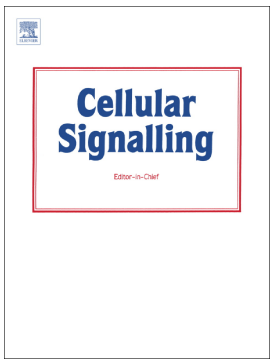

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Wolfgang Eberhardt, Usman Nasrullah, Josef Pfeilschifter

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

Wolfgang Eberhardt*, Usman Nasrullah, Josef Pfeilschifter

pharmazentrum frankfurt/ZAFES, Universitätsklinikum und Goethe-Universität, Frankfurt am Main, Germany

* Corresponding author:

Wolfgang Eberhardt, Ph.D.

pharmazentrum frankfurt/ZAFES
Klinikum der Johann Wolfgang Goethe-Universität Frankfurt am Main

Theodor-Stern-Kai 7

D-60590 Frankfurt am Main, Germany

Phone: +49 69 6301 6954
Fax: +49 69 6301 7942
e-mail: w.eberhardt@em.uni-frankfurt.de

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-κB, nuclear factor κB; ROS, reactive oxygen species; SOD, superoxide dismutase; TGFβ, transforming growth factor β; TβR, TGFβ 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 TGFβ and subsequent activation of TGFβ-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-