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A review on Klotho: FGF23 mediated pathway integration and aging

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Aging is driven by interconnected genetic, metabolic, and environmental factors that manifest as hallmarks including genomic instability, telomere attrition, epigenetic drift, and altered intercellular signaling. The Klotho-FGF23 axis has emerged as a critical regulator linking mineral metabolism to systemic aging processes. Membrane-bound Klotho, primarily in the kidney and parathyroid, acts as an obligate co-receptor for FGF23 to regulate phosphate and vitamin D homeostasis, while soluble Klotho exerts hormone-like effects that modulate Wnt, IGF-1, NF-κB, and TGF-β pathways, influencing oxidative stress, inflammation, and tissue regeneration. Deficiency of Klotho or FGF23 in animal models results in hyperphosphatemia, vascular calcification, and premature aging phenotypes, whereas Klotho overexpression or supplementation extends lifespan and enhances stress resilience. Beyond its renal role, FGF23 can activate Klotho-independent FGFR4 signaling in cardiomyocytes, promoting hypertrophy and contributing to cardiovascular risk. This review integrates current mechanistic insights on Klotho-FGF23 signaling within the framework of aging hallmarks, differentiating protective Klotho-dependent pathways from maladaptive Klotho-independent effects. We evaluate therapeutic strategies including recombinant Klotho protein, gene therapy, dietary phosphate restriction, FGFR4 inhibition, and senolytics approaches that restore Klotho expression. Key translational challenges remain assay variability and poor standardization of soluble Klotho measurement, limited longitudinal human data, and differences between murine models and human aging. Addressing these barriers will be essential to advancing Klotho-FGF23 targeted interventions as a viable strategy to extend health span and delay age-related pathologies.

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INTRODUCTION

Ageing is an inherent phenomenon that every individual experiences in due course. It is a progression that occurs uniquely for each person, following their own timeline and rate. From a broader perspective, ageing encompasses the multitude of transformations occurring throughout one's lifespan. This process initiates from birth, as individuals progress through growth, development, and ultimately reach maturity [1]. Aging progresses at different rates among species, implying the existence of a poorly characterized biological clock. Although the molecular mechanisms governing aging are under extensive investigation, they remain incompletely elucidated. The etiology of age-associated diseases is, however, likely to be multifactorial [2] In humans, only a few genes have been definitively associated with accelerated aging, as observed in progeria, or, conversely, with extended lifespan [3,4]. The longevity-associated protein Klotho, originally identified as a biomarker of aging, is now recognized as an active regulator of lifespan and health span [5]. The gene was first discovered in mice in 1997 [6]. Loss of its protein product leads to a syndrome exhibiting multiple hallmarks of aging, as seen in mutant mice carrying either a hypomorphic Klotho allele (Kl^kl/kl) or a complete Klotho knockout (Kl^−/−) (Fig. 1). Mice lacking Klotho display stunted growth, kidney dysfunction, elevated phosphate and calcium levels, vascular calcification, cardiac hypertrophy, hypertension, organ fibrosis, multi-organ atrophy, reduced bone mass, lung pathology, cognitive decline, and a markedly shortened lifespan [4,7]. Klotho functions as an obligate co-receptor for fibroblast growth factor 23 (FGF23), enabling precise regulation of calcium-phosphate metabolism and vitamin D homeostasis [8]. Loss of Klotho disrupts phosphate excretion, elevates circulating phosphate and 1,25-dihydroxyvitamin D, and promotes vascular calcification pathologies linked to premature mortality. At the cellular level, Klotho suppresses IGF1R/PI3K/Akt signaling, preserving FOXO3-mediated antioxidant defenses and reducing NOX2-derived reactive oxygen species, thereby limiting oxidative stress and ischemia–reperfusion injury [9]. Klotho interferes with pro-oxidant signaling cascades by inhibiting upstream pathways (IGF1R/PI3K/AKT), thereby maintaining FOXO3 in an active state that promotes antioxidant defense, and reduces NOX2-driven ROS production. This combined effect alleviates oxidative stress, protects cardiac tissue and reduce injury IRI (Ischemia-Reperfusion Injury) [10] Beyond systemic mineral regulation, Klotho influences neural and muscular resilience. In the brain, high expression in the choroid plexus limits neuroinflammation [11]. Systemic Klotho deficiency causes hippocampal neuron spine heads to enlarge and spine length to shorten changes linked to reduced synaptic flexibility and impaired cognitive function. In contrast, Klotho overexpression reverses these structural changes, promoting healthier, more dynamic synapses. Overall, Klotho supports synaptic plasticity and brain health, suggesting that higher levels may enhance cognitive performance, while lower levels may contribute to age-related cognitive decline [12]. In skeletal muscle, injury-induced upregulation of Klotho supports regeneration, whereas persistent epigenetic repression in aged muscle limits repair capacity [13]. By integrating endocrine, metabolic, and signaling functions, Klotho modulates multiple hallmarks of aging, positioning it as a key regulator of longevity rather than a passive biomarker.

