In our previous results, we demonstrated the browning of perivascular adipose tissue (PVAT) after all-trans retinoic acid (atRA) treatment in Apo-E and C57BL/6J mice. Therefore, the aim of this study is the identification of molecules and mechanisms by which atRA-induced browning of PVAT regulates endothelial function in Apo-E mice. We also would compare PVAT anti-atherogenic and pro-atherogenic molecules under different conditions (normal diet and high fat diet (HFD); early stage of atherosclerosis and advanced stage of development of atherosclerosis). Our research is based on the hypothesis that molecular changes in PVAT are a consequence of the physiological changes in the body.

Atherosclerosis is the underlying cause of about 50% of all deaths in westernized society. It is the main cause of atherosclerotic cardiovascular disease (ASCVD) resulting in heart attacks, stroke, and peripheral artery disease. Diet modification, exercise, and drugs affected plasma lipids may induce changes in the natural pathology of atherosclerosis plaques in arteries. Atherosclerosis is a progressive chronic metabolic disorder of blood vessels, which still has no effective therapies.

Vitamin A is an important micronutrient involved in maintaining major risk factors for atherogenesis including regulation of glucose concentrations, lipid metabolism, and inflammation. Retinoic acid (RA) is a major active cellular retinoid metabolite. Administration of RA has been shown to promote the WAT browning. It also upregulates the expression of uncoupling protein 1 (UCP1) in both in vivo and in vitro studies in mice.

Perivascular adipose tissue (PVAT), which surrounds most of the blood vessels, is active, regulating component of vascular homeostasis that produces several biologically active molecules including adipokines. Under physiological conditions, PVAT releases several anti-atherosclerotic agents such as NO, H_2S, and adiponectin. Pathophysiological conditions like obesity, hyperlipidemia, and diabetes perturb PVAT homeostasis. Dysfunctional and whitening BAT-like PVAT releases pro-inflammatory adipokines that promote atherosclerosis development. However, the exact mechanisms by which atRA-induced browning of PVAT may regulate endothelial function remain unclear. In the present study, we will investigate the role of atRA browning of PVAT on endothelial function in the Apo-E mice without or with HFD.

Apo-E mice demonstrate the development of severe hypercholesterolemia and all of the known phases of atherogenesis similar to those observed in humans. On this mice model, we will determine glucose, insulin, and lipid profile. Furthermore, we will perform an assessment of the quantification of atherosclerotic lesions by histological and immunohistological analysis. Moreover, we investigated the effect of atRA treatment on PVAT browning in Apo-E mice. Then we will analyze molecular characteristics of PVAT after atRA treatment by microarray genes analysis and validation of the microarray results using qPCR. In the next step, we will select 5 molecules most highly expressed in microarray genes analysis after atRA treatment compared to the vehicle as well as on standard diet and HFD and validation these results using Western blot and/or ELISA. Finally, we will identify the potential mechanism regulation of endothelial function for the PVAT produced and secreted molecules by analysis of its effects on a) inflammation (IL-6); b) adhesion molecules (VCAM); c) NO production and d) ROS (Superoxide) production in Mouse Primary Aortic Endothelial Cells line. This will be done using cytokines/molecules and their suppression by specific receptors or their downstream signal transduction pathways, depending on the analyzed molecules.

To the best of our knowledge, no studies have examined the browning effect of PVAT after atRA treatment on endothelial function. We will also compare PVAT anti-atherogenic and pro-atherogenic molecules under different conditions (normal diet and HFD; early stage of atherosclerosis and advanced stage of development of atherosclerosis).

We hypothesize that on normal diet browning of PVAT improve endothelial function and we identify mechanism connected with endothelial regulation. This study will assist to evaluate whether targeting PVAT function and stimulates browning of PVAT can be used as a novel approach for the treatment of atherosclerosis and subsequent ASCVD.

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