, submucosal layers of the small intestine, and tonsils). MCs containing only chymase are rare and found in synovial tissue. MCs of rodents are also classified in two main subsets: connective tissue MCs (CTMCs) located in the skin, peritoneal cavity, and intestinal submucosa and the mucosal MCs (MMCs) residing in mucosal layers (Komi et al. 2020; Krystel-Whittemore et al. 2016).

The nature of the thymic MCs is still unclear. There are variants of their origin from a bone marrow progenitor (common with blood basophils) (Da Silva et al. 2014; Forsythe 2019) or immature thymocytes (Scripture-Adams et al. 2014; Winandy, Brown 2007). Our results do not allow us to conclude the nature of MCs. But we found out that immature thymic MCs pass all stages of differentiation within one thymic lobule (Gusel'nikova, Polevshchikov 2013). The first MCs appear in the deep cortex and the medulla of the mouse thymus on the 19$^{th}$ day of gestation (Guselnikova et al. 2012). During granule maturation, they move to the subcapsular region as well as to the capsule and connective tissue trabeculae (Gusel'nikova, Polevshchikov 2013), where they come into contact with nerve terminals (Gusel'nikova et al. 2015). The intrathymic stages of MCs maturation indirectly testify in favor of the lymphoid origin of thymic MCs.

The existence of contacts between thymic MCs and nerve terminals gives an opportunity to estimate their role in neuroimmune interactions and a possible mediating function (Schiller et al. 2020). The key molecules in neuro-MC contacts are N-cadherin and CADM1 on both cells, as well as nestin-3 on the nerve terminals (Forsythe 2019). Intrathymic MCs have been linked to neuro(endocrine)-immune circuits involving MCs-peptidergic nerve contacts and changes in the number of MCs inside the organ have been reported in a series of experimental conditions related to the manipulation of the neuroendocrine axis (Ribatti, Crivellato 2016). According to the latest data, MCs interact with the nervous system through degranulation, de novo synthesis, extracellular vesicles, tunneling nanotubes, and extracellular traps (Mittal et al. 2019).

 https://www.doi.org/10.33910/2687-1270-2021-2-1-15-20

MCs express receptors for various neurotransmitters and neuropeptides and are modulated by them, allowing neural control of mast cell function. Conversely, MCs also directly trigger neuron activation through mediators, including cytokines, histamine, neurotransmitters, and neurotrophic factors, causing acute activation and long-lasting changes in excitability and neuronal phenotypes (Forsythe 2019; Xu et al. 2020).

Soluble mediators realize nerve-MC interaction but it is possible to move the whole granule to the neuron cytoplasm (Wilhelm et al. 2005). The Figure 1 shows key mechanisms and a shortlist of the signaling molecules that are exchanged between MCs and neurons. Importantly, MC can act as both a receptor cell and an effector cell. MC can generate an afferent signal to the CNS, as well as translate the efferent signal from the CNS into a set of secreted cytokines and growth factors. This contact is often referred to as a "neuro-MC functional unit" (Kleij, Bienenstock 2005). The role of MC as a receptor cell is effectively illustrated by the presence of serotonin and dopamine in its granules, which may be key mediators for afferent signals to the brain about any inflammatory disorders (Wernersson, Pejler 2014; Herr et al. 2017).

Perivascular localization of MCs in the thymus may be directly related to the thymic endocrine function (Hadden 1992). Until the beginning of the 1990s, the thymus was considered as one of the sources of somatostatin, CGRP, CRF, VIP, SP, oxytocin, and vasopressin (Savino et al. 1999). However, it is MCs that are the only thymic cells capable of secretion. The set of thymus hormones is very close to the set of MC secretory products (Fig. 1). There is a reason to believe that all thymic hormones are the results of neuro-MC interactions synthesized by either MCs or nerve terminals.

