REGIONAL CENTRE FOR BIOTECHNOLOGY

Journal Club

"A Ligand-Independent VEGFR2 Signaling Pathway Limits Angiogenic Responses in Diabetes"
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Abstract

Although vascular complications are a hallmark of diabetes, the molecular mechanisms that underlie endothelial dysfunction are unclear. We showed that reactive oxygen species generated from hyperglycemia promoted ligand-independent phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2). This VEGFR2 signaling occurred within the Golgi compartment and resulted in progressively decreased availability of VEGFR2 at the cell surface. Consequently, the responses of endothelial cells to exogenous VEGF in a mouse model of diabetes were impaired because of a specific deficiency of VEGFR2 at the cell surface, despite a lack of change in transcript abundance. Hyperglycemia-induced phosphorylation of VEGFR2 did not require intrinsic receptor kinase activity and was instead mediated by Src family kinases. The reduced cell surface abundance of VEGFR2 in diabetic mice was reversed by treatment with the antioxidant N-acetyl-L-cysteine, suggesting a causative role for oxidative stress. These findings uncover a mode of ligand-independent VEGFR2 signaling that can progressively lead to continuously muted responses to exogenous VEGF and limit angiogenic events.