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Mast cell tryptase – Marker and maker of cardiovascular diseases

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ABSTRACT

Mast cells are tissue-resident cells, which have been proposed to participate in various inflammatory diseases, among them the cardiovascular diseases (CVDs). For mast cells to be able to contribute to an inflammatory process, they need to be activated to exocytose their cytoplasmic secretory granules. The granules contain a vast array of highly bioactive effector molecules, the neutral protease tryptase being the most abundant protein among them. The released tryptase may act locally in the inflamed cardiac or vascular tissue, so contributing directly to the pathogenesis of CVDs. Moreover, a fraction of the released tryptase reaches the systemic circulation, thereby serving as a biomarker of mast cell activation. Actually, increased levels of circulating tryptase have been found to associate with CVDs. Here we review the biological relevance of the circulating tryptase as a biomarker of mast cell activity in CVDs, with special emphasis on the relationship between activation of mast cells in their tissue microenvironments and the pathophysiological pathways of CVDs. Based on the available *in vitro* and *in vivo* studies, we highlight the potential molecular mechanisms by which tryptase may contribute to the pathogenesis of CVDs. Finally, the synthetic and natural inhibitors of tryptase are reviewed for their potential utility as therapeutic agents in CVDs.

Contents

Abbreviations: AAA, Abdominal aortic aneurysm; ACS, Acute coronary syndrome; AMI, Acute myocardial MI; apo, Apolipoprotein; ApoE−/−, ApoE-deficient; BMMCs, Bone marrow-derived mast cells; CVDs, Cardiovascular diseases; EC, Endothelial cell; ECM, Extracellular matrix; HDL, High-density lipoprotein; KS, Kounis syndrome; LDL, Low-density lipoprotein; IL, Interleukin; LPA, Lysophosphatidic acid; MC, Mast cell; MCAS, MC activation syndrome; PAR-2, Proteinase-activated receptor-2; SMC, Smooth muscle cell.

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1. Introduction

Cardiovascular diseases (CVDs) affected approximately 42 million patients in 2015, and they were the number 1 cause of death globally (Roth et al., 2017). Of these deaths, the majority were due to ischemic heart disease, i.e. coronary heart disease (Roth et al., 2017). Atherosclerosis, the underlying cause of coronary heart disease, is regarded as a chronic inflammatory disease in which many inflammatory cells, including macrophages, T-lymphocytes, and mast cells (MCs) accumulate in the arterial intimal layer, so fueling a local inflammatory reaction in the atherosclerosis-prone arterial segments (Hansson, 2005; Libby, 2002; Lusis, 2000). Though well-known as an inflammatory cell in allergic reactions, MCs were recognized also in human atherosclerotic lesions, implicating them as having role in CVDs (Cairns & Constantinides, 1954). Indeed, the inner layer of the human arterial wall, the intima, which is the site of atherogenesis, contains MCs, and also the perivascular tissue, i.e. the adventitia of healthy arteries harbors MCs (Atkinson, Harlan, Harlan, & Virmani, 1994; Kaartinen, Penttila, & Kovanen, 1994). Most importantly, atherosclerotic changes lead the MC numbers to build up in the atherosclerotic lesions and in the adventitial layer backing them (Kaartinen, Penttila, & Kovanen, 1994; Laine et al., 1999).

Pathological and experimental evidence highlights the key contribution of MCs to the pathogenesis of CVDs (Bot, van Berkel, & Biessen, 2008; Kovanen, 2007b). Once activated, MCs produce a wide range of neutral proteases and other preformed mediators, and also potent cytokines and chemokines (Krishnaswamy, Ajitawi, & Chi, 2006; Mackins et al., 2006; Moon, Befus, & Kulka, 2014). The evidence relating the pathogenesis of CVDs to MC activation has increased substantially, particularly regarding the pathogenesis of atherosclerotic CVDs (Fairweather & Frisancho-Kiss, 2008; Kovanen & Bot, 2017; Kritikou, Kuiper, Kovanen, & Bot, 2016; Levick et al., 2011; Shi, Bot, & Kovanen, 2015). Tryptase, as one of the potentially proatherogenic mediators secreted by MCs, has been shown to be elevated in the venous blood and in atherosclerotic plaques of patients with other cardiometabolic disease markers, and, an elevated tryptase level has been associated with cardiovascular complications, implying a potential role for tryptase in such events (Moreno et al., 2014; Ramalho et al., 2013; Willems et al., 2013).

In this review, we summarize MC triggers that are thought to explain MC-dependent pathologic mechanisms in the progression of CVDs, and tryptase-dependent effects that are pivotal in the formation of an atherosclerotic plaque. Moreover, since defects of MC function and activation (e.g. impaired linker for activation of T cells (LAT) activation (Saitoh et al., 2003) and serglycin gene-disruption (Sutton et al., 2016) have been recognized as contributing to differing medical conditions with an inflammatory background, with or without an allergic component, the latter ones especially when accompanying cardiovascular symptoms, we will discuss the potential role of activated MCs in human CVDs, with a strong focus on the use of tryptase as a biomarker of CVD events.Given the implicit role that tryptase may have as a pathogenic factor of atherogenesis, we also will examine the inhibitors targeting tryptase activity that may have potential therapeutic utility in CVDs.

2. Mast cell biology

MCs are known to have a hematopoietic origin and they are found in all human tissues as tissue-resident cells. They are particularly abundant in front-line tissues exposed to the external environment where, following exposure to allergic or non-immune triggers, they release prestored mediators, including histamine and tryptase, along with many *de novo* synthesized chemokines and cytokines (Galli, Nakae, & Tsai, 2005; Theoharides & Kalogeromitros, 2006). MCs perform both effector and regulatory functions with a pivotal role in reactions of adaptive and innate immunity and a potential role in the maintenance of tissue homeostasis (Cardamone, Parente, De Feo, & Triggiani, 2016; Gri et al., 2012; Payne & Kam, 2004). MC granules are composed of heparin, histamine and neutral proteases, notably tryptase. The secretion of these mediators due to MC degranulation may occur as a response to physical factors (mechanical trauma, high temperature), toxins, venoms, endogenous mediators (proteins, tissue proteases), and immune mechanisms (dependent or not dependent on IgE) through the cross-linking of FcεRI-bound IgE or the activation of G protein-coupled receptors and other recognition sites on the human MC surface (Gorska et al., 2015; He & Xie, 2004; Lappalainen, Lindstedt, Oksjoki, & Kovanen, 2011; Zeng, Zhang, Xu, Yang, & He, 2013). The diversity of MC activation and its response indicate the differing activation stimuli and intracellular pathways mediating that response.

Non-allergic reactions may cause MC activation, thereby giving MCs a potential role in several biological processes (Ibelgaufts, 2015). Diverse stimuli trigger MC activation and induce secretion of various cytokines, chemokines, and growth factors (Mukai, Tsai, Saito, & Galli, 2018). Thus, depending on the type of the activating stimulus, as well as the phenotype of the MCs, the activated MCs secrete granulemedicl stored and/or newly synthesized mediators, so creating organ/tissue-specific variation in MC actions contingent upon many macro- and microenvironmental factors, which can involve physical, anti-body/antigen-mediated or non-antigenic stimuli. Considering their location at the body's outer or inner environmental interfaces (either skin or mucosal surfaces), MC mediators may have evolved to integrate with the immune system, having the ability of attracting granulocytes and T and B lymphocytes to the site of injury, and controlling their function to counteract bacterial, parasitic and viral agents (Marshall, 2004).

The pre-stored mediators are secreted through non-selective MC degranulation (as in anaphylaxis); however, there are morphologically distinct secretory pathways, which allow MCs to exert selective release of mediators via so-called piecemeal degranulation (Dvorak, 1986, 2005; Dvorak et al., 1994). MCs contribute to the processes of wound healing (Carole & Oskeritzian, 2012), hair follicle recycling (Moon et al., 2010), and bone remodeling (Krystel-Whittemore, Dileepan, & Wood, 2016). Furthermore, the potent proteases released by activated MCs may degrade some endogenous toxic peptides, including endothelin-1 and neurotensin produced because of bacterial infection and bacterial toxins (Maurer et al., 2004; Metsärinne et al., 2002). Regarding the expression of the two major neutral proteases in MCs, tryptase and chymase, two types of human MCs have been identified: one is mainly found in alveolar walls and the small intestinal mucosa with granules containing only tryptase, and the other is found in skin, intestinal submucosa, and blood vessels with granules which contain both tryptase and chymase (Irani, Schechter, Craig, DeBlois, & Schwartz, 1986; Payne & Kam, 2004). Like in other human tissues, in the arterial intima, the site of atherogenesis, all MCs contain tryptase, and moreover, a variable fraction (on average 40%) of them also contains chymase (Kaartinen, Penttila, & Kovanen, 1994; Kaartinen, Penttilä, & Kovanen, 1994).

3. Structure, expression and functions of tryptase

Tryptase is a neutral serine-proteinase with trypsin-like characteristics and a molecular weight of 134 kDa. It is the most abundant protease contained in the MC secretory granules. Four non-covalently bound subunits constitute the enzyme. With regard to the amino acid sequences, human MC tryptases are categorized into four major types α,

β, γ, and δ, with tryptase α having two subtypes (α1, α2) and tryptase β having three subtypes (β1, β2, β3) (Kolmar, Sommerhoff, & Wentzel, 2012; Payne & Kam, 2004; Pereira et al., 1998; Presnell & Taft, 2003). The first two types are soluble proteinases and can proteolytically form active tetramers packed in the granules in complex with proteoglycans, largely heparin proteoglycans (Hanna et al., 1993; Schwartz, 1990). Based on an Asp246/Gly246 mutation in its catalytic domain, tryptase α displays very little enzymatic activity. Moreover, it is not stored in MC granules and appears to act as a pro-enzyme (Schwartz et al., 1995). On the contrary, tryptase β is the chief enzymatically active type, and, by being a granule component, it is released from the MCs upon MC activation and ensuing degranulation (Lindstedt, Kokkonen, & Kovanen, 1998). In the extracellular fluid, tryptase can diffuse away from the secretory granules (Payne & Kam, 2004).

3.1. The structural maturation of tryptase in mast cells

Human tryptase genes are clustered on the short arm of chromosome 16, encoding an immature tryptase (protryptase) that, following proteolytic activation, assembles into an active tetramer presenting as a soluble serine proteinase (Fukuoka & Schwartz, 2007; Kido & Nakai, 2002; Maffitt, Niles, & Haak-Frendscho, 2001). The activation process consists of two proteolytic steps (Ni, Cao, Huang, Meng, & Wei, 2017). An autocatalytic intermolecular cleavage comes about in the first step, followed by proteolytic processing by cathepsin C when exposed to heparin or dextran sulphate under the acidic pH and optimal conditions prevailing in the MCs (Le, Gomez, et al., 2011; Le, Min, et al., 2011). The second step is to remove the remaining precursor dipeptide via dipeptidyl peptidase I leading the mature peptide to spontaneously form into the mature tetramer. There has been some evidence that processing of human tryptase involves activation by cathepsin L or B. Though more likely to be involved in a minor portion of protryptase processing, cathepsin C is not critical for mature tryptase synthesis (Le, Gomez, et al., 2011; Le, Min, et al., 2011).

Heparin allows packing and stabilization of the mature tryptase in the secretory granules of MCs (Stevens & Adachi, 2007; Wernersson & Pejler, 2014). In accordance with initial findings on X-ray crystallography, human tryptase appeared as a homotetrameric structure with four independent catalytic sites in a pair-wise distribution, which was indicative of a crystal structure containing four independent monomers arranged at the corners of a flat rectangular frame (Liang et al., 2012; Pereira et al., 1998; Sommerhoff, Bode, Matschiner, Bergner, & Fritz, 2000). The active site of every subunit of the tetramer orientates towards the inner face of the central cavity and protects them against biological inhibitors of serine proteases (Fukuoka & Schwartz, 2006; Payne & Kam, 2004; Pereira et al., 1998). These monomers come into interaction with their neighbors at two distinct interfaces via six loop segments surrounding the active site of tryptase. Tryptase tends to cleave peptides with basic amino acids, and the four active sites provide tryptase properties of an allosteric enzyme with sigmoidal reaction kinetics (Harvima, Harvima, Eloranta, & Fräki, 1988).

