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Targeting the GATM Metabolic Checkpoint via Extracellular Vesicles to Mitigate the AKI to CKD Transition and Fibrosis in Kidney Transplantation

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Objectives : Kidney transplantation is the definitive treatment for end-stage kidney disease, but long-term graft survival is often threatened by borderline T-cell-mediated rejection (BDR) and ischemia-reperfusion injury (IRI). These insults are major drivers of progressive allograft fibrosis and functional decline.
Methods : We analyzed 156 urine samples from a prospective cohort of 51 BDR patients, comparing those with stable versus declining graft function. NMR-based untargeted metabolomics was used to identify key differential metabolites. To elucidate the underlying mechanism, integrated single-cell RNA sequencing was performed on a murine model of unilateral IRI (uIRI) to map cell-specific metabolic signatures. Finally, the therapeutic potential of GATM-enriched extracellular vesicles (GATM-EVs) was evaluated in stress-induced HK-2 cells and a 2-week uIRI model representing the AKI to CKD transition.
Results : Untargeted metabolomic profiling of the prospective cohort revealed that a marked downregulation of urinary guanidinoacetate (GAA) is a primary metabolic signature in patients with subsequent graft dysfunction. Integrated single-cell transcriptomics localized GATM, the rate-limiting enzyme for GAA synthesis, exclusively to proximal tubule (PT) cells, where its expression declined sharply following uIRI in correlation with injury severity. In vitro experiments using HK-2 cells demonstrated that oxidative stress (H2O2) and hypoxia (CoCl2) significantly suppressed GATM expression, a process that was effectively reversed by GATM-EV treatment in a dose-dependent manner. In the uIRI model, GATM levels plummeted within 48 hours and failed to recover to baseline by day 14, marking a critical point in the AKI to CKD transition. Administration of GATM-EVs markedly attenuated histological fibrosis as shown by Sirius Red and Masson's Trichrome staining, significantly reduced the expression of pro-fibrotic markers such as COL1A1, and successfully restored GATM protein levels within the kidney.
Conclusions : GATM deficiency serves as a critical metabolic checkpoint driving the AKI to CKD transition and chronic kidney fibrosis.GATM-EV administration can replenish essential metabolic capacity and mitigate post-ischemic fibrosis.

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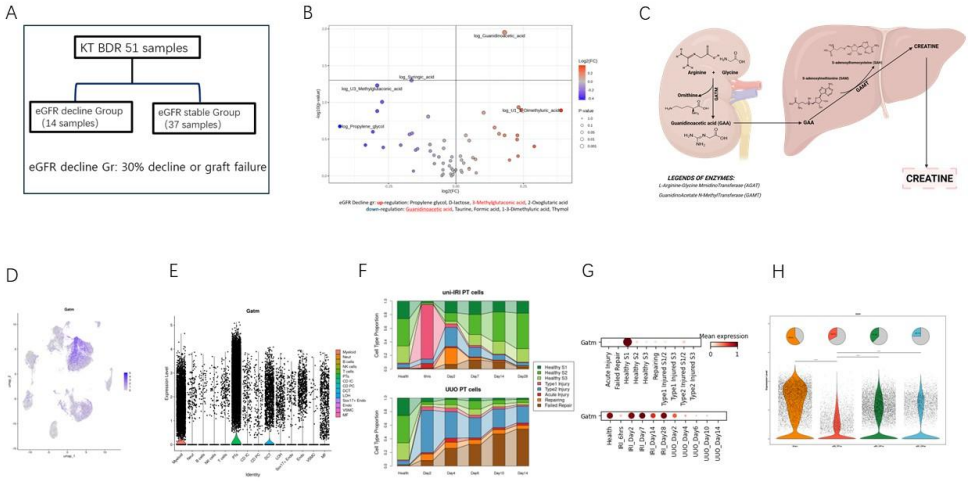

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