CaMK-II is a PKD2 target that stabilizes cilia

Rothschild et al., Development 2011; 138: 3387–3397; doi:10.1242/dev.066340

Constitutively active (T287D) CaMK-II reverses pronephric developmental defects. (a–f) Lateral views of entire embryos (a–c) and the cloaca (d–f; arrows indicate the end of the cloaca) after injection of pkd2 morpholino with or without constitutively active CaMK-II (c). (g–i) Immunostaining α1 Na+/K+-ATPase identifies the pronephric ducts. hpf, hours post-fertilization.

Polycystic kidney disease is a ciliopathy believed to be due to defects in Ca2+ signaling. Autosomal dominant polycystic kidney disease is caused by mutations in the polycystins PKD1 and PKD2. While PKD1 is a large receptor-like integral membrane protein with an extracellular N-terminus with motifs for cell–cell and cell–matrix interactions, PKD2 is a member of the transient receptor potential (TRP) superfamily of nonselective Ca2+-permeable ion channels found in plasma membranes, endoplasmic reticulum, and primary cilium. The intracellular terminals of both PKD1 and PKD2 contain coiled-coil domains that enable formation of a receptor–channel complex where activation of PKD1 induces Ca2+ entry via PKD2 and thus regulates levels of intracellular Ca2+. A large amount of work in a variety of mammalian and zebrafish models has shown that diminished activation of both intracellular Ca2+ signals leads to kidney cyst formation. One potential mediator of normal Ca2+ action is CaMK-II, a conserved calmodulin-dependent protein kinase; prolonged Ca2+ stimulation converts CaMK-II into an activated state that, in the zebrafish, is detected in the forebrain, ear, and kidney. In a recent study, Rothschild et al. found activated CaMK-II during early zebrafish development in specific ciliated tissues, including cells of the nervous system, the inner ear, and the pronephric kidney. Suppression of CaMK-II (camk2g1) induced pronephric cysts and resulted in disassembly of cilia and a decrease in their number, and any remaining cilia were immobile. Moreover, kidney-targeted dominant-negative CaMK-II also caused pronephric cystogenesis. Of great interest is the authors’ finding that expression of constitutively active CaMK-II rescued cyst development in animals with knock-down of pkd2 (Figure).

Thus, in the developing kidney, CaMK-II activation was found to be dependent on PKD2 Ca2+ and was capable of restoring proper kidney development in PKD2-deficient embryos. These findings indicate that CaMK-II is a natural transducer of PKD2 Ca2+ that enables both normal development and cilia stability. This elegant study has implications for other ciliated tissues and identifies a potential new therapeutic target for autosomal dominant polycystic kidney disease.

Juan Oliver

Acute kidney injury after liver transplantation in a rat model of syngeneic orthotopic liver transplantation

Wang et al., Lab Invest 2011; 91: 1158–1169; doi:10.1038/labinvest.2011.59

Orthotopic liver transplantation (OLT) is indicated for patients with end-stage liver disease of almost any etiology. Acute kidney injury (AKI) is a frequent complication after OLT and unfavorably affects prognosis after liver transplantation (LT). AKI occurs in 80% of cases in the first 48 hours after LT. Post-LT AKI increases length of stay, cost, and mortality and is an important risk factor for chronic kidney disease and end-stage renal disease. Although post-LT AKI is common, its mechanism remains unclear. Risk factors such as intraoperative hemodynamic instability, post-reperfusion graft function, infection, and nephrotoxic drugs may predispose to post-LT AKI. Wang and colleagues used the rat model of syngeneic orthotopic LT (SOLT) to investigate the mechanism of post-LT AKI. They hypothesized that the condition of the graft, rather than intraoperative hemodynamic instability, has an important role in post-LT AKI in the SOLT model. Rats were randomly assigned into four groups: sham operated, vessel clamped, full-size LT, and reduced-size LT. The authors identified AKI in both the full-size and the reduced-size LT groups. In addition to renal tubular necrosis and apoptosis, renal peritubular capillary injury was also present. Pathological changes were more severe in the reduced-size than in the full-size LT group. Interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and monocyte chemotactic protein-1 (MCP-1) upregulation was found in liver tissue 6 hours after LT. The serum concentration of IL-6 and TNF-α was also increased at 6 hours after LT. The activated inflammatory response in renal tissue consisted of increased macrophage infiltration and upregulated IL-1β, IL-6, and TNF-α. The circulating proinflammatory cytokines act on distant organs such as the lung and kidney. The systemic inflammatory response induced by LT was the initiating factor in post-LT AKI.

