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Review

Regulation of αKlotho

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αKlotho • FGF23 • CKD • Longevity

Abstract
Since its discovery in 1997, αKlotho has gained a lot of attention due to its powerful anti-aging and health-promoting properties. It exists as a membrane-bound protein or as a soluble factor. Membrane-bound αKlotho is an essential cofactor for fibroblast growth factor 23 (FGF23), thereby being involved in the regulation of renal phosphate and vitamin D metabolism. Soluble αKlotho (sKL) is present in different body fluids and exerts hormone-like effects. Through the αKlotho-FGF23 signaling axis, FGF23 regulates phosphate excretion by downregulating Na^+-dependent phosphate transporter (NaPi-2a). In addition, this axis suppresses expression of 1α-hydroxylase, thereby reducing active vitamin D (calcitriol) serum concentration. Disruptions of this axis lead to deranged mineral metabolism. Low levels of αKlotho and elevated FGF23 are early biomarkers for different diseases, including chronic kidney disease (CKD) and cardiovascular diseases (CVD). In CKD, decreased renal αKlotho expression and enhanced FGF23 production contribute to worsening kidney function. Activated transforming growth factor β1 (TGF-β1) signaling, promoting renal fibrosis, contributes to the pathophysiology. Moreover, FGF23 directly induces left ventricular hypertrophy (LVH) through FGF receptor-induced calcineurin/nuclear factor of activated T cells (NFAT) signaling in CKD. Our review aims to comprehensively summarize the regulation and function of αKlotho, highlighting its central role in maintaining mineral metabolism and its therapeutic potential in age-related and chronic diseases.

Introduction

The anti-aging protein αKlotho owes its name to Greek mythology, in which the goddess Klotho decided over life and death and held the threads of life [1, 2]. Its discovery goes back to experiments with a *kl/kl* mouse strain in 1997 [1]. This mouse strain is characterized by changes in behavior and appearance at a few weeks of age only [1]. Particularly striking is a drastic loss of bone mineral density and further signs of premature aging, leading to early death [1]. Conversely, overexpression of αKlotho delays aging and induces longevity, making αKlotho an interesting target in longevity research [3].

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Klotho family

Three different Klotho proteins exist, termed α-, β- and γ-Klotho, all being expressed in different organs and fulfilling various functions [4], but this review focuses only on αKlotho.

The latter is strongly expressed in the brain and kidney, and to a much lesser extent in the pituitary gland, aorta or pancreas [1]. αKlotho belongs to the group of type I membrane proteins with several structural domains: two extracellular domains KL1 and KL2, a transmembrane domain (TM) and a short cytoplasmic site (CYT) [5–7]. Depending on the cleavage site, membrane-bound αKlotho protein can be split into full-length soluble αKlotho (sKL) or into the respective single fragments KL1 and KL2 by a disintegrin and metalloproteinase (ADAM)10 or 17 [8–10]. In addition, a product of alternative RNA splicing exists, namely secreted αKlotho and identical to KL1 [5, 10]. Both human and mouse transcripts of membrane αKlotho comprise five exons, whereas the human secreted form of αKlotho consists of five and mouse secreted αKlotho only consists of three exons [5, 11]. Secreted αKlotho transcripts can only be detected in mice and humans, but not in rats [12] and the expression of secreted αKlotho in humans is even higher than that of membrane αKlotho [5].

In contrast to soluble and secreted αKlotho (summarized as circulating KL) [13] being humoral factors [14], the function of the membrane-bound form is much better understood: It acts as an essential cofactor for the binding of fibroblast growth factor 23 (FGF23) to its receptor since only αKlotho generates a specific FGF23 receptor (FGFR) complex FGFR1c, FGFR3c or FGFR4 [15, 16].

Membrane-bound αKlotho and FGF23

FGF23 was first described in 2000 [17] and is predominantly expressed by bone cells, i.e. osteoblasts and osteocytes [18]. The discovery of missense mutations in the FGF23 gene accounting for derangements of phosphate metabolism, rickets and further disorders of bone, led to the assumption that FGF23 is a major factor for phosphate and vitamin D metabolism [17, 19].

Altogether, 22 FGF genes exist that can be divided into intracellular and secreted FGFs, the latter having paracrine and endocrine functions [20, 21] and comprising FGF15/FGF19, FGF21, and FGF23 [22]. In contrast to the other FGF subfamilies, endocrine FGFs only have low affinity for heparin, resulting in a weak FGF receptor interaction [21–23]. It is the primary task of αKlotho to facilitate efficient and specific FGF23 signaling in the kidney by forming a FGFR1(IIIc)-αKlotho complex (Fig. 1) [16, 24]. It controls calcitriol synthe-

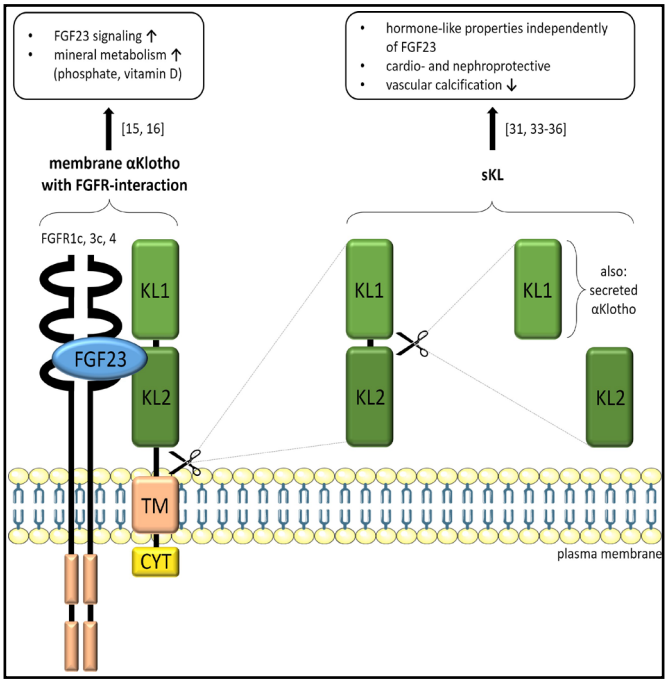

Fig. 1. Structures of membrane-bound αKlotho forming a complex with FGFR and FGF23 (left) and the cleaved forms of soluble αKlotho (KL1/KL2, right) with their respective functions in the organism. Fibroblast growth factor 23 (FGF23), FGF23 receptor (FGFR), transmembrane domain (TM), short cytoplasmic site (CYT), soluble αKlotho (sKL). Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/), Fig. adapted from [6].

sis by regulating the expression of its key enzyme, 1α-hydroxylase, in the proximal tubule [25, 26]. By downregulating the major renal Na^+-dependent phosphate transporter NaPi-2a, FGF23 suppresses phosphate reabsorption [26]. Both, αKlotho or FGF23 deficiency result in similar disorders in mice that are mainly due to deranged vitamin D and phosphate homeostasis and further characterized by growth retardation and a severely reduced life span [4, 24]. Moreover, αKlotho and FGF23 may both serve as biomarkers for the early detection of various diseases. Particularly in chronic kidney disease (CKD), an early rise in FGF23 serum levels as well as a decrease αKlotho serum levels are predictors of CKD progression [27, 28]. In an αKlotho-independent manner, elevated FGF23 binds to FGFR4 on cardiomyocytes and thereby activates phospholipase Cγ (PLCγ)/calcineurin/nuclear factor of activated T cells (NFAT) signaling, inducing left ventricular hypertrophy [29, 30].