TYPES OF AGING

Cellular aging

A cell has the capacity to undergo approximately 50 rounds of replication before encountering a point where the genetic information can no longer be faithfully duplicated. This inability to accurately copy genetic material is known as cellular senescence, a process marked by the decline of functional properties within the cell. The buildup of senescent cells serves as a defining feature of cellular aging, ultimately contributing to the progression of biological aging [14].

Hormonal aging

Hormones exert a significant influence on the process of aging, particularly in the period of childhood, where their function encompasses the promotion of bone and muscle formation as well as the facilitation of the emergence of secondary sexual characteristics in males and females. Gradually, the secretion of numerous hormones will start to decrease, resulting in alterations in the skin such as the emergence of wrinkles and diminished elasticity, alongside a decline in muscle firmness, bone mass, and libido [15].

Accumulative damage

Aging, resulting from the cumulative impact of damage (referred to as "wear and tear"), pertains to the external elements that may gradually amass. Exposure to toxins, ultraviolet radiation, unhealthy dietary choices, and environmental contaminants represent a few instances of factors that can negatively affect the body. Over a period of time, these external factors have the potential to directly harm the DNA within cells (partially through subjecting them to excessive or persistent inflammation). The accrued damage has the capacity to compromise the body's self-repair mechanisms, thereby fostering an accelerated aging process [16].

Metabolic aging

Throughout the course of a typical day, the cells within the human body engage in the continuous conversion of food into energy, leading to the generation of potentially detrimental byproducts. This metabolic activity, crucial for sustaining life, has the capacity to inflict cumulative harm on cellular structures, a condition commonly identified as metabolic aging. Certain scholars posit that the deceleration of metabolic functions, achieved, for instance, through the implementation of dietary restrictions like calorie reduction, could potentially decelerate the aging process in the human population [17].

HALLMARKS OF AGING

Genomic instability

The human genome is under persistent assault from exogenous and endogenous genotoxic agents, including environmental pollutants and the by products of normal cellular metabolism. This continuous exposure leads to the progressive accumulation of DNA damage over an individual's lifespan. Given DNA's role as the fundamental blueprint for cellular processes, this accumulating genetic impairment is a hallmark of biological aging, contributing to the erosion of cellular homeostasis and functional decline [18]. Genomic instability directly triggers cell cycle disruption, changes in gene expression, and dysregulation of gene activity. Over time, these effects lead to cellular deterioration and loss of function, ultimately contributing to aging and the development of degenerative diseases [19]. This stability is also preserved by specialized mechanisms that ensure proper telomere length and function. Besides direct DNA damage, abnormalities in nuclear structure referred to as laminopathies can disrupt genome integrity and lead to premature aging disorders [20].

Reduced telomeres

Telomeres are specialized chromatin structures located at the ends of chromosomes, composed of conserved TTAGGG repeat sequences. They act as protective caps that prevent chromosome ends from undergoing recombination or degradation [18]. Due to the limitations of replicative DNA polymerases, the telomeric regions of eukaryotic DNA cannot be fully duplicated during cell division. As a result, telomeres progressively shorten with each division, leading to genomic instability and eventually triggering either apoptosis or cellular senescence.

