Abstract

Charles University in Prague

Faculty of Pharmacy in Hradec Králové

Department of Biological and Medical Sciences

Candidate: Mgr. Jana Rathouská

Supervisor: Doc. PharmDr. Petr Nachtigal, Ph.D.

Title of Doctoral Thesis: Pharmacological influence on atherogenesis in experimental animal models of atherosclerosis

Atherosclerosis is a slow inflammatory process in arterial walls which is, as a part of cardiovascular diseases, the main source of morbidity and mortality in developed countries. However, searching for the possibilities of atherosclerosis treatment requires detailed knowledge of pathogenesis of the disease itself. The use of mouse models offers one of the possibilities of studying the pathogenesis of atherosclerosis, which enables a number of interventions that would not be acceptable in human medicine. By using the high content lipid diet, we are able to induce the changes of lipid spectrum in mice. Moreover, if a targeted genetic manipulation is used, one can reach considerably advanced plaques in a relatively short time period. It is also possible to interfere in the process of atherogenesis in mouse models by using some hypolipidemic drugs, for example from the statin group that were represented in our studies by atorvastatin. By observing the vessel's reactivity to atorvastatin dosage, one can obtain another figure (besides the influence on the level of lipids), that may reveal some lipid-independent effects of statin, so-called pleiotropic effects, which are getting into the forefront especially over the last years.

In the process of atherogenesis, there are relatively complex changes on the immunological, morphological and functional levels in the organism, accompanied by complex signaling between cells that are involved in the process. One of the significant roles in the process of atherogenesis is attributed to TGF-β cytokine and its signaling, which despite of the signs of atheroprotection has not still been clarified, including the role of TGF-β receptors that apparently play the key role in the process of atherogenesis.

The role of endoglin (TGF-β receptor III, ENG) and its signaling in aorta in chosen mouse models of atherosclerosis, with the consideration to the levels of its serum form

(cleaved from the tissue), was the key topic of papers in this summary dissertation thesis. The pertinent influence of atorvastatin on these processes was taken into account as well. Endoglin was described as a significant TGF-β receptor with the potential of atheroprotection, especially in terms of the influence on the production of eNOS and VEGF, in the atherosclerotic aorta in apoE/LDLR deficient mice. On the other hand, the serum form of this protein (sENG) was identified as a potentially negative marker of the atherosclerotic process. The study of atorvastatin effect in the apoE/LDLR deficient model revealed, besides the influence on serum lipids, the ability of non-lipid effect in terms of the size reduction of atherosclerotic plaques, the expression increase of potentially atheroprotective molecules of TGF-β signaling (ENG/ALK-5/Smad2/eNOS and ENG/ALK-1/Smad1/VEGF pathways) and the reduction of serum endoglin levels.

The study of two mouse strains with a different predisposition to atherosclerosis (C57BL/6J vs. C3H/HeJ) proved a reduced aortic sensitivity in C3H/HeJ atheroprotective strain to the expression of inflammatory (adhesion) molecules P-selectin, VCAM-1, ICAM-1, and showed a possible endoglin participation in the increase of eNOS expression in the aorta of this strain, compared to C57BL/6J sensitive strain.

The histological study with apoE-deficient mouse models evaluated the extra-cardiac part of aorta as a relevant one at studying atherosclerotic process, compared to the area of the aortic sinus, that does not reflect the changes of endoglin in the atherogenetic process and thus probably has a relation more likely to the cardiogenesis and heart valves development. We showed that endoglin is not co-localized with cell adhesion molecules (P-selectin and VCAM-1) involved in atherosclerosis, suggesting it might not participate in leukocyte accumulation in aorta of apoE-deficient mice during atherogenesis.

By summarizing the role of endoglin in atherogenesis in the review article, that also included the results of some above-mentioned studies, it is possible to deduce, that the role of TGF-β receptor III (ENG) in atherogenesis more likely appears as atheroprotective. On the other hand, the role of serum form of this protein (sENG) seems to be hopeful in terms of observing the levels as the marker of atherosclerotic process severity. However, the implementation of these conclusions into human medicine and its use e.g. in the context of the efficiency of statin therapy, still requires a search for deeper understanding.