Renal Obstruction and Transforming Growth Factor-alpha (TGF-alpha), Literatures

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Abstract: Obstructive uropathy is a condition in which the flow of urine is blocked. This causes the urine to back up and injure one or both kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem. If the blockage comes on suddenly, kidney damage is less likely if the problem is detected and treated promptly, and the damage to the kidneys goes away normally. Long-term damage to the kidneys may occur if the blockage has been present for a long time. If the problem is caused by a blockage in the bladder, the bladder may have long-term damage, which may lead to problems emptying the bladder or leakage of urine. Transforming growth factor alpha (TGF-α) is a protein that in humans is encoded by the TGFA gene. As a member of the epidermal growth factor (EGF) family, TGF-α is a mitogenic polypeptide. The protein becomes activated when binding to receptors capable of protein kinase activity for cellular signaling. TGF-α is a transforming growth factor that is a ligand for the epidermal growth factor receptor, which activates a signaling pathway for cell proliferation, differentiation and development. This protein may act as either a transmembrane-bound ligand or a soluble ligand. This gene has been associated with many types of cancers, and it may also be involved in some cases of cleft lip/palate.
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Key words: transforming growth factor- alpha (TGF-alpha); obstruction; renal; life; cell

1. Introduction

Obstructive uropathy is a condition in which the flow of urine is blocked. This causes the urine to back up and injure one or both kidneys. Obstructive uropathy occurs when urine cannot drain through a ureter. Urine backs up into the kidney and causes it to become hydronephrosis. It can occur suddenly, or be a long-term problem. If the blockage comes on suddenly, kidney damage is less likely if the problem is detected and treated promptly, and the damage to the kidneys goes away normally. Long-term damage to the kidneys may occur if the blockage has been present for a long time. If the problem is caused by a blockage in the bladder, the bladder may have long-term damage, which may lead to problems emptying the bladder or leakage of urine.

Transforming growth factor alpha (TGF-α) is a protein that in humans is encoded by the TGFA gene. As a member of the epidermal growth factor (EGF) family, TGF-α is a mitogenic polypeptide. The protein becomes activated when binding to receptors capable of protein kinase activity for cellular signaling. TGF-α is a transforming growth factor that is a ligand for the epidermal growth factor receptor, which activates a signaling pathway for cell proliferation, differentiation and development. This protein may act as either a transmembrane-bound ligand or a soluble ligand. This gene has been associated with many types of cancers, and it may also be involved in some cases of cleft lip/palate.

TGF-α is synthesized internally as part of a 160 (human) or 159 (rat) amino acid transmembrane precursor. The precursor is composed of an extracellular domain containing a hydrophobic transmembrane domain, 50 amino acids of TGF-α, and a 35-residue-long cytoplasmic domain. In its smallest form TGF-α has six cysteines linked together via three disulfide bridges. Collectively all members of the EGF/TGF-α family share this structure. TGF-α can be produced in macrophages, brain cells, and keratinocytes. TGF-α induces epithelial development. When TGF-α binds to EGFR it can initiate multiple cell proliferation events. Cell proliferation events that involve TGF-α bound to EGFR include wound healing and embryogenesis.

When TGF-α binds to EGFR it dimerizes triggering phosphorylation of a protein-tyrosine kinase. The activity of protein-tyrosine kinase causes an autophosphorylation to occur among several tyrosine residues within EGFR, influencing activation and signaling of other proteins that interact in many signal transduction pathways. The EGF/TGF-α family has been shown to regulate luteinizing hormone-releasing hormone (LHRH) through a glial-neuronal interactive process. Produced in hypothalamic astrocytes, TGF-α indirectly stimulates LHRH release through various intermediates. As a result, TGF-α is a physiological component essential to the initiation process of female puberty.

The following introduces recent reports as

references in the related studies.

Akin, M., S. Demirbilek, et al. "Attenuation of ureteral obstruction-induced renal injury by polyenylphosphatidylcholine." Int J Urol. 2007 Apr;14(4):350-6.

The cytoprotective, antioxidant and antifibrotic effects of polyenylphosphatidylcholine (lecithin, PPC) have been demonstrated both experimentally and clinically. The present study investigated whether PPC treatment has any beneficial effect on renal injury in unilateral partial ureteral obstruction (UUO) in rats. 40 Wistar-Albino rats were split into three groups (sham-operated controls, untreated and treated rats). Rats of the untreated and treated groups (n = 15) underwent UUO with two-thirds of the left ureter embedded in the psoas muscle. In group 3, PPC was given orally at a dose of 100 mg/day for 30 days. At the end of the 30th day of the experimental period, obstructed kidneys and blood samples were harvested.

Ardura, J. A., S. Rayego-Mateos, et al. "Parathyroid hormone-related protein promotes epithelial-mesenchymal transition." J Am Soc Nephrol. 2010 Feb;21(2):237-48. doi: 10.1681/ASN.2009050462. Epub 2009 Dec 3.

Epithelial-mesenchymal transition (EMT) is an important process that contributes to renal fibrogenesis. TGF-beta1 and EGF stimulate EMT. Recent studies suggested that parathyroid hormone-related protein (PTHrP) promotes fibrogenesis in the damaged kidney, apparently dependent on its interaction with vascular endothelial growth factor (VEGF), but whether it also interacts with TGF-beta and EGF to modulate EMT is unknown. Here, PTHrP(1-36) increased TGF-beta1 in cultured tubuloepithelial cells and TGF-beta blockade inhibited PTHrP-induced EMT-related changes, including upregulation of alpha-smooth muscle actin and integrin-linked kinase, nuclear translocation of Snail, and downregulation of E-cadherin and zonula occludens-1.

Asanuma, H., B. A. Vanderbrink, et al. "Arterially delivered mesenchymal stem cells prevent obstruction-induced renal fibrosis." J Surg Res. 2011 Jun 1;168(1):e51-9. doi: 10.1016/j.jss.2010.06.022. Epub 2010 Jul 8.

Mesenchymal stem cells (MSCs) hold promise for the treatment of renal disease. While MSCs have been shown to accelerate recovery and prevent acute renal failure in multiple disease models, the effect of MSC therapy on chronic obstruction-induced renal fibrosis has not previously been evaluated. Male Sprague-Dawley rats underwent renal artery injection of vehicle or fluorescent-labeled human bone marrow-derived MSCs immediately prior to sham operation or induction of left ureteral obstruction (UUO).

Bani-Hani, A. H., J. A. Leslie, et al. "IL-18 neutralization ameliorates obstruction-induced epithelial-mesenchymal transition and renal fibrosis." Kidney Int. 2009 Sep;76(5):500-11. doi: 10.1038/ki.2009.216. Epub 2009 Jun 17.

