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Therapeutic role of sirolimus in non-transplant kidney disease

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ABSTRACT

Sirolimus is a member of a novel class of immunosuppressant drug that potently suppresses T cell proliferation and expansion by inhibition of the Target of Rapamycin Complex 1 (TORC1) protein kinase. Sirolimus also has anti-proliferative effects on intrinsic cells of the kidney, and increasing evidence suggests that it may have a therapeutic role in non-transplant renal diseases. In the normal kidney, sirolimus is considered to be non-nephrotoxic. In the diseased kidney, sirolimus may be beneficial or detrimental, depending on the type of renal injury. In polycystic kidney disease, TORC1 activation mediates renal tubular epithelial cell (TEC) proliferation and cyst growth in animals, and Phase III clinical trials are underway to determine the effect of sirolimus in attenuating disease progression in humans. In contrast, in acute kidney injury, sirolimus transiently impairs proximal TEC regeneration and delays renal recovery. In animal models of lupus nephritis and diabetic kidney disease, sirolimus prevents disease progression. However, the efficacy of sirolimus in human glomerulonephritis as well as in diabetic chronic kidney disease remains unclear, as it paradoxically exacerbates renal dysfunction when the baseline glomerular filtration rate is low (< 40 ml/min/1.73 m^2) and there is heavy proteinuria (> 300 mg/day). This may, in part, be due to inhibition of compensatory glomerular capillary repair through the suppression of endothelial cell proliferation and angiogenic growth factor production by podocytes. Therefore, at present, polycystic kidney disease is the most promising therapeutic application for sirolimus in non-transplant renal diseases, and further studies are needed to clarify its role in other situations.

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Abbreviations: AKI, acute kidney injury; AMPK, AMP-activated kinase; ADPKD, autosomal dominant polycystic kidney disease; CAN, chronic allograft nephropathy; CD2AP, CD2-associated protein; Cdk, cyclin-dependent kinase; CNI, calcineurin inhibitor; CTGF, connective tissue growth factor; ELITE, Efficacy Limiting Toxicity Elimination; EGF, epidermal growth factor; 4E-BPs, eukaryotic initiation factor 4E binding proteins; FKBP-12, FK binding protein-12; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; HIF-1α, hypoxia-inducible factor-1 α; PC, polycystin; RME, receptor mediated endocytosis; S6K, S6 ribosomal protein kinase; STZ, streptozotocin; SMA, smooth muscle actin; TORC1, Target of Rapamycin Complex 1; TOR, Target of rapamycin; TORC2, Target of Rapamycin Complex 2; TEC, tubular epithelial cell; TGFβ1, transforming growth factor-β1; VEGF, vascular endothelial growth factor.

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1. Introduction

Sirolimus (rapamycin; $C_{51}H_{79}NO_{13}$, molecular weight 914.2) is a naturally occurring water-insoluble macrolide antibiotic produced by the *Streptomyces hygroscopicus* bacterium, which was serendipitously isolated by Dr. Suren Seghal from soil samples taken from the Vai Atare region of Easter Island (Garber, 2001; Sehgal, 2003). The immunosuppressant properties of sirolimus were recognised within a few years after its initial discovery, when it was noted to suppress humoral IgE production in experimental adjuvant-induced arthritis and allergic encephalomyelitis (Martel et al., 1977). It was also found to be a potent fungicidal (particularly against *Candida* species), and identified as a strong tumoricidal agent in in vitro studies performed by the National Cancer Institute (Martel et al., 1977). However, for various reasons (Garber, 2001), further development was halted, and it was not until 1989 when sirolimus re-emerged in clinical studies as an immunosuppressant for use in organ transplantation in humans (Chapman et al., 2007). This resurrection was probably also partly in response to knowledge that it had structural similarities to FK506 (tacrolimus) (Abraham & Wiederrecht, 1996).

