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REVIEW

Klotho Protein: A Multifaceted Guardian of Healthy Aging and Its Therapeutic Potential

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Abstract: The Klotho protein, encoded by the KL gene, has garnered significant attention as a pivotal biomolecule in the field of aging research. Its expression levels are closely correlated with both lifespan and overall health status, exerting influence over critical physiological processes such as metabolic homeostasis, oxidative stress response, and inflammation modulation. This review aims to systematically examine the multifaceted roles of Klotho within the context of aging and its implications for various age-associated disorders. We highlight the emerging evidence suggesting that Klotho may serve as a key regulator in age-related pathologies, including cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes. Furthermore, we explore the potential of Klotho as a therapeutic target, positing that interventions aimed at enhancing Klotho activity could offer novel strategies for alleviating the health burdens experienced by the aging population.

Keywords: Klotho, aging, oxidative stress, inflammation, population aging

Introduction

With the profound impact of the rapidly aging population trend on the social structure, the Klotho protein, a prodigious product of the KL gene, emerges as a beacon of hope. Its expression, intricately tied to both longevity and healthspan, positions it as a sentinel, overseeing a myriad of vital physiological processes that underpin vitality and resilience. It ensures metabolic equilibrium, mitigates oxidative stress, and regulates inflammation, all of which contribute to the overall well-being and resilience of the body.[1] Klotho protein exists in three forms: α-klotho, β-klotho, and γ-klotho.[2] FGF23 is secreted by osteocytes, and the complex formed by αKlotho and FGF receptor (FGFR) is mainly expressed in the renal tubules of the kidney, and when FGF23 binds to the αKlotho-FGFR complex, it activates the classical FGF signaling pathway, phosphorylating the FGFR substrate 2α (FRS2α),[3] which in turn activates extracellular regulatory protein kinases 1 and 2 (ERK1/2).[4] This not only regulates the transport of minerals by the kidneys, but also affects other related signaling pathways.[5,6] βKlotho FGF19 binds to βKlotho-FGFR4 to activate a signaling pathway that predominantly inhibits bile acid synthesis in the liver.[7] FGF21 binds to βKlotho - FGFR1c, activating a signaling pathway that affects nervous system function in addition to regulating metabolism.[8] As a co-receptor of FGF19 and FGF21, it plays an important role in metabolic regulation. FGF19 is secreted by intestinal epithelial cells and reaches the liver via the portal vein after feeding, where it binds to the βKlotho-FGFR4 complex expressed in the liver.[9,10] Undoubtedly, aging, this profound biological journey, is a complex narrative woven from an intricate web of mechanisms. It encompasses genomic instability, telomere attrition, epigenetic alterations, proteostasis disruption, impaired macroautophagy, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, the depletion of stem cell reservoirs, altered

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intercellular communication, chronic inflammation, and microbial dysbiosis.[11] Each individual mechanism contributes to the intricate and diverse tapestry of aging, and unraveling the complex interplay among them is essential for uncovering the fundamental processes that underlie the deterioration of both the human body and mind.

The prospect of utilizing the Klotho protein as a powerful tool to combat age-related diseases stands as a radiant beacon of hope and promise. By enhancing its expression, we stand poised on the cusp of a revolutionary era, where the course of degeneration may be redirected, and the foundations of health in our aging populace strengthened. This is not merely a speculative endeavor but a tangible approach to intercept and mitigate the relentless march of illnesses, including cardiovascular disorders, renal impairment, and neurological conditions, among a myriad of others.

The road ahead necessitates a comprehensive exploration of Klotho's underlying mechanisms and the development of innovative therapies based on its principles. These endeavors promise to ease the socio-economic strains imposed by an aging population. By fostering investments in Klotho research and therapeutic innovations, societies can envision a future where the later stages of life are characterized not by infirmity but by vitality, autonomy, and independence.

Common Aging Diseases and the Role of Klotho Protein in Them

Among the many research directions, Klotho proteins have attracted much attention for their potential roles in delaying aging and improving cognitive functions. As a single transmembrane protein encoded by the Klotho gene, Klotho is involved in the regulation of various physiological processes, including calcium and phosphorus metabolism, oxidative stress, and apoptosis. Based on the above background, in this paper, we will explore the role of Klotho proteins in different systems in detail. Firstly, we will focus on the nervous system and discuss its function in cardiovascular system, urinary system, motor system and endocrine system in turn and its potential impact on various types of age-related diseases.

Nervous System

Alzheimer's Disease

Alzheimer's disease, a neurodegenerative condition that progressively debilitates, silently infiltrates the central nervous system, stealthily manifesting its pernicious effects over time. Predominantly affecting the elderly, it is the leading manifestation of dementia in this demographic, marked by a relentless erosion of cognitive faculties and behavioral integrity.[12] At its core lie memory impairments, with recent memories being particularly susceptible to swift erasure—memories of events and conversations fading rapidly into the abyss.[13] As the disease advances, afflicted individuals confront challenges in language proficiency, both expressively and receptively, spatial disorientation, and an increased vulnerability to confusion. Judgment, reasoning abilities, and the very essence of personality and behavior undergo profound alterations. Despite concerted medical research endeavors, a definitive pharmacological treatment for Alzheimer's disease remains elusive, leaving a substantial therapeutic void in the management of this devastating condition.[14]

Recent scientific endeavors have unearthed the promising potential of Klotho, a protein acclaimed for its neuroprotective properties. A groundbreaking study involving geriatric rhesus monkeys, sharing an astonishing 93% genetic similarity with humans, received a single, low-dose infusion of Klotho (10 μg/kg body weight). These aged primates, averaging 21.78 years old, exhibited remarkable improvements in cognitive abilities, particularly in working and spatial memory, with these enhancements persisting robustly for at least two weeks post-treatment.[15] Tozer et al injected elderly rhesus macaques with Klotho protein, which improved working memory and ability to complete tasks, and cognitive enhancement at lower doses (equivalent to five times the baseline level).[16] Further investigation has revealed that in rodent models, exogenous Klotho administration elevates plasma levels of platelet-derived factors, notably systemic platelet factor 4 (PF4). PF4, capable of traversing the blood-brain barrier, has demonstrated efficacy in bolstering cognitive function. In aged mice, PF4 was efficacious in mitigating cognitive impairments and rectifying the age-induced surge in specific factors integral to hippocampal cognitive performance. While Klotho's cognitive benefits persist in PF4-deficient mice, this platelet factor is postulated as a potential mediator of Klotho's neurocognitive effects (Figure 1). PF4 may enhance cognitive abilities in younger brains and help mitigate age-related cognitive decline.[17] Recently, a noteworthy discovery is that Klotho influences the expression of various RNA species, including mRNAs, long non-coding RNAs, microRNAs, and tRNA fragments, all are intimately linked to aging and cognition. This includes modulations of neural and glial regulators in murine models of aging and Alzheimer's disease are corroborated by

