Diabetes-Induced Cellular Senescence and Senescence-Associated Secretory Phenotype Impair Cardiac Regeneration and Function Independently of Age

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Diabetes Mellitus (DM) affects the biology of multipotent cardiac stem/progenitor cells (CSCs) and adult myocardial regeneration. We assessed the hypothesis that senescence and senescence-associated secretory phenotype (SASP) are a main mechanism of cardiac degenerative defect in DM. Accordingly, we tested whether that ablation of senescent CSCs would rescue the cardiac regenerative/reparative defect imposed by DM. We obtained cardiac tissue from non-aged (50-64 years old) DM type 2 (T2DM) and non-diabetic (NDM) patients with post-infarct cardiomyopathy undergoing cardiac surgery. A higher ROS production in T2DM associated with an increased number of senescent/dysfunctional T2DM-human(h)CSCs with reduced proliferation, clonogenesis/spherogenesis and myogenic differentiation vs. NDM-hCSCs in vitro. T2DM-hCSCs show a defined pathologic SASP. A combination of two senolytics, Dasatinib (D) and Quercetin (Q), clears senescent T2DM-hCSCs in vitro restoring their expansion and myogenic differentiation capacities. In a T2DM model in young mice, diabetic status per se (independently of ischemia and age) causes CSC senescence coupled with myocardial pathologic remodeling and cardiac dysfunction. D+Q treatment efficiently eliminates senescent cells, rescuing CSC function, which results in functional myocardial repair/regeneration improving cardiac function in murine DM. In conclusions, DM hampers CSC biology inhibiting their regenerative potential through the induction of cellular senescence and SASP independently from aging. Senolytics clear senescence abrogating the SASP restoring a fully proliferative-/differentiation- competent hCSC pool in T2DM with normalization of cardiac function.