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Invited Commentary

Tryptase levels in coronary syndromes and in hypersensitivity episodes: A common pathway towards Kounis syndrome

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Evidence exists today, that the same mediators released from similar cells such mast cells are present in both acute coronary events and acute hypersensitivity episodes [1]. It seems likely that a common pathway exists between the hypersensitivity coronary syndrome the so called Kounis syndrome [2] and non-hypersensitivity coronary syndromes [3]. One of these common mediators is the mast cell derived specific neutral protease tryptase.

In the very important paper, concerning 270 Chinese patients, published in this Journal [4] it was found that serum tryptase levels were significantly higher in patients with substantial coronary heart disease including unstable angina and acute myocardial infarction than in patients with unsubstantial disease namely patients with less than 50% or without luminal narrowing of the main coronary arteries. The authors of this report suggested that tryptase and the brother protease chymase are important independent biomarkers for atherosclerotic plaque vulnerability. Although in this cohort, patients with any kind of autoimmunity, allergic diseases, cancer, and renal failure were correctly excluded other patients with conditions known to have also elevated baseline serum tryptase levels [5] such as mastocytosis, refractory anemias, myelodysplastic syndromes, hypereosinophilic syndrome, and patients receiving recombinant human stem cell factor should have been excluded also.

However, several other studies have also shown that elevated tryptase levels are present during acute coronary syndromes and

they have emphasized the significance of measuring these in patients with coronary events.

In a previous study [6], tryptase levels were elevated in patients with non-allergic acute coronary syndromes with higher concentration in the ST segment depression group of patients and it was postulated that tryptase may be a potential new marker characterizing the unstable plaque and may differentiate patients with distinct types of acute coronary syndromes. Tryptase levels were found also elevated in non-allergic patients with significant coronary artery disease as a result of chronic low-grade inflammatory activity present in the atherosclerotic plaques [7]. It is proposed that tryptase measurements may emerge as a novel way of identifying asymptomatic patients with coronary, artery disease and represent a new biomarker of therapeutic efficacy in these patients [7].

Tryptase is a preformed neutral protease which has been estimated to constitute approximately 20% of the total cellular protein of human mast cells [8]. Mast cells constitute the sole source of tryptase, although negligible amounts of tryptase are found in human basophils (0.04 pg per basophil) [9]. This trypsin-like serine proteinase is stored fully active in the cytoplasmic granules of all human mast cells and is released in the peripheral circulation [10]. This enzyme exists as a tetramer composed of 31 kDa glycoprotein subunits and accounts for more than 20% of the total cellular protein [11].

Tryptase has the following important cardiovascular effects:

1. Activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin that can promote plaque disruption or rupture [12].

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2. Degrades the pericellular matrix components fibronectin and vitronectin and neuropeptides, such as vasoactive intestinal peptide and calcitonin gene related peptide [13].
3. Degrades HDL [14].
4. Activates neighboring cells by cleaving and activating protease-activated receptor (PAR)-2, and thrombin receptors [15,16].
5. Exerts dual action on the coagulation cascade with both thrombotic and fibrinolytic properties [17].

An important question which arises in acute coronary events is whether inflammatory cells including mast cells and their contents such as serum tryptase are the cause and not the result of the event. There is now evidence that mast cells not only enter the culprit lesion before plaque erosion or rupture but also release their contents before an actual coronary episode. For example, tryptase levels were raised during spontaneous ischemic episodes in 8 patients suffering from unstable angina [18], but not after ergonovine-provoked ischemia in 5 patients suffering from variant angina, suggesting that a primary yet unknown stimulus activates mast cells just before the episodes of unstable angina. In another report [19], infiltrates of activated mast cells were found at the site of coronary atheromatous erosion or rupture in a ratio of 200:1 compared with normal adjacent endothelial segments. It is known that circulating blood contains only mast cell precursors and these precursors take several days to weeks to differentiate into morphologically identifiable mast cells filled with cytoplasmic secretory granules [20,21]. Therefore, the mast cells must already have been present at the erosion or rupture sites before the episode in the above patients

Another question is that allergic episodes are common in everyday practice, but only few patients develop severe reaction such as chest pain with/or electrocardiographic changes, manifesting as Kounis syndrome, during these episodes. Therefore, the need to predict severe consequences and the risk of Kounis syndrome in patients with hypersensitivity episodes is always a challenging issue and of paramount importance for the physicians. We had previously suggested that a threshold level of mast cell content (tryptase, chymase, etc.) exists [22] above which it can provoke coronary artery spasm and/or plaque erosion or rupture. Furthermore, the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody-antigen reaction, the allergen concentration and the route of allergen entrance could be some additional factors. Recent reports show that, patients with increased serum baseline tryptase are prone to developed immediate and severe hypersensitivity reaction to hymenoptera sting [23]. Such patients were found to have underlying clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome [24]. In these patients, bone marrow aspiration showed mast cell granulomas and spindle-shaped mast cells, flow cytometric analysis of mast cells revealed mast cells expressing CD2 or CD25 in their surface and KIT mutation analysis showed KIT mutation at codon 816. KIT is the mast cell receptor for the stem cell factor which is essential for mast cell development, proliferation, survival, adhesion, and homing. Therefore, patients with serum baseline tryptase greater than normal might have KIT mutations that lower the stimulus threshold for anaphylaxis, and have hyperresponsive mast cell phenotype [5]

resulting in the development of Kounis syndrome. Research efforts on this matter are currently under progress.

