Pathways to Prevent Early Cellular Senescence

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Aging is characterized by a progressive decline in cell and tissue function in multicellular organisms. Cells continually experience stress and damage from internal and external sources and their responses range from complete recovery to cell death. Proliferating cells initiate an additional response by adopting a state of permanent cell-cycle arrest commonly known as cellular senescence. Cellular senescence is a state characterized by an inability of cells to proliferate despite the presence of sufficient nutrients and mitogens while maintaining cell viability and metabolic activity. There is mounting evidence that stress response termed cellular senescence links multiple pathologies of aging. Great progress has been made in the past decade in understanding an ever growing number of stimuli that induce senescence and linking these mechanisms to cancer protection and aging. Anti-aging compounds regulate energy metabolism and ROS-induced stress pathways. However, there are many gaps in our understanding of the complex role of cellular senescence and accompanying degenerative and hyperplastic diseases of aging.

Role of Adipokines

Oxidative stress plays a critical role in the pathogenesis of age-related diseases. Several lines of evidence support that as reactive oxygen species (ROS) levels increase and antioxidants decline in aging tissues, there is a greater susceptibility to oxidative damage. Recent studies have demonstrated that SIRT1, the mammalian homologue of yeast Sir2, plays an important role in the regulation of cell death/survival and stress response in mammals. Senescent cells upregulate the proinflammatory cytokines IL-6 and IL-8, the main markers of the senescence-associated secretory phenotype (SASP). Adipokines, or cytokines released by adipocytes, have recently been studied due to their unique physiologic properties. Adipocytes have been shown to secrete a variety of bioactive proteins into the circulation. These secretory proteins have been collectively named adipocytokines and include leptin, tumor necrosis factor (TNF)-alpha, adipsin, resistin, and adiponectin. Under normal physiological conditions, adiponectin circulates in high concentrations, but its levels are significantly decreased in obesity, and related disease states such as obesity-linked insulin resistance, type 2 diabetes, and metabolic syndrome. Adiponectin improves glucose uptake by cells and regulates energy expenditure more

efficiently. Several features make adiponectin an attractive marker for cardiovascular risk, including the ability to help regulate levels through medication, lifestyle, and diet.

Therapeutic Potential of Adiponectin

Adiponectin has also been shown to have multiple beneficial anti-apoptotic, anti-inflammatory and anti-oxidative effects. Research suggests that adiponectin may have anti-aging benefits such as cellular damage repair, enhancement of keratinocyte differentiation and moisturization, and improvement of antimicrobial barriers. Adiponectin exerts its biological effects via binding to two structurally and functionally distinct, G protein-coupled, seven-transmembrane receptors, called adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2). However, the underlying mechanism for adiponectin function is not completely understood. Dr. Jin and colleagues from Chung-Ang University in South Korea, developed a senescence model using H2O2 as an ROS stress inducer to investigate the role of adiponectin in correcting premature cellular senescence in keratinocytes. Their results suggest a strong protective effect of adiponectin stimulation in human keratinocytes by countering antimicrobial peptide expression. Using Enzo's FLUOR DE LYS SIRT1 fluorometric drug discovery assay kit, adiponectin was shown to induce keratinocyte differentiation by upregulation of SIRT1 activity, which prevents cellular premature senescence.

Future Questions and Directions

Human β-defensin (hBD-2) is one of the primary biomarkers of the skin's innate immune system. The production and regulation of hBD-2 in keratinocytes maintains the innate immune system. Recent studies have reported abnormally high antimicrobial peptides levels in aged skin compared to young skin tissue, and an abnormal increase in hBD-2 levels after exposure to UVB or H2O2 in keratinocytes. Given that senescent cells increase with age and age-related pathology, scientists are searching for anti-aging therapies targeting senescent cells with the hope of discovering the biological 'fountain of youth'.

Enzo Life Sciences has a very unique portfolio for researchers investigating senescence such as the Cellular senescence activity assay and the Cellular senescence live cell analysis assay. In addition, Enzo offers antibodies, immunoassays, live cell analysis kits, proteins and small molecules.