3.2. Functions of tryptase

In humans, tryptase expresses its biological function via cleaving specific substrates of a wide variety, and via activation of the proteinase-activate receptor 2 (PAR-2), a seven-transmembrane, G protein-coupled receptor (Lan, Stewart, & Henry, 2002; Liu et al., 2016). A variety of cells, such as airway epithelial and smooth muscle cells (SMCs), endothelial and vascular SMCs, terminal bronchial epithelium, MCs, and several other types of inflammatory cell, e.g. mononuclear cells, granulocytes, neutrophils, express PAR-2 (Lan et al., 2002; Niles, Haak-Frendscho, Harris, & Craik, 2004; Schmidlin et al., 2001). Therefore, it is tangible that PAR-2 is involved in many medical conditions such as cancer, as well as inflammatory, gastrointestinal, respiratory and metabolic diseases (Ammendola et al., 2014; Asaduzzaman et al., 2015; Badeanlou, Furlan-Freguia, Yang, Ruf, & Samad, 2011; Jacob et al., 2005; Lan et al., 2002; Lim et al., 2013). Tryptase cleaves PAR-2 near its N-terminus, which causes a conformational change in PAR-2, and so elicits the subsequent signal transduction (Fukuoka & Schwartz, 2007; Lan et al., 2002). Nevertheless, activation of PAR-2 *in vivo* by tryptase is associated with some controversy, as glycosylation of PAR-2 or binding of tryptase to heparin causes an inhibitory effect on tryptase-induced activation of PAR-2 (Compton, Renaux, Wijesuriya, & Hollenberg, 2001; Compton, Sandhu, Wijesuriya, & Hollenberg, 2002).

Cells (dependent or independent on PAR-2 activation), peptides, proteins, and tissues can be considered as targets for the action of tryptase. It has been observed that tryptase is able to increase the secretion of cytokines and chemokines from endothelial (Zhang et al., 2011) and epithelial cells (Caughey, 2007), and from eosinophils (Galdiero et al., 2017; Wong, Ng, Lun, Cao, & Lam, 2009), along with airway SMCs (Berger et al., 2003; Chhabra et al., 2007), which account for the pathogenesis of allergic inflammation. It can trigger the growth of fibroblasts, epithelial cells and SMCs involved in fibrosis and tissue remodeling (Brown et al., 1995; Cairns & Walls, 1996; Ruoss, Hartmann, & Caughey, 1991; Schechter, Brass, Lavker, & Jensen, 1998), as well. Tryptase is responsible for the release of interleukin (IL)-8, intercellular adhesion molecule, and IL-1β. IL-8 results in leukocyte infiltration leading to an amplification and maintenance of the MC response (Compton, Cairns, Holgate, & Walls, 1998).

The secretion of tryptase from activated MCs may trigger the release of more tryptase from neighboring MCs, resulting in an amplification of the signal (He, Gaça, & Walls, 1998). Other mediators, including tumor necrosis factor (TNF) and IL-6, are induced by tryptase through the activation of PAR-2. Together, these inflammatory biomolecules reinforce a positive feedback mechanism and ultimately promote immigration and subsequent proliferation of inflammatory cells in the vascular wall (Compton et al., 1998). Moreover, tryptase can induce smooth muscle spasm in the respiratory tract by means of degradation of the bronchodilator vasoactive intestinal peptide, hydrolysis of the peptide histidine-methionine, and catalysis of the calcitonin gene-related peptide (Caughey, Leidig, Viro, & Nadel, 1988; Walls et al., 1992). Of note, activation of some protein substrates, namely matrix metalloproteinases and pro-urokinase, by tryptase contributes to biological actions of tissue remodeling and tumor invasion (Gruber et al., 1989; Stack & Johnson, 1994; Yamamoto, Kumagai, Fukuda, Fujitsu, & Nishida, 2006). Tryptase-induced damage to fibronectin and collagen can also occur in tissue remodeling, which may contribute to the development of some CVDs, including atherosclerosis and abdominal aortic aneurysms (AAA) (Lindstedt, Mäyränpää, & Kovanen, 2007; Swedenborg, Mäyränpää, & Kovanen, 2011). Elevation of vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor in response to tryptase play a key role in angiogenesis and tumorigenesis (Blair et al., 1997; Hanahan & Folkman, 1996; Iruela-Arispe & Dvorak, 1997; Ribatti, 2006; Ribatti & Crivellato, 2012). There have been some *in vitro* studies highlighting that tryptase can counteract coagulation factors, e.g., the degradation of fibrinogen, and exert an anticoagulant action (He, Xie, & He, 2004; Schwartz, Bradford, Littman, & Wintroub, 1985).

4. Mast cell activators in atherosclerotic cardiovascular disease

Atherosclerosis is a medical condition associated with chronic inflammation of the arterial wall, arising from the accumulation of macrophages or foam cells, along with intracellular cholesterol and lipid (Abdolmaleki, Gheibi Hayat, Bianconi, Johnston, & Sahebkar, 2018; Pentikäinen, Öörni, Ala-Korpela, & Kovanen, 2000; Pirro & Mannarino, 2018). This complex increase of plasma-derived lipoprotein lipids in the arterial intima, notably of cholesterol, results from an imbalance created by low-density lipoprotein (LDL) accumulation that outweighs the removal of fats and cholesterol from the macrophages through functionally competent high-density lipoprotein (HDL). In addition to macrophages, the presence of monocytes, neutrophils, lymphocytes, and

MCs, particularly near foam cells, are also detected in the arterial intima (Lee, Lindstedt, & Kovanen, 1992), indicating the involvement of these inflammatory cells in the transformation of macrophages into foam cells (Raggi et al., 2018).

In an attempt to explore potent therapeutic cues for MC stabilization in various cardiac disorders, it is important to understand the underlying mechanisms for MC activation. MC activation can be induced by many mediators, with IgE being the most recognized and mediating degranulation via the high affinity receptor FcεRI, which affords irreversible IgE binding to MCs (Pulendran & Ono, 2008). Each MC has a diversity of IgE molecules bound to FcεRI with differing antigen specificities and affinities (Sechi, Roller, Willette-Brown, & Kinet, 1996). On exposure to an antigen, MCs are immediately stimulated to degranulate (Yamasaki & Saito, 2005). In an apolipoprotein E-deficient (ApoE−/−) mouse model, the lack of FcεRIα was correlated to diminished lipid deposition in the aortic arch and to decreased burden of atherosclerosis caused by a western diet (Wang et al., 2011). Moreover, there were fewer macrophages, T cells and apoptotic cells, along with lower concentrations of inflammatory cytokines in atherosclerotic lesions. IgE activation may induce inflammatory signaling and apoptosis in macrophages, SMCs and endothelial cells (ECs) (Wang et al., 2011), and ligands at the site of intimal injury or the underlying adventitial tissue have the capability to activate local MCs (Spinas et al., 2014).

The complement system plays an important role in the regulation of the innate and also of the adaptive immunity, and these regulatory functions extend to the cardiovascular system (Oksjoki, Kovanen, Meri, & Pentikäinen, 2007). Importantly, complement component C5a has been observed in human coronary lesions in lipid-rich inflammatory areas (Speidl et al., 2011) and in ruptured coronary plaques in acute myocardial infarction (AMI), complement activation was observed (Laine et al., 2002). Importantly, in human atherosclerotic coronary plaques, macrophages, T cells, endothelial cells, subendothelial smooth muscle cells, and MCs demonstrate the expression of the receptor for C5a (Oksjoki et al., 2007). In a murine vein graft model, it was reported that administration of a C5a receptor antagonist had a lowering influence on plaque size and perivascular treatment with C5a throughout disease initiation promoted plaque formation. Furthermore, when the mice were treated with a combination of C5a and the MC stabilizer cromolyn, the plaque size decreased to control level, and so reversed the impact of MC activation (de Vries et al., 2013). During late stages of vein graft disease, C5a was documented to play a pivotal role in vein graft destabilization via activation of MCs (Wezel et al., 2014). Although MCs are also known to express the receptor for C3a that can cause MC activation, the interactions among C3a, MCs and atherosclerosis have not yet been elucidated.

Toll like receptors (TLRs) are pattern recognition receptors often expressed by various types of cell of the innate immune system (O'Neill, Golenbock, & Bowie, 2013). Murine MCs express TLR1 to TLR9, other than TLR5, while on the contrary human MCs carry TLR1 to TLR7, as well as TLR9 and TLR10 (Sandig & Bulfone-Paus, 2012). However, the mechanism(s) whereby TRLs trigger MC activation is still unclear. There is evidence suggesting a role for peptidoglycan as an activator of TLR2 on murine and human MCs that leads to degranulation, but others have not confirmed this (Sandig & Bulfone-Paus, 2012). MC degranulation likely follows TLR4 activation, and lipopolysaccharide can be a strong trigger of pro-inflammatory cytokines and chemokines release. An *in vivo* study by den Dekker et al. reported that MCs increase the destabilization of atherosclerotic plaques in a TLR4 dependent fashion through chymase-induced SMC apoptosis (den Dekker et al., 2012). Additionally, chymase release as a hallmark of MC degranulation was detected following TLR4 activation. The authors of the above-cited study therefore postulated that TLR4 signaling leads to the formation and release of proinflammatory cytokines, such as IL-6, which further cause autocrine-dependent degranulation of MCs via chymase secretion, and thereby lead to SMC apoptosis. These results were achieved in ApoE−/− mice, in which TLR4 was activated using the *Escherichia coli* lipopolysaccharide and suppressed by a natural TLR4 antagonist suggesting a role of this TLR through MC activation in atherosclerosis (den Dekker et al., 2012).

Recently, a study showed that IL-33 may act as a strong MC activator with signaling akin to lipopolysaccharide (Taruselli, Kolawole, & Ryan, 2017). IL-33 belongs to IL-1 family, causing the differentiation of T cells contingent on phosphorylated MAPK and NFκB, and participating in T cell-mediated immune reactions. Moreover, IL-33 contributes to the generation of IL-5, IL-4, IL-13, and also of many chemokines (Castellani et al., 2009). It was shown that fluvastatin induced an IL-33-dependent elevation of TNF and IL-6 release in primary mouse and human MCs (Taruselli et al., 2017). These changes required the mitogen stem cell factor, as without it no changes were seen. Of note, these events were inhibited by mevalonic acid, the bioproduct of the HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase) reaction, and by geranylgeranyl pyrophosphate as well as by farnesyl pyrophosphate, i.e. two isoprenoids later downstream products in the cholesterol biosynthesis pathway (Taruselli et al., 2017).

Circulating oxidized LDL (oxLDL) is a biomarker for atherosclerosis, and it is also considered as a pathogenic particle intiating and aggravating atherosclerosis, when generated in the arterial intima (Que et al., 2018). Importantly, oxLDL can enhance TLR4 signaling and also thereby contribute to the pathogenesis of atherosclerosis (Howell et al., 2011). OxLDL is more likely to develop antigen-antibody complexes, with autoantibodies against oxLDL being chiefly of the IgG isotype. Such circulating immune complexes are found in patients with CVDs and in atherosclerotic lesions (Willems et al., 2014; Yla-Herttuala et al., 1994). MCs release FcγRs that possess low affinity for monomeric IgG, and high affinity for antigen-antibody complexes (Wezel, Quax, Kuiper, & Bot, 2015). *In vitro* studies have shown that oxLDL-IgG immune complexes can trigger MC activation leading to high levels of tryptase, chymase, histamine, TNFα, IL-6, and CCL2 in the incubation medium (Lappalainen et al., 2011). Lysophosphatidic acid (LPA) is one of the main lipid components of modified LDL that has been shown as a potent MC activator in atherosclerosis (Bot et al., 2013). By applying mass spectrometry, it could be shown that multiple LPA species exist in atherosclerotic plaques, particularly in the necrotic core area of atherosclerotic lesions in mice (Bot et al., 2013). Treating MCs with LPA *in vitro* led to increased degranulation as well as cytokine secretion. Likewise, intraperitoneal administration of LPA to MC-competent mice augmented tryptase concentrations in the peritoneal fluid, while no tryptase was present in the peritoneal fluid of similarly treated MC-deficient Kit (W^{-sh}/W^{-sh}) mice (Bot et al., 2013). Furthermore, the perivascular use of LPA in plaques promoted the macrophage number and intraplaque hemorrhages, which were proposed to be MC-specific events, because treatment of the mice with the MC stabilizer cromolyn diminished both effects (Bot et al., 2013).