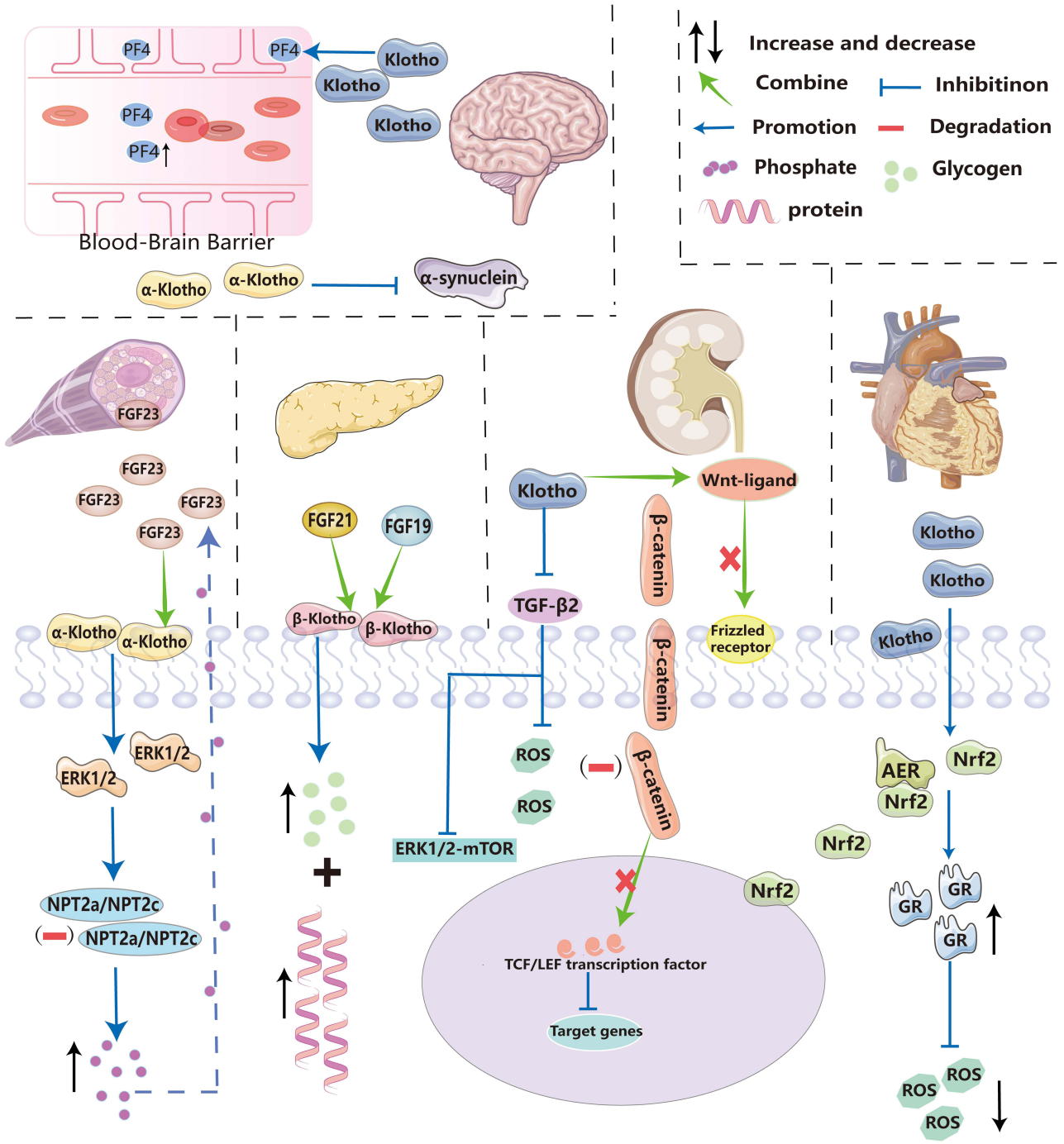

Figure 1 Klotho protein-mediated network of signaling pathways. This figure shows the multiple biological pathways Klotho protein is involved in and its intermolecular interactions. Klotho induces PF4 production, which affects cognitive function after crossing the blood-brain barrier. In calcium and phosphorus metabolism, FGF23 binds to the α-Klotho-FGFR complex, activating the FGF signaling pathway to maintain balance. FGF19 and FGF21 bind to β-Klotho-FGFR complexes for metabolic regulation. In the Nrf2-GR pathway, increased Klotho leads to Nrf2 binding to antioxidant response element (ARE), enhancing glutathione reductase (GR) expression and activity. Klotho is also involved in Wnt/β-catenin and TGF-β pathways. In the Wnt/β-catenin pathway, it may affect β-catenin – related processes, and in the TGF-β pathway, it inhibits receptor binding and reduces oxidative stress. Overall, these pathways highlight Klotho's significance in health maintenance and anti – aging.

findings in post-mortem human brains which affected by the same ailment.[18] In a recent interesting study, Driscoll et al found that the KL-VS heterozygous (KL-VSHET) attenuated age-related neuroinflammation, neurodegeneration, and synaptic dysfunction in a cohort of cognitively unimpaired and at high risk of Alzheimer's disease, protecting the brain from age-related harmful biomolecular changes.[19]

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Even though there has been a lot of progress, the complex ways Klotho affects cognitive function are still not fully understood. We also do not know why its effects last so long or the key paths it uses to change brain functions. Since Klotho cannot get through the blood-brain barrier, which is an important protective system, it is thought that another molecule might be involved.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease,[20] which is a neurodegenerative disease that easily affects the motor function of middle-aged and elderly people. It not only shows motor disorders, but also includes non-motor manifestations, such as depression, cognitive decline and circadian rhythm imbalance.[21] To date, no agents have been shown to have unequivocal evidence of disease-modifying effects in Parkinson's disease.[22]

Scientific research personnel measured α-Klotho in CSF and serum of PD patients at early stage of the disease, finding two distinct pools, the first increased, the second reduced. CSF α-Klotho was inversely associated with CSF α-synuclein levels (Figure 1). The preliminary results suggest α-Klotho as potential biomarker or therapeutic target in PD.[23] Research shows that increasing Klotho levels enhanced cognitive ability and neuroresilience in young, aging, and Parkinson's disease models. Klotho-deficient mice exhibit nigrostriatal neurodegeneration, a feature of Parkinson's disease, in addition to age-related cognitive decline and premature death. But the study did not find a correlation between Klotho levels and clinical indicators of Parkinson's disease (such as the MDS-UPDRS score or the MoCA score) or between Klotho levels and the age of patients with Parkinson's disease.[24]

Major Depression

Major depression is one of the most prevalent and debilitating personal and public health conditions worldwide.[25] Major depressive disorder (MDD) is a chronic, generally episodic and debilitating disease that affects an estimated 300 million people worldwide, but its pathogenesis is poorly understood. The heritability estimate of MDD is 30–40%, suggesting that genetics alone do not account for most of the risk of major depression.[26]

Preliminary investigations have found an association between reduced α-Klotho protein levels and the development of major depressive disorder in older adults, and increasing Klotho protein levels may help alleviate depressive symptoms.[27] Gene therapy trials to increase Klotho levels have now progressed effectively, and behavioral manifestations of depression can be improved in controlled experimental settings.[28] The pharmacological methods used to increase Klotho concentrations have the potential to reduce oxidative stress and inflammatory responses in patients with depression and contribute to symptomatic relief.[29] With more in-depth research and exploration by researchers, we believe that the problem of major depression in the elderly will also be solved in the foreseeable future.

