MEK Inhibition Holds Promise for Polycystic Kidney Disease

James P. Calvet
Department of Biochemistry and Molecular Biology and the Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas

Polycystic kidney disease (PKD) has a number of characteristics that make it uniquely challenging for the development of therapies to slow disease progression. Renal cystic diseases result from the neoplastic growth of numerous fluid-filled cysts, often accompanied by increased apoptosis, tissue remodeling, inflammation, and fibrosis (1–3). The slow, inexorable growth of these renal cysts, particularly in the adult forms of the disease, makes PKD an unlikely candidate for cancer chemotherapeutic drugs designed to attack rapid cell proliferation.

However, unlike cancer chemotherapy, which is designed to eliminate tumors, PKD chemotherapy only has to slow cyst growth to be successful. It is not necessary to eliminate the cysts as long as renal function can be preserved and significantly extended. But any drug used to treat PKD would have to be tolerated over a lifetime, as it is likely that cysts would continue to grow, or new cysts would form de novo from normal renal tubule cells, once therapy was stopped.

A number of therapeutic interventions designed specifically to inhibit cell proliferation have been tested in a variety of animal models of PKD. These interventions include paclitaxel, lovastatin, EGF receptor (EGFR) tyrosine kinase inhibition, TNF-α converting enzyme inhibition, c-Src inhibition, c-Myc antisense oligos, and rapamycin—these therapies have exhibited limited success or mixed outcomes (4–7). The vasopressin receptor antagonists, which have the effect of lowering intracellular cAMP, have shown remarkable success (6,8). In this issue of *JASN*, Omori et al. (9) present a study in which they tested another cell proliferation inhibitor from the cancer chemotherapeutic arsenal. In this paper, the mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) kinase (MEK) inhibitor PD184352 (now named CI-1040) is shown to effectively block cyst growth and kidney enlargement, and to preserve renal function, when given to pcy/pcy mice that have nephronophthisis (NPHP3), an adolescent form of recessive PKD (10).

PD184352 inhibits the Ras/MAPK pathway by targeting the MAPK kinase, MEK, which activates ERK by phosphorylating it on tyrosine and threonine residues (Figure 1). The Ras/MAPK pathway mediates most growth factor (GF) receptor–mediated signaling. Activation of a Ras family member (H-Ras, K-Ras, N-Ras) leads directly to activation of the Raf kinases (Raf-1, A-Raf, B-Raf). The Rafs are also called MAPK kinase kinases because they phosphorylate and activate MEK1 and MEK2. The MEKs, in turn, phosphorylate ERK1 and ERK2, their only known targets. Then ERK, among other things, phosphorylates and activates transcription factors affecting gene expression and ultimately cell proliferation.

Omori et al. (9) showed that pcy/pcy cystic kidneys have elevated levels of activated or phosphorylated ERK (P-ERK), specifically in the cystic epithelium of embryos, newborns, 1-wk postnatal animals, and 8-wk-old mice. While these pcy/pcy mice develop renal cysts before birth, their kidneys do not become abnormally large until about 8 wk of age and the mice usually survive for 6 mo or more, making them an excellent model to study therapeutic agents over a relatively long period of time (11). In this study, mice were fed PD184352 every day for a week starting at 10 wk of age, and then every 3 d up to 17 wk. PD184352 reduced kidney size, % kidney weight/body weight, cystic index, and serum creatinine. Consistent with improved renal function, pcy/pcy mice receiving PD184352 were better able to concentrate urine and had lower BP. The only potential problem was a decrease in (nonkidney) body weight in the treated animals.

The rationale for targeting the MEK/ERK pathway is based on previous studies that showed that cAMP-dependent proliferation of cultured human autosomal dominant PKD (ADPKD) cyst–lining epithelial cells is mediated through the activation of ERK (12–14) and that P-ERK levels are elevated in the cystic epithelium of embryos, newborns, 1-wk postnatal animals, and 8-wk-old mice. While these pcy/pcy mice develop renal cysts before birth, their kidneys do not become abnormally large until about 8 wk of age and the mice usually survive for 6 mo or more, making them an excellent model to study therapeutic agents over a relatively long period of time (11). In this study, mice were fed PD184352 every day for a week starting at 10 wk of age, and then every 3 d up to 17 wk. PD184352 reduced kidney size, % kidney weight/body weight, cystic index, and serum creatinine. Consistent with improved renal function, pcy/pcy mice receiving PD184352 were better able to concentrate urine and had lower BP. The only potential problem was a decrease in (nonkidney) body weight in the treated animals.
calcium (14), and that ADPKD cells can be rescued (switched back) by raising intracellular calcium (16).

The basis for this phenotypic switch appears to be the response of B-Raf to cAMP. In normal cells (Figure 1, left), B-Raf is repressed by Akt (also called protein kinase B) in a phosphoinositide-3 kinase (PI3K)- and calcium-dependent manner. By contrast, in ADPKD cells and in calcium-restricted cells (Figure 1, right), Akt activity is decreased, thus allowing B-Raf to be activated by cAMP. Activation of B-Raf leads to MEK and ERK activation and results in increased cell proliferation. Another MEK inhibitor, PD98059, was shown to block ERK activation and prevent this cAMP-dependent cell proliferation in PKD cells (13,14). Thus, it appears that the key to the aberrant cell proliferation in PKD is cAMP-dependent B-Raf activation, with Akt activity—this B-Raf being activated not by mutation but by cAMP? If so, PD184352 and new-generation MEK-specific inhibitors may hold promise for treating PKD.

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References
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