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Review Article

Mammalian target of rapamycin inhibition in polycystic kidney disease: From bench to bedside

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease in the USA resulting in chronic kidney disease and the need for dialysis and transplantation. Approximately 85% of cases of ADPKD are caused by a mutation in the Pkd1 gene that encodes polycystin-1, a large membrane receptor. The Pkd1 gene mutation results in abnormal proliferation in tubular epithelial cells, which plays a crucial role in cyst development and/or growth in PKD. Activation of the proliferative mammalian target of rapamycin (mTOR) signaling pathway has been demonstrated in polycystic kidneys from rodents and humans. mTOR inhibition with sirolimus or everolimus decreases cysts in most animal models of PKD including Pkd1 and Pkd2 gene deficient orthologous models of human disease. On the basis of animal studies, human studies were undertaken. Two large randomized clinical trials published in the New England Journal of Medicine of everolimus or sirolimus in ADPKD patients were very unimpressive and associated with a high side-effect profile. Possible reasons for the unimpressive nature of the human studies include their short duration, the high drop-out rate, suboptimal dosing, lack of randomization of "fast" and "slow progressors" and the lack of correlation between kidney size and kidney function in ADPKD. The future of mTOR inhibition in ADPKD is discussed.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease in the USA. It affects about 1:400 to 1:1000 people. ADPKD occurs in all racial and ethnic groups. Most patients with ADPKD develop hypertension. Massive cystic disease may also lead to chronic pain and cyst infections. In clinical practice, detection of multiple renal cysts on ultrasound or CT scan is used to make the diagnosis of PKD. Precise determination of kidney and cyst volume on MRI scanning is used for clinical studies. Approximately 50% of people with ADPKD develop chronic kidney disease around age 50 years. ADPKD accounts for about 5% to 10% of end-stage renal failure in the USA, requiring dialysis and renal transplantation [1]. There is no effective treatment for ADPKD.

Approximately 85% of cases of ADPKD are caused by a mutation in the Pkd1 gene that encodes polycystin-1 (PC-1), a large membrane receptor, and approximately 15% caused by a mutation in the Pkd2 gene that encodes polycystin-2 (PC-2) a calcium channel that binds to PC-1. PC-1 and PC-2 have been localized to the cilia where they function as a mechanosensor that mediates flow-dependent calcium entry [2].

It has been determined that inhibitors of cyclic adenosine monophosphate (cAMP), cyclin-dependent protein kinase,

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tumor necrosis factor-α, sarcoma (Src) a proto-oncogene tyrosine-protein kinase, the renin-angiotensin-aldosterone system, and 3-hydroxy-3-methyl-glutaryl-CoA reductase reduce cyst formation and improve renal function in rat and mouse models of PKD, which are thus potential therapeutic targets in PKD. Current developments in the field of PKD research are very exciting. The results of studies in rat and mouse models of PKD have been translated to the bedside. Tolvaptan (a vasopressin V2-receptor antagonist) that inhibits cAMP, somatostatin, bosutinib (a Src/Abl tyrosine kinase inhibitor), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and statins that reduce cyst formation and improve renal function in animal models of PKD are being tested in interventional studies in humans [3,4]. It is likely that current or future interventional studies in patients with ADPKD will result in the discovery of an agent that can slow the growth of the polycystic kidneys and delay the onset of renal failure.

The mammalian target of rapamycin (mTOR) signaling pathway is the focus of the current review. Human and experimental data provide strong evidence that abnormal proliferation in tubular epithelial cells plays a crucial role in cyst development and/or growth in PKD [5]. Genetic manipulations that induce the proliferation of tubular epithelial cells in mice cause cysts to form in the kidney [6,7]. The mTOR signaling pathway regulates cell growth and proliferation that are dysregulated in ADPKD. Sirolimus, an mTOR inhibitor, is an FDA-approved immunosuppressive drug and is a powerful antiproliferative [8]. In view of the importance of tubular cell proliferation in cyst formation and the antiproliferative effects of sirolimus, the hypothesis was developed that sirolimus would reduce cyst formation and disease progression in ADPKD via inhibition of tubular cell proliferation. In addition to inhibition of proliferation, mTOR inhibitors may also have a therapeutic effect in PKD by affecting vascular remodeling, angiogenesis, and fibrogenesis [9]. To understand the mechanism of action of mTOR inhibitors better, the mTOR signaling pathway will first be discussed in detail.

mTOR signaling pathway and PKD kidney

mTOR exists in association with two different complexes: mTORC1 and mTORC2. mTORC1 consists of mTOR and regulatory associated protein of mTOR (Raptor), while mTORC2 consists of mTOR and rapamycin-independent companion of mTOR (Rictor).

