Обзор / Review

Genetic, morphological and functional characteristics of human tryptase

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Abstract

Introduction. Tryptase, a mast cell-derived protease, plays a significant role in the diagnosis and pathogenesis of allergic and inflammatory diseases. The baseline serum tryptase level is used as a biomarker for the diagnosis of conditions associated with mast cell activation, which may be accompanied by severe allergic reactions and anaphylaxis. Studying tryptase isoforms, along with their structural and functional variations, aids in understanding genetic predisposition and the mechanisms underlying inflammatory diseases such as bronchial asthma and chronic inflammation.

Materials and Methods. A detailed investigation of the structure and function of various tryptase isoforms was conducted. Biochemical properties human tryptase isoforms were examined. The analysis included the study of the genes TPSAB1, TPSB2, TPSG1, and TPSD1, which encode different forms of tryptase, and the assessment of their activity. Tryptase secretion has been investigated, along with various factors influencing its release.

Results. Tryptase, a mast cell-derived enzyme, is represented by four major isoforms—α, β, γ, and δ. Among the secreted isoforms, α- and β-tryptases are the most prominent, β-tryptase exhibits the highest catalytic activity, whereas α-tryptase demonstrates limited enzymatic function. The tryptase genes are located on chromosome 16 and show a high degree of homology. Key genes TPSAB1 and TPSB2 encode active forms of tryptase, and an increased number of TPSAB1 copies leads to elevated baseline tryptase levels, heightening the risk of allergic reactions. Tryptase plays a role in inflammatory and allergic processes, including mast cell degranulation, affecting vascular permeability and leukocyte recruitment.

Conclusion. The collected data on the secretion and functions of tryptase produced by mast cells suggest that it can be regarded as a multifunctional mediator, acting through specific molecular and cellular mechanisms. Tryptase is critically involved in the pathogenesis of inflammatory processes and allergic responses across multiple organs and systems, including the respiratory tract and the skin. Understanding the biochemical characteristics and genetic features of tryptase isoforms opens new opportunities for the development of diagnostic and therapeutic approaches for high-impact allergic diseases.

Keywords: tryptase, mast cells, secretion, enzyme, marker

Conflict of interests:
The authors declare no conflict of interest.

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Генетические, морфологические и функциональные особенности триптазы человека

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Аннотация

Актуальность. Триптаза, фермент тучных клеток, играет значимую роль в диагностике и патогенезе аллергических и воспалительных заболеваний. Базовый уровень триптазы в сыворотке используется как индикатор для диагностики заболеваний, сопровождающихся активацией тучных клеток, которые могут сопровождаться тяжелыми аллергическими реакциями и анафилаксией. Изучение изоформ триптазы, их структурных и функциональных вариаций, помогает понять генетическую предрасположенность и механизмы воспалительных заболеваний, таких как бронхиальная астма и хроническое воспаление.

Материалы и методы. Проведено детальное исследование структуры и функций различных изоформ триптазы. Изучены биохимические особенности различных изоформ триптазы человека. Анализ включал изучение генов TPSAB1, TPSB2, TPSG1 и TPSD1, кодирующих разные формы триптазы, а также оценку их активности. Изучена секреция триптазы, а также факторы, влияющие на ее секрецию.

Результаты. Триптаза, фермент тучных клеток, представлена четырьмя основными изоформами — α, β, γ и δ. Среди них α- и β-триптазы являются секретируемыми, при этом β-триптаза обладает наибольшей каталитической активностью, тогда как α-триптаза имеет низкую ферментативную активность. Гетеротетрамеры α/β обладают уникальной активностью по сравнению с гомотетрамерами β, задействуя молекулы-мишени, неактивные для β-гомотетрамеров, что оказывает влияние на активность тучных клеток. Гены триптазы расположены на хромосоме 16 и имеют высокую степень гомологии. Важные гены TPSAB1 и TPSB2 кодируют активные формы, а увеличение числа копий TPSAB1 приводит к повышению базальных уровней триптазы, увеличивая риск развития аллергических реакций. Триптаза играет роль в воспалительных и аллергических процессах, в том числе в дегрануляции тучных клеток, влияя на сосудистую проницаемость и привлечение лейкоцитов.