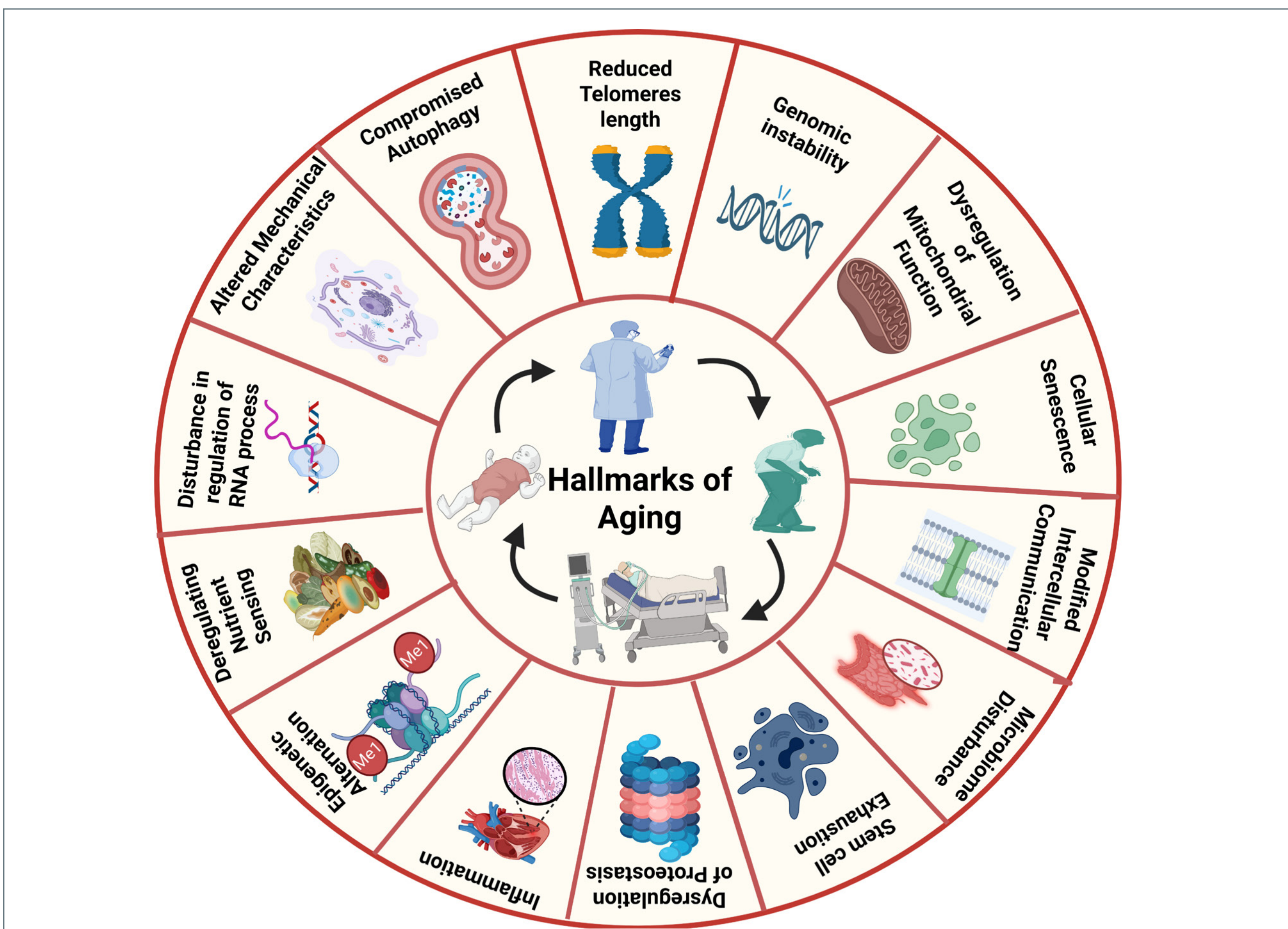

Figure 1. Hallmarks of aging.
Illustration of major aging hallmarks, including telomere shortening, genomic instability, mitochondrial dysfunction, senescence, altered intercellular communication, stem cell exhaustion, proteostasis loss, inflammation, epigenetic changes, deregulated nutrient sensing, RNA processing defects, mechanical alterations, and impaired autophagy.

However, this harmful process can be counteracted by telomerase, an enzyme with reverse transcriptase activity that helps maintain telomere length [20,21]. This enzyme, which plays a key role in elongating telomeres and is highly active in embryonic stem cells, is largely undetectable in most normal human cells. Researchers have discovered that reduced telomerase activity accelerates stem cell senescence [22]. A lack of telomerase in humans is linked to the early onset of disorders like pulmonary fibrosis, aplastic anemia, and dyskeratosis congenita conditions that impair the ability of affected tissues to regenerate [23]. Studies using genetically engineered animal models have demonstrated direct connections between telomere shortening, cellular senescence, and aging at the organism level. Mice with reduced telomere length show shorter lifespans, while those with extended telomeres tend to live longer [20,24].