Soluble αKlotho (sKL)

As the product of cleaved renal membrane-bound αKlotho, sKL serves as a hormone-like factor independently of FGF23 [31]. It can be detected in blood, cerebrospinal fluid, or urine [31] and is effective in different organs, including heart and blood vessels [32]. SKL has organoprotective properties in the heart by reducing susceptibility to stress signals and lowering intracellular calcium levels by inhibition of transient receptor potential channel TRPC6 [33]. It has beneficial effects in blood vessels by reducing vascular calcification [34, 35] and is nephroprotective [36]. SKL controls important intracellular signaling pathways including transforming growth factor-β (TGF-β) or Wnt signaling [31]. Antitumor [37] or antifibrosis effects of sKL may also be due to TGF-β receptor or Wnt signaling inhibition [38, 39]

Hitherto, no receptor for sKL has been characterized, but sKL binds to so-called lipid rafts and thereby negatively affects phosphoinositide 3-kinase (PI3K) signaling [40]. Lipid rafts are considered a promising target for many sKL-induced pathways [40].

Regulation of αKlotho in the kidney

Regulators of renal αKlotho expression are reviewed below and listed in an alphabetical order (summarized in Table 1).

1, 25-dihydroxyvitamin D_3

In cell lines of proximal or distal tubular origin or of the collecting duct, 1, 25-dihydroxyvitamin D_3 (1, 25D) enhances renal αKlotho gene expression, an effect dependent on vitamin D receptor (VDR) [41, 42].

Also, the administration of 1, 25D is paralleled by an increase in αKlotho gene expression in mice [43].

Albumin

Albumin reduces αKlotho mRNA and protein abundance *in vitro* and *in vivo* [44, 45], an effect attributed to albumin-induced endoplasmic reticulum (ER) stress. Conversely, inhibition of ER stress or silencing of activating transcription factor 3 (ATF3) enhance αKlotho protein [44].

Table 1. Regulators of transmembrane αKlotho

Regulator	Impact on transmembrane αKlotho expression
1,25D	↑ [41–43]
Aerobic exercise	↑ [72, 73]
AGK2 (SIRT2-inhibitor)	↑ [50]
Albumin	↓ [44, 45]
Aldosterone	↓ [77, 79]
AMPK	↑ [47]
Angiotensin II	↓ [78]
AST-120	↑ [91, 92]
Berberine	↑ [66]
Cytotoxic agents	↑ [49]
D-galactose	↓ [50]
Dehydration	↓ [77]
EGF	↑ [51]
EPO	↑ [52]
Fosinopril	↑ [83]
HDAC3	↓ [56]
High glucose	↓ [60]
Indoxyl sulfate	↓ [90, 91]
IFN-γ	↓ [59]
KP1	↑ [63, 64]
Lithium	↓ [65]
Losartan	↑ [81, 83]
LPS	↓ [12, 57]
NFκB signaling pathway	↓ [58]
Nicotinamide	↑ [71]
PAC-1	↑ [49]
Phosphorus-rich diet	↓ [69, 70]
PKCγ	↓ [74]
PPARγ activation	↑ [61, 62]
Rapamycin	↑ [75] ↓ [76]
Resveratrol	↑ [67, 68]
ROS	↓ [84, 85]
SGLT2i	↑ [60, 86]
Shiga toxin 2	↓ [93]
Sp1 overexpression	↑ [94]
Spironolacton	↑ [80]
Statins	↑ [87–89]
TGF-β	↓ [64]
TNFα/TWEAK	↓ [58]
Vasopressin	↓ [77]

AMP-dependent kinase

AMP-dependent kinase (AMPK) is activated in cellular states of energy deficiency characterized by high levels of AMP [46]. It stimulates renal αKlotho gene and protein expression *in vitro* [47], but αKlotho itself can activate AMPK signaling, too [48].

Cytotoxic agents

In certain renal cell lines, αKlotho expression is enhanced by cisplatin, paclitaxel, or doxorubicin [49], an effect at least in part involving peroxisome proliferator-activated receptor γ (PPARγ) [49]. The induction of apoptosis with PAC-1 shows a similar effect on αKlotho expression *in vitro* [49]. In contrast, these cytotoxic drugs suppress renal αKlotho gene expression and reduce sKL in human kidney 2 (HK2) cells [49].

D-galactose

D-galactose stimulates renal fibrosis by inducing silent mating type information regulation 2 homolog-2 (SIRT2) and TGF-β1, an effect paralleled by reduced renal αKlotho protein abundance *in vivo* [50]. Conversely, SIRT2 inhibitor acylglycerol kinase (AGK)-2 upregulates αKlotho protein [50].

Epidermal growth factor

Epidermal growth factor (EGF) elevates renal αKlotho mRNA levels *in vitro* [51].

Erythropoietin

Recombinant human erythropoietin (EPO) induces renal αKlotho protein expression in rats with acute nephropathy [52].

Histone deacetylase 3

Histone deacetylase (HDAC) inhibition up-regulates αKlotho mRNA and protein in a kidney cell line or *in vivo* and delays CKD progression [53, 54]. HDAC3 is a regulator of ROS production and is involved in renal fibrosis [55]. TGF-β activates HDAC3 that subsequently decreases αKlotho protein [56]. In contrast, inhibition of HDAC3 stimulates both αKlotho gene and protein expression *in vitro*, while increased αKlotho protein expression is reported *in vivo* [56].

Inflammation

Lipopolysaccharides (LPS) downregulate renal αKlotho gene expression [12] and protein [57] *in vivo* and *in vitro*. Also, tumor necrosis factor α (TNFα) and TNF-like weak inducer of apoptosis (TWEAK) suppress αKlotho mRNA and protein expression through NFκB signaling *in vitro* and *in vivo* [58], as does interferon (IFN)-γ *in vitro* [59].

Metabolic factors

High levels of glucose, especially in type 2 diabetes, are negatively associated with αKlotho mRNA and protein abundance in a proximal tubular cell line [60].

