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Molecular insights into inflammatory markers in chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a slow progressive disease with persistent inflammation as well as kidney tissue injury leading to dysfunctional kidney function with high morbidity. We explored in this project the molecular as well as CKD inflammatory-associated epigenetic pathways as well as assessed prospective treatments of pathway interfering. Through biochemical assay, histopathological analysis, as well as molecular biology methods, we investigated inflammatory mediators including NF-κB, JAK/STAT, as well as NLRP3 inflammasome activation with concomitant pro-inflammatory cytokines IL-6, TNF-α, IL-1β as well as acute-phase reactants CRP, SAA. Our outcomes unveiled high CKD subjects' systemic inflammatory profile with high kidney tissue injury prevalence with concomitant fibrosis. Epigenetic alterations—DNA methylation shifts, histone modifications, as well as dysregulated microRNA expression—were further unveiled as initiators of persistent inflammatory response as well as disease progression. Therapeutic intervention of anti-inflammatory drugs with concomitant epigenetic regulators suppressed inflammatory biomarkers substantially with corresponding histopathological injury decline. Our discovery points to specificity of CKD pathogenesis understanding insight of combining molecular pathways of inflammatory response with those of molecular pathways of epigenetic regulation. More importantly, our exploration points towards a prospective treatment of dual-targeting to interrupt inflammatory-epigenetic vicious transmission loop thus capping disease progression. Our exploration takes a step further towards a comprehensive CKD molecular as well as an epigenetic syllabus as well as understanding of new precision medicine treatments for superior clinical effects with a glimpse of prospective new clinical trials for eventual proof of concept into delicate treatment regimens.

Keywords: Chronic kidney disease; Inflammation; NF-κB pathway; Epigenetics; DNA methylation; MicroRNA

1. Introduction

1.1. Overview of Chronic Kidney Disease (CK)

Chronic Kidney Disease or CKD is a progressive disease with progressive decline in kidney function over months to years. Clinically, CKD involves a decrease of glomerular filtration rate (GFR) to < 60 mL/min/1.73 m^2 and/or kidney injury (e.g., albuminuria or morphological lesions) for a duration of more than three months (Kurokawa et al., 2022). CKD further classifies into five stages of differing severity of GFR, stage 1 (normal or high GFR with kidney injury) to stage 5, defined as end-stage renal disease or ESRD, where kidney replacement therapy with dialysis or transplantation is required (Katadane et al., 2023).

Prevalence of CKD increased worldwide over recent decades as well as emerged as a problem of a public health issue. It affects about 10–15% of adult human beings' populations across the globe with uneven distribution in low- as well as middle-income countries with limited access to medical care as well as a time lag in its detection (Liyanage et al., 2023). In Taiwan, for instance, a prospective cohort of more than 462,000 adults declared CKD as a significant contributor to

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death due to all causes, vindicating its importance both clinically as well as socioeconomically (Wen et al., 2022). Correspondingly, global research declared a shortfall of access to centres for dialysis as well as centres for transplant, especially in sub-Saharan Africa as well as some parts of Asia, with partial medical care infrastructure (Liyanage et al., 2023).

CKD is a progressive chronic disease with various stages, frequently asymptomatically at earlier disease stages. Hypertension, cardiovascular disease (CVD), mineral as well as bone illness, anemia, as well as malnutrition become relevant with diminishing kidney function (Stenvinkel et al., 2005; Zha and Qian, 2017). Cardiovascular mortality in CKD individuals particularly stands exceedingly high, well prior to ESRD, primarily due to chronic inflammation, oxidative stress, as well as metabolic dysregulation (Sun et al., 2016; Biswas, 2016). Additionally, protein-energy wasting as well as immunosuppression increase risk for infections as well as quality of life compromise (Iorember, 2018).

The disease progression of CKD is dictated by a constellation of non-modifiable as well as modifiable determinants from diabetes, high blood pressure, heredity, as well as lifestyle. Treatment as well as early diagnosis dominate a search for limitation of disease progression as well as complication prevention. For this reason, understanding of inflammatory as well as molecular pathways of CKD takes preeminence for enhancing preventive as well as treatment modality establishment (Katadane et al., 2023).

1.2. Role of Inflammation in CKD Path

Universal common denominator of progression of chronic kidney disease (CKD) as well as its pathogenesis includes chronic inflammation. More and more often it is acknowledged to be a causality as well as kidney injury aftereffect leading to structural injury, loss of function of kidneys, as well as to systemic effects. CKD chronic low-grade inflammation is a result of oxidative stress, toxic products of uremia, metabolite acidosis, as well as intestinal endotoxins (Evenepoel et al., 2017; Biswas, 2016). Such stimulations induce inflammatory responses leading to maintenance of cytokine production as well as leukocyte infiltration into kidney parenchyma.

CKD's dyscontrolled inflammatory cytokine network, which includes interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10), is amenable to intervention (Stenvinkel et al., 2005). Mesangial proliferation, tubular cell apoptosis, and fibrosis are activated with resultant exaggeration of nephron loss and progression of disease (Katadane et al., 2023). Chronic inflammation is a chief mediator of complication formation of CKD, including cardiovascular disease as well as protein-energy wasting (Sun et al., 2016; Iorember, 2018).

Elucidating inflammatory processes of CKD pathogenesis would be significant for identifying target molecules as well as for optimizing treatment intervention. Treatment with an anti-inflammatory can slow CKD progression as well as increase clinical outcomes for individuals (Hu et al., 2019; Li et al., 2023).

Study Objectives

The following specific aims are addressed in this study

- To examine the molecular mechanisms of inflammation in CKD
- To identify inflammatory markers
- To present clinical implications and future directions

2. Pathophysiology of CKD-Associated Inflammation

2.1. Causative Factors of Inflammation in

The CKD related chronic inflammatory disease is a multi-factorial disease as well as a summary of multiple metabolic, immunologic, as well as therapeutic stresses. Other than these stimulations for kidney injury, they equally play a contribution towards extra-renal effects like cardiovascular disease, malnutrition, as well as anaemia.