Ureteral obstruction results in renal fibrosis in part due to inflammatory injury. The role of interleukin-18 (IL-18), an important mediator of inflammation, in the genesis of renal fibrosis was studied using transgenic mice overexpressing human IL-18-binding protein. In addition, HK-2 cells were analyzed following direct exposure to IL-18 compared to control media. IL-18 is a significant mediator of obstruction-induced renal fibrosis and epithelial-mesenchymal transition independent of downstream TGF-beta1 or TNF-alpha production.

Beghdadi, W., L. C. Madjene, et al. "Mast cell chymase protects against renal fibrosis in murine unilateral ureteral obstruction." Kidney Int. 2013 Aug;84(2):317-26. doi: 10.1038/ki.2013.98. Epub 2013 Mar 20.

Mast cell release of chymase is important in tissue remodeling and may participate in inflammation leading to fibrosis and organ failure. Here we analyzed the function of chymase in unilateral ureteral obstruction, an established accelerated model of renal tubulointerstitial fibrosis. The mast cell released mMCP4 has anti-fibrotic potential in acutely induced obstructive nephropathy.

Boor, P., A. Konieczny, et al. "Complement C5 mediates experimental tubulointerstitial fibrosis." J Am Soc Nephrol. 2007 May;18(5):1508-15. Epub 2007 Mar 27.

Renal fibrosis is the final common pathway of most progressive renal diseases. C5 was recently identified as a risk factor for liver fibrosis. Using a combined genetic and pharmacologic approach, C5, in particular C5a, is identified as a novel profibrotic factor in renal disease and as a potential new therapeutic target.

Bor, M. V., Y. Shi, et al. "Increased TGF-alpha and EGF Receptor mRNA expression in response to neonatal unilateral partial ureter obstruction in rats." Nephron Exp Nephrol. 2006;104(2):e76-82. Epub 2006 Jun 19.

AIM: To evaluate the potential role of members of the epidermal growth factor (EGF) family in altered renal growth caused by partial ureteral

obstruction in the developing obstructed and non-obstructed kidneys. The increased expression of TGF-alpha and its receptor in the obstructed kidney might be related to a cell-survival function in the affected cells possibly by protecting them from entering apoptosis.

Borgeson, E., N. G. Docherty, et al. "Lipoxin A(4) and benzo-lipoxin A(4) attenuate experimental renal fibrosis." FASEB J. 2011 Sep;25(9):2967-79. doi: 10.1096/fj.11-185017. Epub 2011 May 31.

Unresolved inflammation underlies the development of fibrosis and organ failure. Here, we investigate the potential of the proresolving eicosanoid lipoxinA(4) (LXA(4)) and its synthetic analog benzo-LXA(4) to prophylactically modulate fibrotic and inflammatory responses in a model of early renal fibrosis, unilateral ureteric obstruction (UUO). LXs may represent a potentially useful and novel therapeutic strategy for consideration in the context of renal fibrosis.

Bozic, M., J. de Rooij, et al. "Glutamatergic signaling maintains the epithelial phenotype of proximal tubular cells." J Am Soc Nephrol. 2011 Jun;22(6):1099-111. doi: 10.1681/ASN.2010070701. Epub 2011 May 19.

Epithelial-mesenchymal transition (EMT) contributes to the progression of renal tubulointerstitial fibrosis. NMDAR plays a critical role in preserving the normal epithelial phenotype and modulating tubular EMT.

Campbell, M. T., K. L. Hile, et al. "Toll-like receptor 4: a novel signaling pathway during renal fibrogenesis." J Surg Res. 2011 Jun 1;168(1):e61-9. doi: 10.1016/j.jss.2009.09.053. Epub 2009 Oct 23.

The toll-like receptor (TLR) family serves an important regulatory role in the innate immune system, and recent evidence has implicated TLR signaling in the pro-inflammatory response of a variety of endogenous and exogenous stimuli within the kidney. The role of TLR signaling in fibrotic renal injury, however, remains unknown. TLR4 appears to be a significant mediator of fibrotic renal injury. While TLR4 signaling is recognized as a critical component of the innate immune response, this is the first study to demonstrate a novel role for TLR4 in renal fibroblast accumulation and tubulointerstitial fibrosis.

Chevalier, R. L. "Obstructive nephropathy: towards biomarker discovery and gene therapy." Nat Clin Pract Nephrol. 2006 Mar;2(3):157-68.

Obstructive nephropathy is a major cause of renal failure, particularly in infants and children. Cellular and molecular mechanisms responsible for the progression of the tubular atrophy and interstitial fibrosis-processes that lead to nephron loss-have been elucidated in the past 5 years. Targeted gene deletion and various forms of gene therapy have been used in experimental obstructive nephropathy, mostly rodent models of unilateral ureteral obstruction or cell culture techniques.

Chowdhury, P., S. H. Sacks, et al. "Endogenous ligands for TLR2 and TLR4 are not involved in renal injury following ureteric obstruction." Nephron Exp Nephrol. 2010;115(4):e122-30. doi: 10.1159/000313493. Epub 2010 Apr 28.

Toll-like receptors (TLRs) are a recently described arm of innate immunity. TLR2 and TLR4 do not play a significant role in the development of tubulointerstitial fibrosis following obstruction.

Edgtton, K. L., R. M. Gow, et al. "Plasmin is not protective in experimental renal interstitial fibrosis." Kidney Int. 2004 Jul;66(1):68-76.

The plasminogen-plasmin system has potential beneficial or deleterious effects in the context of renal fibrosis. Recent studies have implicated plasminogen activators or their inhibitors in this process. The effects of proteins such as plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA), and urokinase-type plasminogen activator receptor (uPAR) on renal fibrosis occur independently from the generation of plasmin.

Efrati, S., S. Berman, et al. "Rosiglitazone treatment attenuates renal tissue inflammation generated by urinary tract obstruction." Nephrology (Carlton). 2009 Apr;14(2):189-97. doi: 10.1111/j.1440-1797.2008.01032.x.

Peroxisome proliferator-activated receptor (PPAR)-gamma activation by rosiglitazone decreases manifestation of intrarenal inflammatory hallmarks. Inflammation significantly aggravates renal injury following urinary tract obstruction. The importance of the anti-inflammatory role of rosiglitazone treatment in amelioration of ureteral obstruction-induced renal damage.

El-Sherbiny, M. T., O. M. Mousa, et al. "Role of urinary transforming growth factor-beta1 concentration in the diagnosis of upper urinary tract obstruction in children." J Urol. 2002 Oct;168(4 Pt 2):1798-800.

