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REVIEW

Inflammation-Induced Klotho Deficiency: A Possible Key Driver of Chronic Kidney Disease Progression

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Abstract: Chronic kidney disease (CKD) is influenced by inflammation, a critical factor in its progression. However, the underlying mechanism through which inflammation contributes to CKD is still obscure. The Klotho protein, which is predominantly found in the kidneys, is known for its protective functions, including anti-inflammatory, anti-aging, antioxidant, and anti-fibrotic effects. A myriad of studies have suggested that inflammation in CKD leads to a decrease in Klotho expression, diminishing Klotho protection capabilities and exacerbating kidney damage, thereby promoting CKD progression. These findings suggest that Klotho deficiency could be a crucial link between inflammation and CKD progression. However, the mechanism regarding their relationship is still unclear. The reduction in Klotho due to inflammation may be attributed to epigenetic mechanisms, such as DNA methylation, histone deacetylation, transcription factor, microRNA (miRNA) regulation and long non-coding RNA (lncRNA) regulation or non-epigenetic factors, such as endoplasmic reticulum (ER) stress and ER-associated degradation (ERAD), which affect Klotho protein metabolism. Through these pathways, inflammation triggers a decrease in Klotho expression, further driving CKD progression. Notably, Klotho also exerts a strong anti-inflammatory effect by inhibiting key inflammatory factors and pathways, suggesting that there is intricate crosstalk between inflammatory factors and Klotho in CKD. This review highlights how inflammation suppresses the expression of Klotho and further contributes to the development and exacerbation of CKD. By focusing on the interplay between inflammation and Klotho, the present review provides novel potential therapeutic strategies such as correcting epigenetic and non-epigenetic abnormalities for treating CKD by targeting this specific axis.

Keywords: inflammation, Klotho, chronic kidney disease, epigenetics, non-epigenetics, kidney fibrosis

Introduction

Recent epidemiological surveys have suggested that chronic kidney disease (CKD) affects 13.4% of the global population and 8.2% of China as of early 2019.[1] CKD-associated prevalence rate and mortality remain high, underscoring the critical need to improve patient outcomes.[2] A consistent, low-grade inflammatory response is a central characteristic of CKD and plays a key role in its progression as well as in the transition from acute kidney injury (AKI) to CKD.[3,4] Systemic or localized inflammatory responses contribute to increased oxidative stress, which damages the intrinsic cells of the kidneys.[5] Inflammation also causes endothelial dysfunction, exacerbating renal ischemia.[6] Furthermore, it induces the trans-differentiation of tubular cells into myofibroblasts, leading to enhanced collagen deposition.[7] As a result, the persistent inflammatory response ultimately results in renal fibrosis and a decline in kidney function. Thus, anti-inflammatory therapies are essential for delaying CKD progression and improving patient prognosis.[8,9] However, the specific mechanisms by which inflammation accelerates CKD progression are complex and not yet completely understood. Consequently, gaining deeper insights into these inflammatory pathways could provide potential strategies for the prevention and treatment of CKD.

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Klotho protein was originally identified as an anti-aging protein[10] and exists in three isoforms: α-Klotho, β-Klotho, and γ-Klotho, with α-Klotho being predominantly synthesized in the kidneys.[11] Klotho occurs in two forms: membrane-bound Klotho (mKlotho) and soluble Klotho (sKlotho). mKlotho is a transmembrane protein featuring a long extracellular region that contains two internal repeats, KL1 and KL2. These repeats can be cleaved by proteases such as A Disintegrin and Metalloproteinase (ADAM) 10 and ADAM 17, producing the functionally active circulating form, sKlotho.[12] mKlotho is highly expressed in the kidneys and forms a complex with fibroblast growth factor (FGF) receptors, acting as a coreceptor for FGF-23 and mediating phosphate excretion.[13] In contrast, sKlotho functions as an endocrine substance, participating in both FGF-23-dependent and -independent processes.[14] Several studies have shown that levels of sKlotho decline in CKD[8,15–22] (Table 1), indicating a negative correlation between sKlotho levels and kidney function. Moreover, the downregulation of sKlotho is associated with adverse outcomes, such as creatinine doubling, renal replacement therapy or death during the CKD progression[21,23–30](Table 2).

The Klotho protein, which is predominantly detected in the kidneys, is critical for several protective functions, such as anti-inflammatory, anti-aging, antioxidant, anti-fibrotic,[31] anti-apoptotic[32] and regulating calcium-phosphorus metabolism.[15,33] Previous studies have demonstrated a significant reduction in sKlotho expression in individuals with CKD, which is linked to disease progression and adverse outcomes.[23,34] Thus, sKlotho deficiency plays an important role in CKD pathogenesis and development and is emerging as a potential target for CKD management nowadays.[35] The downregulation of Klotho is driven by a variety of factors, including both epigenetic mechanisms and non-epigenetic mechanisms.[36] A key contributor to this decrease in Klotho levels is abnormal epigenetic regulation, including DNA methylation, histone deacetylation, transcription factor activity, microRNA (miRNA) and long non-coding RNA (lncRNA) activity, which inhibits Klotho synthesis.

