Atherosclerosis is one of the major causes of cardiovascular morbidity. This chronic inflammatory disease is characterized by endothelial dysfunction with accumulation of lipids, leukocytes, smooth muscle cells and extracellular matrix within the vessel intima. This process results in reducing of the vessel lumen that can lead to the obstruction of vessel blood flow. The initiation of atherogenic process is characterized by the alteration of endothelial function which is so-called endothelial dysfunction. The endothelial dysfunction is characterized by the expression of cell adhesion molecules and increased endothelial permeability for monocytes, T-cells and lipoproteins. This is beginning of „vicious"circle of atherosclerosis.

On of the most important cell adhesion molecules participating in the beginning of atherogenesis are members of the immunoglobulin superfamily, VCAM-1 (vascular cell adhesion molekule-1), ICAM-1 (intracellular cell adhesion molekule-1) and PECAM-1 (platelet-endothelial cell adhesion molekule-1).VCAM-1 and ICAM-1 are transmembrane glycoproteins participacing predominantly in the stabilization leukocyte of interaction with endothelium and transmigration of leukocytes into vessel intima.

In this dissertation thesis, the first studies were focused on the endothelial expression of VCAM-1 and ICAM-1 in mouse aorta. Moreover the effects of statin treatment on the expression of these molecules were studied in several mouse models of atherosclerosis.

The changes of endothelial expression of VCAM-1 and ICAM-1 in the vessel wall after the short-term administration of simvastatin, atorvastatin, and micro dispersed derivates of oxidised celulose (MDOC™) in apoE-deficient mice were studied. Mice received normal chow diet or diet containing simvastatin or atorvastatin 10 mg/kg/day or MDOC™ 50 mg/kg/day. Biochemical analysis and stereological analysis of the immunohistochemical staining of VCAM-1 and ICAM-1 were performed. Atorvastatin treatment resulted in reduced expression of both adhesion molecules suggesting that atorvastatin has anti-inflammatory effects independent of hypolipidemic effects.

Furthermore, we compared the effect of 8-week atorvastatin treatment on both lipid parameters and VCAM-1 and ICAM-1 expression in apoE-deficient or wild type C57BL/6J mice that were fed with either chow or atherogenic diet. We

demonstrated that endothelial expression of both VCAM-1 and ICAM-1 does not correlate with cholesterol levels in blood. Moreover, we showed that 8-week administration of atorvastatin decreased endothelial expression of these adhesion molecules in C57BL/6J mice fed by chow diet beyond its lipid lowering effect.

We focused on atorvastatin effects in new mouse model of atherosclerosis – apoE/LDLr deficient mice in other study. Atorvastatin significantly decreased cholesterol levels, monocyte chemotactic protein-1 (MCP-1) levels in blood, and expression of cell adhesion molecules VCAM-1 and ICAM-1 in the vessel wall. We demonstrated strong hypolipidemic and anti-inflammatory effects of atorvastatin in this mouse model. We propose that this model might be a good animal model for the study of effects of statins and other substances that could be used in combination treatment with statins.

The second part of this dissertation was focused on endoglin role in atherogenesis. We studied endoglin expression in the vessel wall and possible effects of atorvastatin treatment on this expression.

Endoglin (CD 105) is a part of the transforming growth factor-β (TGF-β) receptor complex that affects TGF-β1 signaling. The major sources of endoglin are vascular endothelial cells. Endoglin participates in angiogenesis, cardiovascular development and vascular homeostasis. Moreover endoglin is highly expressed in activated macrophages, in tissues undergoing angiogenesis such as healing wounds, infarcts and in wide range of tumors. In addition its enhanced expression was documented in smooth muscle cells of vessels during inflammation, injury and in human atherosclerotic plaques.

In the first study we wanted to evaluate whether endoglin is expressed in normocholesterolemic and hypercholesterolemic C57BL/6J mice as well as whether it is affected by atorvastatin treatment in these mice. Biochemical analysis of blood samples revealed that administration of atherogenic diet significantly increased levels of total cholesterol, VLDL, LDL and decreased levels of HDL. Atorvastatin treatment resulted in a significant decrease of total cholesterol and VLDL only in mice fed by atherogenic diet. Quantitative stereological analysis revealed that atorvastatin significantly decreased endothelial expression of endoglin in C57BL/6J mice fed with atherogenic diet only. In conclusion we demonstrated that endothelial expression of endoglin is upregulated by

hypercholesterolemia and decreased by hypolipidemic effect of atorvastatin in C57BL/6J mice suggesting that endoglin expression could be involved in atherogenesis.

In the second study we hypothesized whether endothelial expression of endoglin is changed in hypercholesterolemia as well as whether its expression is affected by atorvastatin treatment in apoE-deficient mice. This study demonstrated that endoglin was expressed by aortic endothelium showing similar staining patterns like other markers involved in the process of atherosclerosis. In addition, we showed that endoglin expression in endothelium could be affected by the administration of atorvastatin beyond its lipid lowering effects in apoE-deficient mice

On the basis of results of these studies, we concluded endoglin may be possible marker of endothelial dysfunction.

The last study we stepped forward to elucidate whether endoglin is co-expressed with SMAD2, phosphorylated SMAD2/3 proteins and eNOS in vivo in atherosclerotic lesions in ApoE/LDLR double knockout mice. In addition, we sought whether endoglin expression as well as the expression of SMAD2, phosphorylated SMAD2/3 and eNOS is affected by atorvastatin treatment. Immunohistochemical and western blot analysis of endoglin, SMAD2, phosphorylated SMAD2/3 and eNOS expressions in aorta were performed. The biochemical analysis showed that administration of atorvastatin significantly decreased level of total cholesterol, VLDL, LDL, TAG, and significantly increased level of HDL cholesterol. Fluorescence immunohistochemistry showed endoglin co-expression with SMAD2, phosphorylated SMAD2/3 and eNOS in aortic endothelium covering atherosclerotic lesions in both control and atorvastatin treated mice. Western blot analysis demonstrated that atorvastatin significantly increased expression of endoglin, SMAD2, phosphorylated SMAD2/3, and eNOS in mice aorta.

In conclusion, these findings suggest, that endoglin might be interesting marker of endothelial dysfunction and/or atherogenesis which is upregulated by statins implicating potential beneficial role of endoglin and its pathway in atherosclerosis.