Cardiovascular System

Hypertension

In accordance with the World Health Organization (WHO) guidelines for the clinical description of hypertension, hypertension is defined as the absence of treatment with antihypertensive medications and a blood pressure measurement showing a systolic blood pressure equal to or greater than 140mmHg and/or a diastolic blood pressure at or greater than 90mmHg on three different days. These diagnostic thresholds can be adjusted for individual countries and regions to suit their environmental and public health situations. Hypertension is a global epidemic that affects more than 1 billion people and can cause many complications, including stroke, kidney problems, enlarged heart, heart attack and congestive heart failure. It also has significant public health implications.[30]

The development of hypertension is closely linked to dietary habits, and the researchers found that high salt (HS) increased blood pressure in both old and young heterozygous Klotho-Knockout mice and was associated with increased expression of Wnt5a and p-MYPT1 in the vasculature.[31] Klotho controls blood pressure by coordinating the renin-angiotensin-aldosterone system (RAAS) and preventing its over-activation.[32] The antioxidant properties of Klotho are also effective in counteracting the increased oxidative stress in hypertensive disorders. By protecting the vascular endothelium from oxidative stress damage, Klotho enhances endothelial cell integrity and plays an important role in

stabilizing blood pressure.[33] Klotho also has an effect on calcium-phosphorus balance, a key aspect in the development of hypertension, and these studies emphasize the critical role of Klotho in regulating blood pressure.[34]

Klotho protective measures include protecting some important organs, such as heart, brain and kidney, shielding from the harmful effects of high blood pressure. Also Klotho can adjust the inflammatory process and reduce the apoptosis, create a protective barrier prevent organ damage induced by hypertension.[35] It is worth mentioning that the complex interaction of Klotho's mechanism in the context of hypertension is still an active area of research. Understand the Klotho in this mechanism in the process of various diseases and interaction is the mission of scientific research personnel, and realizing the Klotho effects against clinical potential of high blood pressure.

Cardiac Aging

Cardiac aging is the inevitable deterioration of the structural integrity and functional capacity of the heart as a natural consequence of the progression of time. Structurally, senescent cardiomyocytes atrophy and diminish, accompanied by an insidious progression of interstitial fibrosis. This fibrotic transformation disrupts myocardial compliance and leads to thickening of the ventricular walls. Coronary arteries may also undergo atherosclerotic degeneration, which affects myocardial blood supply. Functionally, the heart's systolic and diastolic function declines, as evidenced by a decrease in per-beat volume, impaired heart rate regulation, and decreased cardiac reserve function. These cumulative changes reduce the heart's ability to adapt to higher physiologic demands.[36]

Klotho plays a pivotal role in orchestrating the complex process of cardiac aging, and there is a strong association between reduced Klotho expression and multiple cardiac aging manifestations. Decreased levels of Klotho exacerbate oxidative stress, triggering cardiomyocyte damage and accelerating cardiac aging. Klotho's regulation of the renin-angiotensin-aldosterone system (RAAS) further affects cardiac structure and function, thereby exacerbating the aging process.[32] Klotho deficiency catalyzes cardiac senescence by disrupting the Nrf2-GR (Figure 1) pathway, a line of cellular defense. Supplementation with exogenously secreted Klotho holds promise as a therapeutic avenue against senescence-associated cardiomyopathy and heart failure.[37] Klotho is essentially an important substance in slowing down cardiac aging and mitigating related cardiovascular diseases. We need to fully understand the complex mechanisms by which Klotho plays a role in cardiac aging.

Vascular Calcification

Vascular calcification is a pathological process characterized by an abnormal accumulation of calcium salts within the arterial wall. Chief among these factors are chronic inflammation, oxidative stress, dysregulation of lipid metabolism (especially hyperlipidemia), and diabetes.[38] Chronic inflammation causes damage to vascular endothelial cells, which can lead to vascular calcification. Oxidative stress disrupts the balance between oxidants and antioxidants, exacerbating this damage and compromising the integrity of the vascular wall. Taking cholesterol accumulation in turn leads to dysregulation of lipid metabolism, exacerbating the calcification process through these series of biochemical reactions.[39]

In the realm of vascular calcification, a recurring observation across animal models is the diminished expression of Klotho protein—a deficiency that is profoundly implicated in the inception and propagation of calcific lesions.[40,41] Mechanistic insights have revealed that Klotho protein exerts a protective role by suppressing the expression of genes linked to osteogenesis, thereby preventing the transformation of vascular smooth muscle cells into osteoblast-like entities. This action effectively modulates the extent of calcification. Clinical data echoes these findings, showcasing significantly reduced levels of Klotho protein in the serum of patients suffering from chronic kidney disease, diabetes, and other conditions that predispose to vascular calcification. Notably, lower serum Klotho concentrations inversely correlate with the severity of vascular calcification, highlighting its potential as both a biomarker and a therapeutic target.[42]

Experimental strategies designed to augment Klotho protein expression or to administer it exogenously have yielded encouraging outcomes in preclinical settings, demonstrating a capacity to mitigate vascular calcification. However, the journey from bench to bedside necessitates a thorough and systematic investigation, along with rigorous validation in clinical trials, to ensure safety and efficacy before these interventions can be integrated into standard medical practice.

Urinary System

Renal Fibrosis

Renal fibrosis is a debilitating condition characterized by the pathological accumulation of extracellular matrix components like collagen and fibronectin within the renal parenchyma, ultimately leads to structural distortion and functional deterioration.[43]

Many studies have consistently emphasized the downregulation of Klotho protein expression in animal models of renal fibrosis, highlighting the key role of Klotho in this disease.[44] Mechanistically, Klotho protein is a potent antifibrotic substance that attenuates fibrosis by modulating multiple pathways. It has an inhibitory effect on the Wnt/β-catenin signaling cascade (Figure 1), which inhibits the activation and proliferation of fibroblasts, and in turn inhibits the synthesis of extracellular matrix components.[45] Klotho proteins also have a role in controlling cellular autophagy, a process that is essential for the removal of damaged cells, and it is because of this process that there is less renal cellular damage and fibrosis.[46] In addition, Qian Yuan et al showed that in a mouse model of renal fibrosis, intravenous injection of Klotho-derived peptide 1 (KP1) led to its preferential accumulation in injured kidneys. KP1 preserved renal function, inhibited TGF-β signaling, ameliorated renal fibrosis and restored endogenous Klotho expression.[47] Zhang et al found that KP1 inhibits cellular senescence and induces Klotho expression through miR-223-3p and lncRNA-TUG1-mediated post-transcriptional regulation. By restoring endogenous Klotho, it can be used as a promising therapeutic agent for fibrotic nephropathy.[48]

These studies are still in the early stages, and deep and broad explorations are needed to understand the complex mechanisms behind the role of Klotho proteins in renal fibrosis.[49]

Chronic Kidney Disease

Chronic Kidney Disease (CKD) is characterized by a persistent anomaly in kidney structure or function, typically evidenced by a glomerular filtration rate (GFR) below 60 mL/min/1.73 m² or an albumin excretion rate exceeding 30 mg over 24 hours, persisting for more than three months.[50]

