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Mechanism and modulators of kidney fibrosis after tubular injury

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Kidney fibrosis is unavoidable consequence of chronic kidney disease irrespective of the primary underlying insults. Fibrogenesis starts with an initial tissue injury that causes inflammation as the physiological host defense response. When this response becomes uncontrolled and sustains itself with continuous production of chemotactic cytokines, inflammation does not resolve and can create the optimal microenvironment for tissue fibrogenesis.
Over the past several decades, many studies have been conducted to identify the pathophysiology involved in the development of AKI. However, much remains unknown about the mechanism of transition from AKI to CKD. Recent studies have focused on the role of damaged tubules and a subpopulation of incompletely recovered tubules after AKI, which lead to abnormal growth arrest, failure to redifferentiate into normal tubules, and finally atrophy, as the result of abnormal wound healing. If abnormal wound healing persists or when metabolic derangements impair normal wound healing, atrophic tubules produce persistent and progressively increasing levels of profibrotic signalling molecules such as TGF-β1 and Shh. These paracrine factors intrinsically play a role in mediating normal wound repair. However, persistent activation of these signalling pathways and abnormal cross talk between unhealed tubular cells and interstitial cells such as infiltrating immune cells or activated fibroblasts eventually leads to myofibroblast transformation of pericyte-like fibroblast or bone marrow-derived precursor cells, the final and common pathological feature of renal fibrosis.
In the context of abnormal wound healing, several intrinsic and extrinsic modulators affect the fate of kidney fibrosis after tubular injury. These are Type, degree and duration of injury, metabolic derangement such as diabetes and ectopic intrarenal lipid accumunlation, presence of underlying CKD, renal aging and impairment of normal wound repair mechanism with intrarenal or BM derived stem cells.
This lecture will highlight the mechanisms of renal fibrosis after tubular injury and the effect of some modulators, especially diabetes and mobilized BM derived stem cells.