Clinical studies have shown that reduced sKlotho levels in the general population are associated with an increase in inflammatory biomarkers such as uric acid, C-reactive protein (CRP), and white blood cell count.[37] In CKD patients, an inverse relationship between inflammation and sKlotho was observed as well, suggesting a significant interplay where inflammation may lead to reduced sKlotho levels.[33,38] Animal studies on kidney diseases have shown that inflammatory biomarkers can decrease mKlotho expression through various mechanisms.[39] Critically, the downregulation of Klotho aggravates kidney damage and accelerates CKD progression in the presence of chronic inflammation.[40,41]

Table 1 Characteristics of the Clinical Studies Regarding the Relationship of sKlotho with Kidney Function

First Author	Year	N	Age	Samples	eGFR	sKlotho level	Klotho and eGFR
Donate-Correa[8]	2024	102 CKD and diabetics	65.4±8.2	Serum	39 (35.8–49.7)	628±211.3 pg/mL	sKlotho levels correlated with eGFR
Liu[20]	2024	3870 (46.35) CKD 673 (39.91) controls	53.11 (0.17) 59.81 (0.33)	-	91.59 (0.31) 74.72 (0.90)	863.18 (6.36) pg/mL 834.54 (9.88) pg/mL	sKlotho had a positive association with eGFR
Martín[17]	2023	43 CKD 38 controls	66.65±8.58 66.50±4.63	Serum	49.0 (47.0–53.0) 81.5 (75–87.8)	670.6 (604.2–746.0) pg/mL 809.2 (680.3–1042.2) pg/mL	sKlotho levels were positively correlated with eGFR
Thaís B[18]	2023	31 CKD	58±4.06	Serum	64.99±2.09	499±60.12 pg/mL	sKlotho levels correlated with eGFR
Iyengar[19]	2022	90 CKD	9.3 (7.0, 14)	Serum	51.3 (36.0, 67.7)	992.0 (641.0, 1350) pg/mL	sKlotho levels were positively correlated with eGFR
Qian[21]	2018	112 CKD	64.5±12.7	Serum	37.5±1.9	523.4±192.4 pg/mL	sKlotho levels showed a significant positive correlation with eGFR
Rotondi[22]	2015	68 CKD	58±15	Serum	45±21	519±183 pg/mL	There was a positive correlation between sKlotho and eGFR

Abbreviations: CKD, chronic kidney disease; N, number; eGFR, estimated glomerular filtration rate.

Table 2 Characteristics of the Clinical Studies Regarding the Relationship of sKlotho with Adverse Clinical Outcomes in CKD

Author	Year	Study Design	N	Sample	Age	eGFR (mL/min)	Follow-up	Outcomes	Conclusion
Han[23]	2024	Prospective	2446	Serum	62 (53, 71)	63.73 (52.91, 91.64)	82 months (medium)	Death	sKlotho levels (when sKlotho concentration was less than 760 pg/mL) negatively correlated with mortality rates
Liu[24]	2024	Prospective	2418	Serum	62.4±10.7	69.3±24.3	87.9 months (mean)	All-cause and CV death	Lower sKlotho levels were linked with higher risk of CV mortality
Milovanova[25]	2024	Prospective	75	Serum	53 (24, 65)	38.4 (55.6, 23.2)	8 years (medium)	All-cause and CV death	α-Klotho levels were associated with all-cause and CV mortality
Gao[27]	2024	Observational	108	Serum	55.63±13.51	CKD3-5	-	Abdominal aortic calcification	Low sKlotho protein levels were independent risk factors for abdominal aortic calcification in CKD
Li[28]	2023	Observational	239	Serum	49.25±13.22	25.7±36.0	-	anemia	α-Klotho levels were correlated with anemia severity
Martins[29]	2023	Prospective	200	Serum	67.23±13.53	No data hemodialysis	66months (medium)	Death, CV events	α-Klotho was associated with the occurrence of CV events
Manou[30]	2020	Prospective	128	Plasma	67 (18–86)	41.5 (8.5–119.5)	5 years	Initiation of RRT, all-cause and CV death	sKlotho levels were associated with progression to end-stage kidney disease and CV mortality
Qian[21]	2018	Prospective	112	Serum	64.5±12.7	37.5±1.9	6 years	Initiation of RRT	α-klotho was an independent predictor of RRT in CKD patients

Abbreviations: N, number; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CV, cardiovascular; RRT renal replacement therapy.

Indeed, enhanced inflammatory responses and Klotho deficiency commonly occur together in CKD, suggesting their potential role in CKD pathogenesis and progression. These findings indicate that the inflammation-mediated suppression of Klotho may be a novel mechanism through which inflammation contributes to CKD progression. However, the underlying mechanisms are not yet fully understood. Understanding how inflammation leads to Klotho downregulation is crucial for developing novel therapeutic approaches for CKD. Increasing evidence suggests that inflammation can significantly reduce *Klotho* transcription through epigenetic mechanisms and influence Klotho protein degradation via non-epigenetic pathways, ultimately playing a role in CKD development and progression, which may not have been covered comprehensively in existing reviews. Thus, in this review, we summarized the potential mechanisms involved in the downregulation of Klotho associated with inflammation and we aimed to provide a theoretical basis for better CKD management by targeting the inflammation-Klotho axis in the future.