This is the first study to investigate the pathological mechanism of AKI in an animal model of SOLT. The results demonstrate that protection of the liver graft and inhibition of the systemic inflammatory response are vital in reducing the risk of post-LT AKI. This interesting study has several limitations, as some important risk factors of AKI in human LT are not included in the study. When syngeneic rats are used, immunosuppressive antirejection therapy
is not required. The operation was carried out on healthy animals, chronic liver disease was not present in the recipients, and the long-term effects of LT on the kidneys need to be clarified.

Marc De Broe

Vasopressin-independent targeting of aquaporin-2


Vasopressin controls water balance by regulating water permeability in the kidney collecting duct; by binding to its GS protein-coupled type 2 receptor (V2R) in principal cells, it triggers accumulation of aquaporin-2 (AQP2) in the apical plasma membrane, thereby allowing water to be reabsorbed and the urine to concentrate. Vasopressin intracellular signaling in the collecting duct includes increased cyclic adenosine monophosphate (cAMP) and protein kinase-dependent phosphorylation of AQP2. Although there is little doubt that urinary concentration is critically dependent on vasopressin, there is some evidence that alternative mechanisms may also regulate water permeability. For example, dehydration was found to reverse the diuresis and AQP2 downregulation induced by an antagonist to the V2R. In a recent communication, Olesen et al. examined the hypothesis that E-prostanoid signaling might be involved in AQP2 regulation. Prostaglandin E2 (PGE2) has multiple actions, probably due to its ability to stimulate four different receptors (EP1–EP4) and potentially initiate different intracellular signaling cascades. PGE2 is synthesized and released in the collecting duct, which expresses all four EP receptors, and both EP2 and EP4 can signal via increased cAMP. Interestingly, at sites where EP1–EP4 are present, including the collecting duct, PGE2 is known to have opposing effects; for example, PGE2 has been shown both to increase water permeability and to decrease the effect of high levels of vasopressin in the cortical collecting duct. In vitro, Olesen et al. found that PGE2 increased phosphorylation and apical targeting of AQP2 in Madin–Darby canine kidney (MDCK) cells, that the EP4 receptor antagonist CAY10580 had similar effects, and that the EP2 agonist butaprost had effects identical to those of PGE2. Moreover, both PGE2 and butaprost (but not CAY10580) increased cAMP in the cells. In cortical kidney slices, the authors found that administration of PGE2 and butaprost increased AQP2 membrane abundance in collecting ducts. Importantly, in vivo, the polyuria and severe concentrating defect induced by a V2R antagonist were greatly alleviated by treatment with butaprost (Figure). In conclusion, EP2 and EP4 agonists increase AQP2 phosphorylation and trafficking, probably through different signaling pathways. Furthermore, EP2-selective agonists can partially compensate for a nonfunctional V2R, providing a rationale for new treatment strategies for hereditary nephrogenic diabetes insipidus, which is due to a loss-of-function mutation of the receptor.

Juan Oliver

Effect of dietary protein supplementation on blood pressure: a randomized, controlled trial

He et al., Circulation 2011; 124: 589–595; doi:10.1161/CIRCULATIONAHA.110.009159

Observational studies have suggested that protein restriction can result in a slower progression of kidney disease, although this observation was not confirmed in randomized trials. Conversely, studies suggest that protein supplementation can result in lower blood pressure (BP). The Protein and Blood Pressure (ProBP) study was a randomized double-blinded trial to test whether a soy protein or mild protein supplement would reduce systolic BP as compared with a complex carbohydrate supplement. The trial used a crossover design with each patient receiving each of the three supplements, randomized as to the order in which the supplements were received. Participants received 40 g soy protein, 40 g milk protein, and 40 g complex carbohydrate per day for a period of 8 weeks each. Subjects were 48 years old on average and had a mean systolic BP between 120 and 159 mm Hg at two screening visits. At initiation of the study, the mean systolic and diastolic BP of the patients was at 126.7/82.4 mm Hg. As compared with the period during which subjects were taking the carbohydrate supplement, the BP was 2 mm Hg lower when they were receiving the soy protein supplement and 2.3 mm Hg lower when they were receiving milk protein. Body weight, fasting plasma glucose, and serum lipids did not vary significantly among intervention phases, except for a slightly higher high-density lipoprotein measurement among participants receiving the soy protein supplement. Adverse events were related mostly to gastrointestinal intolerance.

This trial underscores the importance of randomized trials in confirming a cause-and-effect relationship between protein supplementation and BP. This study demonstrated a small, but significant, improvement at 6 months. Although not generalizable to those with kidney function, this study suggests a role for protein supplementation in the treatment of hypertension. Further studies will be required to understand the mechanism by which blood pressure is linked to nutrient intake.

Lynda Szczecz