Asadi *et al.*
European Journal of Medical Research (2024) 29:412
https://doi.org/10.1186/s40001-024-01951-z

European Journal of Medical Research

RESEARCH

Open Access

Non-dialyzable uremic toxins and renal tubular cell damage in CKD patients: a systems biology approach

Roya Asadi[1], Pejman Shadpour[2*] and Akram Nakhaei[3*]

Abstract

Background Chronic kidney disease presents global health challenges, with hemodialysis as a common treatment. However, non-dialyzable uremic toxins demand further investigation for new therapeutic approaches. Renal tubular cells require scrutiny due to their vulnerability to uremic toxins.

Methods In this study, a systems biology approach utilized transcriptomics data from healthy renal tubular cells exposed to healthy and post-dialysis uremic plasma.

Results Differential gene expression analysis identified 983 up-regulated genes, including 70 essential proteins in the protein–protein interaction network. Modularity-based clustering revealed six clusters of essential proteins associated with 11 pathological pathways activated in response to non-dialyzable uremic toxins.

Conclusions Notably, WNT1/11, AGT, FGF4/17/22, LMX1B, GATA4, and CXCL12 emerged as promising targets for further exploration in renal tubular pathology related to non-dialyzable uremic toxins. Understanding the molecular players and pathways linked to renal tubular dysfunction opens avenues for novel therapeutic interventions and improved clinical management of chronic kidney disease and its complications.

Keywords Non-dialyzable uremic toxins, Renal tubular cells, Systems biology, Pathological pathways, Therapeutic targets

Background

Chronic kidney disease (CKD) represents a significant global public health concern, contributing to increased risks of cardiovascular disease, hospitalization, and mortality. Hemodialysis is a common treatment for CKD, particularly in the advanced stages of the condition. However, its limitations in eliminating all uremic toxins necessitate a deeper understanding of the pathological mechanisms activated by non-dialyzable uremic toxins and the identification of potential therapeutic interventions [29, 45, 47, 55, 69, 92].

Among the key cellular players involved in toxin filtration are renal tubular cells, alongside glomerular cells. Notably, renal tubular cells are at the forefront of exposure to uremic toxins, making them crucial targets for investigation due to their vital role in kidney function and susceptibility to toxin-induced injury [29, 45, 47, 69, 92].

Uremic toxins fall into three categories: small water-soluble solutes, medium molecules, and protein-bound solutes [31]. While numerous uremic toxins contribute to chronic kidney disease (CKD) progression, prior

*Correspondence:
Pejman Shadpour
pshadpour@gmail.com
Akram Nakhaei
a.nakhaee.66@gmail.com
[1] Industrial Engineering Department, Faculty of Technical and Engineering, University of Science and Culture (USC), Tehran, Iran
[2] Hospital Management Research Center (HMRC), Hasheminejad Kidney Center (HKC), Iran University of Medical Sciences (IUMS), Tehran, Iran
[3] Computer Engineering Department, Mazandaran University of Science and Technology (MUST), Babol, Iran

research has primarily focused on indoxyl sulfate (IS) and p-cresyl sulfate (PCS), two protein-bound compounds. These studies unveiled that IS activates the aryl hydrocarbon receptor (Ahr), a ligand-activated transcription factor receptor. Research indicates that Ahr activation correlates with vascular inflammation, leukocyte activation, thrombosis, reactive oxygen species, and cardiotoxicity [70]. Additionally, IS triggers the activation of the epidermal growth factor receptor (EGFR), thereby promoting renal tissue remodeling and arteriosclerosis [80]. IS expedites kidney fibrosis by upregulating expressions of transforming growth factor beta (TGF-β), tissue inhibitors of metalloproteinases-1 (TIMP-1), and pro-collagen [57]. Within kidney tubular cells, IS accumulation wreaks havoc on the anti-oxidative system, fostering cellular dysfunction and heightened oxidative stress [26]. Moreover, IS amplifies the expression of plasminogen activator inhibitor-1 (PAI-1), leading to renal tubular cell dysfunction [58].

PCS exhibits renal toxicity akin to IS [31]. Investigations have unveiled that PCS triggers cellular immune and inflammatory reactions, notably activating the TGF-β signaling pathway [79]. Furthermore, PCS activates rat sarcoma (RAS) and augments oxidative stress generation by stimulating leukocytes, thereby instigating renal tubular epithelial-to-mesenchymal transition. These alterations significantly fuel the advancement of kidney fibrosis [78].

Prior studies have investigated the impact of individual uremic toxins, such as IS and PCS, protein-bound compounds, on renal tubular cells, revealing their tubule-toxic effects and contributions to CKD progression. However, a comprehensive understanding of the effects of non-dialyzable uremic toxins, which can be of any type, on renal tubular cells remains lacking, emphasizing the need for further research to unravel their intricate responses.

This study aims to adopt a systems biology approach to gain a holistic understanding of the comprehensive pathological mechanisms activated by non-dialyzable toxins and identify essential proteins as potential targets for therapeutic intervention.

The primary objectives of this study are twofold: (1) to gain insights into the comprehensive pathological mechanisms of retained uremic toxins on healthy tubular cells, and (2) to identify essential proteins as potential targets for antagonist drugs to control CKD progression. Focusing on antagonist drugs emerges as a justifiable approach for treating CKD due to their proven efficacy in slowing disease progression [59, 89].

Methodology

A flowchart illustrating the overall methodology and data analysis pipeline is provided in Fig. 1. The figure summarizes the step-by-step approach, from data acquisition to pathway enrichment analysis, employed in this study. These steps are explained in the following subsections.

Data acquisition

Transcriptomics data for this study were obtained from the GEO database under the accession number GSE45709 (n.d.). The dataset includes gene expression measurements from healthy renal tubular cells exposed to both healthy plasma (control group) and post-dialysis uremic plasma (case group). All samples from each group were utilized to ensure consistency and statistical power in the analysis.

By utilizing this dataset, we were able to investigate the differential gene expression profiles between the two groups and identify potential cellular mechanisms underlying the pathological effects of non-dialyzable uremic toxins in CKD.

Data normalization

This study seeks to investigate the effects of non-dialyzable uremic toxins on the gene expression of healthy renal tubular cells. In other words, we seek to measure the variance of gene expression between case (post-dialysis plasma) and control (healthy plasma) groups. However, in addition to this variance, there are also technical and biological variances between samples. To measure the intended variance, we must neutralize the others [13]. Biological variance can be neutralized by repeating samples and technical variance by normalization. We have several samples in each group, which neutralizes the biological variance. For technical variance, we used quantile normalization. This method assumes that technical variance appears as differences in the general characteristics of samples. So, quantile normalization equalizes the statistical distribution of gene expression values across samples, effectively removing technical variance [36]. Figure 2 shows the distribution of gene expression values of samples before and after utilizing quantile normalization.

Identification of differentially expressed genes (DEGs)

To identify DEGs between the control and case groups, we employed the limma package in R programming language, a widely accepted method for microarray data analysis that provides reliable results [67], to perform the statistical t-test. We used the FDR technique for adjusting the p-value and genes with a p-value less than 0.05 were considered differentially expressed. We used the fold change (FC) metric to determine the upregulation

