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

Abstract Submission No.: A-0595

Inhibition of PTP1b via milk exosome-mediated siRNA delivery is a novel therapeutic approach for acute kidney injury

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Objectives : Protein tyrosine phosphatase-1B (PTP1b) plays a crucial role in regulating insulin, leptin sensitivity, and inflammatory responses, rendering it a promising therapeutic target for diseases like diabetes, obesity, and neuroinflammation. Despite its well-established significance in various conditions, its involvement in kidney disease remains largely unexplored.
Methods : In this study, we developed an innovative siRNA delivery system using exosomes derived from milk to encapsulate PTP1b siRNA (PTP1b siR@mExo), with the aim of investigating its impact on acute kidney injury (AKI). C57BL/6 mice were subjected to bilateral ischemia reperfusion injury (IRI), and PTP1b siR@mExo was pretreated at -6, -4, and -2 hrs.
Results : In vitro studies demonstrated better cellular uptake of Cy3-labeled PTP1b siR@mExo by human proximal tubule cells (HK2) with superior stability compared to treatment with PTP1b siRNA alone. Moreover, in mice, PTP1b siR@mExo exhibited highly efficient kidney delivery, reaching maximum absorption at 2 hours, sustaining elevated levels up to 48 hours, followed by accumulation in the liver and spleen, indicating milk exosomes as a novel siRNA delivery system. PTP1b expression was notably observed on tubules and glomeruli, and pre-treatment with PTP1b siR@mExo in IRI effectively reduced PTP1b levels in the kidney. This reduction was accompanied by decreased expression of inflammatory cytokines (TNF-α, IL-6, IL-1β), alleviated endoplasmic reticulum stress (CHOP), diminished DMAP signal (HMGB1), and a significant improvement in renal function.
Conclusions : Our results demonstrated that milk-derived exosomes, with superior structural stability, serve as efficient carriers for siRNA, and showed the efficacy of milk-derived exosomes carrying PTP1b siRNA in treating IRI. The inhibition of PTP1b emerges as a promising novel therapeutic target for AKI, providing a new perspective for further exploration and intervention strategies in kidney disease.