PPARγ agonists including troglitazone upregulate renal αKlotho gene and protein expression *in vitro* and *in vivo* [61, 62]

Klotho-derived peptide 1

Klotho-derived peptide 1 (KP1), an inhibitor of TGF-β1 signaling pathway as a ligand of TGF-β receptor 2, is positively associated with αKlotho protein expression *in vitro* and *in vivo* [63, 64].

Lithium

Lithium reduces renal αKlotho protein abundance *in vivo* [65].

Nutrition and lifestyle

Berberine, a natural plant compound has anti-inflammatory, anti-oxidative and anti-apoptotic properties [66]. In acute kidney injury, it upregulates renal αKlotho gene expression [66].

Resveratrol, a polyphenol available in many plant-based foods, stimulates renal αKlotho gene and protein expression *in vitro* and *in vivo* [67, 68].

A high phosphate diet suppresses renal αKlotho protein abundance in wild type mice [69]. Its impact is stronger in adolescent mice compared to adult animals [70].

Nicotinamide attenuates the decrease of αKlotho protein expression in mice with glycerol-induced AKI by altering NFκB and histone deacetylase 1 activity [71].

Aerobic exercise elevates renal αKlotho gene and protein expression and reduces ROS production [72] as well as TGF-β1 signaling [73].

PKC

Protein kinase C (PKC), especially isoform PKCγ, activation downregulates αKlotho gene expression *in vitro* [74].

Rapamycin

Rapamycin is an mTOR (molecular target of rapamycin) inhibitor [75]. One study found upregulation of renal αKlotho protein in mice by rapamycin [75] whereas another one reported rapamycin-induced downregulation of αKlotho transcripts and protein abundance in rats [76].

Renin-angiotensin system

Water homeostasis controls renal αKlotho expression. Dehydration induces angiotensin II, an effect paralleled by suppression of αKlotho mRNA and protein levels [77]. Angiotensin II is a direct negative regulator of αKlotho gene and protein expression *in vitro* [78].

In vitro or *in vivo*, vasopressin [77] and aldosterone [77, 79] reduce the expression of renal αKlotho gene and protein, while aldosterone antagonist spironolactone induces it [80]. Both losartan (angiotensin II receptor antagonist [81]) and fosinopril (inhibitor of angiotensin-converting enzyme (ACE) [82]), enhance renal αKlotho gene and protein expression in a mouse model of primary hypertension [83].

Reactive oxygen species

Reactive oxygen species (ROS) are negative regulators of renal αKlotho gene and protein expression *in vitro* [84, 85] with nuclear factor erythroid 2-related factor 2 (Nrf2) being involved [85].

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 inhibitors *(*SGLT2i) canagliflozin, dapagliflozin, empagliflozin or sotagliflozin are reported to exert contrasting effects on αKlotho gene and protein expression in different renal cell lines and attenuate the decrease of αKlotho triggered by albuminuria or inflammation [60, 86].

Statins

Statins upregulate renal αKlotho mRNA and protein expression *in vitro* and *in vivo* [87–89]. The upregulation is dependent on inhibition of RhoA pathway [88].

Toxins

αKlotho gene and protein expression is downregulated in the presence of uremic toxin indoxyl sulfate *in vitro* and *in vivo* [90, 91]. AST-120, an adsorbent of indole, reverses the suppressive effect on αKlotho protein [91, 92].

Shiga toxin 2 downregulates renal αKlotho mRNA and protein abundance in mice [93].

Transcription factor Sp1

Overexpression of the ubiquitously expressed transcription factor Sp1 upregulates αKlotho transcripts and protein *in vitro* [94].

Regulation of αKlotho in organs and tissues other than kidney

Regulators of αKlotho expression in extrarenal organs or tissues are reviewed below and listed in alphabetical order (summarized in Table 2).

Table 2: Regulators of αKlotho in extrarenal organs/tissues

Regulator	Impact on αKlotho expression in extrarenal organs/tissues
Aerobic exercise	↑ [72]
Cadmium	↓ [95]
CGRP	↑ [96]
Estradiol	↑ [97]
HDAC inhibition	↑ [54]
Matrix stiffness	↓ [98]
Rapamycin	↑ [75, 99]
Resveratrol	↑ [67]
T_3	↑ [100]

Aerobic exercise

Aerobic exercise upregulates αKlotho gene and protein expression in rat brain [72].

Cadmium

Cadmium exposure is negatively associated with αKlotho protein expression in rat hippocampus and in a cell line derived from the adrenal gland [95].

Calcitonin gene-related peptide

In endothelial progenitor cells, calcitonin gene-related peptide (CGRP) upregulates αKlotho gene and protein expression and reverses angiotensin II-induced senescence [96].

Estradiol

αKlotho protein is enhanced by estradiol E2 in rat hippocampus, an effect related to cognitive function and synapse formation [97].

Histone deacetylase inhibition

Inhibition of HDAC elevates αKlotho mRNA levels in femurs of mice [54].

Matrix stiffness

Matrix stiffness, a typical feature of aging, is implicated in decreased αKlotho expression in chondrocytes, and abolishment of stiffness enhances αKlotho expression *in vivo* [98].

Rapamycin

In addition to the kidney, αKlotho protein is also upregulated by rapamycin in adipose tissue, lung, muscle, brain and heart [75].

Rapamycin also increases αKlotho mRNA and protein levels in some cell lines derived from the aorta or in the aorta of mice or rats and thus counteracts vascular calcification [99].

Resveratrol

Treatment with resveratrol elevates αKlotho gene and protein abundance in mouse brain dose-dependently [67].

Triiodothyronine

Triiodothyronine (T_3) increases mRNA levels of the membrane form of αKlotho in preadipocytes during differentiation [100].

Regulation of sKL and secreted αKlotho

Regulators of sKL or secreted αKlotho expression are reviewed below and listed in alphabetical order (summarized in Table 3).

Table 3. Regulators of sKL and secreted αKlotho

Regulator	Impact on sKL/secreted αKlotho
1,25D	↑ [41, 101]
Adiponectin	↓ [111]
Aerobic exercise	↑ [109]
Albumin	↓ [44, 45]
Calcimimetics	↑ [104]
Cholecalciferol	→ [102] ↓ [103]
HDAC inhibition	↑ [54]
Hypertension	↓ [108]
GABA	↑ [112]
Insulin	Shedding ↑ [8]
KP1	↑ [64]
Rapamycin	↑ [99]
SGLT2i	↑ [60]
Sleep	↑ [110]
T_3	→ [100]
Thyroid dysfunction	↓ [107]

1, 25-dihydroxyvitamin D_3

In a cell line of distal tubular origin or of the collecting duct, 1,25-dihydroxyvitamin D_3 (1, 25D) enhances mRNA levels of secreted αKlotho identified with a primer pair that specifically amplifies the secreted αKlotho splice form [41].

An increase in serum and urinary αKlotho also occurs in mice with CKD on a high phosphate diet treated with vitamin D receptor agonists [101]. In contrast, cholecalciferol does not significantly change sKL [102] or even reduces it [103] in patients on dialysis.