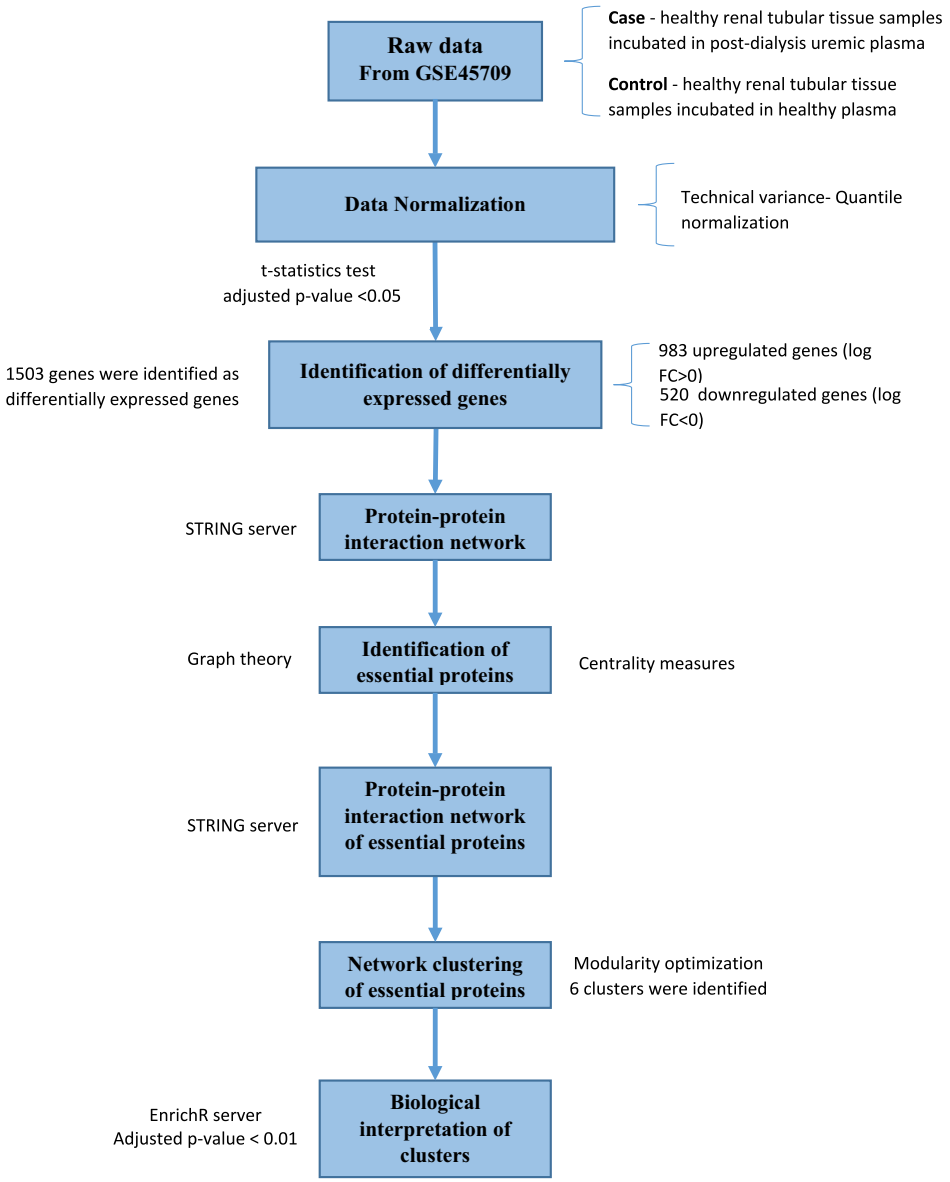

Fig. 1 Flowchart of the study's methodology and data analysis pipeline

(log FC > 0) or downregulation (log FC < 0) of DEGs. As the focus of this study is on potential antagonist drug targets, we specifically examined up-regulated genes.

Construction of protein–protein interaction (PPI) network

To explore potential interactions between the up-regulated DEGs, we constructed a PPI network using the STRING server. The network was built using active interaction sources, including text mining, experiments, and databases, with a minimum required interaction score of 0.7 (high confidence).

Identification of essential proteins

Previous studies have shown that centrality measures are capable of identifying essential proteins in PPI networks [19, 28, 98]. So, to identify essential proteins in the PPI network, we assessed several centrality measures, including closeness, betweenness, degree, and eigenvector centrality. Specific thresholds were applied for each centrality measure to identify essential proteins. The thresholds were 8E-4 for closeness, 1E-9 for betweenness, 3 for degree, and 1.24E-6 for eigenvector, based on prior knowledge.

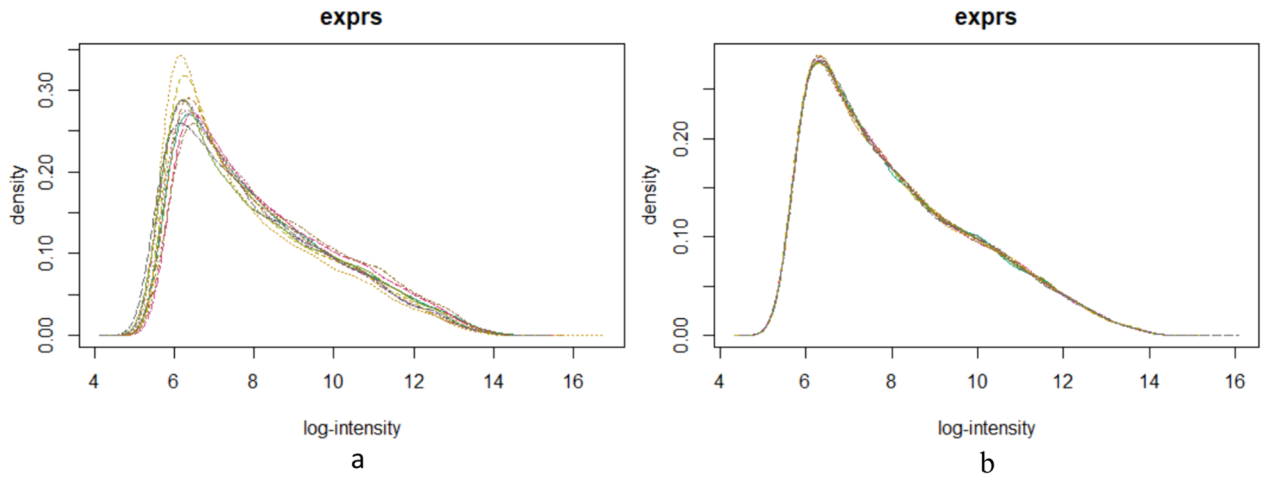

Fig. 2 **a** and **b** Show the distribution of log of gene expression values of samples before and after quantile normalization

Clustering of essential proteins

We extracted the PPI network of essential proteins from the STRING server using active interaction sources and a minimum required interaction score of 0.4. To identify potential functional modules, we employed a heuristic method based on modularity optimization proposed by Blondel et al. [6]. This approach maximizes the modularity of the resulting clusters, revealing densely connected groups of proteins.

Pathway enrichment analysis

To gain insights into the functions of each protein cluster, we performed pathway enrichment analysis using the Enrichr server. The WikiPathway 2021 Human Library was utilized to identify enriched biological pathways associated with each cluster. Pathways were ranked by adjusted p-value [12].

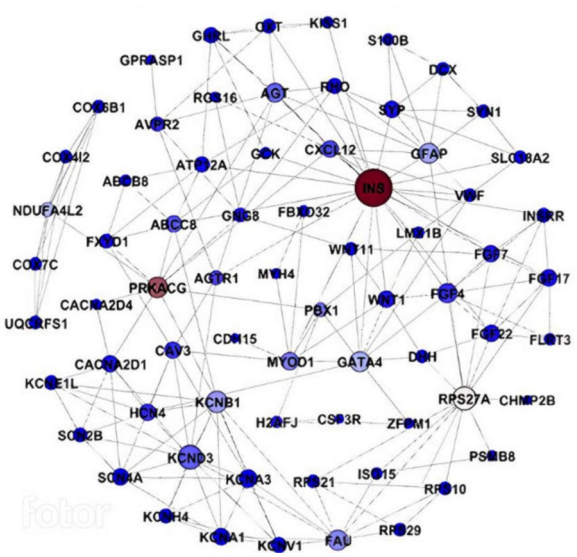

Fig. 3 PPI network of essential proteins

Results

In this section, we present the results of our data analysis pipeline, aiming to gain insights into the effects of non-dialyzable uremic toxins on healthy renal tubular cells and identify potential therapeutic targets.

Identifying essential proteins

After performing the t-test, we identified 1503 DEGs, with 983 up-regulated and 520 down-regulated genes. Among the up-regulated DEGs, a PPI network analysis using centrality measures (degree, betweenness, closeness, and eigenvector centrality) and predefined thresholds allowed us to identify 70 essential proteins. The resulting PPI network of the 70 essential proteins is depicted in Fig. 3, comprising 195 edges representing protein–protein interactions. In this figure, the size of the node represents the degree. The larger the size, the higher the degree of the node. The color of the node represents the betweenness. The color of the node changes in a spectrum from red to blue. Red indicates a higher betweenness, and blue indicates a lower betweenness.