The Epigenetic Mechanisms Through Which Inflammation Suppresses Klotho Expression

Epigenetic regulation involves hereditary changes in gene expression without alterations to the DNA sequence. These alterations include DNA methylation, histone modifications, transcription factor interactions, non-coding RNA interactions, RNA modifications, and chromatin remodeling. A myriad of studies have shown that abnormal epigenetic mechanisms play a significant role in reducing Klotho transcription activity, which is a key factor contributing to

decreased Klotho expression.[42] Inflammation can inhibit Klotho expression by targeting various epigenetic processes, ultimately impacting gene regulation and contributing to disease progression.[43]

DNA Methylation of Klotho

DNA methylation involves the addition of a methyl group to the 5′-carbon of the cytosine residue in the CpG dinucleotide, a process facilitated by DNA methyltransferase (DNMT), leading to gene silencing. Previous research has shown that the *Klotho* gene promoter and first exon region are rich in CpG islands. Unlike regions with TATA or CAAT boxes, the *Klotho* promoter contains five GC boxes, making it susceptible to high levels of methylations.[44] Related studies have indicated that the inflammation can lead to telomere shortening, which is often associated with increased DNA methylation.[45] Additionally, inflammatory factors such as CRP have been shown to directly promote DNA methylation,[46] an effect that can be reversed through anti-inflammatory treatment.[47] Therefore, inflammation is not only positively correlated with DNA methylation but also serves as an inducer of this epigenetic modification.

A cross-sectional study revealed that the level of sKlotho protein in the peripheral blood of cardiovascular disease patients was inversely correlated with that of tumor necrosis factor-α (TNF-α), and pro-inflammatory markers were directly connected to *DNMT1* gene expression. Furthermore, the observed downregulation of sKlotho expression was negatively associated with DNMT1-mediated hypermethylation in the *Klotho* promoter region.[48] These findings suggest that vascular inflammation associated with atherosclerosis may cause *Klotho* promoter methylation, leading to reduced sKlotho expression. Further animal studies have demonstrated that in fibrotic kidney tissues, TGF-β promotes the methylation of *Klotho* in renal tubular epithelial cells, thereby inhibiting mKlotho expression.[49] Thus, elevated levels of inflammatory cytokines may lead to increased methylation of *Klotho* in renal tissues, resulting in reduced Klotho expression.

DNMTs are critical enzymes responsible for DNA methylation, with DNMT1 playing a significant role in regulating the methylation of the *Klotho* gene. Several studies have demonstrated that inflammation can influence DNMT1 expression through multiple mechanisms, subsequently affecting the methylation of the *Klotho* gene. First, inflammation can activate NF-κB, which further binds to the *DNMT1* promoter region, increasing DNMT1 expression.[50–52] This increase in DNMT1 activity results in increased methylation levels of *Klotho*. Moreover, inflammatory cytokines such as IL-1β and TNF-α can upregulate miRNAs such as miR-29C, miR-26B, and miR-20A, which in turn inhibit the *methylcytosine dioxygenase* gene, further increasing DNMT activity.[53] Furthermore, the inflammatory marker C-C chemokine ligand 5 (CCL5) can activate signal transducer and activator of transcription 3 (STAT3), promoting downstream *DNMT1* transcription and accelerating *Klotho* promoter hypermethylation.[54]

Thus, inflammation may target DNMT1-mediated DNA methylation to suppress *Klotho* transcription, leading to reduced Klotho expression and the progression of CKD (Figure 1). Additionally, the role of DNA demethylases may be significant in Klotho deficiency, particularly in the context of inflammation. However, further investigation is needed, as there are currently very few studies exploring this relationship.

Histone Deacetylation

Histone deacetylation is a process mediated by histone deacetylase (HDAC), which removes acetyl groups from lysine residues on core histones, restoring the positive charge of the histone. This positively charged histone binds more tightly to the negatively charged DNA, causing chromatin condensation. This condensation blocks the transcription factor access and subsequently inhibits gene transcription. The kidneys are particularly rich in acetylated lysine protein,[55] and histone deacetylation has been shown to promote the development of renal interstitial fibrosis in CKD.[56,57] Inflammatory processes can activate histone deacetylation.[58,59] For example, TNF-α and IL-1β can recruit HDAC2 to gene promoter sites, thereby activating histone deacetylation.[60] Research has shown that HDAC8 inhibitors can reverse mKlotho reduction induced by unilateral ureteral obstruction (UUO)[61] and that HDAC3 can promote histone deacetylation at the *Klotho* promoter, inhibiting *Klotho* transcription and aggravating kidney damage.[62] These findings suggest that inflammation can activate histone deacetylation to regulate the mKlotho expression. Animal experiments further confirmed that TNF-like weak inducer of apoptosis can promote the binding of the NF-κB family protein RelA to the mouse *Klotho* promoter, enhancing histone H3 and H4 deacetylation and suppressing *Klotho* transcription.[39]

