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Identification of Mitochondria-related Genes in Renal Tubular Epithelial Cells of Chronic Kidney Disease

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Abstract: *Background*: Mitochondria treatment has a broad application prospect in relieving CKD. This study's objective was to employ bioinformatics and experimental strategies to identify and validate the Mitochondria-related genes and CKD association induced by TGF-β1. *Methods*: 266 differentially expressed genes (DEGs) were identified in GSE66494 database from GEO. Then we picked 1136 mitochondria-related genes which were from Mitocart3.0 database for obtaining intersecting genes between the former and the latter. Subsequently, the intersecting genes were analyzed by Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) axis enrichment assessments and Gene Set Enrichment Analysis (GSEA). Furthermore, we did Immune invasion assessment and a Protein-Protein Interaction (PPI) axis was conducted. Finally, the gene expression levels of some intersecting genes with the most abundant connections in control and TGF-β1 groups, as evidenced by reverse transcription-quantitative polymerase chain reaction (RT-QPCR) analysis. *Results*: 26 intersecting genes among DEGs and mitochondria-related genes were identified. GO and KEGG enrichment analysis demonstrated biological processes namely small molecule catabolic, response to peptide hormone, hormone metabolic, organic acid catabolic and carboxylic acid catabolic processes are significantly affected, then a lot of intersecting genes were mainly concentrated in processes like the small molecule catabolic, response to peptide hormone, hormone metabolic, organic acid catabolic processes and so on. Gene Set Enrichment Analysis demonstrated that DEG was concentrated in mitochondrial related gene expression, mitochondrial autophagy, mitochondrial electron chain transmission, Jak/Stat signaling pathway regulation, histone H2A ubiquitination, and cell cycle pathways, Protein-Protein Interaction (PPI) network demonstrated these intersecting genes interacted with each another. Finally, via RT-QPCR evaluation, we revealed that the four gene expressions with the most connections were substantially reduced, relative to the normal group. *Conclusion*: In conclusion, the present study aimed to indicated that during the process of a global transcriptional reprogramming in TGF-β1 induced CKD, mitochondria-related genes plays a significant role. Mitochondria-related genes were strongly upregulated by treatment and then to reduce CKD.

Keywords: Mitochondria; CKD; Bioinformatics analysis; Renal tubule; TGF-β1

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1. Introduction

Chronic renal disease (CKD), which can lead to functional organ failure. It is an important global public health issue, both morbidity and mortality have increased in recent years [1,2]. Chronic kidney disease (CKD) was referred to persistent renal damage and/or renal insufficiency, with strongly elevated global morbidity and mortality, resulting in a weighty social burden. However, at present, there is no good treatment plan for the late stage of CKD, which mainly depends on dialysis and kidney transplantation. however, dialysis cannot stop the progress of the disease, and kidney transplantation resources are scarce. In addition, late CKD causes kidney failure and increases cardiovascular disease (CVD) risk. According to studies, CVD is the major contributor of mortality among CKD patients [3,4]. Although the prevention, diagnosis and therapy of CKD obtained some advancement, the disease remains a significant threat to world public health. Therefore, demanding to develop more practical schemes for CKD as soon as possible.

Mitochondria, also known as "power chambers", are very active double membrane organelles. Mitochondria are the main energy source for most cells. Adenosine triphosphate (ATP) is synthesized by oxidative phosphorylation [5]. Considering their primary function in energy metabolism and cell death, they critically modulate life cycle of organisms [6]. Proximal renal tubule are particularly vulnerable to mitochondrial toxicity because they rely mainly on aerobic respiration to provide energy [5]. All filtered nutrients are reabsorbed by the kidney's proximal tubule, which also secretes certain toxins and most electrolytes. Reabsorbing nutrients and electrolytes require a lot of energy, so the renal tubule is one of the human tissue human tissues in the body with the largest mitochondrial content. The organ with the highest mitochondrial density is the kidney. Energy crises may result from mitochondrial malfunction. Mitochondrial abnormalities in renal tubules can cause cell death, inflammation, or epithelial shrinkage, which can accelerate the progression of CKD [7,8].

Bioinformatics is an interdisciplinary method, which combines molecular biology analysis and technological innovation. It is increasingly becoming an important approach to clarify the underlying signaling network of disease [9]. Transforming growth factor-β (TGF- β) is a diverse functional regulating factor, TGF-β1 is a secondary subtype of TGF-β family, its amino acid homology is 70-82%, and has similar activity in different systems [10]. TGF-β1 can damage the kidney in many ways and play a pathogenic role [11]. Therefore, TGF-β1 is widely used in the establishment of CKD model. Bioinformatics was employed in this study to analyze the GSE66494 dataset from the Gene expression General Table (GEO) database, including the CKD group and control group (49 discovery CKD,5 discovery control, 5 validation CKD and 3 validation control).

Therefore, based on the role of mitochondria in kidney, we aimed to elucidate and verify the important association of mitochondrial genes in CKD therapy, in order to find the accurate targeted molecular therapy of CKD.

2. Materials and methods

2.1. Bioinformatics and experimental design

CKD-related gene expression profiles are obtained from the GEO webpage of the National Biotechnology Information Center (NCBI). There are 61 samples in GSE66494, which is consisted of 49 discovery CKD,5 discovery control,5 validation CKD and 3 validation control. Differentially expressed genes (DEGs) screening utilized R (R 4.2.3). Using LIMMA package to perform normalization and log2 transformations for the dataset. To use Unpaired Student's *t*-test to acquire corresponding *p*-values for gene symbols based on the prespecified threshold, $p < 0.05$ and |log [fold-change (FC)] | > 1 were considered statistically significant, thus the DEGs

between discovery and control groups were confirmed. The heatmap, volcano map and violin map were drawn by using the R software.

2.2. Screening intersecting genes

This study screened 266 DEGs by using R software, in order to obtain genes that intersect with mitochondria, we picked 1136 genes related to mitochondria which were from Mitocart 3.0 database. Then comparing DEGs and mitochondria-associated genes were assessed employing R to obtain intersecting genes, and display them using Venn diagrams [12].

2.3. Functional enrichment analysis (FEA)

Finally, via Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment axis assessments results were acquired. Using enrichment for gene function analysis. The GO terms analysis included biological process (BP), molecular function (MF), cellular component (CC).

