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Prostaglandin E2 receptors as therapeutic targets in renal inflammation and fibrosis

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Chronic kidney disease (CKD) is characterized by the development of renal fibrosis and progressive loss of renal function, ultimately CKD leads to end-stage renal disease (ESRD). CKD is a leading cause of mortality, and the global incidence is steadily increasing, currently about 10% of the population suffers from CKD. Yet, despite the overwhelming efforts to find potential therapeutics to reduce renal fibrosis, current treatment strategies are ineffective in preventing disease progression in CKD patients.

The cyclooxygenase/prostaglandin system plays a key role in renal injury and holds great promise as a suitable therapeutic target. We have developed a variety of experimental animal models of renal injury enabling us to study clinically relevant cases of CKD with the aim to identify therapeutics to target fibrosis. Using pharmacological intervention, transgenic mouse models and in vivo gene silencing approaches, we have previously identified specific inflammatory mechanisms evolving around the cyclooxygenase type 2 (COX2)/prostaglandin (PG) system, which seem to be involved in renal injury.

The EP receptors (EP1-4) are downstream targets of COX/PGE2 cascade, thus we have explored directly targeting the EP receptors as therapeutic intervention for prevention of renal fibrosis. Based on our findings that COX2 is involved in renal fibrosis we hypothesize that targeting renal EP receptors directly will reduce fibrosis development in CKD. Using a translational approach we have to this end evaluated the role of the EP1 and EP2 receptor in the pathogenesis of renal fibrosis in several models of kidney injury, including human (fibrotic) kidney slices.

Our data demonstrated that targeting the EP1 (EP1 antagonist SC-19220) or the EP2 (EP2 agonist Butaprost) receptor reduced TGFβ-induced fibronectin expression and epithelial-to-mesenchymal transition (EMT) in epithelial Madin Darby Canine kidney (MDCK) cells. Moreover, treatment with SC-19220 or Butaprost attenuated development of fibrosis in mice that underwent unilateral ureteral obstruction (UUO) surgery. More importantly, a similar anti-fibrotic effect of SC-19220 or Butaprost was observed directly in human fibrotic kidney slices.

These studies highlight both the EP1 and the EP2 receptor as promising targets for preventing both the onset and late stage of renal fibrosis. The findings provide a strong evidence that the effect of SC-19220 or Butaprost may translate to clinical care since the effects were observed in UUO mice and directly in human kidney tissue.