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Tryptase in all its states: from allergy to mastocytosis

La tryptase dans tous ses états: de l'allergie aux mastocytoses

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Abstract

In normal humans, tryptase, a serine protease with multiple biological activities, is synthesized nearly exclusively by mast cells (MCs). While immature forms of tryptase (α- and β- monomers) are constantly released by MCs and can be measured in the serum of normal individuals as the basal serum tryptase (BST) level, mature tryptases (mostly tetramers of β-tryptase) are retained in the secretory granules of MCs and are released only upon cell activation. Such MC activation occurs during IgE-mediated allergic reactions and increased levels of tryptase, which can be measured immediately after degranulation, are involved in the pathophysiology of immediate hypersensitivity. Interestingly, recent studies have reported that around 5% of the general population present with a genetic trait called hereditary alpha-tryptasemia (HαT). In HαT+ patients, the BST level is increased. Mastocytosis are a group of hematologic neoplasms characterized by an accumulation of atypical MCs in one or several organs/tissues, often accompanied by MC activation. Increased BST level is a hallmark of systemic mastocytosis (SM) and a diagnostic, prognostic and follow-up marker. Interestingly, the incidence of the HαT trait has been found increased in SM patients (up to 18% of the cases) and HαT+ SM patients are more prone to develop anaphylaxis, making HαT a disease penetrance and phenotype modifier.

Résumé

Chez le sujet normal, la tryptase, une sérine protéase aux multiples activités biologiques, est synthétisée presque exclusivement par les mastocytes (MCs). Alors que les formes immatures de tryptase (monomères α- et β-) sont constamment libérées par les MCs et peuvent être mesurées dans le sérum des sujets normaux en tant que taux basal de tryptase, les tryptases matures (principalement des tétramères de β-tryptase) sont retenues dans les granules de sécrétion des MC et ne sont libérées que lors de l'activation cellulaire. Une telle activation des MCs se produit au cours des réactions allergiques IgE-dépendantes et des niveaux accrus de tryptase, qui peuvent être mesurés immédiatement après la dégranulation, sont impliqués dans la physiopathologie de l'hypersensibilité immédiate. Fait intéressant, des études récentes ont rapporté qu'environ 5% de la population générale présente un trait génétique appelé alpha-tryptasémie héréditaire (HαT). Chez les patients HαT+, le taux basal de tryptase sérique est augmenté. Les mastocytoses sont un groupe d'hémopathies malignes caractérisées par une accumulation de MCs atypiques dans un ou plusieurs organes/tissus, souvent accompagnée d'une activation de ces cellules. L'augmentation du taux basal de tryptase sérique est une caractéristique des mastocytoses systémiques (MS) et un marqueur du diagnostic, du pronostic et du suivi de ces maladies. Fait intéressant, l'incidence du trait HαT est augmentée chez les patients avec MS (jusqu'à 18% des cas) et les patients MS HαT+ sont plus enclins à développer des réactions anaphylactiques, faisant de l'HαT un modulateur de la pénétrance et du phénotype de la maladie.

1. Introduction

Mast cells (MCs) are tissue fixed immune cells derived from hematopoietic stem cells in the bone marrow (BM) [1]. In humans, at least two subtypes of MCs exist: 1) in serosal tissues, such as the skin, MC_{TC} express three different proteases, namely Tryptase, a tetrameric neutral serine protease, Chymase and carboxypeptidase A and 2) in mucosal tissues, such as the lung, MC_T express only Tryptase [1]. In fact, all types of human MCs express abundantly tryptase. In addition, in normal conditions, tryptase is nearly fully specific for MCs, since apart MCs, only peripheral blood basophils express very low amounts of the enzyme [1]. Indeed, human tryptase amount per cell is ~11 pg in lung MCs and ~ 35 pg in skin MCs, and can reach up to 25% of the total cellular protein content in MCs, while the tryptase amount in normal blood basophils is only ~0.05 pg/cell [1]. In resting tissue MCs, tryptase is present in two different forms - monomeric pro-α- and pro-β-tryptase and mature tetrameric α- and β-tryptase [2]. Figure 1 depicts the different forms of tryptase found in human MCs. Monomeric pro-α- and pro-β-tryptase, which are spontaneously and constitutively secreted into tissues and diffuse into the systemic circulation, are the predominant forms of tryptase in the serum in the absence of systemic MC activation, constituting thus the basal serum tryptase (BST) level [2]. BST level in normal individuals is usually ≤ 11.4 μg /L [2]. However, around 5% of the general population present with a genetic trait called hereditary alpha-tryptasemia (HαT) and may have higher BST level [3].

