**CELL LONGEVITY PATHWAYS GOVERN VASCULAR AND INFLAMMATORY RESPONSES TO OXIDANT STRESS**

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More than 170 million individuals world wide are affected by diabetes mellitus (DM). Although complications of DM as a result of oxidative stress are broad in nature, disability in the cardiovascular system can be the most severe. It is therefore vital to understand the cell pathways that determine cell longevity and inflammatory responses of the vascular system. Here we show that the wingless pathway with Wnt1 confers endothelial cell (EC) protection during elevated D-glucose exposure, since application of a Wnt1 neutralizing antibody, treatment with the Wnt1 antagonist DKK-1, or gene silencing of Wnt1 with Wnt1 siRNA transfection blocks cell protection. Wnt1 controls the post-translational phosphorylation of the forkhead member FoxO3a and blocks the trafficking of FoxO3a to the cell nucleus to prevent apoptosis. Intimately linked to this pathway is the sirtuin SIRT1. During elevated D-glucose exposure, SIRT1 is sequestered in the cytoplasm of ECs, but specific activation of SIRT1 shuttles the protein to the nucleus to allow for cytoprotection. The ability of SIRT1 to prevent apoptotic injury requires activation of protein kinase B (Akt1) and the inhibition of FoxO3a as shown by complimentary gene knockdown studies of FoxO3a. SIRT1 modulates mitochondrial membrane permeability, cytochrome c release, Bad activation, and caspase 1 and 3 activation. Our work identifies vascular Wnt1 and SIRT1 signaling as novel strategies for the treatment of DM vascular complications.