Bladder urine TGF-beta1 is a useful noninvasive tool for diagnosis of upper urinary tract obstruction. At 3 months following corrective surgery there is a trend towards decrease in bladder TGF-beta1 concentration in comparison to the preoperative value.

Fintha, A., A. Gasparics, et al. "Characterization and role of SCAI during renal fibrosis and epithelial-to-mesenchymal transition." Am J Pathol. 2013 Feb;182(2):388-400. doi: 10.1016/j.ajpath.2012.10.009. Epub 2012 Nov 22.

TGF-beta1 treatment of LLC-PK1 cells attenuated SCAI protein expression. These data suggest that SCAI is a novel transcriptional cofactor that regulates EMT and renal fibrosis.

Galichon, P., S. Finianos, et al. "EMT-MET in renal disease: should we curb our enthusiasm?" Cancer Lett. 2013 Nov 28;341(1):24-9. doi: 10.1016/j.canlet.2013.04.018. Epub 2013 Apr 21.

Renal epithelial cells arise during embryogenesis by mesenchymal to epithelial transition (MET). In opposition to the EMT occurring during embryogenesis, EMT in fibrosis as well as in cancer is an anarchic cellular process actually developing at the expense of the whole organ(ism).

Ito, K., H. Yoshii, et al. "Adrenomedullin increases renal nitric oxide production and ameliorates renal injury in mice with unilateral ureteral obstruction." J Urol. 2010 Apr;183(4):1630-5. doi: 10.1016/j.juro.2009.12.002. Epub 2010 Feb 20.

Adrenomedullin increased renal nitric oxide, and suppressed tubular apoptosis, interstitial fibrosis and inflammatory cell infiltration in mice with unilateral ureteral obstruction. The renoprotective peptide adrenomedullin may be useful for that condition.

Kamijo-Ikemori, A., T. Sugaya, et al. "Liver-type fatty acid-binding protein attenuates renal injury induced by unilateral ureteral obstruction." Am J Pathol. 2006 Oct;169(4):1107-17.

Liver-type fatty-acid-binding protein (L-FABP), which has high affinity for long-chain fatty acid oxidation products, may be an effective endogenous antioxidant. The renal L-FABP may reduce the oxidative stress in the UUO model, ameliorating tubulointerstitial damage.

Kato, N., T. Kosugi, et al. "Basigin/CD147 promotes renal fibrosis after unilateral ureteral obstruction." Am J Pathol. 2011 Feb;178(2):572-9. doi: 10.1016/j.ajpath.2010.10.009.

Regardless of their primary causes, progressive renal fibrosis and tubular atrophy are the main predictors of progression to end-stage renal disease. The first time that basigin is a key regulator of renal fibrosis. Basigin could be a candidate target molecule for the prevention of organ fibrosis.

Kawai, T., T. Masaki, et al. "PPAR-gamma agonist attenuates renal interstitial fibrosis and inflammation through reduction of TGF-beta." Lab Invest. 2009 Jan;89(1):47-58. doi: 10.1038/labinvest.2008.104. Epub 2008 Nov 10.

Thiazolidinediones (TZDs), synthetic peroxisome proliferator-activated receptor (PPAR)-gamma ligands, have a central role in insulin sensitization and adipogenesis. TGF-beta1 mRNA and TGF beta R-I mRNA and protein expression were decreased in the group treated with troglitazone compared with the control group. The beneficial effects of troglitazone treatment were also dose dependent. PPAR-gamma agonist significantly reduced TGF-beta and attenuated renal interstitial fibrosis and inflammation in the model of UUO.

Kishimoto, K., K. Kinoshita, et al. "Therapeutic effect of retinoic acid on unilateral ureteral obstruction model." Nephron Exp Nephrol. 2011;118(3):e69-78. doi: 10.1159/000322409. Epub 2011 Jan 13.

Retinoic acids, a group of natural and synthetic vitamin A derivatives, have potent anti-proliferative, anti-inflammatory and anti-fibrotic properties. ATRA treatment is not only an effective prophylactic strategy, but also a therapeutic strategy for the treatment of progressive renal fibrosis in diseased kidneys.

Klahr, S. and J. Morrissey "Obstructive nephropathy and renal fibrosis: The role of bone morphogenic protein-7 and hepatocyte growth factor." Kidney Int Suppl. 2003 Nov;(87):S105-12.

The nephropathy induced by ureteral obstruction is associated with increased interstitial volume due to matrix deposition, fibroblast differentiation/proliferation, and monocyte infiltration. Both BMP-7 and HGF attenuate the tubulointerstitial fibrosis due to ureteral obstruction. They also increase GFR and renal plasma flow.

Koca, O., C. Kaya, et al. "Analysis of expression of TNF-alpha and TGF-beta3 in intrinsic ureteropelvic junction obstruction." Bratisl Lek Listy. 2013;114(9):498-502.

Ureteropelvic junction (UPJ) obstruction is of critical importance to understand the histopathology of UPJ obstruction in terms of therapy planning and follow-up. TGF-beta3 and TNF-alpha may play a role in the histopathogenesis of UPJ obstruction.

Kushibiki, T., N. Nagata-Nakajima, et al. "Delivery of plasmid DNA expressing small interference RNA for TGF-beta type II receptor by cationized gelatin to prevent interstitial renal fibrosis." J Control Release. 2005 Jul 20;105(3):318-31.

Renal interstitial fibrosis is the common pathway of chronic renal disease, while it causes end-stage renal failure. Transforming growth factor-beta (TGF-beta) is well recognized to be one of the primary mediators to induce accumulation of extracellular matrix (ECM) in the fibrotic area.

Maeshima, A., K. Mishima, et al. "Follistatin, an activin antagonist, ameliorates renal interstitial fibrosis in a rat model of unilateral ureteral obstruction." Biomed Res Int. 2014;2014:376191. doi: 10.1155/2014/376191. Epub 2014 May 5.

Activin, a member of the TGF-beta superfamily, regulates cell growth and differentiation in various cell types. Activin A acts as a negative regulator of renal development as well as tubular regeneration after renal injury. The activin A produced by interstitial fibroblasts acts as a potent profibrotic factor during renal fibrosis. Blockade of activin A action may be a novel approach for the prevention of renal fibrosis progression.

Manson, S. R., J. B. Song, et al. "HDAC dependent transcriptional repression of Bmp-7 potentiates TGF-beta mediated renal fibrosis in obstructive uropathy." J Urol. 2014 Jan;191(1):242-52. doi: 10.1016/j.juro.2013.06.110. Epub 2013 Jun 29.

