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Spatial regulation of vascular gene expression by glucose

Olga Stenina Adognravi

Cleveland Clinic, USA

Abstract

Remodeling of the vascular wall initiates and defines the development of cardiovascular disease, diabetic complications, tumor growth, and many other devastating chronic diseases. Remodeling and growth of the blood vessels is guided and regulated by the extracellular matrix (ECM), which signals through the cell surface receptors, controls adhesion, migration, survival and proliferation of the vascular cells. Composition of ECM and its interactions with cells are cell-type-specific and local. Hyperglycemia causes profound changes in composition of vascular ECM, and these changes are hallmark of diabetic vascular complications (the primary cause of the mortality and the morbidity of diabetics). We have been exploring the cell- and tissue-specific molecular mechanisms that regulate the production of ECM in response to glucose and can explain the tissueand organ-specific effects of hyperglycemia on vasculature. We have described molecular details of a cell-type-specific transcriptional mechanism controlling production of thrombospondin-1 (TSP-1)(one of the most potent anti-angiogenic ECM proteins implicated in cancer development, diabetic complications and atherogenesis) in endothelial cells (EC) and vascular smooth muscle cells (SMC). In addition to cell-specific transcriptional pathways activated by hyperglycemia, we have discovered a novel tissue-specific post-transcriptional microRNA-dependent mechanism inhibiting the production of TSP-1 to increase angiogenesis in selected tissues in response to hyperglycemia. This novel pathway offers a breakthrough explanation for the tissue- and organ- specific vascular complications of diabetes and for the welldocumented but poorly understood association between hyperglycemia and several cancers. It also suggests a new target for the prevention and treatment of vascular diabetic complications and cancers in diabetic patients. A combination of cell- and tissue-specific transcriptional and post-transcriptional pathways maintains the spatial and temporal regulation of production of the ECM proteins in response to hyperglycemia.

Biography

Stenina-Adognravi has acquired her PhD at the National Cardiology Center in Moscow, Russia. The regulation of vascular gene expression, mechanisms of atherogenesis and functions of the vascular extracellular matrix are her long-standing interests. Her professional activities include more than 30 publications related to vascular biology problems, most of them in high impact journals; peer review of manuscripts for reputable journals and participation in vascular biology grant review groups. She is currently an Associate Staff (Associate Professor) at the Cleveland Clinic, Department of Molecular Cardiology. Stenina is currently working on the molecular mechanisms of association between diabetes and cardiovascular disorders.