The monogenic disorder called alpha-tryptasemia fosters our understanding of the biologic and pathobiologic roles of human α/β-tryptases

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α/β-Tryptases are preferentially expressed by mast cells in humans, where they serve as biomarkers for systemic anaphylaxis, systemic mastocytosis and mast cell cytoreductive therapies. Their biologic or pathobiologic clinically-relevant activities are less well understood. Recently, a monogenic autosomal-dominant condition called alpha-tryptasemia has been described due to a copy number variation in the gene encoding alpha-tryptase, TPSAB1. Affected patients present with multi-organ system defects, including autonomic dysfunction, joint hyper-extensibility, gastrointestinal symptoms and vibratory urticaria along with elevated baseline tryptase levels, but with a normal bone marrow biopsy and no c-kit mutation. As α-tryptase tetramers are ineffective as proteases due to a G245D change in which the aspartic acid side chain clogs the substrate binding pocket, essentially all tryptase proteolytic activity resides with β-tryptase, primarily via β-tryptase tetramers, because monomers, when active, unlike tetramers, are rapidly inactivated by biologic protease inhibitors. So how might alpha-tryptasemia provide new insights in the function of these tryptases? New research aiming to better understand the relationship between tryptases and the clinical phenotype of alpha-tryptasemia patients and how this might lead to better therapeutic options for such patients will be discussed.

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