Modularity-based clustering

The PPI network of essential proteins was subjected to modularity-based clustering, leading to the identification of six distinct clusters of essential proteins which are depicted in Fig. 4. The first cluster, cluster 0, comprises 19 interactions and 13 proteins, including MYOD1, CDH15, CSF3R, H2AFJ, DHH, GATA4, WNT1, FBXO32, MYH4, WNT11, ZFPM1, PBX1, and LMX1B.

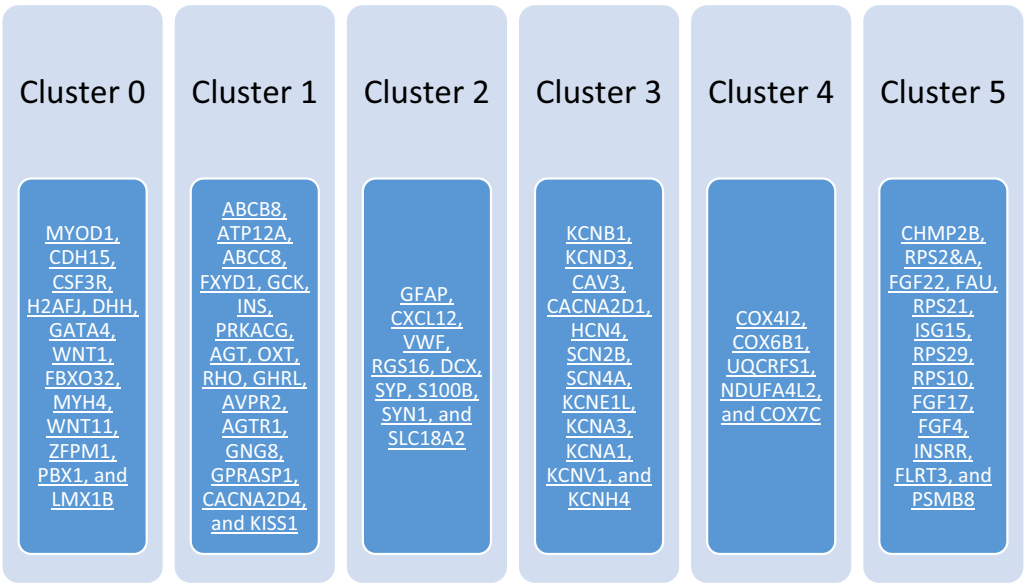

Fig. 4 Modularity classes of essential proteins

The second cluster, cluster 1, encompasses 38 interactions and 17 proteins, including ABCB8, ATP12A, ABCC8, FXYD1, GCK, INS, PRKACG, AGT, OXT, RHO, GHRL, AVPR2, AGTR1, GNG8, GPRASP1, CACNA2D4, and KISS1.

The third cluster, cluster 2, encompasses 15 interactions and nine proteins, including GFAP, CXCL12, VWF, RGS16, DCX, SYP, S100B, SYN1, and SLC18A2.

The fourth cluster, cluster 3, encompasses 37 interactions and 12 proteins, including KCNB1, KCND3, CAV3, CACNA2D1, HCN4, SCN2B, SCN4A, KCNE1L, KCNA3, KCNA1, KCNV1, and KCNH4.

The fifth cluster, cluster 4, comprises ten interactions and five proteins, including COX4I2, COX6B1, UQCRFS1, NDUFA4L2, and COX7C.

The sixth cluster, cluster 5, comprises 31 interactions and 13 proteins: CHMP2B, RPS2&A, FGF22, FAU, RPS21, ISG15, RPS29, RPS10, FGF17, FGF4, INSRR, FLRT3, and PSMB8. Notably, these clusters represent functionally related groups of essential proteins, potentially serving distinct roles in response to retained uremic toxins.

Enrichment analysis

After clustering, we performed enrichment analysis to identify biological pathways activated by proteins of each cluster and map proteins to their functions. We considered pathways with adjusted p-value < 0.01 as statistically significant pathways. The important enriched pathways associated with each cluster are summarized in the following tables:

- Cluster 0: Significantly enriched pathways are listed in Table 1. These pathways had adjusted p-value < 0.01.
- Cluster 1: Significantly enriched pathways are listed in Table 2. These pathways had adjusted p-value < 0.01.
- Cluster 2: Significantly enriched pathways are presented in Table 3. These pathways had adjusted p-value < 0.01.

Table 1 Enriched pathways of cluster 0

Pathway	ID	*p*-value	Adjusted *p*-value
Mammalian disorder of sexual development	WP4842	4.89E-07	0.00002642
Somatic sex determination	WP4814	0.00003533	0.000954
Osteoblast differentiation	WP4787	0.00005484	0.0009871
Dopaminergic neurogenesis	WP2855	0.0001679	0.002267
Wnt signaling in kidney disease	WP4150	0.0002427	0.002621

Table 2 Enriched pathways of cluster 1

Pathway	ID	*p*-value	Adjusted *p*-value
SARS-CoV-2 and angiotensin-converting enzyme 2 receptor: molecular mechanisms	WP4883	0.00001424	0.0004202
Prader–Willi and Angelman syndrome	WP3998	1.81E-07	0.00001067
ACE inhibitor pathway	WP554	0.00009179	0.001805
RAS and bradykinin pathways in COVID-19	WP4969	0.0002724	0.004018
Sleep regulation	WP3591	0.0004695	0.00554
Renin–angiotensin–aldosterone system (RAAS)	WP4756	0.0006299	0.006194

Table 3 Enriched pathways of cluster 2

Pathway	ID	*p*-value	Adjusted *p*-value
EV release from cardiac cells and their functional effects	WP3297	0.000003775	0.00004342
Synaptic vesicle pathway	WP2267	0.000001298	0.00002985

- Cluster 3: We found no statistically significant pathways for proteins of cluster 3.
- Cluster 4: Significantly enriched pathways are listed in Table 4. These pathways had adjusted p-value < 0.01.
- Cluster 5: Significantly enriched pathways are presented in Table 5. These pathways had adjusted p-value < 0.01.

Table 5 Enriched pathways of cluster 5

Pathway	ID	*p*-value	Adjusted *p*-value
Cytoplasmic ribosomal proteins	WP477	3.02E-09	6.95E-08
ESC pluripotency pathways	WP3931	0.000001028	0.00001182
Regulation of actin cytoskeleton	WP51	0.00000287	0.00001832
Breast cancer pathway	WP4262	0.000003187	0.00001832
MAPK signaling pathway	WP382	0.00002029	0.00009335
Focal adhesion PI3K–Akt–mTOR signaling pathway	WP3932	0.00004586	0.0001758
PI3K–Akt signaling pathway	WP4172	0.00007178	0.0002359
Osteoblast differentiation	WP4787	0.002999	0.008621

Discussion

In this study, we aimed to gain a holistic view of the pathological effects of non-dialyzable uremic toxins on healthy renal tubular cells by adopting a systems biology approach. Our analysis revealed 983 up-regulated DEGs and 70 essential proteins. Subsequently, we identified six dense communities of essential proteins, each representing potential functional modules within the network.

Through pathway enrichment analysis, we identified 24 statistically significant pathways associated with the identified clusters. While these pathways were not directly associated with renal tubular dysfunction, we found indirect evidence linking them to cellular processes involved in inflammation, fibrosis, apoptosis, metabolic dysfunction, and oxidative stress. This association is presented in Table 6. This table shows the participation of each pathway in the mentioned pathological processes.