2.4. Gene set enrichment analysis (GSEA)

GSEA was conducted as mentioned earlier against the gene sets from intersecting genes. All intersecting genes were then enriched and sequenced according to Log FC from large to small. This study then visualized the results of GSEA by employing R.

2.5. Protein-protein interaction (PPI) axis generation and evaluation

Applying the screening implement STRING database to assess the PPI axis (STRING;http://string-db.org). Via analyzing the functional interactions between proteins for demonstrating the relationships among intersecting genes. Cytoscape software (http://cytoscape.org/) was utilized to visualize the interactions and generate PPI axis.

2.6. Immune infiltration analysis

The proportion of DEGs and 22 forms of immune cells in four groups were detected using the Cibersort. Such as macrophage series, plasma cells, eosinophils, neutrophils and so on. In the end, we probed the association between DEGs and immune cells.

2.7. Cell culture

Acquired HK-2 human proximal tubular cells from the Procell Life Science &Technology Co. Culturing HK-2 cells in medium (added 10% FBS and antibiotics) in an atmosphere which contains 5% carbon dioxide and 95% humidified air at 37 °C. For experiments, HK-2 cells were separated into two cohorts: control (untreated) treatment and experimental (add 10 ng/ml recombinant human TGF-β1 to the cells for 48 hours).

2.8. Transmission electron microscope

The cell precipitates were collected by centrifugation, removed from the culture medium and fixed with electron microscope solution, and then dehydrated and embedded at room temperature. The cells were polymerized in an oven at 60 ℃ for 48 hours, and finally dyed and dried at room temperature overnight. Using transmission electron microscope to observe and collect image information to observe the ultrastructural changes of mitochondria in cells.

2.9. Reverse transcription-quantitative polymerase chain reaction (RT-QPCR)

In light of the producer's instructions, extract with RNA extract (Trizol Reagent:Lifetech 15596026), reverse transcribe the total RNA (2 μ g) into cDNA using reverse transcriptase kit [FastKing RT Kit (With gDNase) FastKing cDNA first chain synthesis kit: KR116], and for qPCR, use premixed solution (Taq Pro Universal SYBR qPCR Master Mix: Vazyme Q712-02). Then, we employed Biosystems 7500 Real-Time PCR System for all RT-qPCR studies. Finally, calculated relative gene profiles via the 2-ΔΔCt formula. **Table 1** lists the primer sequences.

Table 1. Primer sequences

Sequence	Name	Length (bp)
TTGCCCTCAACGACCACTTT	GAPDH(H)-F	120
TGGTCCAGGGGTCTTACTCC	GAPDH(H)-R	
GACAACACGGGCTATGAC	D2HGDH(H)-F	87
TGGACACAAGATGGACAC	D2HGDH(H)-R	
TGAGGAAGCAGCAGAATT	GRHPR(H)-F	75
ACGACGATGAAATCAGATTG	GRHPR(H)-R	
TGAGGAGGAACTTAACACTAACA	HAO2(H)-F	83
GCTGATAGGAGTCATCTGGAA	HAO2(H)-R	
TATGGAGAATGTGTATGAC	HMGCS2(H)-F	122
TACGGTATGATGTGTAAC	HMGCS2(H)-R	

2.10. Statistical analysis

All data analyses employed SPSS. Presented data are mean value ± standard deviation of three independent experiments. Using Unpaired Student's *t* test in order to analyzing gene expression profiles of specimens. Significance was set at $p < 0.05$.

3. Results

3.1. Screening of DEGs

As shown in **Figure 1(A)**, according to the preset standard {$p < 0.05$ and |log [fold-change (FC)] | > 1}, 266 DEGs were determined which include 29 highly expressed and 237 scarcely expressed genes, and as demonstrated in **Figure 1(B)** that the clustering analysis demonstrated these DEGs could clearly express the control samples and TGF-β1 samples. In order to obtain genes that intersect with mitochondria, we picked 1136 genes related to mitochondria which were from Mitocart3.0 database. Then comparing differentially expressed genes (DEGs) and mitochondria-associated genes to obtain 26 intersecting genes as shown in **Figure 1(C)**.

