

LETTER TO THE EDITOR

Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), Acute Myocardial Infarction and the Kounis Syndrome

To the Editor:

In their very important paper published in *Archives of Medical Research* (1), the authors found that EMMPRIN and matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 expression was increased in the area surrounding the infarct zone in human acute myocardial infarction (AMI) and this may play a critical role in left ventricular remodeling.

However, they have omitted to comment on the role of MMPs in degrading the fibrous cap of vulnerable atheromatous plaque, which is the primary step in the development of coronary thrombosis. Elevated plasma levels of different MMPs have been found in patients with acute myocardial infarction and are associated with severe coronary stenosis and cardiovascular mortality (2).

In AMI, MMP-9 has been found to be secreted into the plasma and therefore can serve as a marker of AMI (3). The vulnerability of atheromatous plaques is characterized by the accumulation of inflammatory cells, mainly mast cells, T-lymphocytes and macrophages, as well as MMPs that have been incriminated to degrade the fibrous plaque cap.

In recent AMI, infiltration of activated mast cells has been found in a ratio of 200:1 at the site of coronary atheromatous erosion or rupture compared with normal endothelial segments (4). Mast cells, when stimulated, degranulate and release their neutral proteases (tryptase and chymase) into the surrounding microenvironment. Every mast cell at the erosion or rupture site was found to contain tryptase, and a significant fraction of these also contained chymase. Furthermore, in this study the proportion of mast cells that released at least some of their tryptase (and chymase) contents was highest at the site of erosion or rupture. Even though tryptase and chymase have limited activity against the various components of the extracellular matrix, they have both been shown to effectively activate the zymogen forms of metalloproteinases (5) such as interstitial collagenase, gelatinase and stromelysin (the pro-MMPs), tryptase-activating prostromelysin (pro-MMP-3) and chymase activating the zymogen form of interstitial collagenase (pro-MMP-1). It should be emphasized that activated interstitial mast cells constitute the sole source of plasma tryptase.

In Kounis syndrome type II variant patients, with culprit but quiescent pre-existing atheromatous disease, the acute release of inflammatory mediators from these inflammatory

cells can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as AMI (6).

Therefore, it seems that a new possibility emerges for the prevention of the progression of coronary plaques to unstable lesions and, that is, apart from inhibition of inflammatory cell degranulation, the EMMPRIN inhibition. The first has already been achieved experimentally by abrogating late thrombotic events via stabilization of mast cell membrane with sodium chromoglycate and reduction of inflammation with dexamethasone (7).

References

1. Nie R, Xie S, Du B, et al. Extracellular matrix metalloproteinase inducer (EMMPRIN) is increased in human left ventricle after acute myocardial infarction. *Arch Med Res* 2009;40:605–611.
2. Muzzio ML, Miksztoewicz V, Brites F, et al. Metalloproteinases 2 and 9, Lp-PLA(2) and lipoprotein profile in coronary patients. *Arch Med Res* 2009;40:48–53.
3. Kai H, Ikeda H, Yasukawa H, et al. Peripheral blood levels of matrix metalloproteinases-2 and -9 are elevated in patients with acute coronary syndromes. *J Am Coll Cardiol* 1998;32:368–372.
4. 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;92:1083–1088.
5. Johnson JC, Jackson CL, Angelini GD, et al. Activation of matrix-degrading metalloproteinases by mast cell proteases in atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 1998;18:1707–1715.
6. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
7. Nemmar A, Hoet PHM, Vermylen J, et al. Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. *Circulation* 2004;110:1670–1677.

NICHOLAS G. KOUNIS
GEORGE N. KOUNIS
GEORGE ALMPANIS
ANDREAS MAZARAKIS
and CONSTANTINOS KOUTSOJANNIS

Address reprint requests to: Nicholas G. Kounis
Department of Medical Sciences
Patras Highest Institute of Education and Technology
7 Aratou Street, Queen Olga's Square
Patras 26221, Greece
Phone/Fax: +302610279579
E-mail: ngkounis@otenet.gr