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The Mammalian Target of Rapamycin

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The mammalian target of rapamycin plays a critical role in cell differentiation, migration, and survival. Inhibitors of rapamycin, such as sirolimus or everolimus, have demonstrated anti-inflammatory, antifibrotic, antitumor, and antifungal properties that underscore the involvement of rapamycin signalling in various cellular functions. Activation of rapamycin phosphorylates p70 ribosomal S6kinase (p70S6K) and eukaryotic initiation factor-4E (4E-BP1), leading to cell hypertrophy, macrophage and T cell proliferation, and infiltration. Recently, rapamycin inhibitors have been applied in anticancer therapy 3, preventing restenosis of coronary arteries after angioplasty, and in clinical trials and research on the tuberous sclerosis complex and Alzheimer's disease. The clinical use of rapamycin inhibitors in kidney disease is limited by the risk of exacerbation of pre-existing proteinuria possibly because of the inhibition of vascular endothelial growth factor 8, but it ameliorated the tubulointerstitial disease associated with chronic proteinuria in experimental animal models 9. In steroid-resistant nephrotic syndrome patients, a rapamycin inhibitor decreased proteinuria values more than 90% in 9 of 13 patients [1-4].

Monocytes, which can differentiate into macrophages and dendritic cells, contributes to the pathogenesis of glomerulonephritis (GN) by secreting chemokines that increase the permeability of the glomerulus to plasma proteins, and stimulate cellular and antibody responses. Chemokines comprise a large family of low-molecular-weight cytokines that primarily recruit and activate leukocyte subsets that play various roles in inflammation through interactions with chemokine receptors. Monocyte chemoattractant protein-1(MCP-1)/CCL2, CXCL3, the regulated on activation, normal T cell-expressed, and presumably secreted protein (RANTES)/CCL5, macrophage inflammatory protein (MIP-1α)/CCL3, MIP-1β/CCL4, interleukin-8 (IL-8)/CXCL8, and their corresponding receptors, are implicated in monocyte recruitment during inflammation . Increased urinary levels of MCP-1 have been reported in children with glomerular proteinuria and as a diagnostic and prognostic marker in patients with lupus nephritis flare. Urinary IL-8 was significantly higher in relapsed steroid-resistant nephrotic-syndrome (NS) patients than in steroid-sensitive NS patients in remission 16. RANTES plays an essential role in the modulation of primary glomerulonephritis, and urinary excretion of RANTES was increased in steroid no responder GN patients. The mRNA of MIP-1α, MIP-1β, and MCP-1 are expressed in glomeruli and tubulointerstitial sites in GN patients [5-7].

However, studies investigating the effect of rapamycin inhibitors on the expression of chemokines are lacking. We hypothesized that rapamycin inhibitors had a modulating effect on GN-related chemokines in monocytes, and aimed to elucidate the detailed intracellular pathway mechanisms by which this occurred, including mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB).

Studies show that rapamycin inhibitor suppresses GN-related chemokines, including MCP-1, RANTES, IL-8, and MIP- 1β in THP-1 cells and MCP-1, RANTES, IL-8, MIP-1α, and MIP-1β in human primary monocytes. We also determined that the suppressive effects of sirolimus in monocytes are mediated by the MAPK-p38 and NF-κB-p65 signalling pathways.