Albumin

Albumin reduces secreted αKlotho mRNA expression *in vivo* [44]. Furthermore, αKlotho protein levels are reduced in the urine of patients with renal dysfunction as a consequence of severe albuminuria [45].

Calcimimetics

The calcium-sensing receptor CaSR activates ADAM10 in the kidney, thereby being involved in Klotho shedding [104]. SKL is elevated upon treatment with calcimimetics or alkali *in vitro* and *in vivo* [104], an effect dependent on CaSR, ADAM10, and tetraspanin 5 [104, 105].

Histone deacetylase inhibition

Inhibition of HDAC elevates αKlotho protein levels in mouse serum [54].

Hormones

According to a human study, the sKL serum concentration is positively correlated with total and free triiodothyronine (T_3) [106]. T_3 increases αKlotho but not sKL gene expression in a preadipocyte cell line during differentiation [100]. In patients with hyper- or hypothyroidism sKL protein is reduced [107].

Hypertension

Elevated blood pressure lowers serum sKL levels [108].

KP1

KP1 increases sKL protein levels in mice with fibrotic kidney [64].

Lifestyle

Aerobic exercise is associated with elevated sKL plasma levels in a human study [109] as is adequate sleep [110].

Metabolic factors

Insulin elevates sKL by enhancing ADAM10- and ADAM17-mediated shedding of transmembrane Klotho [8]. SKL and secreted αKlotho are downregulated by adiponectin *in vivo* and *in vitro* [111].

In mice treated with streptozotocin that induces type 1 diabetes, gamma-aminobutyric acid (GABA) enhances sKL[112].

Rapamycin
In rats with CKD, rapamycin elevates serum sKL levels [99].

SGLT2 inhibitors
In patients treated with SGLT2 inhibitors for type 2 diabetes, sKL in serum and urine is upregulated [60].

Administration of exogenous Klotho as therapeutic agent

The administration of exogenous Klotho protein may be a promising approach in the treatment of different diseases. Exogenous Klotho may be comparable to sKL and may thus provide resistance of cells to oxidative stress via inhibition of the insulin/PI3K/Akt signaling pathway and FoxO-mediated upregulation of anti-oxidative enzymes [113, 114]. Moreover, sKL not only ameliorates renal fibrosis and CKD [115, 116], but also acts as a tumor suppressor in various types of cancer [117–119]. Further health-promoting effects of exogenous Klotho administration are part of current research and already reviewed elsewhere [120].

Conclusion

αKlotho in both of its forms (membrane-bound or soluble) is an important regulator of health and disease. Due to its anti-aging effects, αKlotho has gained attention as a putative therapeutic target. It not only preserves kidney function, but also positively affects the heart, blood vessels or cognitive functions and improves outcomes in cancer or diabetes. As summarized in this article, regulation of αKlotho is complex and dependent on several factors. For sure, more research is needed to better understand the physiological and pathophysiological roles of membrane-bound αKlotho and sKL.

Acknowledgements

Fig. 1 was partly generated using Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). No AI was applied.

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Statement of Ethics
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References

1 Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI: Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 1997;390:45–51.
2 Lichtenauer M, Altwein A-K, Kopp K, Salmhofer H: Uncoupling fate: Klotho-Goddess of fate and regulator of life and ageing. Australasian journal on ageing 2020;39:161–3.
3 Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, McGuinness OP, Chikuda H, Yamaguchi M, Kawaguchi H, Shimomura I, Takayama Y, Herz J, Kahn CR, Rosenblatt KP, Kuro-o M: Suppression of aging in mice by the hormone Klotho. Science (New York, N.Y.) 2005;309:1829–33.
4 Hu MC, Shiizaki K, Kuro-o M, Moe OW: Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annual review of physiology 2013;75:503–33.
5 Matsumura Y, Aizawa H, Shiraki-Iida T, Nagai R, Kuro-o M, Nabeshima Y: Identification of the human klotho gene and its two transcripts encoding membrane and secreted klotho protein. Biochemical and biophysical research communications 1998;242:626–30.
6 Prud'homme GJ, Kurt M, Wang Q: Pathobiology of the Klotho Antiaging Protein and Therapeutic Considerations. Frontiers in aging 2022;3:931331.
7 Tohyama O, Imura A, Iwano A, Freund J-N, Henrissat B, Fujimori T, Nabeshima Y: Klotho is a novel beta-glucuronidase capable of hydrolyzing steroid beta-glucuronides. The Journal of biological chemistry 2004;279:9777–84.
8 Chen C-D, Podvin S, Gillespie E, Leeman SE, Abraham CR: Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. Proceedings of the National Academy of Sciences of the United States of America 2007;104:19796–801.
9 van Loon EPM, Pulskens WP, van der Hagen EAE, Lavrijsen M, Vervloet MG, van Goor H, Bindels RJM, Hoenderop JGJ: Shedding of klotho by ADAMs in the kidney. American journal of physiology. Renal physiology 2015;309:F359-68.
10 Wang Y, Sun Z: Current understanding of klotho. Ageing research reviews 2009;8:43–51.
11 Shiraki-Iida T, Aizawa H, Matsumura Y, Sekine S, Iida A, Anazawa H, Nagai R, Kuro-o M, Nabeshima Y: Structure of the mouse klotho gene and its two transcripts encoding membrane and secreted protein. FEBS letters 1998;424:6–10.
12 Ohyama Y, Kurabayashi M, Masuda H, Nakamura T, Aihara Y, Kaname T, Suga T, Arai M, Aizawa H, Matsumura Y, Kuro-o M, Nabeshima YI, Nagail R: Molecular cloning of rat klotho cDNA: markedly decreased expression of klotho by acute inflammatory stress. Biochemical and biophysical research communications 1998;251:920–5.
13 Xu Y, Sun Z: Molecular basis of Klotho: from gene to function in aging. Endocrine reviews 2015;36:174–93.
14 Mitani H, Ishizaka N, Aizawa T, Ohno M, Usui S, Suzuki T, Amaki T, Mori I, Nakamura Y, Sato M, Nangaku M, Hirata Y, Nagai R: In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. Hypertension (Dallas, Tex. 1979) 2002;39:838–43.
15 Kuro-o M: Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. Current opinion in nephrology and hypertension 2006;15:437–41.
16 Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T: Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006;444:770–4.
17 Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nature genetics 2000;26:345–8.
18 Liu S, Guo R, Simpson LG, Xiao Z-S, Burnham CE, Quarles LD: Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. The Journal of biological chemistry 2003;278:37419–26.
19 White KE, Carn G, Lorenz-Depiereux B, Benet-Pages A, Strom TM, Econs MJ: Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. Kidney international 2001;60:2079–86.
20 Ornitz DM, Itoh N: Fibroblast growth factors. Genome biology 2001;2:REVIEWS3005.
21 Ornitz DM, Itoh N: The Fibroblast Growth Factor signaling pathway. Wiley interdisciplinary reviews. Developmental biology 2015;4:215–66.
22 Martin A, David V, Quarles LD: Regulation and function of the FGF23/klotho endocrine pathways. Physiological reviews 2012;92:131–55.