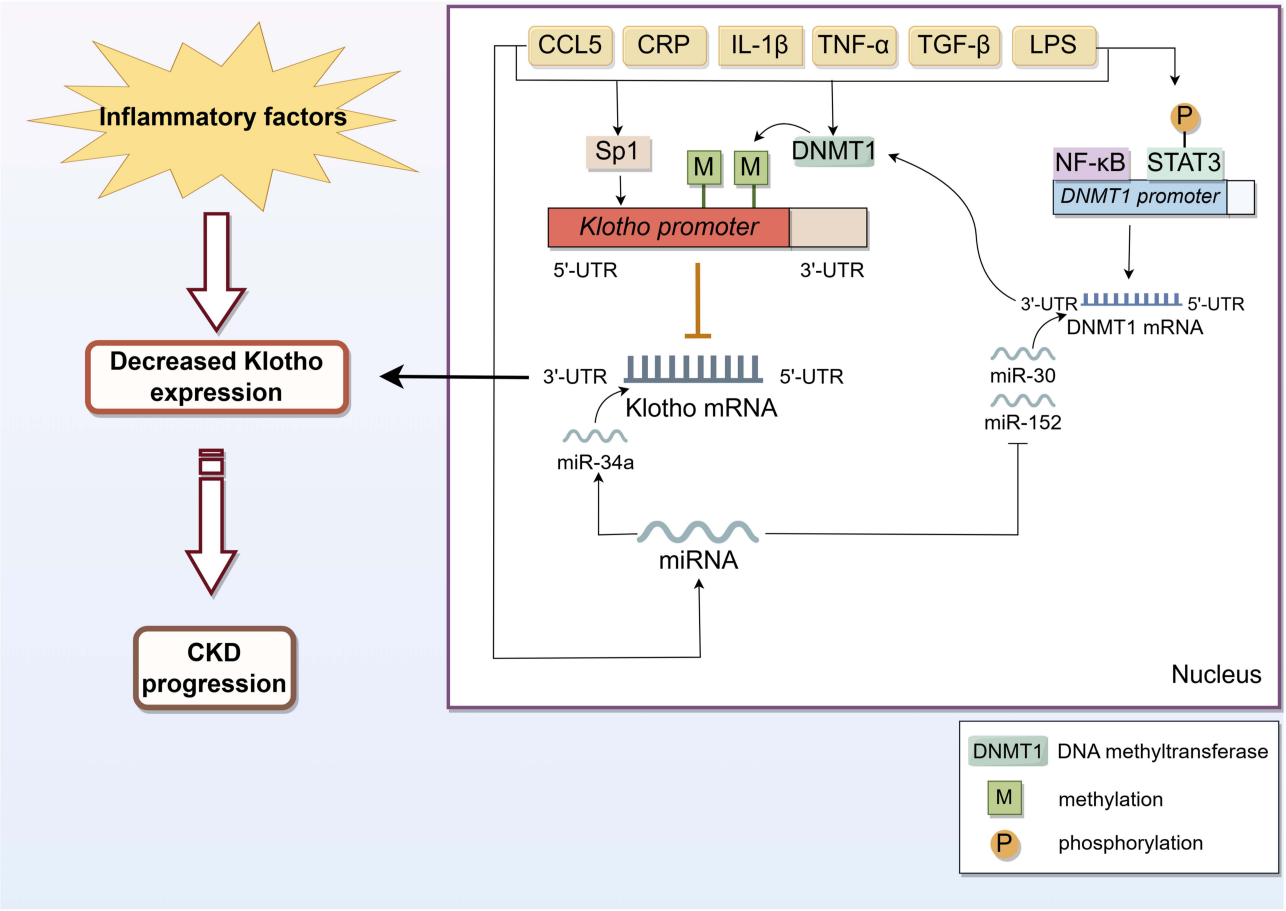

Figure 1 Roles of DNA methylation and miRNA in inflammation-induced Klotho deficiency. By Figdraw.

Additionally, inflammation can activate HDAC3 via the TGF-β/Smad signaling pathway. HDAC3 forms a repressive complex with the nuclear receptor inhibitor protein/NF-κB that binds to the *Klotho* promoter, leading to histone deacetylation and gene transcription suppression.[62] Therefore, inflammation may downregulate *Klotho* transcription by activating histone deacetylation, thereby inhibiting the renoprotective effect of Klotho, which is linked to CKD progression (Figure 2). Similarly, histone acetyl transferases (HATs) are also involved in Klotho regulation. P300-mediated histone acetylation has been shown to suppress Klotho expression through regulating Akt signaling pathway.[63] Yet it remains unclear whether HATs also contribute to the regulation of Klotho deficiency induced by inflammation and further research is needed to clarify this relationship.

Transcription Factors

Transcription factors influence the initiation and extension of gene expression, regulating it by binding to enhancer elements and recruiting co-activators and RNA polymerase II to target genes. The *Klotho* promoter region contains binding sites for multiple transcription factors, which means that Klotho expression is regulated by these factors.[64] These transcription factors can directly bind to their specific sites on the *Klotho* promoter to regulate its expression. Additionally, they can indirectly modulate *Klotho* transcription through other mechanisms, thereby affecting its expression levels.

Direct Regulation of Klotho Expression by Transcription Factors That Bind to the Klotho Promoter

Certain transcription factors, such as specificity protein 1 (Sp1) and peroxisome proliferator-activated receptor-γ (PPAR-γ), can directly bind to the *Klotho* promoter to regulate its expression. The Sp family of transcription factors typically functions as transcription activator. For example, Sp1 can bind to GC-rich sequences in the regulatory regions of genes,