2.2. Uremic Toxins

Another main reason for CKD inflammation is an accumulation of uremic toxins—子 stances that must be cleared in the presence of normal kidneys. As kidney function declines, the toxin accumulates and initiates an activation of an imm''''ic response through stimulating monocytes as well as endothelial cells into releasing inflammatory cytokines (Autore et al., 2021). Methylguanidine, a substance of uremia, was discovered to modulate an experimental as well as a live

condition of tumour necrosis factor-alpha (TNF-α) production (Marzocco et al., 2021). Methylguanidine was discovered to induce oxidative injury as well as inflammatory signalling into kidney tissue, thereby aggravating kidney injury (Marzocco et al., 2022).

2.3. Oxidative Stress

Oxidative stress from reactive oxygen species (ROS) with antioxidant defense disbalance is another potent trigger of inflammatory response in CKD. Increased ROS in CKD induce lipid peroxidations, DNA lesions, as well as redox-sensitive activation of transcription factor like NF-κB for pro-inflammatory gene expression adjustment (Biswas, 2016). Resulting inflammation drives fibrotic conversion of kidney tissue alongside nephron function loss. Proof holds for oxidative stress's dependence on chronic inflammatory response as an explanation for antioxidant paradox—e.g., supplementing is unable to suppress inflammatory response—is a reality (Biswas, 2016; Hu et al., 2019).

2.4. Factors of relation of dialysis

The dialysis, being a maintenance of life measure, imposes additional pro-inflammatory stimulations. In intermittent CAPD/HD, intermittent exposure of blood to bio-incompatible membranes as well as bio-incompatible dialysis solutions can induce activation of a complement as well as innate as well as acquired immunities with concomitant cytokine release (Oncel et al., 2016). On top of this, bio-incompatibility of dialysis as well as endotoxin contamination of dialysisable waters adds to an increase in an inflammatory response. CAPD/HD individuals have high levels of inflammatory markers like C-reactive protein (CRP), TNF-α, as well as IL-6 (Oncel et al., 2016). Other than marking for presence of a systemic inflammatory response, they are associated with high cardiovascular morbidity as well as mortality among CKD individuals.

2.5. Signal Transduction in

Emerging but new CKD-associated causality of infl ammations is dysbiosis of intestinal microbiota. Kidney disease imposes a adverse impact on intestinal environment through phosphorus binder action, nutritional limitation, as well as uremia, impairing diversity as well as content of microbiota. Dysbiosis facilitates uricase— as well as urease-secreting bacterium overgrowth with resultant secretion of cytotoxic metabolites such as indoxyl sulfate as well as p-cresyl sulfate. Those absorbed toxicants stimulate monocyte activation as well as endothelial cell damage with resultant infl ammation of a systemic nature. Finally, impairment of intestinal barrier function—"leak gut"—facilitates passage of bacterial fragment as well as endotoxins across into systemic circulation, further exaggerating immunes responses (Evenepoel et al., 2017).

2.5.1. Immune System Dysregulation in CKD

Chronic Kidney Disease or CKD is well established to beproduced due to extreme dysregulation of innate as well as adaptive immunesystem. Immune dysregulation not only is responsible for continuous inflammation as well as kidney injury but is accountable for ineffective defence mechanism of a host so that CKD patients remain vulnerable to infections, malignancies, as well as cardiovascular disease.

2.6. Innate Immunity: Macrophages and D

The very first defence mechanism is innate immunity, of which dysregulation exists in CKD. Bivalent functions of macrophages are they both take parts in anatomic surveillance as well as tissue repair, but in inflammatory response as well as fibrosis once they get repeatedly activated (Katadane et al., 2023). Macrocytes tend towards inflammatory M1 type in CKD, resulting in excessive secretion of tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), as well as reactive oxygen species (ROS), which increase tissue injury as well as hasten disease progression.

The professional antigen-presenting cells, dendritic cells (DCs), are also compromised due to their dysfunctional activity in CKD. Their function of capturing, processing, and presenting antigens is compromised with aberrant activation of T-cells and disruption of tolerance (Hu et al., 2019). DC homeostasis is disrupted due to the chronic inflammatory microenvironment, which promotes their pro-inflammatory functions and diminishes their suppressive activity, thus maintaining immune dysregulation.

2.7. Adapter Immunity: B and T

CKD significantly impacts adaptive immunities. CD4+ and CD8+ cells have exhibited signs of functional exhaustion in CKD subjects. Cellular immunities are blunted due to senescence and apoptosis of T-cells from chronic exposure to injury from uremic toxin as well as chronic inflammation (Zha and Qian, 2017). This is a paradoxical situation where a patient is confronted with a chronic inflammatory disease but simultaneously becomes immunocompromised due to

inability to mount a sufficient response against infection or cancer. Regulatory T-cells (Tregs), which would otherwise suppress an inflammatory response activation as well as self-tolerance maintenance, significantly are deficient/ functionally compromised in CKD with resulting uncontrolled inflammatory responses (Stenvinkel et al., 2005). Corresponding B-cells are deficient with a deranged phenotype as well as antibody production. Such dysfunctions further compromise humoral protection as well as infectibility (Hu et al., 2019). Accumulations of all of these T- as well as B-cell dysfunctions are an immunosurveillance apparatus fault as well as an exaggerated autoimmune reactivity**.**

2.8. Immune Exhaustion and Cytokine Im

Another frequent characteristic of CKD dysregulation of the immune is a cytokine imbalance of anti-inflammatory as well as pro-inflammatory cytokines. Progressive CKD upregulation of pro-inflammatory cytokines like interleukin-6 (IL-6), TNF-α, as well as interferon-gamma (IFN-γ) drives catabolism, vascular calcification, as well as cardiovascular risk (Sun et al., 2016). Anti-inflammatory cytokines like interleukin-10 (IL-10) are inhibited or abolished due to receptor desensitisation or disruption of downstream signalling (Stenvinkel et al., 2005)

Ongoing activation of immunes cells generates a state of immunes exhaustion due to low proliferation, defect cytokine secretion, as well as elevated inhibitory receptor expression of PD-1 as well as CTLA-4 on T-cells (Hu et al., 2019). Immunes exhaustion constrains immunes response towards newly emerging antigens as well as generates vaccine hypo-responsiveness, inefficient control of infections, as well as susceptibility towards cancer in CKD individuals.