Adventitial MCs are present near sensory nerve fibers in human coronary arteries, and the number of MC-nerve contacts have been found to be increased with lesion progression (Laine, Naukkarinen, Heikkila, Penttila, & Kovanen, 2000). The sensory nerves were positive for the neuropeptides substance P and calcitonin gene-related peptide, both of which can activate MCs. The numbers of adventitial MCs were demonstrated as a correlate of neurofilament^{+} nerve fibers in coronary artery specimens, and it was suggested that neuronal activation might contribute to activation and ensuing mediator release of adventitial MCs in atherosclerosis. This hypothesis received strong support from experiments in mice, in which it could be demonstrated that local administration of substance P in aApoE−/− mice increased the numbers of MCs and activated them (Bot et al., 2010). MC activation also associated with increased frequency of intraplaque hemorrhages, which were MC-dependent, as substance P treatment in MC-deficient Kit(W^{-sh}/W^{-sh}) mice was without effect (Bot et al., 2010). More recently, the presence of neuropeptide Y has been shown in human endarterectomy lesions with a twofold increase in unstable lesions compared to stable plaques (Lagraauw et al., 2014). In addition, in the carotid artery of

ApoE−/− mice perivascular MCs became activated and atherosclerotic lesion formation was increased following local lentiviral overexpression of NPY. In an experimental setting, the exposure of murine MCs to NPY enhanced IL-6 and tryptase release (Lagraauw et al., 2014).

It is recognized that high-perceived stress associates with an increased risk of coronary artery disease, and that cardiovascular events may be triggered by acute psychological stress (Richardson et al., 2012; Steptoe & Brydon, 2009). Given that stress can stimulate sensory nerves with further secretion of various neuropeptides, it is postulated to act as a mediator of MC activation in atherosclerotic plaque destabilization, which is a prerequisite for plaque erosion or rupture (Alevizos, Karagkouni, Panagiotidou, Vasiadi, & Theoharides, 2014; Huang, Pang, Letourneau, Boucher, & Theoharides, 2002). In another study, using a model of ApoE−/− mice treated with compound 48/80 caused a decrease in plaque stability with elevation of macrophage content and increased neovascular density (Tang et al., 2009). This pharmacological induction of MCs could also cause MC degranulation and microvascular inflammation (Steiner, Gonzalez, & Wood, 2003). In a more physiological setting, in the Langendorff perfusion system, hypoxia was found to activate rat myocardial MCs, which only contain the neutral protease chymase, to degranulate (Kareinen et al., 2018). The released chymase then C-terminally truncated apolipoprotein A-I, the major component of HDL and so compromised its endothelial-healing ability, as assessed in a wound-healing assay system. In another experimental system, both the application of either the MC stabilizer cromolyn to prevent granule release, or the pretreatment with compound 48/80 to reduce the number of MC granules before ischemia/reperfusion resulted in the reduced severity of hepatic injury (Yang et al., 2014). Moreover, MC recruitment and degranulation by compound 48/80 treatment were shown effective for arteriogenesis, thereby having protective effects on tissue against severe ischemic damage, a finding providing a basis for a therapeutic approach to manage vascular occlusive diseases (Chillo et al., 2016).

5. Role of mast cells and tryptase in direct myocardial damage

MCs are present in the human heart in the interstitial space between the cardiomyocytes, and frequently near nerves that may be associated with the formation and progression of arrhythmias (Dvorak, 1986; Forman et al., 1985; Marone et al., 1995; Morrey et al., 2010; Reid, Silver, & Levi, 2007; Silver et al., 2004). Activation of cardiac MCs induces the generation of various potent pro-inflammatory and profibrotic mediators (Koda et al., 2010; Mackins et al., 2006; Morrey et al., 2010; Reid et al., 2007; Silver et al., 2004). Both chymase and tryptase are within the majority of the MCs in the human heart (90%) (Weidner & Austen, 1993). Cardiac MCs take part in a wide variety of physiological functions, namely angiogenesis, formation of atrial natriuretic peptide, as well as local generation of angiotensin II using renin and in the absence of angiotensin-converting enzyme (Frangogiannis et al., 1998; Miyazaki, Takai, Jin, & Muramatsu, 2006; Proctor, Chan, Garrett, & Smith, 1991; Rakusan, Sarkar, Turek, & Wicker, 1990; Silver et al., 2004; Wei et al., 2010). Chymase and tryptase in association with other mediators (e.g., cytokines, TNFα, chemokines, leukotrienes, transforming growth factor, histamine) promote tissue repair (Douaiher et al., 2014). Cardiac MCs have been found to be involved also in different pathophysiological processes of the myocardium, including ventricular remodeling, that is, alterations in size, shape, structure, and function of the heart caused by MI (through atherosclerotic lesions or coronary vasospasm), volume overload, chronic hypertension or myocarditis (Gilles, Zahler, Welsch, Sommerhoff, & Becker, 2003; Higuchi et al., 2008; Huang et al., 2013; Levick et al., 2011; Melendez et al., 2011; Palaniyandi, Inagaki, & Mochly-Rosen, 2008), arrhythmias (Koda et al., 2010; Mackins et al., 2006; Morrey et al., 2010), graft rejection following cardiac transplantation (Li et al., 1992; Zweifel et al., 2002), dilated cardiomyopathy (Palaniyandi et al., 2005), cardiac hypertrophy, heart failure (Balakumar et al., 2008; Batlle et al., 2006; Hara et al., 2002; Joseph et al., 2003; Kim et al., 2006; Shiota et al., 2003), Takotsubo cardiomyopathy (Cheng & Kounis, 2012; Vultaggio et al., 2007). Moreover, MCs within the arterial walls are involved in the progression of atherosclerosis in epicardial coronary arteries, in carotid arteries (Jeziorska, McCollum, & Woolley, 1997; Lehtonen-Smeds et al., 2005; Willems et al., 2013) and in the aorta (Ramalho et al., 2013) and its clinical complications, such as the ACSs (Deliargyris et al., 2005; Forman et al., 1985; Kaartinen et al., 1998; Kervinen et al., 2005; Steffel, Akhmedov, Greutert, Luscher, & Tanner, 2005), and in the development of AAA (Wang & Shi, 2012; Zhang et al., 2011).

6. Role of tryptase in the formation and progression of atherosclerosis

In relation to healthy subjects, patients with coronary artery disease have presented considerably higher serum levels of tryptase, implying its potential role in atherosclerosis. Intraluminal exposure of human coronary arteries to recombinant tryptase led to impairment in endothelium, as shown by retraction and desquamation secondary to disrupted EC adhesion (Deliargyris et al., 2005; Mäyränpää, Heikkilä, Lindstedt, Walls, & Kovanen, 2006; Xiang et al., 2011). The involvement of tryptase in the vascular system has been related to lipoprotein disruption, proenzyme or procytokine activation, as well as matrix protein degradation (Fig. 1). Among the various lipoprotein classes, the lipid-poor subclass of HDL particles, the pre-beta HDL particles, which effectively remove cholesterol from macrophage foam cell, the hallmark of atherosclerosis, are highly sensitive to extracellular degradation by various proteolytic enzymes, among them tryptase (Lee et al., 2002; Lee-Rueckert & Kovanen, 2006, 2015). The pre-beta HDL particles contain apolipoprotein A-I, which normally mediates initiation of cholesterol removal from macrophage foam cells via interaction with the cell surface ATP-binding cassette transporter A1 (ABCA1), but loses this activity upon degradation by tryptase (Lee et al., 2002; Lee-Rueckert & Kovanen, 2006, 2015). Overall, since tryptase is released by activated MCs in atherosclerotic plaques, and the co-secreted heparin proteoglycans prevent rapid inactivation of the released tryptase in extracellular fluid (Lindstedt et al., 1998), we can surmise that activated MCs in atherosclerotic plaques contribute to inhibition of HDL-dependent removal of cholesterol from macrophage foam cells, and by inhibiting reverse cholesterol transport, contribute to formation and maintenance of foam cells in the lesions.

As for pericellular matrix protein degradation, tryptase has the ability to similarly degrade pericellular fibronectin, vitronectin, and collagen type IV, which further induce angiogenesis, tissue remodeling, and maybe vascular cell apoptosis (Mäyränpää et al., 2006; Meyer, Creer, & McHowat, 2005; Ribatti, Levi-Schaffer, & Kovanen, 2008). Proteolytic release of tryptase leads to activation of pro-matrix metalloproteinases (MMPs), which also contribute to the development and remodeling of atherosclerotic plaques. Indeed, tryptase generates active matrix metalloproteinases (MMP)-1, -2, and -3 (Johnson, Jackson, Angelini, & George, 1998), all of which have been involved in plaque development and AAA (Galis et al., 2002; Kuzuya et al., 2006; Longo et al., 2002; Wågsäter, Zhu, Björkegren, Skogsberg, & Eriksson, 2011). It has been reported that tryptase can augment the expression of chemokines (monocyte chemoattractant protein-1, IL-8) and adhesion molecules (ICAM, VCAM, selectin) in human ECs, which are important elements of leukocyte homing (Bianconi, Sahebkar, Atkin, & Pirro, 2018; Pejler, Abrink, Ringvall, & Wernersson, 2007). Upon release of MMPs and MC tryptase, different components of the pericellular and extracellular matrix (ECM) undergo degradation, thereby predisposing a plaque to rupture (Kovanen, 2007a).

Angiogenesis as an important hallmark of atherosclerosis is also affected by MC tryptase. Indeed, they induce the formation of microvessel tubes and elevate the growth of microvessel ECs (Blair et al., 1997). In a model of atherosclerosis using *ApoE*−/− mice, targeted treatment of perivascular MC with activators such as dinitrofluorobenzene and

