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ABSTRACT N. CO18

LABORATORIO E FATTORI PREDITTIVI

RELATIONSHIP BETWEEN GUT PERMEABILITY AND PCSK9 IN HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA.

V. Castellani[1], V. Cammisotto[2], F. Baratta[2], S. Bartimoccia[3], C. Nocella[2], L. D'erasmo[1], N. Cocomello[2], C. Barale[4], R. Scicali[5], I. Russo[4], F. Purrello[5], R. Carnevale[3], F. Violi[2], M. Arca[1], P. Pignatelli[2].

1_Department of Translational and Precision Medicine, Sapienza University of Roma, Roma; [2]Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Roma; [3]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Roma, Roma; [4]Department of Clinical and Biological Sciences, University of Turin, Turin; [5]Department of Clinical and Experimental Medicine, Internal Medicine, University of Catania, Catania;.

Background: Gut dysbiosis is a major determinant of low-grade endotoxaemia via dysfunction of the intestinal barrier scaffold, which is a prerequisite for Lipopolysaccharide (LPS) translocation into the systemic circulation. Endotoxaemia is associated with atherosclerotic burden and its clinical sequelae. Moreover, current data show that LPS is cleared from the circulation via low-density lipoprotein receptors (LDLR) on hepatocytes, which are downregulated by proprotein convertase subtilisin/kexin type 9 (PCSK9), protein directly associated with circulating LDL cholesterol (LDL-C) level and in the onset of hypercholesterolemia.

The aim was to analyze the relationship between PCSK9, gut permeability and endotoxemia after the treatment with PCSK9 inhibitors (PCSK9i).

Methods: We performed a before-after study including 40 patients with heterozygous familial hypercholesterolemia (HeFH) on treatment with maximum tolerated statin dose ± ezetimibe before and after six months of PCSK9i therapy. We analysed plasma PCSK9 levels, intestinal permeability marker such as zonulin, endotoxemia marker such as LPS and oxidized-LDL (ox-LDL) that play a central role in atherosclerotic process, by enzyme-linked immunosorbent assay (ELISA). To study a potential mechanism of intestinal permeability, Caco2 cells, a well characterized intestinal in vitro model, were treated in vitro with PCSK9, and the expression of occludin, an integral membrane thigh junction protein, and zonulin levels were evaluated.

Results: We observed a significant decline in LDL-C, zonulin, LPS, and ox-LDL levels after six months of PCSK9i compared to baseline. Furthermore, linear regression analysis showed that LPS levels were associated with LDL-C and zonulin reduction, suggesting a relationship between gut permeability and PCSK9 levels. In vitro, PCSK9, at concentration of 50-150-300 ng/ml, significantly reduced the protein levels of occludin compared to unstimulated cells whereas increased levels of zonulin. The treatment with NOX2ds-tat and PCSK9i significantly improve occludin expression and reduced zonulin levels in cell media.

Conclusions: This study provides evidence that PCSK9i could improve intestinal permeability by reducing circulating endotoxemia as well as oxLDL production by counteracting the atherosclerotic process in HeFH patients.

Email: *valentina.castellani@uniroma1.it*