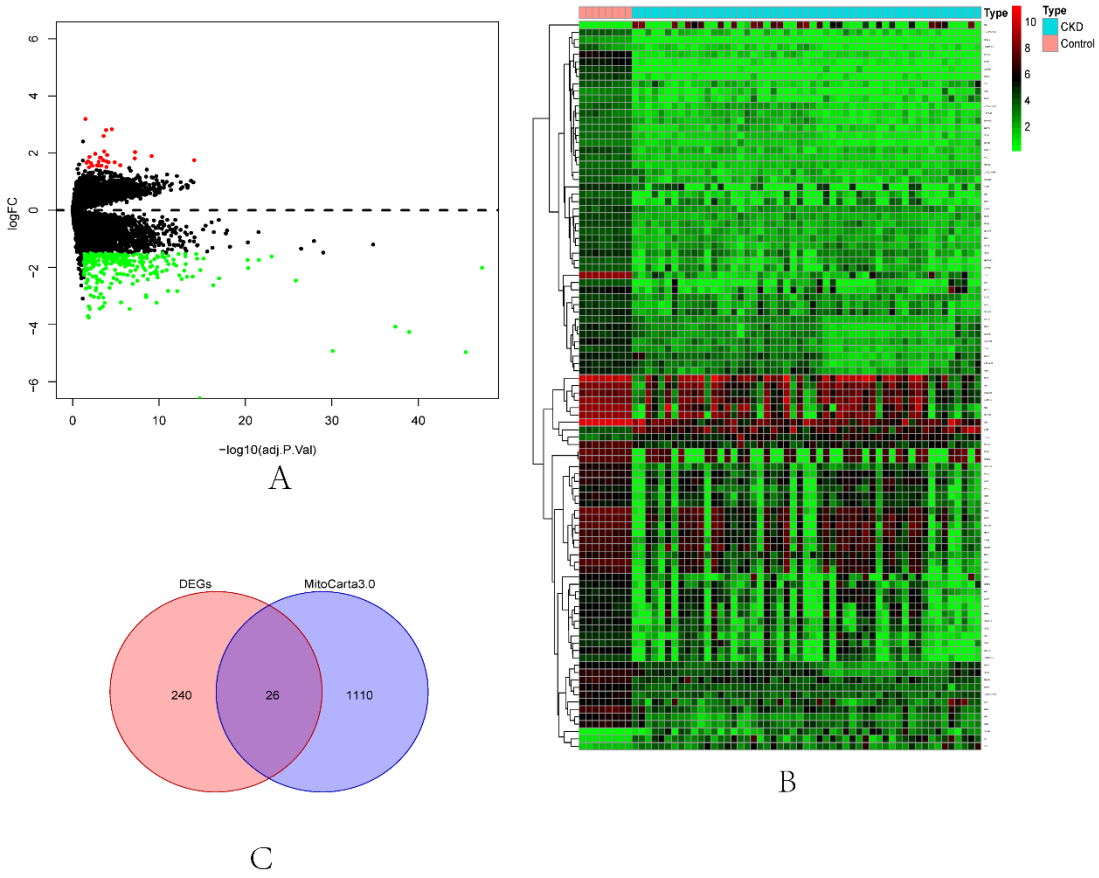

Figure 1. Differential expression analysis and mitochondrial related genes. (A, B) The heatmap and volcanic map for differential expression analysis of the GSE66494; (C) Genes related to mitochondria in differential genes.

3.2. FEA

Exploring the physiological relevance of these intersecting genes, using R software for building GO and KEGG enrichment assessments. GO evaluation returned abundant messages according to the MF, BP, and CC of intersecting genes. As shown in **Figure 2(A)**, the following biological progresses were conspicuously affected: small molecule catabolic, response to peptide hormone, hormone metabolic, organic acid catabolic, carboxylic acid catabolic processes and so on. The most abundant cellular component terms were apical part of cell, secretory granule lumen, cluster of actin−based cell projections, cytoplasmic vesicle lumen and so on. The most abundant molecular function terms included glycosaminoglycan binding, sulfur compound interaction, oxidoreductase action, modulators of CH−OH group of donors, Regulatory activity of polypeptidase and so on. To further analyze concentration and signal pathways of intersecting genes function via KEGG enrichment analysis. As shown in **Figure 2 (B)**, a lot of intersecting genes were mainly concentrated in small molecule catabolic, response to peptide hormone, hormone metabolic, organic acid catabolic processes and so on.

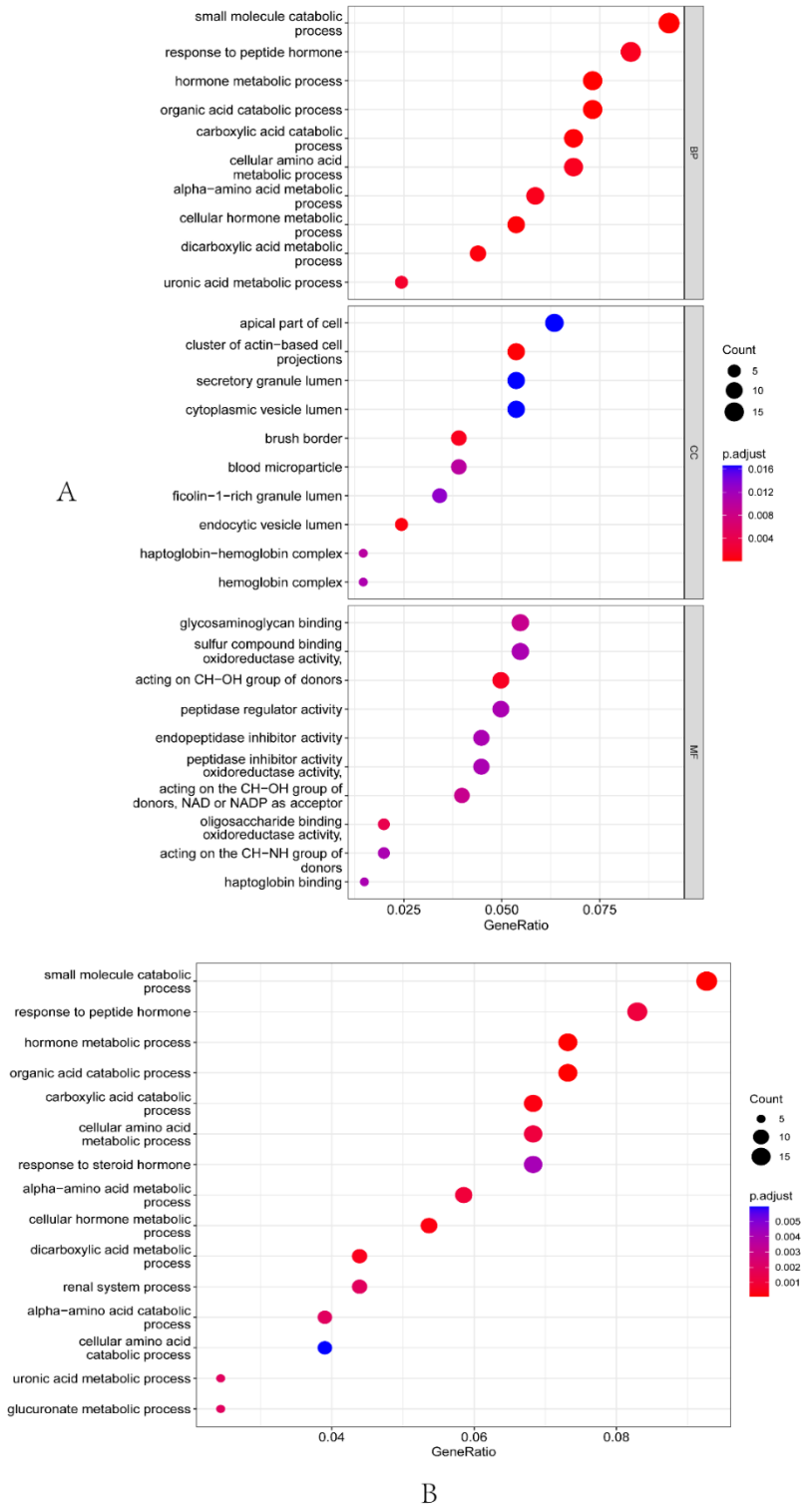

Figure 2. GO and KEGG analyses of DEGs. (A) GO; (B) KEGG. BP, biological process; CC, cellular composition; MF, molecular function; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEG, differentially expressed genes.

