SOLUBLE ENDOGLIN COMBINED WITH HYPERCHOLESTEROLEMIA AFFECTS VASCULAR AND ENDOTHELIAL FUNCTION IN MICE

Petr Nachtigal¹, Barbora Vitverova¹, Matej Vicen¹, Iveta Najmanova¹, Eva Dolezelova¹, Carmelo Bernabeu², Miguel Pericacho³

¹Charles University, Faculty of Pharmacy in Hradec Kralove, Hradec Kralove, Czech Republic; ²Center for Biological Research, Spanish National Research Council (CSIC), Biomedical Research Networking Center on Rare Diseases, Madrid, Spain; ³Department of Physiology and Pharmacology, Renal and Cardiovascular Physiopathology Unit, University of Salamanca, Salamanca, Spain

Objective: A soluble form of tissue/membrane endoglin (sEng) circulating in plasma is increased in hypercholesterolemia, atherosclerosis and type II diabetes mellitus patients. Moreover, it has been proposed that sEng might be least partially responsible for the induction of endothelial dysfunction (but not studied in atherosclerosis prone blood vessels so far) and related to the presence of hypercholesterolemia. We provided couple of experiments in order to reveal whether high levels of sEng combined with hypercholesterolemia might affect vascular/endothelial function and inflammation in mice aorta.

Methods: Three-month-old female transgenic mice on CBAxC57BL/6J background with high levels of sEng (*Sol-Eng*⁺ high HFD) and their littermates with low levels of sEng (*Sol-Eng*⁺ low HFD) were fed high fat diet (HFD) for either 3 months or 6 months. Plasma samples were used for biochemical analyses of total cholesterol and ELISA analyses of sEng and inflammatory markers. Functional parameters of aorta were assessed by means of wire myograph 620M. Western Blot analysis endothelial dysfunction/inflammation markers in aorta was performed.

Results: 3 months exposure to high sEng levels and HFD resulted in induction of inflammation (increased expression of P-selectin, ICAM-1, pNFkB and COX-2) in aorta of high *Sol-Eng*⁺ high HFD. Moreover, 6 months exposure to high sEng levels and HFD resulted in impaired KCl induced vasoconstriction, endothelial-dependent relaxation after administration of acetylcholine, endothelial-independent relaxation induced by sodium nitroprusside. In addition, the expressions of endoglin, p-eNOS/eNOS, pSmad2/3/Smad2/3 signaling pathway were significantly lower in *Sol-Eng*⁺ high HFD group compared to *Sol-Eng*⁺ low HFD group.

Conclusions: Current results show that high levels of soluble endoglin in combination with hypercholesterolemia induce signs of inflammation and endothelial/vascular dysfunction in aorta with possible alteration of membrane endoglin/eNOS signaling. Thus, we might propose that high levels of soluble endoglin presented in patients with hypercholesterolemia, atherosclerosis and type II diabetes mellitus might worsen endothelial dysfunction in combination with hypercholesterolemia, thus soluble endoglin might be considered as a risk factor of cardiovascular diseases.

Funding: This work was supported by a grant from Czech Health Research Council AZV CR #17-31754A.