Recombinant BMP-7 inhibits the pathogenesis of renal injury in response to various stimuli. The histone deacetylase dependent repression of Bmp-7 transcription is a critical event during the pathogenesis of renal injury in obstructive uropathy. Accordingly, treatment with histone deacetylase inhibitors represents a potentially effective strategy to restore BMP-7 expression and its renal protective functions during treatment of obstructive uropathy.

Masterson, R., T. D. Hewitson, et al. "Relaxin down-regulates renal fibroblast function and promotes matrix remodelling in vitro." Nephrol Dial Transplant. 2004 Mar;19(3):544-52.

Renal fibroblasts are important effector cells in tubulointerstitial fibrosis, with experimental antifibrotic strategies focusing on the functional down-regulation of these cells.

Mazzei, L. J., I. M. Garcia, et al. "Rosuvastatin preserves renal structure following unilateral ureteric obstruction in the neonatal rat." Am J Nephrol. 2012;35(2):103-13. doi: 10.1159/000334935. Epub 2011 Dec 29.

Unilateral ureteric obstruction (UUO) in neonatal rodents can be used as a paradigm for in utero obstruction in humans and a platform for studying the potential of novel therapies for congenital obstructive nephropathy. Ros treatment was unable to completely salvage glomerular development. Together these data highlight the therapeutic potential and limitations of Ros in neonatal obstruction.

Meldrum, K. K., R. Misseri, et al. "TNF-alpha neutralization ameliorates obstruction-induced renal fibrosis and dysfunction." Am J Physiol Regul Integr Comp Physiol. 2007 Apr;292(4):R1456-64. Epub 2006 Dec 14.

Upper urinary tract obstruction results in tubulointerstitial fibrosis and a progressive decline in renal function. TNF-alpha mediates obstruction-induced renal fibrosis and identify TNF-alpha neutralization as a potential therapeutic option for the amelioration of obstruction-induced renal injury.

Metcalfe, P. D., J. A. Leslie, et al. "Testosterone exacerbates obstructive renal injury by stimulating TNF-alpha production and increasing proapoptotic and profibrotic signaling." Am J Physiol Endocrinol Metab. 2008 Feb;294(2):E435-43. Epub 2007 Dec 11.

Upper urinary tract obstruction is a common cause of renal dysfunction in children and adults. The endogenous testosterone production in normal male rats and testosterone exogenously administered to oophorectomized females significantly increases TNF production and proapoptotic and profibrotic signaling during renal obstruction, resulting in increased apoptotic cell death, tubulointerstitial fibrosis, and renal dysfunction.

Misseri, R. and K. K. Meldrum "Mediators of fibrosis and apoptosis in obstructive uropathies." Curr Urol Rep. 2005 Mar;6(2):140-5.

Upper urinary tract obstruction, regardless of its cause, often poses a significant clinical challenge to the urologist. Renal cellular and molecular events that occur in response to upper urinary tract obstruction result in a progressive and permanent loss in renal function when left untreated. These pathologic changes include the development of renal fibrosis, tubular atrophy, interstitial inflammation, and apoptotic renal cell death.

Misseri, R., R. C. Rink, et al. "Inflammatory mediators and growth factors in obstructive renal injury." J Surg Res. 2004 Jun 15;119(2):149-59.

Obstruction of the upper urinary tract poses a significant clinical challenge to the urologist, and the cascade of renal cellular and molecular events triggered by upper urinary tract obstruction result in a progressive, and eventually permanent, loss in renal function.

Moridaira, K., J. Morrissey, et al. "ACE inhibition increases expression of the ETB receptor in kidneys of

mice with unilateral obstruction." Am J Physiol Renal Physiol. 2003 Jan;284(1):F209-17.

Unilateral ureteral obstruction (UUO) is a well-established model for the study of interstitial fibrosis in the kidney. It has been shown that the renin-angiotensin system plays a central role in the progression of interstitial fibrosis.

Morimoto, Y., Z. Gai, et al. "TNF-alpha deficiency accelerates renal tubular interstitial fibrosis in the late stage of ureteral obstruction." Exp Mol Pathol. 2008 Dec;85(3):207-13. doi: 10.1016/j.yexmp.2008.08.003. Epub 2008 Sep 18.

TNF-alpha and TGF-beta1 have a complementary relationship in fibrogenesis. This study was performed to investigate the role of TNF-alpha in renal tubular interstitial fibrosis. In the chronic stage of renal fibrosis, TNF-alpha suppresses the infiltration of macrophages by inducing TNF-alpha type 2 receptor expression, resulting in the amelioration of fibrosis.

Morinaga, J., Y. Kakizoe, et al. "The antifibrotic effect of a serine protease inhibitor in the kidney." Am J Physiol Renal Physiol. 2013 Jul 15;305(2):F173-81. doi: 10.1152/ajprenal.00586.2012. Epub 2013 May 22.

Interstitial fibrosis is a final common pathway for the progression of chronic kidney diseases. CM might represent a new class of therapeutic drugs for the treatment of renal fibrosis through the suppression of TGF-beta(1) signaling.

Munoz-Felix, J. M., J. M. Lopez-Novoa, et al. "Heterozygous disruption of activin receptor-like kinase 1 is associated with increased renal fibrosis in a mouse model of obstructive nephropathy." Kidney Int. 2014 Feb;85(2):319-32. doi: 10.1038/ki.2013.292. Epub 2013 Aug 14.

Tubulointerstitial fibrosis is characterized by an accumulation of extracellular matrix in the renal interstitium, myofibroblast activation, cell infiltration, and tubular cell apoptosis, leading to chronic renal failure. Activin receptor-like kinase 1 (ALK1) is a transforming growth factor-beta1 type I receptor with a pivotal role in endothelial proliferation and migration, but its role in the development of renal fibrosis is unknown.

Murer, L., E. Benetti, et al. "Clinical and molecular markers of chronic interstitial nephropathy in congenital unilateral ureteropelvic junction obstruction." J Urol. 2006 Dec;176(6 Pt 1):2668-73; discussion 2673.

In congenital unilateral ureteropelvic junction obstruction chronic interstitial nephropathy and poor postoperative recovery seem to be associated with an earlier diagnosis of hydronephrosis, functional loss greater than 10% and worse scintigraphic drainage. Moreover, there is a strong correlation between molecular fibrogenic markers and histologically and scintigraphically demonstrated renal damage.

Nagatoya, K., T. Moriyama, et al. "Y-27632 prevents tubulointerstitial fibrosis in mouse kidneys with unilateral ureteral obstruction." Kidney Int. 2002 May;61(5):1684-95.