3.3. GSEA

GSEA assessment of GSE66494 revealed that DEG was concentrated in mitochondrial related gene expression, mitochondrial autophagy, mitochondrial electron chain transmission, Jak/Stat signaling pathway regulation, histone H2A ubiquitination, and cell cycle pathways. As demonstrated in **Figure 3**.

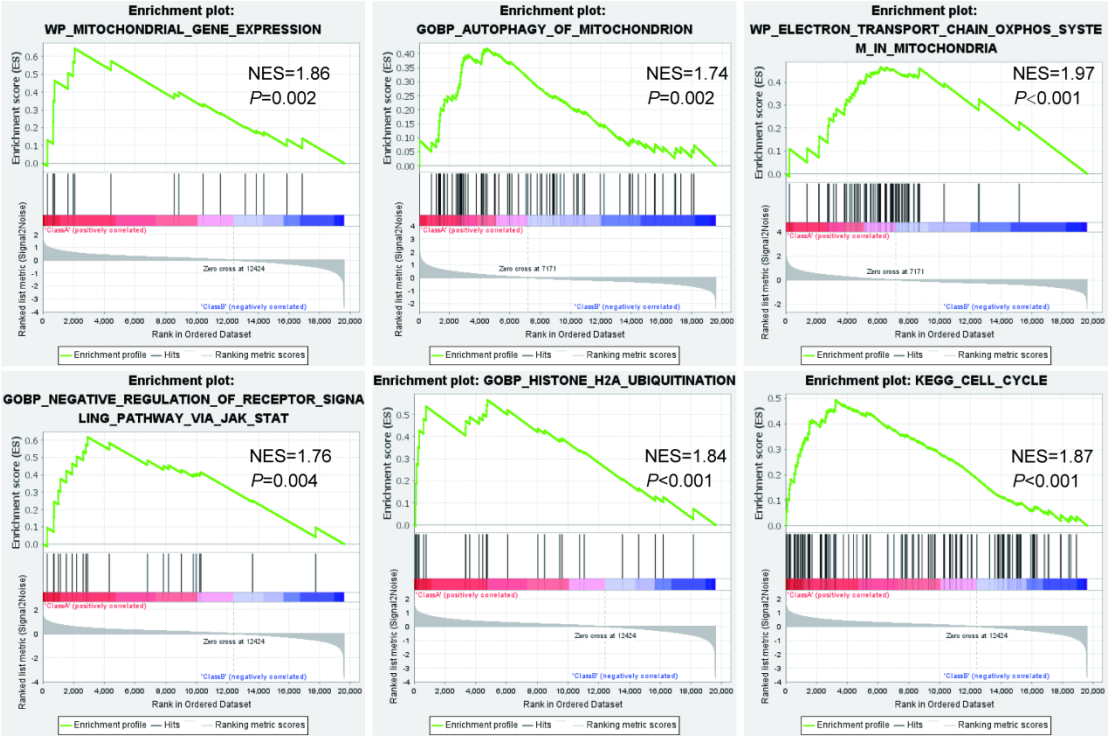

Figure 3. Gene set enrichment analysis.

3.4. PPI axis generation and evaluation

The PPI axis is conducted by Cytoscape software,adopting STRING database analyze intersecting genes function. The degree to which proteins act as a node in the PPI axis demonstrates the protein numbers that interact with specific nodes. Regarding central node as a node with high degree. the PPI network of intersecting genes was conducted and consisted of 26 nodes as shown is **Figure 4**.

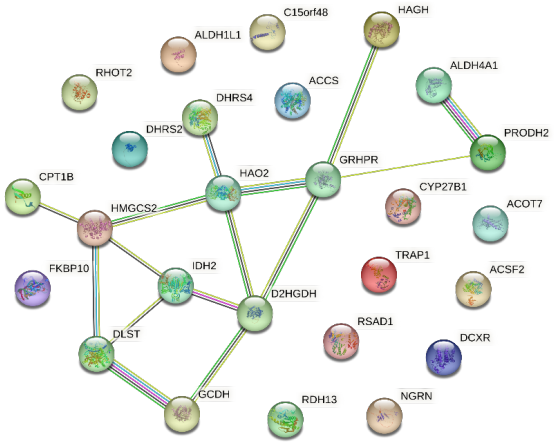

Figure 4. Mitochondrial related differential gene PPI.

3.5. Immune infiltration analysis

Using immune score $p < 0.05$, 61 samples which include discovery CKD group, discovery control group, validation CKD group and validation control group were picked for immune infiltration assessment. To explore alterations in immune invasion between control group and TGF-β1 group in 22 kinds of immune cell, the CIBERSORT software was employed. **Figure 5** (A) demonstrates the abundant results. Compared with control group, TGF-β1 group generally exhibited more plasma cells, memory B cells, naive B cells, neutrophils, eosinophils, monocytes and macrophages (M0). On the contrary, the ratio of gamma delta T cells, regulatory T cells and activated mast cells were lower.