Заключение. Собранные данные о секреции и функциях триптазы, продуцируемой тучными клетками, позволяют считать ее многофункциональным медиатором, воздействующим посредством специфических молекулярных и клеточных механизмов. Триптаза играет важную роль в патогенезе воспалительных процессов и аллергических реакций в разнообразных органах и системах, включая респираторную систему и кожу. Понимание биохимических характеристик и генетических особенностей изоформ триптазы открывает возможности для разработки новых методов диагностики и лечения аллергических заболеваний с высокой социальной значимостью.

Ключевые слова: триптаза, тучные клетки, секреция, фермент, маркер

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INTRODUCTION

Tryptases belong to the family of serine proteases of mast cells. In healthy individuals, baseline serum tryptase levels are stable. Baseline serum tryptase concentration is an important diagnostic marker, as its elevation may indicate the presence of diseases associated with mast cell dysfunction and increase the risk of severe allergic reactions. Studies show that even tryptase levels within the normal range may be associated with an increased likelihood of allergic conditions. In acute cases, such as anaphylaxis, tryptase levels rise significantly, reaching peak values. Therefore, it is extremely important to perform sequential peak and baseline measurements of serum tryptase in acute situations, especially during the assessment of anaphylaxis [1].

Tryptases can have different genetic variants, perform different functions, and participate in the development of diseases in different ways. Future research on tryptase requires the improvement of laboratory methods that will allow for a more accurate assessment of its biological functions, participation in pathological processes, and clinical significance.

ISOPHORMS AND STRUCTURE OF HUMAN TRYPTASE

Human tryptases consist of four isoforms, including secreted α- and β-tryptases encoded by the TPSAB1 and/or TPSB2 genes, δ-tryptase encoded by the TPSD1 gene, and membrane-bound γ-tryptase encoded by the TPSG1 gene (Table 1).

Human δ-tryptase has a C-terminal truncation and lacks important substrate-binding residues. Thus, human δ-tryptase is considered a protein with no biological activity.

Tryptase, a mast cell enzyme, is represented by four main isoforms: α, β, γ, and δ. Among them, α- and β-tryptase are secreted, with β-tryptase having the highest catalytic activity, while α-tryptase has low enzymatic activity. In most serine proteases, including β-tryptase, a glycine residue is found at position 216, which is necessary for the proper functioning of the active site. α-tryptase has virtually no catalytic activity, partly due to the replacement of aspartic acid at this position. In α-tryptase, this position is occupied by aspartic acid, which reduces its catalytic ability. In addition, the amino acid substitutions p.G216D and

Table 1. **Biochemical characteristics and enzyme formats of various human tryptase isoforms (author's table)**
Таблица 1. **Биохимические особенности и форматы ферментов различных изоформ триптазы человека (таблица автора)**

Tryptase isoforms	Gene	Activity	Protein-enzyme format
α-tryptase	*TPSAB1*	inactive	Inactive promo number
			Inactive homotetramer
			Active heterotetramer α/β
βI-tryptase	*TPSAB1* или *TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
βII-tryptase	*TPSAB1 или TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
βIII-tryptase	*TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
γ-tryptase	*TPSG1*	triptych	Active; with membrane mounting
δ-tryptase	*TPSD1*	inactive	Truncated; probably monomeric

p.D189K cause changes in segment 214–220, which leads to partial filling of the S1 pocket, the active site region necessary for substrate binding. These structural features prevent substrate access to the active site, which explains the low activity of α-tryptase [2].

β-tryptase has three main isoforms: βI-tryptase, βII-tryptase, and βIII-tryptase. These three isoforms of β-tryptase have more than 95% homology and similar catalytic activity. Among β-tryptases, approximately 23% of people of European descent carry a nonsense variant of βIII-tryptase, resulting from the insertion of a single base pair, which leads to a reading frame shift and a premature stop codon (βIII FS). In the case of expression, the resulting protein will have a large truncation at the C-terminus and will not have an active site [3].

The ratio of active β-tryptase alleles to inactive alleles (including α-tryptase and βIII FS-tryptase) determines the activity of tryptase in mast cell granules. [2].

The genetic basis of frequent and recurrent loss-of-function variants that led to the formation of α-tryptase, truncated βIII FS-tryptase, and δ-tryptase during human evolution, as well as how active and inactive tryptase alleles affect human disease and host defense, is not fully understood at present [2]. α-tryptase does not have a functional active site and does not possess any catalytic activity of its own. However, pairs of α-tryptase with β-tryptase form active α/β-tryptase heterotetramers.