Among the 24 pathways, 11 were found to be involved in these cellular processes, suggesting their potential relevance to renal tubular dysfunction. To further explore the role of essential proteins in the identified pathways, we investigated their participation rates. To this end, we investigated each pathway. Notably, 22 essential proteins, including WNT1/11, AGT, FGF4/17/22, LMX1B, GATA4, CXCL12, KISS1, COX6B1/7C, UQCRFS1, AGTR1, NDUFA4L2, INS, RGS16, RPS10/21/27A, FAU, and SLC18A2 were found to play a role in the pathways associated with inflammation, fibrosis, apoptosis, metabolic dysfunction, and oxidative stress. Figure 5 shows the participation of these proteins in the 11 identified

Table 4 Enriched pathways of cluster 4

Pathway	ID	*p*-value	Adjusted *p*-value
Nonalcoholic fatty liver disease	WP4396	2.62E-11	1.31E-10
Electron transport chain (OXPHOS system in mitochondria)	WP111	0.000001317	0.000003291
Mitochondrial CIV assembly	WP4922	0.00002965	0.00004942
Mitochondrial complex III assembly	WP4921	0.003994	0.004992

Table 6 Mapping pathological pathways to their roles in renal tubular dysfunction

Pathway	Role in CKD progression				
	Inflammation	Fibrosis	Apoptosis	Metabolic dysfunction	Oxidative stress
Mammalian disorder of sexual development WP4842 [25]	✓			✓	
Dopaminergic Neurogenesis WP2855 [2]					✓
Wnt signaling in kidney disease WP4150 [32, 33, 72]	✓	✓	✓	✓	✓
SARS-CoV-2 and angiotensin-converting enzyme 2 receptor: molecular mechanisms WP4883 [1, 10, 24, 52]	✓	✓	✓	✓	✓
Prader–Willi and Angelman syndrome WP3998 [9]	✓			✓	
ACE inhibitor pathway WP554 [21, 30]	✓		✓		
EV release from cardiac cells and their functional effects WP3297 [16, 53]	✓	✓		✓	✓
Nonalcoholic fatty liver disease WP4396 [23, 46, 63, 82, 102]	✓	✓	✓	✓	✓
Cytoplasmic ribosomal proteins WP477 [40, 62, 68, 99]	✓	✓	✓	✓	✓
ESC pluripotency pathways WP3931 [34]			✓		
Breast cancer pathway WP4262 [4, 20, 22, 51, 61]	✓	✓	✓	✓	✓

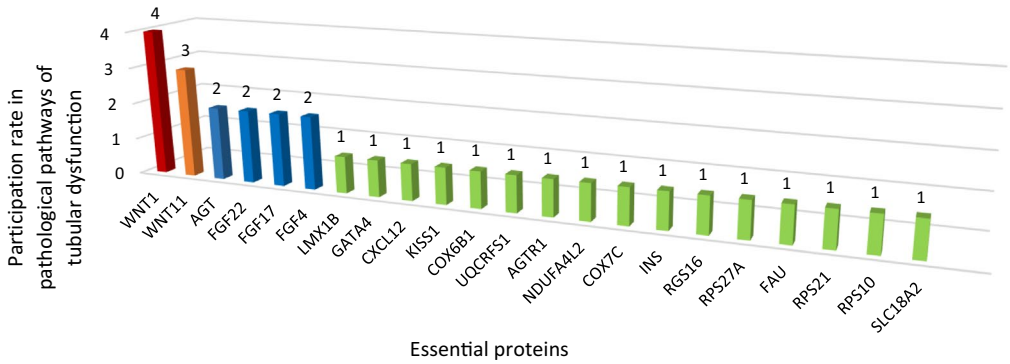

Fig. 5 The participation rate of essential proteins in pathological pathways which lead to renal tubular dysfunction. WNT1 participates in 4 pathological pathways. WNT 11 participates in 3 pathological pathways. Each of AGT and FGF4/7/22 participates in 2 pathological pathways. Each of LMX1B, GATA4, CXCL12, KISS1, COX6B1, UQCRFS1, AGTR1, NDUFA4LC, COX7C, INS, RGS16, RPS27A, FAU, RPS21, RPS10 and SLC18A2 participates in 1 pathological pathway

pathological pathways. WNT1 participates in 4 pathological pathways. WNT 11 participates in 3 pathological pathways. Each of AGT and FGF4/7/22 participates in 2 pathological pathways. Each of LMX1B, GATA4, CXCL12, KISS1, COX6B1, UQCRFS1, AGTR1, NDUFA4LC, COX7C, INS, RGS16, RPS27A, FAU, RPS21, RPS10 and SLC18A2 participates in 1 pathological pathway.

WNT1/11

Figure 5 shows that WNT1 and WNT11 have the highest participation rate in pathological pathways of renal tubular cells. WNT1 participates in breast cancer pathway WP4262, dopaminergic neurogenesis WP2855, ESC pluripotency pathways WP3931, and Wnt signaling in kidney disease WP4150. WNT11 participates in breast cancer pathway WP4262, ESC pluripotency pathways WP3931, and Wnt signaling in kidney disease WP4150.

WNT1/11 plays a pivotal role in kidney development and function, modulating proliferation, differentiation, and apoptosis [66]. However, its upregulation leads to renal cell dysfunction. Previous studies have reported elevated levels of WNT1 and WNT11 in various kidney diseases, including cystic kidney diseases, nephropathy, and tubulointerstitial fibrosis [66, 81, 90]. In vivo experiments demonstrated that WNT1/11 overexpression in renal tubules caused dysfunction in tubular cells, supporting their potential role in renal tubular dysfunction [43].

In exploring the potential clinical applications of targeting WNT1/11 to mitigate the pathological pathways activated by non-dialyzable uremic toxins, several promising avenues have emerged. Small molecule inhibitors,

exemplified by LGK974 and XAV939, offer a targeted approach to disrupt WNT secretion and downstream signaling components, potentially attenuating renal damage in CKD patients [48, 93]. Monoclonal antibodies like OMP-18R5 and vantictumab could serve as adjunct therapies by specifically blocking WNT proteins, thereby inhibiting aberrant signaling cascades associated with CKD progression [60, 74].

Moreover, RNA interference (RNAi) strategies hold promise in silencing WNT1/11 gene expression, offering a potential avenue for personalized treatment approaches tailored to CKD patients' specific molecular profiles [49, 54]. Additionally, the therapeutic potential of natural compounds such as curcumin, Tripterygium wilfordii, and astragaloside IV cannot be overlooked. Derived from plants or other sources, these compounds exhibit promising capabilities in downregulating WNT1/11 expression or activity through various mechanisms, providing alternative or complementary therapeutic options for CKD management [11, 15, 38, 91].

AGT/AGTR1

Figure 5 shows that AGT/R1 has a high participation rate in pathological pathways of renal tubular cells. AGT participates in ACE inhibitor pathway WP554 and ESC pluripotency pathways WP3931. AGT is produced in the kidney and cleaved by renin to form angiotensin I and II, regulating blood pressure, sodium reabsorption, and fluid balance in renal tubules [96]. However, elevated AGT levels in the kidney have been associated with renal tubular dysfunction in humans and animal models [86, 87]. Studies with AGT overexpression in animal models have observed tubular cell apoptosis, inflammation, fibrosis, and other signs of tubular injury, supporting the association between elevated renal AGT levels and tubular dysfunction [50, 97].

In considering the translation of identified targets into clinical applications, AGT emerges as a promising candidate for therapeutic intervention in CKD. AGT overexpression contributes to renal tubular dysfunction, highlighting its significance as a target for antagonist drugs aimed at mitigating disease progression.

Several pharmacological agents have been proposed to target AGT, primarily for managing conditions like hypertension and heart failure, which commonly coexist with CKD. For example, angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril have demonstrated efficacy in reducing AGT-mediated effects on blood pressure and fluid balance, thereby potentially attenuating renal damage [27, 37]. Similarly, angiotensin receptor blockers (ARBs) like losartan and valsartan offer alternative therapeutic avenues by blocking downstream effects of AGT activation, contributing to the regulation of blood pressure and renal function. Additionally, renin inhibitors like aliskiren provide another approach to modulating the renin–angiotensin–aldosterone system, targeting AGT-mediated pathways implicated in CKD progression [17, 73].

FGF4/17/22

As Fig. 5 shows, FGF4/17/22 has a high participation rate in pathological pathways of renal tubular cells. FGF 4/17/22 participate in breast cancer pathway WP4262 and ESC Pluripotency pathways WP3931. FGF signaling plays an important role in kidney development and function by modulating cell proliferation, differentiation, survival, and repair [3, 85]. FGFs are expressed in the adult kidney, particularly in the renal tubules [3, 8]. Some studies have found elevated levels of these FGFs in animal models and patients with kidney diseases like polycystic kidney disease, nephropathy, and tubulointerstitial fibrosis [44, 77, 83].

