Intraluminal autocrine purinergic signaling within cysts: implications for the progression of diseases that involve encapsulated cyst formation

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PURINERGIC LIGANDS ARE LOCAL mediators, autacoids, or paracrine factors (5, 7–10, 12, 16, 47–49, 51, 63, 70). The role of extracellular nucleotides and nucleosides in physiology and pathophysiology has been studied for decades (5, 7–10, 12, 16). However, it was slow to be appreciated because of trepidations with regard to the loss of ATP as an intracellular biochemical fuel (9, 12, 16). Before the release of purinergic ligands from cells was studied extensively and systematically, multiple types of receptors for nucleotides (ATP, UTP, UDP, ADP, etc.) and nucleosides (adenosine, etc.) emerged from molecular cloning (1, 14, 27, 41, 49). The study of purinergic ligand’s effects on cell function has exploded recently, as has the study of purinergic ligand release and the binding of these ligand's effects on cell function has exploded recently, as has the study of purinergic ligand release and the binding of these ligand's effects on cell function has exploded recently, as has the study of purinergic ligand release and the binding of these ligand's effects on cell function has exploded recently, as has the study of purinergic ligand release and the binding of these ligand's effects on cell function has exploded recently, as has the study of purinergic ligand release and the binding of these ligand's effects on cell function has exploded recently, as has

The current paper by Turner et al. (63), in this issue of the American Journal of Physiology-Renal Physiology, speaks directly to the concepts delineated above. In particular, it illustrates how important and robust purinergic ligands and their signal transduction systems are when cells and tissue remodel to form an ideal “purinergic signaling microenvironment” such as a cyst that is fully encapsulated and closed off from the rest of the tissue by a single monolayer of cyst-lining epithelial cells. In pathophysiological terms, the lumen of this encapsulated cyst becomes this ideal microenvironment. In a renal tubule or in a duct emanating from an endocrine gland (mammary tissue, ovary, etc.), the tubule or duct is an “open system,” where the tubule fluid or glandular secretion enters one end and leaves the other. In an encapsulated cyst, solutes, ions, fluid, autocrine/paracrine ligands, etc. enter the lumen but they then become trapped. The creation of this abnormal yet robust microenvironment for autocrine and paracrine signaling within an encapsulated cyst is shown in Fig. 1.

Turner et al. (63) use a three-dimensional collagen gel culture system in which Madin-Darby canine kidney (MDCK) cells are seeded into this gel matrix as it forms. The cells organize into cyst structures and grow and expand in diameter and volume over time in vitro within this gel matrix. Turner et al. show elegantly and comprehensively that release of endogenous purinergic ligands into the microenvironment surrounding and within these MDCK cell cysts drives their growth and expansion. Use of apyrase, the ATP and ADP scavenger, as well as some nonspecific antagonists of P2 receptors inhibited cyst expansion markedly. Inhibitors of the ERK kinases slow cyst growth and expansion more dramatically. Both P2Y and P2X receptors can trigger ERK kinase activation (2, 37, 38), as can growth factor receptors (13). It is well known that purinergic receptor systems can “transactivate” growth factor receptor systems and cytokine receptor systems (14, 65). It is well known that purinergic ligands can act as mitogens in their own right or comitogens with growth factors (21, 26, 34, 42, 45, 46, 60, 63). As illustrated in the paper by Turner et al. (63) and discussed in the poly cystic kidney disease (PKD) literature (11, 17, 57–59, 66–69), the interplay between local purinergic signaling and growth factor signaling may be critically important in the progression of PKD during remodeling and after cysts have formed. The monocilium of the ductal epithelium and the protein products of genes mutated in PKD may have a central galvanizing role in purinergic and growth factor signaling cross talk (15, 22–24, 31, 32, 39, 40, 43, 44, 71–73).

In past work, our laboratory showed that ATP content was robust in a subset of cyst fluid samples from autosomal dominant polycystic kidney disease (ADPKD) kidneys (70). We also showed that ADPKD cell monolayers released ATP across the apical membrane as or more readily than normal kidney cell monolayers (50, 70). This work was almost exclusively

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performed using primary cultures of human kidney cells grown as polarized cell monolayers. We also showed that multiple P2X and P2Y purinergic receptor subtypes were expressed by normal and ADPKD primary human cell monolayers and that nucleotide ligands to both types of P2 receptors could increase cell calcium and stimulate chloride secretion (50). Purinergic receptor-driven stimulation of chloride secretion has been well documented in MDCK cells as well as in other renal epithelial cell model systems from the collecting duct and in many other epithelial cell and tissue models (3, 11, 17, 20, 28, 29, 34, 35, 36, 50, 52–56, 74, 75). The CFTR chloride channel is often expressed in cyst-lining renal epithelial cells (20, 28, 29, 34, 35, 50, 52). It may also be detrimental in cyst fluid accumulation and expansion (11, 17, 20, 28, 29, 34, 35, 50, 52) and/or the chronic mitogenic effects on the cells that lined the encapsulated cysts (2, 11, 17, 21, 26, 34, 37, 38, 46–48, 50, 60, 63, 66–70). Not only could this be detrimental to the progression of ADPKD cysts in the kidney but it could also play a deleterious role in cysts observed in extrarenal tissues in ADPKD (11, 17) as well as in polycystic syndrome in other tissues such as ovary and breast (25) where P2Y and P2X receptors are also expressed. This being said, autocrine and paracrine purinergic signaling may play a very different role in autosomal recessive PKD (ARPKD), where encapsulated cysts rarely form and only dilation of renal collecting ducts and biliary duct is observed in the human condition (18, 19). ARPKD and ADPKD are very different diseases with

From this abundant work by us and others, we argued that autocrine and paracrine ATP and adenosine signaling could be detrimental to ADPKD cyst growth and expansion (11, 17, 20, 28, 29, 34, 35, 50, 52, 63). The detrimental pathophysiological effects could be the continual stimulation of chloride and fluid secretion into the encapsulated cysts (11, 17, 20, 28, 29, 34, 35, 50, 52, 63) and/or the chronic mitogenic effects on the cells that lined the encapsulated cysts (2, 11, 17, 21, 26, 34, 37, 38, 46–48, 50, 60, 63, 66–70). Not only could this be detrimental to the progression of ADPKD cysts in the kidney but it could also play a deleterious role in cysts observed in extrarenal tissues in ADPKD (11, 17) as well as in polycystic syndrome in other tissues such as ovary and breast (25) where P2Y and P2X receptors are also expressed. This being said, autocrine and paracrine purinergic signaling may play a very different role in autosomal recessive PKD (ARPKD), where encapsulated cysts rarely form and only dilation of renal collecting ducts and biliary duct is observed in the human condition (18, 19). ARPKD and ADPKD are very different diseases with
respect to the type of tissue remodeling that occurs (17–19); this is an important caveat that needs to be voiced.

Our laboratory is extremely excited about the work of Unwin and colleagues (63, 64) because the current paper (63) has clearly reawakened the concepts that autocrine and paracrine purinergic and growth factor signaling may indeed be detrimental to the progression of cystic diseases during the remodeling of tissue and after formation of encapsulated cysts has occurred. It is our hope that the ADPKD research community applies these findings to collagen gel studies of primary human ADPKD cell cysts or to kidney organ culture models where cyst formation can be visualized. In these models, it is also highly likely that antagonism of local purinergic signaling may slow cyst progression and that existing as well as novel therapeutics may be brought to bear on ADPKD pathogenesis.

REFERENCES