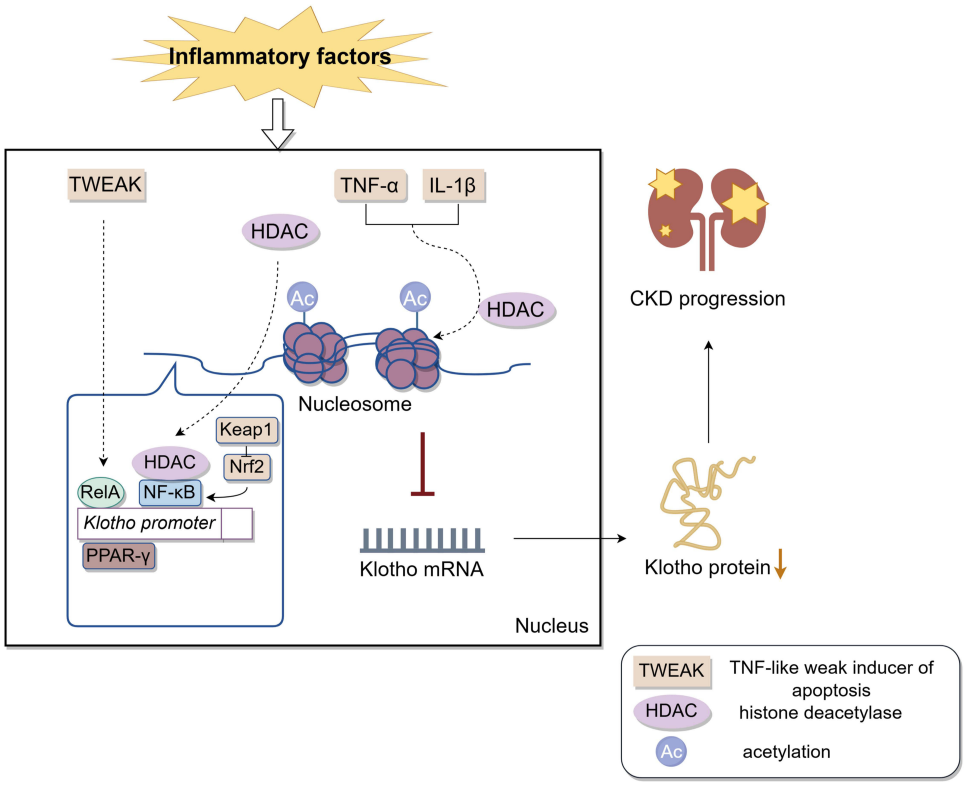

Figure 2 Roles of histone deacetylation and transcription factors in Klotho regulation. By Figdraw.

preventing them from undergoing methylation and activating transcription.[65] The *Klotho* promoter region contains five GC boxes that serve as binding sites for Sp1. This interaction can activate gene transcription and increase Klotho expression. Studies have demonstrated that the overexpression of Sp1 not only induces mKlotho expression but also mitigates renal fibrosis, suggesting the involvement of Sp1 in mKlotho regulation.[66] Under inflammatory conditions, such as lipopolysaccharide (LPS)-induced damage, LPS can activate NF-κB, which in turn increases the activity of Sp1-degrading enzymes.[67] This may lead to a further degradation of Sp1 and a subsequent reduction in Klotho expression. These findings suggest that inflammation-induced Klotho suppression may be partly mediated through Sp1 modulation (Figure 1).

PPAR-γ, a member of the ligand-activated nuclear hormone receptor and transcription factor family, plays a significant role in regulating Klotho expression. Studies have shown that a functional non-classical PPAR response element sequence located in the 5′-flank region of the *Klotho* gene can be recognized by PPAR-γ, thereby promoting *Klotho* transcription.[68] However, inflammation can reduce PPAR-γ expression, subsequently affecting mKlotho levels. Some studies have shown that inflammation can lead to PPAR-γ deacetylation, which weakens its binding to the *Klotho* promoter, inhibiting *Klotho* transcription and expression[69] (Figure 2).

Other Mechanisms by Which Transcription Factors Affect Klotho Expression

Transcription factors, such as STATs, can influence Klotho expression through various pathways, in addition to directly binding to promoters. STATs, which are activated by phosphorylation, regulate gene transcription and are implicated in CKD progression.[70,71] When activated in mesangial cells, the JAK/STAT3 pathway promotes renal fibrosis by increasing TGF-β1, IV collagen and fibronectin production.[72] Furthermore, phosphorylated STAT3 (p-STAT3) binds to the *DNMT1* promoter, inducing DNMT1 expression and affecting *Klotho* transcription. Inflammation triggers STAT activation,[73] and our previous studies revealed that, in CKD, the inflammatory factor CCL5 activates p-STAT3/DNMT1, leading to *Klotho* methylation and reduced expression[54] (Figure 1).

Kelch-like ECH-associated protein 1 (Keap1) and nuclear factor erythroid 2- related factor 2 (Nrf2) play critical roles in anti-inflammatory and antioxidant responses. Normally, Keap1 binds Nrf2, leading to its ubiquitination and degradation. However, during inflammation, Keap1 undergoes sulfhydryl modification, releasing Nrf2, which then translocates to the nucleus to exert anti-inflammatory effects. Nrf2 inhibits NF-κB by upregulating heme oxygenase-1 and blocking NF-κB inhibitory protein α phosphorylation. Additionally, Nrf2 competes with NF-κB for CREB binding proteins, preventing *Klotho* methylation and histone deacetylation.[74,75] Studies have shown that in CKD, chronic inflammation can upregulate Keap1, enhancing Keap1-Nrf2 binding and Nrf2 degradation,[76] ultimately reducing *Klotho* transcription through NF-κB-dependent epigenetic mechanisms and promoting CKD progression (Figure 2).