Expanding on the potential translation of the identified targets into clinical applications, the overexpression of FGF4, FGF17, and FGF22 in renal tubules has emerged as a significant factor contributing to dysfunction. Understanding their context-dependent functions is crucial for developing targeted FGF-based therapies aimed at addressing tubule disorders in CKD patients.

Several therapeutic approaches have been proposed to target FGF4/17/22, offering potential avenues for personalized treatment in CKD. For example, small molecule inhibitors like erdafitinib indirectly inhibit FGF activity by targeting FGFRs, thereby modulating FGF-mediated signaling pathways [56]. Similarly, antibodies such as R3Mab have shown promise in blocking FGF activity by preventing their interaction with receptors or promoting their degradation, offering targeted interventions to mitigate renal dysfunction [35].

RNAi-based approaches, exemplified by molecules like AZD4547, offer a mechanism to silence FGF expression by targeting their mRNA, potentially reducing aberrant FGF signaling and mitigating tubule disorders in CKD [64]. Additionally, peptides like FGF Trap competitively inhibit FGF binding to receptors, disrupting FGF signaling pathways and offering therapeutic potential in CKD management [84].

Furthermore, proteins or molecules like FP-1039/GSK3052230 can bind and sequester FGF ligands, effectively inhibiting FGF signaling pathways and providing a targeted approach to modulating FGF-mediated effects on renal function [5].

LMX1B

LMX1B participates in dopaminergic neurogenesis WP2855. This protein plays an important role in kidney

function and development. Previous studies have shown that LMX1B is expressed in renal tubular epithelial cells and is required for proper podocyte differentiation [7]. Our results initially hypothesized that overexpression of LMX1B leads to tubule injury and dysfunction. However, there is also evidence that LMX1B overexpression may have a healing function. Some studies have found that elevated LMX1B expression is seen in regenerating tubules after injury, suggesting that LMX1B may promote renal tubular repair and regeneration [100].

As LMX1B is primarily a transcription factor involved in developmental processes, there are currently no specific molecules designed to target LMX1B directly for therapeutic purposes.

GATA4

GATA4 participates in mammalian disorder of sexual development WP4842. This protein plays an important role in kidney function, particularly in renal tubular cells [14]. Our results hypothesize that GATA4 overexpression leads to renal tubular cell dysfunction and injury. This is supported by evidence from the literature.

Studies have shown that high GATA4 levels in renal tubular epithelial cells correlate with tubular cell dysfunction and injury, contributing to diabetic nephropathy [14]. Both articles find that inhibiting GATA4 activity, such as by promoting its degradation, attenuates tubular cell damage and fibrosis.

Expanding on the potential translation of the identified targets into clinical applications, various strategies have been proposed to target GATA4, offering promising avenues for personalized treatment in CKD.

Compounds like histone deacetylase (HDAC) inhibitors provide indirect modulation of GATA4 activity by affecting proteins interacting with GATA4 or downstream targets. These compounds have shown efficacy in contexts like cardiac regeneration, suggesting their potential utility in mitigating GATA4-related abnormalities associated with CKD [101].

Experimental techniques involving adeno-associated virus (AAV) vectors offer another approach to target GATA4, with the aim of delivering GATA4 gene constructs to cells with mutations, potentially restoring normal expression and function. While initially explored in the context of cardiac disease, similar gene therapy approaches could hold promise for addressing GATA4-related abnormalities in CKD [65].

RNAi approaches, utilizing small interfering RNAs (siRNAs) or antisense oligonucleotides, present a mechanism to silence GATA4 expression at the mRNA level, potentially reducing aberrant protein levels associated with CKD progression [75].

Furthermore, targeting pathways regulated by GATA4, such as Wnt/β-catenin signaling, offers alternative therapeutic approaches. Compounds modulating these pathways, such as Wnt antagonists or β-catenin inhibitors, may offer potential interventions to mitigate GATA4-related abnormalities and improve outcomes for CKD patients [41].

CXCL12

CXCL12 participates in EV release from cardiac cells and their functional effects WP3297. While CXCL12 is known to promote the regeneration of renal tubules after acute kidney injury [71, 95], sustained CXCL12 overexpression may have detrimental effects [76]. Studies involving tubule-specific CXCL12 overexpression in mouse models found that sustained CXCL12 overexpression in adult renal tubular cells led to tubular damage, inflammatory cell infiltration, interstitial fibrosis, and impairment of genes related to electrolyte transport [94].

In exploring the translation of the identified targets into clinical applications, several promising approaches have emerged for targeting CXCL12, offering potential avenues for personalized treatment in CKD.

Small molecule inhibitors like AMD3100 represent one such approach, disrupting the CXCL12-CXCR4 interaction and inhibiting downstream signaling pathways. AMD3100's application in stem cell transplantation and its exploration in cancer therapy highlight its potential utility in mitigating CXCL12-mediated effects in CKD patients [18].

Compounds like NOX-A12 offer another avenue for targeting CXCL12, interfering with its binding to CXCR4. As a PEGylated Spiegelmer, NOX-A12 has been studied in clinical trials for hematological malignancies and solid tumors, suggesting its potential as a therapeutic intervention in CKD-associated conditions [39].

RNAi approaches utilizing siRNAs or antisense oligonucleotides provide yet another mechanism to target CXCL12, aiming to silence its expression at the mRNA level and potentially inhibiting its function in diseases such as cancer and inflammatory disorders [88].

Conclusion and limitations

In conclusion, our systems biology analysis has yielded valuable insights into potential molecular mechanisms contributing to renal tubular dysfunction in CKD. The identification of up-regulated proteins such as WNT1/11, AGT, FGF4/7/17/22, LMX1B, GATA4, CXCL12, KISS1, COX6B1/7C, UQCRFS1, AGTR1, NDUFA4L2, INS, RGS16, RPS10/21/27A, FAU, and SLC18A2 highlights promising targets for further investigation. However, several limitations need to be acknowledged.

Firstly, the sample size of the gene expression data used in this study was very small, comprising only five controls and five cases, which may limit the generalizability of our findings. Additionally, the reliance on a single dataset (GSE45709) may also restrict the generalizability of our findings. Future studies should aim to validate our results using larger and more diverse datasets to enhance the robustness and applicability of our findings.

Moving forward, experimental validation of the identified targets is imperative. Plans or strategies for validation through in vitro cell culture experiments or in vivo animal models based on key target proteins and potential pathways need to be outlined comprehensively. This would provide crucial evidence to support the significance of our findings and facilitate their translation into clinical applications.

Despite these limitations, our study sheds light on the molecular players and pathways associated with renal tubular dysfunction, offering potential avenues for novel therapeutic interventions and enhanced clinical management of CKD and its complications. Emphasizing the need for continued research in this direction will drive progress toward better understanding and tackling CKD, ultimately benefiting patients' outcomes and overall healthcare.

Abbreviations

CKD	Chronic kidney disease
IS	Indoxyl sulfate
PCS	P-Cresyl sulfate
Ahr	Aryl hydrocarbon receptor
EGFR	Epidermal growth factor receptor
TGF-β	Transforming growth factor beta
TIMP-1	Tissue inhibitors of metalloproteinases-1
PAI-1	Plasminogen activator inhibitor-1
RAS	Rat sarcoma
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
GEO	Gene Expression Omnibus
DEGs	Differentially expressed genes
FC	Fold change
PPI	Protein–protein interaction
HDAC	Histone deacetylase
AAV	Adeno-associated virus
siRNAs	Small interfering RNAs

Acknowledgements
Not applicable.

Author contributions
All authors contributed equally to this work.

Funding
Not applicable.