In the ever-evolving arena of CKD research, Klotho has emerged as a pivotal player. A multitude of studies have revealed a pronounced diminution in the expression of the Klotho gene within the renal tissue as CKD advances. This decline is not only correlated with the degree of renal function deterioration but also with the severity of kidney pathology.[51] Mechanistically, Klotho deficiency stands accused of expediting CKD progression via intricate, multifaceted pathways. Research substantiates that Klotho restrains oxidative stress signaling pathways, thereby ameliorating oxidative damage inflicted upon renal cells.[51] Additionally, it exerts a modulatory effect on the synthesis and secretion of inflammatory cytokines, alleviating renal inflammatory responses.[35] Hongyu Li et al demonstrated that a single low-dose injection of PPSK NPs is sufficient to maintain normal renal structure and prevent renal fibrosis in a mouse model of unilateral ischemia-reperfusion injury and folic acid-induced transition of acute kidney injury (AKI) to CKD. The protective effect of polydopamine-polyethylenimine-l-serine-Klotho plasmid nanoparticles (PPSK NPs) relies on upregulating the key molecule peroxisome proliferator-activated receptor α (PPARα) by inhibiting p38 and JNK phosphorylation, which in turn improves renal tubular fatty acid β oxidation and reduces renal lipid accumulation, thereby preventing renal fibrosis. This result highlights the translational potential of nanoparticle-based Klotho gene therapy in preventing AKI-CKD transitions.[52] Makoto Kuro-O's team also found that not only does the Klotho protein play a key role in regulating phosphate metabolism, but its deficiency may cause renal tubular cells to be more sensitive to a high-phosphate environment, thereby promoting the formation of calcium phosphate crystallites and aggravating kidney damage.[53] Clinically, the potential of Klotho as an innovative biomarker for CKD diagnosis and prognosis is gaining increasing recognition. Monitoring Klotho levels in blood or urinary excretion could serve as a powerful tool for early CKD identification, providing insights into disease severity, and enabling the prediction of clinical outcomes.[54,55]

In summation, the meticulous exploration of Klotho's role in CKD furnishes a critical theoretical bedrock and opens up prospective therapeutic avenues. By harnessing the potential of Klotho, we can forge ahead in the quest for more effective CKD management strategies.

Motor System

Osteoarthritis

Osteoarthritis (OA) is a pervasive and incapacitating chronic joint ailment. It poses a colossal global challenge, afflicting over half a billion individuals. Long regarded as solely a result of articular cartilage deterioration, OA is now recognized as a sophisticated, whole-joint disorder intricately intertwined with biochemical and cellular alterations within synovial joint tissues. These changes start a series of histological and structural transformations, eventually resulting in joint dysfunction. The lack of a definitive cure for OA is partly due to the incomplete understanding of the complex pathological mechanisms that control its onset and progression.[56]

The burgeoning field exploring Klotho's role in OA, while still in its nascent stages, has ignited fascinating hypotheses and sparked preliminary investigations. Accumulating evidence hints at Klotho's potential to modulate OA pathogenesis and progression by harnessing its robust antioxidant properties to quell oxidative stress and its prowess in suppressing inflammatory processes.[57,58] Nevertheless, the precise mechanisms underpinning Klotho's interactions with OA pathophysiology remain veiled in mystery, necessitating extensive and meticulous research endeavors to unravel the complexities of this intricate relationship.

Sarcopenia

Sarcopenia, a progressive skeletal muscle disorder predominantly linked to aging yet exacerbated by factors such as disease, malnutrition, or sedentary lifestyles, manifests as a relentless erosion of muscle mass, strength, and function. This decline translates into diminished physical capabilities, impaired balance, heightened susceptibility to falls, frailty, metabolic disturbances, and ultimately, a cascade of consequences impacting quality of life, disability, and mortality rates.[59] Pathophysiologically, sarcopenia is a multifarious condition, encompassing complex alterations in hormonal profiles (encompassing growth hormone, testosterone, and estrogen), chronic inflammation, oxidative stress, neuromuscular dysfunction, disruptions in protein metabolism, and mitochondrial inefficiencies. Accurate diagnosis typically necessitates a comprehensive evaluation that encompasses assessments of muscle strength, mass, and overall physical performance.[59]

Klotho, a protein of profound significance in sarcopenia research, has emerged as a critical player in the condition's etiology. Research delineates the following pivotal observations regarding Klotho's role:

Experimental use of Klotho in older mice significantly increased muscle strength and function. Treatment with Klotho mice after injury can improve muscle twitch response, enhance the force of production and the increase of the body's endurance. Researchers studying mice in different age groups found that Klotho had a significant effect on age-related genes. In aging mice, Klotho supplementation resulted in a 17% increase in strength and a 60% increase in endurance, along with an increase in body weight. Older rats showed signs of abnormal gene responses, suggesting a complex interaction between Klotho and the aging musculoskeletal system.[60] FGF19 also attenuates muscle atrophy in a mouse model through the ERK1/2 signaling pathway and mTOR effectors (Figure 1), and its therapeutic effect is mainly dependent on the activation of its receptor.[61] Recent studies by Da Zhou et al showed increased hepatic secretion of FGF21 during the decompensated phase of cirrhosis. FGF21 inhibits the PI3K/Akt pathway by binding to β-klotho on the surface of satellite cells, hindering satellite cell proliferation and differentiation, resulting in sarcopenia. Neutralization of circulating FGF21 or knockout of klotho beta in satellite cells improves sarcopenia.[62]

These findings suggest that Klotho plays a crucial role in the complex development of sarcopenia, an increase in muscle atrophy as they age, and life becomes inconvenient in old age as a result, making Klotho a promising therapeutic target. However, much of the current research is based on animal models, and more experimental studies are needed to see if Klotho has the same therapeutic potential in humans.

Osteoporosis

Osteoporosis is a bone disease characterized by impaired bone structure and strength, leading to a progressively higher risk of fragility fractures. As the population ages, the prevalence of osteoporosis is rising globally.[63] The causes of this complex situation include, among others, natural aging and changes in hormone levels, such as lower estrogen levels and sex hormones in older people, as well as poor lifestyles, such as malnutrition due to picky eating, especially low intake of

calcium and vitamin D, lack of physical activity, smoking and alcohol consumption, and the adverse effects of certain medications that can also lead to osteoporosis.[64]

There is a clear association between Klotho gene expression and bone mineral density (BMD), and Klotho affects phosphate homeostasis through the regulation of the fibroblast growth factor 23 (FGF23) signaling pathway, which has a significant impact on bone mineralization.[65] In experimental animal models, Klotho knockout mice exhibit significant osteoporosis features, such as reduced bone mass, thinning and reduced density of the trabecular network, and impaired bone strength.[66] These findings emphasize the important role of Klotho in maintaining healthy bone metabolism and bone structural integrity.

Endocrine System

Diabetes

Diabetes is mainly divided into type 1 and type 2: Type 1 usually manifests in childhood or adolescence, and type 2 is generally associated with adults and is now increasingly observed in younger populations. There is an increasing number of cases of type 2 diabetes mellitus (T2DM) and a transition to an aging population. Almost half of all people with diabetes are now aged 65 and over.[67]

Klotho is a protein that has been implicated in diabetes and has anti-aging properties. Klotho proteins interfere with downstream events of these signaling pathways by inhibiting autophosphorylation of insulin and IGF1 receptors, thereby influencing intracellular insulin signaling. This suggests that Klotho may influence metabolic status by modulating insulin signaling.[68] β-Klotho is an influential component of the fibroblast growth factor (FGF) receptor complex, highly expressed in key metabolic tissues such as adipose, liver, and pancreas, and plays an important role in high-affinity binding to the endocrine factors FGF19 and FGF21 (Figure 1). The balance between glucose metabolism and energy utilization is maintained by this interaction. Having this endocrine axis, which is largely controlled by the interaction of β-Klotho and FGFs, is essential for glucose regulation in patients with type 2 diabetes mellitus.[69]

Complications of T2DM include diabetic nephropathy,[70] cardiovascular disease,[71] and retinopathy.[70] In diabetic nephropathy, decreased levels of Klotho in the patient's body will accelerate renal fibrosis and disrupt glomerular filtration, triggering metabolic disorders that can exacerbate the condition.[72] Studies of diabetic retinopathy have shown that Klotho regulates retinal cell homeostasis and function through several key mechanisms. These mechanisms include cellular phagocytosis, calcium signaling, vascular endothelial growth factor-A secretion, REDOX homeostasis, and melanin synthesis, and Klotho positively affects these mechanisms, which may help to reduce diabetic retinopathy.[73] Studying how to increase Klotho expression in diabetic patients is important for controlling diabetes and its complications.