## Role of thymic MCs in stress

Stress-induced thymic atrophy is the classic and most obvious manifestation of thymic responses to the effects of the hypothalamic-pituitary-adrenal axis, and MCs are actively involved in this process (James et al. 2018). The number of degranulating thymic MCs increases in 4–8 hrs after an increase in corticosteroid levels in the blood (Guselnicova, Polevshchikov 2013). The triggering of degranulation may be associated with signals from adrenergic and noradrenergic nerve endings (Bellinger et al. 1992). The perivascular localization of thymic MCs and the set of MC mediators suggest their participation in the processes of cell extrathymic migration in response to a stress stimulus (Godinho-Silva et al. 2019). Direct morphological data confirm the exit

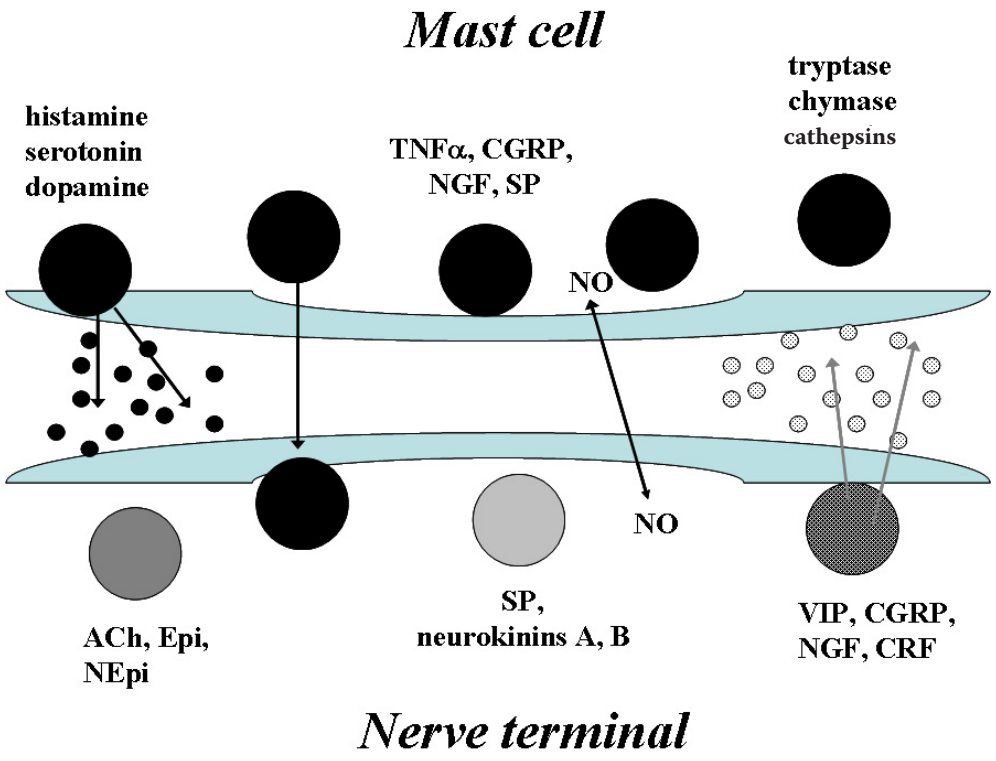


Fig. 1. The main mediators and ways of transferring molecules in neuro-mast cell contacts

of a significant part of living cells from the thymus throughout the lymphatic vessels in response to glucocorticoid hormone releasing (Kato, Schoefl 1989). This result was indirectly confirmed by the results of a cytometric assessment of thymocyte viability during stress-induced atrophy. Inside the thymic cortex, only 60–70% of immature DP thymocytes die by apoptosis under stress, while the rest of the cortical cells leave the organ (Starskaya et al. 2015). The role of the alive DP-thymocyte releasing during the stress reaction from the thymus to the bloodstream remains unclear.

The subsequent involvement of thymic MCs in the repopulation of cortical thymocytes after the stress reaction has also been studied in detail. It was found that the number of thymic MCs significantly increases within 4–7 days after stress-induced thymic involution. It is assumed that peptidergic nerve terminals play an important role in this process stimulating the differentiation and degranulation of new MCs (Bellinger et al. 1992; Forsythe 2019; Varricchi et al. 2019). MC growth factors and cytokines (especially SCF, VEGF, TGF-β, NGF, PDGF, GM-CSF, FGF-β, IL-2, -3, -4, -10) provide accelerated repopulation of cortical thymocytes after stress (Da Silva et al. 2014).