Availability of data and materials
The dataset utilized in this study is publicly available from the GEO database under the accession number GSE45709. Researchers interested in accessing the data can retrieve them directly from the GEO database at [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE45709].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 2 August 2023 Accepted: 25 June 2024
Published online: 09 August 2024

References

1. Andrade Silva M, da Silva AR, de Amaral MA, Fragas MG, Câmara NOS. Metabolic alterations in SARS-CoV-2 infection and its implication in kidney dysfunction. Front Physiol. 2021;12:624698.
2. Barzilai A, Melamed E. Molecular mechanisms of selective dopaminergic neuronal death in Parkinson's disease. Trends Mol Med. 2003;9:126–32.
3. Bates CM. Role of fibroblast growth factor receptor signaling in kidney development. Am J Physiol-Renal Physiol. 2011;301:F245–51. https://doi.org/10.1152/ajprenal.00186.2011.
4. Bhatelia K, Singh K, Singh R. TLRs: linking inflammation and breast cancer. Cell Signal. 2014;26:2350–7.
5. Blackwell C, Sherk C, Fricko M, Ganji G, Barnette M, Hoang B, Tunstead J, Skedzielewski T, Alsaid H, Jucker BM. Inhibition of FGF/FGFR autocrine signaling in mesothelioma with the FGF ligand trap, FP-1039/GSK3052230. Oncotarget. 2016;7:39861.
6. Blondel VD, Guillaume J-L, Lambiotte R, Lefebvre E. Fast unfolding of communities in large networks. J Stat Mech: Theory Exp. 2008;2008:P10008.
7. Burghardt T, Kastner J, Suleiman H, Rivera-Milla E, Stepanova N, Lottaz C, Kubitza M, Böger CA, Schmidt S, Gorski M. LMX1B is essential for the maintenance of differentiated podocytes in adult kidneys. J Am Soc Nephrol. 2013;24:1830–48.
8. Cancilla B, Davies A, Cauchi JA, Risbridger GP, Bertram JF. Fibroblast growth factor receptors and their ligands in the adult rat kidney. Kidney Int. 2001;60:147–55.
9. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Gene Med. 2012;14:10–26.
10. Cecchini R, Cecchini AL. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Med Hypotheses. 2020;143: 110102.
11. Chang B, Chen W, Zhang Y, Yang P, Liu L. Tripterygium wilfordii mitigates hyperglycemia-induced upregulated Wnt/β-catenin expression and kidney injury in diabetic rats. Exp Ther Med. 2018;15:3874–82.
12. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV, Clark NR, Ma'ayan A. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinf. 2013;14:1–14.
13. Chen JJ, Delongchamp RR, Tsai C-A, Hsueh H, Sistare F, Thompson KL, Desai VG, Fuscoe JC. Analysis of variance components in gene expression data. Bioinformatics. 2004;20:1436–46.
14. Chen K, Chen J, Wang L, Yang J, Xiao F, Wang X, Yuan J, Wang L, He Y. Parkin ubiquitinates GATA4 and attenuates the GATA4/GAS1 signaling and detrimental effects on diabetic nephropathy. FASEB J. 2020;34:8858–75.
15. Chen X, Tan H, Xu J, Tian Y, Yuan Q, Zuo Y, Chen Q, Hong X, Fu H, Hou FF. Klotho-derived peptide 6 ameliorates diabetic kidney disease by targeting Wnt/β-catenin signaling. Kidney Int. 2022;102:506–20.
16. Chiaradia E, Tancini B, Emiliani C, Delo F, Pellegrino RM, Tognoloni A, Urbanelli L, Buratta S. Extracellular vesicles under oxidative stress conditions: biological properties and physiological roles. Cells. 2021;10:1763.
17. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667–75. https://doi.org/10.1056/NEJMoa010713.

