THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-1086

tRF-Ala-CGC-023 Aggravates Renal Tubular Cell injury by Inhibiting MFN2 Expression and Promoting Mitochondrial Damage in Mouse AKI model

Xian Xie[1], Hao Zhang[1], Wei Zhang[1]
[1]Department of Internal Medicine, The Third Xiangya Hospital, Central South University, China
[2]Department of The Critical Kidney Disease Research Center, Central South University, China

Objectives : Acute kidney injury (AKI) is a severe clinical condition lacking effective treatments and early diagnostics. tRNA-derived small RNA fragments (tRFs) are generated from tRNAs under stress conditions and exert various biological effect in gene expression, but their roles in AKI are unclear. This study investigates the role and potential mechanisms of tRF-Ala-CGC-023 in AKI.
Methods : tRFs sequencing were confirmed on mouse renal tissues from ischemia-reperfusion-induced AKI model. tRF levels in renal tissues and tubular epithelial cells (TECs) were measured via qRT-qPCR. In both IRI and cisplatin induced AKI mouse models, tRF-Ala-CGC-023 mimic/inhibitor transfection simulated in vivo and in vitro effects. Mechanism investigation assays included RNA blotting, RNA immunoprecipitation (RIP), dual-luciferase reporter assays, protein blotting, qPCR, ELISA, and rescue experiments.
Results : tRF-Ala-CGC-023, a 30-nt tRF from 5' tRNA, significantly increased in IRI-AKI renal tissues and CIS-AKI TECs. Overexpressing tRF-Ala-CGC-023 promoted apoptosis, upregulated cleaved-caspase3, and downregulated BCL2. It exacerbated mitochondrial damage, decreased mitochondrial fusion protein MFN2, and increased mitochondrial fission protein DRP1. Electron microscopy showed severer mitochondrial damage, including cristae dissolution, vacuolization, and reduced quantity. tRF-Ala-CGC-023 increased MDA content, while its inhibition improves the aforementioned damage. RIP results demonstrate the recruitment of tRF-Ala-CGC-023 by AGO in TECs, with mRNA sequencing revealing significant effect of MFN2 expression. Dual-luciferase assays indicated tRF-Ala-CGC-023 reduced MFN2 mRNA levels via binding its 3'UTR. Overexpressing MFN2 reversed tRF-Ala-CGC-023-induced effect, and siRNA-mediated AGO knockdown eliminated tRF-Ala-CGC-023's inhibitory effect on MFN2.
Conclusions : This study identifies a novel tRNA-derived fragment, tRF-Ala-CGC-023, involved in the progression of AKI. tRF-Ala-CGC-023 is upregulated in AKI models induced by ischemia-reperfusion and CIS and exacerbates TECs damage. It primarily inhibits MFN2 expression through the formation of AGO/RISC complexes, thereby aggravating mitochondrial damage and cell apoptosis, thus promoting AKI progression.