Title	5-aminolaevulinic acid with sodium ferrous citrate alleviated kidney injury and fibrosis in a unilateral ureteral obstruction model
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論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Ｎａｍｅ	馬 快（MA KUAI）
論文題名 Title	5-aminolaevulinic acid with sodium ferrous citrate alleviated kidney injury and fibrosis in a unilateral ureteral obstruction model　（5-アミノレブリン酸とクエン酸第一鉄ナトリウムは片側性尿管閉塞モデルにおいて腎障害と線維化を緩和した）

論文内容の要旨

〔目　的(Objective)〕

This study aimed to investigate the potential therapeutic effects of 5-aminolaevulinic acid (5-ALA) combined with sodium ferrous citrate (SFC) on kidney injury and fibrosis in a mouse model of unilateral ureteral obstruction (UUO)-induced chronic kidney disease (CKD).

〔方法ならびに成績(Methods/Results)〕

Methods: A murine UUO model was used to mimic human CKD. The mice received daily intragastric administration of 5-ALA/SFC for 7 and 14 consecutive days. Serum creatinine (Cr) and blood urea nitrogen (BUN) levels and histological evaluations were performed to assess the renal function parameters underlying 5-ALA/SFC treatment in the UUO model. Differentially expressed genes (DEGs) were analyzed by RNA sequencing (RNA-Seq), and the results were validated by quantitative real-time PCR (qRT-PCR). The severity of renal fibrosis was evaluated using Sirius red and Masson's trichrome (MT) staining techniques, while the expression of fibrosis-related genes was examined using western blotting and immunohistochemistry.

Results: Our findings demonstrated that 5-ALA/SFC treatment improved UUO-induced renal dysfunction, attenuated tubular damage, and significantly reduced serum Cr and BUN levels as well as the mRNA expression and secretion of pro-inflammatory and pro-apoptotic cytokines in kidney tissues. Furthermore, 5-ALA/SFC suppressed renal tissue fibrosis and downregulated the mRNA and protein expression of fibrosis-related genes. Notably, treatment with 5-ALA/SFC led to the significant upregulation of protein expression levels of PPAR gamma-coactivator-1α (PGC-1α), indicating its role in inhibiting inflammation and fibrosis through the activation of the PGC-1α signaling pathway.

〔総　括(Conclusion)〕

5-ALA/SFC exhibits renoprotective effects in UUO-induced CKD by attenuating inflammation, apoptosis, and suppressing renal fibrosis. These findings suggest a specific renal protective mechanism for 5-ALA/SFC, highlighting its potential as a novel therapeutic agent for human CKD treatment.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

This study aimed to investigate the potential therapeutic effects of 5-aminolaevulinic acid (5-ALA) combined with sodium ferrous citrate (SFC) on kidney injury and fibrosis in a mouse model of unilateral ureteral obstruction (UUO)-induced chronic kidney disease (CKD). A murine UUO model was used to mimic human CKD. The mice received daily intragastric administration of 5-ALA/SFC for 7 and 14 consecutive days. Differentially expressed genes (DEGs) were analyzed by RNA sequencing (RNA-Seq), and the results were validated by quantitative real-time PCR (qRT-PCR). Our findings demonstrated that 5-ALA/SFC treatment improved UUO-induced renal dysfunction, attenuated tubular damage, and significantly reduced serum Cr and BUN levels as well as the mRNA expression and secretion of pro-inflammatory and pro-apoptotic cytokines in kidney tissues. Furthermore, 5-ALA/SFC suppressed renal tissue fibrosis and downregulated the mRNA and protein expression of fibrosis-related genes.

The primary feature of UUO is tubular injury as a result of obstructed urine flow. Stressed and injured tubular cells release inflammatory mediators that can exacerbate tubular damage either directly or indirectly by recruiting inflammatory cells, including macrophages. Inflammation plays a pivotal role in the progression of renal fibrosis, with activated macrophages assuming critical functions. In human studies, the degree of macrophage infiltration has been shown to correlate with the severity of kidney injury in patients with glomerulonephritis, suggesting their pathogenic role in kidney diseases. Macrophages infiltrate the renal interstitium, producing cytokines and releasing inflammatory mediators that induce tissue inflammation and subsequent renal fibrosis. The release of pro-inflammatory cytokines further amplifies the inflammatory cascade, activates pro-fibrotic factors, promotes ECM deposition, and facilitates epithelial-to-mesenchymal transition. Interstitial fibroblasts can be activated and transformed into myofibroblasts, which are characterized as chronically activated fibroblasts that express a-SMA. Renal fibrosis can be quantified by assessing the distribution of renal collagen using Masson staining or Sirius red staining. These methods effectively identify collagen types I, III, and IV, with type IV being the predominant component of the tubular basement membrane. TGF-β is the main factor that activates fibroblasts to produce ECM and myofibroblasts are the principal cells that produce fibrotic ECM. The activation and reprogramming of macrophages are particularly important, as they not only regulate the inflammatory response but also promote the transformation of myofibroblasts. This transformation is facilitated by the secretion of growth factors, such as TGF-β, which significantly contributes to the progression of fibrosis and the systemic decline in renal function.

This research is worth being granted a doctoral degree (medicine).