Hypothyroidism

Hypothyroidism is characterized by a deficiency of thyroid hormones in the body. Patients typically experience symptoms such as fatigue, weight gain, and decreased tolerance to cold.[74,75] Hypothyroidism is prevalent in all age groups and is expected to increase steadily as the population ages. Once hypothyroidism has been confirmed, treatment requires caution, frequent cardiovascular monitoring, and individualized (precision) medicine.[76]

The researchers analyzed the relationship between serum Klotho levels and hypothyroidism in the elderly through one-way analysis of variance, multiple linear regression modeling, subgroup analysis, interaction test, smoothing curve fitting, and threshold effect, and concluded that serum Klotho levels were negatively correlated with hypothyroidism in the elderly.[77] Future research directions could be based on exploring the therapeutic potential of modulating Klotho expression and its activity in the treatment of hypothyroidism. It is hoped that increasing Klotho levels will alleviate symptoms and slow the progression of the disease.

Obesity

The global epidemic of obesity is a major public health issue today.[78] By reviewing the literature related to obesity, we find that there is a close link between obesity and many diseases, such as asthma,[79] cardiovascular diseases[80] and

hyperlipidemia.[81] In the process of the slow decline of the body of the elderly, if the emergence of obesity, will inevitably increase the risk of suffering from diseases.

A cross-sectional study investigating visceral adiposity index (VAI) and serum levels of Klotho in selected adults showed a negative correlation, ie, the greater the visceral adiposity, the lower the concentration of Klotho. This suggests that Klotho is associated with the pathogenesis of obesity, the exact mechanistic basis of which is currently unknown. Future studies are needed to understand how Klotho affects fat metabolism, energy balance and obesity-related processes.[82] Klotho has great potential for the treatment of obesity, and perhaps in the future it could reveal more effective ways to control obesity.

Respiratory System

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death in the world. Affected patients not only suffer from impaired lung function, but also from a variety of complications,[83] such as heart failure, vascular disease, diabetes, and cancer are at increased risk, which may complicate the course of the disease. Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous chronic inflammatory lung disease that usually presents with clinical symptoms later in life and may result in significant morbidity and risk of early death. COPD is more common in the elderly population, and cigarette smoking is the greatest risk factor for developing COPD in susceptible individuals.[84]

Studies have shown that when Klotho expression is reduced in bronchial epithelial cells, COPD may progress at an accelerated rate. This is because it plays a key role, along with other anti-aging molecules, in orchestrating cellular senescence, regulating oxidative stress and controlling inflammatory responses.[85] Min Li et al's study found that Klotho can affect the development of COPD by regulating the senescence and differentiation of goblet cells, and when exposed to cigarette smoke, Klotho deficiency can exacerbate lung inflammation, goblet cell senescence, and ciliated cell dysfunction. Treatment of neddylation may be a promising strategy to reverse lung senescence and goblet cell senescence.[86] However, the complex mechanisms behind this relationship are unclear and require more in-depth studies by researchers.

Ophthalmic Diseases

Retinal Pigment Epithelium (RPE) Degenerative Changes

Aging is a major cause of retinal degenerative diseases.[87] The retina consists of a multilayered network of cells, including photoreceptor cells (optic rod and cone cells), bipolar cells, and ganglion cells, and is a key ocular tissue responsible for visual perception and signaling. The retinal pigment epithelium (RPE), a hexagonal layer of pigment cells located between retinal neurons and the choroid, plays an important role in maintaining the function of masking photoreceptor cells. RPE integrity is strongly associated with the etiology of retinal degenerative diseases, especially age-related macular degeneration.[88]

The experimental results showed that α-Klotho was able to prevent senescence-like morphological changes induced by TGF-β2. When co-treated with TGF-β2, α-Klotho inhibited TGF-β2 receptor binding, reduced Smad2/3 phosphorylation, and decreased oxidative stress brought about by the up-regulation of NADPH oxidase 4 (NOX4), as well as reduced the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and rapamycin targeting protein (mTOR). It can be concluded that the anti-aging protein α-Klotho has a protective effect on preventing Epithelial-Mesenchymal Transition (EMT) and RPE degeneration, and the experiments also suggest that α-Klotho may serve as a promising treatment for degenerative RPE lesions.[88]

Cataract

Cataracts, characterized by the clouding of the lens, rank among the foremost culprits behind vision impairment. Their genesis is multifactorial, encompassing aging, genetics, ocular trauma, systemic diseases like diabetes, prolonged exposure to medications such as corticosteroids, and ultraviolet radiation.[89] Predominantly emerging postnatally, cataracts share aging and oxidative stress as their chief instigators, notwithstanding the acceleration imparted by both immutable and modifiable risk elements.[90] Currently, surgical intervention remains the singular efficacious treatment for cataracts, offering restoration of sight.[91]

The lens is a crystalline structure in the eye that focuses light to project images clearly onto the retina, similar to what a camera lens does. Aging, injury, or certain diseases can cause changes in the protein of the lens, causing it to denature and aggregate, resulting in a clouded lens that marks the beginning of cataract formation. Klotho has shown a good therapeutic effect in treatment by enhancing antioxidant defense through Nrf2 and inhibiting the NF-κB pathway to reduce inflammation.[92]

Studies of lens epithelial cells from cataract patients have shown significantly higher levels of methylation of the Klotho gene and significantly lower expression of Klotho genes and proteins compared to healthy controls. These findings suggest that Klotho may have a positive impact on the complex pathogenesis of senile cataract.[93] This makes Klotho a promising cure for cataracts, bringing hope to seniors facing cataracts with vision problems.

The Role of Klotho in Aging

In terms of cognitive function, Klotho proteins can enhance memory in aged primates, suggesting that Klotho proteins could be used clinically to address cognitive decline in the elderly in the future.[15] Certain neurological disorders such as Alzheimer's disease[18] and Parkinson's disease[94] are characterized by cognitive dysfunction, manifested by progressive deterioration of memory and cognitive abilities. Cognitive dysfunction is a common symptom in later life and can lead to a decline in their quality of life and a lack of independence in their lives. The ability of Klotho to improve cognitive dysfunction in aged rhesus monkeys is a major breakthrough and lays the foundation for the future use of Klotho proteins in the treatment of age-related cognitive disorders.[15]

Klotho counteracts the accumulation of senescent cells, protects the functional integrity of tissues and organs, and possesses high antioxidant capacity. Klotho also delays cellular senescence by regulating the expression of antioxidant proteins and reducing deleterious signals to counteract oxidative stress.[33,37,95,96] Klotho also modulates mitochondrial health. Mitochondria are an essential component of cellular viability, orchestrating a complex network of regulatory mechanisms, with regulation of mitochondrial uncoupling protein 1 (UCP1) to control energy expenditure, stabilization of B-cell lymphoma-2 (BCL-2) to prevent apoptosis, and influencing cell proliferation and differentiation through the Wnt/β-catenin signaling pathway. Klotho further interacts with mitochondrial biogenesis peroxisome proliferation-activated receptor γ coactivator 1-α (PGC-1α), transcription factor EB (TFEB) and peroxisome proliferation-activated receptor γ (PPAR-γ).[96–98] Through these complex mechanisms, Klotho plays a key role in maintaining mitochondrial health. It ensures efficient energy production while minimizing the accumulation of reactive oxygen species (ROS). The protective effects of Klotho at the cellular level include antioxidant defense, mitochondrial integrity, and regulation of important signaling pathways.