The mTORC1 pathway involves the following major players: insulin-like growth factor-I (IGF-1), serine/threonine kinase Akt (also known as protein kinase B), tuberous sclerosis complex 1 and 2 (TSC1/2), mTOR, and the serine/threonine kinase p70 S6 ribosomal protein kinase (p70S6K) [10,11,12] (Fig. 1). IGF-I is a major regulator of the mTOR pathway via signaling to PI3K/Akt/mTOR. Phosphoinositide-3-kinase (PI3K) converts the lipid phosphatidylinositol (4,5)-bisphosphate (PIP_2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), which localizes Akt to the membrane. The TSC1 (hamartin) and TSC2 (tuberin) complex is inactivated by Akt-dependent phosphorylation. Inactivation of TSC2 results in activation of mTOR via the Ras-related small GTPase (Rheb). mTORC1 is a complex that is made up of mTOR and Raptor. mTOR phosphorylates both p70S6K and eukaryotic initiation factor 4E-binding protein (4E-BP1) via independent pathways. Increased p70S6K and 4E-BP1 act independently to promote cell proliferation (cell growth and cell cycle progression). The mode of action of sirolimus is to bind the cytosolic protein FK-binding

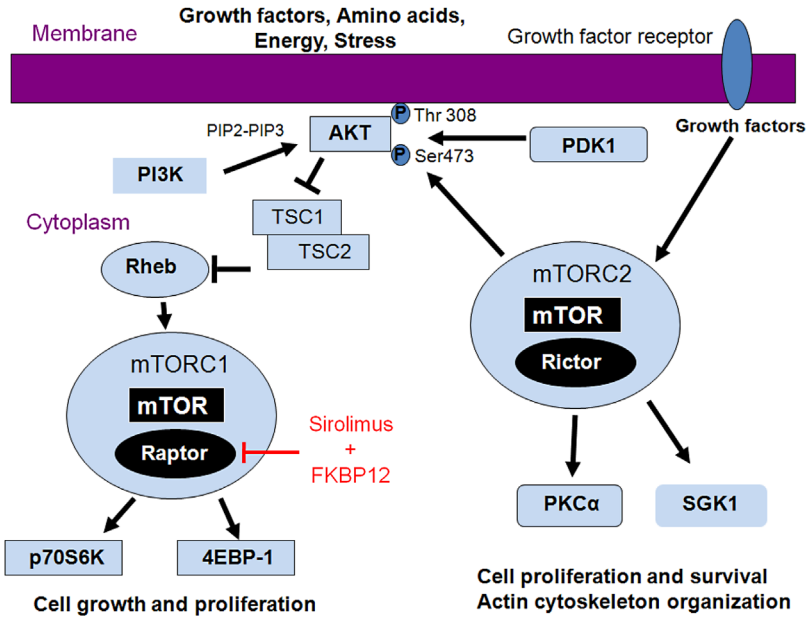

Figure 1. mTOR signaling. mTOR exists in association with two different complexes, mTORC1 and mTORC2. mTORC1 consists of mTOR and regulatory associated protein of mTOR (Raptor), while mTORC2 consists of mTOR and rapamycin-independent companion of mTOR (Rictor). In the mTORC1 pathway, PI3K converts PIP_2 into PIP_3, which localizes Akt to the membrane. The TSC1 (hamartin) and TSC2 (tuberin) complex is inactivated by Akt-dependent phosphorylation. Inactivation of TSC2 results in activation of mTOR via the GTPase, Rheb. mTOR phosphorylates both p70 S6 kinase (p70S6K) and 4E-BP1 via independent pathways that promote cell proliferation. The mode of action of sirolimus is to bind the cytosolic protein FK-binding protein 12 (FKBP12) to destabilize the association between mTORC1 and raptor, preventing the downstream phosphorylation of p70S6K. In the mTORC2 pathway, there is downstream signaling to the AGC kinases Akt, PKCα, and SGK1. Phosphorylation of Akt at Serine 473 by mTORC2 primes Akt for further phosphorylation at Threonine 308.