The small GTPase Rho is involved in cell-to-substratum adhesion and cell contraction. These actions of Rho mediated by downstream Rho effectors such as Rho-associated coiled-coil forming protein kinase (ROCK) may be partly responsible for the progression of renal interstitial fibrosis. The Rho-ROCK system may play an important role in the development of tissue fibrosis, and the Rho-ROCK signaling pathway may be a new therapeutic target for preventing interstitial fibrosis in progressive renal disease.

Nakamura, H., Y. Isaka, et al. "Introduction of DNA enzyme for Egr-1 into tubulointerstitial fibroblasts by electroporation reduced interstitial alpha-smooth muscle actin expression and fibrosis in unilateral ureteral obstruction (UUO) rats." Gene Ther. 2002 Apr;9(8):495-502.

The phenotypic alteration of interstitial fibroblasts into 'myofibroblasts', acquiring characteristics of both fibroblasts and smooth muscle cells is a key event in the formation of tubulointerstitial fibrosis. The electroporation-mediated retrograde gene transfer can be an ideal vehicle into interstitial fibroblasts, and molecular intervention of Egr-1 in the interstitium may become a new therapeutic strategy for interstitial fibrosis.

Nasu, T., M. Kinomura, et al. "Sustained-release prostacyclin analog ONO-1301 ameliorates tubulointerstitial alterations in a mouse obstructive nephropathy model." Am J Physiol Renal Physiol. 2012 Jun 15;302(12):F1616-29. doi: 10.1152/ajprenal.00538.2011. Epub 2012 Mar 14.

Tubulointerstitial injuries are crucial histological alterations that predict the deterioration of renal function in chronic kidney disease. The potential therapeutic efficacies of ONO-1301 in suppressing tubulointerstitial alterations partly mediated via inducing HGF, an antifibrotic factor counteracting TGF-beta.

Nishida, M., Y. Okumura, et al. "Delayed inhibition of p38 mitogen-activated protein kinase ameliorates renal fibrosis in obstructive nephropathy." Nephrol

Dial Transplant. 2008 Aug;23(8):2520-4. doi: 10.1093/ndt/gfn309. Epub 2008 May 30.

The p38 mitogen-activated protein kinase (MAPK) pathway is an important intracellular signalling pathway involved in the production of proinflammatory and profibrotic mediators. Previous reports indicated the role of p38 MAPK activation in renal fibrosis. The p38 MAPK blockade is an appealing therapeutic target, even after the emergence of established fibrosis.

Noh, H., H. J. Kim, et al. "Heat shock protein 90 inhibitor attenuates renal fibrosis through degradation of transforming growth factor-beta type II receptor." Lab Invest. 2012 Nov;92(11):1583-96. doi: 10.1038/labinvest.2012.127. Epub 2012 Sep 10.

The accumulation of extracellular matrix proteins in the interstitial area is the final common feature of chronic kidney diseases. The 17AAG blocked the interaction between Hsp90 and TGF-beta type II receptor (TbetaRII) and promoted ubiquitination of TbetaRII, leading to the decreased availability of TbetaRII. Smurf2-specific siRNA reversed the ability of 17AAG to inhibit TGF-beta1 signaling.

Oliveira, F. A., A. C. Moraes, et al. "Low-level laser therapy decreases renal interstitial fibrosis." Photomed Laser Surg. 2012 Dec;30(12):705-13. doi: 10.1089/pho.2012.3272. Epub 2012 Nov 7.

The purpose of this study was to investigate the effect of low-level laser therapy (LLLT) on chronic kidney disease (CKD) in a model of unilateral ureteral obstruction (UUO). The LLLT can prevent tubular activation and transdifferentiation, which are the two processes that mainly drive the renal fibrosis of the UUO model.

Omori, H., N. Kawada, et al. "Use of xanthine oxidase inhibitor febuxostat inhibits renal interstitial inflammation and fibrosis in unilateral ureteral obstructive nephropathy." Clin Exp Nephrol. 2012 Aug;16(4):549-56. doi: 10.1007/s10157-012-0609-3. Epub 2012 Feb 18.

Renal interstitial fibrosis is the common pathway in progressive renal diseases, where oxidative stress promotes inflammation and macrophage infiltration. Febuxostat is a novel nonpurine xanthine oxidase (XO)-specific inhibitor for treating hyperuricemia. While some reports suggest a relationship between hyperuricemia and chronic kidney disease (CKD), the renoprotective mechanism of an XO inhibitor in CKD remains unknown.

Oujo, B., J. M. Munoz-Felix, et al. "L-Endoglin overexpression increases renal fibrosis after unilateral ureteral obstruction." PLoS One. 2014 Oct 14;9(10):e110365. doi: 10.1371/journal.pone.0110365. eCollection 2014.

Transforming growth factor-beta (TGF-beta) plays a pivotal role in renal fibrosis. Endoglin, a 180 KDa membrane glycoprotein, is a TGF-beta co-receptor overexpressed in several models of chronic kidney disease, but its function in renal fibrosis remains uncertain. Obstructed kidneys from L-ENG+ mice showed higher amounts of type I collagen and fibronectin but similar levels of alpha-smooth muscle actin (alpha-SMA) than obstructed kidneys from WT mice.

Poncelet, A. C., H. W. Schnaper, et al. "Cell phenotype-specific down-regulation of Smad3 involves decreased gene activation as well as protein degradation." J Biol Chem. 2007 May 25;282(21):15534-40. Epub 2007 Mar 30.

Signaling by transforming growth factor-beta (TGF-beta), a regulator of several biological processes, including renal fibrosis, is mediated, in part, by the Smad proteins. Tight control of Smad level and activity is critical for proper TGF-beta biological functions.

Pradere, J. P., J. Klein, et al. "LPA1 receptor activation promotes renal interstitial fibrosis." J Am Soc Nephrol. 2007 Dec;18(12):3110-8. Epub 2007 Nov 14.

Tubulointerstitial fibrosis in chronic renal disease is strongly associated with progressive loss of renal function. LPA, likely acting through LPA1, is involved in obstruction-induced TIF. Therefore, the LPA1 receptor might be a pharmaceutical target to treat renal fibrosis.

Prakash, J., M. H. de Borst, et al. "Cell-specific delivery of a transforming growth factor-beta type I receptor kinase inhibitor to proximal tubular cells for the treatment of renal fibrosis." Pharm Res. 2008 Oct;25(10):2427-39. doi: 10.1007/s11095-007-9515-x. Epub 2008 Jan 9.

Activation of tubular epithelial cells by transforming growth factor-beta (TGF-beta) plays an important role in the pathogenesis of renal tubulointerstitial fibrosis. The free TKI at an equimolar (low) dosage exhibited little effects. Inhibition of TGF-beta signaling by local drug delivery is a promising antifibrotic strategy, and demonstrated the important role of tubular activation in renal fibrosis.