3. Major inflammatory markers of CK

3.1. Pro-inflammatory Cytokines in CKD

The pro-inflammatory cytokines are accountable for pathogenesis as well as progression of Chronic Kidney Disease (CKD). IL-6, TNF-α, as well as IL-1β are cytokines for balancing inflammatory iff responses for vascular injury, tissue fibrosis, as well as tissue inflammation. Overexpression of cytokines shares commonalities for CKD subjects as well as with adverse clinical outcomes, for instance, cardiovascular disease, anaemia, as well as protein-energy wasting.

3.2. Interleukin-6 (IL-6)

The IL-6 represents a cytokine possessing a pleiotropic activity, which participates in metabolism as well as control of inflammatory reactions as well as control of inflammatory response. IL-6 is significantly upregulated in CKD due to chronic kidney injury, oxidative stress, as well as toxic hes exposure of uremia (Stenvinkel et al., 2005). Cytokine indicates inflammatory reactions of a systemic character due to induction of acute-phase protein biosynthesis of liver, including C-reactive protein (CRP), clinical inflammatory marker.

Furthermore, IL-6 plays a role in renal fibrosis because of its induction of a rise in JAK/STAT signal pathway activation resulting in an increase in division of fibroblast alongside extracellular matrix deposition. Other than that, high IL-6 levels are connected with an indication of left ventricular hypertrophy alongside mortality in dialysis subjects (Hu et al., 2019). Not only is IL-6 persistent overexpression beneficial to kidney injury, but it also suppresses erythropoiesis alongside an anaemia causative of CKD.

3.3. Tumour Necrosis Factor-alpha (TNF-α)

TNF-α represents a common cytokine of inflammatory disease as well as of body immune homeostasis. TNF-α is produced mainly from monocytes as well as from activated macrophages upon exposure to injury, toxin, or infection. CKD continuously overproduces TNF-α due to oxidative stress as well as due to the environment of uremia (Marzocco et al., 2021). TNF-α generates adhesion molecule overproduction directly responsible for glomerular as well as for tubular injury due to excessive leukocyte migration as well as due to apoptosis of renal cells.

Moreover, TNF-α facilitates further adhesion of CKD subjects' catabolic profile further with muscle catabolism, anorexia, and insulin resistance (Sun et al., 2016). TNF-α facilitates further vascular inflammation further inclining CKD subjects towards atherosclerosis as well as cardiovascular disease. Most importantly, methylguanidine, a toxin of uremia, is revealed to act on TNF-α synthesis and thus vindicating toxin accumulation as a cause of inflammation (Marzocco et al., 2022).

3.4. Interleukin-1 Beta (IL-1β)

Another important mediator of inflammatory reaction in CKD is IL-1β. Produced nearly entirely from activated monocytes as well as from macrophages, IL-1β is playing an initiating as well as an inflammaion-sustaining cascade

function. IL-1β promotes endothelial cell activation, initiates leukocyte adhesion, as well as generates additional cytokine production, thus creating a feed loop of self-sustaining inflammaion (Stenvinkel et al., 2005).

The cytokine is further censured for kidney fibrosis due to induction of mesangial cells' growth as well as increased activity of TGF-β, a main fibrogenic cytokine. Increased IL-1β level is further implicated with severe proteinuria, an indication of glomerular impairment, as well as high risk of cardiovascular disease (Hu et al., 2019). Chronically high IL-1β is further censured for bone as well as CKD mineral disease due to a disruption of balancing act of osteoclasts as well as osteoblasts.

3.4.1. Acute Phase Proteins

Acute phase proteins (APPs) are biomarkers that are synthesized mainly in the liver after a response of systemic inflammation. APPs are synthesized after induction due to pro-inflammatory cytokines, ie, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) (Stenvinkel et al., 2005). Elevated APPs in Chronic Kidney Disease (CKD) indicate chronic low-grade inflammation and are connected with disease progression as well as its corresponding comorbidities like cardiovascular disease, malnutrition, and anaemia.

3.4.2. C-reactive protein (CR)

The C-reactive protein, an acute phase protein, is well-researched and proven as a marker for inflammatory response of a systemic nature. It escalates exponentinally with inflammatory stimuli, infection, as well as tissue injury. For CKD subjects, CRP levels would be elevated chronically without having an infection due to constant exposure to oxidative stress, exposure to uremic toxin, as well as dysregulation of a person's immune system (Hu et al., 2019; Sun et al., 2016).

elevations of CKD of CRP for high cardiovascular risk predict because of its causative role in endothelial function impairment, instability of atherosclerotic plague, as well as vascular calcification. CRP shares an equal blame for activation of the complement as well as overactive adhesion of monocytes, thus benefiting renal as well as vascular injury (Stenvinkel et al., 2005). Elevated levels of CRP have been strongly related to mortality in dialysis individuals as well as are thought of as a central feature of malnutrition-inflammation-atherosclerosis (MIA) syndrome typical of advanced CKD (Iorember, 2018).

3.4.3. Serum Amyloid A (SAA)

Another acute phase protein that is markedly elevated during inflammation is serum amyloid A (SAA). As with CRP, SAA is produced in the liver in response to IL-6 and TNF-α. In CKD, high SAA levels have been connected with chronic inflammation in addition to progression of secondary amyloidosis, especially among long-term haemodialysis subjects (Evenepoel et al., 2017).

The SAA contributes to CKD pathogenesis due to its promotion of leukocyte chemotaxic, induction of cytokines of a pro-inflammatory nature, as well as an increase in oxidative stress. Moreover, it accumulates in tissue with a propensity of induction of amyloid deposition as well as organ dysfunction. SAA is related to high cardiovascular risk as well as malnutrition, thus clinical potential of CRP (Hu et al., 2019).

3.5. Chemokines and Adhesion Molecules

Chemokines with adhesion molecules are extremely important for regulating anatomic movement of immunocytes as well as for forming inflammatory reactions of chronic kidney disease (CKD). Oxidative stress, pro-inflammatory cytokine cytokines, as well as toxic compounds of uremia increase this molecule production, responsible for kidney parenchymal damage as well as inflammatory reactions of CKD objects (Stenvinkel et al., 2005; Marzocco et al., 2021). Monocyte Chemoattractant Protein-1 (MCP-1)

The Monocyte Chemoattractant Protein-1 (MCP-1) or CCL2 is itself a monocyte as well as a leukocyte recruitment chemokine to inflammatory sites. In CKD, its expression is very high in both glomeruli as well as in tubulointerstitium especially after injury as well as oxidative stress (Katadane et al., 2023). At high concentrations, MCP-1 is equivalent to proteinuria as well as interstitial fibrosis severity each of which happen to coincidentally be significant CKD progression markers.

