SDF-1β PRETECTS CARDIAC CELLS FROM HIGH FAT-INDUCED FIBROSIS THROUGH ITS RECEPTOR CXCR7-MEDIATED AMPK/P38 MAPK ACTIVATION AND IL-6 EXCRETION

Poster Contributions
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Authors: Yuguang Zhao, Wei Li, Xiao Chen, Junying Dai, Yi Tan, Lu Cai, the First Hospital of Jilin University, Changchun, People’s Republic of China, KCHRI at the Department of Pediatrics, University of Louisville, Louisville, KY, USA

Hyperlipemia often occurs in the patients with obesity and type 2 diabetes, and is also primary trigger for cardiac remodeling and dysfunction. Stromal cell-derived factor-1beta (SDF-1β) was cardiac protective, but whether it also protects the cardiac cells from high fat-induced remodeling remains unknown. By using H9c2 cardiac cell line, we observed the effect of SDF-1β on saturated free fatty acid-induced fibrotic response. Exposure of H9c2 cells to palmitate at 62.5 µM for 15 h caused a significant fibrotic effect, shown by up-regulation of CTGF, TGF-β and KLF4, which is by activating NADPH oxidase-associated nitrosative damage and endoplasmic reticulum stress. Pretreatment with SDF-1β significantly prevented palmitate-induced fibrosis along with significant increases in AMPK-mediated p38 MAPK activation and IL-6 generation. AMPK activator significantly prevents palmitate-induced cardiac fibrosis while AMPK inhibitor prohibited SDF-1β’s protective effect. P38β MAPK siRNA significantly prevents SDF-1β’s anti-fibrotic effect. Direct addition of recombinant human IL-6 to cell cultures prevented palmitate-induced fibrosis whereas IL-6 siRNA abolished the protective effect of SDF-1β. CXCR7 siRNA, but not CXCR4 siRNA, abolished SDF-1β’s protective effect and above related signaling pathways. The anti-fibrotic effect of SDF-1β observed in H9c2 cells was also confirmed in the primary cultures of neonatal cardiomyocytes. These in vitro results suggest that SDF-1β prevents palmitate-induced cardiac fibrosis via its receptor CXCR7 and further activating AMPK/p38 MAPK-mediated IL-6 excretion. In vivo studies, by using type 2 diabetes models, we confirmed that high-fat diet induced cardiac fibrosis, and that SDF-1β prevented high fat diet-induced cardiac fibrosis along with its activation of AMPK. This important finding opens a new road for the research of SDF-1β’s cardiac protection that is irrelevant with its well-known function of stem cell mobilization.