Mature β-tryptase heterotetramers have high biological activities on tissues, cells and molecules (as depicted in Table 1), and consist of four non-covalently bound subunits, each monomer containing an active enzyme site. Alpha-tryptase also forms mature homotetramers but at lower amounts. Both tetrameric α- and β-tryptase are released by activated (degranulating) MCs and a transient increase in serum tryptase level reflects such process [4].

For instance, in IgE-dependent allergic reactions, increased concentrations of serum tryptase can be measured as soon as 15 min. after activation, peaking after 2 hours [5].

By contrast to the normal situation, an aberrant expression of tryptase by neoplastic cells can be found in myeloid blast cells and/or neoplastic immature basophils during acute and chronic myeloid leukemias, other myeloproliferative syndromes, myelodysplastic syndromes and in all the conditions accompanied by an increase in tissue MCs, such as, but not limited to mastocytosis or chronic eosinophilic leukemia [4],

2. Tryptase in mast cell disorders with special focus on mastocytosis

The global classification of human MC disorders distinguishes four different conditions: reactive MC hyperplasia, MC activation syndromes (MCAS), myelomastocytic overlap disorders and mastocytosis [6]. Mastocytosis is a term used to define a group of hematopoietic neoplasms characterized by a pathological accumulation of clonal MCs in the skin (cutaneous mastocytosis: CM) or in one or more extra-cutaneous organ systems (gastrointestinal tract, BM, liver, spleen, lymph nodes, others), namely systemic mastocytosis (SM) [7]. Mastocytosis can occur at any age, presents variable mediator-related symptoms and have heterogeneous clinical courses, ranging from mild, sometimes self-limiting forms to severe, advanced forms with a shorter overall survival [7]. According to the World Health Organization (WHO) classification, mastocytosis are divided into CM, SM, and mast cell sarcoma (MCS). SM is classified into indolent SM (ISM), smouldering (slowly progressive) SM (SSM), SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL) [8]. Patients with CM and ISM have a good prognosis with a normal or near normal life-expectancy, while patients with SSM may or may not progress to a more advanced form of the disease [7]. By contrast, patients with advanced SM, e.g. SM-

AHN, ASM, MCL and MCS have an unfavourable prognosis often with rapid disease progression [7].

The diagnostic of SM, according to the WHO, is based on one major and four minor diagnostic criteria [8]. The major SM criterion is the multi-focal clustering of MCs (≥15 cells per aggregate) in the BM or in another extra-cutaneous organ [8]. Minor criteria relate to an abnormal morphology of MCs, an aberrant expression of CD2 and/or CD25 on MCs, an activating mutation in codon 816 of *KIT*, and an elevated BST level exceeding 20 μg/L [8]. When at least one major and one minor or at least three minor criteria are fulfilled, the diagnosis SM can be established [8].

An elevated BST level is thus an important diagnostic parameter and clinical biomarker in MC disorders [8]. As seen above, an elevated persistent BST level >20 μg/L is a minor SM criterion [8]. However, this criterion is only valid in the absence of an AHN because the AHN component of the disease may contribute to the increased BST level [7]. It is also worth noting that an elevated BST level (even if very high) is not a marker of MC activation (MCA). Rather severe MCA and MCA syndrome (MCAS) are more frequently seen in those SM patients who have a lower BST level and only the acute event-related increase in tryptase above the individual´s baseline (following the + 20% + 2 μg/L equation) qualifies as a biomarker of systemic MCA and thus as a criterion of MCAS [9]. In SM, very high BST levels are associated with less favourable prognosis and represent a B-finding (>200 μg/L + >30% infiltration of the BM biopsy by MCs) [7].

3. Hereditary Alpha-Tryptasemia (HαT)

Hereditary alpha-tryptasemia (HαT) is a common genetic trait (4–6% of all individuals in Western populations) caused by increased copy number of the *TPSAB1* gene encoding α-tryptase, which induces elevated BST level [3]. Among individuals with HαT, a gene dosage

effect is observed, increasing *TPSAB1* copy numbers being associated with higher BST levels [3]. The possibility that HαT might modify clonal MC disease was first suggested by a study where the investigators examined the prevalence of HαT in clonal MC diseases, and reported that 12.2% of individuals with SM followed at the U.S. National Institutes of Health (NIH) had concomitant HαT, a rate over twice that of the general population [10]. A subsequent study performed within the European Competence Network on Mastocytosis (ECNM) centers on 241 SM patients validated this association with an even greater prevalence observed in these patients (17.2% found to have HαT) [11].

