ApoE−/− PGC-1α−/− mice display reduced IL-18 levels and do not develop enhanced atherosclerosis

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BACKGROUND: Atherosclerosis is a chronic inflammatory disease that evolves from the interaction of activated endothelial cells, macrophages, lymphocytes and modified lipoproteins (LDLs). In the last years many molecules with crucial metabolic functions have been shown to prevent important steps in the progression of atherogenesis, including peroxisome proliferator activated receptors (PPARs) and the class III histone deacetylase (HDAC) SIRT1. The PPARγ coactivator 1 alpha (Ppargc1a or PGC-1α) was identified as an important transcriptional cofactor of PPARγ and is activated by SIRT1. The aim of this study was to analyze total PGC-1α deficiency in an atherosclerotic mouse model. METHODOLOGY/PRINCIPAL FINDINGS: To investigate if total PGC-1α deficiency affects atherosclerosis, we compared ApoE−/− PGC-1α−/− and ApoE−/− PGC-1α+/+ mice kept on a high cholesterol diet. Despite having more macrophages and a higher ICAM-1 expression in plaques, ApoE−/− PGC-1α−/− did not display more or larger atherosclerotic plaques than their ApoE−/− PGC-1α+/+ littermates. In line with the previously published phenotype of PGC-1α−/− mice, ApoE−/− PGC-1α−/− mice had marked reduced body, liver and epididymal white adipose tissue (WAT) weight. VLDL/LDL-cholesterol and triglyceride contents were also reduced. Aortic expression of PPARα and PPARγ, two crucial regulators for adipocyte differentitation and glucose and lipid metabolism, as well as the expression of some PPAR target genes was significantly reduced in ApoE−/− PGC-1α−/− mice. Importantly, the epididymal WAT and aortic expression of IL-18 and IL-18 plasma levels, a pro-atherosclerotic cytokine, was markedly reduced in ApoE−/− PGC-1α−/− mice. CONCLUSIONS/SIGNIFICANCE: ApoE−/− PGC-1α−/− mice, similar as PGC-1α−/− mice exhibit markedly reduced total body and visceral fat weight. Since inflammation of visceral fat is a crucial trigger of atherogenesis, decreased visceral fat in PGC-1α-deficient mice may explain why these mice do not develop enhanced atherosclerosis.
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