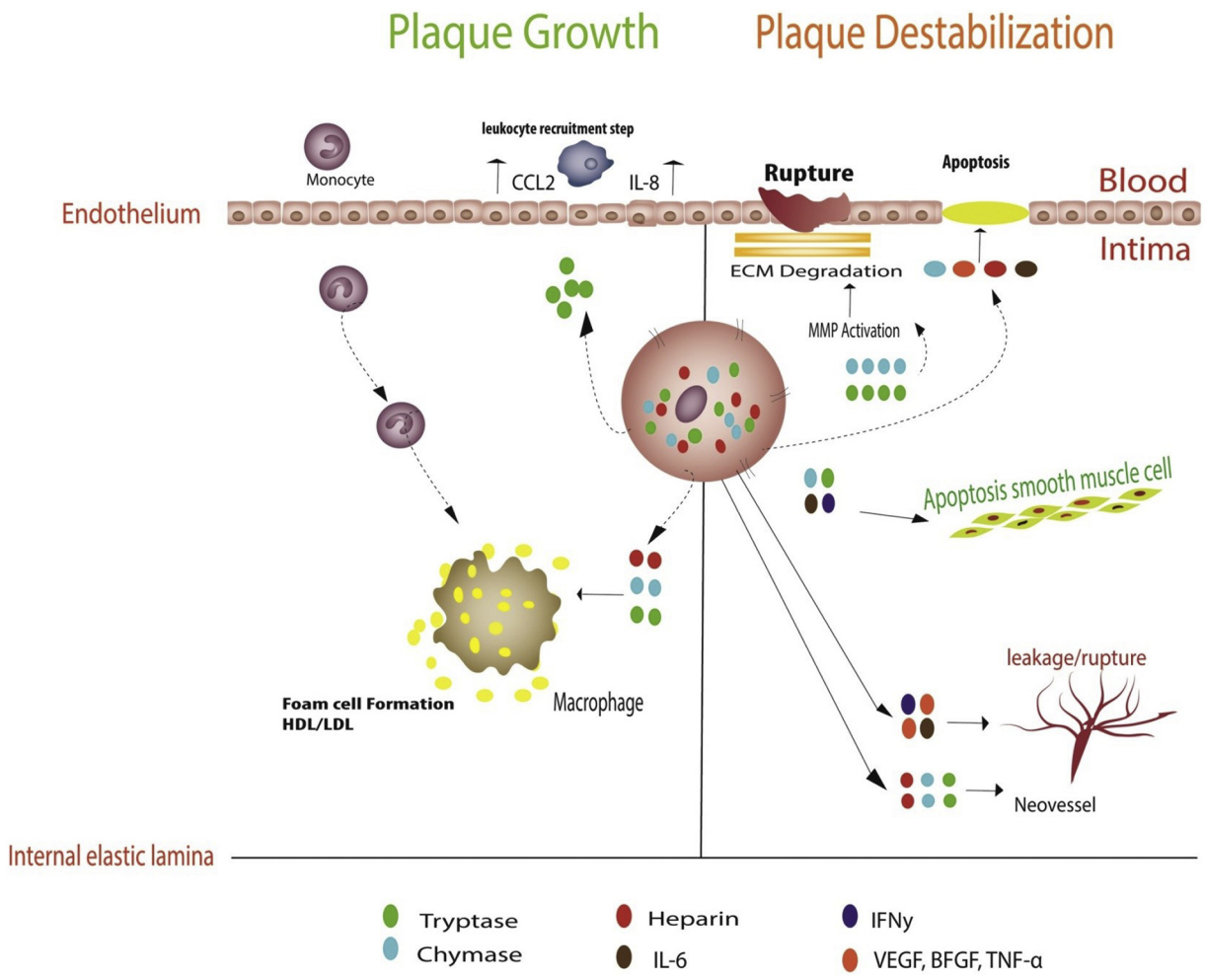

Fig. 1. The role of activated mast cells in plaque growth (left) and destabilization (right) during the formation and progression of atherosclerosis. An activated mast cell (center) releases an array of proatherogenic mediators. Depending on the type of the activating stimulus, as well as the phenotype of the MCs, the activated MCs secrete granule stored and/or newly synthesized mediators. The mediators are listed at the bottom of the Figure, and their sites of action are shown. *Plaque growth*: endothelial cells are activated to secrete monocyte-inviting chemokines. In the subendothelial intima, the monocytes become differentiated into macrophages, and further converted to cholesterol-containing foam cells. *Plaque destabilization*: apoptosis of endothelial cells exposes thrombogenic subendothelial layer. Plaque rupture results from activation of matrix metalloproteinases (MMPs) with ensuing degradation of the extracellular matrix (ECM). Moreover, apoptosis of smooth muscle cells and induction of neovascular sprouts and their leakage and rupture, all destabilize the plaque and render it susceptible to rupture. Both loss of endothelial cells (erosion) and plaque rupture expose subendothelial prothrombotic tissue, and so trigger formation of a local arterial thrombus. Mast cell-derived tryptase is involved directly and/or indirectly in the pathways described.

dinitrophenyl enhanced the frequency of intraplaque hemorrhage, histamine- and tryptase-mediated macrophage apoptosis, vascular leakage, and chemokine receptor CXCR2/very late antigen-4-mediated leukocyte recruitment to the lesions (Bot et al., 2007).

Thus, MC tryptase can cause plaque erosion and atherothrombotic complications via inducing apoptosis of endothelial cells in plaques with thick caps (11). Plaques at high risk are composed of a large acellular lipid-laden necrotic core and an overlying thin fibrous cap. Indeed, the development of new fragile and leaky vessels leads the necrotic core to enlarge that culminates in increased plaque vulnerability to rupture. In addition, physical factors (e.g., biomechanics, hemodynamics) are associated with plaque destabilization. Plaque rupture is responsible for exposing necrotic core constituents to the circulation, enabling the stimulation of tissue factor, development of the coagulation cascade, and recruitment of platelets and inflammatory cells, notably neutrophils in this late atherothrombotic stage (Kolodgie et al., 2017).

7. Role of tryptase in the formation and progression of abdominal aortic aneurysm

The interplay among components of atherosclerotic plaque exposed to flowing blood, platelet receptors, and clotting factors, results in platelet stimulation, aggregation, and the ensuing generation of atherothrombosis (Badimon & Vilahur, 2014). AAA is a good example of this sequence of events that exemplifies a specifically localized form of atherothrombosis where increased proteolytic activity impairs the ECM, resulting, not only in inward growth, but also in outward growth of the affected site of the aortic wall, which ultimately result in the wall rupture (Michel et al., 2010). Histopathological characteristics of the arterial wall in case of AAA present lipid deposits trapped in foam cells, free cholesterol crystals in the extracellular space, calcifications, thrombosis, angiogenesis, inflammatory cell infiltration in the adventitia, along with ulceration of the endothelial layers and sometime of the whole arterial wall, often resulting in sudden death of the patient.

A variety of inflammatory cells (i.e., macrophages, lymphocytes, neutrophils, and MCs) residing at the site of injury generate cytokines and proteases, which further trigger inflammatory responses, aortic medial SMC apoptosis, ECM disruption, as well as neovascularization that largely contribute to AAA pathogenesis (Rizas, Ippagunta, & Tilson 3rd., 2009). It was documented that MCs induce vascular cells (i.e., SMC, EC) to express proteases via secreting their inflammatory cytokines (i.e., IL-6, TNFα, IFNγ), thereby promoting angiogenesis, vascular cell apoptosis, and ECM degradation (Sun et al., 2007). The study by Mäyränpää and colleagues substantiated the association of MCs with

inflammation, neovascularization, and intraluminal thrombus in human AAA (Mäyränpää et al., 2009). The findings of real-time PCR analysis highlighted the significantly higher concentrations of vascular endothelial growth factor, its receptor FLT1, vascular endothelial-cadherin, CD31, tryptase, chymase, and cathepsin G in AAA compared to normal arteries showing increased angiogenesis levels in AAA lesions. Moreover, human AAA luminal surface demonstrated $CD42b^{+}$ platelets adherence contributing to endothelial erosion of the AAA wall (Furubayashi et al., 2007).

The role of MCs in angiogenesis and vascular cell apoptosis discussed earlier likely contributes to AAA pathogenesis with the involvement of tryptase. Importantly, serum tryptase concentrations correlated with AAA annual expansion rate in a follow-up study on Danish patients with AAA (Zhang et al., 2011). By an unknown mechanism, tryptase controls cathepsin expression related to atherosclerosis development in AAA (Kaschina et al., 2009; Sun et al., 2009). Of note, high serum tryptase levels were associated with increased risks of later surgical repair of AAA or death of the patient. In mice, after experimental AAA formation caused by elastase perfusion, those animals without tryptase mMcp6 showed notably smaller AAA lesions than did wild-type mice. This study also emphasized the involvement of tryptase in apoptosis of vascular SMCs, infiltration of inflammatory cells, as well as expression and activities of elastinolytic cathepsin by vascular cells, rather than in enhancement of angiogenesis (Zhang et al., 2011). Interestingly, both human and animal affected by AAA exhibit augmented levels of MC-specific tryptase and their AAA lesions possess macrophage-specific enzymes (Zhang et al., 2011). What is more, monocytes as well as MCs from tryptase-deficient mice were similarly found with the decreased expression of the cathepsins (B, K, L, S) (Zhang et al., 2011). The key role of cathepsins K, L, and S in AAA pathogenesis has been unraveled employing experimental AAA caused by aortic elastase perfusion or angiotensin-II infusion (Qin et al., 2012; Sun et al., 2011; Sun et al., 2012). The lack of tryptase can considerably inhibit AAA formation or progression.

Another study compared the effect of bone marrow-derived MCs (BMMCs) from wild-type or tryptase-deficient mice, and found that the wild-type BMMCs promoted mouse aortic SMC death, whereas the tryptase-deficient BMMCs did not participate in the induction of aortic SMC apoptosis in the studied AAA model (Zhang et al., 2011). Although not addressed in this study, BMMCs from tryptase-deficient mice are more likely to fail the induction of EC apoptosis. Furthermore, monocytes from tryptase mouse MC protease-6–deficient (Mcpt6−/−) mice notably diminished the expression and activities of cathepsins B, S, K, and L (Zhang et al., 2011). Taking together, the above findings imply both direct and indirect effects of tryptase on AAA development.

8. Tryptase in systemic circulation as a biomarker of mast cell activation

Tryptase levels in biological fluids can be representative of MC number and/or activation (Schwartz, 2001). There exists only one commercial method now available for the measurement of human tryptase in body fluids (ImmunoCAP Tryptase, Thermo Fisher Scientific, Phadia, Sweden). Though verified for serum and plasma it has not been verified for other fluids such as *in vitro* cell culture supernatants. This technique considers the total concentration of α- and β-tryptase in the form of mature (tetrameric) and immature (monomeric) molecules, i.e. the "total tryptase" level (Schwartz et al., 1994); put differently, it does not differentiate between the α and β forms, neither between tetrameric and monomeric forms. Importantly, as tryptase are the only proteins known to be expressed in all human MCs, and only in the MCs of the human body, their plasma level ("total tryptase") is the only currently available convenient and reliable marker of the activation status and the total body burden of MCs, i.e. the size a person's total tryptase-secreting MC population.

In healthy individuals the tryptase baseline levels have been reported to range approximately between 1 and 15 μg/L (or ng/mL). The median value of serum tryptase at baseline in adults hovers around 3.8 μg/L. Of note, the findings collected from Thermo Fisher in 126 apparently healthy subjects (61 males, 65 females, age range 12–61 years) indicated that the majority of healthy people (95%) had tryptase values of 11.4 μg/L or less (Thermo Scientific, 2017). A state without MC activation or MC disorders retains tryptase values of a given donor rather constant over time. As for children, a median value for tryptase is 3.5 μg/L when aged 6 months–18 years, in accordance with a study including 197 US children, and two others recruiting 213 French children (Belhocine et al., 2011; Ibrahim, Bongrand, Carayon, & Vitte, 2009; Komarow et al., 2009). A recent study carried out in infants during the first three months of life pinpointed significantly higher levels of serum tryptase (median 6.1 μg/L) (Belhocine et al., 2011). With the exception of serum tryptase levels in younger than 6-month-old infants, the levels do not differ notably between adults and children. Elderly patients have slightly but considerably augmented levels of tryptase, with a median of 4 μg/L in age category of 18–30 years and 6.6 μg/L in individuals over 80 years of age (Blum, Gunzinger, Muller, & Helbling, 2011; Gonzalez-Quintela et al., 2010). A reduced renal excretion of tryptase might be responsible for the higher levels in old persons, a notion supported by the observation that tryptase levels are on the rise as renal failure gets worse, which commonly occurs amongst older patients (Simon et al., 2010; Sirvent et al., 2010).

In case of MC disorders, four chief categories have been established with applications for diagnostic frameworks (Valent et al., 2012). The first is MC activation syndrome (MCAS), a notable transient elevation in serum tryptase levels (or in another MC-derived mediator, e.g., PGD2, histamine), and clinical responsiveness to drugs with inhibitory effects over MC mediators (Valent, 2013; Valent et al., 2012). This category itself includes primary MCAS (monoclonal *KIT*-mutated MCs), secondary MCAS (IgE-dependent allergy or any other inflammatory disorder), and idiopathic MCAS (neither underlying disease nor clonal MC abnormality). The second category refers to mastocytosis, as characterized by clonal MC growth and MC accumulation in different tissues and organs, such as skin and bone marrow. Cutaneous and systemic mastocytosis are typical examples in this regard. Of note, the clinical manifestations of mastocytosis are various, and so are the underlying MC mutations and laboratory results (e.g., serum tryptase levels) (Alvarez-Twose et al., 2014; Bonadonna et al., 2009; Valent et al., 2012). MC hyperplasia, the third class, was observed to ensue certain pathologic conditions (e.g., parasitosis with a tissue phase) and diseases (i.e., variants of mastocytosis) (Metcalfe, 2008). The last category regards myelomastocytic conditions with substantial clinical and pathologic overlap with systemic mastocytosis (Chiu & Orazi, 2012). Representative example of this category is myelomastocytic leukemia with rare incidence and grave prognosis (Valent et al., 2001). Given that MC hyperplasia and myelomastocytic conditions are truly rare, whereas MCAS is as a relatively common disorder, the following parts of this section deal with the pathogenesis of MCAS and mastocytosis with a particular focus on clinical cardiovascular symptoms, which may be caused by MC activation and ensuing release of various bioactive molecules, among them the tryptase both as a causal factor and as a biomarker of the activation process (Ballesteros-Martinez et al., 2017; Fassio & Almerigogna, 2012; Molderings, Brettner, Homann, & Afrin, 2011; Sun et al., 2007; Xiang et al., 2011).