Tryptase is a tetrameric trypsin-like protease with a strictly controlled assembly mechanism. Full-length tryptases contain a propeptide at their N-terminus (protryptase zymogen); cleavage of the propeptide by cathepsins in mast cell granules appears to be necessary for tryptase activation [4]. Mature tryptase monomers (with removed propeptide sequences) form tetramers in the secretory granules of mast cells, which have an acidic pH environment and abundant heparan glycosaminoglycans. Since tryptase monomers have negligible catalytic activity under physiological conditions, tetrameric tryptases are the predominant enzymatically active protease in mast cell granules. Tetramer formation is facilitated under low pH conditions and by binding to heparin glycosaminoglycan. Structural analysis of mature tryptases reveals a toroidal, doughnut-like tetramer comprising protomers that interact with their neighbors at both large and small interfaces. In this tetrameric form, each tryptase protomer serves as a cofactor to stabilize the neighboring tryptase in a catalytically active conformation [5]. Although α-tryptase does not possess any intrinsic catalytic activity, the α-tryptase promoter can stabilize and activate the adjacent β-tryptase in the α/β-tryptase heterotetrameric format. Interestingly, α/β-tryptase heterotetramers are reported to have altered catalytic activity toward certain substrates, such as EMR2 and PAR2 cell surface receptors, compared to β-tryptase homotetramers. In addition, tryptase may have unique effects when interacting with neighboring β-tryptases to regulate the overall catalytic conformations of β-tryptase and/or substrate accessibility [6]. Interactions between promoters within tryptases are stabilized by heparin, which is negatively charged and binds to a large positively charged surface encompassing both small interface surfaces. Since there are no known endogenous inhibitors of tetrameric tryptase, low concentrations of extracellular heparin in the peripheral circulation may serve as a natural mechanism of inactivation. The concentration gradient of heparin from high concentrations inside cells to low concentrations in the extracellular space promotes the gradual dissolution of active tryptase tetramers, i.e., their conversion into inactive forms [7]. A distinctive feature of α-tryptase compared to β-tryptase is its ability to activate independently of heparin, as well as at lower pH values in insufficiently vascularized areas, which is particularly important for tissues with chronic inflammation or in the pathogenesis of bronchial asthma [8].