Sirolimus has a novel mechanism of immunosuppressant action involving the suppression of T-lymphocyte proliferation through inhibition of the target of rapamycin protein kinase complex (TORC) 1 (Brown et al., 1994; Y. Chen et al., 1994; Chiu et al., 1994; Faivre et al., 2006; Heitman et al., 1991; Rohde et al., 2001; Sabatini et al., 1994; Sabers et al., 1995; Sarbassov et al., 2006; Tsang et al., 2007). In organ transplantation, sirolimus was initially viewed as a new approach to overcome the problem of chronic calcineurin-inhibitor (CNI)-nephrotoxicity, without increasing the risk of allograft rejection (Fellstrom, 2004; Nankivell et al., 2003). Many head-to-head comparisons in experimental and clinical studies revealed that sirolimus exhibited little or minimal nephrotoxicity at standard immunosuppressant doses, when compared to cyclosporin (Sehgal, 1998). Consequently, sirolimus was approved by the United States Food and Drug Administration in 1999, as an immunosuppressant to prevent allograft rejection, and it is now a well-established agent used in kidney, islet cell, liver and heart transplantation. However, the precise role of sirolimus in the therapy of renal transplantation continues to evolve, and the results of recent clinical trials suggest that it might best serve as a maintenance immunosuppressant following early CNI withdrawal in patients with low immunological risk (Russ et al., 2005, 2006), and/or in the prevention of post-transplantation malignancy (Augustine et al., 2007; Campistol et al., 2006; Gutierrez-Dalmau & Campistol, 2007; Russ et al., 2006).

The purpose of the current review is to assess the therapeutic role of sirolimus in non-transplant renal diseases. Sirolimus has been shown to attenuate the progression of immune-mediated renal diseases in animal models (Warner et al., 1994). In addition, the TORC1 has a ubiquitous cellular distribution and is a non-discriminate transducer of mitogenic stimuli in many non-immune cell types (Buhaescu et al., 2006). Hence, sirolimus also has direct anti-proliferative effects on intrinsic cells of the kidney (Lieberthal et al., 2001). Therefore, increasing evidence from animal models and humans suggests that sirolimus may have a therapeutic role in many different types of kidney disease through a dual mechanism of action that involves modulation of TORC1 in the immune system as well in local resident renal cells (Liu, 2006). However, the effects of sirolimus in kidney disease have turned out to be complex, as it has been found to be both beneficial and detrimental (Table 1). Hence, a secondary aim of this review is to clarify the potential mechanisms of these conflicting data in more detail (Tomlanovich & Vincenti, 2007).

2. Molecular pharmacology and cell-specific sensitivity of sirolimus

2.1. Molecular mechanisms of action

Target of Rapamaycin (TOR) is a 289 kDa phosphatidylinositol 3-kinase-related kinase which is evolutionarily conserved from yeast to mammals (Sarbassov et al., 2005). It has a critical role in promoting cellular growth and differentiation, cell cycle progression, apoptosis and organ size (Guertin & Sabatini, 2005; Tsang et al., 2007). Extracellular nutrients (growth factors, amino acids, glucose) and intracellular signals (such as due to AMP/ATP levels *via* AMP-activated protein kinase, AMPK), acting through the PI3K-Akt-Rheb pathway, are the principal regulators of TOR (Fig. 1) (Guertin & Sabatini, 2005; Tsang et al., 2007). AMPK is a serine/threonine protein kinase, which is activated when intracellular ATP is depleted and intracellular AMP levels are increased (that is, increased AMP/ATP ratio), such as in glucose deprivation, hypoxia, ischaemia and heat shock (Motoshima et al., 2006). The activation of AMPK suppresses TORC1 pathway activation (Motoshima et al., 2006).

Table 1
Summary of the therapeutic effects of sirolimus in kidney disease.

Likely to be beneficial (Level II evidence)[a]	Potentially beneficial (Level III evidence)[a]	Unresolved efficacy	High-risk for adverse effects (Level I–II evidence)[a]
• Preservation of renal function following early CNI withdrawal	• Malignancy post-transplantation • Polycystic kidney disease	• Glomerulonephritis • Anti-fibrotic effects in chronic renal diseases	• Potentiation of cyclosporin nephrotoxicity in renal transplant recipients • May delay renal recovery in acute kidney injury or in severe nephrotic syndrome • Moderate risk of proteinuria following late conversion from a CNI in patients with renal transplant recipients with chronic allograft nephropathy • May exacerbate renal function in long-standing pre-existent chronic renal injury (GFR <40 ml/min/1.73 m^2 and proteinuria >300 mg/day)

[a] According to the National Health and Medical Council of Australia criteria. Level I: evidence from a systematic review of all relevant randomised controlled trials; Level II: evidence from at least one properly designed RCT; Level III: evidence from a well-designed pseudorandomised controlled trial, comparative study or case–control study; IV: evidence obtained from case series.

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