Targeting B-Raf as a treatment strategy for polycystic kidney disease

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POLYCYSTIC KIDNEY DISEASE (PKD) is a genetic disorder characterized by the formation of fluid-filled cysts, primarily within the kidneys but also in the liver. Autosomal dominant PKD (ADPKD) has an incidence rate of 1:400–1,000 and is the most common genetic cause of renal failure. ADPKD has been mapped to mutations in the genes PKD1 and PKD2, which encode polycystin-1 (PC1) and PC2, respectively (2). While the specific function of PC1 is still not completely known, PC2 is a member of the transient receptor potential superfamily and is a calcium-permeable cation channel. These two proteins (PC1 and PC2) form a complex in several cellular locations, including on the primary cilium. Primary cilia bend in response to mechanosensory stimuli, such as fluid flow through kidney tubules, resulting in changes in channel activity. Most notably, bending of the primary cilium has been shown to result in increased calcium ($Ca^{2+}$) influx through the PC2 channel (2).

In ADPKD cyst epithelial cells, mutations in the PKD genes disrupt $Ca^{2+}$ signaling and reduce steady-state intracellular $Ca^{2+}$ levels (5, 13). Along with disruption of intracellular $Ca^{2+}$ homeostasis, intracellular cAMP levels were found to be elevated in the kidneys of PKD animals (14). In ADPKD, cAMP not only stimulates fluid secretion, but it also causes abnormal cellular proliferation by activating the mitogen-activated protein kinase (MAPK)/extracellular signal-related kinase (ERK) pathway. The increased activation of MEK/ERK signaling and ADPKD cell proliferation has been attributed to cAMP activation of B-Raf (15). Blocking cAMP or the MAPK pathway has been associated with decreases in cyst formation and disease progression in several animal models (6, 9).

Currently, there are no effective clinical treatments that prevent or slow the progression of PKD. Tolvaptan, a vasopressin V2 receptor antagonist, has been shown to reduce renal cAMP and inhibit PKD progression in animal models (8). Octreotide, a long-lasting analog of somatostatin, binds to somatostatin receptors and reduces cAMP production in the kidney and liver (8). Both compounds are currently being investigated in clinical trials. Other pathways being investigated for treatment of PKD include the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is important for protein synthesis, and there is crossstalk between the ERK pathway and the mTOR pathway. Inhibitors of the mTOR pathway are currently being tested in animal models and clinical trials; however, recent studies suggested that mTOR inhibition alone is not fully capable of slowing disease progression and maintaining renal function (7, 11). Therefore, new or combined therapies still need to be developed that would effectively treat PKD.

In an issue of the American Journal of Physiology-Renal Physiology, Yamaguchi et al. (16) tested the multi-kinase inhibitor Sorafenib (BAY 43–9006) on cAMP-induced cellular proliferation of human ADPKD cells. Sorafenib was initially identified in a wide-screen Raf kinase assay, followed by examination of its effects on tumor cell proliferation (4). Sorafenib primarily targets the Raf kinases, which are serine/threonine kinases, but Sorafenib also inhibits several tyrosine kinases including vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, platelet-derived growth factor receptor beta, c-KIT, and RET (12). Sorafenib has been approved for the treatment of renal cell carcinomas and hepatocellular carcinomas (1, 3). In patients with renal cell carcinomas, Sorafenib was able to prolong progression-free survival and reduce death for patients in which previous therapies had been ineffective (1). While there were increases in adverse events (primarily diarrhea and rash), the risk-benefit ratio was deemed acceptable. From the clinical trials, the authors suggest that beneficial effects seen with Sorafenib are due to its anti-angiogenic properties following VEGF inhibition, as the results were comparable to clinical trials with other VEGF inhibitors. In addition to use in renal cell and hepatocellular carcinomas, Sorafenib is currently in clinical trials for a variety of other cancers (3).

In the current work by Yamaguchi et al. (16), the authors examined the effects of Sorafenib on cell proliferation in primary cultures of human ADPKD cells. The rationale for these experiments came from the authors’ hypothesis that B-Raf is the link between elevated cAMP levels and increased cellular proliferation in PKD. The authors show that relatively low doses of Sorafenib inhibited B-Raf, ERK activation, and cellular proliferation induced by cAMP and/or epidermal growth factor (EGF). Additionally, Sorafenib limited cyst growth of ADPKD cells in a collagen gel. The proliferation of cyst-lining cells and cyst growth can be stimulated by a variety of factors including EGF, insulin-like growth factor 1, and VEGF. Interestingly, VEGF is present in cyst fluid where it may promote cyst growth by increasing cellular proliferation and angiogenesis (8). Since Sorafenib is not selective for B-Raf and can target other kinases including the VEGF receptor, future studies should examine the effects of Sorafenib on other signaling pathways involved in PKD. It is also possible that B-Raf inhibition in combination with other therapies such as mTOR inhibition may be an even more effective means of slowing or preventing cyst growth. Even though other B-Raf inhibitors exist, such as PLX4720 and GSK2118436, these two pharmacological agents selectively target a cancer-associated mutated B-Raf (B-Raf$^{V600E}$), which has not been reported in PKD (10). The study by Yamaguchi et al. (16) points out the important role of the cAMP/B-Raf/MEK/ERK pathway in the proliferation of ADPKD cells and that inhibition of the Raf kinases may be an effective means of altering the progression of PKD.

REFERENCES