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Antibiotics-induced intestinal microbiota depletion can attenuate acute kidney injury transition to chronic kidney disease via NOX2 and trimethylamine-N-oxide inhibition

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Objectives: Intestinal microbiota and their metabolites affect systemic inflammation and kidney disease outcomes. We aimed to investigate the key metabolites associated with acute kidney injury (AKI)-to-chronic kidney disease (CKD) transition, and the effect of antibiotics-induced microbiota depletion (AIMD) on this transition.

Methods: Among 152 patients with AKI, admitted to intensive care unit and underwent continuous renal replacement therapy (CRRT), 59 plasma metabolites were measured. The risk of AKI-to-CKD transition was evaluated. AKI-to-CKD transition murine model was established 4 weeks after unilateral ischemia-reperfusion injury (IRI), and effects of AIMD on gut microbiome, metabolites, and the pathological response related with CKD transition was explored. Human proximal tubular epithelial cells were challenged with CKD-transition related metabolite and inhibitory effects through NOX2 signals was tested.

Results: Plasma trimethylamine N-oxide (TMAO) was associated with increased risk for AKI-to-CKD transition [adjusted OR 4.437 (95% CI 1.298-15.198), P-value = 0.017] in clinical metabolomics study. AKI-to-CKD transition mice with AIMD showed significantly decreased apoptosis and kidney tissue fibrosis. Expression of TGFβ, periostin, IL-18, macrophage infiltration, and tubular NOX2 decreased after AIMD. AIMD inhibited unilateral IRI induced metabolite increase of betaine, trimethylamine, and TMAO. In vitro, TMAO induced fibrosis response with NOX2 activation, and NOX2 inhibition successfully attenuated apoptosis, inflammation, and fibrosis with suppression of G2/M arrest.

Conclusions: TMAO is a key metabolite associated with AKI-to-CKD transition. NOX2 activation is identified as a key regulator of TMAO-related AKI-to-CKD transition both in vivo and in vitro model. AIMD successfully inhibited gut-microbiome originated metabolites including TMAO and attenuated inflammation, apoptosis, G2/M arrest, and fibrosis with NOX2 suppression.