Epigenetic alteration

Epigenetic alterations are non-genomic modifications that influence gene expression and alter chromatin structure without changing the underlying DNA sequence. These changes regulate how genes function and are typically defined as modifications in gene regulation that are not directly programmed into the DNA itself [25]. Epigenetic changes associated with aging involve shifts in DNA methylation patterns, irregular post-translational modifications of histones, disrupted chromatin remodeling processes, and impaired regulation of non-coding RNAs (ncRNAs) [23]. These often reversible regulatory modifications influence gene expression and various cellular functions, contributing to the onset and advancement of numerous age-related diseases, including cancer, neurodegenerative disorders, metabolic syndrome, and skeletal conditions [23].

Dysregulation of proteostasis

Proteostasis refers to the balance and stability of functional proteins within cells. As aging progresses, this protein quality control system deteriorates. Consequently, aging cells begin to accumulate damaged or misfolded proteins due to the decline in proteostasis mechanisms, leading to reduced cellular function and the emergence of protein misfolding disorders commonly known as proteinopathies or conformational diseases such as Alzheimer's and Huntington's disease [18]. The key components responsible for maintaining proteostasis include molecular chaperones, the ubiquitin-proteasome system, and the lysosomal-autophagy pathway involved in protein degradation. Chaperones assist and protect proteins throughout their various structural transitions, including initial folding, assembly and disassembly, membrane transport, and marking them for degradation [18].The ubiquitin-proteasome system and autophagy serve as the cell's main pathways for protein degradation, but their efficiency diminishes with age [26]. Enhancing proteasome or autophagy function by overexpressing key proteasome subunits or critical autophagy-related genes has been shown to extend lifespan and increase stress resistance in model organisms such as S. cerevisiae, C. elegans, and D. melanogaster [27].

Stem cell exhaustion

Stem cell exhaustion, characterized by a decrease in stem cell quantity and activity, occurs in nearly all tissues and organs that depend on adult stem cells for maintenance, such as the bones, forebrain, and muscles [28]. The functionality of these hematopoietic stem cells declines with age, potentially resulting in various pathological outcomes, including weakened adaptive immune responses, a higher risk of developing anemia, and a reduction in lymphoid cell populations [26]. The reduction in stem cell activity is driven by multiple factors, such as accumulated cellular damage, shifts in gene expression patterns, and changes in the surrounding stem cell niche or microenvironment [18]. Research has demonstrated that stem cell exhaustion plays a significant role in the age-related decline of tissue regeneration, contributing to conditions like muscle loss, delayed bone repair, and reduced skin elasticity. Additionally, it heightens the risk of age-related diseases such as Alzheimer's, cardiovascular conditions, and cancer [29].

Cellular senescence

Cellular senescence is a state in which cells permanently stop dividing but remain metabolically active. This process is typically triggered by various forms of stress, such as DNA damage, oxidative stress, telomere shortening, or oncogene activation. Senescent cells become non-functional and cease to divide; additionally, they promote increased inflammation, which can accelerate the aging process [30]. These cells show altered metabolic activity, experience major shifts in gene expression, and acquire a complex senescence-associated secretory phenotype (SASP). This phenotype includes proinflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes, all of which can influence and disrupt the surrounding cellular environment [18]. Studies have shown that the ongoing elimination of senescent cells through genetic or pharmacological methods can enhance both lifespan and health in aged mice, confirming the crucial role of cellular senescence in the aging process. Therefore, targeting and clearing senescent cells may help reduce age-related tissue damage and promote a longer, healthier life [31].

