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Mediators of Tubulointerstitial Injury

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Regardless of the underlying causes, tubulointerstitial fibrosis is closely associated with disease progression in chronic kidney disease. During this process, tubular cells play a dominant role by secreting inflammatory and fibrogenic molecules that are activated by insults. In our recent study, we showed that Growth Arrest and DNA Damage 45gamma (GADD45gamma) is upregulated in unilateral ureteral obstruction, and GADD45gamma activates p38 MAPK and regulates various molecules in cultured renal tubular cells (Abstract S-A16). In this lecture, several GADD45gamma associated molecules that have been implicated in the tubulointerstitial pathogenesis will be reviewed.

It has been have suggested that p38 MAPK activation contributes to the pathogenesis of kidney disease. In cultured renal tubular cells, p38 has been shown to mediate TGF-beta1 induced generation of reactive oxygen species, tumor necrosis factor-alpha production in ischemic stress, and TGF-beta1 induced generation of procollagen-Ialpha1. In rodent models, p38 activation has been associated with renal inflammation and fibrosis. Moreover, it has been demonstrated that p38 activation contributed to the pathogenesis of various progressive kidney diseases in humans. CX3CL1 (fractalkine) is a transmembrane molecule with an extracellular chemokine domain and mucin stalk. Soluble CX3CL1 promotes chemotaxis of target leucocytes, whereas the membrane anchored form function as an adhesion molecule for monocytes, NK cells and subsets of CD8+ T cells. In cultured renal tubular cells, it has been shown that CX3CL1 enhanced leukocyte adhesion to the luminal surface of the cells. In acute renal allograft rejection, there was increased expression of CX3CL1 mRNA by tubular epithelial cells and its mRNA expression correlated with infiltrating leukocyte subsets. In addition, CX3CL1 was upregulated by albumin overload in cultured renal tubular cells. CCL20 is a chemokine mainly expressed by epithelial cells. It plays an important role under inflammatory conditions by chemoattracting immature dendritic cells, T cells and B cells. It has been shown that CCL20 expression is markedly increased in renal tubular epithelium during allograft rejection episodes, which suggests CCL20 attracts inflammatory cells to the acutely rejecting kidney. IL8 is a member of the CXC chemokine family, and it causes chemotaxis of neutrophils and T-lymphocytes. In human glomerular diseases, IL8 was increased in patients urine and in renal tissue. In addition, a pathogenetic role of IL8 in antineutrophil cytoplasmic antibody associated glomerulonephritis has been addressed. It has been historically considered that MMPs degrade matrix, thereby reduce renal fibrosis. However, recent studies challenge such concept. A decrease in MMP-9 by knockout of tissue-type plasminogen activator preserved the integrity of tubular basement membrane in the obstructed kidneys. Similarly, it has been shown that MMP-9 disrupted cell barrier function in kidney cells. Decorin is an extracellular proteoglycan which binds TGF-1, hence it has been suggested that decorin neutralizes the profibrotic effect of TGF-beta1. However, accumulating studies showed that decorin actually contributes to the development of glomerular and tubulointerstitial fibrosis.