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Autotaxin Inhibition Alleviates Kidney Fibrosis and Improves Kidney Function

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Objectives : Autotaxin (ATX) is an enzyme that converts lysophosphatidylcholine into lysophosphatidic acid (LPA) and choline. LPA receptor(LPAR) 1-ligand binding is known to promote fibroblast proliferation, contributing to fibrosis progression. Given that ATX is also overexpressed in kidney, lung, and liver fibrosis, and its inhibition has been explored as a potential strategy to regulate fibrosis. However, research on ATX in kidney remains limited. This study aims to evaluate whether a newly developed ATX inhibitor (ATXi) has a kidney protective effect in chronic kidney disease (CKD).
Methods : In vivo study, CKD model was induced by administering a single dose of folic acid (FA, 250 mg/kg) in C57BL/6 mice. Experiment was conducted with a total of three groups: control group, FA group, and FA+ATXi group. ATXi was administered orally at a dose of 30 mg/kg once daily. Kidney function was evaluated by measuring blood urea nitrogen (BUN) and cystatin C, while histological changes were assessed via immunostaining. We also analyzed the effect of the ATXi on the expression of each LPA receptor (LPAR) type using qPCR. In vitro study, to evaluate whether the ATXi suppresses fibroblast proliferation, we used NRK-49F (rat kidney fibroblast). Cells were treated with TGF-β and ATXi for immunofluorescence analysis.
Results : In FA-induced CKD mice, administration of the ATXi improved kidney dysfunction, indicated by BUN and cystatin C, reduced tubular atrophy and fibrosis, and suppressed marker upregulations such as α-SMA and collagen 1A1. Additionally, ATXi inhibited LPAR1 and LPAR6 mRNA levels, which were elevated in FA mice. In vitro, the ATXi concentration of 20μM effectively suppressed TGF-β-induced NRK-49F cell proliferations. Immunofluorescence analysis further confirmed that ATXi effectively attenuated TGF-β-induced overexpression of α-SMA and Ki-67 in NRK-49F cells.
Conclusions : This study demonstrated that ATXi improves kidney function and reduces kidney fibrosis, suggesting that ATXi is a novel therapeutic agent for kidney fibrosis.