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, antibiotic, antitumor, and antifungal properties that underscore the involvement of rapamycin signalling in various cellular functions. Activation of rapamycin phosphorylates p70 ribosomal S6 kinase (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 non 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 KB (NF-kB).

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-kB-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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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


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.