According to the Kidney Disease Improving Global Outcomes guideline for GN 19, the immune system plays a crucial role not only in disease pathogenesis but also in disease evaluation and treatment. With the signalling of chemokines and their corresponding receptors, monocytes recruit to the kidney following injury and differentiate into macrophages and dendritic cells. The inflammatory chemokine MCP-1 is a member of the cysteine-cysteine (CC) chemokine family. An increased level of MCP-1 expression in renal tissues is pivotal to monocyte/macrophage infiltration in the pathogenesis of renal injury. Evidence also suggests that the role of MCP-1 extends beyond chemotaxis. A previous study showed that when serum-deprived human mesangial cells were exposed to MCP-1, the expression of the intercellular adhesion molecule-1 (ICAM-1) protein increased significantly at 24 h post treatment. In clinical studies as well as bench studies, increased urine levels of MCP-1 were reported in children with IgA nephropathy, and focal segmental glomerulosclerosis was shown to correlate with proteinuria 14. Evidence from clinical studies and animal models has demonstrated that MCP-1 plays a critical role in the pathogenesis of various renal diseases. The RANTES protein is also a member of the CC chemokine family. Previous studies have shown that increased expression of the RANTES protein 3 to 5 d after the activation of T cells facilitated leukocyte infiltration and increased the duration of the inflammatory response. In an animal model of autoimmune nephritis, RANTES-deficient DBA/1 mice developed significantly less proteinuria, azotemia, and renal inflammation, demonstrating reduced crescent formation and tubulointerstitial nephritis [8-11]. Another study showed that the expression of the MCP-1 and RANTES proteins by tubular epithelial cells correlated with proteinuria, and was associated with interstitial cell infiltration and fibrosis. The up regulation of RANTES and MCP-1 expression in response to infiltrating macrophages might play a crucial role in the development and progression of diabetic nephropathy. Thus, manipulating the expression of RANTES might provide a beneficial treatment for various renal diseases, such as acute renal failure, nephritis, transplant rejection, and nephropathies of various aetiologies. The plasma level of IL-8 was significantly higher during nephrotic-syndrome relapse than during remission 28. After administration of IL-8 antibodies, proteinuria in experimental acute immune complex-induced GN animal model was decreased. A previous study showed that MIP-1α and MCP-1 were expressed by infiltrating leukocytes, the renal tubular cells, and peritubular capillaries of patients with crescent glomerulonephritis. In addition, serum MIP-1β and IL-8 levels are associated with the clinical status of idiopathic steroid-sensitive nephrotic syndrome in children [12-15].

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Rapamycin is a component of two major intracellular signalling complexes (rapamycinC1 and rapamycinC2) that play different roles downstream. RapamycinC1 is activated by growth factors and amino acids, and controls cellular proliferation, promoting processes such as DNA translation, RNA transcription, ribosomal biogenesis, and cell cycle progression. Immunosuppressant in the rapamycin inhibitor family, which includes sirolimus and everolimus, is frequently used for their proliferation signal inhibiting properties in nephrology. Although application of rapamycin inhibitors in kidney disease may be limited by the risk of exacerbation of pre-existing proteinuria, rapamycin inhibitors have been shown to decrease proteinuria and to be renoprotective in animal models of nephrotic syndrome. rapamycin inhibitors not only ameliorated the tubulointerstitial disease associated with chronic proteinuria and the loss of renal mass in rats 9 but also decreased proteinuria and restored nephrin and podocin expression in experimental membranous nephropathy. In clinical studies, sirolimus (4 to 8 ng/mL), combined with an angiotensin-converting enzyme inhibitor and statin, stabilized renal function and reduced glomerular proliferation in patients with proteinuria greater than 1 g/day and hypertension IgA nephropathy. The majority of nephrotic-syndrome patients are steroid-responsive, and treatment with levamisole, cyclophosphamide, cyclosporine, tacrolimus, and mycophenolate mofetil is beneficial in a variable proportion of patients who suffer frequent relapses or steroid dependence [16-19]. Evaluation of the role of rapamycin inhibitors in the treatment of GN-related nephrotic syndrome is warranted.

In this review, we determined that suppressive effect of rapamycin inhibitors on GN-related chemokines in cell model and human primary monocytes. The results indicated that rapamycin inhibitors may play a therapeutic role in GN treatment. We further investigated the intracellular signal pathway to explore the detailed mechanism by which this occurred. The NF-κB-, ERK-, and p38-mediated activation of MAPK signal transduction pathways plays an essential role in the inflammatory response in GN. The suppressive effect of sirolimus on the expression of LPS-induced phosphorylation of p38 and p65, but not JNK or ERK, suggested that rapamycin inhibitor suppresses the expression of GN-related chemokines through the modulation of the p38- and p65-mediated signalling pathways. The immunosuppressive effect of glucocorticoids in nephrotic syndrome occurs through MAPKs; the calcineurin inhibitors, cyclosporine and tacrolimus, blunt the responses of NF-κB activation and therapeutically regulate the expression of MAPKs in steroid-resistant nephrotic syndrome; mycophenolate mofetil inhibits the phosphorylation of NF-κB and JNK as an alternative treatment for steroid-resistant nephrotic syndrome [20-23]. Our results suggested that rapamycin inhibitors suppress the expression of GN-related chemokines through the inhibition of the NF-κB-p65 and MAPK-p38 signalling pathways in monocytes. Further pathway investigation may be necessary.

Commercial Development of Rapamycin

The standard script is being followed for drug development based on rapamycin, by the look of things. Rapamycin reliably extends life in mice, which is more than can be said for the last set of overhyped alleged longevity-enhancing drugs, but it's still not worth getting excited about this sort of thing. The most likely end result is a rapamycin-like drug that lacks the worst side-effects, is of marginal benefit to humans, and which is only legally available as a palliative treatment for people suffering late-stage age-related disease - the regulatory environment in the US blocks all other options. Pharmacology to slow aging is simply not a viable path to greatly extended healthy life, and is of very limited use for old people.