miRNAs

miRNA is an endogenous, non-coding small RNA that can directly bind to the 3'UTR of the target mRNA, negatively regulating gene expression.[77] In CKD, inflammation leads to the upregulation of certain miRNAs, such as miR-29-5p, miR-21-5p and miR-196a-5p,[78] indicating that inflammatory responses can increase the expression of miRNAs. Notably, the inflammatory factor TGF-β1 activates p53/Smad3 signaling, resulting in increased miR-34a expression, which in turn reduces Klotho expression by directly binding to its 3′UTR.[79,80] Furthermore, TGF-β suppresses the expression of the miR-152 and miR-30 families. The 3′UTRs of *DNMT1* and *DNMT3a* mRNAs contain binding sequences for these miRNA families. Inflammation can prevent miRNA from binding to the 3′UTR of *DNMT* mRNA, increasing the post-transcriptional translation of DNMT, promoting hypermethylation of the *Klotho* gene and a subsequent decrease in Klotho expression.[80] In summary, the targeted regulation of miRNAs may be another epigenetic mechanism by which inflammation modulates Klotho expression, contributing to CKD progression (Figure 1).

lncRNAs

LncRNA represent a large and diverse class of transcripts longer than 200 nucleotides, involved in gene transcription and post-transcriptional regulation.[81,82] Recent studies have identified lncRNAs as potential biomarkers for CKD.[83] For instance, lncRNA TCONS_00088786 has been shown to promote renal interstitial fibrosis through the regulation of miR-132.[84] Conversely, the knockdown of lncRNA-ATB can inhibit the progression of renal fibrosis in vitro,[85] indicating that lncRNAs play a significant role in CKD progression. Furthermore, available studies have revealed that inflammation can upregulate lncRNA expression.[86] In high glucose-induced human renal glomerular endothelial cells (HRGECs), both lncRNA MALAT1 and inflammatory markers, such as IL-6 and TNF-α, were found to be elevated. This phenomenon has also been observed in the vitreous humor of diabetic patients.[87] Inflammation serves as a positive inducer of lncRNAs, where MALAT1 can recruit the methyltransferase G9a to increase H3K9me1 levels, subsequently binding to the *Klotho* promoter and epigenetically inhibiting mKlotho expression, leading to HRGEC injury.[88] Thus, inflammation promotes lncRNA interactions with the *Klotho* promoter, resulting in reduced mKlotho expression. Additionally, some lncRNAs can interact with miRNAs to decrease the levels of fibrotic or inflammatory miRNAs, thereby functioning in an anti-inflammatory and anti-fibrotic capacity.[89] However, the precise relationship between these lncRNAs and Klotho remains unclear. In summary, the regulation of lncRNAs that target the *Klotho* promoter may represent one of the mechanisms by which inflammation suppresses Klotho expression, thereby exacerbating the progression of CKD.

Non-Epigenetic Mechanisms by Which Inflammation Inhibits Klotho Expression

Inflammation can suppress Klotho expression via several epigenetic mechanisms, such as DNA methylation, histone deacetylation, transcription factor expression, miRNA and lncRNA expression. However, in addition to these epigenetic mechanisms, inflammation can also inhibit Klotho expression via non-epigenetic mechanisms, which include endoplasmic reticulum (ER) stress and ER-associated degradation (ERAD).

ER Stress and ERAD

The ER is a primary organelle responsible for protein synthesis, folding, and post-translational modification. CKD is often associated with increased ER stress, which plays a critical role in its progression.[90] While ER stress can help restore ER homeostasis, persistent ER stress, which is commonly observed in CKD, disrupts protein folding and post-translational modifications, leading to the accumulation of unfolded or misfolded proteins in the ER and preventing proper protein maturation.[91] Studies have shown that inhibiting ER stress increases mKlotho protein levels without altering *Klotho* mRNA levels.[92] Additionally, the inhibition of ER stress has been demonstrated to restore mKlotho expression and ameliorate AKI.[93] These findings suggest that ER stress may promote the degradation of the mKlotho protein. Given that inflammation can trigger ER stress, the mechanisms by which inflammation suppresses mKlotho expression may involve ER stress[94] (Figure 3).

ERAD and the unfolded protein response (UPR) are two critical pathways activated by ER stress. When unfolded or misfolded proteins accumulate in the ER, both ERAD and UPR are triggered to restore ER homeostasis.[95] If the UPR fails to restore ER homeostasis, ERAD is activated to ubiquitinate and degrade these unfolded or misfolded proteins.[96] Our previous research involved a mouse model of renal interstitial fibrosis induced by UUO and revealed that blocking ERAD with Eeyarestatin I significantly restored mKlotho expression and alleviated kidney fibrosis, suggesting that mKlotho may be a potential substrate of ERAD.[97] Therefore, inflammation may degrade mKlotho by inducing ER stress and activating ERAD, contributing to further kidney damage (Figure 3).