23 Zhang X, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M, Ornitz DM: Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. The Journal of biological chemistry 2006;281:15694–700.
24 Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu M-C, Moe OW, Kuro-o M: Regulation of fibroblast growth factor-23 signaling by klotho. The Journal of biological chemistry 2006;281:6120–3.
25 Erben RG, Andrukhova O: FGF23-Klotho signaling axis in the kidney. Bone 2017;100:62–8.
26 Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T: FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. Journal of bone and mineral research the official journal of the American Society for Bone and Mineral Research 2004;19:429–35.
27 Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu C, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M: Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 2011;305:2432–9.
28 Shimamura Y, Hamada K, Inoue K, Ogata K, Ishihara M, Kagawa T, Inoue M, Fujimoto S, Ikebe M, Yuasa K, Yamanaka S, Sugiura T, Terada Y: Serum levels of soluble secreted α-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. Clinical and experimental nephrology 2012;16:722–9.
29 Faul C, Amaral AP, Oskouei B, Hu M-C, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-o M, Kusek JW, Keane MG, Wolf M: FGF23 induces left ventricular hypertrophy. The Journal of clinical investigation 2011;121:4393–408.
30 Grabner A, Amaral AP, Schramm K, Singh S, Sloan A, Yanucil C, Li J, Shehadeh LA, Hare JM, David V, Martin A, Fornoni A, Di Marco GS, Kentrup D, Reuter S, Mayer AB, Pavenstädt H, Stypmann J, Kuhn C, Hille S, Frey N, Leifheit-Nestler M, Richter B, Haffner D, Abraham R, Bange J, Sperl B, Ullrich A, Brand M, Wolf M, Faul C: Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left Ventricular Hypertrophy. Cell metabolism 2015;22:1020–32.
31 Dalton GD, Xie J, An S-W, Huang C-L: New Insights into the Mechanism of Action of Soluble Klotho. Frontiers in endocrinology 2017;8:323.
32 Erben RG: Update on FGF23 and Klotho signaling. Molecular and cellular endocrinology 2016;432:56–65.
33 Xie J, Cha S-K, An S-W, Kuro-o M, Birnbaumer L, Huang C-L: Cardioprotection by Klotho through downregulation of TRPC6 channels in the mouse heart. Nature communications 2012;3:1238.
34 Hu MC, Shi M, Zhang J, Quiñones H, Griffith C, Kuro-o M, Moe OW: Klotho deficiency causes vascular calcification in chronic kidney disease. Journal of the American Society of Nephrology JASN 2011;22:124–36.
35 Liu Q, Yu L, Yin X, Ye J, Li S: Correlation Between Soluble Klotho and Vascular Calcification in Chronic Kidney Disease: A Meta-Analysis and Systematic Review. Frontiers in physiology 2021;12:711904.
36 Hu M-C, Shi M, Zhang J, Quiñones H, Kuro-o M, Moe OW: Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. Kidney international 2010;78:1240–51.
37 Tang X, Wang Y, Fan Z, Ji G, Wang M, Lin J, Huang S, Meltzer SJ: Klotho: a tumor suppressor and modulator of the Wnt/β-catenin pathway in human hepatocellular carcinoma. Laboratory investigation; a journal of technical methods and pathology 2016;96:197–205.
38 Doi S, Zou Y, Togao O, Pastor JV, John GB, Wang L, Shiizaki K, Gotschall R, Schiavi S, Yorioka N, Takahashi M, Boothman DA, Kuro-o M: Klotho inhibits transforming growth factor-beta1 (TGF-beta1) signaling and suppresses renal fibrosis and cancer metastasis in mice. The Journal of biological chemistry 2011;286:8655–65.
39 Zhou L, Li Y, Zhou D, Tan RJ, Liu Y: Loss of Klotho contributes to kidney injury by derepression of Wnt/β-catenin signaling. Journal of the American Society of Nephrology JASN 2013;24:771–85.
40 Dalton G, An S-W, Al-Juboori SI, Nischan N, Yoon J, Dobrinskikh E, Hilgemann DW, Xie J, Luby-Phelps K, Kohler JJ, Birnbaumer L, Huang C-L: Soluble klotho binds monosialoganglioside to regulate membrane microdomains and growth factor signaling. Proceedings of the National Academy of Sciences of the United States of America 2017;114:752–7.