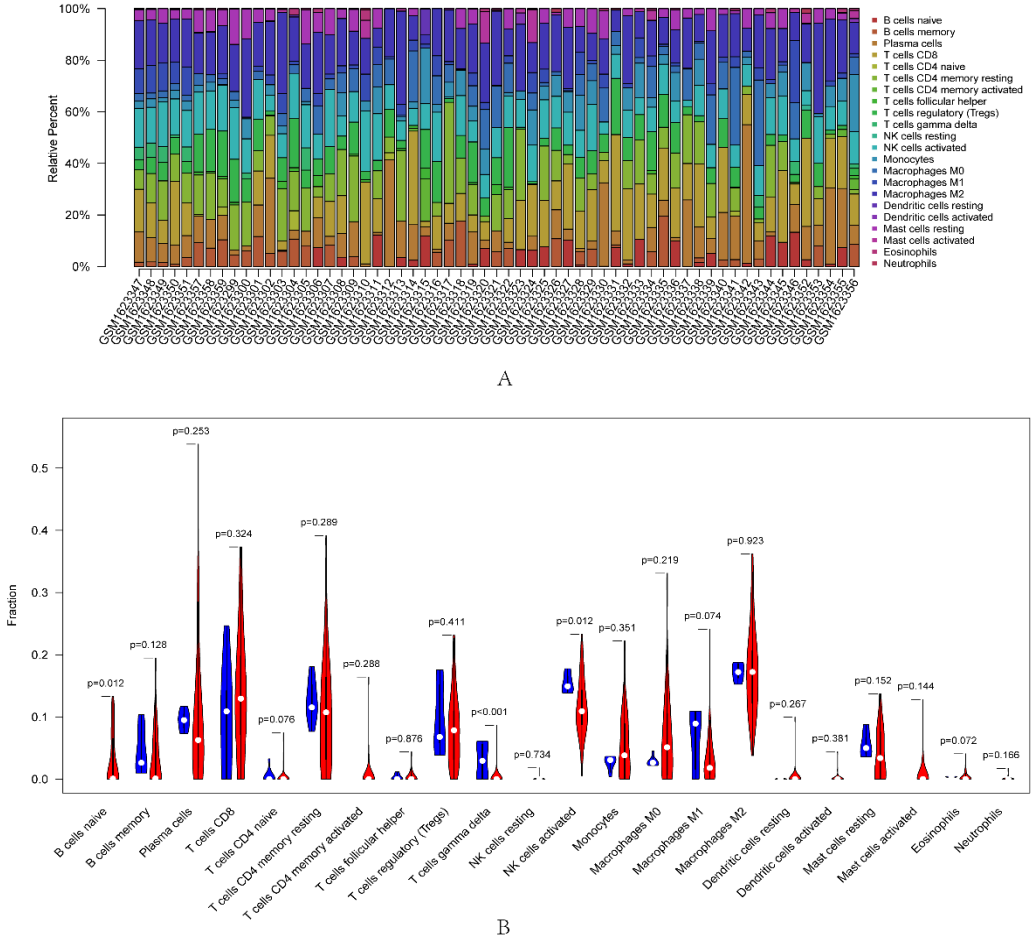

Figure 5. GSE66494 cohort immune invasion analysis. (A) Bar plot. (B) violin plot of immune invasion status.

3.6. Association between intersecting genes and immune cells

It is not clear whether mitochondrial related genes affect immune cell recruitment in CKD microenvironment. Hence, herein, we analyzed the relationship between mitochondrial genes and CKD immune invasion. The level of immune infiltration of Macrophage M0 was directly associated with ACOT7 and C15orf48 expressions (**Figure 6**). However, the Macrophage M2 immune invasion was inversely associated with ACOT7, ALDH1L1, ALDH4A1, DCXR, HAO2, PRODH2 and TRAP1 expressions (**Figure 6**). The degree of Monocyte immune invasion was negatively associated with ACCS, DLST, GCDH, GRHPR, NGRN, RDH13 and RHOT2 expressions (**Figure 7**). The degree of NK cells activated immune invasion was inversely proportional to the C15orf48 expression, but directly associated

with the CPT1B, DLST, HMGCS2 and RSAD1 expressions (**Figure 8**). The degree of immune infiltration of T cells regulatory was directly associated with the ALDH4A1, CYP27B1 and D2HGDH expressions (**Figure 8**). The immune infiltration level of Mast cells resting was negatively correlated with the expression of C15orf48, but positively correlated with the expression of HMGCS2, IDH2 and NGRN (**Figure 8**). T cells CD4 memory resting and T cells CD8 were negatively associated with the C15orf48 and CPT1B expressions, respectively (**Figure 8**). Therefore, through this study, it is found that mitochondrial genes associated with CKD immune invasion.

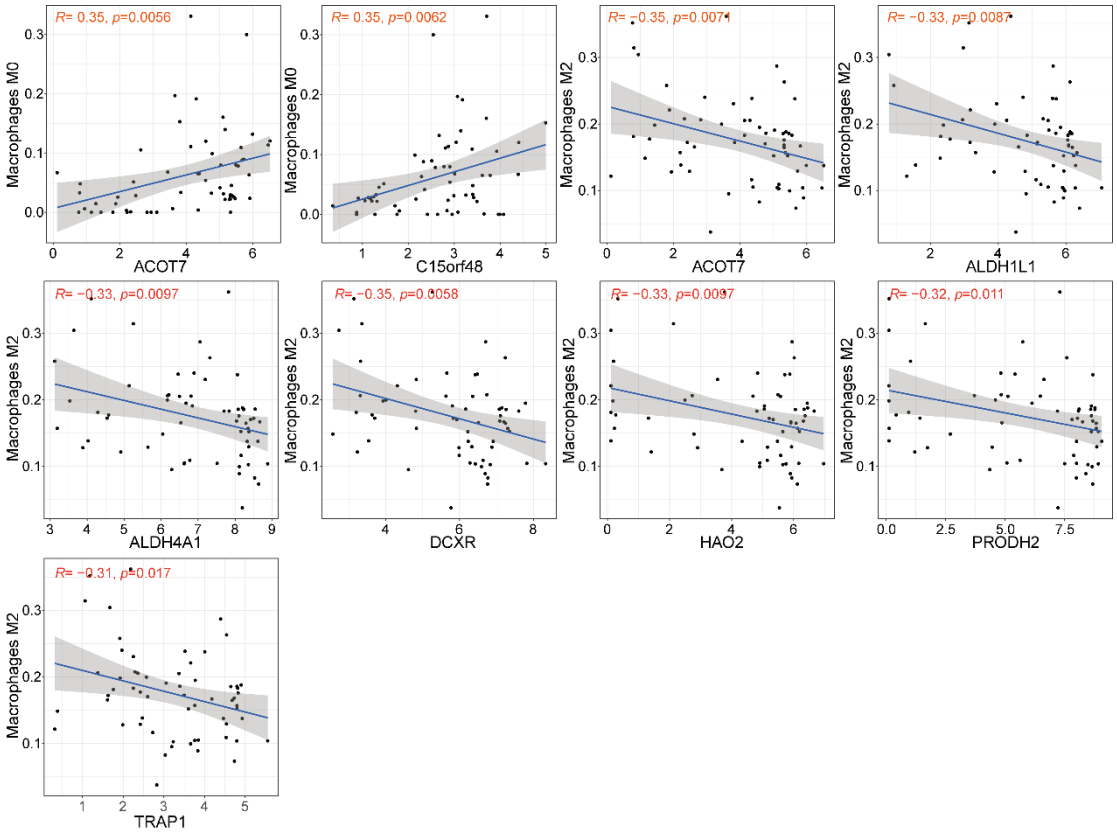

Figure 6. Association between Mitochondrial gene expressions and immune infiltration of Macrophage M0 and Macrophage M2.