Other Non-Epigenetic Mechanisms

Other non-epigenetic mechanisms, such as the renin-angiotensin-aldosterone system (RAAS) and mineral imbalances, influence Klotho regulation. Inflammation can activate the RAAS, which in turn increases the expression of pro-inflammatory cytokines.[98] The activated RAAS is known to suppress sKlotho expression, whereas blocking the RAAS can help restore sKlotho levels in CKD.[21,99] Additionally, RAAS activation is associated with triggering ER stress, which can be alleviated via the use of RAAS inhibitors.[100] Inflammation can also impact vitamin D regulation, leading to decreased Klotho expression; however, the underlying mechanism is not yet fully understood and requires further research.[101–103]

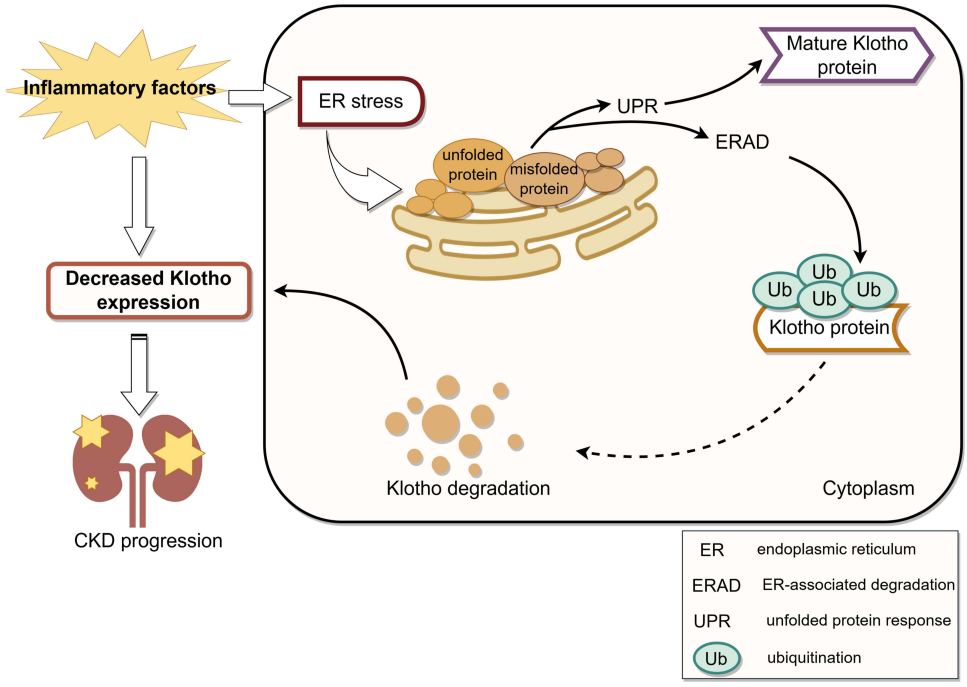

Figure 3 Roles of ER stress and ERAD in inflammation-induced Klotho deficiency. By Figdraw.

Mechanisms by Which Klotho Inhibits the Inflammatory Response

Klotho protein also exhibits strong anti-inflammatory properties by inhibiting key inflammatory factors and pathways. In eukaryotic cells, members of the NF-κB family exist as dimers in the cytoplasm. IκB acts as an NF-κB dimer inhibitor by binding to NF-κB, thereby preventing its translocation to the nucleus and keeping it inactive in the cytoplasm. Klotho inhibits inflammation by modulating the NF-κB signaling pathway.

First, Klotho prevents NF-κB pathway activation via the inhibition of IκB phosphorylation. Both in vitro and in vivo, Klotho reduces phosphorylated IκB levels and consequently lowers inflammatory factor levels.[104] Second, Klotho also inhibits the non-classical NF-κB pathway via RelA-Ser536 phosphorylation, preventing NF-κB from binding to target gene promoters and thereby inhibiting the inflammatory response.[105] Additionally, Klotho upregulates the expression of PDZ and LIM domain-containing proteins, which function as ubiquitin E3 ligases. These proteins target the NF-κB p65 subunit, promoting its ubiquitination and degradation, which in turn inhibits NF-κB activation.[106]

Furthermore, sKlotho exhibits glycoside activity that inhibits downstream inflammatory signals by deglycosylation of toll-like receptor 4.[107] mKlotho also reduces CKD-associated systemic inflammation by suppressing the RIG-I signaling pathway and monocyte activation.[41] Studies have reported that Klotho promotes the polarization of anti-inflammatory M2 macrophages, mitigating inflammation induced by indoxyl sulfate and resulting in reduced levels of urine, serum urea nitrogen, and creatinine.[108,109] Finally, the anti-inflammatory effects of Klotho may also involve modulation of the Wnt/β-catenin signaling pathway.[110] Overall, Klotho can effectively suppress inflammation and potentially improve CKD outcomes by targeting various inflammatory pathways (Figure 4).

Taken together, a complex network exists between inflammation and Klotho in CKD. Inflammation may suppress Klotho expression via both epigenetic mechanisms, such as DNA methylation, histone deacetylation, transcription factors, miRNAs and lncRNAs, and non-epigenetic mechanisms, including ER stress and ERAD. This suppression of Klotho compromises its protective effects, thereby aggravating inflammation and kidney function in CKD and promoting its progression. This establishes a vicious cycle between inflammation and Klotho, underscoring the critical role of the inflammation-Klotho axis in the initiation and progression of CKD.

