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The Role of TXNIP in mitochondrial dysfunction, mitophagy deregulation and inflammasome activation in diabetic retinopathy

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Chronic hyperglycemia (HG)-associated oxidative stress, low grade inflammation and apoptosis play critical roles in the pathogenesis diabetes and its complications such asdiabetic cardiomyopathy, diabetic nephropathy, neuropathy and retinopathy (DR). Excess glucose metabolic flux through various biochemical pathways are implicated in thesediabetic complications.The retina is a part of the central nervous system, which requires large amounts of glucose and oxygen to generate ATP for its visual function. During ATP generation in the mitochondrial electron transport chain,mtROS is generated as a byproduct.Although anti-oxidants are present in the mitochondrion to counter free radicals, the mtROS dodamage mitochondrial proteins, mtDNA, and membrane lipids. The damaged mitochondria are inefficient in ATP production but release excess ROS.The mitochondrion being a symbiotic bacterium when released its components into the cytosol are recognized as danger-associated molecular patterns (DAMPS) by cytosolic pattern recognition NOD-like receptor, the NLRP3 inflammasome. These inflammasomes process inactive pro-caspase-1 to active caspase-1, which cleaves pro-inflammatory IL-1 mature IL-1 causing inflammation and pyroptosis. To counter the damaging action of mtROS and inflammasomes in fully differentiated retinal cells, the removal of damaged and dysfunctional mitochondria is needed via mitophagy, aspecific form of autophagy. Mitophagy is critical for mitochondrial quality control, homeostasis and cell survival. Nonetheless, under chronic diseases including DR, mitophagy dysregulation, lysosome destabilization and NLRP3 inflammasome activation occurs causinginflammation and disease progression. Recently, the thioredoxin-interacting protein TXNIP has been shown to be induced strongly by high glucose and diabetes inhibitingthe anti-oxidant function of thioredoxin.Thus, TXNIPhas been implicated in mitochondrial dysfunction, mitophagy dysregulation, oxidative stress and inflammation in DR. Because TXNIP gene expression itself is strongly induced in cells by high glucose, nucleic acid constructs containing the TXNIP promoter linked with a therapeutic gene such as insulin or inhibitory RNAs targeting disease-associated genes (e.g., VEGF-A or TXNIP itself) can be used to prevent or slow down the progression of DR.

Biography

Lalit Singh Pukhrambam is an Associate Professor at Wayne State University School of Medicine, Detroit, Michigan, USA, in the Departments of Anatomy/Cell Biology and Ophthalmology. He obtained his Ph.D. from the Indian Institute of Science, Bangalore, India. He was a recipient of the American Diabetes Association Career Development Award and the Robert Schrier MD Young Investigator Grant of the National Kidney Foundation (NKF), USA. His research has also been supported by JDRF, USA, Eye-Banks, USA, and NIH/NEI grants. His research interests involve molecular and cellular mechanisms of diabetes and its complications particularly of the eye and kidney and gene therapy approaches.

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