Targeting stem cell senescence to rejuvenate the aged heart

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Adult cardiac stem cells (CSCs) are a small population of cells contributing to tissue homeostasis and regeneration by differentiating in all cell types of the heart. CSC senescence has been associated with physiological and pathological processes encompassing both non-age and age-related decline in cardiac tissue repair, organ dysfunction and disease. Because senescent cells contribute to the outcome of a variety of cardiac diseases, including age-related and unrelated cardiac diseases like diabetic cardiomyopathy, therapies that target senescent cell clearance are actively being explored. Aging and Diabetes Mellitus (DM), independently but also additively, increase cardiovascular risk and affect the biology and regenerative potential of adult CSCs. Thus, we investigated whether Diabetes affects cell senescence and whether CSCs acquire typical hallmarks of aging that likely contribute to the loss of their regenerative potential. We obtained biopsies from non-aged patients with type 2DM (T2DM) and non-diabetic (NDM) patients with post-infarct cardiomyopathy undergoing surgical coronary revascularization. We found an increased oxidative stress in heart sections from T2DM patients as revealed by the expression of 8-OH-deoxyguanosine, nitrotyrosine, and 4-hydroxinonenal in CSCs and cardiomyocytes. CSCs from T2DM patients shown a senescence-associated secretory phenotype (SASP), with the secretion of MMP-3, PAI1, IL-6, IL-8, IL-1β and GM-CSF, an increased number of p16INK4a positive cells, reduced telomerase activity and length, reduced proliferation, clonogenesis/spherogenesis and myogenic differentiation when compared to CSCs from NDM patients. A combination of two senolytics, dasatinib and quercetin, clear senescent T2DM-CSCs in vitro abrogating the SASP, restoring expansion and myogenic differentiation capacities of the diabetic CSC pool.