Deregulated nutrient sensing

Nutrients are essential compounds required by the body to maintain vital functions necessary for survival, growth, and reproduction, and they are best acquired through a well-balanced diet. Therefore, glucose, along with other carbohydrates, amino acids, and lipids, are vital nutrients for cells, and mammalian cells possess specific mechanisms to detect their presence and availability. Cells need the ability to store nutrients during times of abundance and retrieve them when nutrients are in short supply [18]. The regulation of nutrient availability in cells involves four major nutrient-sensing pathways: Insulin and Insulin-like Growth Factor 1 (IGF-1) signaling (IIS), the mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins. These interconnected pathways play a crucial role in maintaining cellular homeostasis by sensing nutrient levels, regulating energy metabolism, and coordinating cellular growth, repair, and survival in response to nutrient abundance or scarcity [32]. The IIS and mTOR pathways serve as indicators of nutrient abundance, and their inhibition has been shown to extend lifespan by limiting cellular growth and anabolic metabolism [18]. Researchers have discovered that fibroblast growth factor 21 (FGF21) may promote longevity in mammals by stimulating the AMPK signaling pathway [33]. A major nutrient-sensing impairment associated with human aging is insulin resistance. As people age, various factors such as oxidative stress, chronic inflammation, disrupted enzyme activity, and the buildup of fatty acids in cells can lead to reduced insulin sensitivity [18].

Modified intercellular communication

Intercellular communication involves the different mechanisms by which cells connect and share a wide range of signals with one another The methods of communication in these processes involve multiple mechanisms that can function separately or simultaneously, depending on the physiological or pathological conditions. The specific patterns of cell-to-cell signaling that emerge with aging are especially important [34]. Aging is associated with gradual changes in intercellular communication that introduce increased signaling disturbances, disrupting the body's ability to maintain balance and respond adaptively to stress [23]. Changes in intercellular communication reflect disruptions in the signaling between cells, which can contribute to the development of age-related diseases and functional decline [18]. Cell-to-cell communication is also crucial in the aging process, as it helps regulate functions at the neuroendocrine, endocrine, and neuronal levels [22].

Dysregulation of mitochondrial function

Mitochondria are commonly called the cell's powerhouses because they generate energy by converting nutrients into a form the cell can utilize. Damage to mitochondria reduces their capacity to generate energy needed to power the cell [18]. Mitochondrial dysfunction can lead to impairments in the respiratory chain, elevated production of reactive oxygen species (ROS), decreased ATP generation, and the activation of apoptosis and inflammation, all of which contribute to the development of various age-related diseases [26]. Reactive oxygen species (ROS) comprise a group of molecules such as hydrogen peroxide (H_2O_2), superoxide ion (O_2•–), and hydroxyl radical (•OH). These highly reactive molecules are considered a major cause of oxidative stress originating within the body [30]. Senescent cells experience notable alterations in mitochondrial function, structure, and dynamics. They show reduced membrane potential, increased proton leakage, enhanced enzyme release, greater mitochondrial mass, and elevated levels of tricarboxylic acid (TCA) cycle metabolites [18]. Despite being present in large numbers, mitochondria in senescent cells generally have a diminished capacity to generate ATP. Physical exercise can help counteract the aging effects associated with mitochondrial dysfunction [26].

Compromised autophagy

Compromised autophagy represents a fundamental feature of the aging process [35,36]. Aging is characterized by the build-up of incorrectly folded proteins and dysfunctional mitochondria that have reached senescence, primarily due to the breakdown of cellular repair mechanisms [37]. The elimination of misfolded proteins is essential for the survival of cells, as protein misfolding hinders normal biological processes and enhances the propensity to form harmful aggregates a defining trait of age-related neurodegenerative condition [38]. Under normal circumstances, misfolded proteins are initially eliminated by the ubiquitin-proteasomal system (UPS); nonetheless, large cargos like protein oligomers, aggregates, and impaired mitochondria are too sizeable to be processed by the proteasome of the UPS mechanism, and therefore undergo degradation through autophagy [39]. A harmonized interplay between UPS and autophagy has been recognized as crucial for sustaining the equilibrium of functional protein levels. The ubiquitin markers attached to misfolded or aggregated proteins facilitate their delivery and subsequent degradation via either the UPS or autophagy [40]. Strategies involving pharmaceutical interventions or genetic manipulations that aim to impede the UPS stimulate autophagy by boosting the expression of specific autophagy-related genes, such as ATG5 and ATG7, enhancing Beclin-1 levels, and activating AMPK, among other mechanisms [41]. Likewise, impaired autophagy triggers the activation of the UPS by elevating the levels of proteasomal subunits [39]. Detailed discussions on the interaction between UPS and autophagy can be found in other sources. The significance of autophagy is particularly pronounced in long-lived post-mitotic cells, such as neurons, which are seldom renewed throughout the lifespan of the adult organism. This protective mechanism diminishes with age, leading to the accumulation of damaged structures both inside and outside of lysosomes [35,42].