For the entire human organism, Klotho may play a key role in maintaining health throughout the aging process.[34,99] Klotho's anti-inflammatory capabilities are also important in its role in the body as a whole, modulating the inflammatory response, inhibiting the cascade of inflammatory cytokines, and mitigating tissue damage caused by inflammation.[35,100,101] Klotho possesses anti-aging properties that protect the structural integrity and operational stability of tissues by inhibiting the proliferation of senescent cells. As a key mediator in the aging process, Klotho emerges as a promising therapeutic target aimed at addressing the myriad of challenges posed by aging and its associated pathologies. This observation also highlights the significance of exploring the biological mechanisms of Klotho. Such research could unlock its potential applications in promoting healthy longevity and in the therapeutic approaches targeting age-related conditions.

The Application of Klotho Protein in Clinical Practice

The wide range of functions of Klotho proteins in various physiological systems suggests that they hold great promise for clinical applications, especially in aging and aging-related diseases. Klotho proteins have anti-aging potential and may play a key role in the complex aging process. By regulating Klotho protein levels, physicians may be able to intervene in disease in the future, while simultaneously mitigating aging and promoting health and vitality in the elderly population[54] (Figure 2). Pair with is correlated have been associated with the development and progression of diseases such as atherosclerosis,[102] hypertension,[31] and heart failure.[103] In the future clinical monitoring of Klotho levels could be used as a marker of cardiovascular risk.[104,105] Studies are currently exploring how drugs and gene therapy can be used to increase

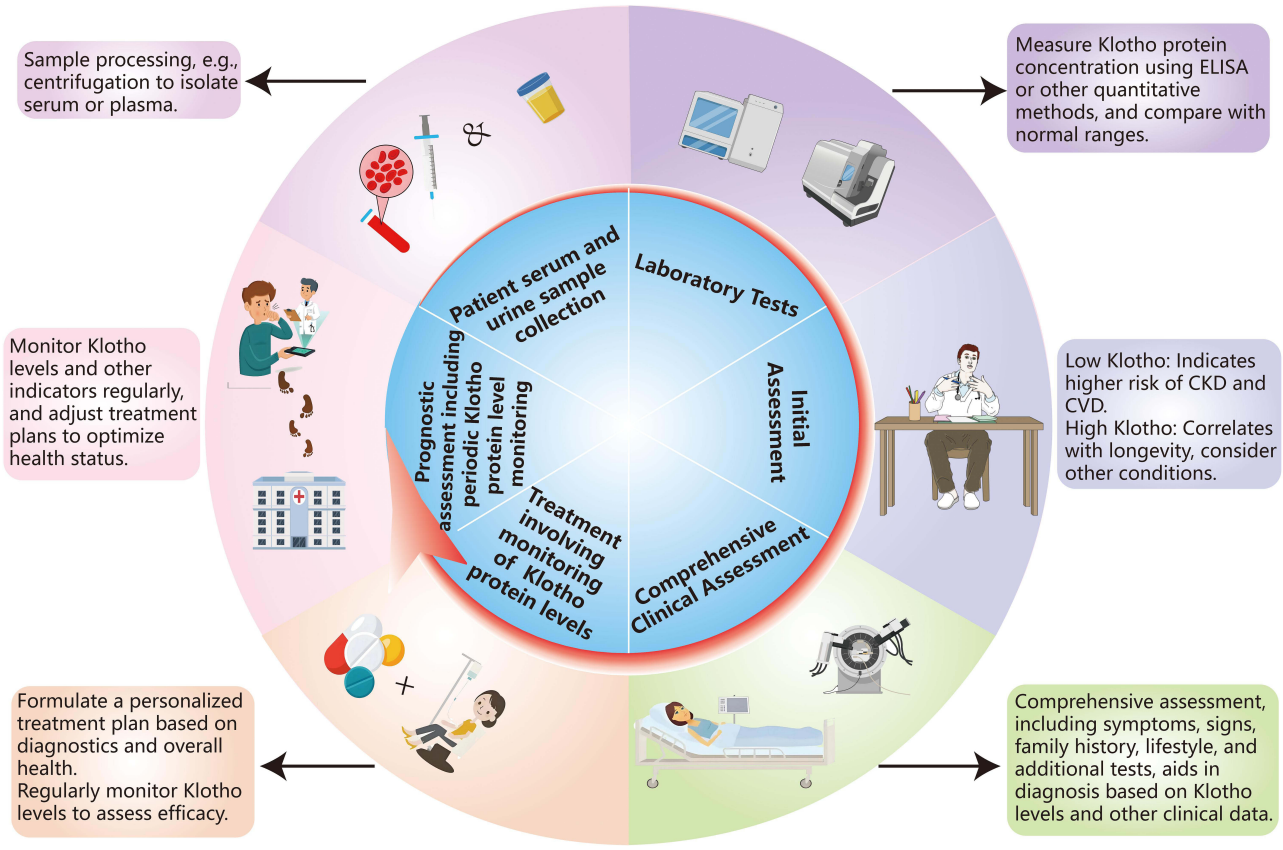

Figure 2 Klotho Protein Detection Protocol and Clinical Application. This diagram presents the clinical application scenario of Klotho protein. Firstly, blood and urine samples of patients are collected, these are then subjected to laboratory testing using quantitative methods such as ELISA to measure Klotho protein concentrations. Secondly, the test results will be compared. Lower levels of Klotho may indicate a higher risk of chronic kidney disease (CKD) and cardiovascular disease (CVD), while higher levels might be associated with longevity or other conditions. Finally, combined with all diagnostic information such as clinical examination and laboratory tests, personalized treatment strategies are regularly monitored to evaluate therapeutic efficacy. (Some of the icons above are from BioGDP.com).