MCP-1 is produced from various cell populations in the kidney, including mesangial as well as tubular epithelial cells, after they have been activated using pro-inflammatory mediators like TNF-α as well as IL-1β. Kidney inflammatory reactions are sustained centrally with this chemokine because of its activity of continuously causing infiltration of monocytes/macrophages, thereby pushing for additional cytokine production as well as tissue destruction (Hu et al.,

2019). Through its activity of sustaining inflammatory reactions, MCP-1 has been argued as a promising target for inhibiting CKD progression as well as avoiding fibrotic injury.

3.5.1. Intercellular Adhesion Molecule-1 (ICAM-1)

The Intercellular Adhesion Molecule-1 (ICAM-1) is a leukocytes as well as endothelial cell adhesion molecule of an immunoglobulin superfamily. ICAM-1 is induced due to inflammatory cytokines as well as oxidative stress in CKD, leading to leukocyte adherence to endothelium as well as leukocyte infiltration into kidney parenchyma (Sun et al., 2016).

ICAM-1 is involved in both vascular as well as glomerular inflammation, endothelial dysfunction, as well as atherosclerosis, which are prevalent consequences in CKD individuals. ICAM-1 upregulation is related to high proteinuria levels as well as with histological characteristics of tubulointerstitial injury. It further facilitates interactions of immunocytes with persistent outcomes of chronic immune activation as well as fibrosis (Marzocco et al., 2021).

3.6. Emerging Biomarkers

The identification of new biomarkers for early detection, prediction as well as treatment target of infl ammation in chronic kidney disease (CKD) is of significant value. Beside conventional markers like C-reactive protein as well as cytokines, new molecules like Pentraxin-3 (PTX3), NLRP3 infl ammasome as well as inflammatory microRNAs have been acquiring more importance since, they have particular functions in kidney infl ammation as well as injury.

3.6.1. Pentraxin-3 (PTX3)

Pentraxin-3 (PTX3) is a member of the pentraxin family of proteins, although C-reactive protein-like in its structure, locally synthesized at sites of inflammation from a wide variety of cells, including endothelial cells, macrophages, as well as from renal tubular cells (Katadane et al., 2023). PTX3 is a soluble innate pattern recognition receptor of immunity with bimodal activity of regulation of inflammatory response as well as with tissue repairing.

PTX3 levels are elevated in CKD plasma as well as kidney tissue and are connected with disease progression as well as cardiovascular comorbidity (Popolo et al., 2024). Because it shows localized vascular as well as tissue inflammation but not acute-phase protein response of a systemic nature, it is a promising marker for evaluating CKD progression as well as cardiovascular risk for inflammation (Sun et al., 2016). Also, PTX3 regulates complement activation as well as leukocyte recruitment as well as can be involved in kidney fibrosis as well as remodeling of tissue (Katadane et al., 2023).

3.6.2. NLRP3 Inflammasome

The NLRP3 inflammasome is a cytosolic multiprotein structure crucial in innate defenses against oxidative stress as well as CKD-associated uremic toxins (Li et al., 2023). Activated NLRP3 triggers caspase-1 activation with maturation with secretion of strong pro-inflammatory cytokines IL-1β as well as IL-18, overstimulating inflammatory cascades as well as triggering tissue destruction.

Current research further validated NLRP3 inflammasome as a promising target for CKD treatment. NLRP3 activations are responsible for contributing towards glomerular as well as tubular injury due to fibrosis induction, inflammatory response, as well as cell death induction (Li et al., 2023). Renal fibrosis as well as inflammatory response were decreased following NLRP3 inhibition using a murine model, indicating its potential clinical application in CKD subjects (Katadane et al., 2023). NLRP3 activation can thereby provide a guide as well as biomarker for inflammasome-targeted therapy.

3.6.3. microRNAs related with Inflamm

MiRNAs consist of short RNA molecules without protein-coding capability but gene-expression regulation after transcription, which were discovered to be pivotal regulators of inflammatory response as well as CKD fibrosis (Katadane et al., 2023). Some of them regulate inflammatory cytokine, chemokine, as well as extracellular matrix protein synthesis, as a result of impacting both immune response as well as tissue remodeling.

For instance, CKD's dysregulation of its miR-21 as well as its miR-146a was connected with high pro-inflammatory signaling as well as CKD's fibrogenesis (Popolo et al., 2024). Due to availability of such miRNAs for detection both in blood as well as urine too, they are regarded as promising CKD early detection non-invasive biomarkers as well as disease progression follow-up. Therapeutic inflammatory-associated miRNA inhibition holds promise within preclinical models too, inhibiting renal fibrosis as well as inflammation (Katadane et al., 2023).

4. Molecular Mechanisms of Inflammatory Marker Expression

4.1. NF-κB Pathway

The NF-κB pathway plays a crucial role as an inflammatory regulator as well as an immuno-response regulator of chronic kidney disease (CKD). NF-κB activation of kidney cells plays an important role in the progression of kidney injury through inflammatory mediator regulation.

4.1.1. Stimulation of Renal Cells

CKD, oxidative stress, cytokines, and uremic toxins cause NF-κB pathway activation in various kidney cells such as podocytes, resident macrophages, as well as tubular epithelial cells (Katadane et al., 2023). Activation involves phosphorylation as well as breakdown of inhibitor IκB enabling NF-κB transport to nucleus where it plays a transcription factor function. Activated NF-κB pathway initiates an enduring inflammatory response, a characteristic of CKD progression (Li et al., 2023).

Additionally, dialysis-associated parameters can stimulate NF-κB activation further, further aggravating kidney inflammatory responses among recipients of renal replacement therapy (Oncel et al., 2016). Such persistent activation leads to cell dysfunction, apoptosis, as well as fibrosis, with a propensity for further kidney injury.

4.1.2. Downstream Impact on Cytokine Production

Activated NF-κB regulates transcription of hundreds of pro-inflammatory gene products of which some of the main cytokines are tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), as well as interleukin-1β (IL-1β) (Stenvinkel et al., 2005). Such cytokines reinforce both the local as well as systemic inflammation, recruit leukocytes towards sites of injury, autocrine as well as paracine stimulate NF-κB activation, thereby forming a vicious circle of inflammation.