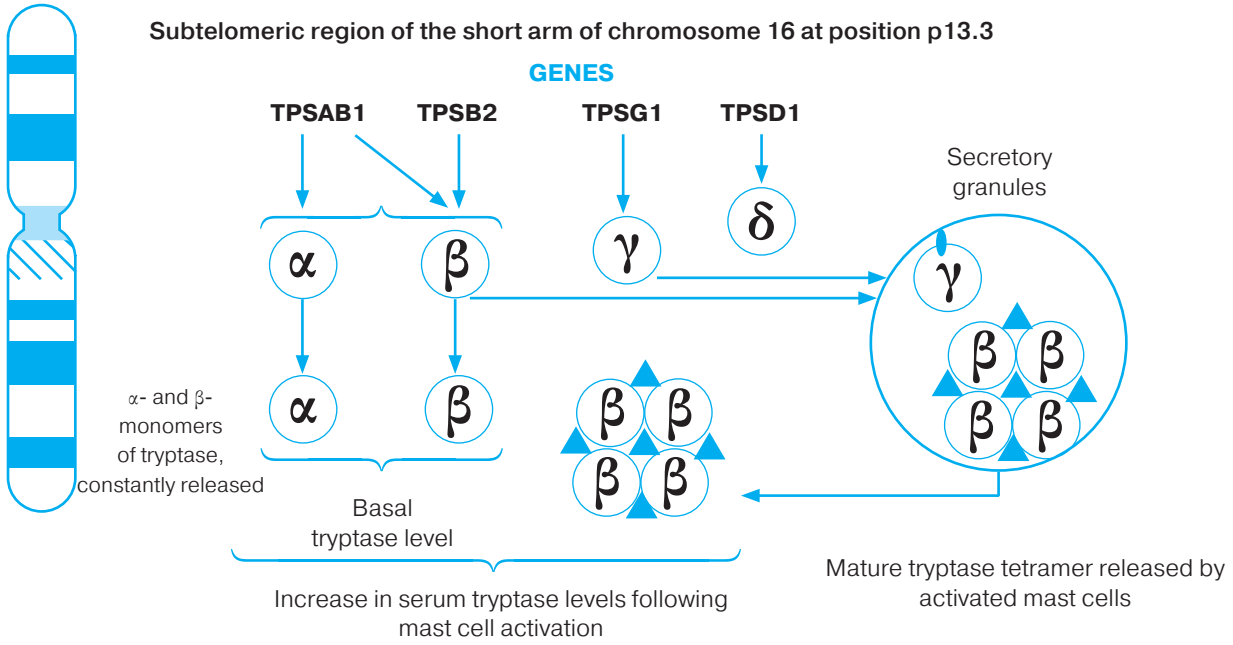

Fig. 1. **Production and intracellular transport of human α-, β-, and γ-tryptases in mast cells (illustration by the author)**
Рис. 1. **Производство и внутриклеточный перенос человеческих α-, β- и γ-триптаз в тучных клетках (иллюстрация автора)**

HUMAN TRYPTASE GENETICS

The human tryptase locus is located in the subtelomeric region of the short arm of chromosome 16 at position p13.3. All four known genes encoding tryptase (TPSG1, TPSB2, TPSAB1, and TPSD1) are located in this locus [9, 10]. As it is typical for subtelomeric regions, the tryptase locus contains large segments of homologous repetitive sequences that facilitate gene conversion and replication. Human tryptases are believed to have evolved in this region through tandem duplication, which may help explain the high degree of homology between human tryptase isoforms. The two most studied loci are TPSB2 and TPSAB1, which encode biologically important secreted tryptase isoforms consisting of α- and β-tryptase. While TPSAB1 can encode either α or β-tryptase, TPSB2 encodes only β-tryptase (βI, βII, or βIII-tryptase) [2].

Elevated basal serum tryptase levels, consisting of secreted zimogen α-protryptase and β-protryptase, consisting of secreted zimogen α-protryptase and β-protryptase, are inherited in an autosomal dominant manner in humans. This increase in basal serum tryptase levels is the result of TPSAB1 duplications, which encode α-tryptase, a genetic trait known as hereditary α-tryptasemia. However, the increase in basal serum tryptase levels far exceeds what would be expected based solely on the excess number of copies. It has been suggested that the increase in basal serum tryptase levels is mainly the result of overexpression of tryptase on the replication-competent allele, but this has not been proven. Indeed, individuals carrying up to four additional copies of TPSAB1 have been reported to date, and it has been shown that basal serum tryptase levels follow a dose-response effect, with each additional replication of TPSAB1 increasing basal serum tryptase levels by approximately 9.5 ng/ml [11, 12].

There have also been reports of copy number loss in the tryptase locus, but it is unclear whether these structural variants exist in the TPSAB1 or TPSB2 locus. An increase in the number of copies encoding β-tryptase has also been reported, but where it is present, it has not been shown to correlate with elevated basal serum tryptase levels, and it is currently unknown whether these replicates exist in TPSAB1 or TPSB2. Ultimately, the location of these duplications or deletions may be arbitrary, given that any locus can encode any of the known active versions of β-tryptase (βI- III) [13].

The tryptase gene undergoes various mutations, leading to insufficient transcription, zymogen activation, catalytic site conformation, and even gene deletion as a whole [14]. Tryptase gene polymorphisms are numerous, and the number of functional

tryptase alleles that a person can carry varies from two to four [15]. The number and type of functional alleles carried by an individual can alter baseline systemic tryptase levels. Genetics affects baseline serum tryptase levels [16, 17].

TRYPTASE SECRETION

Tryptase is produced in the form of α-, β-, γ-, and δ-subunits in the endoplasmic reticulum. While the γ subunit remains bound to the membrane of secretory granules, α and β monomers are continuously released as enzymatically inactive propeptides into the bloodstream without a specific stimulus and constitute the tryptase normally present in serum [18]. In addition, the α- and β-subunits undergo sequential proteolytic cleavage (activation). Initially, various forms of tryptase are expressed as pre-tryptases, then they rapidly convert to pro-tryptases to become mature (mainly β) tetrameric tryptase, which is active, stabilized by heparin, and stored in secretory granules, awaiting appropriate stimuli to induce degranulation. Cathepsins B, L, or C are also required for conversion to mature tryptase. In addition, β-tryptase remains stable after proteolysis with the help of heparin. Heparanase deficiency leads to an increase in tryptase stores in mast cells due to the formation of larger heparin chains [4, 18]. Conversely, defects in heparin synthesis contribute to a decrease in the accumulation of the active form of tryptase [4].

