Targeting c-fms Kinase Attenuates Aristolochic Acid Nephropathy in Mice

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Background: Aristolochic acid nephropathy (AAN) is a progressive chronic kidney disease related to the use of Chinese herbal medicine and is characterized by extensive tubulointerstitial fibrosis and inflammation with macrophage infiltration. However, treatment of AAN remains ineffective. Thus, the present study aimed to develop a new therapeutic strategy for chronic AAN by targeting macrophages with a selective inhibitor of tyrosine kinase activity of macrophage colony-stimulating factor receptor (fms-I).

Methods: Chronic AAN was induced in C57BL/6 mice by intraperitoneal injection of aristolochic acid at a dose of 5 mg/kg every other day for 4 weeks. Fms-I in an optimal dose of 10 mg/kg twice daily (i.p) was given at the beginning of induction of AAN or at the established AAN on day 14. The therapeutic effect of fms-I on chronic AAN was examined at day 28.

Results: Treatment with fms-I largely suppressed F4/80 macrophage and CD3+ T cell infiltration and upregulation of proinflammatory cytokines (MIF, TNFα, MCP-1), resulting in protection against acute and chronic AAN by inhibiting 24-hour proteinuria, elevated levels of serum creatinine, upregulation of KIM-1, and progressive renal fibrosis including accumulation of α-SMA+ myofibroblasts and collagen I. Moreover, administration of fms-I to the established AAN at day 14 also halted the disease progression of chronic AAN at day 28. Further studies revealed that the therapeutic effect of fms-I on chronic AAN was associated with blockade of both NF-kB and TGF-β/Smad pathways.

Conclusion: Macrophages play a pathogenic role in the development of chronic AAN. Targeting macrophages with fms-I has therapeutic potential for chronic AAN.

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Effect of RGMb on Cyst Development in ADPKD

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Objective: Autosomal dominant polycystic kidney disease (ADPKD), an inherited disease characterized by massive enlargement of fluid-filled cysts in the kidney with an incidence rate of 1:1000–1:4000, is a common cause of renal failure. There is no effective therapy for ADPKD. Repulsive guidance molecule b (RGMb), a co-receptor for bone morphogenetic protein signaling and also a ligand for neogenin, is expressed at the epithelial cells in kidney. RGMb has been reported to induce apoptosis in renal tubular cells. The aim of this study was to determine if RGMb played a role in ADPKD development.

Methods: MDCk cyst model, embryonic kidney cyst model and Pkd2fl/f−/−; Ksp-Cre PKD mouse model were used to assess the effect of RGMb in ADPKD. Results: The experimental results showed that RGMb overexpression inhibited MDCK cyst formation in 3D collagen matrix. Compared with control MDCK cells whose cysts contained a single lumen with forskolin stimulation, RGMb-MDCK cells sprawled into the colonies without cystic structure. A few of identifiable cysts contained multiple smaller lumens and thicker walls. H&E staining showed that RGMb null kidneys had interstitial hyperplasia and decreased tubular structures, especially in the boundary area of renal cortex and medulla. DBA staining revealed less branched uretic bud in E13.5 RGMb null mouse embryonic kidney, which suggested that deficiency of RGMb would retard uretic bud branching and negatively modulate collecting duct development. Western blot analysis exhibited increased phosphorylation of Smad1/5/8 in RGMb-MDCK cells, indicating BMP-Smad1/5/8 pathway was important in ADPKD development.

Conclusion: Our data suggest that RGMb plays an important role in kidney development and inhibits ADPKD by regulating BMP-Smad1/5/8 pathway.

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Bortezomib Before, During and After Autologous Hematopoietic Stem Cell Transplantation in Patients with Newly Diagnosed AL Amyloidosis

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Objective: We demonstrated that the outcome of treating AL amyloidosis with bortezomib-dexamethasone (BD) induction followed by autologous hematopoietic stem cell transplantation (ASCT) was superior to the outcome of the ASCT treatment alone previously. To further improve the hematologic response rate, we conducted a prospective trial of bortezomib before, in and after ASCT in patients with newly diagnosed AL amyloidosis.

Methods: Newly diagnosed AL amyloidosis patients who met the criteria of ASCT could be included. Treatment schedule consisted of two cycles of BD induction therapy (bortezomib 1.3 mg/m² and dexamethasone 40 mg/d on days 1, 4, 8 and 11 followed by 10 days of rest), ASCT treatment (the conditioning regimen consisted of melphalan and bortezomib, the dose of bortezomib before, in and after ASCT in patients with newly diagnosed AL amyloidosis. Further cycles of bortezomib treatment (with a dose of 1.6 mg/m² on days 1 and 8 of the cycle) will be conducted as consolidation therapy after ASCT. Hematologic response, tolerability and survival were observed.

Conclusion: Macrophages play a pathogenic role in the development of chronic AAN. Targeting macrophages with fms-I has therapeutic potential for chronic AAN.