Mechanistic target of Rapamycin

The mechanistic target of rapamycin, also known as mammalian target of rapamycin (mTOR) or FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1), is a protein that in humans is encoded by the MTOR gene. MTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. MTOR belongs to the phosphatidylinositol 3-kinase-related kinase protein family.

References

1. Liu Y (2006) Rapamycin and chronic kidney disease: beyond the inhibition of inflammation. Kidney Int 69: 1925-1927.
2. Brunskill NJ (2005) Rapamycin: a new string to the antiproteinuric bow? J Am Soc Nephrol 16: 1878-1879.
3. Guertin DA, Sabatini DM (2005) An expanding role for mTOR in cancer. Trends Mol Med 11: 353-361.
4. Fajadet J, Morice MC, Bode C, Barragan P, Serruys PW, et al. (2005) Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation 111: 1040-1044.
5. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, et al. (2008) Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 358: 140-151.
6. Gouras GK (2013) mTOR: at the crossroads of aging, chaperones, and Alzheimer's disease. J Neurochem 124: 747-748.
7. Kirsch AH, Riegelbauer V, Tagwerker A, Rudnicki M, Rosenkranz AR et al. (2012) The rapamycin-inhibitor rapamycin mediates proteinuria in nephrotoxic serum nephritis by activating the innate immune response. Am J Physiol Renal Physiol 303: 569-575.
8. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, et al. (2002) Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 8: 128-135.
9. Bonegio RG, Fuhro R, Wang Z, Valeri CR, Andry C, et al. (2005) Rapamycin ameliorates proteinuria-associated tubulointerstitial inflammation and fibrosis in experimental membranous nephropathy. J Am Soc Nephrol 16: 2063-2072.
10. Liern M, De Reyes V, Fayad A, Vallejo G (2012) Use of sirolimus in patients with primary steroid-resistant nephrotic syndrome. Nefrologia 32: 321-328.
11. Sarbassov DD, Ali SM, Sabatini DM (2005) Growing roles for the mTOR pathway. Curr Opin Cell Biol 17: 596-603.
12. Schuler W, Sedrani R, Cottens S, Häberlin B, Schulz M, et al. (1997) SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. Transplantation 64: 36-42.
13. Nashan B (2002) Review of the proliferation inhibitor everolimus. Expert Opin Investig Drugs 11: 1845-1857.
14. Rangan GK, Coombes JD (2007) Renoprotective effects of sirolimus in non-immune initiated focal segmental glomerulosclerosis. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 22: 2175-2182.
15. Ramadan R, Faour D, Awad H, Khateeb E, Cohen R et al. (2012) Early treatment with everolimus exerts nephroprotective effect in rats with adriamycin-induced nephrotic syndrome. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 27: 2231-2241.
16. Stratakis S, Stylianou K, Petrakis I, Mavroeidi V, Poulidaki R, et al. (2013) Rapamycin ameliorates proteinuria and restores nephrin and podocin expression in experimental membranous nephropathy. Clin Dev Immunol 2013: 941893.
17. Cruzado JM, Poveda R, Ibernon M, Diaz M, Fulladosa X et al. (2011) Low-dose sirolimus combined with angiotensin-converting enzyme inhibitor and statin stabilizes renal function and reduces glomerular proliferation in poor prognosis IgA nephropathy. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 26: 3596-3602.
18. Bagga A, Mantan M (2005) Nephrotic syndrome in children. Indian J Med Res 122: 13-28.

19. Moudgil A, Bagga A, Jordan SC (2005) Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions. Pediatr Nephrol 20: 1376-1381.

20. Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, et al. (2010) Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin J Am Soc Nephrol 5: 2207-2212.

21. Indian Society of Pediatric Nephrology, Gulati A, Bagga A, Gulati S, Mehta KP, et al. (2009) Management of steroid resistant nephrotic syndrome. Indian Pediatr 46: 35-47.

22. Ohashi R, Nakagawa T, Watanabe S, Kanellis J, Almirez RG, et al. (2004) Inhibition of p38 mitogen-activated protein kinase augments progression of remnant kidney model by activating the ERK pathway. Am J Pathol 164: 477-485.

23. Schieppati A, Remuzzi G (2003) Proteinuria and its consequences in renal disease. Acta Paediatr Suppl 92: 9-13.