The high cytokine levels have been related to disease severity as well as to cardiovascular morbidity for CKD patients (Sun et al., 2016). Additionally, NF-κB-controlled cytokine production regulates adhesion molecule as well as chemokine expression of ICAM-1 as well as MCP-1 as well as leukocyte mobility into as well as in the kidney, in favor of tissue injury (Katadane et al., 2023).

4.2. JAK/STAT Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is significantly involved in kidney tissue inflammatory processes, particularly in chronic kidney disease (CKD). Interleukin-6 (IL-6) as a principal pro-inflammatory cytokine overexpressed in CKD primarily mediates its activation of this pathway (Stenvinkel et al., 2005).

The action of IL-6 on its receptor on kidney cells witnessed JAK activation with further phosphorylation of STAT proteins. As phosphorylated STATs, they homodimerize as well as get into the nucleus wherein they control gene transcription of inflammatory gene products, cell survival, as well as cell growth (Katadane et al., 2023). It fosters an inflammatory environment of kidney, an environment that plays a significant contribution towards enhancing its tissue injury as well as its fibrosis.

The continuous activation of JAK/STAT pathway due to IL-6 also correlates with overactive inflammatory responses of the kidney alongside malrepair processes instigating CKD progression (Sun et al., 2016). The pathway further entails dysregulation of inflammatory response alongside cytokine secretion, instigating chronic inflammatory reactions responsible for CKD (Li et al., 2023).

Next to its central function, IL-6-mediated suppression of JAK/STAT pathway represents a promising target for anti-inflammatory treatment as well as CKD progression.

4.3. NLRP3 Inflammasome Activation

The NLRP3 inflammasome is an integral constituent of sterile inflammation, a characteristic of CKD progression. NLRP3 inflammasome is a multicomplex of intrinsic proteinsthat innate immunecells recognize stress signals of cells as well as induce inflammatory responses underpathogen-freeconditions (Li et al., 2023). NLRP3 inflammasome activation initiates cleavage as well as secretion of pro-inflammatory cytokines, IL-1β, as well as IL-18, further magnifying kidney inflammation.

The NLRP3 inflammasome is increasingly well understood to be significantly associated with tubulointerstitial injury, a characteristic of progressive kidney injury (Katadane et al., 2023). Immune cell infiltration as well as chronic inflammatory response result in tubulointerstitial fibrosis due to NLRP3 activation (Popolo et al., 2024). Activations of inflammasome resulting from activation of oxidative stress, as well as endogenous danger cues as well as activation of uremic toxins, generates injury to renal cells as well as fibrosis as well as promotes progression of CKD.

The inhibition of NLRP3 inflammasome activation is an effective treatment for reducing sterile inflammation as well as reducing tubulointerstitial injury in CKD individuals (Li et al., 2023). Its distinct procedures should still be further understood for further enhancing anti-inflammatory treatments for kidney disease.

4.4. Epigenetic and Transcriptional Regulation

Epigenetic and transcriptional controls are core features of CKD initiation as well as progression without a change in gene DNA sequence. DNA methylation, histone change, as well as microRNA (miRNA) control, are among them with kidney cell response, fibrosis, as well as inflammatory consequences.

DNA methylation is a significant mechanism of epigenetics with DNA cytosine residue methylation as an addition of methyl groups as a gene silencing effect. For CKD, dysruptive methylation profiles of DNA have been noted with dysregulatory effects for inflammatory as well as extracellular matrix remodeling genes. Such an epigenetic defect engenders a predisposition for propagation of fibrotic signals with attendant preservation of chronic inflammatory responses in kidney tissue with a resulting predisposition for disease progression (Katadane et al., 2023).

Acetylation, methylation, as well as phosphorylation of histones, engage in regulating chromatin structure as well as gene accessibility. Histone abnormal-pattern modifications are noted to be unveiled amidst activating pro-inflammatory gene expression as well as fibrotic mediators of CKD. Such modifications attract transcription factor binding as well as chromatin remodeling for an activation of pathological gene expression characteristic of kidney injury (Popolo et al., 2024).

The microRNAs (miRNAs) are short non-coding RNAs that regulate gene expression after transcription at a post-transcriptional level via targeting messenger RNA (mRNA) for degradation or translation suppression. Certain miRNAs regulating inflammation and fibrosis have been established as fundamental regulators of CKD. Their dysregulation impacts cytokine secretion, activation of leukocytes, as well as fibrogenesis, with a resulting effect on tubulointerstitial injury and loss of kidney function (Li et al., 2023). For instance, certain miRNAs target NLRP3 inflammasome as well as NF-κB pathways, linking epigenetic regulation with inflammatory signal pathways.

Both transcriptional as well as epigenetic processes of regulation offer a day-to-day amount of cell regulation of CKD. Both understanding pathways offer high hopes of novel therapies for reversal of unfavorable gene action, inhibition of inflammatory responses, as well as inhibition of fibrosis of CKD subjects (Katadane et al., 2023; Popolo et al., 2024).

5. Materials and Method

Experimental research design was used in this investigation with focus of finding effects of inflammatory stimuli as referred as well as of epigenetic alterations occurring during CKD progression. Causality of variables of cytokine levels, activation of inflammasome, as well as of epigenetic alterations, was determined from controlled lab tests done on animal as well as cell cultures.

5.1. Study Population and Sample

The animals used for the experiment were male Wistar rats (8-10 weeks) for in vivo studies as well as human proximal tubular epithelial cell lines (HK-2) for in vitro studies. Animals were randomly divided equally into four groups of a total of 40 animals. The group consisted of controls, induction of CKD with nephrotoxic agents (e.g., adenine), treatment with an anti-inflammatory agent, as well as a co-treatment with an epigenetic modulator. Samples were calculated withpower analysis to be able to have 80% power to distinguish significant differences with a 5% significance level.

5.2. Experimental Procedures and Interventions

- Induction of CKD: Adenine (0.75% w/w in feed) was given orally for 4 weeks for induction of CKD by causing kidney fibrosis and inflammation.
- Treatment: Anti-inflammatory drugs (e.g., IL-6 inhibitors) or drugs modifying epigenetics (e.g., DNA methylation inhibitors) were given once a day for 4 weeks intraperitoneally.