Sakai, N., T. Wada, et al. "The renin-angiotensin system contributes to renal fibrosis through regulation of fibrocytes." J Hypertens. 2008 Apr;26(4):780-90. doi: 10.1097/HJH.0b013e3282f3e9e6.

The renin-angiotensin system is a major pathway in the pathogenesis of cardiovascular and renal diseases. Bone marrow-derived fibrocytes, which are dual positive for CD45 and type I collagen, are now considered to contribute to the pathogenesis of various fibrotic diseases. The AT1R/AT2R signaling may contribute to the pathogenesis of renal fibrosis by at least two mechanisms: by regulating the number of fibrocytes in the bone marrow, and by activation of fibrocytes.

Sakairi, T., K. Hiromura, et al. "Effects of proteasome inhibitors on rat renal fibrosis in vitro and in vivo." Nephrology (Carlton). 2011 Jan;16(1):76-86. doi: 10.1111/j.1440-1797.2010.01367.x.

Transforming growth factor-beta (TGF-beta) is involved in renal tubulointerstitial fibrosis. Recently, the ubiquitin proteasome system was shown to participate in the TGF-beta signalling pathway. Proteasome inhibitors attenuate TGF-beta signalling by blocking Smad signal transduction in vitro, but do not inhibit renal interstitial fibrosis in vivo.

Sakuraya, K., A. Endo, et al. "The synergistic effect of mizoribine and a direct renin inhibitor, aliskiren, on unilateral ureteral obstruction induced renal fibrosis in rats." J Urol. 2014 Apr;191(4):1139-46. doi: 10.1016/j.juro.2013.10.053. Epub 2013 Oct 16.

Renal fibrosis, the major histopathological change in various renal disorders, is closely related to renal dysfunction. Unilateral ureteral obstruction is a well established model of experimental renal disease that results in tubulointerstitial fibrosis. After unilateral ureteral obstruction the tubular dilatation, interstitial volume and alpha-SMA expression scores were significantly decreased by combination therapy compared with monotherapy with aliskiren or mizoribine.

Samarakoon, R., A. D. Dobberfuhl, et al. "Induction of renal fibrotic genes by TGF-beta1 requires EGFR activation, p53 and reactive oxygen species." Cell Signal. 2013 Nov;25(11):2198-209. doi: 10.1016/j.cellsig.2013.07.007. Epub 2013 Jul 18.

While transforming growth factor-beta (TGF-beta1)-induced SMAD2/3 signaling is a critical event in the progression of chronic kidney disease, the role of non-SMAD mechanisms in the orchestration of fibrotic gene changes remains largely unexplored.

Sawashima, K., S. Mizuno, et al. "Protein restriction ameliorates renal tubulointerstitial nephritis and reduces renal transforming growth factor-beta expression in unilateral ureteral obstruction." Exp Nephrol. 2002;10(1):7-18.

In contrast to the substantial evidence for attenuation of the glomerular lesions by a low-protein (LP) diet, it remains to be determined whether and how such a diet lessens the progression of tubulointerstitial lesions, which show the strongest correlation with renal function. Chronic unilateral ureteral obstruction (UUO) results in interstitial fibrosis of the affected kidney.

Schinner, E., A. Schramm, et al. "The cyclic GMP-dependent protein kinase Ialpha suppresses kidney fibrosis." Kidney Int. 2013 Dec;84(6):1198-206. doi: 10.1038/ki.2013.219. Epub 2013 Jun 12.

Cyclic guanosine monophosphate (cGMP) is synthesized by nitric oxide or natriuretic peptide-stimulated guanylyl cyclases and exhibits pleiotropic regulatory functions in the kidney. The cGMP, acting primarily through cGKIalpha, is an important suppressor of kidney fibrosis.

Soofi, A., P. Zhang, et al. "Kielin/chordin-like protein attenuates both acute and chronic renal injury." J Am Soc Nephrol. 2013 May;24(6):897-905. doi: 10.1681/ASN.2012070759. Epub 2013 Mar 28.

The secreted kielin/chordin-like (KCP) protein, one of a family of cysteine-rich proteins, suppresses TGF-beta signaling by sequestering the ligand from its receptor, but it enhances bone morphogenetic protein (BMP) signaling by promoting ligand-receptor interactions. The extracellular regulation of the TGF-beta/BMP signaling axis by KCP, and by extension possibly other cysteine-rich domain proteins, can attenuate both acute and chronic renal injury.

Srisawat, N., K. Manotham, et al. "Erythropoietin and its non-erythropoietic derivative: do they ameliorate renal tubulointerstitial injury in ureteral obstruction?" Int J Urol. 2008 Oct;15(11):1011-7. doi: 10.1111/j.1442-2042.2008.02149.x. Epub 2008 Aug 26.

Pleiotropic effects of recombinant human erythropoietin (EPO) have recently been discovered in many non-renal animal models. The renoprotective effects of EPO and carbamylated-erythropoietin (CEPO), a novel EPO which has a small stimulatory effect on hemoglobin, have never been explored in unilateral ureteral obstruction (UUO), a chronic tubulointerstitial (TI) disease model which is independent of systemic factors. EPO and CEPO can limit 14-day UUO-induced TI injury by reducing inflammation, interstitial fibrosis, and tubular apoptosis.

Sugiura, H., T. Yoshida, et al. "Reduced Klotho expression level in kidney aggravates renal interstitial fibrosis." Am J Physiol Renal Physiol. 2012 May 15;302(10):F1252-64. doi: 10.1152/ajprenal.00294.2011. Epub 2012 Feb 15.

Renal expression of the klotho gene is markedly suppressed in chronic kidney disease (CKD). The low renal Klotho expression is a result of renal fibrosis. Taken together, renal fibrosis can trigger a deterioration spiral of Klotho expression, which may be involved in the pathophysiology of CKD progression.

Summers, S. A., P. Y. Gan, et al. "Mast cell activation and degranulation promotes renal fibrosis in experimental unilateral ureteric obstruction." Kidney Int. 2012 Sep;82(6):676-85. doi: 10.1038/ki.2012.211. Epub 2012 Jun 6.

Progressive renal fibrosis is the final common pathway leading to renal failure irrespective of the initiating cause. Clinical studies of renal fibrosis found that prominent mast cell accumulation correlated with worse outcomes. Mast cells are pluripotent innate immune cells that synthesize and secrete profibrotic mediators. A mast cell stabilizer that impairs degranulation, disodium chromoglycate, significantly attenuated renal fibrosis following ureteric ligation in wild-type mice. Thus, mast cells promote renal fibrosis and their targeting may offer therapeutic potential in the treatment of renal fibrosis.