Klotho levels in patients to reduce cardiovascular damage.[106] Klotho expression decreases significantly in kidney disease. So its level is also an important biomarker for assessing kidney function and disease progression.[107,108] Future therapeutic interventions to increase Klotho expression could provide a new approach to treating kidney disease and slow the progression of renal fibrosis in chronic kidney disease.[6]

Klotho has been shown to protect the nervous system from neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[15] Modulating Klotho to prevent or ameliorate these aging-related diseases has great potential for future clinical therapies. Preliminary animal model studies have shown that increasing Klotho expression reduces neuroinflammation and neuronal damage, highlighting its importance as a potential therapeutic target for the treatment of neurological disorders, particularly those associated with cognitive decline.[109–112]

The use of Klotho proteins in clinical practice is still in the exploratory phase and their diagnostic potential in a wide range of disease states should not be overlooked.[113–115] For instance, in patients with CKD, the degree of absence of Klotho protein in a patient's serum correlates with the severity of renal impairment. By quantifying Klotho protein levels, healthcare professionals can gain a more precise understanding of kidney function and thus more accurately assess a patient's condition. There is also a therapeutic strategy that utilizes the body's own mechanisms to increase the concentration of Klotho protein. Specific pharmacological interventions can be used to modulate specific pathways to elevate Klotho protein levels.[116] An illustrative example is recent research on the clinical treatment of OA. Researchers have developed an injectable peptide-hydrogel conjugate, pPNP + TIIA@PFS, which incorporates a stem cell homing peptide (PFSSTKT) to deliver plasmid DNA-laden nanoparticles and Tanshinone IIA. This groundbreaking therapy aims to arrest OA progression by rejuvenating senescent tissue microenvironments and fostering cartilage regeneration. The

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pPNP + TIIA@PFS therapy achieves this by dual mechanisms: it augments the levels of the anti-aging protein Klotho while simultaneously disrupting the dissemination of senescence signals to adjacent healthy chondrocytes. This concerted action significantly mitigates chondrocyte senescence, fortifying cartilage integrity and potentially reshaping the therapeutic landscape for osteoarthritis.[117]

Regarding the application of clinical treatment, although large-scale clinical application is yet to materialize, preliminary application is expected to be realized in continuous research and efforts. In preliminary clinical trials for cardiovascular disease, researchers are exploring how to increase Klotho protein levels in patients through drug intervention or gene therapy to enhance heart function and improve patient outcomes.[118]

There are still many obstacles to widespread clinical use based on Klotho proteins. The basis of Klotho mechanism has not been fully understood, and further research is needed. While gene therapy has potential, harbors inherent risks cannot be ignored which is ethical concerns. Meanwhile, for drug-based approaches, identifying precise targets with high specificity and minimal adverse effects remains an ongoing challenge. In summary, although Klotho protein demonstrates compelling potential for clinical application, it still needs substantial research and practical development to verify if it is really used in clinic.

The Current Controversies Regarding Klotho Protein

The controversy surrounding Klotho protein is intricate and multifaceted, mainly regarding clinical applications. One is the duration of the treatment's effects, despite evidence suggesting Klotho's potential in enhancing cognitive function and decelerating aging, the longevity of these effects remains uncertain, necessitating additional longitudinal studies to ascertain the sustained efficacy of Klotho protein over extended periods.[15] The other one is the dose and safety of the drug, the therapeutic window for Klotho protein is yet to be conclusively defined. Klotho may have a number of potential adverse effects at high dose levels, and it will be necessary to conduct comprehensive clinical trials to determine the optimal dose and confirm safety parameters for clinical use. Finally, in the current research, no clinical application of Klotho protein has been found, and most of the existing studies use new materials (such as hydrogels, nanoparticles, etc) combined with Klotho protein to achieve therapeutic purposes, and it is only used in animals and has not been used in clinical practice.[52,119] Therefore, if Klotho protein is to be turned into a clinically viable treatment option, research from all walks of life will need to work together to create a new and cost-effective treatment. Another controversy relates to Klotho's interaction with FGF23, where studies have indicated that α-Klotho promotes anti-aging through a pathway, suggesting that α-Klotho itself may not have anti-aging effects. This complexity elucidates the importance of the precise mechanisms behind Klotho function.[120]

Coordination and collaboration are needed to resolve these controversies and to facilitate the development of Klotho in clinical applications. Researchers need to delve deeper into the complex mechanisms of Klotho and rigorously assess the feasibility and safety of clinical applications in compliance with ethical regulations. Large-scale clinical trials must also be conducted to demonstrate the efficacy of Klotho in age-related diseases to establish a solid foundation for its therapeutic potential.

The Concluding Remarks and Future Directions

The Klotho Protein Plays an Important Role in Anti-Aging

Revered as the quintessential "longevity protein", Klotho is deeply interlaced within the very essence of aging, its levels serving as a poignant inverse barometer to the crescendo of age-related diseases.[15,31,37,121] Masterfully orchestrating the modulation of Klotho expression, we stand on the precipice of unlocking its innate potential—a potential to not merely decelerate the relentless march of time but to fortify the sanctity of healthspan, rejuvenating the golden years with renewed vigor and vitality.[54] Its protective aura blankets the cardiovascular domain with an invisible shield, warding off the specters of atherosclerosis, hypertension, and heart failure.[103,122–124] Klotho, in its vigilant sentry role, not only safeguards the heart but also heralds as a harbinger of cardiovascular risk, unveiling its therapeutic prowess and heralding a new dawn in the management of cardiac afflictions.[104] In the realm of renal health, Klotho's diminished presence amidst the tempest of kidney disease illuminates its dual role—as a beaconing biomarker for disease progression and

a tantalizing therapeutic target for intervention.[125] Its neuroprotective mantle extends beyond mere boundaries, enfolding Alzheimer's and Parkinson's diseases within its protective embrace, intimating its profound utility in the prophylaxis and palliation of neurodegenerative disorders.

Klotho, with its multifarious nature, transcends the limitations of being merely a protein; it stands as a vital lifeline, an indispensable cog in the intricate machinery of human longevity and wellbeing. Its abundance or scarcity paints a vivid picture of the dichotomy between health and disease, granting us a panoramic glimpse into the horizons of aging. By tapping into the profound potential of Klotho, we embark on an odyssey not merely to endure the years but to flourish within them, envisioning a future where the golden years are reimagined as an era of robust health, boundless joy, and unwavering vitality.

The Prospects of the Klotho Protein for the Aging Population

In the face of escalating demographic aging—a global phenomenon that strains healthcare systems and social infrastructures—the Klotho protein ascends as a luminary figure, casting light upon a path towards healthier longevity. Its multifaceted regulatory roles within the human body, particularly in maintaining the delicate balance of calcium-phosphate homeostasis.[34,126] Mitigating the ravages of oxidative stress,[95,97,127] and modulating the complex processes of apoptosis,[128] are indispensable in preserving physiological integrity and resilience against the onslaught of time. By harnessing the power to amplify Klotho expression, we stand on the precipice of a new era where the trajectory of age-related degeneration can be redirected. This is not merely a theoretical proposition; it is a tangible strategy to intercept and mitigate the progression of a spectrum of diseases, encompassing cardiovascular ailments, renal dysfunction, and neurological disorders. The very fabric of health in our aging population could be fortified by fortifying the levels of this vital protein. Moreover, the Klotho protein's predictive prowess as a biomarker for both aging and disease susceptibility offers a glimpse into the future, allowing for preemptive insights and timely medical interventions.[54,55,104] It is akin to having a vanguard, a sentinel at the forefront of the battle against the inevitable march of age, enabling us to prepare and act before the onset of debilitating conditions.

The urgency to delve deeply into Klotho's intricate mechanisms and to pioneer groundbreaking Klotho-centric therapies cannot be underestimated. These endeavors represent the cornerstone in alleviating the societal and economic pressures imposed by an aging population. By fostering research endeavors and therapeutic innovations centered around Klotho, we envision a future where the golden years are not synonymous with decline but rather embody vitality and autonomy. The promise of Klotho as a pivotal force in the quest for healthy aging transcends mere optimism; it is a clarion call for researchers, policymakers, and healthcare practitioners to unite in their endeavors. By harnessing this scientific breakthrough, we can transform the inevitable process of aging into a reality of tangible benefits for the countless individuals impacted by its relentless march.