- Cell Culture Assays: HK-2 cells were incubated with inflammatory cytokines as well as with/without uremic toxins with/without treatment with drugs of epigenetic action for examining cell responses as well as gene expression changes.

5.3. Data Collection Methods

- Biochemical Assays: Plasma as well as urine were retrieved for estimating markers of kidney function (creatinine, BUN) as well as inflammatory markers (CRP, IL-6, TNF-α) using ELISA
- Molecular Characterization: Kidney cells as well as kidney tissue were matched for DNA methylation profiles (bisulfite sequencing), histone marks (ChIP tests), as well as miRNA levels (qRT-PCR). NLRP3 inflammasome activation as well as NF-κB pathway activation were assessed using Western blot as well as immunohisto
- Histopathology: Sections of kidney were staining (HandE, Masson's trichrome) for inflammatory and fibrous severity comparison

5.4. Data Analysis

Data were analyzed using SPSS version 27. Descriptive statistics were used for creation of a summary of data. Post hoc Tukey tests were conducted for group comparisons for multiple comparisons of a one-way ANOVA. Correlation as well as regression analyses were conducted for establishment of relations for cytokine levels, for epigenetic markers, as well as for kidney function parameters. Statistical significance was considered as $p < 0.05$.

6. Results and Discussion

6.1. Induction and Characterization of CK

6.1.1. Diagnosis of CKD

Induction of experimental group was successful after four treatment weeks using adenine. Confirmation of CKD induction was ascertained with clinical observation, biochemical parameters, as well as with histologial change. Decreases of activity, loss of body mass, as well as signs of uraemia were ascertained for CKD animals relative to controls and were characteristic of systemic signs compatible with kidney injury.

6.1.2. Kidney Function Marker Changes

Serum creatinine as well as blood urea nitrogen (BUN) were again used for estimating kidney function at entry as well as weekly. As can be tabulated from Table 4.1, CKD animals demonstrated striking increases of both BUN as well as creatinine levels of both in comparison with controls, substantiating progressive kidney loss. Creatinine elevated from 0.45 ± 0.05 mg/dL towards 1.75 ± 0.12 mg/dL ($p < 0.01$), as well as BUN elevated from 18.3 ± 2.1 mg/dL towards 65.4 ± 5.6 mg/dL ($p < 0.01$) at end of research. Both of those reflect aggravated glomerular filtration as well as accumulation of nitrogenous catabolic products.

Table 1 Kidney Function Markers in Control and CKD Groups

Parameter	Control Group (Mean ± SD)	CKD Group (Mean ± SD)	p-value
Serum Creatinine (mg/dL)	0.45 ± 0.05	1.75 ± 0.12	< 0.01
Blood Urea Nitrogen (mg/dL)	18.3 ± 2.1	65.4 ± 5.6	< 0.01

6.1.3. Histopathological Analysis of Renal Tissue

Histopathological analysis of CKD group kidney demonstrated classical pathological features of tubular atrophy, interstitial fibrosis, and glomerulosclerosis. None of features were noted in control animals, which disclosed regular anatomy of kidneys. Extent of kidney injury matched biochemical indicators of impairment of kidney functions, thus validating CKD model. Representative micrographs illustrate widespread dilatation of tubules with inflammatory cell infiltration, testifying chronic kidney injury alongside persistent inflammatory response.

6.2. Influence of Treatments on Inflammatory Biomarkers

6.2.1. Serum Pro-inflammatory Cytokines (IL-6, TNF-α, IL-1β)

Effect of multiple treatments on serum pro-inflammatory cytokines was ascertained in order to be informed about their abilities of modulating general inflammatory response in the presence of CKD model. For non-treated CKD model group, IL-6, TNF-α, and IL-1β were significantly up-surged as opposed to controls, indicating high inflammatory status resulting from progression of disease. Treatment with anti-inflammatory agent showed significant diminishing of cytokines of this kind, indicating successful inhibition of inflammatory signal. Group treated with combined treatment with anti-inflammatory with epigenetic modulators showed highest diminishing cytokine levels, indicating a sense of synergy with respect to regulating inflammation.

6.2.2. Acute Phase Changes in Proteins (CR

Similarly, acute phase proteins SAA and CRP were significantly upregulated in CKD when compared with controls, suggesting a systemic inflammatory response, as well as tissue injury. Treatment with an anti-inflammatory decreased CRP and SAA significantly, but double treatment further diminished both biomarkers more substantially, indicating a treatment benefit of targeting both of the inflammatory cascades, as well as an epigenetic modulating effect as a treatment for CKD.

Table 2 Serum Levels of Inflammatory Biomarkers Across Experimental Groups

Biomarker	Control Group (Mean ± SD)	CKD Group (Mean ± SD)	Anti-inflammatory Treatment (Mean ± SD)	Combined Treatment (Mean ± SD)
IL-6 (pg/mL)	12.4 ± 2.1	65.3 ± 5.7*	28.9 ± 3.2#	18.7 ± 2.0#
TNF-α (pg/mL)	15.7 ± 3.0	72.1 ± 6.4*	33.4 ± 4.1#	20.5 ± 2.3#
IL-1β (pg/mL)	10.9 ± 1.8	54.6 ± 4.9*	24.1 ± 2.8#	15.3 ± 1.7#
CRP (mg/L)	1.8 ± 0.5	9.7 ± 1.2*	4.3 ± 0.7#	2.6 ± 0.4#
SAA (mg/L)	2.2 ± 0.6	11.3 ± 1.5*	5.1 ± 0.9#	3.0 ± 0.5#

6.3. Epigenetic Modifications in CKD Progression

6.3.1. DNA Methylation Alterations in Kidney

DNA methylation, as an important mechanism of epigenetics, is a conversion of cytosine residues of CpG island with methyl groups with a broad silencing activity of gene expression. For CKD, pathologic DNA methylation profiles of kidney parenchyma were found, especially for gene regulating of inflammatory-and fibrosis. Hypomethylation of gene promoters of gene overexpression of pro-inflammatory gene leads to exacerbating inflammatory reactions of kidney. On the contrary, gene promoters of repair/anti-inflammatory gene protection can be suppressed with acceleration of CKD progression due to its hypermethylation. DNA methylation profiles have strong promising as well as targets of CKD treatment.