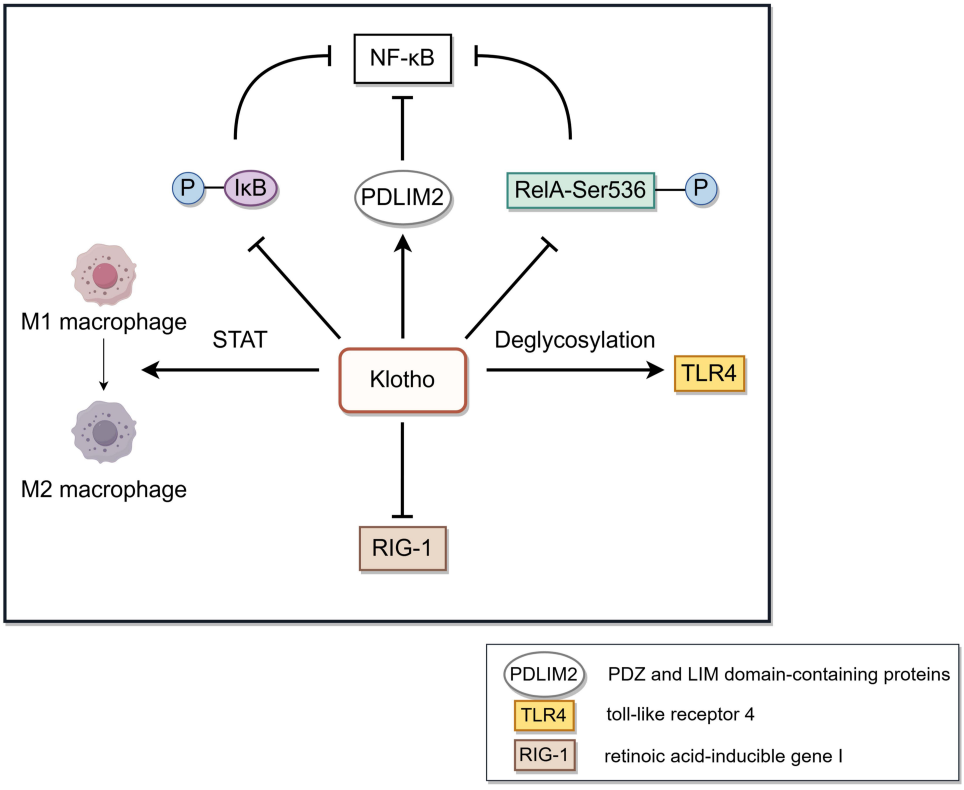

Figure 4 Anti-inflammatory actions of Klotho. By Figdraw.

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Therapeutic Applications of the Inflammation-Klotho Axis

Recent research exploring the inflammation-Klotho axis has been on the rise. Numerous pharmacological agents have been shown to enhance Klotho expression through anti-inflammatory mechanisms. For instance, rapamycin has been demonstrated to reverse the decline in mKlotho and sKlotho levels by inhibiting inflammatory pathways such as mTOR signaling.[111] The TNF-α inhibitor infliximab inactivates Wnt/β-catenin signaling by upregulating mKlotho, which helps suppress the progression of CKD.[112] Animal studies indicate that baicalin can exert anti-inflammatory effects in diabetic kidneys and mitigate renal fibrosis by reversing Klotho suppression induced by DNA methylation.[113] However, it remains to be determined whether this compound upregulates Klotho expression through the inhibition of DNA methylation in an anti-inflammatory context. Additionally, the selective class IIa HDAC inhibitor MC1568 has been shown to upregulate Klotho expression and may impede the initiation and progression of inflammation-induced renal fibrosis by suppressing NF-κB phosphorylation.[114] As a key transcription factor, NF-κB regulates Klotho through multiple epigenetic mechanisms, suggesting that MC1568 may target NF-κB to counteract the inflammation-induced downregulation of Klotho. Current research on the epigenetic regulation of Klotho expression through anti-inflammatory mechanisms is still limited, and this study provides novel insights into potential therapeutic strategies in this under-explored area.

Furthermore, several interventions have been found to upregulate Klotho expression, thereby mediating anti-inflammatory effects. For example, pentoxifylline has been shown to ameliorate inflammatory responses during the atherosclerotic process by increasing sKlotho levels.[8] Recombinant human α-Klotho used as an adjunctive therapy to telmisartan has demonstrated anti-inflammatory effects, thereby attenuating diabetic kidney disease.[115] Additionally, novel therapeutic targets related to the *Klotho* gene have been identified. Mutations in the *Klotho* gene may be linked to severe systemic inflammatory responses.[116] Clinical trials have shown that the KL-VS mutation of the *Klotho* gene is associated with lower serum levels of inflammatory markers, such as CRP and TNF-α.[117] Moreover, delivering *Klotho*-expressing plasmid DNA via stem cell-homing hydrogels has been found to alleviate osteoarthritis.[118] Therefore, targeting *Klotho* gene interventions may offer innovative strategies for combating inflammation.

Conclusion

Overall, Klotho deficiency, particularly under inflammatory conditions, is a significant factor in CKD. The suppression of Klotho by inflammation involves various epigenetic and non-epigenetic mechanisms, which may represent a novel mechanism by which inflammation promotes CKD progression. Conversely, Klotho exerts a protective effect by inhibiting key inflammatory factors and pathways, thereby reducing inflammation. This interplay forms a closed-loop relationship, suggesting that targeting the inflammation-Klotho axis could serve as a potential therapeutic strategy for CKD. Existing pharmacological therapies and genetic interventions targeting this axis have been reported, while the approaches remain relatively limited in scope. Understanding the regulatory dynamics between inflammation and Klotho could provide new insights for managing inflammation, regulating Klotho expression, and ultimately preventing and treating CKD. Although anti-inflammatory therapy has been shown to effectively protect kidney function and improve prognosis, the therapeutic effects of enhancing Klotho by targeting Klotho regulators in clinical settings have not yet been investigated under the inflammatory conditions during CKD. Therefore, translational research is needed to evaluate and confirm the clinical significance of the inflammation-Klotho axis in the CKD population in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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