Takeda, Y., T. Nishikimi, et al. "Beneficial effects of a combination of Rho-kinase inhibitor and ACE inhibitor on tubulointerstitial fibrosis induced by unilateral ureteral obstruction." Hypertens Res. 2010 Sep;33(9):965-73. doi: 10.1038/hr.2010.112. Epub 2010 Jul 22.

The combination of imidapril and fasudil further improved fibrotic area (-52%), DHE-positive area (-26%), alpha-SMA-positive area (-33%), F4/80-positive area (-62%) and the expression of various mRNA (all $P<0.05$ vs. monotherapy).

Tasanarong, A., S. Kongkham, et al. "Vitamin E ameliorates renal fibrosis by inhibition of TGF-beta/Smad2/3 signaling pathway in UUO mice." J Med Assoc Thai. 2011 Dec;94 Suppl 7:S1-9.

One striking feature of chronic kidney disease (CKD) is tubular atrophy and interstitial fibrosis (TA/IF). During chronic renal injury, transforming growth factor-beta (TGF-beta) is involved in this process causing progression of renal fibrosis. The increasing of TGF-beta1 protein and upregulation of TGF-beta1 mRNA in UUO mice were confirmed by western blot and real time RT-PCR. In contrast, vitamin E treatment significantly inhibited the expression of TGF-beta1 protein and mRNA in UUO mice compared with placebo treatment. Interestingly, Smad2/3 protein expression became progressive increasing in UUO mice on day 3, 7 and 14 compared with sham controls.

Tasanarong, A., S. Kongkham, et al. "Vitamin E ameliorates renal fibrosis in ureteral obstruction: role of maintaining BMP-7 during epithelial-to-mesenchymal transition." J Med Assoc Thai. 2011 Dec;94 Suppl 7:S10-8.

Epithelial to mesenchymal transition (EMT) is a process which tubular epithelial cells (TEC) undergo a phenotypic conversion to the matrix-producing fibroblasts and myofibroblasts. The renoprotective effects of vitamin E could have some therapeutic value to inhibit the progression of renal fibrosis in human.

Terashima, H., M. Kato, et al. "A sensitive short-term evaluation of antifibrotic effects using newly established type I collagen reporter transgenic rats." Am J Physiol Renal Physiol. 2010 Oct;299(4):F792-801. doi: 10.1152/ajprenal.00141.2009. Epub 2010 Jul 21.

Fibrosis is the final common pathway for various tissue lesions that lead to chronic progressive organ failure, and consequently effective antifibrotic drugs are strongly desired. Although both an ANG II type 1 receptor blocker (ARB), olmesartan, and a transforming growth factor-beta (TGF-beta) type I receptor kinase (ALK5) inhibitor, SB-431542, inhibited renal luciferase activities in UUO, only SB-431542 inhibited luciferase activity induced by TGF-beta1 in isolated glomeruli.

Thangada, S., L. H. Shapiro, et al. "Treatment with the immunomodulator FTY720 (fingolimod) significantly reduces renal inflammation in murine unilateral ureteral obstruction." J Urol. 2014 May;191(5 Suppl):1508-16. doi: 10.1016/j.juro.2013.10.072. Epub 2014 Mar 26.

The S1P signaling pathway represents an important potential target for the modulation of tissue inflammation/injury. The immunomodulator FTY720, also known as fingolimod, is a potent agonist for multiple S1P receptors that was approved by the Food and Drug Administration to treat multiple sclerosis.

Venkatachalam, M. A. and J. M. Weinberg "New wrinkles in old receptors: core fucosylation is yet another target to inhibit TGF-beta signaling." Kidney Int. 2013 Jul;84(1):11-4. doi: 10.1038/ki.2013.95.

Shen et al. exploit glycobiology to dampen transforming growth factor-beta (TGF-beta) signaling and ameliorate renal fibrosis after ureteral obstruction.

Vidyasagar, A., S. Reese, et al. "HSP27 is involved in the pathogenesis of kidney tubulointerstitial fibrosis." Am J Physiol Renal Physiol. 2008 Sep;295(3):F707-16. doi: 10.1152/ajprenal.90240.2008. Epub 2008 Jul 2.

We hypothesized that heat shock protein 27 (HSP27), a small heat shock protein with actin-remodeling properties, is involved in the pathogenesis of kidney tubulointerstitial fibrosis. We first examined its expression in the rat unilateral ureteral obstruction (UUO) model of kidney fibrosis and epithelial-to-mesenchymal transition (EMT). The HSP27 is involved in the pathogenesis of TGF-beta1-induced EMT and chronic tubulointerstitial fibrosis. HSP27 overexpression may delay injury by upregulating E-cadherin through downregulation of Snail.

Vieira, J. M., Jr., E. Mantovani, et al. "Simvastatin attenuates renal inflammation, tubular transdifferentiation and interstitial fibrosis in rats with unilateral ureteral obstruction." Nephrol Dial Transplant. 2005 Aug;20(8):1582-91. Epub 2005 Apr 26.

The pleiotropic actions of statins have been largely explored. These drugs have been tested in several models of progressive renal disease, most of them accompanied by hypertension. We sought to investigate more closely the effects of simvastatin on renal interstitial fibrosis due to unilateral ureteral obstruction (UUO).

White, L. R., J. B. Blanchette, et al. "The characterization of alpha5-integrin expression on tubular epithelium during renal injury." Am J Physiol Renal Physiol. 2007 Feb;292(2):F567-76. Epub 2006 Oct 3.

The hallmark of progressive chronic kidney disease is the deposition of extracellular matrix proteins and tubulointerstitial fibrosis. Integrins mediate cell-extracellular matrix interaction and may play a role tubular epithelial injury. Murine primary tubular epithelial cells (TECs) express alpha(5)-integrin, a fibroblast marker and the natural receptor for fibronectin. Microscopy localized alpha(5)-integrin on E-cadherin-positive cells, confirming epithelial expression.

Wojcikowski, K., H. Wohlmuth, et al. "Effect of Astragalus membranaceus and Angelica sinensis combined with Enalapril in rats with obstructive uropathy." Phytother Res. 2010 Jun;24(6):875-84. doi: 10.1002/ptr.3038.

ACE inhibitors (ACEi) reduce renal tubulointerstitial fibrosis but are not completely effective. Combined extract of Astragalus membranaceus and Angelica sinensis (A&A) is a traditional antifibrotic agent in China.