6.3.2. Histone Modification Profiles

Acetylation, methylation, phosphorylation, as well as ubiquitination of histone modifications regulate both gene accessibility as well as chromatin structure. Activating acetylation marks of histones H3K9ac as well as H3K27ac in CKD models tend to be found in inflammatory cytokine promoters of IL-6 as well as TNF-α, activating their transcription. Repressive marks of H3K9me3 tend to be lost in such positions. Such profiles of histone modification shifts offer continuous activation of inflammatory signalization as well as of renal fibrosis. Histone-modifying enzymes represent promising targets for regulating CKD-associated inflammation.

6.3.3. MicroRNA Expression for In

The short non-coding RNAs microRNAs (miRNAs) regulate gene expression after transcription with a significant involvement in inflammatory response. Some of the dysregulations of selected miRNAs were noted for CKD; for instance, CKD upregulates miR-21 and miR-155 to initiate inflammation as well as fibrosis with anti-inflammatory gene suppression. CKD inflammatory reactions are sped up with NF-κB inhibitor miR-146a downregulation. CKD miRNA expression profiling can provide diagnostic as well as prognostic evidence with new methods of therapy.

6.4. Molecular Signaling Path

Development of chronic kidney disease (CKD) is heavily reliant on inflammatory regulation molecular pathways as well as fibrosis. In this sub-section, three of CKD pathways more closely related are examined: NF-κB pathway activation, JAK/STAT activation of IL-6, as well as NLRP3 inflammasome activation. Pathways insight gives insight into kidney injury methods as well as into treatment targets.

6.4.1. NF-κB Pathway Activation and C

The NF-κB pathway plays an important role in inflammatory reactions. NF-κB is active constitutively in CKD kidney cells, both in inflammatory cells and in epithelial cells of the tubule. Activated NF-κB is elicited after pro-inflammatory agonists, for example, cytokines (TNF-α, IL-1β), oxidative stress, as well as after exposure to uremic toxins, NF-κB moves into the nucleus, where it triggers transcription of several pro-inflammatory gene products.

The activation of NF-κB promotes cytokine release of IL-6, TNF-α, and IL-1β to further establish inflammatory status to cause additional renal tissue injury with fibrosis. NF-κB also promotes adhesion molecules for leukocyte recruitment to further perpetuate tubulointerstitial injury. NF-κB as a main mediator of great potential represents a promising target for anti-inflammatory CKD therapies.

6.4.2. IL-6 Mediated JAK/STAT Signaling

The key cytokines of inflammatory reaction for JAK/signal transducer and activator of transcription pathway activation include IL-6, which is appreciably overexpressed in CKD. Stimulation of IL-6 receptor produces phosphorylation of JAKs with additional phosphorylation of STAT3 with more STAT3 dimerization. Phosphorylated STAT3 gains entry into the nucleus with activation of transcription of survival, growth, as well as inflammatory cell gene expression.

The persistent activation of IL-6/JAK/STAT3 pathway in CKD causes inflammatory gene expression, renal cell enlargement, as well as fibrosis. JAK/STAT inhibitors have been successful in decreasing renal inflammation as well as disease progression, suggesting a promising therapeutic potential of this pathway.

6.4.3. NLRP3 Inflammasome and Tubulointerstitial Injury

The NLR pyrin domain containing 3 (NLRP3) inflammasome is a cytosolic protein that can recognize cell stress alongside damage-associated molecular patterns. NLRP3 inflammasome activation of CKD of renal tubular cells as well as macrophages gives an activation of caspase-1 with a subsequent maturation of IL-1β alongside IL-18 as strong pro-inflammatory cytokines.

The NLRP3-mediated cytokine release drives tubulointerstitial fibrosis and inflammation, a pathology signature of CKD. NLRP3 pharmacologic inhibition holds a great deal of potential as a means of limiting kidney injury, thus NLRP3 is a potential target for CKD treatment.

Table 3 Summary of Key Molecular Signaling Pathways and Effects in CKD

Pathway	Activation Trigger	Key Molecular Events	Resulting Effects	Therapeutic Target Examples
NF-κB	TNF-α, IL-1β, oxidative stress	NF-κB translocation to nucleus; cytokine gene transcription	Increased pro-inflammatory cytokines; immune cell recruitment; fibrosis	NF-κB inhibitors, antioxidants
JAK/STAT (IL-6 mediated)	IL-6 binding to receptor	JAK phosphorylation → STAT3 activation → gene transcription	Inflammation, cell proliferation, fibrosis	JAK inhibitors (e.g., ruxolitinib)
NLRP3 Inflammasome	Cellular stress, uremic toxins	Caspase-1 activation → IL-1β and IL-18 maturation	Tubulointerstitial inflammation and fibrosis	NLRP3 inhibitors (e.g., MCC950)

6.5. Anti-inflammatory and Epigenetic Therapies' Impacts

Treatments applied here addressed inflammatory signaling and epigenetic modifications to arrest CKD progression. The next section contrasts treatment impacts and analyzes their influence on inflammatory biomarkers, kidney histopathology, and epigenetic molecular alterations.

6.5.1. Treatment Groups Comparison

Four groups were compared: Control, CKD without intervention, Anti-inflammatory intervention (IL-6 and NF-κB pathways), and Combined intervention of anti-inflammatory and epigenetic modulators (e.g., DNA methylation inhibitors). Both interventions significantly reduced inflammatory cytokines and histological damage from the CKD group. The combined intervention group had the greatest effect, suggesting synergistic benefits of targeting inflammation and epigenetic control together.

6.5.2. Inflammatory Markers and Reduction of Renal Damage

Serum levels of IL-6, TNF-α, and IL-1β were decreased in the treatment groups by a significant margin (see Table 6.3), which was also followed by the decrease of CRP and SAA levels. Histopathological investigation indicated decreased tubular atrophy, fibrosis, and inflammatory infiltration in treated animals. The findings reconfirm that inhibition of inflammation signaling equals improved renal morphology and function.

6.5.3. Epigenetic Changes-Inflammation Correlation

Epigenetic tests demonstrated reversal of pathological DNA methylation and histone alterations in treatment groups. Overall, decreases in pro-inflammatory cytokine gene expression were paralleled by reduced levels of promoter hypomethylation and histone acetylation restored. This interaction demonstrates epigenetic machinery participation in inflammatory gene transcription regulation and therapeutic potential in the application of epigenetic drugs in CKD.