8.1. Supraventricular tachycardia and cardiac arrest

Patients with systemic mastocytosis (29%) and MCAS (at least 20%) have been observed to typically present with palpitations and episodes of supraventricular tachycardia (Alvarez-Twose et al., 2010; Bazan-Socha, Rudzki, Maciejewicz, Witkos, & Szczeklik, 2001; Crawhall & Wilkinson, 1987; Horan & Austen, 1991; Molderings et al., 2011; Ricciardi et al., 2005; Rohr, Rich, & Silver, 2005). In MCAS patients, hyperadrenergic postural tachycardia syndrome is frequent (Molderings, Likungu, Hentrich, & Göthert, 1988). Rohr et al. reported

a case developing recurrent syncope, acute myocardial injury and ventricular fibrillation (Rohr et al., 2005). A biopsy specimen derived from the skin rash area denoted mastocytosis in this patient. According to the WHO diagnostic criteria (sensitivity >80%, specificity ~ 100%), increased levels of MC mediators support the diagnosis of mastocytosis, particularly, when serum tryptase level is higher than 20 ng/mL (Rohr et al., 2005). Ridolo et al. proposed cardiac arrest or ventricular fibrillation as initial indications of anaphylaxis associated with systemic mastocytosis and suggested the evaluation of serum tryptase in case on such cardiac emergencies (Ridolo et al., 2013). In their study, three patients had very high values of serum tryptase ranging from 75 to 200 ng/mL in different conditions, such as several days after the cardiac arrest, few hours after the cardiac arrest or even 3–6 months after a wasp sting (normal range < 11.4 ng/mL) (Ridolo et al., 2013).

8.2. Irregularities of blood pressure regulation

Hemodynamic presentations of MCAS are variable. Several patients present with a notable and even dramatically reduced blood pressure, whereas others develop a substantially enhanced blood pressure. There are some MCAS cases displaying both hypotension and hypertension or an occasional condition promptly fluctuating from one to the other. Dramatic acute symptoms, including episodes of hypotension, lightheadedness or syncope are manifest in 22–55% of the MCAS patients (Alvarez-Twose et al., 2010; Molderings, Haenisch, Bogdanow, Fimmers, & Nöthen, 2013; Travis, Li, Bergstralh, Yam, & Swee, 1988; Valabhji et al., 2000). In an observational study, Alvarez-Twose et al. indicated that the mean value of serum baseline tryptase was 15.4 (RR 2.7–30) μg/L among nonclonal MCAS patients (Alvarez-Twose et al., 2010). Additionally, the prevalence of hypotension did not significantly differ from nonclonal MCAS patients displaying high (30% of patients) or normal (33% of patients) levels of serum baseline tryptase. The cut-off values of <11.5 or 15 μg/L, and >25 μg/L were used to indicate normal and high serum baseline tryptase in their study (Alvarez-Twose et al., 2010). In a comparative study between adults and children with mastocytosis, Brockow et al. unraveled that the cumulative incidence of anaphylaxis was higher in adults (49%) than in children (9%) (224). The adult patients were at high risk for developing anaphylaxis with cardiovascular symptoms as primary events, i.e., in 44% dizziness/presyncope, in 47% tachycardia, and in 50% hypotension or shock. The authors reported that patients with anaphylaxis possessed greater basal tryptase values than their peers without anaphylaxis (60.2 ± 55 vs. 21.2 ± 33 ng/mL) (Brockow, Jofer, Behrendt, & Ring, 2008). On the other hand, up to 31% of MCAS patients may experience significant recurrent or sustained increases in arterial blood pressure due to MC activation (Alvarez-Twose et al., 2010; Jennings et al., 2014; Roberts & Oates, 1991).

8.3. Chronic heart failure

Though supported by animal experiments (Balakumar et al., 2008; Batlle et al., 2006; Hara et al., 2002; Joseph et al., 2003; Kim et al., 2006; Shiota et al., 2003), the involvement of MCs in the development of congestive heart failure in humans is unclear (Clarke, 2012; McElroy Jr, Phyliky, & Li, 1998; Sotlar, Horny, Lebherz, Leser, & Bültmann, 1997). In a retrospective cohort study including 548 Danish adults with mastocytosis, patients presented with congestive heart failure (2%), perivascular disease (2%), and MI (2%) (Cohen et al., 2014). A prospective study was conducted on seventeen MCAS patients to elucidate the suspected cardiac effect on an elevated systemic MC activation (Kolck, 2009). This study demonstrated no pathological changes in systolic left ventricular function, systolic or diastolic left ventricular diameter, neither in the shortening fraction. Nevertheless, twelve of the seventeen patients had a diastolic left ventricular dysfunction, as manifested in pulse wave- and/or tissue-Doppler imaging. Moreover, left ventricular hypertrophy occurred in five of these twelve patients (Kolck, 2009). The same study group also noted that despite some signs of heart failure in MCAS patients, the prevalence of symptomatic chronic heart failure in this setting seemed not to be greater than in the general population (Kolck, Haenisch, & Molderings, 2016). Unfortunately, none of the above-listed studies reported about serum tryptase levels in the studied patients.

8.4. Acute coronary syndromes

The clinical implication of MC activation has been shown in patients with variant angina and coronary spasm (Forman et al., 1985; Sakata et al., 1996), denoting a role for coronary MCs as a potent ultimate trigger of anginal attacks (Forman et al., 1985). There have been many case reports of MCAS patients who might have developed Prinzmetal (variant) angina or an allergic ACS (i.e., Kounis syndrome; KS) (Fassio & Almerigogna, 2012; Gonzalez-de-Olano et al., 2012; Ward & Schwartz, 2011). González-de-Olano et al. described 10 patients, of whom, five were diagnosed with nonclonal MCAS, two with clonal MCAS, and another two with indolent systemic mastocytosis (Gonzalez-de-Olano et al., 2012). One case was also identified with the probability of clonal MCAS/indolent systemic mastocytosis. All patients had been admitted due to a history of oppressive chest pain indicative of ischemic heart disease. On coronary angiography, three were categorized as type I variant KS, one as type II variant, and the other four remained unclassifiable. In addition to the probable case (3.08 μg/L), only one nonclonal MCAS patient (6.3 μg/L) presented normal tryptase levels (i.e., <11.4 μg/L). Hypertension occurred both in the patients with the highest (60 μg/L) and with the lowest (3.08 μg/L) level of tryptase. Therefore, serum tryptase levels during acute coronary symptoms might provide evidence for a potential role of MC activation in the pathogenesis of ACSs (Gonzalez-de-Olano et al., 2012).

A baseline tryptase level of 57 ng/mL was documented by Ward and Schwartz in a male patient presenting with a history of flushing and substernal chest pain preceding episodes of syncope (Ward & Schwartz, 2011). ECG findings exhibited marked ST-segment elevations, and the patient was diagnosed to have both Prinzmetal angina and systemic mastocytosis. The authors of this study concluded that MC mediators, notably the tryptase, was involved in the coronary vasospasm. Considering the rarity of cardiac manifestations of systemic mastocytosis, it is more likely that mastocytosis coincided with recurrent episodes of cardiac instability (Ward & Schwartz, 2011). A contrasting view was expressed by Paratz et al., who concluded that even lethal cardiac manifestations due to a coronary spasm might be the first sign of systemic mastocytosis (Paratz, Khav, & Burns, 2017). They reported about a 72-year-old male patient with a long-standing history of unexplained syncope, who proceeded to percutaneous coronary intervention for a tight coronary artery stenosis. Thirty minutes after the intervention, the patient suffered cardiac arrest, and an urgent repeat angiography demonstrated profound coronary artery spasm in two coronary arteries with only moderate atherosclerotic changes, a finding consistent with KS. Serum tryptase levels were >200 μg/L shortly after the cardiac arrest, and declined to 56 μg/L after 24 h. A second arrest occurred three days later, and systemic mastocytosis was ultimately diagnosed. The authors then undertook a structured systematic review of cardiac presentations of adult patients with systemic mastocytosis. They concluded that such patients are predominantly male, and that short-term mortality is high, and that unexplained cardiac arrest may be in the first presentation of systemic mastocytosis.

Regarding the mechanism of coronary artery spasm caused by activated MC, it is important to recognize that histamine, which is a major vasodilator of the microvasculature, actually causes vasospasm in atherosclerotic coronary segments, where endothelial dysfunction prevails (Ginsburg, Bristow, Davis, Dibiase, & Billingham, 1984). Some previous clinical observations strongly support this conclusion. Accordingly, a patient with variant angina, who ultimately experienced unexpected cardiac death, showed a higher extent of adventitial MCs in the spastic coronary segment (Forman et al., 1985). Importantly, the adventitial

MCs in atherosclerotic coronary segments contain histamine and are highly activated to degranulate and release histamine. Since the MCs are located next to the adventitial microvessels which extend to the medial layer of the coronary artery, the secreted histamine can reach the contractile smooth muscle cells of the medial layer and cause their contraction. In a clinical study, eight patients with variant angina were found with the increased level of histamine in the great cardiac vein, followed by coronary spasms with ensuing attacks of angina (Sakata et al., 1996). Finally, the serum concentration of tryptase elevated during spontaneous ischemic episodes in unstable angina as a sign of MC activation and mediator release (Cuculo et al., 1998).

In another report, a case of type I variant of KS was diagnosed on the basis of increased cardiac biomarkers during an anaphylactic reaction to hymenoptera venom (Leli, 2012). The patient had hypotension with no history of cardiac risk factors or allergy. Measurement of serum tryptase was not possible at baseline, but it reached 3.59 (RR 2–10) μg/L following intravenous treatment with hydrocortisone sodium succinate, chlorphenamine, and ranitidine (Leli, 2012). Filipiak et al. highlighted an elevation of serum tryptase in 52 ACS patients (11.90 ± 10.46 ng/mL) compared to 10 control subjects without ischemic heart disease (4.88 ± 1.85 ng/mL) (Filipiak et al., 2003). The lowest levels of serum tryptase were observed in the acute phase of ACS (8.05 ± 4.63 ng/mL). On the other hand, the highest concentrations were associated with ST-segment depression both in the acute phase (12.71 ± 11.36 ng/mL) and at follow-up (17.55 ± 15.39 ng/mL). These results suggested that serum tryptase levels can afford to discern patients with distinct types of ACSs (Filipiak et al., 2003). Similarly, in a study by Cuculo et al. 8 patients with unstable angina during a spontaneous ischemic episode and 5 patients with variant angina during ergonovine-induced coronary spasm were evaluated in terms of tryptase levels in their peripheral blood samples after the onset of chest pain and ECG changes (Cuculo et al., 1998). The patient in the former group experienced a significant increase in the serum level of tryptase (multiplied by a 5 factor) at 5 min after the onset of pain, normalizing after 15 min, while in the second group, no change in serum tryptase was detected. Put differently, tryptase levels did increase during spontaneous episode of myocardial ischemia, rather than after ergonovine-induced ischemia in variant angina, implying that MC activation in ACS is a primary event, and not secondary to coronary spasm itself (Cuculo et al., 1998).

On the other hand, among patients without ACSs, but who were undergoing cardiac catheterization because of chronic coronary artery disease, those with significant coronary atherosclerosis (≥50% stenosis in ≥1 artery) had significantly higher serum tryptase levels than patients with normal angiography or with only non-significant coronary artery stenosis (<50%) (Upadhya et al., 2004).

