Abstract

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Title of Doctoral Thesis: Tissue and soluble endoglin relation to the endothelial dysfunction and possible treatment

Atherosclerosis is a complex inflammatory disease and it represents a major source of morbidity and mortality in the world as a part of cardiovascular diseases. Endothelial dysfunction represents the first step in the development of atherosclerosis and it is characterized by disruption of endothelial homeostasis. Statins are drugs of choice in the treatment of atherosclerosis and they can decrease LDL cholesterol levels and positively affect levels of HDL cholesterol. Statins, however have a wide range of other effects, which are referred to non-lipid or pleotropic effects. The most important non-lipid effects of statins are lipid-independent modulation of endothelial function, antioxidant, anti-inflammatory, antithrombogenic and antiproliferative effects.

The most widely used animal model for the study of atherosclerosis is the mouse model. Thanks to a high fat diet and genetic modification, we are able to modify lipid profile in mice and induce atherosclerotic changes even at early age of mice. During the process of atherogenesis in the arteries, pathological changes occur on the immunological, morphological and functional levels. Signaling pathway of transforming grow factor beta (TGF-β) plays an important role during these processes.

The publications presented in this thesis mainly focus on the role of endoglin (auxiliary TGF-β receptor III) and its soluble form in endothelial dysfunction in selected mouse models.

Changes of endoglin expression and increased levels of soluble endoglin were demonstrated in many cardiovascular diseases including atherosclerosis, hypertension, type II diabetes mellitus and preeclampsia.

We have demonstrated that endoglin is not expressed with adhesion molecules (ICAM-1, P-selectin) in aortic endothelium of atherosclerotic plaques in apoE deficient mice during atherogenesis and thus endoglin is probably not involved in the accumulation and transmigration of leukocytes during atherogenesis.

We could not demonstrate endothelial dysfunction in the aorta of mice with high levels of human soluble endoglin (Sol-Eng^{+}) in plasma on chow diet. Administration of high fat diet to these mice resulted in activation of pro-inflammatory markers (ICAM-1, P-selectin, COX-1 and pNFκB) and induced oxidative stress (NOX-1, NOX-2 and HO-1) in aorta. The endothelium-dependent vasodilatation of aorta was more impaired in the group with low levels of soluble endoglin in plasma and preserved in group with high levels of soluble endoglin in plasma. These results suggest that high concentrations of soluble endoglin in plasma induce the activation of pro-inflammatory, pro-oxidative as well as vasoprotective mechanisms in the vessel wall. The role of soluble endoglin in endothelial dysfunction and its relationship with hypercholesterolemia were discussed in our review article. We have demonstrated a positive correlation of soluble endoglin and hypercholesterolemia in C57BL/6J mice, apoE deficient mice on chow diet, apoE deficient and apoE/LDLR deficient mice on cholesterol diet. The highest levels of soluble endoglin were observed in apoE/LDLR deficient mice fed cholesterol diet – the group with the highest progression of atherosclerosis. In this study, we also summarized current knowledge of soluble endoglin and its relation to endothelial dysfunction and atherogenesis. We suggest that soluble endoglin represents an interesting biomarker of progression and treatment of many cardiovascular diseases associated with endothelial dysfunction.