Substitution of the SERCA2 Cys674 reactive thiol accelerates atherosclerosis by inducing endo-plasmic reticulum stress and inflammation

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Abstract

BACKGROUND AND PURPOSE The cysteine674 (C674) thiol of Sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2 (SERCA2) is easily and irreversibly oxidized under atherosclerotic conditions. However, contribution of the C674 thiol redox status in the development of atherosclerosis remains unclear. Our goal was to elucidate the possible mechanism involved. EXPERIMENTAL APPROACH Heterozygous SERCA2 C674S knock-in (SKI) mice in which half of the C674 was substituted by serine674 were used to mimic removal of the reactive C674 thiol which occurs under patholog-ical conditions. The whole aorta and aortic root were isolated for histological analysis. Bone marrow derived macrophages (BMDMs) and a cardiac endothelial cell line were used for intra-cellular Ca2+, macrophage adhesion and protein expression analysis. KEY RESULTS SKI mice developed more severe atherosclerotic plaque and macrophage accumulation. Cell cul-ture studies suggest the partial substitution of SERCA2 C674 increased intracellular calcium lev-els and ER stress in both BMDMs and ECs. The release of pro-inflammatory factors and macro-phage adhesion increased in SKI BMDMs. In normal ECs, the overexpression of C674S mutant induced endothelial inflammation and promoted macrophage recruitment. Additionally, 4-phenyl butyric acid (4-PBA), an ER stress inhibitor, prevented the increased atherosclerosis observed in SKI mice, and alleviated ER stress and inflammatory responses in BMDMs and ECs exposed to 4-PBA. CONCLUSIONS AND IMPLICATIONS The substitution of SERCA2 C674 thiol accelerates the development of atherosclerosis by in-ducing ER stress and inflammation. Our findings highlight the importance of SERCA2 C674 redox status in the context of atherosclerosis, and open up a novel therapeutic strategy to combat atherosclerosis.

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