8.5. Atherosclerosis

The relationship between blood tryptase levels and atherosclerotic plaque instability has been investigated (Deliargyris et al., 2005; Filipiak et al., 2003; Xiang et al., 2011). A recent study on patients with non-alcoholic fatty liver disease showed the positive association of circulating tryptase levels with body mass index, fat mass, glycated haemoglobin, homeostasis model assessment of insulin resistance, fasting insulin, fasting triglycerides, and the high-sensitive C-reactive protein (Moreno et al., 2014). The measured values of tryptase ranged from <7.9 μg/L to >15.7 μg/L. Tryptase levels were significantly related to carotid intima-media thickness measurements, and were greater in those patients with carotid plaque. It was shown that tryptase levels could independently predict subclinical atherosclerosis variance following adjustment for other cardiovascular risk factors (i.e., body mass index, blood pressure, LDL-cholesterol). More importantly, the area under the curve for tryptase with contribution to atherosclerosis was 0.653 (0.532–0.774) in both genders (Moreno et al., 2014). Likewise, a cohort study on Chinese population with coronary heart disease suggested the role of serum tryptase as an independent biomarker for coronary plaque stability (Xiang et al., 2011). Patients with angiography-established coronary heart disease had higher values of serum tryptase than did their counterparts with <50% or without luminal coronary narrowing in angiography (7.81 ± 0.52 *vs.* 6.11 ± 0.51 ng/mL). Adjustment for covariates (i.e., age, fasting glucose, total cholesterol, LDL cholesterol, triglycerides) did not change this finding. The highest values of tryptase were seen in AMI patients (11.13 ± 1.55 ng/mL). Further analyses showed that serum tryptase were associated remarkably with age, whereas the levels of fasting glucose, total cholesterol, LDL cholesterol, and triglyceride showed a week correlation to serum tryptase levels (Xiang et al., 2011).

Willems et al. found that the plasma levels of tryptase were significantly higher in patients with any cardiovascular event (5.3 ng/mL with RR 4.2–6.9) than in control subjects (4.5 ng/mL with 3.7–5.8) (Willems et al., 2013). Interestingly, the term "any cardiovascular events" included a wide variety of clinical condition, such as non-fatal or fatal stroke, non-fatal or fatal myocardial infarction, sudden death, other vascular death, or any arterial vascular intervention that had not been planned at the time of inclusion, e.g., carotid surgery or angioplasty, coronary artery bypass, percutaneous coronary artery intervention, peripheral vascular surgery or angioplasty. Additionally, in the above-cited study, the tryptase levels had a positive correlation with the number of degranulating MCs in the plaque, suggesting that the accumulation of degranulating MCs at the site of injury not only causes the local matrix degradation, but is also indicative of the systemic changes that contribute to the secondary events (Willems et al., 2013). Another study conducted on patients without ACS undergoing cardiac catheterization indicated that MC tryptase values were higher in patients with a significant coronary artery disease characterized by coronary stenosis ≥50% than in those with only a mild stenosis (i.e., <50%) (8.38 *vs.* 6.78 μg/L) (Deliargyris et al., 2005). Conversely, other studies have not shown such correlation in patients with ACS (Kervinen et al., 2005; van Haelst et al., 2001). Thus, in patients enrolled in the study by van Haelst and colleagues (van Haelst et al., 2001), the levels of tryptase were 7.9 ± 4.6, 6.0 ± 2.1, and 6.9 ± 4.1 μg/L in patients with AMI, unstable angina pectoris, and controls (without ischaemic CVDs), respectively. This conflicting evidence may arise from immeasurable small release of tryptase into the systemic circulation from acutely activated MCs in a ruptured plaque, or due to constant state of activation of plaque MCs, also with immeasurable release of tryptase. This latter option is more probable, since in patients without an acute allergic reaction, the MCs in the inflamed plaque are in a state of permanent low-grade activation, and, accordingly, they only slowly weaken the cap or the vulnerable shoulder regions of the plaque, thereby predisposing them to ultimate erosion or rupture (Kervinen et al., 2005; Kovanen, Kaartinen, & Paavonen, 1995).

As noted above, AAA has the potential to directly increase serum tryptase levels, and a population-based randomized screening study, that included a 100 Danish men with defined AAA and 35 age-matched male controls, showed a substantial increase in log transformed data of plasma tryptase levels (1.80 ± 0.35 ng/mL) compared to controls (1.69 ± 0.20 ng/mL) (Zhang et al., 2011). However, a number of patients in the control group (25.7%) reported another comorbidity such as, AMI, angina pectoris, stroke, or hypertension. Serum tryptase levels before the log transformation were 103.6 ± 1881.1 and 56.2 ± 55.6 ng/mL in AAA patients and their controls, respectively. Smokers approximately constituted nearly half of them (42.9%). There existed a weaker correlation between initial AAA size and tryptase levels. Furthermore, the results of Cox regression analysis demonstrated that high plasma tryptase levels in AAA patients accounted for the risk of later surgical repair prior to (hazard ratio [HR]: 1.74) and following (HR: 2.15) adjustment for confounders, i.e., AAA size, use of glucocorticoids, body mass index, diastolic blood pressure, use of aspirin, current smoking, lowest ankle–brachial blood pressure index, coexisting cardiovascular and pulmonary disease, and age. Importantly, a high plasma tryptase level was found to associate with overall mortality prior to (HR: 1.43) and following (HR: 3.17) adjustment. These findings were

Table 1
Circulating tryptase levels in patients with various atherosclerotic cardiovascular diseases.

Authors	Numbers of study subjects	Participants/subgroups	Disorder(s)	Major findings and interpretations by the authors of the cited papers
Patella et al. (1995)	2 subjects	2 patients undergoing heart transplantation for cardiomyopathy	Mast cells from the transplanted heart were isolated and cultured for analysis	Strong correlation between histamine and tryptase release from mast cells caused by addition of anti-IgE suggested that the human myocardial mast cells contained IgE-receptor-bound IgE on their surfaces
Filipiak et al. (2003)	62 subjects	52 patients with ACS 10 control subjects	34 patients with ST-elevation MI and 18 patients with unstable angina or non-ST-elevation MI	At each time point (admission; 2nd week; 3rd month) tryptase levels were higher in unstable angina/non-ST-elevation MI than in -ST-elevation MI. Lowest levels in Controls. Mast cell-derived tryptase was postulated as potential new marker of unstable plaque, and also to reflect the fibrinolytic status of the patient
Upadhya et al. (2004)	85 subjects	Patients undergoing diagnostic cardiac catheterization	CAD in 56 patients and congestive heart failure in 13 patients	Elevated tryptase levels in patients with CAD. Low typtase levels in patients with congestive heart failure due to clinically significant cardiomyopathy (in contrast to increased levels of IL-6 and TNFα)
Deliargyris et al. (2005)	102 subjects	Angiographic evaluation of all subjects: 66 patients with significant CAD (> 50% stenosis), 23 patients with non-significant CAD (< 50% stenosis), 13 patients with normal angiography (evaluation of heart failure)	Stable CAD or hearth failure	Significantly higher tryptase levels in patients with significant CAD than in patients with non-significant CAD or patients with normal angiography. Tryptase may emerge as a new biomarker of patients with CAD without clinical instability
Kervinen et al. (2005)	183 subjects	ACS and acute MI	64 with acute angina 60 with unstable angina, 59 with myocardial infarction 41control subjects	Tryptase levels within 24 h after onset of chest pain remained stable and did not differ from those in the control subjects. Local activation of coronary mast cells with release of immeasurable low amounts of tryptase into the systemic circulation was speculated as a potential final trigger of plaque rupture
Filipiak et al. (2007) (Available in ResearchGate)	70 subjects	All patients with ACS	34 patients with ST-elevation MI 36 patients with unstable angina or non-ST-elevation MI	Serum tryptase concentrations were higher in unstable angina/non-ST-elevation MI patients than in ST-elevation MI patients. The authors extrapolated the results to reflect degranulation of myocardial mast cells rather than mast cells in the culprit coronary lesion
Caroselli, Perfetti, and Bruno (2009)	A single 38 y-old cocaine addict	No control subjects	Massive acute MI	Tryptase levels strongly increased, suggestive of cocaine-induced mast cell activation and coronary vasospasm
Xiang et al. (2011)	270 subjects	Chinese patients with varying degrees of CHD (unsubstantial CHD, stable or unstable angina pectoris, or MI)	CHD	Serum tryptase levels were nearly doubled in MI, when compared with those in any other studied group
Willems et al. (2013)	270 subjects	264 patients (6 of 270 were excluded) with a stenosing carotid artery plaque. All underwent carotid endarterectomy 175 control patients	A 3-year follow-up for any cardiovascular event. 89 patients with an event 175 patients without an event (designated as “controls”)	Carotid plaques with a high number of mast cells showed unstable and vulnerable phenotypes. Patients with high numbers of activated intraplaque mast cells had increased plasma tryptase levels and more cardiovascular event during the follow-up. This implied that the carotid tryptase-secreting mast cells were representative for the systemic changes responsible for the secondary cardiovascular events
Chen et al. (2014)	124 subjects	99 consecutive patients with first-time ST-elevation MI 25 control patients with atypical chest pain and normal coronary arteries verified by coronary angiography	Patiens with MI were treated with PCI	Serum tryptase levels were significantly increased at admission, and decreased after PCI. High tryptase levels after PCI associated with poor myocardial reperfusion and poor cardiac function, suggesting that blocking of tryptase release may beneficial for improving myocardial reperfusion after PCI
Laroche, Gomis, Gallimidi, Malinovsky, and Mertes (2014)	100 subjects	75 patients in allergy group 25 patients in control group	Patients having life-threatening allergic reactions under anesthesia Patients resuscitated from cardiac or other types of shock	Tryptase (and histamine) levels were significantly elevated in patients with allergic reactions. The resuscitation manoeuvers *per se* did not increase tryptase or histamine levels
Moreno et al. (2014)	228 subjects	Consecutively recruited patients from FLORINASH Project	Varying degrees of carotid atherosclerosis, which ranged from increased carotid intima-media thickness to carotid plaques	Tryptase levels were significantly elevated in obese individuals and associated positively with various parameters indicating insulin resistance. Tryptase levels associated strongly with pathologically increased carotid intima-media thickness values, and were higher in the presence than in the absence of carotid plaques. Thus, tryptase may independently contribute to subclinical carotid atherosclerosis in obese subjects, and its determination could be used as a surrogate marker for subclinical atherosclerosis in obese subjects

Table 1 (*continued*)

Authors	Numbers of study subjects	Participants/subgroups	Disorder(s)	Major findings and interpretations by the authors of the cited papers
Pastorello et al. (2014)	100 subjects	65 consecutive ACS patients 35 healthy controls	ACS	In ACS patients, tryptase levels could predict the composite measure of clinical and angiographic cardiovascular complexity more reliably than other relevant biomarkers (C-reactive protein and high-sensitivity troponin)
Kazim and Zayr (2015)	62 subjects	40 patiens with cardiorenal syndrome 22 patients in control group	Cardiorenal syndrome	Elevated tryptase in serum of patients with cardiorenal syndrome, in contrast to normal subjects
Lewicki et al. (2015)	52 subjects	33 patients with ST-elevation MI 19 controls	CAD of varying severity Healthy volunteers	Serum tryptase levels were higher in ST-elevation MI patients than in healthy volunteers. Patients with one-, two-, or three-vessel CAD had similarly increased tryptase leves, like had the patients with or without significant LAD stenosis. Thus, tryptase levels did not correlate with the severity of CAD
Pastorello et al. (2015)	65 subjects	23 patients with MACE during 2-year follow-up 42 patients without MACE during 2-year follow-up	ACS	Tryptase level measured during admission was significantly correlated to development of MACE up to 2 years, revealing a long-term predictive value for tryptase
Kazim, Hadree, and Zayr (2016)	52 subjects	30 Patients with CVD (not clinically specified) and diabetes in Baghdad, Iraq 22 healthy controls	Diabetes and CVD	Tryptase levels were significantly higher in patients with CVD and diabetes than in healthy controls
Morici et al. (2016)	190 subjects	140 consecutive patients with ACS 50 control patients	62 ACS patients with ST-elevation 78 ACS patients without ST-elevation	In patients with ACS, tryptase measurement at admission, when added to conventional validated biomarkers (high-sensitivity troponin, high-sensitivity C-reactive protein and SYNTAX score), improves risk stratification regarding recurrent MI within 2 years. No difference between the 2 types of ACS were reported

ACS = Acute coronary syndrome; CAD = Coronary artery disease; CHD = Coronary heart disease; CVD = Cardiovascular disease; FLORINASH Project = The role of intestinal microflora in non-alcoholic fatty liver disease (NAFLD) Project; LAD = Left anterior descending coronary artery; MI = Myocardial infarction; MACE = Major adverse cardiac event; PCI = Percutaneous coronary intervention.

also substantiated by those of immunostaining and immunoblotting; aortic sections from AAA lesions presented considerable tryptase immunoreactivity in the adventitia and media versus non-AAA and extracts prepared from these lesions were found to contain more tryptase than those from normal aortas (Zhang et al., 2011).

