ABSTRACTS

Angiopoietin-like protein 2 mediates vasculopathy-driven fibrogenesis in a mouse model of skin fibrosis

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Fibrosis is a pathological condition wherein excessive deposition of extracellular matrix components leads to tissue hardening and loss of function. Though fibrosis contributes to ~40% of deaths worldwide, the lack of effective treatments highlights the need for a molecular understanding of fibrogenesis. Vasculature abnormalities are a foundational cause of fibrotic disorders such as the skin fibrotic disease scleroderma, however the underlying mechanisms are largely unknown.

Therefore, the current team investigated the contribution of vasculature defects in scleroderma-like fibrotic conditions and the molecular basis of such vasculopathy. Given that the transcription factor Snail is upregulated in various fibrotic conditions, the researchers engineered a transgenic mouse model expressing Snail in the basal keratinocytes of the epidermis that recapitulates the hallmark features of scleroderma. Noteworthy among these pathological features is vasculopathy such as deformed vessels, endothelial cell dysfunction and vascular leakage leading to increased immune cell infiltration. Immunostaining, qPCR analysis of gene expression, vascular leakage assays, knock-out mouse studies, *ex vivo* explant assays, and *in vitro* experiments with endothelial cells were carried out to investigate the role of vasculopathy in fibrosis development.

The study revealed that vasculature defects arise earlier than significant increase in dermal thickness in the Snail transgenic skin recapitulating the disease progression in scleroderma patients. Investigations of the underlying molecular mechanisms revealed that *Angiopoietin-like protein 2 (Angptl2)*, secreted by the Snail transgenic keratinocytes, is a major contributor towards fibrotic vasculopathy. *Angptl2* upregulates pro-fibrotic genes in endothelial cells, downregulates the tight junction protein *Claudin 5*, and drives acquisition of mesenchymal markers. Furthermore, *Claudin 5* potentially acts as a master regulator of *Angptl2*-mediated effects, as overexpression of this tight junction protein in endothelial cells reduced *Angptl2*-induced acquisition of mesenchymal characteristics. Inhibiting endothelial cell junctional instability and consequently vascular leakage with a synthetic analog (*UAS03*) of the microbial metabolite Urolithin A decreased the fibrotic phenotype in the Snail tg skin. The researchers found that *UAS03* counteracts the effects of *Angptl2* in endothelial cells. This posits *UAS03* as a novel anti-fibrotic therapeutic strategy.

The study has identified an early biomarker of the disease in the form of *Angptl2* and discovered novel therapeutic strategies via use of *UAS03*, which can potentially aid in reducing the disease severity.

Presented by: Dyuti Saha
SIRCON 2023 held at IISC, Bengaluru
DOI: 10.15305/ijir.v7i1.386