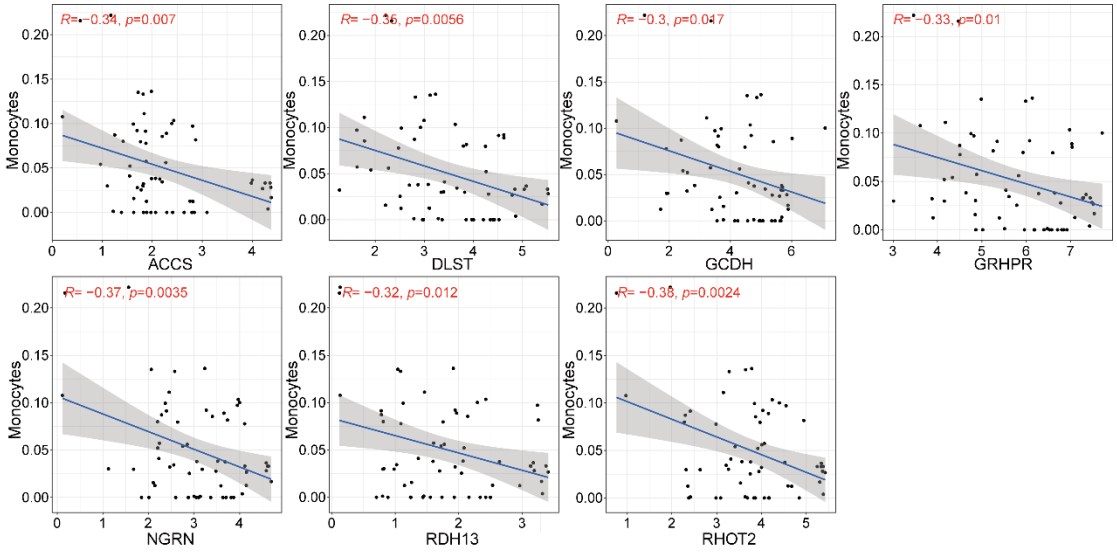

Figure 7. Association between mitochondrial gene expressions and immune infiltration of Monocytes.

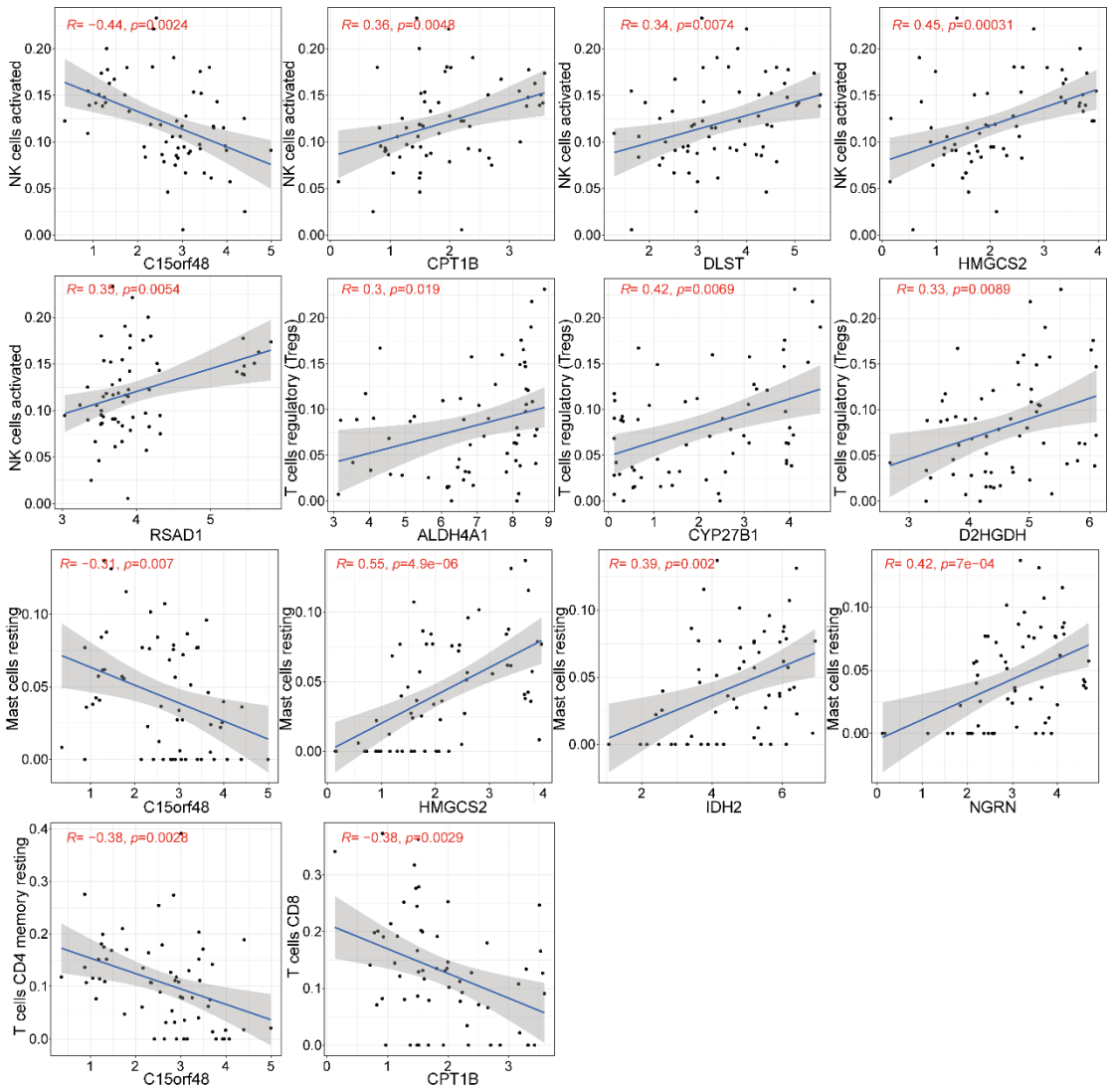

Figure 8. Association between mitochondrial gene expressions and immune infiltration of NK cells activated, T cells regulatory, Mast cells resting, T cells CD4 memory resting and T cells CD8.