9. Medicinal inhibitors of mast cell tryptase

Initially, human tryptase was extracted from human lung MCs in 1981 and afterwards directly from a number of other human tissues, including pituitary, lung, and skin (Hernández-Hernández et al., 2012). Because of its significant influences on allergic and inflammatory events, tryptase has garnered more attention from scholars and has been viewed as a potent therapeutic agent for over two decades (Sismanopoulos et al., 2012; Zhang & Shi, 2012). Considering past reports, there are three classes of tryptase inhibitors (Caughey, Raymond, Bacci, Lombardy, & Tidwell, 1993; Clark et al., 1995; Hopkins et al., 2005). The first class is composed of a reactive functional group capable of forming a covalent bond between the inhibitor and the enzyme with no selectivity and yet possibility of being toxic due to the overall binding affinity (Rice, Tanaka, Katz, Numerof, & Moore, 1998). The second class consists of a basic P1 group, namely amidino, benzylamine, or guanidino that develops a hydrogen-bonding network, which can identify the substrates, participate in the cleaving reactions, and ultimately inhibit tryptase's activity (Burgess et al., 1999). The first inhibitors of this class with the basic P1 group (pKa > 11) and high molecular weight were shown with poor oral bioavailability. Accordingly, a series of new inhibitors were created using a less basic P1 group (pKa~9) and low molecular weight. The best examples are APC366 (MW: 440.5) (Krishna et al., 2001) and (5-amidino-2-benzimidazolyl) methane (BABIM) (MW: 332.4) (Caughey et al., 1993), both of which have revealed marked improvements in pharmacokinetic properties. The inhibitors belonging to the third class mainly counteract a part of serine proteinases (e.g., thrombin) carry a non-basic P1 group, and fail to produce a direct H-bonding interaction with Asp189 (Stubbs et al., 1997), that culminates in more favorable pharmacokinetic properties, oral bioavailability in particular, but no applicability for tryptase (Liang et al., 2012).

10. Synthetic inhibitors of tryptase

10.1. Benzene sulfonamide-based tryptase inhibitors

Tryptase inhibitors are compounds characterized as bisaryl benzamidine sulfonamides (Burgess & Rizzi, 2001). The two sulfonamide groups are able to promptly bind two adjacent S1 active sites of the tryptase and more likely to subsequently suppress the proteolysis of protein substrates, namely vasoactive intestinal peptide. A well characterized compound of this type is 1,5-bis-{4-[(3-carbamimidoylbenzenesulfonylamino)-methyl]-phenoxy-pentane (AMG-126737) with a relatively high molecular weight (MW: 678.8) and selective inhibition of serine proteases, including tryptase (Ki = 90 nM) (Burgess et al., 1999; Pereira et al., 1998). Whilst there is evidence from experimental studies (guinea pig and sheep models) supporting its intratracheal therapeutic application in antigen-induced airway responses, further studies will be required to investigate its effectiveness in CVDs both *in vitro* and *in vivo* (Burgess & Rizzi, 2002; Wright et al., 1999).

10.2. Benzimidazole-based tryptase inhibitors

This class of inhibitors consists of a benzimidazole that interferes with the hydrogen-bonding interaction with residue Asp189 of tryptase (Anderskewitz et al., 2002, 2003; Sommerhoff et al., 1994). In general, bis(benzimidazole) difluoromethane (CRA-9249) and bis(5-amidino-2-benzimidazo-lyl)methane (BABIM) are two examples of benzimidazole-based tryptase inhibitors, similarly having two benzimidazoles in their structures (Anderskewitz et al., 2002). The former is orally bioavailable and still in preclinical studies due to rapid degradation when exposed to liver microsomes in models of rabbit, dog,

Table 2
Serum tryptase levels: forensic studies after cardiovascular and non-cardiovascular deaths.

Authors	Numbers of study cases	Cases/subgroups	Disorder(s)	Major findings and interpretations by the authors of the cited papers
Edston and van Hage-Hamsten (1995)	56 autopsy cases	29 cases of sudden coronary death 27 non-cardiac fatalities as controls	Coronary artery thrombosis and/or recent acute MI	Increased numbers of coronary mast cells in coronary death cases, but no increase in circulating tryptase or IgE levels. Therefore, allergic mechanisms or anaphylactic reactions in the pathogenesis of acute myocardial infarction were excluded
Edston and van Hage-Hamsten (1998)	193 autopsy cases	176 with known causes of death 10 unexplained deaths 7 anaphylactic or anaphylactoid deaths	Known cause of death Unknown Anaphylactic or anaphylactoid deaths	Tryptase cut-off level = 10 ng/mL was found optimal for post-mortem detection of anaphylactic or anaphylactoid mode of death in unexplained cases. Such tryptase cut-off level could also reflect contribution of mast cell activation in other causes of death with anaphylactoid reactions (e.g. of idiopathic origin or after exercise)
Edston, Gidlund, Wickman, Ribbing, and Hage-Hamsten (1999)	44 autopsy cases	Infants younger than 1.5 years	Sudden infant death	Association between a prone position (hypoxia) at death and elevated tryptase level. In 40% elevated tryptase levels. Hypothetically, mast cell degranulation due to a hypoxic stimulus in the infants. No support for and allergic mechanism of mast cell activation in sudden infant death
Horn, Halsey, and Zumwalt (2004)	57 autopsy cases	Cases categorized into 4 groups: Presence or absence of atherosclerotic cardiovascular disease and/or chest trauma	Non-anaphylactic deaths. Widely differing intervals between death and sampling time	No significant differences between the groups. Both tryptase and IgE levels demonstrated a significant elevation with increasing postmortem interval, which ranged from 1 to 126 h. It follows that chiefly the early postmortem period remains a helpful suggestive test for antemortem anaphylaxis
Edston, Eriksson, and van Hage (2007)	60 autopsy cases	39 cardiovascular deaths within minutes 16 deaths caused by prolonged asphyxia 5 anaphylactic deaths	Sudden cardiac death or acute aortic dissection Traumatic chest compression/suffocation Anaphylaxis	No increase of tryptase level in acute cardiovascular death or in asphyxia, but strong increase in anaphylaxis. In all studied groups had higher values in cardiac ventricular blood and in femoral blood
Ramalho et al. (2013)	44 autopsy cases	16 cardiovascular deaths 28 non-cardiovascular deaths	All patients had atherosclerosis of various degrees in thoracic and/or abdominal aorta: 24 with discrete, 13 with moderate, and 7 with severe degree of atherosclerosis	Positive correlation between degree of atherosclerosis and the density of tryptase- and chymase-containg mast cells in the lesions. The results support a role for tryptase and chymase in aggravation of atherosclerotic lesions
Comment, Bonetti, Mangin, and Palmiere (2014)	94 autopsy cases	A wide variety of causes of death. No control group	Both anaphylactic and non-anaphylactic causes of death	In patients who had died of anaphylaxis, β -tryptase levels were very high in serum, and they were increased also in the pericardial fluid, but much less than in the serum. In other types of death, tryptase levels were similar in the serum and pericardial fluid. In the vitreous humor of the eye and in urine, typtase levels were normal in all patients
Sravan, Tse, and Cala (2015)	1 autopsy case	Death from ant bite	Anaphylactic death	Two separate serum tryptase measurements were taken from the same femoral vein 24 h apart (at days 2 and3 after death), and the levels were 130 and 84.4 μg/L, respectively. The patient had reportedly early childhood asthma, previous anaphylactic reactions to ant bite, atopic disease, and indolent mastocytosis with baseline tryptase level of 40 μg/L.
Xiao et al. (2017)	74 autopsy cases	20 patients with anaphylactic shock 17 patients with acute cardiovascular death 13 patients with ACS 10 patients with acute dissecting aneurysm rupture 14 patients with pneumonia or methamphetamine poisoning (serving as controls)	Acute cardiac deaths compared with other types of acute deaths	All groups of patients with cardiovascular deaths had elevated levels of tryptase. Among them, the patients with ACS had the highest levels. Attention should be paid to the differential diagnosis between anaphylactic death and non-anaphylactic acute cardiovascular death
Tse, Garland, and Ahn (2018)	1 autopsy case	Death from intravenous antibiotic administration	Anaphylactic death	Serum tryptase level was measured from femoral blood 3 and 6 days after death, and yielded values of 522 μg/L and 300 μg/L, respectively (baseline value before before intravenous injection of benzylpenicillin was 5.6 μg/L). Since in living subjects tryptase returns to baseline 24 to 72 h after anaphylactic stimulus, the postmortem decline is much slower.

ACS = Acute coronary syndrome; MI = Myocardial infarction.

Table 3
Experimental *in vivo* studies evaluating selected roles of tryptase in cardiovascular diseases.

Authors	Species	Gender	Animal model	Major findings and conclusions
Kitaura-Inenaga et al. (2003)	Mice	Inbred	DBA/2J	Mouse mast cell proteases with tryptic and chymotryptic activities participate in the progression of heart failure and cardiac remodeling
Judström et al. (2010)	Mice	Female	NMRI	Proteolytic inactivation of HDL by mast cell-derived tryptase and chymase inhibits the ability of HDL to induce cholesterol efflux from macrophage foam cells. By preventing cholesterol removal from atherosclerotic plaques, tryptase may accelerate atherogenesis
Sharma and McHowat (2011)	Rabbit	Both sexes	Hearts obtained from normal adult rabbits	PGE2 release from tryptase-stimulated rabbit ventricular myocytes is mediated primarily by iPLA2γ, suggesting mast cells a role in cardiac inflammation
Zhi et al. (2013)	Mice	Male	ApoE−/−	Tryptase promotes atherosclerotic plaque hemorrhage by promoting angiogenesis via altering the balance of PAI-1 and TPA. Thus, regulating tryptase expression in mast cells may provide a potential target for atherosclerosis treatment

cynomolgus monkey, and human (Yu et al., 2006). Conversely, BABIM has considerable selectivity and can bind to the active site of tryptase in the presence of a zinc ion that strengthens the binding (Anderskewitz et al., 2004); the zinc ion is bound to two nitrogens of BABIM and two residues of tryptase (i.e., His57 imidazole, Ser195 hydroxyl) (Tidwell, Geratz, Schwab, Pryzwansky, & Anderle, 1990). Moreover, the amidine group of BABIM forms a hydrogen-bonding interaction with Asp189 of tryptase to stabilize the tryptase-inhibitor complex (Katz et al., 1998). In a study by Clark et al. it was shown to inhibit allergen-induced asthma-like airway inflammatory responses in allergic sheep model (Clark et al., 1995); particularly, at the treatment regimen of 9 mg/3 mL H_20 given 0.5 h before, 4 h after, and 24 h after antigen challenge it reduced both peak early and late increases in specific lung resistance. Also, in a study by Geratz et al. it was proved to be effective in the treatment of arthritis induced by streptococcal cell wall fragments in Lewis rats; the results from this study pave the way to further investigations aimed at exploring its potential application in the treatment of similar conditions in humans (Clark et al., 1995; Geratz, Pryzwansky, Schwab, Anderle, & Tidwell, 1988).

