# Mast Cell–Restricted Tetramer-Forming Tryptases and Their Beneficial Roles in Hemostasis and Blood Coagulation

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**KEYWORDS**

• Mast cell • hTryptase-β • mMCP-6 • mMCP-7 • Fibrinogen
• Fibrin thrombin-dependent coagulation • Anaphylaxis

**KEY POINTS**

- Tryptase-β–dependent proteolysis of the α chain of hFibrinogen impairs its ability to form thrombin-dependent fibrin.
- The antithrombotic activity of hTryptase-β hinders the internal accumulation of life-threatening fibrin deposits and fibrin-platelet clots in tissues when activated mast cells (MCs) exocytose histamine and other vasopermeability factors which, in turn, induce vasodilation and edema of tissues.
- The anticoagulant activity of MC-restricted tryptases explains why there are 2 genes in mice and humans that encode similar tetramer-forming tryptases that can proteolytically damage fibrinogen, and why there is no endogenous protease inhibitor in normal blood that can rapidly inactivate these enzymes.
- The anticoagulant activity of tetramer-forming tryptases also explains the presence of hemorrhagic disorders in some patients with anaphylaxis or mastocytosis.
- Recombinant hTryptase-β could be a more effective and safer anticoagulant in the clinic than porcine-derived heparin oligosaccharides.
- C-terminal fragments of the α chain of hFibrinogen in blood and/or urine potentially could be biomarkers for the identification of patients who have undergone systemic anaphylaxis, have mastocytosis, or have an MC activation disorder.

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## INTRODUCTION

Mast cells (MCs) are key effector cells in immediate hypersensitivity reactions because of their release of numerous proinflammatory mediators. The presence of too many MCs in tissues leads to mastocytosis (**Fig. 1**). However, the conservation of MCs in evolution and the failure to identify a human who lacks MCs suggests critical beneficial roles for these immune cells in our survival. In that regard, it has been demonstrated that the tetramer-forming tryptases exocytosed from activated MCs are needed for efficient host defense against certain bacterial, helminth, and virus infections.[1–6] Moreover, the loss of human immunodeficiency virus 1–infected hTryptase-$\beta^+$ MCs and their progenitors in patients with AIDS is now believed to be a contributing factor in their inability to combat opportunistic infections.[7–9]

Tetramer-forming tryptases are stored in the MC's secretory granules ionically bound to serglycin proteoglycans (SGPGs), which usually have heparin chains. These serine proteases are useful clinical and experimental biomarkers for mastocytosis, anaphylaxis, and the MC activation syndrome. Such markers can be measured by enzyme-linked immunosorbent assays and can be detected in peripheral blood for longer periods of time than other mediators exocytosed from activated MCs (eg, histamine and arachidonic acid metabolites).[10–12] The expression of hTryptase-$\beta$ is also highly restricted to MCs. Despite its diagnostic value, the biological function of the hTryptase-$\beta$ in plasma and blood has largely remained unknown.

The ability to form fibrin when the skin and other connective tissues are wounded is essential for preventing blood loss and the entry of pathogens into the body. Nevertheless, the formation of intravascular fibrin deposits and fibrin-platelet clots can have dangerous consequences. When the MCs in skin and other connective tissue sites degranulate, these immune cells quickly release the contents of their secretory granules, which include histamine and tetramer-forming tryptases bound to SGPGs that usually contain heparin glycosaminoglycans (GAGs). Histamine is the major

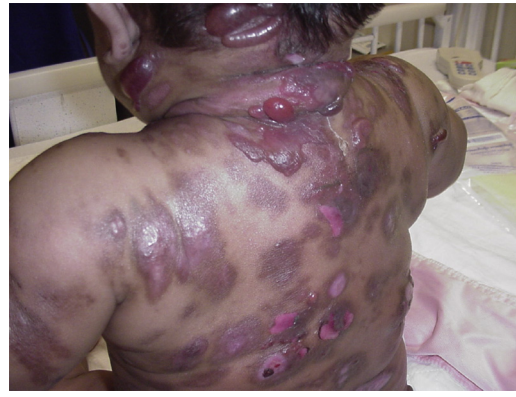

**Fig. 1.** Mastocytosis. The presence of an activating mutation in the tyrosine kinase receptor Kit/CD117 in the mast cell (MC)-committed progenitors of a mastocytosis patient eventually causes the accumulation of too many mature hTryptase-$\beta^+$ MCs in the skin and other connective tissues. The activation of these MCs and the exocytosis of their granule mediators can lead to numerous clinical problems, as occurred in the skin of this patient with bullous mastocytosis. Because the C-terminus of the $\alpha$ chain of hFibrinogen is preferentially cleaved by hTryptase-$\beta$, the identification of peptides derived from the protein's $\alpha$ chain in the circulation via an enzyme-linked immunosorbent assay could be of therapeutic valuable in the early identification of mastocytosis patients, as well as monitoring their treatment.