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Mechanisms of Renal Fibrosis. Can we Cure this Disease?

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Chronic renal failure is still one of the biggest challenges in nephrology and the number of patients presenting with endstage renal failure (ESRF) (1-5) is steadily increasing. At present in the western industrial countries diabetic nephropathy is the main cause for ESRF (6).

In recent years progress has been made in understanding the pathogenesis of chronic progressive renal disease, however, treatment of chronic renal failure still aims at delaying the onset of ESRF rather than prevention or reversal, while specific treatments to prevent or even reverse established chronic renal disease are not available in the clinic, yet (4, 7, 8). However, recent therapeutic success in animal models of chronic renal diseases raise hope, that effective treatment for chronic kidney disease will be available for patients in the future (7).

Although most common renal diseases that lead to ESRF differ significantly in their underlying primary pathomechanisms (5, 9, 10) finally they all present with an indistinguishable scarred/fibrotic kidney (5, 10). Thus we and others speculate that a common pathogenic pathway leading to ESRF will be associated with renal fibrosis.

The progression of these diseases is often associated with an expansion of the renal tubulointerstitial area. Furthermore, excretory renal function strictly correlates with the increase of the tubulointerstitial area, especially with the extent of tubulointerstitial fibrosis (10-12). These tubulointerstitial lesions are mainly characterized by cellular infiltrates, tubular atrophy and different degrees of fibrosis (12).

Renal fibroblasts differentiate along a terminal differentiation lineage (12-14). They can be identified and characterized by morphological criteria as well as by the expression of different cell surface molecules and intercellular proteins (12-14). These cells play a key role in the process of organ fibrosis for they secrete most of the accumulating matrix components such as type I collagen, fibronectin, and furthermore, present with a significant multiplication during fibrosis and increased migratory activity (14-17). These interstitial cells interact with infiltrating inflammatory cells as well as with tubular epithelial or vascular endothelial cells. Activated renal fibroblasts in part positive for α-smooth muscle actin are considered the main mediators of kidney fibrosis 17, 18).

These activated fibroblasts derive from at least three different sources (8, 19, 20). Resident quiescent renal fibroblasts can become activated and furthermore, they can be of epithelial origin due to epithelial mesenchymal transition (EMT) (20-23). In part bone marrow-derived cells also contribute via the circulation to the pool of activated fibroblasts in the kidney (20).

The process of EMT seems to be one of the key players in the progression of renal fibrosis (22, 23). Epithelial cells (tubular epithelial cells) loose their typical epithelial characteristics and acquire typical characteristics of fibroblasts (24). In the adult kidney EMT of epithelial cells is considered a physiological response to injury as it serves as a means for epithelial cells to escape cell death and as it serves an additional source of myofibroblasts/fibroblasts, which are essential to repair injured tissue (8, 20, 25). However, during renal fibrosis the enhanced conversion of renal tubular epithelial cells into myofibroblasts / fibroblasts is considered unfavourable, as it leads to disruption of polarized renal tubular cells and an increase in fibrotic scar formation (20). A combination of cytokines associated with proteolytic digestion of basement membranes is considered to induce EMT in the kidney. Among numerous growth factors, TGF-ß1 has been identified as the principal inducer of EMT in the kidney (8, 23, 26). This cytokine is either secreted by inflammatory cells surrounding tubular epithelial cells (paracrine) or in an autocrine fashion by the epithelial cell itself undergoing the process of EMT (19). Furthermore, in experimental analysis it has been shown that the expression of the adhesion molecule E-cadherin stabilizes the cellular epithelial phenotype. Thus the loss of E-cadherin is associated with EMT (19). Although the knowledge in understanding the disease progress has increased there are still only a few options to prevent or treat renal interstitial fibrosis.

Bone morphogenic proteins (BMPs) are a major subgroup of the TGF-ß superfamily (27). These proteins control morphogenic pathways at different stages of development in a broad range of organs (28). BMP-7 was primarily identified as a factor that induces bone formation, however, studies performed in knock out mice revealed the importance of BMP-7 in the kidney (29, 30) . BMP-7 has been shown to play a major role during mammalian kidney development (32, 33). BMP-7 is expressed mainly in the collecting duct, distal tubular epithelial cells and podocytes (33). However, the expression of BMP-7 is significantly decreased in acute and chronic renal injury (34). After recovery of renal function the level of BMP-7 is normalized in the kidney, thus BMP-7 may have a reno-protective effect (34).