10.3. Benzylamine-based tryptase inhibitors

These inhibitors are regarded as the structural analogues of the second class, which possess a benzylamine to interact with the two adjacent active sites (Asp189 residues) in tryptase. In this regard, MOL 6131 is a potent inhibitor with notably selective action because of the interaction occurring between an aniline ring of MOL 6131 and Asp189 residue of tryptase (Aydt, Kranich, Vollhardt, & Wolff, 2011; Oh et al., 2002). Its effectiveness was shown in the context of allergic airway inflammation and airway hyper-reactivity using a murine model of asthma induced by inhalation of tryptase (Molinari et al., 1996).

10.4. Dipeptide-based tryptase inhibitors

Dipeptide-based tryptase inhibitors have a dipeptide at the center of their structure (Costanzo et al., 2003). The guanidine group of these inhibitors interact with the active site forming a complex with Asp189 residue (Caughey et al., 1993). Structurally, the presence of a benzothiazole and ketone is necessary for bonding to His57 of tryptase and Ser195, respectively (Costanzo et al., 2005). This class includes RWJ-51084, RWJ-56423, RWJ-58643, and APC-366. RWJ-51084 only has a single amino acid residue, a low molecular weight (MW = 387.5), and effective inhibition of tryptase (Ki =88 nM) (Costanzo et al., 2003; Recacha et al., 1999). RWJ-56423 is another potential with reversible activity, low molecular weight, and protection against tryptase (Ki =10 nM) and its activity has been studied (Sperandio et al., 2006). The potent RWJ-56423-mediated inhibition of antigen-induced asthmatic responses (70–75% blockade of the early response and complete inhibition of the late response) in an allergic sheep model have suggested its application in the treatment of asthma(Costanzo et al., 2003; Kenney et al., 2007). RWJ-58643 is the L-Arg diastereoisomer for RWJ-56423. It is not orally bioavailable, while it is well-absorbed following intranasal injection. In a randomized double-blind crossover clinical study, its intranasal administration was tested as a potential novel approach to treat allergic rhinitis; in this study RWJ-56423 showed a dose-dependent therapeutic action in allergic inflammation (Erin et al., 2006). Although its action against tryptase is time-dependent, poorly selective, and irreversible, APC-366 has been substantiated as a potential candidate for treating allergen-induced late-phase airway obstruction, hepatic fibrosis, asthma, and other inflammatory diseases (Bunnett & Corvera, 1999; Levell et al., 2005; Lu, Chen, Li, & Sun, 2014; Rice et al., 1998; Sylvin, Dahlbäck, Van Der Ploeg, & Alving, 2002). Noteworthy, APC-366-mediated inhibition of tryptase was found to block ox-LDL-induced foam cell formation from macrophages through the upregulated expression of ATP-binding cassette transporters (Yeong, Ning, Xu, Li, & Yin, 2010). Thus, further studies should investigate the potential anti-atherosclerotic activity of this compound.Finally, other analogues of these inhibitors, APC-2059 as an example, have been investigated for the development of anti-inflammatory drugs (Tremaine et al., 2002).

10.5. Guanidino-based tryptase inhibitors

An extension of the fourth class for the purpose of anti-inflammatory drugs results in guanidino-based tryptase inhibitors (Costanzo, Maryanoef, & Yabut, 2006; Costanzo, Maryanoff, & Yabut, 2002). APC-2059 and nafamostat mesilate are the most typical examples of this class of inhibitors. The second generation of APC-366, APC-2059, is 10,000 times more selective than the previous generation drugs. Its application in case of psoriasis, inflammatory bowel disease, of note ulcerative colitis, have attracted more attention recently. Particularly, it has entered phase I/II clinical trials for the treatment of ulcerative colitis, showing promising results. (Bayes, Rabasseda, & Prous, 2003; Gangloff, Kuo, Dener, & Rice, 2003; Tremaine et al., 2002).

Nafamostat mesilate or FUT-175 (6-amino-2-naphtlyl p-guanidinobenzoate dimethansulfonate) shows significant but nonspecific inhibition against human tryptase (Ishizaki et al., 2008; Sendo et al., 2003). There is evidence from experimental studies of nafamostat-mediated tryptase inhibition in different inflammatory conditions. In a murine model of allergic asthma nafamostat administration was associated with suppression of airway eosinophilic inflammation and remodeling of airway epithelium. In an experimental model of colitis nafamostat inhibited significantly the colonic mucosal inflammation, suggesting tryptase inhibition as a potential therapeutic strategy against inflammatory bowel diseases (Isozaki et al., 2006). In addition, there is evidence from animal studies for its use in the treatment of allergic inflammation, acute pancreatitis, periodontitis and disseminated intravascular coagulation (Fujii, Okutome, Nakayama, Yaegashi, & Kurumi, 1984; Holzhausen et al., 2011; Hwang, Hyun, Moon, Lee, & Yoon, 2013; Ishizaki et al., 2008). Finally, there is preliminary evidence suggesting that nafamostat-mediated tryptase inhibition may have beneficial effects on vascular function. Accordingly, in human umbilical vein endothelial cell (HUVEC) cultures, nafamostat was shown to reduce the expression of endothelial cell adhesion molecules and to increase nitric oxide (NO) generation (Choi et al., 2016; Kang et al., 2015).

10.6. Beta lactam-based tryptase inhibitors

Beta lactam-based tryptase inhibitors possess a beta lactam in the middle of their structure to establish a covalent binding to Ser195 (Bisacchi et al., 2002). In addition to C2 carbonyl in the beta lactam, these inhibitors are composed of guanidin groups at C-3, which tend to reside in the S1 pocket of tryptase via forming a salt bridge between Asp189 and substituents at N-1 of the azetidinone nucleus (Sutton et al., 2004). Typical compounds of this class are BMS-262084 and BMS-363131. BMS-262084 was found an influential inhibitor (Ki = 4 nM) with a moderate-to-good selectivity with aqueous stability (Qian, Zheng, Burke, Saindane, & Kronenthal, 2002). However, it exhibited poor absorption and oral bioavailability in a murine model (Kamath et al., 2005; Molinari et al., 1996). There has been some animal-based evidence in support of its use for reducing the bronchoconstriction and the airway infiltration of inflammatory cells (Sutton et al., 2002). BMS-363131 has a high potency (Ki < 1.7 nM), marked selectivity, and enhanced hydrolytic stability making it a potent inhibitor of tryptase. Using the ovalbumin-sensitized guinea pig model of lung inflammation, it was found that the intratracheal administration of BMS-363131 carried a lowering effect on inflammatory cell numbers (Sutton et al., 2002; Treuner et al., 1999).

10.7. Spirocyclic piperidine amide-based tryptase inhibitors

The seventh class refers to those inhibitors with a spirocyclic piperidine and an amino group on the same side of their structure. They have selectivity for tryptase and good oral bioavailability, desiderable characteristics for potential clinical applications. As an example, JNJ-27390467 exerts its inhibitory effects on tryptase through the interaction between the phenylethynyl group and a hydrophobic pocket in the active site of tryptase (Ki = 3.7 nM). Extensive investigations in sheep and guinea pig asthma models have shown its oral efficacy as well as ability to effectively block the late-phase and airway inflammation responses (Costanzo et al., 2008). Data on JNJ-27390467-mediated tryptase inhibition in experimental models of atherosclerosis are lacking.

11. Tryptase inhibitors from natural sources

There have been some reports concerning tryptase inhibitors from natural sources, such as leech-derived tryptase inhibitor (LDTI), lactoferrin, myeloperoxidase (MPO), and the peptide leucine arginine (pLR). LDTI is a small peptide (46 amino residues) produced by the medicinal leech *Hirudo medicinalis* that is composed of three disulfide bridges (Ribatti, 2016; Sperandio et al., 2006) and the presence of the amino-terminal Lys-Lys sequence selectively inhibits human lung tryptase with Ki = 1.4 nM by electrostatic interactions (Ribatti, 2016; Sperandio et al., 2006; Stubbs et al., 1997; Tanaka et al., 1999). LDTI has been shown to inhibit tryptase *in vitro* and to mitigate the tryptase-induced growth of human fibroblasts and keratinocytes (Pohlig et al., 1996). Lactoferrin is produced by mucosal epithelium and neutrophils when exposed to inflammatory stimuli. It has an iron-binding capacity with the potential to suppress tryptase activity (78 kDa). *In vitro* studies have reported that this natural molecule offered a selective and time-dependent inhibition against tryptase (Ki = 24 nM) in a heparin-dependent manner (Mann, Romm, & Migliorini, 1994). Lactoferrin exert this inhibitory action by decreasing tryptase stabilization without interfering with tryptase enzymatic activity (He et al., 2003). In the allergic sheep model of asthma, it was shown to inhibit the late-phase bronchoconstriction as well as airway hyperresponsiveness (Elrod, Moore, Abraham, & Tanaka, 1997). The third product, MPO, is a cationic neutrophil protein with a molecular weight of 118-kDa. Its secretion from activated neutrophils constitutes the main part of host response to microbial infection (Schleimer, 1988). Also, it is utilized as an indicator of neutrophil infiltration in inflammatory conditions, namely asthma and rhinitis (Linder, Venge, & Deuschl, 1987). Besides this antimicrobial activity, MPO has shown a potent and time-dependent inhibitory action against tryptase *in vitro* (Ki = 16 nM) (Cregar, Elrod, Putnam, & Moore, 1999). MPO inhibits human MC tryptase in a time-dependent manner by promoting the disruption of tryptase tetramers to inactive monomers. Heparin can prevent MPO-mediated tryptase inhibition by inducing tryptase tetramer stabilizazion (Cregar et al., 1999).

Last but not least, pLR comes from a class of cyclic peptides derived from frog skin (Salmon et al., 2001). It shows potent inhibitory effects on tryptase (Ki = 8 nM). In a murine model, pLR was reported as a compound of utmost importance to decline the acute and the chronic asthma phenotype (Polte, Fuchs, Behrendt, & Hansen, 2009).

The tryptase inhibition ability of none of these compounds has been investigated in experimental models of atherosclerosis. Thus, further studies should investigate this issue.

12. Conclusions and future perspective

Compelling evidence from clinical, clinico-pathological and experimental studies suggests that activation of MCs with ensuing release of tryptase may exert significant roles in the pathogenesis of atherosclerosis and its clinical complications (Tables 1, 2 and 3; Fig. 1). The fact that tryptase is a MC-specific enzyme, and the knowledge that after MC activation in any tissue, a fraction of the released tryptase finds its way into the circulation, where its concentration can be reliably measured by a specific immunoassay, have allowed to perform clinical studies in patients with various forms of cardiovascular diseases. The circulating levels tryptase have been observed to be increased in patients with various atherosclerotic CVDs, particularly after acute coronary events, so revealing a local or systemic activation of MCs in this group of diseases. Importantly, in patients with an acute coronary event, an increased tryptase level at admission to the hospital has been found to significantly correlate to the future development of a major adverse cardiac event, revealing a long-term predictive value for tryptase (Pastorello et al., 2015). However, also normal tryptase levels have been reported in patients with subclinical atherosclerosis or after an acute coronary event. Thus, more clinical studies are needed to define whether an increased plasma level of tryptase is a causative factor or a late marker of an acute cardiovascular event, i.e., whether it is a cause or a consequence of the event. In this respect, the study by Pastorello and coworkers is of great interest, as it demonstrated that in patients with acute coronary events, the level of circulating tryptase could predict the composite measure of clinical and angiographic cardiovascular complexity (Pastorello et al., 2014). Moreover, clinical and experimental studies suggest a role for activated MCs in other forms of CVDs. Thus, activated MCs in the aortic wall and the myocardium may contribute to the formation and progression of abdominal aortic and various forms of myocardial damage, respectively (See Table 2).

Accumulated evidence from numerous studies in animal models and in humans proves that tryptase inhibitors possess therapeutic potential in different inflammatory conditions, particularly in allergic asthma. To date, two distinct types of tryptase inhibitors from synthetic or natural resources have been developed, but no clinical trial has yet directly addressed their inhibitory effect against MC activation for the purpose of prevention or treatment of CVDs. The development of new and specific inhibitors targeting tryptase activities with high specificity and bioavailability would allow such studies to be performed. The results of such clinical trials would also help us in defining the role of tryptase, and, in more general terms, also the role of MCs – the only cellular source of tryptase in the human body – in various forms of cardiovascular diseases.

Conflict of interest

None of the authors have any competing interests to disclose.

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