Role of Cellular Aging in Cardiovascular and Metabolic Disease

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Cellular senescence is a state of irreversible cell growth arrest induced by excessive replication or various stresses, including oncogenic stimuli. It is thought to be a defensive mechanism against malignant transformation. This response is controlled by negative regulators of the cell cycle like the p53 tumor suppressor protein. Accumulating evidence has suggested a role of p53 activation in various age-associated conditions, including vascular senescence, heart failure, and diabetes. It has also been reported that diabetes promotes vascular senescence and accelerates the development of cardiovascular complications. However, it remains unclear whether the senescence of vascular cells per se contributes to metabolic abnormalities and obesity in diabetic patients. We here identified a crucial role of endothelial p53 activation in the regulation of glucose homeostasis and obesity. Endothelial expression of p53 was markedly up-regulated when mice were fed a high-calorie diet. Disruption of endothelial p53 activation improved dietary inactivation of endothelial nitric oxide synthase that up-regulated the expression of peroxisome proliferator-activated receptor-γ coactivator-1α in skeletal muscle, thereby increasing mitochondrial biogenesis and oxygen consumption. Mice with endothelial cell-specific p53 deficiency fed a high-calorie diet showed improvement of insulin sensitivity and less fat accumulation compared with control littermates. Conversely, up-regulation of endothelial p53 caused metabolic abnormalities and increased fat accumulation. These results indicate that inhibition of endothelial p53 could be a novel therapeutic target to block the vicious cycle of cardiovascular and metabolic abnormalities occurring in diabetic patients.

The Functional Implication of DNA Damage in Cardiometabolic Disease

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Accumulation of DNA damage has been implicated in the phenotypic manifestations of aging in rodents and humans. DNA damage can be caused by various endogenous or exogenous stresses, including telomere erosion, oxidative stress, oncogenic mutations, and genotoxic stress. p53 is a key player in the intrinsic cellular responses to DNA damage, and activation of p53 leads to cell cycle arrest, apoptosis, and senescence. Cellular senescence is originally described as the finite replicative lifespan of human somatic cells in culture. Cellular senescence is accompanied by a specific set of phenotypic changes in morphology and gene expression. Primary cultured cells from patients with premature aging syndromes are known to have a shorter lifespan than cells from age-matched healthy persons. It is also reported that the number of senescent cells increases in various tissues with advancing age. Interestingly, such accumulation of senescent cells in aged animals is attenuated by caloric restriction that regulates the lifespan regulatory system and delays age-associate phenotypes. I therefore hypothesize that cellular senescence in vivo contributes to the pathogenesis of age-associated disease. An important feature shared by several types of senescent cells is persistent up-regulation of inflammatory molecules and accumulating evidence has suggested a critical role of senescence-induced inflammation in metabolic and cardiovascular disease. Here I will present our recent data on the role of cellular senescence in age-related pathologies and will discuss the potential of anti-senescence as a novel therapeutic strategy for age-associated diseases.

Therapeutic Angiogenesis in Japan

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Improved understanding of the mechanisms involved in vessel formation has led to the development of a novel strategy for the treatment of ischemic cardiovascular disease, called as ‘therapeutic angiogenesis’. In the first phase of therapeutic angiogenesis, a single angiogenic growth factor, or its cognate DNA sequence, was injected into ischemic tissue. Although the initial non-randomized clinical trials showed beneficial effects, the results of controlled clinical trials have not been consistent. The second phase of therapeutic angiogenesis began with the identification of circulating bone marrow–derived endothelial progenitors. The first clinical trial showed that implantation of bone marrow–mononuclear cells significantly improved tissue oxygenation and blood flow in ischemic tissue. Early preclinical studies suggested that replenishment of endothelial progenitors was attributed to the efficacy of cell therapy. However, the studies in the third phase suggest that angiogenic factors secreted by implanted cells play a critical role in achieving neovascularization with cell therapy. Recently, we have demonstrated that cell transplantation enhances muscle regeneration and that regenerating myoblasts produce various growth factors that promote neovascularization and thus accelerate the regeneration of ischemic muscle tissue via a Notch-dependent pathway. In this symposium, I will introduce the current status of therapeutic angiogenesis in Japan and discuss about future direction of therapeutic angiogenesis for ischemic cardiovascular disease.