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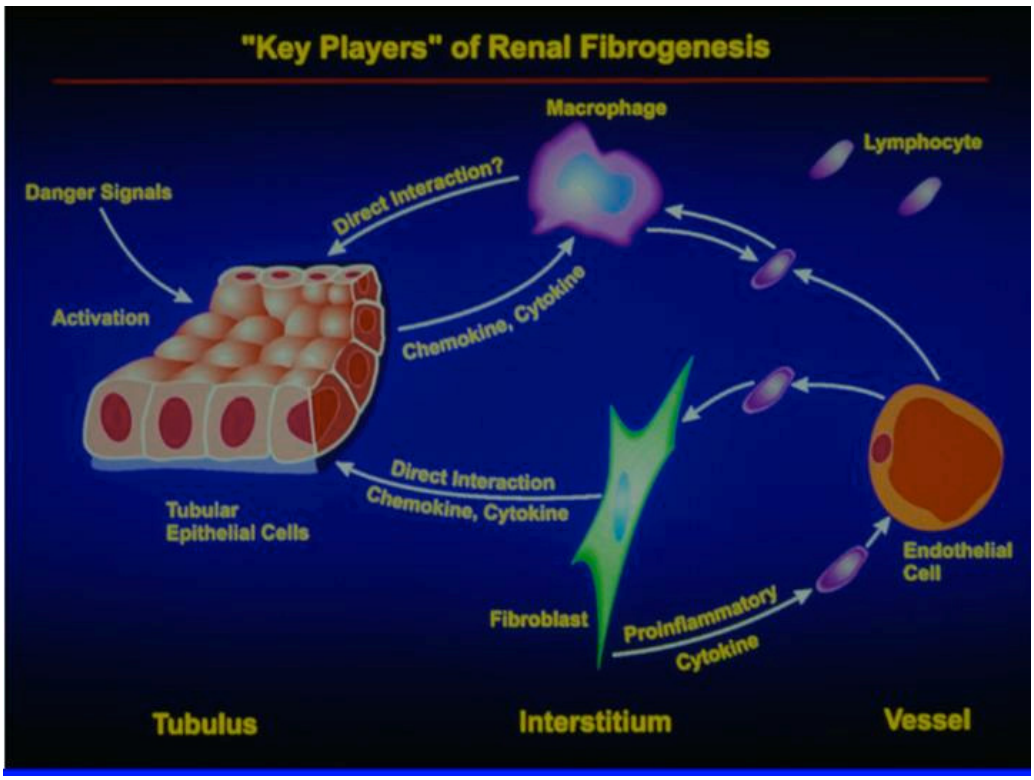
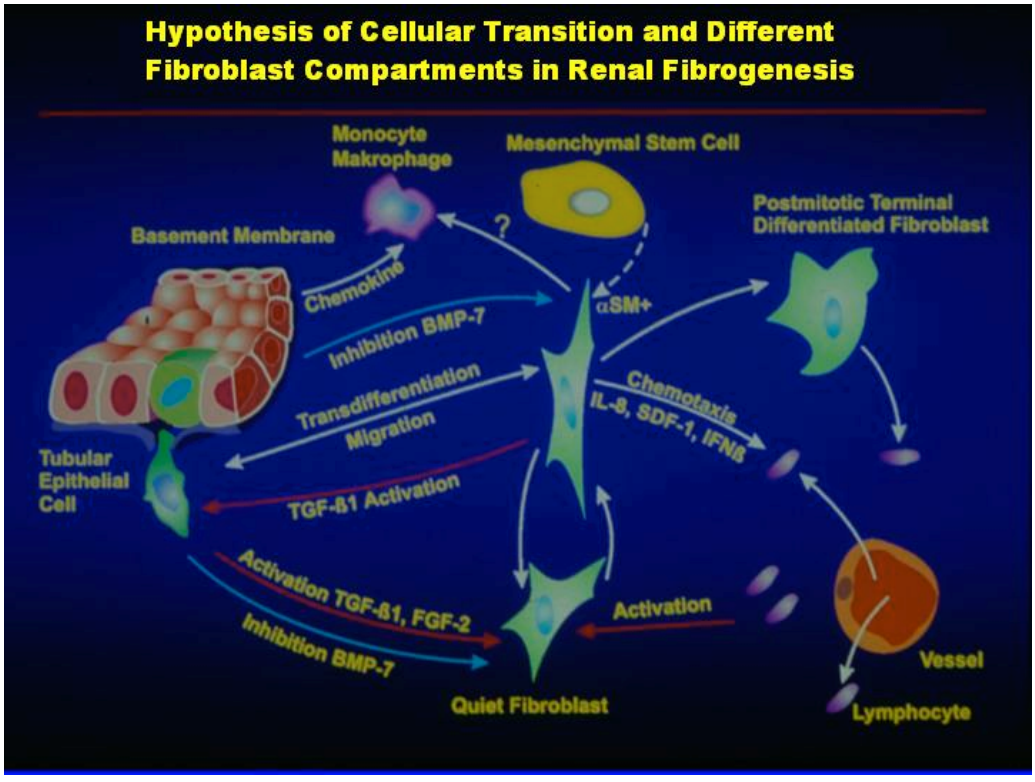


Due to the **results** obtained by cellular and molecular biological analyses as well as by animal experiments it became clear that BMP-7 and TGF-ß1 function as physiological counterparts during kidney development and kidney regeneration (8, 36). In the adult kidney it has been shown that TGF-ß1 is associated with progression of chronic renal disease, while the expression of BMP-7 in the kidney is significantly decreased in injured kidneys (35 36).



Furthermore, an endogenous molecule named decorin inhibits TGF-ß1 activity by trapping it extracellularly and ameliorates progression of TGF-ß1 induced chronic renal fibrosis (37). If the kidney possesses endogenous molecules, which provide from injury, then these molecules can constitute a new line of therapeutic agents against renal failure.

Recently several independent studies revealed encouraging therapeutic effects of exogenous recombinant BMP-7 (rhBMP-7) in several animal models of chronic renal diseases. In comparative studies the renoprotective effect of rh-BMP-7 was significantly better than the effect of enalapril in rat models of diabetic nephropathy and unilateral uretral obstruction (38, 39). These positive reno-protective effects by rhBMP-7 were demonstrated in rats (40) as well as in mice (41). Treatment with rhBMP-7 ameliorated glomerular pathology and tubulointerstitial fibrosis in a model of STZ-induced diabetes (34). Furthermore, in the model of nephrotoxic serum nephritis the extent of interstitial renal fibrosis was reduced and excretory renal function improved by giving the animals rhBMP-7 some days after renal fibrosis was established (36). Thus the administration of rhBMP-7 could inhibit the progression of renal fibrosis in different animal models of chronic renal insufficiency. The results obtained in animals using rhBMP-7 to prevent renal fibrosis or to reduce the extent of renal fibrosis are very encouraging for nephrologists to perform in the near future clinical trials to prevent or reduce renal fibrosis in patients, a major cause of ESRF.

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