Tenascin-X mediates flow-induced suppression of EndMT and atherosclerosis

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Abstract

Background: Endothelial-to-mesenchymal transition (EndMT) has been identified as a critical driver of vascular inflammation and atherosclerosis, and TGF-β (transforming growth factor β) is a key mediator of EndMT. Both EndMT and atherosclerosis are promoted by disturbed flow, whereas unidirectional laminar flow limits EndMT and is atheroprotective. How EndMT and endothelial TGF-β signaling are regulated by different flow patterns is, however, still poorly understood.

Methods: Flow chamber experiments in vitro and endothelium-specific knockout mice were used to study the role of tenascin-X in the regulation of EndMT and atherosclerosis as well as the underlying mechanisms.

Results: In human endothelial cells as well as in human and mouse aortae, unidirectional laminar flow but not disturbed flow strongly increased endothelial expression of the extracellular matrix protein TN-X (tenascin-X) in a KLF4 (Krüppel-like factor 4) dependent manner. Mice with endothelium-specific loss of TN-X (EC-Tnxb-KO) showed increased endothelial TGF-β signaling as well as increased endothelial expression of EndMT and inflammatory marker genes. When EC-Tnxb-KO mice were subjected to partial carotid artery ligation, we observed increased vascular remodeling. EC-Tnxb-KO mice crossed to low-density lipoprotein receptor-deficient mice showed advanced atherosclerotic lesions after being fed a high-fat diet. Treatment of EC-Tnxb-KO mice with an anti-TGF-beta antibody or additional endothelial loss of TGF-beta receptors 1 and 2 normalized endothelial TGF-beta signaling and prevented EndMT. In in vitro studies, we found that TN-X through its fibrinogen-like domain directly interacts with TGF-β and thereby interferes with its binding to the TGF-β receptor.

Conclusions: In summary, we show that TN-X is a central mediator of flow-induced inhibition of EndMT, endothelial inflammation and atherogenesis, which functions by binding to and by blocking the activity of TGF-β. Our data identify a novel mechanism of flow-dependent regulation of vascular TGF-β, which holds promise for generating new strategies to prevent vascular inflammation and atherosclerosis.