3.7. Verify intersecting genes

In order to verify the reliability of GSE66494 dataset, HK-2 cells were treated with TGF-β1 to create CKD conditions, and the expression of four intersecting genes in CKD was evaluated by RT-qPCR. According to the experimental, the results of electron microscope showed that the mitochondria of the normal group were full and regular in **Figure 9 (A)** control group. As shown in **Figure 9 (A)**TGF-β1 group, there were mitochondrial swelling, mitochondrial vacuoles, cristae-like structure disorder and disappearance, mitochondrial pyknosis and so on. It can be seen that TGF-β1 can affect the mitochondrial structure of HK-2 human proximal tubular cells. The above results show that the CKD model has been established successfully. The results of RT-qPCR in **Figure 9 (B)** revealed that the D2HGDH and GRHPR contents in TGF-β1 group were drastically reduced, relative to the controls. However, no discernible alterations were present in HAO2 and HMGCS2 expressions between the two cohorts.

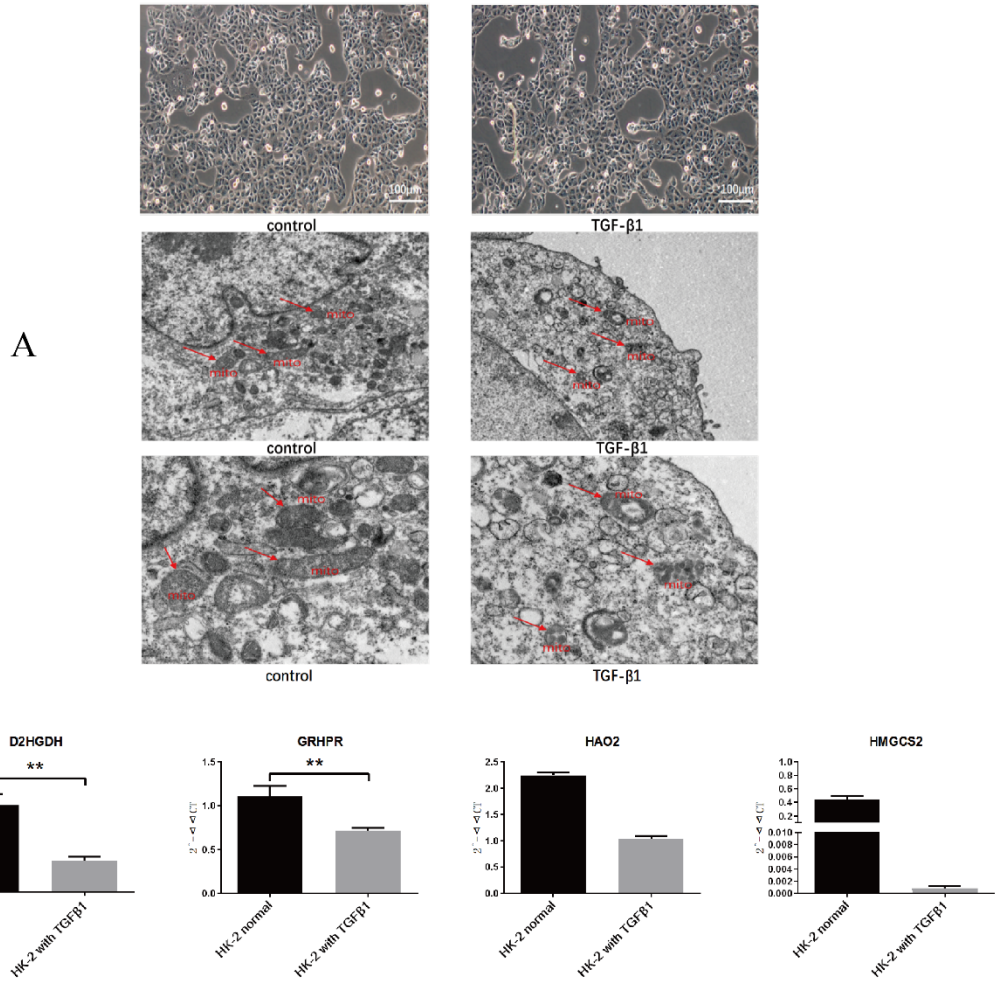

Figure 9. The ultrastructural changes of mitochondria were analyzed by transmission electron microscope. the arrow in the Figure 9 (A) refers to mitochondria and their corresponding magnified structures. Figure 9 (A)control group,the mitochondria are full and regular. Figure 9 (A) TGF-β1 group, mitochondrial vacuoles, cristae-like structure disorder and disappearance, mitochondrial pyknosis. Figure 9 (B). CKD model induced by TGF-β1. The above results show that the CKD model with good characteristics has been constructed successfully. RT-qPCR analysis revealed that the D2HGDH and GRHPR expressions were substantially lower than those in normal conditions. There existed no obvious alterations in HAO2 and HMGCS2 expressions between the two cohorts.

4. Discussion

CKD is considered to be an independent, irreversible and progressive pathological condition [13]. CKD are associated with another organ dysfunction [14]. Previous studies have found that mitochondrial function is often impaired before apoptosis [15]. Therefore, herein, we attempted to validate the important relationship of mitochondrial related genes in alleviating CKD injury. It may be helpful to study the mechanism of Mitochondrial therapy in improving renal function injury in the future.

In the present research, intersecting genes were first confirmed by comparing DEGs and mitochondria-associated genes. There are 26 intersecting Mitochondria-relater genes were found, which suggest that

mitochondrial related genes participated the mitigation process of injury and provide a potential pharmacological target for healing human renal proximal tubular epithelial cells injury. The intersecting genes were analyzed by GO, KEGG axis enrichment analyses and GSEA. The results show that these 26 intersecting genes were primarily associated with 'small molecule catabolic process', 'response to peptide hormone', 'apical part of cell', 'cell projection clusters based on actin', 'glycosaminoglycan binding' and 'sulfur compound binding' and so on. These pathways were involved in healing human renal proximal tubular epithelial cells injury. Prior investigations revealed that human body can deploy subcellular structures namely mitochondria by generating tunnel nanotubes, releasing extracellular capsules (EV) and cellular fusion [16]. Therefore, the mitochondria treatment can significantly up-regulate the expression of mitochondrial-related genes, which may be a new approach to treating CKD injury.

