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Gabor Csanyi
Augusta University, USA

Co-Authors
Hui-Ping Lin, Bhupesh Singla
Pushpankur Ghoshal,
Mary Cherian-Shaw and **David Fulton**
Vascular Biology Center, USA

Receptor-independent LDL macropinocytosis by macrophages contributes to the pathogenesis of atherosclerosis

Aims: Hypercholesterolemic mice lacking CD36 and SRA, two major scavenger receptors (SRs), are only partially protected from atherosclerosis. These results support the existence of an alternative, receptor-independent pathway of lipid internalization that contributes to the pathogenesis of atherosclerosis. This study was designed to examine the role of macrophage macropinocytosis in the development of atherosclerosis.

Methods: Macropinocytosis was stimulated in wild type (WT), CD36-/-, SRA-/- and CD36-/-/SRA-/- bone marrow-derived macrophages using pharmacological approaches (M CSF) and overexpression of constitutively active Ras (H RasG12V). Atherosclerosis was induced by a single PCSK9-AAV injection (ip), partial left carotid artery ligation and Western diet (three weeks). Macropinocytosis was inhibited by the amiloride derivative EIPA and deletion of NHE1 in myeloid cells (LysmCre+ NHE1f/f mice).

Results: MCSF and overexpression of H RasG12V stimulated nLDL (50 µg/ml) internalization in WT, CD36-/-, SRA /- and CD36-/-/SRA-/- macrophages approximately 3-fold compared to respective controls. Stimulation of macropinocytosis significantly increased uptake of ox- and ac-LDL (50 µg/ml) in WT and CD36-/-/SRA-/- macrophages. The macropinocytosis inhibitor EIPA abolished lipid internalization in MCSF-treated and H RasG12V-overexpressing macrophages, confirming the uptake mechanism as macropinocytosis. Both wild type (WT) and CD36-/-/SRA-/- mice treated with EIPA using an osmotic pump developed significantly less atherosclerosis compared to controls. Loss of NHE1 in myeloid cells decreased lesion size by ~80% compared to Cre- mice. Body weight, blood pressure and plasma cholesterol levels were not different between groups.

Conclusions: To our knowledge, the findings of the present study demonstrate for the first time that macrophage macropinocytosis contributes to the pathogenesis of atherosclerosis.

Biography

Gábor Csányi has received his PhD from the University of Szeged, Hungary in 2008 and completed his Post-doctoral training in 2013 in the Vascular Medicine Institute at the University Pittsburgh. He is an Assistant Professor of Pharmacology in the Vascular Biology Center at Augusta University, USA. His research focuses on the mechanisms that regulate blood vessel function, and in particular, how macrophages and vascular cells contribute to the development of vascular disease.

gcsanyi@augusta.edu