18. De Clercq E. Potential clinical applications of the CXCR4 antagonist bicyclam AMD3100. Mini Rev Med Chem. 2005;5:805–24.
19. Dempsey K, Ali H. 2011. Evaluation of essential genes in correlation networks using measures of centrality, in: 2011 IEEE International Conference on Bioinformatics and Biomedicine Workshops (BIBMW). IEEE, pp. 509–515.
20. Devericks EN, Carson MS, McCullough LE, Coleman MF, Hursting SD. The obesity–breast cancer link: a multidisciplinary perspective. Cancer Metastasis Rev. 2022;41:607–25.
21. Di Raimondo D, Tuttolomondo A, Buttà C, Miceli S, Licata G, Pinto A. Effects of ACE-inhibitors and angiotensin receptor blockers on inflammation. Curr Pharm Des. 2012;18:4385–413.
22. Ding J-H, Xiao Y, Zhao S, Xu Y, Xiao Y-L, Shao Z-M, Jiang Y-Z, Di G-H. Integrated analysis reveals the molecular features of fibrosis in triple-negative breast cancer. Mol Ther-Oncol. 2022;24:624–35.
23. Dongiovanni P, Paolini E, Corsini A, Sirtori CR, Ruscica M. Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: from epidemiology to drug approaches. Eur J Clin Invest. 2021;51: e13519.
24. Donia A, Bokhari H. Apoptosis induced by SARS-CoV-2: can we target it? Apoptosis. 2021;26:7–8.
25. Elyasi F, Kashi Z, Tasfieh B, Bahar A, Khademloo M. Sexual dysfunction in women with type 2 diabetes mellitus. Iran J Med Sci. 2015;40:206.
26. Enomoto A, Takeda M, Tojo A, Sekine T, Cha SH, Khamdang S, Takayama F, Aoyama I, Nakamura S, Endou H. Role of organic anion transporters in the tubular transport of indoxyl sulfate and the induction of its nephrotoxicity. J Am Soc Nephrol. 2002;13:1711–20.
27. Essig J, Belz G, Wellstein A. The assessment of ACE activity in man following angiotensin I challenges: a comparison of cilazapril, captopril and enalapril. Brit J Clinical Pharm. 1989. https://doi.org/10.1111/j.1365-2125.1989.tb03485.x.
28. Estrada E. Virtual identification of essential proteins within the protein interaction network of yeast. Proteomics. 2006;6:35–40. https://doi.org/10.1002/pmic.200500209.
29. Falconi CA, Junho CV, Fogaça-Ruiz F, Vernier IC, Da Cunha RS, Stinghen AE, Carneiro-Ramos MS. Uremic toxins: an alarming danger concerning the cardiovascular system. Front Physiol. 2021;12:686249.
30. Filippatos G, Uhal BD. Blockade of apoptosis by ACE inhibitors and angiotensin receptor antagonists. Curr Pharm Des. 2003;9:707–14.
31. Fujii H, Goto S, Fukagawa M. Role of uremic toxins for kidney, cardiovascular, and bone dysfunction. Toxins. 2018;10:202.
32. Fuster JJ, Zuriaga MA, Ngo DT-M, Farb MG, Aprahamian T, Yamaguchi TP, Gokce N, Walsh K. Noncanonical Wnt signaling promotes obesity-induced adipose tissue inflammation and metabolic dysfunction independent of adipose tissue expansion. Diabetes. 2015;64:1235–48.
33. George SJ. Wnt pathway: a new role in regulation of inflammation. Arterioscler Thromb Vasc Biol. 2008;28:400–2.
34. Guo WT, Wang XW, Yan YL, Li YP, Yin X, Zhang Q, Melton C, Shenoy A, Reyes NA, Oakes SA. Suppression of epithelial–mesenchymal transition and apoptotic pathways by miR-294/302 family synergistically blocks let-7-induced silencing of self-renewal in embryonic stem cells. Cell Death Differ. 2015;22:1158–69.
35. Hadari Y, Schlessinger J. FGFR3-targeted mAb therapy for bladder cancer and multiple myeloma. J Clin Investig. 2009;119:1077–9.
36. Hicks SC, Irizarry RA. 2014. When to use quantile normalization? BioRxiv 012203.
37. Hirsch AT, Talsness CE, Smith AD, Schunkert H, Ingelfinger JR, Dzau VJ. Differential effects of captopril and enalapril on tissue renin-angiotensin systems in experimental heart failure. Circulation. 1992;86:1566–74. https://doi.org/10.1161/01.CIR.86.5.1566.
38. Ho C, Hsu Y-C, Lei C-C, Mau S-C, Shih Y-H, Lin C-L. Curcumin rescues diabetic renal fibrosis by targeting superoxide-mediated Wnt signaling pathways. Am J Med Sci. 2016;351:286–95.
39. Hoellenriegel J, Zboralski D, Maasch C, Rosin NY, Wierda WG, Keating MJ, Kruschinski A, Burger JA. The Spiegelmer NOX-A12, a novel CXCL12 inhibitor, interferes with chronic lymphocytic leukemia cell motility and causes chemosensitization. Blood. 2014;123:1032–9.
40. Huang G, Li H, Zhang H. Abnormal expression of mitochondrial ribosomal proteins and their encoding genes with cell apoptosis and diseases. Int J Mol Sci. 2020;21:8879.
41. Iyer LM, Nagarajan S, Woelfer M, Schoger E, Khadjeh S, Zafiriou MP, Kari V, Herting J, Pang ST, Weber T. A context-specific cardiac β-catenin and GATA4 interaction influences TCF7L2 occupancy and remodels chromatin driving disease progression in the adult heart. Nucleic Acids Res. 2018;46:2850–67.
42. Jhawar SR, Lowenstein J, Zavadil J, Singh P, Torres D, Ramirez-Valle F, Kassem H, Fernandez T, n.d. The molecular basis of the renal and vascular consequences of Uremia.
43. Kawakami T, Ren S, Duffield JS. Wnt signalling in kidney diseases: dual roles in renal injury and repair. J Pathol. 2013;229:221–31.
44. Kuo N-T, Norman JT, Wilson PD. Acidic FGF regulation of hyperproliferation of fibroblasts in human autosomal dominant polycystic kidney disease. Biochem Mol Med. 1997;61:178–91.
45. Lauriola M, Farré R, Evenepoel P, Overbeek SA, Meijers B. Food-derived uremic toxins in chronic kidney disease. Toxins. 2023;2023(15):116.
46. Li J, Xie S, Teng W. Sulforaphane attenuates nonalcoholic fatty liver disease by inhibiting hepatic steatosis and apoptosis. Nutrients. 2021;14:76.
47. Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins. 2021;13:142.
48. Liu J, Pan S, Hsieh MH, Ng N, Sun F, Wang T, Kasibhatla S, Schuller AG, Li AG, Cheng D, Li J, Tompkins C, Pferdekamper A, Steffy A, Cheng J, Kowal C, Phung V, Guo G, Wang Y, Graham MP, Flynn S, Brenner JC, Li C, Villarroel MC, Schultz PG, Wu X, McNamara P, Sellers WR, Petruzzelli L, Boral AL, Seidel HM, McLaughlin ME, Che J, Carey TE, Vanasse G, Harris JL. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. Proc Natl Acad Sci USA. 2013;110:20224–9. https://doi.org/10.1073/pnas.1314239110.
49. Liu Y, Huang T, Zhao X, Cheng L. MicroRNAs modulate the Wnt signaling pathway through targeting its inhibitors. Biochem Biophys Res Commun. 2011;408:259–64.
50. Lo C-S, Liu F, Shi Y, Maachi H, Chenier I, Godin N, Filep JG, Ingelfinger JR, Zhang S-L, Chan JS. Dual RAS blockade normalizes angiotensin-converting enzyme-2 expression and prevents hypertension and tubular apoptosis in Akita angiotensinogen-transgenic mice. Am J Physiol-Renal Physiol. 2012;302:F840–52.
51. Longhitano L, Forte S, Orlando L, Grasso S, Barbato A, Vicario N, Parenti R, Fontana P, Amorini AM, Lazzarino G. The crosstalk between GPR81/IGFBP6 promotes breast cancer progression by modulating lactate metabolism and oxidative stress. Antioxidants. 2022;11:275.
52. Lowery SA, Sariol A, Perlman S. Innate immune and inflammatory responses to SARS-CoV-2: Implications for COVID-19. Cell Host Microbe. 2021;29:1052–62.
53. Loyer X, Zlatanova I, Devue C, Yin M, Howangyin K-Y, Klaihmon P, Guerin CL, Kheloufi M, Vilar J, Zannis K. Intra-cardiac release of extracellular vesicles shapes inflammation following myocardial infarction. Circ Res. 2018;123:100–6.
54. Ma C, Shi L, Huang Y, Shen L, Peng H, Zhu X, Zhou G. Nanoparticle delivery of Wnt-1 siRNA enhances photodynamic therapy by inhibiting epithelial–mesenchymal transition for oral cancer. Biomater Sci. 2017;5:494–501.
55. Maheshwari V, Tao X, Thijssen S, Kotanko P. Removal of protein-bound uremic toxins using binding competitors in hemodialysis: a narrative review. Toxins. 2021;13:622.
56. Markham A. Erdafitinib: first global approval. Drugs. 2019;79:1017–21. https://doi.org/10.1007/s40265-019-01142-9.
57. Miyazaki T, Ise M, Seo H, Niwa T. 1997. Indoxyl sulfate increases the gene expressions of TGF-β1 TIMP-1 and pro-α1 (1) collagen in uremic rat kidneys. Kidney international supplement.
58. Motojima M, Hosokawa A, Yamato H, Muraki T, Yoshioka T. Uremic toxins of organic anions up-regulate PAI-1 expression by induction of NF-κB and free radical in proximal tubular cells. Kidney Int. 2003;63:1671–80.
59. Norris K, Vaughn C. The role of renin–angiotensin–aldosterone system inhibition in chronic kidney disease. Expert Rev Cardiovasc Ther. 2003;1:51–63.
60. O'Cearbhaill RE, McMeekin DS, Mantia-Smaldone G, Gunderson C, Sabbatini P, Cattaruzza F, Fischer M, Kapoun AM, Xu L, Dupont J, Brachmann RK, Farooki A, Moore KN. Phase 1b of WNT inhibitor ipafricept (IPA, decoy receptor for WNT ligands) with carboplatin (C) and paclitaxel (P) in