Using STRING to conduct PPI axes and Cytoscape software to identify four genes with the most abundant connections in intersecting genes: D2HGDH, GRHPR, HAO2, HMGCS2. For bioinformatics, verifying the four genes via RT-qPCR. The main function of D2HGDH is to prevent the accumulation of potentially harmful cells such as D2-HG [17,18]. Severe autosomal recessive neurometabolic diseases are caused by the loss of function, mutation, and deletion of D2HGDH [19]. The relationship between D2HGDH activity and mitochondrial metabolism, as well as its potential to facilitate metabolic diseases that are carcinogenic, have not yet been thoroughly investigated [17]. GRHPR gene mutations can produce the recessive hereditary disease primary hyperoxaluria type II, which is featured by excess urinary oxalate excretion, refractory calcium oxalate kidney stones and usually progressive renal insufficiency [20,21]. HAO2 is mainly expressed in the kidney and liver, oxidizing Lmur2-hydroxy acid to ketoacid, and then ketoacid to hydrogen peroxide [22]. These processes help to upregulate reactive oxygen species (ROS) levels, thereby causing cellular damage. Alternately, the increase of ROS level may also indicate a stimulus that induces cell proliferation [23]. HMGCS2, a mitochondrial enzyme of the HMG-CoA protein family, is the rate-limiting enzyme that accelerates the first ketogenesis reaction. Ketogenesis facilitates the deployment of lipid energy to a variety of organs during the absence of carbohydrate intake [24]. High HMGCS2 expression leads to ROS aggregation and mitochondrial membrane potential (MMP) loss. It has been found that mitochondrial HMGCS2 accumulation destroys mitochondrial function and aggravates CKD damage [25].

Mitochondria are the metabolic center of cells, and disruption in their delicate balance causes chronic kidney disease (CKD) [25]. Mitochondrial dysfunction heavily contributes to several acute kidney diseases and chronic nephropathy pathogenesis [26]. Data show that mitochondrial dysfunction is the core of progression to CKD, because targeting mitochondria can reverse pro-inflammatory and fibrogenic phenotypes, and persistent mitochondrial damage is the basis of CKD progress [27]. Renal proximal tubular epithelial cells are very dependent on mitochondria to maintain their life and function. Mitochondrial autophagy clears damaged mitochondria [28]. Previous studies have shown that induced autophagy can reduce nephrotoxicity, inhibition of mitochondrial autophagy can lead to the deterioration of mitochondrial function and aggravate cell injury. On the contrary, enhanced mitochondrial autophagy can prevent mitochondrial dysfunction and cell injury. Moreover, mitochondrial autophagy protects against cellular apoptosis by promoting the degradation of damaged mitochondria [5]. Therefore, the intersecting genes involved in this study play an important part in inducing mitochondrial catabolic process and there is a process of intracellular catabolism is mitochondrial autophagy. So, mitochondria therapy can up-regulate mitochondrial-related intersecting genes to induce mitochondrial autophagy catabolic process to treat and reduce human renal proximal tubular epithelial cells injury.

In our successful model, RT-qPCR revealed that the D2HGDH and GRHPR expressions in TGF-β1 group were substantially decreased and statistically significant. According to previous studies, mitochondrial D2HGDH accelerates the D-2-HG oxidation to α-KG, which promotes cell dynamic balance to some extent by regulating the α-KG-dependent dioxygenase activity. Signals regulating D2HGDH expression are thought to widely affect physiology and pathology [29]. And it is necessary to strictly control the expression of D2HGDH, because its level changes can participate in the IDH2- α-KG- dioxygenase axis, which may have a profound impact on cell regulation through epigenetic remodeling [17]. The mutation and expression of GRHPR gene can not only lead to renal stone formation and type 2 primary hyperoxaluria, but also cause renal failure and some late effects [30,31]. Although there has been no special report on the expression of mitochondrial D2HGDH and GRHPR in the context of CKD, we believe that there is a relationship between them via this study, which may provide some theoretical basis for the future mitochondrial targeting therapy of CKD.

TGF-β1 is not only beneficial, but also closely related to the pathological changes of various renal diseases. This article mainly talks about its "evil side". TGF-β is considered to be the key molecule leading to glomerulosclerosis [32]. According to some studies, TGF-β can start certain pathophysiological processes at the beginning of kidney damage, such as renal tubular epithelial cell apoptosis and internal cell dedifferentiation, which are directly related to the acute decline in renal activity and renal fibrosis development [33]. TGF-β signal transduction in proximal tubules has an adverse effect on the reaction of acute renal injury because of apoptotic effect [34]. According to previous conclusions, TGF-β1 has significant role in the pathophysiological process of glomeruli and tubulointerstitium by promoting pathological changes, inducing changes in glomerular filtration barrier, glomerular sclerosis and fibrosis, and tubular degeneration that leads to persistent renal dysfunction [10]. At this study, the experimental cells were scanned by transmission electron microscope. Compared with the normal group, mitochondrial damage could be found in TGF-β1 group under ultrastructure, such as mitochondrial swelling, vacuole, cristae-like structure disorder and disappearance, mitochondrial pyknosis and so on. Therefore, we used TGF-β1 for inducing human renal proximal tubular epithelial cells injury to obtain CKD condition.

However, our study had limitations at present. First of all, the quantity of data analyzed is not large enough. Secondly, the current data should be further verified in more clinical samples. Then, intersecting mitochondrial-related genes and their functions need to be further studied. Intersecting genes are identified by bioinformatics, which may supply a theoretical basis for further treatment research, although still needing a lot of clinical studies to verify it.

5. Conclusion

In summary, the results show that mitochondrial-related genes are critical for CKD treatment. Although it is not perfect, these results still supply a basis for guiding the design of future studies aimed at understanding deeper mechanisms in mitochondrial therapy.

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Disclosure statement

The authors declare no conflict of interest.

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