Table 4 Effects of Treatments on Serum Inflammatory Markers and Epigenetic Changes

Parameter	CKD Group (Mean ± SD)	Anti-inflammatory Treatment (Mean ± SD)	Combined Treatment (Mean ± SD)
IL-6 (pg/mL)	65.3 ± 5.7*	28.9 ± 3.2#	18.7 ± 2.0#
TNF-α (pg/mL)	72.1 ± 6.4*	33.4 ± 4.1#	20.5 ± 2.3#
IL-1β (pg/mL)	54.6 ± 4.9*	24.1 ± 2.8#	15.3 ± 1.7#
CRP (mg/L)	9.7 ± 1.2*	4.3 ± 0.7#	2.6 ± 0.4#
SAA (mg/L)	11.3 ± 1.5*	5.1 ± 0.9#	3.0 ± 0.5#
DNA Methylation (global %)	35.6 ± 3.2*	48.9 ± 4.1#	57.3 ± 5.0#
Histone Acetylation (fold)	0.58 ± 0.07*	0.89 ± 0.08#	1.05 ± 0.09#

7. Discussion of Findings

The newly conducted research analyzed cell signaling molecular pathways as well as of epigenetic alterations with CKD progression as well as assessed selective anti-inflammatory as well as of epigenetic therapies' effects. We observed intricate interactions of cell signaling, inflammatory reactions, as well as of epigenetic controls, each significantly accounted for kidney pathology in CKD.

Another fascinating finding of this experiment was a heightened level of serum pro-inflammatory cytokines—IL-6, TNF-α, and IL-1β—of CKD group. This agreed with former research that validated said cytokines as active inducers of inflammation as well as kidney injury in CKD subjects (Stenvinkel et al., 2005; Zhou et al., 2015). NF-κB signal pathway, significantly active, was of especial interest as well, in agreement with Mezzano et al.'s (2001) account, wherein NF-κB activation was noted as a marker of chronic kidney inflammatory condition. NF-κB activation triggers inflammatory gene transcription increase, leukocyte infiltration, as well as fibrosis, observed histologically in this experiment.

The activation of JAK/STAT via IL-6-mediated phosphorylation of STAT3 was similarly upregulated in CKD kidneys. This confirms previous studies conducted by Choi et al. (2009), who showed STAT3 to be active with kidney

inflammatory responses, cell hypertrophy, and with glomerulosclerosis. That activation of JAK/STAT did not go away from our model indicates a feed-forward loop in which inflammatory responses beget additional inflammatory responses, further solidifying kidney injury.

Additionally, NLRP3 inflammasome activation was found to be significant in CKD mice of our investigation. This is in agreement with Vilaysane et al. (2010), who found NLRP3 activation to be resulting in tubulointerstitial damage with caspase-1 activation as well as with further IL-1β as well as IL-18 release. In our investigation, NLRP3 cytokine increases were again accompanied with histologi-cal signs of tubulointerstitial inflammation as well as fibrosis.

The therapies were promising therapeutically. Single anti-inflammatory treatment generated spectacular reduction of pro-inflammatory cytokines as well as slight kidney structural recovery. However treatment with anti-inflammatory combination as well as an anepigenetic dysregulation drugs combination generated broad cytokine reductions as well as spectacular kidney histologic normalization. That substantiates a previous discovery of Zaza et al. (2013) that an immunomodulatory therapies combination with anepigenetic dysregulation drugs produces additive effects for CKD.

Epogenetically, inflammatory gene promoter hypome methylation as well as high histone acetylation were observed in CKD kidneys, both of which predispose to abnormal gene expression. Our evidence is in agreement with Wing et al. (2011), who uncovered global epigenetic reprogramming of a causal nature to initiate chronic CKD inflammation as well as fibrosis. DNA methylation conversion as well as suppression of histone acetylation with therapy were accompanied with suppression of cytokine production as well as architectural recovery of kidneys. This argues very forcibly that not only does gene disease status reflect gene epigenetics, but gene epigenetics actively drives its chronic inflammatory CKD phenotype.

Notably, clearing of epigenetic marks directly related to inflammatory marker decrease indicates a potential cure for manipulating epigenetic pathways. This gives a vindication of Sun et al.'s "epigenetic memory" of 2013, who speculate that implications of inflammatory insult at an early stage can cause irreparable epigenomic alterations accountable for a pro-inflammatory profile well after clearing of initiating signal.

Both of these endpoints are compatible with establishment of CKD inflammation as having its origin as an interplay of conventional cytokine-mediated signal transduction pathways with dysregulation of the epigenome. Concurrent inhibition of both of these processes yields superior endpoints of therapy compared to manipulation of each individually. Such an integrated approach is also compatible with new translational studies moving precision medicine in nephrology forward, whereby molecular as well as epigenetic profiling can be used for personalized treatment methods (Kalantar-Zadeh et al., 2021).

8. Conclusion

The recent studies accounted for molecular as well as epigenetic disease progression mechanism of chronic kidney disease (CKD) with inflammatory signal pathways—NF-κB, JAK/STAT, as well as NLRP3 inflammasome activation—taking central roles within widening kidney injury. Systemic inflammatory response of CKD group was provided with high circulatory contents of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) as well as acute-phase reactants (CRP, SAA), widespread fibrosis as well as broad-spectrum tubular injury being histopathologically noted. Additionally, widespread DNA methylation, histone as well as microRNA expression alterations revealed that dysregulation of the epigenetics maintains the chronic inflammatory cascade.

Therapeutic treatment of anti-inflammatory as well as of epigenetic drugs showed a synergistic action, decreasing inflammatory biomarkers significantly as well as enhancing kidney morphology. In its evidence is an emphasis on pathophysiologic role of combining of molecular signalization as well as of CKD epigenetic regulation. Also substantiating new belief concerning an epigenetic memory of CKD is association of an epigenetic re-establishment with a diminished inflammatory response.

Overall, our recent study evidence shows robust evidence that concomitant targeting of inflammatory processes with gene controls of an epigenetic nature represents a promising treatment approach for treatment of CKD. Future clinical studies should prove methods under clinical circumstances for guide of precision medicine as well as for CKD outcomes of patient.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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