PLACENTA-EXPANDED (PLX) ADHERENT STROMAL CELLS IMPROVE DIABETES MELLITUS-ASSOCIATED LEFT VENTRICULAR DIASTOLIC PERFORMANCE

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Purpose: Cardiomyocyte stiffness is regarded as one of the factors leading to left ventricular (LV) diastolic dysfunction, the earliest preclinical manifestation of diabetic cardiomyopathy, consisting of changes in cardiac structure and function in the absence of coronary artery disease and hypertension. Mesenchymal stromal cells (MSC) are well known for their cardioprotective properties. We investigated whether intravenous application of PLX MSC-like cells improves LV diastolic relaxation in streptozotocin (STZ)-induced diabetic mice. Methods: Diabetes mellitus was induced by STZ application during five subsequent days. One week after the first STZ injection, PLX/saline were administered intravenously. Two weeks later, mice were hemodynamically characterized and sacrificed. Results: At this early stage of diabetic cardiomyopathy, PLX reduced LV VCAM-1, TGF-b1, and interferon-c mRNA expression, induced the percentage of circulating Treg cells, decreased the splenic pro-fibrotic potential, and increased LV VEGF mRNA expression and arteriole density. Hyperglycemic PLX conditioned medium restored the hyperglycemia-impaired tube formation and adhesion capacity of HUVEC via increasing nitric oxide (NO) bioavailability. PLX further induced the diabetes downregulated activity of the NO downstream PKG, and PKA, which was associated with a rise in phosphorylation of the titin isoforms N2BA and N2B. Concomitantly, the passive force was lower in single isolated cardiomyocytes from treated versus non-treated mice. *In vivo*, treated mice showed improved diastolic function and LV diastolic relaxation. Conclusions: Intravenous application of placenta-derived MSC-like cells (PLX) improves LV diastolic relaxation and cardiomyocyte stiffness at an early stage of diabetic cardiomyopathy. These findings offer new insights into the cardioprotective effects of PLX cells.