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CD31EV CARGO PROVIDES NOVEL BIOMARKERS OF VASCULAR SMOOTH MUSCLE CELL DYSFUNCTION IN DIABETES

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Cardiovascular complications are a relevant cause of morbidity and mortality in diabetic setting. Vessel wall alterations lead to intima-media thickening (IMT) which predicts a high risk group of cardiovascular events. In addition, restenosis still represents a major vascular complication in diabetic patients. Intimal hyperplasia is a major cause of re-occlusion. It is mainly due to the migration and/or excessive growth of vascular smooth muscle cells (VSMCs). A dysregulated balance between apoptosis and the proliferation of VSMCs seems to play a crucial role in this process. Although circulating high glucose concentration might per se drive VSMC dysfunction, events independent of hyperglycaemia can contribute to this process *in vivo*. Extracellular vesicles (EVs) are broadly distributed in human body fluids, while circulating EV cargo generally reproduces the cell of origin in its physiological and/or pathological condition. Increased levels of circulating platelet and endothelial cell (EC) derived micro particles have been proposed as biomarkers of cell dysfunction. At this regard, we investigated the roles of endothelial derived EVs (CD31EVs) as biomarkers and mediators of smooth muscle cell (VSMC) dysfunction in type 2 diabetes (T2D) setting. We discovered that VSMCs, from human atherosclerotic arteries of T2D individuals, express low Bax/Bak and high bcl-2-miR-296-5p levels. These effects were recapitulated in VSMCs subjected to high glucose (HG) and translated into increased apoptosis resistance. We demonstrated that miR-296-5p post-transcriptionally regulates Bak. Moreover, diabetic (D-CD31EVs), but not non-diabetic (ND-CD31EVs) sera-derived EVs further decreased apoptotic cell number and Bax/Bak levels, while increased Bcl-2 and miR-296-5p. D-CD31EVs were found almost depleted of miR-296-5p, suggesting that VSMC-miR-296-5p content did not depend on D-CD31EV transfer. Conversely, D-CD31EVs were enriched in Platelet-derived growth factor with two B subunits (PDGF-BB). By depleting CD31EVs of PDGF-BB, it was demonstrated that PDGF-BB contributes to D-CD31EV-mediated miR-296-5p expression and downstream events. This study identifies Bak as a novel miR-296-5p target and D-CD31EVs as relevant mediators of diabetes-associated VSMC dysfunction. This study also recognizes CD31EV-miR-296-5p-PDGF-BB content as novel diabetes-associated biomarkers.

Biography

Maria Felice Brizzi (female) has a long lasting experience on the study of tumor microenvironment and angiogenesisis. Moreover, she recently focused on the paracrine mechanisms regulating angiogenesis and both in physiological and pathological settings. In particular, she is mainly involved in studying the role of extracellular vesicles in the regulation of regenerative processes in different diseases and in tumor growth. Maria Felice Brizzi' s cumulative impact factor sums 582,038, Average Impact Factor: 6.258, Impact Factor first/last/corresponding author: PhD in Cytomorphology, 1998 Academic Specialty in Internal Medicine, 1993

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