論 文 要 旨

Estrogen-SIRT1 Axis Plays a Pivotal Role in Protecting Arteries Against Menopause-induced Senescence and Atherosclerosis

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Aim: Menopause causes arterial senescence and atherosclerotic development through decrease of estrogen. Recently, histone deacetylase SIRT1 have been reported to have protective effects against arterial senescence and atherosclerosis. However, the relationship between estrogen and SIRT1 in the context of menopause-induced alteration is not well understood. The present study aims to investigate whether SIRT1 is involved in the etiology of menopause-induced arterial senescence and atherosclerotic development.

Methods: Twelve-week old female apolipoprotein E-knockout (ApoE-KO) mice underwent ovariectomy (OVX) or sham surgery.

Results: SIRT1 expression and endothelial nitric oxide synthase (eNOS) activation in the aorta were significantly lower in OVX mice than in sham mice. Senescence-associated β-galactosidase activity, protein expression of Ac-p53 and PAI-1, and aortic atherosclerosis lesions were significantly greater in OVX mice than those in sham mice. Administration of 17β-estradiol (E2) for 8 weeks to OVX mice restored aortic SIRT1 expression, activated eNOS, and retarded OVX-induced arterial senescence and atherosclerotic development, which were attenuated by administration of a SIRT1 inhibitor, sirtinol. In vitro experiment using human endothelial cells demonstrated that E2 also increased SIRT1 expression and retarded oxidized low density lipoprotein-induced premature senescence, which were also abolished by sirtinol. These results suggested that estrogen modulated arterial senescence and atherosclerosis through SIRT1. In addition, a selective estrogen receptor modulator (SERM), bazedoxifene, also augmented SIRT1 and inhibited arterial senescence and atherosclerotic development.

Conclusions: Downregulation of SIRT1 causes OVX-induced arterial senescence and atherosclerosis in ApoE-KO mice. Administration of estrogen or SERM enables OVX mice to restore these alterations by SIRT1 induction.