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Mechanisms of Endothelial Progenitor Cells Senescence Induced by Oxidative Stress

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Endothelial progenitor cells (EPC) are the precursors of mature endothelial cells and are involved in neovascularization and reendothelization. Previous studies have shown that oxidative stress can induce EPC senescence. However, the potential molecular mechanisms involved are still not clearly elucidated.

Reduced telomerase activity may be one of the mechanisms. Telomeres, the physical ends of the chromosomes, are necessary for chromosome stability and genetic integrity. Because telomeres are shortened during each cell division, they can function as a mitotic clock. The enzyme telomerase counteracts the shortening of telomeres. Since oxidative stress is involved in telomere-shortening and regulation of cellular life span, it can result in EPC senescence and dysfunction through shortening the telomeres. It is reported that angiotensin Ⅱ could induce EPC senescence through oxidative stress. However, estrogen reduced EPC senescence through augmentation of telomerase activity. Moreover, C-reactive protein (CRP) not only enhanced reactive oxygen species (ROS) production but also resulted in a significantly reduced activity of the catalytic subunit of telomerase, telomerase reverse transcriptase (TERT). Most importantly, ROS appeared to stimulate the export of TERT from the nucleus into the cytosol, which may result in a loss in the ability to prolong telomeres, leading to progressive telomere shortening, reduced replicative ability and increased sensitivity toward apoptotic stimuli. In addition, overexpression of human TERT in EPC prevented downregulation of endothelial nitric oxide synthase (eNOS), improved the functional activity of EPC for vascular regeneration, and enhanced EPC survival.

It is considered that p53, p21, and pRb are the major regulators of senescence, whose activation in EPC may induce cellular senescence. Studies have shown that oxidative stress could lead to accelerated onset of EPC senescence through the activation of Akt/p53/p21 signaling pathway. Furthermore, Akt was constitutively activated in EPC cultured in the presence of oxidized small and dense low density lipoprotein, which then caused an accumulation of p53 in the nucleus and an increase of p21. Activated p21 further inhibited the cyclin-dependent kinase (CDK), which maintained Rb in an underphosphorylated state, thereby causing EPC senescence-like growth arrest.

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