The Application Prospect and Significance of Klotho Protein in Anti-Aging Diseases

In recent years, significant progress has been made in the field of Klotho protein research. There has been a significant increase in the number of research papers on how Klotho protein affects the aging process and its role in a variety of diseases, and several studies have revealed its potential therapeutic value. In particular, it is important to improve cognitive function,[15,16] alleviate aging-related diseases,[129,130] and develop novel therapeutic strategies[52,119] (Table 1).

The Klotho protein's application in the realm of anti-aging diseases heralds a paradigm shift of monumental proportions, encapsulating a vision where the ravages of time are tempered and the vibrancy of youth is reclaimed. Its multi-faceted influence weaves a tapestry of hope across the expanse of geriatric science:

Decelerating the Inevitable March of Time: Through its intricate orchestration of metabolic pathways, suppression of inflammation, and attenuation of oxidative stress, Klotho emerges as a maestro, conducting the symphony of longevity. It holds the potential to recalibrate the aging clock, bestowing upon us the gift of extended lifespans, not merely in terms of years, but in the richness of health and vitality they contain.[131–133]

Protection against disease: Klotho acts as a protective shield against disease in the elderly. Cardiovascular diseases,[37,129] the insidious progression of neurodegenerative disorders[13,29] and the pernicious grip of metabolic syndrome[134–136] are promising to be overcome in the future, and Klotho acts as a guardian to prevent the progression

Table 1 The Table Reflects the Progress Made in Recent Years in the Research of Klotho Protein

Year	Research Focus/Theme	Key Findings/Conclusions
2023	To validate the activity of the Klotho protein in the rhesus form and to study its effects on cognitive function in older rhesus macaques.	The resulting rhesus Klotho protein is bioactive in mice and enhances synaptic plasticity and cognitive function. A single injection of Klotho protein at a low dose (10 μg/kg) of older rhesus macaques enhances their performance on a spatially delayed memory task and the effect lasts for at least 2 weeks, compared with high doses.[15]
2023	To study Klotho's platelet-inducing factor and its promoting effect on angiogenesis.	It was found that Klotho can induce platelets to produce a variety of pro-angiogenic factors, which can promote the proliferation, migration and lumen formation of endothelial cells, play an important role in the angiogenesis process, and provide new potential targets for the treatment of ischemic diseases.[17]
2023	To investigate the effects of Klotho protein injections on cognitive function in elderly primates.	Elderly rhesus macaques were injected with Klotho protein, their working memory and ability to complete tasks were improved, and the lower dose (equivalent to five times the baseline level) could enhance cognitive ability, indicating that the clinical use of Klotho to improve cognitive performance or become a new treatment for neurodegenerative diseases, but the specific mechanism is unknown.[16]
2024	Local delivery of Klotho-expressing plasmid DNA and tanshinone IIA by stem cell homing hydrogel slows osteoarthritis (OA) progression.	An injectable peptide-hydrogel complex (pPNP TIIA@PFS) was constructed, which could increase the concentration of the anti-aging protein Klotho, inhibit chondrocyte senescence, promote the recruitment and differentiation of bone marrow mesenchymal stem cells, reduce osteophyte formation, and alleviate articular cartilage degeneration in the OA rat model.[117]
2024	To investigate the effects of KL-VS heterozygosity of the Klotho gene on neuroinflammation, neurodegeneration, and synaptic dysfunction in cognitively impaired older adults.	In cohorts with unimpaired cognition and increased risk for Alzheimer's disease, KL-VS heterozygous ($KL\text{-}VS_{HET}$) reduces age-related neuroinflammation, neurodegeneration, and synaptic dysfunction and protects the brain from age-related changes in harmful biomolecules.[19]
2024	To investigate the effect of FGF21 secreted by the liver during the decompensated phase of cirrhosis on satellite cell myogenesis through klotho beta and its relationship with sarcopenia.	During the decompensated phase of cirrhosis, the liver secretes more FGF21, which is inversely correlated with skeletal muscle mass. FGF21 inhibits the PI3K/Akt pathway by binding to klotho beta on the surface of satellite cells, hindering satellite cell proliferation and differentiation, resulting in sarcopenia. Neutralization of circulating FGF21 or knockout of klotho beta in satellite cells improves sarcopenia.[62]
2025	Modulation of the regenerative capacity of nucleus pulposus progenitor cells (NPPCs) using a nanoparticle-hydrogel system for the treatment of aging-associated intervertebral disc degeneration (IVDD).	An NPPC-targeted lipid thymine nanoparticle (NT-LNP) was designed to introduce Klotho circular ribonucleic acid (circRNA) into NPPCs to regulate cell regeneration and extracellular matrix metabolic homeostasis. Combined with a hydrogel system that can scavenge chemokines, it can improve the inflammatory environment and synergistically promote the regeneration of degenerative intervertebral discs, providing a reversible therapeutic strategy for IVDD.[119]

(*Continued*)

Table 1 (Continued).

Year	Research Focus/Theme	Key Findings/Conclusions
2025	To investigate the long-term effects of secretory Klotho (s-KL) on aging progression in wild-type mice.	Expression of s-KL through an adeno-associated virus type 9 (AAV9) vector increased the concentration of s-KL in mouse serum, increasing the lifespan of male mice by 20%. s-KL treatment also improved physical fitness in mice, reduced muscle fibrosis, enhanced muscle regeneration, improved bone microstructural parameters associated with osteoporosis, and increased cellular markers of adult neurogenesis and immune response.[112]
2025	Effect and mechanism of nanoparticle-mediated Klotho gene therapy on the transition from acute kidney injury to chronic kidney disease.	The use of nanoparticle-mediated Klotho gene therapy can alleviate acute kidney injury and prevent the transition from acute kidney injury to chronic kidney disease by modulating the PPARα signaling pathway in renal tubular epithelial cells, inhibiting inflammation and apoptosis.[52]

of diseases associated with aging. Easing the burden of suffering: For patients who already suffer from age-related diseases, Klotho offers hope for future treatments. It not only improves symptoms and prognosis and quality of life, but more importantly, enables elderly patients to live with greater dignity in their later years.[124] Driving therapeutic innovation: The emerging field of Klotho research is a prerequisite for the development of new therapies and pharmaceutical formulations. It can enrich our therapeutic arsenal and provide healthcare professionals with a powerful tool for treating age-related diseases. Charting the Path to Healthy Aging: when we unravel Klotho's complex anti-aging mechanisms, we can paint a new picture of hope for the challenges posed by aging. This vision will lead us to look at aging in a new light, not as a decline, but as a beautiful process of staying strong and healthy.

In conclusion, the Klotho protein is a beacon of optimism that lights the way toward healthier aging. Its mechanism and role in combating age-related diseases and prolonging life underscores its importance. However, future development is fraught with complexity and requires a thorough understanding of its complex mechanisms and ensuring its safety and efficacy in clinical applications. Future efforts must embody a multidisciplinary spirit, advance through meticulous clinical trials, and address the ethical implications inherent in research. As we delve into the mysteries of Klotho, one fact that emerges is that the potential for this protein to reshape the aging landscape is profound. It allows us to embrace the unknown, challenge the boundaries of what is possible, and strive to ensure that the golden years are filled with robust health and unyielding vitality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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