41 Forster RE, Jurutka PW, Hsieh J-C, Haussler CA, Lowmiller CL, Kaneko I, Haussler MR, Kerr Whitfield G: Vitamin D receptor controls expression of the anti-aging klotho gene in mouse and human renal cells. Biochemical and biophysical research communications 2011;414:557–62.
42 Haussler MR, Haussler CA, Whitfield GK, Hsieh J-C, Thompson PD, Barthel TK, Bartik L, Egan JB, Wu Y, Kubicek JL, Lowmiller CL, Moffet EW, Forster RE, Jurutka PW: The nuclear vitamin D receptor controls the expression of genes encoding factors which feed the „Fountain of Youth" to mediate healthful aging. The Journal of steroid biochemistry and molecular biology 2010;121:88–97.
43 Tsujikawa H, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y: Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. Molecular endocrinology (Baltimore, Md.) 2003;17:2393–403.
44 Delitsikou V, Jarad G, Rajaram RD, Ino F, Rutkowski JM, Chen C-D, Santos CXC, Scherer PE, Abraham CR, Shah AM, Feraille E, Miner JH, Seigneux S de: Klotho regulation by albuminuria is dependent on ATF3 and endoplasmic reticulum stress. FASEB journal official publication of the Federation of American Societies for Experimental Biology 2020;34:2087–104.
45 Fernandez-Fernandez B, Izquierdo MC, Valiño-Rivas L, Nastou D, Sanz AB, Ortiz A, Sanchez-Niño MD: Albumin downregulates Klotho in tubular cells. Nephrology, dialysis, transplantation official publication of the European Dialysis and Transplant Association - European Renal Association 2018;33:1712–22.
46 Hardie DG, Hawley SA, Scott JW: AMP-activated protein kinase--development of the energy sensor concept. The Journal of physiology 2006;574:7–15.
47 Vogt J, Wolf L, Hoelzle LE, Feger M, Föller M: AMP-dependent kinase stimulates the expression of αKlotho. FEBS open bio 2024;14:1691–700.
48 Lee J, Tsogbadrakh B, Yang S, Ryu H, Kang E, Kang M, Kang HG, Ahn C, Oh K-H: Klotho ameliorates diabetic nephropathy via LKB1-AMPK-PGC1α-mediated renal mitochondrial protection. Biochemical and biophysical research communications 2021;534:1040–6.
49 Münz S, Wolf L, Hoelzle LE, Chernyakov D, Edemir B, Föller M: Impact of cytotoxic agents or apoptosis stimulants on αklotho in MDCK, NRK-52E and HK2 kidney cells. Aging 2022;14:7282–99.
50 Protective Effect of Pharmacological SIRT2 Inhibition on Renal Dysfunction, Fibrosis, TGF-β1/β-Catenin, and Klotho Signaling in D-Galactose-Induced Aging Model. J Biol Regul Homeost Agents 2023;37.
51 Choi BH, Kim CG, Lim Y, Lee YH, Shin SY: Transcriptional activation of the human Klotho gene by epidermal growth factor in HEK293 cells; role of Egr-1. Gene 2010;450:121–7.
52 Sugiura H, Yoshida T, Mitobe M, Shiohira S, Nitta K, Tsuchiya K: Recombinant human erythropoietin mitigates reductions in renal klotho expression. American journal of nephrology 2010;32:137–44.
53 Kale A, Sankrityayan H, Anders H-J, Gaikwad AB: Epigenetic and non-epigenetic regulation of Klotho in kidney disease. Life sciences 2021;264:118644.
54 Lin W, Li Y, Chen F, Yin S, Liu Z, Cao W: Klotho preservation via histone deacetylase inhibition attenuates chronic kidney disease-associated bone injury in mice. Scientific reports 2017;7:46195.
55 He R, Liu B, Geng B, Li N, Geng Q: The role of HDAC3 and its inhibitors in regulation of oxidative stress and chronic diseases. Cell death discovery 2023;9:131.
56 Chen F, Gao Q, Wei A, Chen X, Shi Y, Wang H, Cao W: Histone deacetylase 3 aberration inhibits Klotho transcription and promotes renal fibrosis. Cell death and differentiation 2021;28:1001–12.
57 Tsai K-D, Lee W-X, Chen W, Chen B-Y, Chen K-L, Hsiao T-C, Wang S-H, Lee Y-J, Liang S-Y, Shieh J-C, Lin T-H: Upregulation of PRMT6 by LPS suppresses Klotho expression through interaction with NF-κB in glomerular mesangial cells. Journal of cellular biochemistry 2018;119:3404–16.
58 Moreno JA, Izquierdo MC, Sanchez-Niño MD, Suárez-Alvarez B, Lopez-Larrea C, Jakubowski A, Blanco J, Ramirez R, Selgas R, Ruiz-Ortega M, Egido J, Ortiz A, Sanz AB: The inflammatory cytokines TWEAK and TNFα reduce renal klotho expression through NFκB. Journal of the American Society of Nephrology JASN 2011;22:1315–25.
59 Thurston RD, Larmonier CB, Majewski PM, Ramalingam R, Midura-Kiela M, Laubitz D, Vandewalle A, Besselsen DG, Mühlbauer M, Jobin C, Kiela PR, Ghishan FK: Tumor necrosis factor and interferon-gamma down-regulate Klotho in mice with colitis. Gastroenterology 2010;138:1384-94, 1394.e1-2.
60 Mora-Fernández C, Sánchez-Niño MD, Donate-Correa J, Martín-Núñez E, Pérez-Delgado N, Valiño-Rivas L, Fernández-Fernández B, Ortiz A, Navarro-González JF: Sodium-glucose co-transporter-2 inhibitors increase Klotho in patients with diabetic kidney disease: A clinical and experimental study. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2022;154:113677.

61 Yamagishi T, Saito Y, Nakamura T, Takeda S, Kanai H, Sumino H, Kuro-o M, Nabeshima Y, Kurabayashi M, Nagai R: Troglitazone improves endothelial function and augments renal klotho mRNA expression in Otsuka Long-Evans Tokushima Fatty (OLETF) rats with multiple atherogenic risk factors. Hypertension research official journal of the Japanese Society of Hypertension 2001;24:705–9.
62 Zhang H, Li Y, Fan Y, Wu J, Zhao B, Guan Y, Chien S, Wang N: Klotho is a target gene of PPAR-gamma. Kidney international 2008;74:732–9.
63 Yuan Q, Ren Q, Li L, Tan H, Lu M, Tian Y, Huang L, Zhao B, Fu H, Hou FF, Zhou L, Liu Y: A Klotho-derived peptide protects against kidney fibrosis by targeting TGF-β signaling. Nature communications 2022;13:438.
64 Zhang X, Li L, Tan H, Hong X, Yuan Q, Hou FF, Zhou L, Liu Y: Klotho-derived peptide 1 inhibits cellular senescence in the fibrotic kidney by restoring Klotho expression via posttranscriptional regulation. Theranostics 2024;14:420–35.
65 Fakhri H, Pathare G, Fajol A, Zhang B, Bock T, Kandolf R, Schleicher E, Biber J, Föller M, Lang UE, Lang F: Regulation of mineral metabolism by lithium. Pflugers Archiv European journal of physiology 2014;466:467–75.
66 Salah TM, Rabie MA, El Sayed NS: Renoprotective effect of berberine in cisplatin-induced acute kidney injury: Role of Klotho and the AMPK/mtor/ULK1/Beclin-1 pathway. Food and chemical toxicology an international journal published for the British Industrial Biological Research Association 2025;196:115179.
67 Chu S-H, Yang D, Wang Y-P, Yang R, Qu L, Zeng H-J: Effect of resveratrol on the repair of kidney and brain injuries and its regulation on klotho gene in d-galactose-induced aging mice. Bioorganic & medicinal chemistry letters 2021;40:127913.
68 Hsu S-C, Huang S-M, Chen A, Sun C-Y, Lin S-H, Chen J-S, Liu S-T, Hsu Y-J: Resveratrol increases anti-aging Klotho gene expression via the activating transcription factor 3/c-Jun complex-mediated signaling pathway. The international journal of biochemistry & cell biology 2014;53:361–71.
69 Morishita K, Shirai A, Kubota M, Katakura Y, Nabeshima Y, Takeshige K, Kamiya T: The progression of aging in klotho mutant mice can be modified by dietary phosphorus and zinc. The Journal of nutrition 2001;131:3182–8.
70 Fukuda-Tatano S, Yamamoto H, Nakahashi O, Yoshikawa R, Hayashi M, Kishimoto M, Imi Y, Yamanaka-Okumura H, Ohnishi K, Masuda M, Taketani Y: Regulation of α-Klotho Expression by Dietary Phosphate During Growth Periods. Calcified tissue international 2019;104:667–78.
71 Lin W, Wu X, Wen J, Fei Y, Wu J, Li X, Zhang Q, Dong Y, Xu T, Fan Y, Wang N: Nicotinamide retains Klotho expression and ameliorates rhabdomyolysis-induced acute kidney injury. Nutrition (Burbank, Los Angeles County, Calif.) 2021;91-92:111376.
72 Ji N, Luan J, Hu F, Zhao Y, Lv B, Wang W, Xia M, Zhao X, Lao K: Aerobic exercise-stimulated Klotho upregulation extends life span by attenuating the excess production of reactive oxygen species in the brain and kidney. Experimental and therapeutic medicine 2018;16:3511–7.
73 Zhao J, Guan Y, Jia Y, Chen Y, Cai Y: Aerobic exercise up-regulates Klotho to improve renal fibrosis associated with aging and its mechanism. PloS one 2024;19:e0311055.
74 Wolf L, Vogt J, Alber J, Franjic D, Feger M, Föller M: PKC regulates αKlotho gene expression in MDCK and NRK-52E cells. Pflugers Archiv European journal of physiology 2024;476:75–86.
75 Szőke K, Bódi B, Hendrik Z, Czompa A, Gyöngyösi A, Haines DD, Papp Z, Tósaki Á, Lekli I: Rapamycin treatment increases survival, autophagy biomarkers and expression of the anti-aging klotho protein in elderly mice. Pharmacology research & perspectives 2023;11:e01091.
76 Espartero A, Vidal A, Lopez I, Raya AI, Rodriguez M, Aguilera-Tejero E, Pineda C: Rapamycin downregulates α-klotho in the kidneys of female rats with normal and reduced renal function. PloS one 2023;18:e0294791.
77 Tang C, Pathare G, Michael D, Fajol A, Eichenmüller M, Lang F: Downregulation of Klotho expression by dehydration. American journal of physiology. Renal physiology 2011;301:F745-50.
78 Zhou Q, Lin S, Tang R, Veeraragoo P, Peng W, Wu R: Role of Fosinopril and Valsartan on Klotho Gene Expression Induced by Angiotensin II in Rat Renal Tubular Epithelial Cells. Kidney & blood pressure research 2010;33:186–92.
79 Lai L, Cheng P, Yan M, Gu Y, Xue J: Aldosterone induces renal fibrosis by promoting HDAC1 expression, deacetylating H3K9 and inhibiting klotho transcription. Molecular medicine reports 2019;19:1803–8.
80 Alesutan I, Feger M, Pakladok T, Mia S, Ahmed MSE, Voelkl J, Lang F: 25-Hydroxyvitamin D3 1-α-hydroxylase-dependent stimulation of renal klotho expression by spironolactone. Kidney & blood pressure research 2013;37:475–87.

