Regulation of KLF2 and KLF4 by Syndecan-4: a novel signaling pathway to target atherosclerosis

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Atherosclerosis, the formation of plaques inside arteries, leads to severe conditions such as coronary heart disease (CAD), stroke and peripheral arterial disease (PAD). Although current treatments and healthy lifestyle can slow down disease progression, cure for atherosclerosis remains an unmet medical need.Atherosclerotic plaques often develop in defined arterial vessel locations named atheroprone regions. Biomechanical studies of arterial blood flow have later demonstrated that atheroprone regions are exposed to turbulent blood flow (e.g. blood vessel bifurcations) while atheroresistant regions (e.g. descending thoracic aorta) are exposed to laminar blood flow. Atheroprone regions are characterized by inability of endothelial cells (EC) to align parallel to blood flow direction, a defect that associate with loss of intrinsic antiinflammatory properties of the endothelium.

In this context we have found that transmembrane proteoglycan Syndecan-4 (Sdc4) mediates protection of athero-resistant regions by promoting EC alignment and upregulation of antinflammatory transcription factors KLF2 and KLF4. This hypothesis is supported by a series of observations. First, Sdc4 knock-out mice(Sdc4-/-) aortas show a generalmisalignment of endothelium. Second, ina hypercholesterolemic mouse model (DKO) we find that Sdc4 knock-out (Sdc4-/-) mice develop massive accumulation of atherosclerotic plaques in thoracic aortawhile wild-type (WT) mice show plaques only atbifurcation points (intercostal arteries). Third, we observe a marked downregulation of antiinflammatory transcription factors KLF2 and KLF4 in Sdc4 -/- EC, which are believed to conferantiinflammatory, antithrombotic, antiadhesive properties to the endothelium.

KLF2 and KLF4 upregulation may offer a real therapeutic opportunity to treat atherosclerosis, unfortunately the upstream regulation ofthese factor expression remain poorly understood. Preliminarydata generated in our laboratory, suggest that Sdc4 may regulate KLF2/KLF4 expression via a novel PKCalpha/ERK5 pathway. More work is ongoing in order to elucidate the molecular link between Sdc4 and endothelial cell alignement.In summary, we have identified a novel molecule (Sdc4) that modulates KLF2/KLF4 expression, endothelial cell alignment and promotes atheroprotection.