Therefore, the above Chinese study [4] is important because it may shed light in both predicting coronary plaque instability and foreseeing severe reaction leading to an actual coronary event such as Kounis syndrome, but further studies are needed to corroborate it.

References

- [1] Lopez PR, Peiris AN. Kounis syndrome. *South Med J* 2010;103:1148–55.
- [2] Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
- [3] Kounis NG, Kouni SN, Koutsojannis CM. Myocardial infarction after aspirin treatment, and Kounis syndrome. *J R Soc Med* 2005;98:296.
- [4] Xiang M, Sun J, Lin Y, et al. Usefulness of serum tryptase level as an independent biomarker for coronary plaque instability in a Chinese population. *Atherosclerosis* 2011;215:494–9.
- [5] Metcalfe DD, Schwartz LB. Assessing anaphylactic risk? Consider mast cell clonality. *J Allergy Clin Immunol* 2009;123:687–8.
- [6] Filipiak KJ, Tarchsalska-Krynska B, Opolski G, et al. Tryptase levels in patients with acute coronary syndromes: the potential new marker in unstable plaque? *Clin Cardiol* 2003;26:366–72.
- [7] Deliargyris EN, Upadhyay B, Sane DC, et al. Mast cell tryptase: a new biomarker in patients with stable coronary artery disease. *Atherosclerosis* 2005;178:381–6.
- [8] Schwartz LB. Tryptase from human mast cells: biochemistry, biology and clinical utility. *Monogr Allergy* 1990;27:90–113.
- [9] Castells M, Irani AA, Schwartz LB. Evaluation of human peripheral blood leukocytes for mast cell tryptase. *J Immunol* 1987;138:2814–9.
- [10] Thomas VA, Wheelless CJ, Stack MS, Johnson DA. Human mast cell tryptase fibrinogenolysis: kinetics, anticoagulation mechanism, and cell adhesion disruption. *Biochemistry* 1998;37:2291–8.
- [11] Schwartz LB, Lewis RA, Austen KF. Tryptase from human pulmonary mast cells. Purification and characterization. *J Biol Chem* 1981;256:11939–43.
- [12] Jackson CL, Angelini GD, George SJ. Activation of matrix-degrading metalloproteinases by mast cell proteases in atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 1998;18:1707–15.
- [13] Fajardo I, Pejler G. Human mast cell beta-tryptase is a gelatinase. *J Immunol* 2003;171:1493–9.
- [14] Lee-Rueckert M, Kovanen PT. Mast cell proteases: physiological tools to study functional significance of high density lipoproteins in the initiation of reverse cholesterol transport. *Atherosclerosis* 2006;189:8–18.
- [15] Meyer MC, Creer MH, McHowat J. Potential role for mast cell tryptase in recruitment of inflammatory cells to endothelium. *Am J Physiol Cell Physiol* 2005;289:C1485–91.
- [16] Molino M, Barnathan ES, Numerof R, et al. Interactions of mast cell tryptase with thrombin receptors and PAR-2. *J Biol Chem* 1997;272:4043–9.
- [17] Lombardini C, Helia RE, Boehlen F, Merlani P. Heparinization and hyperfibrinolysis by wasp sting. *Am J Emerg Med* 2009;27. p. 1176.e1–1176.e3.
- [18] Cuculo A, Summari F, Schiavino D, et al. Tryptase levels are elevated during spontaneous ischemic episodes in unstable angina but not after ergonovine test in variant angina. *Cardiologia* 1998;43:189–93.
- [19] Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995;92:1083–8.
- [20] Valent P, Spanbloshe E, Sperr WR, et al. Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor (CSF)/kit ligand (KL) in long-term culture. *Blood* 1992;80. 2337–2245.
- [21] Irani AA, Nilsson G, Miettinen U, et al. Recombinant human stem cell factor stimulates differentiation of mast cells from dispersed human fetal liver cells. *Blood* 1992;80:3009–21.
- [22] Mazarakis A, Koutsojannis CM, Kounis NG, Alexopoulos D. Cefuroxime-induced coronary artery spasm manifesting as Kounis syndrome. *Acta Cardiol* 2005;60:341–5.
- [23] Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol* 2009;123:680–6.
- [24] Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. *Blood* 2007;110:2331–3.