Abstract

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Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction.

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BACKGROUND: The functional changes associated with cellular senescence may be involved in human aging and age-related vascular disorders. We have shown the important role of telomere and telomerase in vascular cell senescence in vitro. Progressive telomere shortening in vivo has been observed in the regions susceptible to atherosclerosis, implying contributions to atherogenesis. However, whether senescent vascular cells are present in the vasculature and contribute to the pathogenesis of atherosclerosis remains unclear.

METHODS AND RESULTS: Senescence-associated beta-galactosidase (beta-gal) activity was examined in the coronary arteries and the internal mammary arteries retrieved from autopsied individuals who had had ischemic heart diseases. Strong beta-gal stainings were observed in atherosclerotic lesions of the coronary arteries but not in the internal mammary arteries. An immunohistochemical analysis using anti-factor VIII antibody demonstrated that beta-gal stained cells are vascular endothelial cells. To determine whether endothelial cell senescence causes endothelial dysfunction, we induced senescence in human aortic endothelial cells (HAECs) by inhibiting telomere function and examined the expression of intercellular adhesion molecule (ICAM)-1 and endothelial nitric oxide synthase (eNOS) activity. Senescent HAECs exhibited increased ICAM-1 expression and decreased eNOS activity, both of which are alterations implicated in atherogenesis. In contrast, introduction of telomerase catalytic component significantly extended the life span and inhibited the functional alterations associated with senescence in HAECs.

CONCLUSIONS: Vascular endothelial cells with senescence-associated phenotypes are present in human atherosclerotic lesions, and endothelial cell senescence induced by telomere shortening may contribute to atherogenesis.

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