Wolak, T., H. Kim, et al. "Osteopontin modulates angiotensin II-induced inflammation, oxidative stress, and fibrosis of the kidney." Kidney Int. 2009 Jul;76(1):32-43. doi: 10.1038/ki.2009.90. Epub 2009 Apr 8.

Osteopontin, a secreted glycoprotein has been implicated in several renal pathological conditions such as those due to ureteral obstruction, ischemia, and cyclosporine toxicity. The osteopontin is a promoter and an inhibitor of inflammation, oxidative stress, and fibrosis that is capable of modulating angiotensin II-induced renal damage.

Wongmekiat, O., D. Leelarungrayub, et al. "Alpha-lipoic acid attenuates renal injury in rats with obstructive nephropathy." Biomed Res Int. 2013;2013:138719. doi: 10.1155/2013/138719. Epub 2013 Oct 3.

Pretreatment with ALA significantly minimized all the changes elicited by ureteral obstruction. These findings demonstrate that ALA supplementation attenuates renal injury in rats with obstructive nephropathy and further suggest that oxidative stress inhibition is likely to be involved in the beneficial effects of this compound.

Yamate, J., M. Kuribayashi, et al. "Differential immunoexpressions of cytoskeletons in renal epithelial and interstitial cells in rat and canine fibrotic kidneys, and in kidney-related cell lines under fibrogenic stimuli." Exp Toxicol Pathol. 2005 Nov;57(2):135-47. Epub 2005 Aug 15.

Myofibroblasts play an important role in chronic renal interstitial fibrosis. However, the origin and developmental mechanisms remain to be elucidated. The myofibroblasts may express various cytoskeletons during the development. The derivation of renal myofibroblasts may be heterogeneous, such as renal epithelia, interstitial cells or immature mesenchymal cells.

Yokoi, H., M. Mukoyama, et al. "Role of connective tissue growth factor in fibronectin expression and tubulointerstitial fibrosis." Am J Physiol Renal Physiol. 2002 May;282(5):F933-42.

Connective tissue growth factor (CTGF) is one of the candidate factors mediating downstream events of transforming growth factor-beta (TGF-beta), but its role in fibrogenic properties of TGF-beta and in tubulointerstitial fibrosis has not yet been clarified.

The CTGF plays a crucial role in fibronectin synthesis induced by TGF-beta, suggesting that CTGF blockade could be a possible therapeutic target against tubulointerstitial fibrosis.

Yokoi, H., A. Sugawara, et al. "Role of connective tissue growth factor in profibrotic action of transforming growth factor-beta: a potential target for preventing renal fibrosis." Am J Kidney Dis. 2001 Oct;38(4 Suppl 1):S134-8.

Tubulointerstitial fibrosis is a crucial process determining the progression and prognosis of various renal diseases. Connective tissue growth factor (CTGF), a novel fibrogenic protein induced by transforming growth factor-beta (TGF-beta), is upregulated in various clinical and experimental nephropathies, but the significance of CTGF in the profibrotic action of TGF-beta is still poorly defined. The CTGF has a crucial role in the profibrotic action of TGF-beta in renal fibroblasts, providing a potential therapeutic target against tubulointerstitial fibrosis.

Yoon, H. E., S. J. Kim, et al. "Tempol attenuates renal fibrosis in mice with unilateral ureteral obstruction: the role of PI3K-Akt-FoxO3a signaling." J Korean Med Sci. 2014 Feb;29(2):230-7. doi: 10.3346/jkms.2014.29.2.230. Epub 2014 Jan 28.

This study investigated whether tempol, an anti-oxidant, protects against renal injury by modulating phosphatidylinositol 3-kinase (PI3K)-Akt-Forkhead homeobox O (FoxO) signaling. Tempol attenuates oxidative stress, inflammation, and fibrosis in the obstructed kidneys of UUO mice, and the modulation of PI3K-Akt-FoxO3a signaling may be involved in this pathogenesis.

Yoshio, Y., K. Ishii, et al. "Effect of transforming growth factor alpha overexpression on urogenital organ development in mouse." Differentiation. 2010 Sep-Oct;80(2-3):82-8. doi: 10.1016/j.diff.2010.06.006. Epub 2010 Jul 17.

Transforming growth factor-alpha (TGFalpha) promotes cell proliferation by binding to the epidermal growth factor receptor (EGFR). TGFalpha and EGFR overexpression have been reported in various human cancers. The TGFalpha overexpression in mouse urogenital organs alone may not be responsible for tumor formation and epithelial hyperplasia, but is involved in bladder outlet obstruction.

Zager, R. A., A. C. Johnson, et al. "Uremia impacts renal inflammatory cytokine gene expression in the setting of experimental acute kidney injury." Am J Physiol Renal Physiol. 2009 Oct;297(4):F961-70. doi: 10.1152/ajprenal.00381.2009. Epub 2009 Aug 5.

Inflammatory cytokines are evoked by acute kidney injury (AKI) and may contribute to evolving renal disease Changes in gene transcription (as reflected by Pol II recruitment), and possible posttranscriptional modifications (known to be induced by microRNAs), are likely involved.

Zarjou, A., S. Yang, et al. "Identification of a microRNA signature in renal fibrosis: role of miR-21." Am J Physiol Renal Physiol. 2011 Oct;301(4):F793-801. doi: 10.1152/ajprenal.00273.2011. Epub 2011 Jul 20.

Renal fibrosis is a final stage of many forms of kidney disease and leads to impairment of kidney function. The molecular pathogenesis of renal fibrosis is currently not well-understood. The targeting specific miRNAs could be a novel therapeutic approach to treat renal fibrosis.

Zieg, J., K. Blahova, et al. "Urinary transforming growth factor-beta1 in children with obstructive uropathy." Nephrology (Carlton). 2011 Aug;16(6):595-8. doi: 10.1111/j.1440-1797.2011.01459.x.

Obstructive uropathies (OU) in childhood constitute one of the major causes of chronic renal insufficiency. Transforming growth factor-beta1 (TGF-beta1) is considered to be the major fibrogenic growth factor. Urinary TGF-beta1 may be a useful non-invasive tool for the differential diagnosis between OU and NOU in children. A positive correlation of TGF-beta1 with markers of renal tissue damage in patients with OU was found.

Zimmerman, D. L., J. Zimpelmann, et al. "The effect of angiotensin-(1-7) in mouse unilateral ureteral obstruction." Am J Pathol. 2015 Mar;185(3):729-40. doi: 10.1016/j.ajpath.2014.11.013. Epub 2015 Jan 24.

Angiotensin-(1-7) is a ligand for the Mas receptor and may protect against tissue injury associated with renin-angiotensin system activation.

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