81 Yoon HE, Ghee JY, Piao S, Song J-H, Han DH, Kim S, Ohashi N, Kobori H, Kuro-o M, Yang CW: Angiotensin II blockade upregulates the expression of Klotho, the anti-ageing gene, in an experimental model of chronic cyclosporine nephropathy. Nephrology, dialysis, transplantation official publication of the European Dialysis and Transplant Association - European Renal Association 2011;26:800–13.
82 Weber MA: Fosinopril: a new generation of angiotensin-converting enzyme inhibitors. Journal of cardiovascular pharmacology 1992;20 Suppl 10:S7-12.
83 Tang R, Zhou Q-L, Ao X, Peng W-S, Veeraragoo P, Tang T-F: Fosinopril and losartan regulate klotho gene and nicotinamide adenine dinucleotide phosphate oxidase expression in kidneys of spontaneously hypertensive rats. Kidney & blood pressure research 2011;34:350–7.
84 Mitobe M, Yoshida T, Sugiura H, Shirota S, Tsuchiya K, Nihei H: Oxidative stress decreases klotho expression in a mouse kidney cell line. Nephron. Experimental nephrology 2005;101:e67-74.
85 Zhang D, Li Z, Gao Y, Sun H: MiR-556-3p mediated repression of klotho under oxidative stress promotes fibrosis of renal tubular epithelial cells. Scientific reports 2025;15:12182.
86 Wolf L, Föller M, Feger M: The impact of SGLT2 inhibitors on αKlotho in renal MDCK and HK-2 cells. Frontiers in endocrinology 2023;14:1069715.
87 Kuwahara N, Sasaki S, Kobara M, Nakata T, Tatsumi T, Irie H, Narumiya H, Hatta T, Takeda K, Matsubara H, Hushiki S: HMG-CoA reductase inhibition improves anti-aging klotho protein expression and arteriosclerosis in rats with chronic inhibition of nitric oxide synthesis. International journal of cardiology 2008;123:84–90.
88 Narumiya H, Sasaki S, Kuwahara N, Irie H, Kusaba T, Kameyama H, Tamagaki K, Hatta T, Takeda K, Matsubara H: HMG-CoA reductase inhibitors up-regulate anti-aging klotho mRNA via RhoA inactivation in IMCD3 cells. Cardiovascular research 2004;64:331–6.
89 Yoon HE, Lim SW, Piao SG, Song J-H, Kim J, Yang CW: Statin upregulates the expression of klotho, an anti-aging gene, in experimental cyclosporine nephropathy. Nephron. Experimental nephrology 2012;120:e123-33.
90 Adijiang A, Shimizu H, Higuchi Y, Nishijima F, Niwa T: Indoxyl sulfate reduces klotho expression and promotes senescence in the kidneys of hypertensive rats. Journal of renal nutrition the official journal of the Council on Renal Nutrition of the National Kidney Foundation 2011;21:105–9.
91 Shimizu H, Bolati D, Adijiang A, Adelibieke Y, Muteliefu G, Enomoto A, Higashiyama Y, Higuchi Y, Nishijima F, Niwa T: Indoxyl sulfate downregulates renal expression of Klotho through production of ROS and activation of nuclear factor-κB. American journal of nephrology 2011;33:319–24.
92 Adijiang A, Niwa T: An oral sorbent, AST-120, increases Klotho expression and inhibits cell senescence in the kidney of uremic rats. American journal of nephrology 2010;31:160–4.
93 Feger M, Mia S, Pakladok T, Nicolay JP, Alesutan I, Schneider SW, Voelkl J, Lang F: Down-regulation of renal klotho expression by Shiga toxin 2. Kidney & blood pressure research 2014;39:441–9.
94 Li Y, Liu Y, Wang K, Huang Y, Han W, Xiong J, Yang K, Liu M, Xiao T, Liu C, He T, Bi X, Zhang J, Zhang B, Zhao J: Klotho is regulated by transcription factor Sp1 in renal tubular epithelial cells. BMC molecular and cell biology 2020;21:45.
95 Liu S, Yu D, Wei P, Cai J, Xu M, He H, Tang X, Nong C, Wei Y, Xu X, Mo X, Zhang Z, Qin J: JAK2/STAT3 Signaling Pathway and Klotho Gene in Cadmium-induced Neurotoxicity In vitro and In vivo. Biological trace element research 2023;201:2854–63.
96 Zhou Z, Hu C-P, Wang C-J, Li T-T, Peng J, Li Y-J: Calcitonin gene-related peptide inhibits angiotensin II-induced endothelial progenitor cells senescence through up-regulation of klotho expression. Atherosclerosis 2010;213:92–101.
97 Tan Z, Li Y, Guan Y, Iqbal J, Wang C, Yan R, Ma X-M: Klotho Regulated by Estrogen Plays a Key Role in Sex Differences in Stress Resilience in Rats. International journal of molecular sciences 2023;24.
98 Iijima H, Gilmer G, Wang K, Bean AC, He Y, Lin H, Tang W-Y, Lamont D, Tai C, Ito A, Jones JJ, Evans C, Ambrosio F: Age-related matrix stiffening epigenetically regulates α-Klotho expression and compromises chondrocyte integrity. Nature communications 2023;14:18.
99 Zhao Y, Zhao M-M, Cai Y, Zheng M-F, Sun W-L, Zhang S-Y, Kong W, Gu J, Wang X, Xu M-J: Mammalian target of rapamycin signaling inhibition ameliorates vascular calcification via Klotho upregulation. Kidney international 2015;88:711–21.
100 Mizuno I, Takahashi Y, Okimura Y, Kaji H, Chihara K: Upregulation of the klotho gene expression by thyroid hormone and during adipose differentiation in 3T3-L1 adipocytes. Life sciences 2001;68:2917–23.