Interestingly, in these two studies, the authors reported not only a higher frequency of HαT carriers in mastocytosis patients but also more severe mediator-related symptoms in HαT+ SM than in patients without HαT [10,11]. Of note, the authors also reported a strong association between HαT and Hymenoptera venom hypersensitivity reactions (30%) as well as severe cardiovascular mediator-related symptoms (anaphylaxis and hypotension; 35.5%) [10,11]. Based on these observations, HαT is considered a new biomarker to identify patients at risk of developing severe anaphylaxis in mastocytosis. Moreover, the determination of *TPSAB1* alpha extra copies by droplet digital PCR (ddPCR) is currently discussed as an important biomarker to be included in risk assessment models and in diagnostic algorithms in patients with mastocytosis.

4. Conclusions and key-messages

Tryptase is a MC-specific serine-protease with various biological activities, which is constitutively secreted in an immature form by resting MC at low levels, but rapidly released under the form of mature β-tryptase following MC activation (MCA). Serial determination of serum tryptase levels showing transient increase of the circulating enzyme may allow detecting MCA. The various biological activities of mature β-tryptase on cells, tissues and

molecules, are deleterious and account for the pathophysiology of early and late phase events following IgE-dependent reactions. The basal serum tryptase (BST) level in the general population is below 11.4 mg/L, excepted for ~ 5% of the humans who harbor the genetic trait called hereditary alpha-tryptasemia (so-called HαT+ individuals).

In SM, a rare neoplastic condition characterized by abnormal accumulation of MCs in several internal organs including the BM, BST level is a minor diagnostic criterion and has a prognostic significance. Of note, serial measurements of BST level in SM allow also the follow-up of the disease and the monitoring of therapeutic effects. Finally, the incidence of the genetic trait HαT appears to be increased (~ 18%) in SM patients and this genetic trait seems to be a strong disease modifier, since HαT+ SM patients are more prone to develop recurrent anaphylaxis. Thus, in the future, in light of HαT-mediated increases in BST level and of the disease modifier property of the genetic trait, the search for HαT in all SM patients and an adjustment of the diagnostic BST threshold levels (determining SM criteria) in HαT+ SM patients should probably be considered.

Table 1: The various biological activities of human tryptase on tissues, cells and molecules.

TARGETS	BIOLOGICAL ACTIVITIES
Tissues	• Degrades extracellular matrix
Cells	• Fibroblasts: - Increases proliferation - Increases collagen synthesis and IL-6 production - Increases chemotaxis - Increases differentiation to myofibroblasts - Increases contractility - decreases apoptosis
	• Promotes neutrophil recruitment
	• Activates epithelial cells
	• Promotes angiogenesis
Molecules	• Clives and inactivates CCL5 and -11
	• Increases IL-33 activity by proteolytic cleavage
	• Indirectly activates collagenase
	• Activates pro-matrix metallo-proteases (MMP) -3 and -13
	• Activates TGFβ1

Legend to the Figure

Figure 1. Synthesis of tryptases by human mast cells.

