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AI-Based Drug Repositioning Technologies: The Role of 17-DMAG in Mitigating Kidney Fibrosis by Targeting METTL3 mRNA Synthesis

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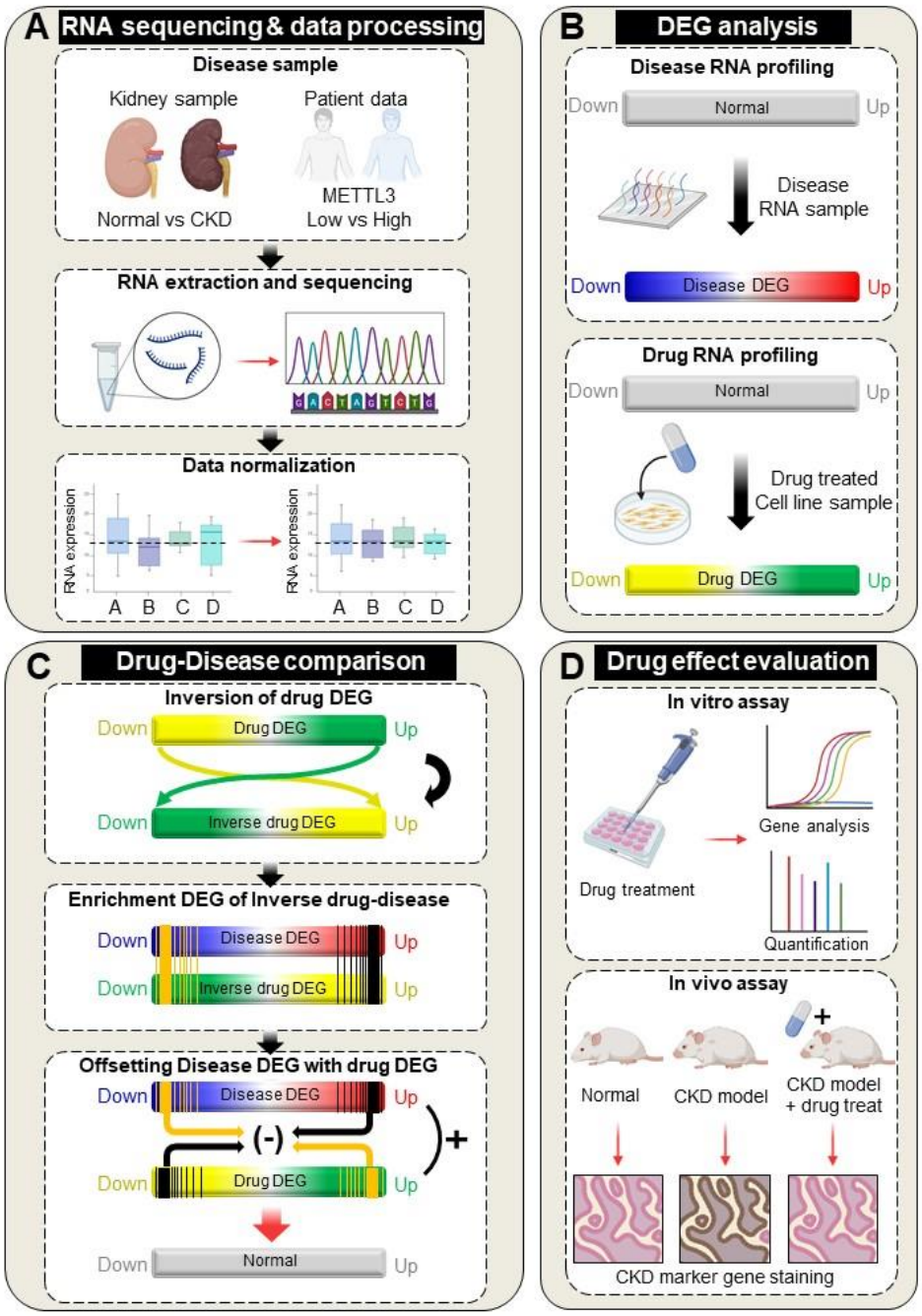
Objectives : The role of N6-methyladenosine (m6A) modifications, facilitated by methyltransferase-like 3 (METTL3), is significantly prominent in the progression of kidney fibrosis, positioning METTL3 as a viable therapeutic target. Leveraging differential gene expression (DEG) analysis, our study has identified a potential inhibitor of METTL3. This research is dedicated to examining the effectiveness of this inhibitor in reducing kidney fibrosis, thus proposing it as an innovative treatment approach.
Methods : Potential METTL3 inhibitors were selected according to enrichment score from disease DEG and drug DEG results. For in vitro experiments, ACHN and H460 cell lines were employed. The unilateral ureteral obstruction (UUO) mouse was selected as in vivo CKD model. Assessments of protein and mRNA levels were conducted via Western blotting and quantitative real-time polymerase chain reaction, respectively. To examine fibrosis and METTL3 expression in tissues, Sirius Red staining and immunohistochemistry (IHC) were applied. Ultrasonography was utilized to evaluate kidney parenchymal thickness and blood flow.
Results : 17-Dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), a heat-shock protein (HSP) 90 inhibitor, was identified as a potent METTL3 inhibitor. Comparative analyses between HSP90 N-terminal and C-terminal binding inhibitors (17-DMAG and Novobiocin respectively), revealed that only N-terminal binding inhibitors decreased METTL3 levels, indicating that METTL3 expression is not directly altered by HSP90 inhibition. Co-treatment of Actinomycin-D and 17-DMAG hindered the recovery of METTL3 levels following mRNA degradation, suggesting that 17-DMAG impedes the de novo synthesis of METTL3 mRNA. In the UUO model, 17-DMAG was shown to mitigate kidney fibrosis, decrease the expression of TGF-β-induced fibrosis markers, lower tissue METTL3 expression, and alleviate impairments in blood flow and parenchymal thickness.
Conclusions : 17-DMAG serves as a METTL3 inhibitor by obstructing the de novo synthesis of METTL3 mRNA. This dual action contributes to the attenuation of kidney fibrosis in the UUO mouse model, underscoring the potential of 17-DMAG as a novel therapeutic option for treating kidney fibrosis

23.11.14 METTL3 figure.jpg


A RNA sequencing & data processing
Disease sample
Kidney sample
Patient data
Normal vs CKD
METTL3
Low vs High
RNA extraction and sequencing
Data normalization
RNA expression
A B C D
B DEG analysis
Disease RNA profiling
Down
Normal
Up
Disease RNA sample
Disease DEG
Drug RNA profiling
Drug treated Cell line sample
Drug DEG
C Drug-Disease comparison
Inversion of drug DEG
Inverse drug DEG
Enrichment DEG of Inverse drug-disease
Offsetting Disease DEG with drug DEG
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D Drug effect evaluation
In vitro assay
Drug treatment
Gene analysis
Quantification
In vivo assay
Normal
CKD model
CKD model + drug treat
CKD marker gene staining