The influence of MC neuropeptides on the thymocytes maturation and differentiation occurs after a stress reaction as well as during the normal T-cell development and the immune response. VIP has an anti-inflammatory effect and inhibits the functions of Th1 and Th17 (Ran et al. 2015). CGRP has a similar anti-inflammatory effect, which provides the predominant formation of Th2 in the thymus and their production of IL-4 (Assas et al. 2014). It is CGRP, acting together with somatostatin and neuropeptide Y, that very effectively ensures the attachment of proliferating thymocytes to fibronectin of the thymic stroma and their proliferation (Springer et al. 2003). On the contrary, tachykinins have opposite proinflammatory effects on maturing thymocytes. SP and neurokinin A have a particularly significant effect at all the stages of intrathymic T-cell development and their activation in peripheral lymphoid organs. At the same time, both nerve terminals and MCs can be the source of all these neuropeptides, however, the local concentration of peptides created by MCs will be much higher (Forsythe 2019). It was found that both CD4 and CD8 T-cells express functional NK1R that, together with SP and hemokinin-1, co-localize within the immune synapse during cognate activation of T-cells. Simultaneous TCR and NK1R stimulation is necessary for the survival of activated T-cells, helper 1 (Th1) and Th17 bias (Morelli et al. 2020).

## From integrative physiology to personalized medicine

MCs are a good example of the relevance of an integrative approach in physiology. The history of MC study over 140 years has led to the description of many phenomena, but the real role of MCs is being revealed only now. Probably, MCs are a unique addition to the nervous system capacities. Their combination of receptor and effector capacities and their localization in all organs and tissues simultaneously supply the CNS with information about any local changes in tissue homeostasis and enhance the local regulatory effects of the nervous system. MCs are instrumental in the communication of the nervous and immune systems as well as in their mutual control of the barrier epithelium.

At present, the prospects for the application of knowledge about MC physiology in the clinical practice of many diseases are already being considered. Data on neuro-MC interactions are already used in the study and treatment of solid and hematologic cancers (Sammarco et al. 2019; Varricchi et al. 2017). New approaches to the therapy of heart diseases and atherosclerosis are also based on the information about neuro-MC interactions. The new data on MC functions are extremely important for solving the problems of Crohn's disease, intestinal and upper respiratory tract polyposis, atypical forms of bronchial asthma and rhinitis of unknown etiology (Da Silva et al. 2014; Varricchi et al. 2019). Within a few years the image of neuro-mast cell contacts may be found on the cover of new guidelines on integrative physiology.

## Conflict of interest

The authors declare no conflicts of interest.

## Author contributions

V. V. Guselnikova: writing, editing and approval of the final version of the article;

A. V. Polevshchikov: the concept and design of the article, writing, editing and approval of the final version of the article, responsibility for the integrity of all parts of the article.

## Abbreviations

***ACh*** — acetylcholine, ***CADM1*** — cell adhesion molecule-1, ***CGRP*** — calcitonin gene-related peptide, ***CNS*** — central nervous system, ***CRF*** — corticotropin-releasing factor, ***DP*** — double positive ($CD4^+CD8^+$)


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immature thymocytes, ***Epi*** — epinephrine (adrenaline), ***FGFβ*** — fibroblast growth factor-β, ***GM-CSF*** — granulocyte-macrophage colony-stimulating factor, ***IL*** — interleukin, ***LT*** — leukotriene, ***MC*** — mast cell, ***MCP-1*** — monocyte chemoattractant protein-1, ***MCSF*** — macrophage colony-stimulating factor, ***MIP-1*** — macrophage inflammatory protein-1, ***NEpi*** — norepinephrine (noradrenaline), ***NGF*** — nerve growth factor, ***PAF*** — platelet-activating factor, ***PDGF*** – platelet-derived growth factor, ***PG*** — prostaglandin, ***RANTES*** — chemokine CCL5 (Regulated on Activation, Normal T-cell Expressed and Secreted), ***SCF*** — stem cell factor, ***SP*** — substance P, ***TARC*** — chemokine CCL-17 (Thymus and Activation Regulation Chemokine), ***TGFβ*** — transforming growth factor-β, ***Th*** — T-helper, ***TNFα*** — tumor necrosis factor-α, ***VEGF*** — vascular endothelial growth factor, ***VIP*** — vasoactive intestinal peptide

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