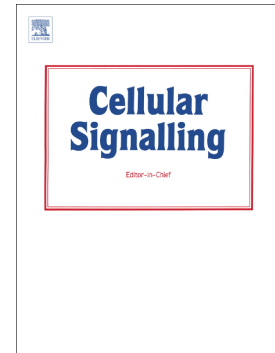


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Activation of renal profibrotic TGF β controlled signaling cascades by calcineurin and mTOR inhibitors

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Abbreviations: AP-1, activator protein 1; CNI, calcineurin inhibitor(s); ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; ERK, extracellular signal regulated kinase; FKBP, FK506 binding protein; JNK, Jun N-terminal kinase; LAP, latency-associated protein; MAPK, mitogen activated protein kinase; MC, mesangial cells; MEK, MAPK/ERK kinase; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor κ B; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF β , transforming growth factor β ; T β R, TGF β receptor

Abstract

The calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus represent potent immunosuppressive agents frequently used for solid organ transplantation and treatment of autoimmune disorders. Despite of their immense therapeutic benefits, residual fibrosis mainly in the kidney represents a common side effect of long-term therapy with CNI. Regardless of the immunosuppressive action, an increasing body of evidence implicates that a drug-induced increase in TGF β and subsequent activation of TGF β -initiated signaling pathways is closely associated with the development and progression of CNI-induced nephropathy. Mechanistically, an increase in reactive oxygen species (ROS) generation due to drug-

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