KLF5

Reduced expression of endothelial nitric oxide synthase (eNOS) is a hallmark of endothelial dysfunction in diabetes, which predisposes diabetic patients to numerous cardiovascular complications including blunted angiogenesis. The Krüppel-like factor (KLF) five has been implicated as a central regulator of cardiovascular remodeling, but its role in endothelial cells (ECs) remains poorly understood. We show here that expression of endothelial KLF5 was significantly increased in the ECs from mouse diabetes mellitus type 2 (T2DM) model, when compared to non-diabetic or T1DM mouse. KLF5 up-regulation by insulin was dependent on activation of multiple pathways, including mammalian target of rapamycin, oxidative stress and Protein kinase C pathways. Hyperinsulinemia-induced KLF5 inhibited endothelial function and migration, and thereby compromised in vitro and in vivo angiogenesis. Mechanistically, KLF5 acted in concert with the MTA1 coregulator to negatively regulate NOS3 transcription, thereby leading to the diminished eNOS levels in ECs. Conversely, potentiation of cGMP content (the essential downstream effector of eNOS signaling) by pharmacological approaches successfully rescued the endothelial proliferation and in vitro tube formation, in the HUVECs overexpressing the exogenous KLF5. Collectively, the available data suggest that the augmentation of endothelial KLF5 expression by hyperinsulinemia may represent a novel mechanism for negatively regulating eNOS expression, and may thus help to explain for the T2DM-related endothelial dysfunction at the transcriptional level [1)].

1)
Wang XH, Yan CY, Liu JR. Hyperinsulinemia-induced KLF5 mediates endothelial angiogenic dysfunction in diabetic endothelial cells. J Mol Histol. 2019 May 2. doi: 10.1007/s10735-019-09821-3. [Epub ahead of print] PubMed PMID: 31049798.