recurrent platinum-sensitive ovarian cancer (OC). JCO. 2016;34:2515–2515. https://doi.org/10.1200/JCO.2016.34.15_suppl.2515.
61. Parton M, Dowsett M, Smith I. Studies of apoptosis in breast cancer. BMJ. 2001;322:1528–32.
62. Pecoraro A, Pagano M, Russo G, Russo A. Ribosome biogenesis and cancer: overview on ribosomal proteins. Int J Mol Sci. 2021;22:5496.
63. Petrescu M, Vlaicu SI, Ciumărnean L, Milaciu MV, Mărginean C, Florea M, Vesa ŞC, Popa M. Chronic inflammation—a link between nonalcoholic fatty liver disease (NAFLD) and dysfunctional adipose tissue. Medicina. 2022;58:641.
64. Phanhthilath N, Hakim S, Su C, Liu A, Subramonian D, Lesperance J, Zage PE. Mechanisms of efficacy of the FGFR1–3 inhibitor AZD4547 in pediatric solid tumor models. Invest New Drugs. 2020;38:1677–86. https://doi.org/10.1007/s10637-020-00933-2.
65. Prendiville TW, Guo H, Lin Z, Zhou P, Stevens SM, He A, VanDusen N, Chen J, Zhong L, Wang D-Z. Novel roles of GATA4/6 in the postnatal heart identified through temporally controlled, cardiomyocyte-specific gene inactivation by adeno-associated virus delivery of Cre recombinase. PLoS ONE. 2015;10: e0128105.
66. Pulkkinen K, Murugan S, Vainio S. Wnt signaling in kidney development and disease. Organogenesis. 2008;4:55–9.
67. Ritchie ME, Phipson B, Wu DI, Hu Y, Law CW, Shi W, Smyth GK. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015;43:e47–e47.
68. Rius-Pérez S, Pérez S, Martí-Andrés P, Monsalve M, Sastre J. Nuclear factor kappa B signaling complexes in acute inflammation. Antioxid Redox Signal. 2020;33:145–65.
69. Rysz J, Franczyk B, Ławiński J, Olszewski R, Ciałkowska-Rysz A, Gluba-Brzózka A. The impact of CKD on uremic toxins and gut microbiota. Toxins. 2021;13:252.
70. Sallée M, Dou L, Cerini C, Poitevin S, Brunet P, Burtey S. The aryl hydrocarbon receptor-activating effect of uremic toxins from tryptophan metabolism: a new concept to understand cardiovascular complications of chronic kidney disease. Toxins. 2014;6:934–49.
71. Sander V, Naylor RW, Davidson AJ. Mind the gap: renal tubule responses to injury and the role of Cxcl12 and Myc. Annal Transl Med. 2019;7:S30.
72. Shao J-S, Aly ZA, Lai C-F, Cheng S-L, Cai JUN, Huang E, Behrmann ABE, Towler DA. Vascular Bmp–Msx2–Wnt signaling and oxidative stress in arterial calcification. Ann NY Acad Sci. 2007;1117:40–50.
73. Sica DA, Gehr TWB, Ghosh S. Clinical pharmacokinetics of Losartan. Clin Pharmacokinetics. 2005;44:797–814. https://doi.org/10.2165/00003088-200544080-00003.
74. Smith DC, Lee Rosen MW, Zhang C, Xu L, Chugh R, Tolcher A, Goldman J, Dupont J, Rainer K, Brachmann KP, Kapoun AM. 2013. Biomarker analysis in the first-in-human Phase 1a study for vantictumab (OMP-18R5; anti-Frizzled) demonstrates pharmacodynamics (PD) modulation of the Wnt pathway in patients with advanced solid tumors, in: Molecular cancer therapeutics. amer assoc cancer research 615 chestnut st, 17th floor, Philadelphia, PA ….
75. Soini T, Pihlajoki M, Kyrönlahti A, Andersson LC, Wilson DB, Heikinheimo M. Downregulation of transcription factor GATA4 sensitizes human hepatoblastoma cells to doxorubicin-induced apoptosis. Tumour Biol. 2017;39:101042831769501. https://doi.org/10.1177/1010428317695016.
76. Song A, Jiang A, Xiong W, Zhang C. The role of CXCL12 in kidney diseases: a friend or foe? Kidney Dis. 2021;7:176–85.
77. Strutz F. The role of FGF-2 in renal fibrogenesis. Front Biosci. 2009;1:125–31.
78. Sun C-Y, Chang S-C, Wu M-S. Uremic toxins induce kidney fibrosis by activating intrarenal renin–angiotensin–aldosterone system associated epithelial-to-mesenchymal transition. PLoS ONE. 2012;7: e34026.
79. Sun C-Y, Hsu H-H, Wu M-S. p-Cresol sulfate and indoxyl sulfate induce similar cellular inflammatory gene expressions in cultured proximal renal tubular cells. Nephrol Dial Transplant. 2013;28:70–8.
80. Sun C-Y, Young G-H, Hsieh Y-T, Chen Y-H, Wu M-S, Wu V-C, Lee J-H, Lee C-C. Protein-bound uremic toxins induce tissue remodeling by targeting the EGF receptor. J Am Soc Nephrol. 2015;26:281–90.
81. Tan RJ, Zhou D, Zhou L, Liu Y. Wnt/β-catenin signaling and kidney fibrosis. Kidney Int Suppl. 2014;4:84–90.
82. Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, Ishigami M, Toyoda H, Wong VW-S, Peleg N. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology. 2020;158:1611–25.
83. Titan SM, Zatz R, Graciolli FG, dos Reis LM, Barros RT, Jorgetti V, Moysés RM. FGF-23 as a predictor of renal outcome in diabetic nephropathy. Clin J Am Soc Nephrol. 2011;6:241–7.
84. Tolcher AW, Papadopoulos KP, Patnaik A, Wilson K, Thayer S, Zanghi J, Gemo AT, Kavanaugh WM, Keer HN, LoRusso PM. A phase I, first in human study of FP-1039 (GSK3052230), a novel FGF ligand trap, in patients with advanced solid tumors. Ann Oncol. 2016;27:526–32.
85. Trueb B, Amann R, Gerber SD. Role of FGFRL1 and other FGF signaling proteins in early kidney development. Cell Mol Life Sci. 2013;70:2505–18. https://doi.org/10.1007/s00018-012-1189-9.
86. Tseng M-H, Huang S-M, Huang J-L, Fan W-L, Konrad M, Shaw SW, Lien R, Chien H-P, Ding J-J, Wu T-W. Autosomal recessive renal tubular dysgenesis caused by a founder mutation of angiotensinogen. Kidney International Reports. 2020;5:2042–51.
87. Tseng M-H, Huang S-M, Konrad M, Huang J-L, Shaw SW, Tian Y-C, Chueh H-Y, Fan W-L, Wu T-W, Ding J-J. Effect of hydrocortisone on angiotensinogen (AGT) mutation-causing autosomal recessive renal tubular dysgenesis. Cells. 2021;10:782.
88. Uemae Y, Ishikawa E, Osuka S, Matsuda M, Sakamoto N, Takano S, Nakai K, Yamamoto T, Matsumura A. CXCL12 secreted from glioma stem cells regulates their proliferation. J Neurooncol. 2014;117:43–51. https://doi.org/10.1007/s11060-014-1364-y.
89. Viazzi F, Bonino B, Cappadona F, Pontremoli R. Renin–angiotensin–aldosterone system blockade in chronic kidney disease: current strategies and a look ahead. Intern Emerg Med. 2016;11:627–35.
90. Wang H, Zhang R, Wu X, Chen Y, Ji W, Wang J, Zhang Y, Xia Y, Tang Y, Yuan J. The wnt signaling pathway in diabetic nephropathy. Front Cell Dev Biol. 2022;9: 701547.
91. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage M1–M2 polarization balance. Front Immunol. 2014;5: 113523.
92. Wojtaszek E, Oldakowska-Jedynak U, Kwiatkowska M, Glogowski T, Malyszko J. Uremic toxins, oxidative stress, atherosclerosis in chronic kidney disease, and kidney transplantation. Oxid Med Cell Longev. 2021;2021:1.
93. Wu X, Luo F, Li J, Zhong X, Liu K. Tankyrase 1 inhibitor XAV939 increases chemosensitivity in colon cancer cell lines via inhibition of the Wnt signaling pathway. Int J Oncol. 2016;48:1333–40.
94. Wu X, Qian L, Zhao H, Lei W, Liu Y, Xu X, Li J, Yang Z, Wang D, Zhang Y. CXCL12/CXCR4: an amazing challenge and opportunity in the fight against fibrosis. Ageing Res Rev. 2022;83:101809.
95. Yakulov TA, Todkar AP, Slanchev K, Wiegel J, Bona A, Groß M, Scholz A, Hess I, Wurditsch A, Grahammer F. CXCL12 and MYC control energy metabolism to support adaptive responses after kidney injury. Nat Commun. 2018;9:3660.
96. Yim HE, Yoo KH. Renin-angiotensin system-considerations for hypertension and kidney. Electrolytesn Blood Pressure. 2008;6:42–50.
97. Ying J, Stuart D, Hillas E, Gociman BR, Ramkumar N, Lalouel J-M, Kohan DE. Overexpression of mouse angiotensinogen in renal proximal tubule causes salt-sensitive hypertension in mice. Am J Hypertens. 2012;25:684–9.
98. Zaidi FS, Fatima U, Usmani BA, Jafri AR. Comprehending nodes essentiality through centrality measures in biological networks. IJCSNS. 2019;19:65.
99. Zhang L, Lu P, Yan L, Yang L, Wang Y, Chen J, Dai J, Li Y, Kang Z, Bai T. MRPL35 is up-regulated in colorectal cancer and regulates colorectal cancer cell growth and apoptosis. Am J Pathol. 2019;189:1105–20.
100. Zhou T-B, Ou C, Jiang Z-P, Xiong M-R, Zhang F. Potential signal pathway between all-trans retinoic acid and LMX1B in hypoxia-induced renal tubular epithelial cell injury. J Recept Signal Transduct. 2016;36:53–6. https://doi.org/10.3109/10799893.2015.1018434.
101. Zhou W, Jiang D, Tian J, Liu L, Lu T, Huang X, Sun H. Acetylation of H3K4, H3K9, and H3K27 mediated by p300 regulates the expression of GATA4 in cardiocytes. Genes Dis. 2019;6:318–25.
102. Ziolkowska S, Binienda A, Jablkowski M, Szemraj J, Czarny P. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. Int J Mol Sci. 2021;22:11128.

Publisher's Note