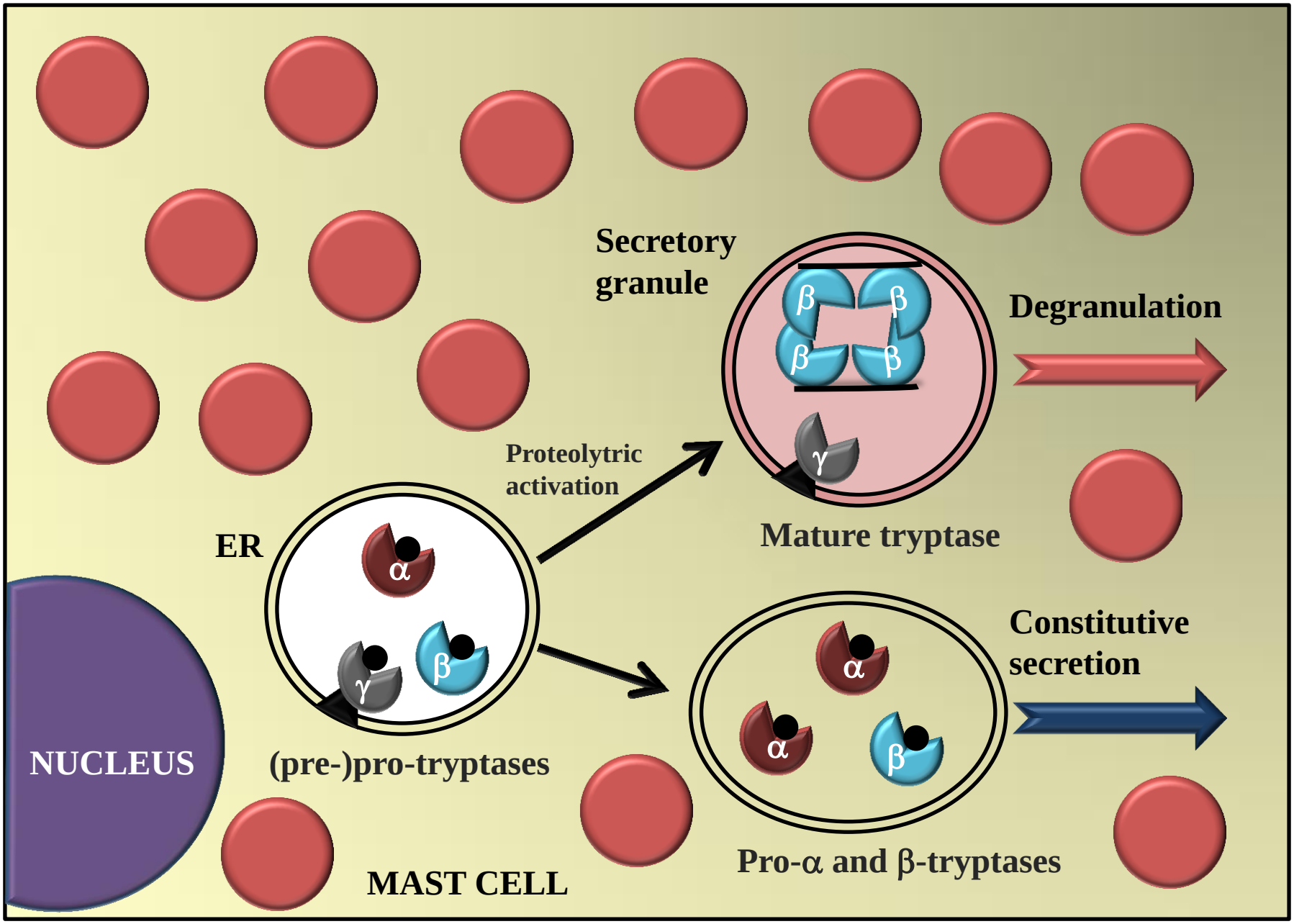
Tryptase is produced in the form of alpha, beta, gamma and epsilon subunits in the endoplasmic reticulum (ER). While the gamma subunit remains bound to the membrane of the secretory granules, alpha and beta monomers are continuously released as enzymatically inactive pro-peptides into the circulation without specific stimulus and constitute the tryptase usually present in serum (down). Furthermore, the alpha and beta subunits undergo sequential proteolytic cleavage (activation) to become a mature (essentially β) tetrameric tryptase, active, stabilized by heparin and stored in secretory granules (top) while awaiting the appropriate stimuli to induce degranulation. ER: endoplasmic reticulum.

References

1. Valent P, Akin C, Hartmann K, et al. . Mast cells as a unique hematopoietic lineage and cell system: From Paul Ehrlich's visions to precision medicine concepts. Theranostics 2020;10:10743-10768.
2. Sprinzl B, Greiner G, Uyanik G, et al. . Genetic Regulation of Tryptase Production and Clinical Impact: Hereditary Alpha Tryptasemia, Mastocytosis and Beyond. Int J Mol Sci 2021;22.
3. Lyons JJ, Yu X, Hughes JD, et al. . Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016;48:1564-1569.
4. Valent P, Sperr WR, Sotlar K, et al. . The serum tryptase test: an emerging robust biomarker in clinical hematology. Expert Rev Hematol 2014;7:683-690.
5. Vitte J, Sabato V, Tacquard C, et al. . Use and Interpretation of Acute and Baseline Tryptase in Perioperative Hypersensitivity and Anaphylaxis. J Allergy Clin Immunol Pract 2021;9:2994-3005.
6. Niedoszytko M, Valent P, Nedoszytko B. Mastocytosis, MCAS, and Related Disorders-Diagnosis, Classification, and Therapy. Int J Mol Sci 2021;22.
7. Valent P, Akin C, Hartmann K, et al. . Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future. Cancer Res 2017;77:1261-1270.
8. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017;129:1420-1427.
9. Valent P, Bonadonna P, Hartmann K, et al. . Why the 20% + 2 Tryptase Formula Is a Diagnostic Gold Standard for Severe Systemic Mast Cell Activation and Mast Cell Activation Syndrome. Int Arch Allergy Immunol 2019;180:44-51.
10. Lyons JJ. Hereditary Alpha Tryptasemia: Genotyping and Associated Clinical Features. Immunol Allergy Clin North Am 2018;38:483-495.
11. Greiner G, Sprinzl B, Górska A, et al. . Hereditary α tryptasemia is a valid genetic biomarker for severe mediator-related symptoms in mastocytosis. Blood 2021;137:238-247.

Conflict of interest: none

Conflit d’intérêt : aucun


Secretory granule
Degranulation
Proteolytric activation
ER
Mature tryptase
NUCLEUS
(pre-)pro-tryptases
Constitutive secretion
Pro-α and β-tryptases
MAST CELL