ATP as a death factor: purinergic signaling in renal epithelial-fibroblast cross talk

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Peritubular fibroblasts are a major fraction of interstitial cells in the kidney that produce erythropoietin. In an issue of the American Journal of Physiology-Renal Physiology, Ponnusamy and colleagues (14) have explored the mechanism linking renal tubular epithelial cell death and injury to peritubular fibroblasts. The results of this work provide new insights into the mechanisms underlying the progression of acute kidney injury to renal fibrosis in chronic kidney disease.

Evolution has made it possible for different organs and cells to have a meticulously orchestrated way of communication. Such processes are vital to maintain homeostasis, stimulate adaptation, and induce an appropriate response to injury. This cross talk embraces various systems, including cytokines, receptors, ion flows, signal transduction pathways, and others. One such way of interaction is via the family of purinergic “P” receptors that are classified into P1 and P2 according to their sequence (19). Recent evidence suggests that P2X receptors open in response to the binding of extracellular ATP. In vertebrates, there are seven distinct genes that encode P2X receptor subunits (P2X1-P2X7) sharing ~50% homology in amino acid sequence (19). Recent evidence suggests that P2X receptors are widely distributed among tissues including neurons, hematopoietic cells, epithelium, bone, and muscle (11, 13, 19).

One of the intriguing members of this family is the P2X7 receptor, which is somewhat unusual among other members in that its persistent activation by high levels of extracellular ATP induces the formation of a reversible plasma membrane pore permeable to hydrophilic solutes up to 900 Da (18, 19). This implies that apart from activating a diverse array of cellular pathways, including activation of phospholipase D, phospholipase A2, and mitogen-activated protein kinases, it could also mediate cell permeabilization to an extent that may lead to cell death. Other unique traits of these receptors are their inability to form functional heteromers with other members of the P2X family and their low affinity for ATP that requires concentrations up to 100 µM for activation (11, 19). Under physiological circumstances the ATP-sensitive P2X7 receptors are predominately present on cells of immunological origin including peripheral macrophages and glial cells in the central nervous system (3, 4). Accumulating evidence suggests that these receptors are critical mediators of cell growth, apoptosis, and necrosis, and their activation is known to have proinflammatory effects (3). Taken together, these observations and recent advances in understanding P2X7 receptor signaling pathways have led to promising avenues that are exploring the potential of inhibiting this receptor in inflammatory and neurodegenerative diseases (15, 20).

Although it has been shown that P2X7 receptors are expressed during kidney development, its presence in the renal parenchyma is very limited under normal conditions (9, 19). However, studies have shown that this receptor is upregulated following injury, and its induction has been documented in animal models of glomerulonephritis and diabetic kidney disease in various cell types, including podocytes, mesangial cells, and proximal tubular cells. More importantly, human kidney biopsies from patients with lupus nephritis also display upregulation of P2X7 receptors in glomeruli and proximal tubules (10, 22, 23).

In an issue of the journal, Ponnusamy and colleagues (14) have explored the mechanism linking renal tubular epithelial cell death and injury to renal interstitial peritubular fibroblasts and provide novel insights. Peritubular fibroblasts are critical interstitial cells in the kidney that produce erythropoietin (12). These cells also mediate extracellular matrix expansion following injury to maintain a careful equilibrium between repair and exaggerated fibrosis that could potentially progress into chronic kidney disease (8). Using an in vitro system, they demonstrate that the cell supernatant from damaged renal proximal tubular epithelial cells and not the cell debris is responsible to induce death of renal peritubular fibroblasts. These damaging effects were identified to be due to release of ATP as the "pro-death factor." They further demonstrate that these effects are mediated through P2X receptors, specifically P2X7, using multiple complementary approaches with chemical inhibitors, small interference RNA knockdown, and overexpression of P2X7. The findings in this work are consistent with recent reports that have demonstrated an important role for P2X7 receptors in the context of glomerulonephritis and suggested that deficiency of this receptor was associated with significant renoprotection (21). Another recent study reported that the tubulointerstitial damage following unilateral ureteral obstruction was attenuated in the P2X7−/− mice (7). The results of this work could provide new insights into the mechanism(s) underlying the progression of acute kidney injury (where the proximal tubule bears the brunt of injury) to renal fibrosis in chronic kidney disease.

In the normal kidney, ATP is released at nanomolar concentrations from thick ascending limb and collecting duct cell lines and micromolar concentrations from proximal tubular epithelial cultures (17). However, accumulating evidence suggests that higher concentrations of ATP are released from abnormal cystic epithelial cells derived from both human and mouse polycystic kidneys (17, 24). Furthermore, it is obvious that any type of insult that can lead to cell death can generate high levels of intracellular ATP and thereby increase the extracellular ATP concentration. Such high concentrations of ATP can,
in turn, activate the P2X7 receptors and cause cellular apoptosis and necrosis and may (at least in part) explain the decreased erythropoietin levels and subsequent anemia that is associated with chronic kidney disease.

There has been great progress in the development of P2X7 receptor antagonists (5). Such agents have already shown impressive results in treating chronic neuropathic pain and rheumatoid arthritis (6). An imperative next step is to confirm the results of the present work in relevant in vivo models of both acute and chronic kidney disease. Once validated and tested in clinical settings, these findings could offer innovative preventive and therapeutic modalities and has the potential to impact morbidity and mortality associated with kidney injury.

REFERENCES