101 Lau WL, Leaf EM, Hu MC, Takeno MM, Kuro-o M, Moe OW, Giachelli CM: Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. Kidney international 2012;82:1261–70.
102 Seibert E, Heine GH, Ulrich C, Seiler S, Köhler H, Girndt M: Influence of cholecalciferol supplementation in hemodialysis patients on monocyte subsets: a randomized, double-blind, placebo-controlled clinical trial. Nephron. Clinical practice 2013;123:209–19.
103 Hryszko T, Rydzewska-Rosołowska A, Goździkiewicz J, Brzósko S, Koc-Żórawska E, Zelazowska-Rutkowska B, Myśliwiec M: Cholecalciferol supplementation reduces soluble Klotho concentration in hemodialysis patients. Polskie Archiwum Medycyny Wewnetrznej 2013;123:277–81.
104 Yoon J, Liu Z, Lee E, Liu L, Ferre S, Pastor J, Zhang J, Moe OW, Chang AN, Miller RT: Physiologic Regulation of Systemic Klotho Levels by Renal CaSR Signaling in Response to CaSR Ligands and pH o. Journal of the American Society of Nephrology JASN 2021;32:3051–65.
105 Liu Z, Yoon J, Lee E, Chang AN, Miller RT: Calcium-sensing receptor- and ADAM10-mediated klotho shedding is regulated by tetraspanin 5. FEBS letters 2025;599:866–75.
106 Dong J, Liu M, Xiang G, Yue L, Xu X, Xiang L: The association between serum soluble α-Klotho and thyroid profile among adults from NHANES 2007-2012. BMC endocrine disorders 2024;24:161.
107 Abdullah NAA-H, Hassan EA: Serum Klotho protein level in patients with thyroid dysfunction. Irish journal of medical science 2025.
108 Awasthi R, Manger PT, Khare RK, Alam R: Klotho protein: a new insight into the pathogenesis of essential hypertension. Clinical hypertension 2024;30:36.
109 Amaro-Gahete FJ, De-la-O A, Jurado-Fasoli L, Espuch-Oliver A, Haro T de, Gutierrez A, Ruiz JR, Castillo MJ: Exercise training increases the S-Klotho plasma levels in sedentary middle-aged adults: A randomised controlled trial. The FIT-AGEING study. Journal of sports sciences 2019;37:2175–83.
110 Mochón-Benguigui S, Carneiro-Barrera A, Castillo MJ, Amaro-Gahete FJ: Is Sleep Associated with the S-Klotho Anti-Aging Protein in Sedentary Middle-Aged Adults? The FIT-AGEING Study. Antioxidants (Basel, Switzerland) 2020;9.
111 Rutkowski JM, Pastor J, Sun K, Park SK, Bobulescu IA, Chen CT, Moe OW, Scherer PE: Adiponectin alters renal calcium and phosphate excretion through regulation of klotho expression. Kidney international 2017;91:324–37.
112 Prud'homme GJ, Glinka Y, Kurt M, Liu W, Wang Q: The anti-aging protein Klotho is induced by GABA therapy and exerts protective and stimulatory effects on pancreatic beta cells. Biochemical and biophysical research communications 2017;493:1542–7.
113 Olejnik A, Radajewska A, Krzywonos-Zawadzka A, Bil-Lula I: Klotho inhibits IGF1R/PI3K/AKT signalling pathway and protects the heart from oxidative stress during ischemia/reperfusion injury. Scientific reports 2023;13:20312.
114 Yamamoto M, Clark JD, Pastor JV, Gurnani P, Nandi A, Kurosu H, Miyoshi M, Ogawa Y, Castrillon DH, Rosenblatt KP, Kuro-o M: Regulation of oxidative stress by the anti-aging hormone klotho. The Journal of biological chemistry 2005;280:38029–34.
115 Neyra JA, Hu MC: Potential application of klotho in human chronic kidney disease. Bone 2017;100:41–9.
116 Shi M, Flores B, Gillings N, Bian A, Cho HJ, Yan S, Liu Y, Levine B, Moe OW, Hu MC: αKlotho Mitigates Progression of AKI to CKD through Activation of Autophagy. Journal of the American Society of Nephrology JASN 2016;27:2331–45.
117 Abramovitz L, Rubinek T, Ligumsky H, Bose S, Barshack I, Avivi C, Kaufman B, Wolf I: KL1 internal repeat mediates klotho tumor suppressor activities and inhibits bFGF and IGF-I signaling in pancreatic cancer. Clinical cancer research an official journal of the American Association for Cancer Research 2011;17:4254–66.
118 Shu G, Xie B, Ren F, Liu D, Zhou J, Li Q, Chen J, Yuan L, Zhou J: Restoration of klotho expression induces apoptosis and autophagy in hepatocellular carcinoma cells. Cellular oncology (Dordrecht, Netherlands) 2013;36:121–9.
119 Wolf I, Levanon-Cohen S, Bose S, Ligumsky H, Sredni B, Kanety H, Kuro-o M, Karlan B, Kaufman B, Koeffler HP, Rubinek T: Klotho: a tumor suppressor and a modulator of the IGF-1 and FGF pathways in human breast cancer. Oncogene 2008;27:7094–105.
120 Hajare AD, Dagar N, Gaikwad AB: Klotho antiaging protein: molecular mechanisms and therapeutic potential in diseases. Molecular biomedicine 2025;6:19.