



The role of TMAO in renal interstitium and chronic kidney disease

av

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Abstract

Chronic kidney disease (CKD) is defined by progressive kidney damage and loss of renal function over time. Its global prevalence in 2022 was more than 10% of the world's population and this is steadily increasing. Several mouse and clinical studies found that trimethylamine N-oxide (TMAO), a uremic toxin generated through gut microbiota metabolism, is associated with CKD. However, these studies do not elucidate the role of TMAO in CKD at the cellular level. To fill this knowledge gap, this thesis investigates the role of TMAO in the renal tubulointerstitium and CKD. We found that TMAO promotes cell proliferation and collagen production in renal fibroblasts via PERK/Akt/mTOR pathway, NLRP3, and caspase-1 signaling and enhances TNF- α mediated proliferation of renal fibroblasts and collagen production via Akt/mTOR and ERK. Furthermore, TMAO enhances TNF- α -mediated secretion of inflammatory proteins known to be associated with kidney disease. In addition, we found that TMAO in proximal tubular cells decreases albumin uptake and megalin expression via PI3K and ERK signaling. The effect of TMAO on megalin was counteracted by candesartan, dapagliflozin, and enalaprilat, which are widely used anti-proteinuric drugs. In patients with CKD, we identified significant concentration differences and correlations between TMAO or its precursors and urine megalin, urine lysine, urine albumin and markers of tubular damage compared to healthy controls. The results of this thesis can form the basis of future research to further elucidate the contribution of TMAO to CKD pathogenesis and progress and to identify new therapeutic targets for CKD.

Keywords: TMAO, chronic kidney disease, renal fibroblasts, proximal tubular cells, proliferation, collagen, fibrosis, inflammation, TNF- α , megalin, proximal tubular cells, albumin uptake, lysine, albuminuria

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