Genetic factors (number and type of functional alleles) or activation of mast cells for other reasons also affect tryptase content. Thus, mast cell activation and tryptase levels are determined by genetic, exogenous, and cellular factors [19].

Mature heterotetrameric β-tryptase has high biological activity against tissues, cells, and molecules and consists of four non-covalently bound subunits, each monomer containing an active enzyme site. α-tryptase also forms mature homotetrameric complexes, but in smaller quantities. Both tetrameric α- and β-tryptase are released by activated (degranulating) mast cells, and a temporary increase in serum tryptase levels reflects this process. For example, in IgE-dependent allergic reactions, an increase in serum tryptase concentration can be measured as early as 15 minutes after activation, with a peak in 2 hours [3, 20].

When mast cells are activated, the release of contents into the extracellular space occurs within minutes. Regardless of the cause, as a result of mast cell degranulation, a rapid increase in histamine levels in peripheral blood is observed within 5 minutes after the onset of the first symptoms, while the detection of tryptase is delayed by 15 or 20 minutes due to the bulky heparin shell. This difference cannot be overlooked in human medicine because it explains why histamine and tryptase cannot be optimally measured in the same blood sample. Indeed, while histamine can peak 5–10 minutes after the onset of anaphylaxis symptoms, tryptase measurements at such early time points often yield values below 12 μg/L, which are mistakenly considered “normal” or even “negative” [21, 22].

Baseline serum tryptase levels are the result of continuous release of immature α- and β-tryptase monomers; mature tetrameric β-tryptase is stored in specialized secretory granules, where it is stabilized by the interaction of proteoglycans with heparin [19, 22]. Mature β-tryptase is not released continuously, but as a result of mast cell activation. Thus, serum tryptase levels measured after mast cell degranulation include both immature and mature forms of α- and β-tryptase. γ-tryptase is a membrane-bound monomer [23].

From a functional point of view, mature tryptase performs sequential actions (Fig. 2) After degranula-

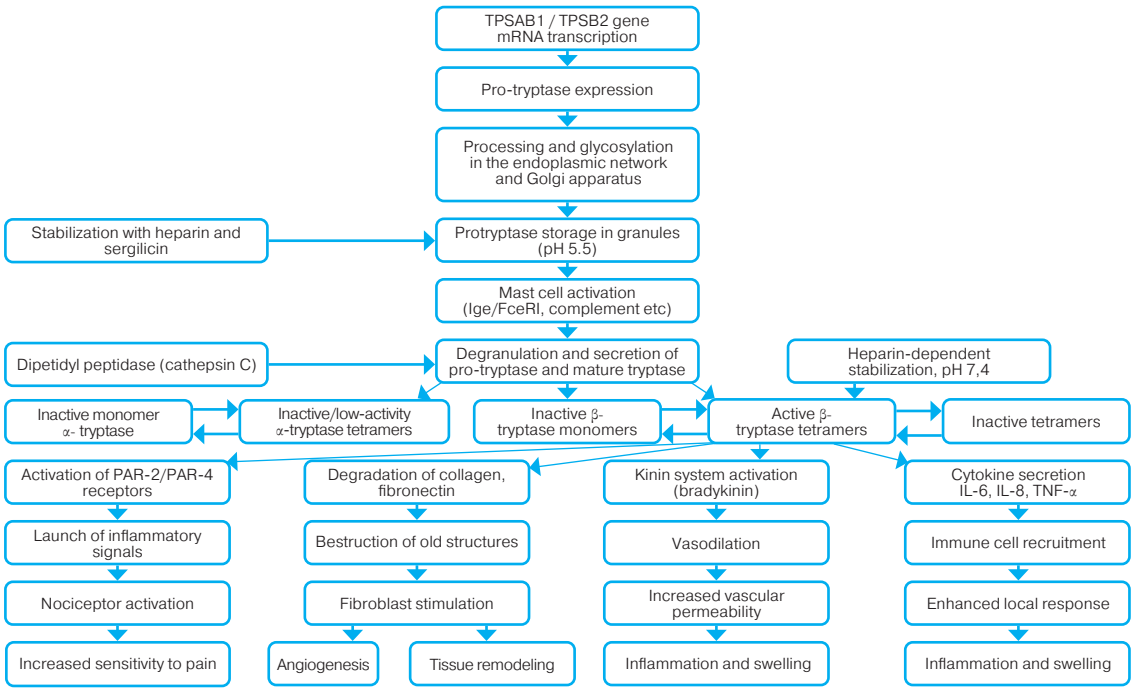

Fig. 2. **The biochemical mechanism of action of tryptase (illustration by the author)**
Рис. 2. **Биохимический механизм действия триптазы (иллюстрация автора)**

