Role of COX-2 in unilateral ureteral obstruction: what is new?

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PROSTANOIDs are metabolites of arachidonic acid through the activity of cyclooxygenase (COX). COX exists in two major isoforms: constitutive COX-1 and inducible COX-2. PGE₂ is the major prostanoi produced in the kidney, and it induces biological function by binding to four G protein-coupled receptors (EP₁-EP₄), which each couple to a distinct signaling pathway. COX-derived prostanoi affect a wide spectrum of renal function in health and disease (2).

Obstructive nephropathy is a common cause of chronic kidney disease in both children and adults. In addition, unilateral ureteral obstruction (UUO) readily induces tubulointerstitial fibrosis, a common pathophysiology of chronic kidney disease, irrespective of the causes, which leads to the end stage of renal disease (1). Accordingly, UUO in rodents is a widely used experimental model of renal fibrosis. It has been reported that PGE₂ generation is elevated in obstructed kidneys. The heightened PGE₂ synthesis is associated with increased COX-2 expression in the UUO model. In vitro evidence demonstrates that COX-2 expression in renal medullary interstitial cells is increased in response to pressure, dependent on the endogenous production of ROS. ROS dependence of COX-2 induction was also observed in rats subjected to UUO. A number of studies using pharmacological inhibitors of COX-2 have attempted to address the functional role of COX-2 fibrosis but direct measurement of ROS production is still insufficient. The expression of antioxidant genes such as HO-1, SOD1, and SOD2 has been determined to antioxidative stress in UUO. However, the assessment of ROS production in the obstructed kidney is insufficient. The expression level of HO-1, SOD1, and SOD2 has been determined to antioxidative stress [heme oxygenase (HO)-1, SOD1, and SOD2], apoptosis (TUNEL staining and caspase-3), and tubular injury (histology and kidney injury molecule-1) were determined. Consistent findings showed the indexes of these three categories of tissue injury were induced by UUO in WT mice, all of which were exaggerated in COX-2 KO mice. These results represent the first genetic evidence to prove a protective role of COX-2 against renal injury in UUO.

This study has a number of limitations. ROS have been postulated to be a major molecular target of COX-2-derived prostaglandins in UUO. However, the assessment of ROS production in the obstructed kidney is insufficient. The expression level of HO-1, SOD1, and SOD2 has been determined to indirectly reflect ROS production. Direct measurement of ROS production using methods such as the electron paramagnetic resonance spin-trapping technique will be extremely helpful. The COX-2 KO kidney exhibits a greater increase in the expression of antioxidant genes such as HO-1, SOD1, and SOD2 compared with WT control kidneys after UUO. However, the causal relationship between COX-2 deletion and the antioxidant gene upregulation is unclear. The detailed mechanism of how COX-2-derived prostaglandins affect a specific antioxidant gene awaits further investigations.

In a sharp contrast to the protective role of COX-2 in UUO as described above, COX-2 plays a pathogenic role in other models of kidney injury, such as cisplatin nephropathy. In a mouse model of cisplatin nephrotoxicity, renal expression of COX-2 and microsomal prostaglandin synthase-1 was elevated accompanied with increased PGE₂ levels. Inhibition of prostaglandin synthesis by celecoxib or meloxicam or by microsomal prostaglandin synthase-1 deletion consistently attenuated cisplatin-induced renal dysfunction, oxidative stress, and inflammation. It is interesting to note that even in the same model of UUO, macrophage COX-2 has been shown to mediate renal inflammation, oxidative stress, and apoptosis.

In this study, a novel technique involving the use of chitosan/small interfering RNA nanoparticles was successfully used to achieve macrophage-specific knockdown of COX-2. This technique helps address the pathogenic role of macrophage COX-2 during UUO and also represents a novel intervention for the management of obstructive nephropathy. This study also brings up a question as to the cell type responsible for the protective role of COX-2, which should be distinct from macrophages.

EP₃ has been shown to mediate the protective role of COX-2 against UUO-induced tubulointerstitial fibrosis (9). It will be

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Obstruction

ROS

Apoptosis, fibrosis, inflammation

COX-2/PGE$_2$/EP$_4$

Tissue remodeling

Fig. 1. Illustration of the protective role of cyclooxygenase (COX)-2 in obstructive nephropathy. In the unilateral ureteral obstruction model, ROS play a central role in mediating obstruction-induced apoptosis, fibrosis, and inflammation. On the other hand, ROS also activate the protective COX-2/PGE$_2$/EP$_4$ pathway, which mitigates oxidant-induced tissue damage.

interesting to determine the EP subtype responsible for the pathogenic role of COX-2 in kidney injury.

In summary, COX-2 deletion in mice exacerbates obstruction-induced renal oxidative stress, apoptosis, and tubular injury. These results represent a strong genetic evidence supporting a protective role of COX-2 against obstructive nephropathy. Such protective action of COX-2 is likely mediated by the PGE$_2$/EP$_4$ pathway (Fig. 1). COX-2 inhibitors should be used with caution in patients with this disease.

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