ER Protein TXNDC5 as a Novel Therapeutic Target against Organ Fibrosis and Atherosclerosis

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Fibrosis, a non-physiological repair in multiple organs, is associated with end-stage pathological manifestation of a wide variety of vascular injury and inflammation related diseases. In response to chemical, immunological and physical insults, the body's defense system and matrix synthetic machinery respond to repair and maintain tissue homeostasis. However, uncontrolled repair process leads to scarring or fibrosis, a pathological condition characterized by excessive synthesis and accumulation of extracellular matrix (ECM) proteins, loss of tissue homeostasis and organ failure.

In the past few years, we have identified thioredoxin domain containing 5 (TXNDC5), a cardiac fibroblast (CF)-enriched endoplasmic reticulum (ER) protein, as a novel mediator of cardiac fibrosis (*Shih et al, Circ Res 2018*). We showed that TXNDC5 promotes cardiac fibrosis by redox-dependent CF activation, as well as by enhancing ECM production via facilitating ECM protein folding. In addition, targeted deletion of *Txndc5* protects against β agonist-induced cardiac fibrosis and LV dysfunction in mice. These results suggest that targeting TXNDC5 could be a powerful novel approach to mitigate cardiac fibrosis and dysfunction. Based on these findings, we hypothesize that TXNDC5 could also contribute to the development of fibrosis in non-cardiac organs, including lung and kidney fibrosis.

Consistent with this hypothesis, our recent work revealed that TXNDC5 was upregulated in both human and mouse fibrotic lungs/kidneys and its expression levels showed strong positive correlation with that of numerous fibrogenic protein genes. Knockdown of TXNDC5 in primary human lung/kidney fibroblasts attenuated TGFβ1-induced lung/kidney fibroblast activation, proliferation and ECM protein upregulation, whereas increasing expression of TXNDC5 triggered lung/kidney fibroblast activation and proliferation and increased ECM protein production. Further experiments revealed a novel cellular mechanism for regulating TGFβ signaling activity and fibrogenesis: we found that TXNDC5, a protein disulfide isomerase, augments TGFβ signaling activity by facilitating the folding and stabilization of TGFβ receptor 1 (TGFBR1), leading to the activation of both canonical and non-canonical TGFβ pathways and hence excessive lung/kidney fibroblast proliferation and ECM accumulation. TGFβ1-induced TXNDC5 upregulation in lung/kidney fibroblasts was dependent on ER stress and activating transcription factor 6-mediated transcriptional control. Finally, fibroblast-specific deletion of *Txndc5* in mice revealed significant protective effects against bleomycin (BLM)-induced lung fibrosis as well as post-injury renal fibrosis, suggesting that targeting TXNDC5 could be a powerful new therapeutic approach to mitigate excessive lung/kidney fibrosis and improve lung/renal function and outcomes in patients with lung/kidney fibrosis.

Interestingly, TXNDC5, also called endo-PDI, is a protein disulfide isomerase also enriched in the endothelium. Our latest work revealed that TXNDC5 is induced in the arterial endothelium by atherogenic disturbed flow and contributes critically to the development of atherosclerosis. In this presentation, I will discuss our recent findings on the mechanisms by which TXNDC5 regulates

endothelial function and the potential insights in the treatment of atherosclerotic vascular diseases.