tion of mast cells, mature tryptase acts as a vasoactive agent in the early stages, increasing vascular permeability and promoting edema, as a pro-inflammatory mediator activating various types of immune cells, including neutrophils and eosinophils, as a chemotactic factor attracting leukocytes and enhancing the inflammatory response, and as a priming agent increasing tissue sensitivity to affect other inflammatory mediators, including histamine and prostaglandins [24, 25]. Under the action of degranulated tryptase, the formation of bradykinins from kinins contributes to increased vascular permeability, while the extracellular matrix is destroyed, which promotes cell migration. Tryptase induces the recruitment and activation of leukocytes with a specific chemotactic effect on neutrophils and eosinophils, which participate in the late phase of allergic inflammation. Tryptase promotes interaction between mast cells and the mononuclear phagocytic system. In the late stages of the inflammatory process, tryptase activates a regenerative function, promoting tissue repair [26]. It stimulates the proliferation and activation of fibroblasts, which promotes the synthesis of extracellular matrix components such as collagen and fibronectin. Tryptase also promotes angiogenesis to activate endothelial cells and induce the formation of new capillaries. These processes are an important part of tissue remodeling and ensure the restoration of tissue structure and function after inflammatory damage. More recent data indicate the role of tryptase in the onset of pain, such as postoperative pain due to the activation of nociceptive receptors activated by protease [27, 28].

Research has traditionally focused almost exclusively on tryptase as an extracellular mediator, but the latest data indicate the role of tryptase in the homeostasis of nuclear histones in mast cells and in the disorganization of histone frameworks during cell death [29].

Human tryptase is considered to be almost specific to mast cells, which can contain large amounts, up to 35 pg per cell. Basophils also contain and release

tryptase, but they do not contribute significantly to tryptase levels, according to reports that showed their tryptase content was 100 times lower than that of mast cells [30]. Tryptase load varies greatly both in mast cells, depending on their microenvironment, and in basophils, ranging from 1 to 100 in different human donors. Human basophils are capable of secreting tryptase upon IgE-mediated activation [31]. In accordance with tryptase synthesis and exocytosis, as described above, it is important to bear in mind that the level of circulating tryptase measured at any given time in a given individual is the combined result of the activation of the total number of mast cells ("mast cell load"), their genetically determined level of α- and β-tryptase production, and their status leading to the release of mature tryptase.

CONCLUSION

The collected data on the secretion and functions of tryptase produced by mast cells allow us to consider it a multifunctional mediator that acts through specific molecular and cellular mechanisms. Tryptase attracts particular attention due to its involvement in the pathogenesis of inflammatory processes and allergic reactions in various organs and systems, including the respiratory system and skin. In addition, tryptase plays a key role in the regulation of tissue remodeling and healing processes, ensuring homeostasis and tissue repair after damage. Studying the biological effects of tryptase helps deepen our understanding of the functional capabilities of mast cells, opening up new avenues for the diagnosis and treatment of diseases of high social significance.

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AUTHORS CONTRIBUTIONS TO THE WORK

Natalia E. Tarasova — conceptualization, methodology, data curation, writing — review & editing — preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision — including pre- or post-publication stages.

Alexander A. Lebedenko — supervision, project administration.

Olga E. Semernik — conceptualization, validation, project administration.

Natalya V. Dobaeva — supervision, project administration.

Viktoriya O. Skosar — investigation, writing.

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Скосарь В. О. — подготовка текста.

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Кривохлябов И. П. — подготовка, работа с данными.

Шкильнюк С. П. — визуализация.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association “Ethical Principles of Conducting Scientific Medical Research with human Participation” as amended in 2000 and the “Rules of Clinical Practice in the Russian Federation” approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the Interdisciplinary Local Ethics Committee of the Pacific State Medical University of the Ministry of Health of the Russian Federation.

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