Disruption in the regulation of RNA processing

Dysregulation of mRNA processing meets all the requirements to be classified as a novel hallmark of aging. The initial requirement is that a hallmark must manifest during the typical aging process [26]. RNA is processed in cells becomes abnormal or imbalanced, a phenomenon known as dysregulation of RNA processing. RNA processing is crucial for creating proteins that cells need to function properly. Studies have shown that certain treatments or interventions aimed at reversing signs of cellular aging (senescent phenotypes) can work, at least in part, by restoring the normal, youthful patterns of expression of splicing factors. Splicing factors are proteins that help edit RNA during processing, ensuring that the RNA is properly prepared for protein production. By bringing these splicing factors back to their youthful levels, these interventions can help restore healthier cellular function [43]. In a similar fashion, the alternative polyadenylation of messenger RNAs, a phenomenon previously identified as a factor in cancer development, exhibits modifications as an individual ages and could potentially play a role in cellular senescence [26]. As we age, several mechanisms that regulate gene expression – such as genome stability, transcriptional efficiency, epigenetic changes, and RNA processing – undergo alterations. Genome stability refers to the preservation of DNA integrity, which becomes compromised over time. Transcriptional efficiency, the process of converting DNA into RNA, also declines with age. Epigenetic changes, such as DNA modifications that regulate gene activity without altering the DNA sequence, accumulate over time. Together, these changes disrupt normal gene expression and contribute to the aging process [26].

Altered mechanical characteristics

Altered mechanical characteristics pertain to both cells and the extracellular environment. In instances such as fibroblast senescence, a significant transition occurs from a dynamic pool of actin that can be easily polymerized and depolymerized during cellular movement, to enduring stress fibers of f-actin connected via focal adhesions to the underlying substrate [44]. This phenomenon is especially evident in cells derived from individuals suffering from syndromes associated with accelerated aging, potentially influencing both cellular motility and intercellular communication and is expected to have an impact on both cell motility and intercellular communication [44]. Interventions that target the signaling pathways of small G proteins responsible for regulating cytoskeletal motility, such as the administration of statins, have shown significant enhancements in the functionality of aged neutrophils in laboratory settings. These improvements have led to a pronounced reduction in mortality rates over a six-month period following hospitalization in the intensive care unit due to pneumonia among older patients [45]. Elevated rigidity and diminished flexibility, for instance due to glycation cross-links among collagen molecules, may result in various age-related pathological conditions such as hypertension accompanied by renal and neurological impairments - these cross-links might play a role in the hastened aging observed in individuals with diabetes [44,46].

Microbiome disturbances

The crucial role of the gut microbiome in various aspects of human health is now widely acknowledged [18]. Advancements in next-generation sequencing technologies have enabled the detection of significant alterations in the gut microbiome with aging, revealing specific shifts in microbial communities and a decline in species diversity [47]. Age-related alterations in the gut microbiota are marked by reduced microbial diversity, a rise in potentially harmful bacterial populations, and a decline in beneficial microbes. Specifically, there is often an increase in potentially pathogenic groups like Proteobacteria and a decrease in beneficial bacteria such as Bifidobacteria [18]. These shifts in the gut microbiota may lead to several health problems frequently observed in older adults, including constipation, increased inflammation, and weakened immune responses [48].

Inflammation

As people age, inflammation associated with aging becomes more persistent and increases over time, even in the absence of infection or injury. This chronic inflammation significantly contributes to the development of numerous age-related diseases, leading to tissue damage, impaired organ function, and a decline in immune system efficiency [49]. As people age, the levels of various inflammatory mediators also increase, indicating an ongoing inflammatory response. Among these mediators are interleukin-1 and interleukin-6, which play a crucial role in regulating immune responses and inflammation [44,50]. Initially, inflammation was regarded as a component of the hallmark 'altered intercellular communication'; however, it merits consideration as an independent phenomenon due to its substantial impact on the ageing process and its interplay with other hallmarks, such as cellular senescence and the recently identified gut microbiota [44,49].

THE ROLE OF KLOTHO IN AGING: EXPRESSION, FUNCTION, AND THERAPEUTIC POTENTIAL

Discovery of Klotho as anti-aging protein

The klotho (KL) gene was identified in 1997 from a mutant mouse line showing multisystem premature-aging phenotypes and shortened lifespan due to disrupted α-klotho expression, establishing KL as an aging-suppressor in mice [6]. In gain-of-function models, transgenic overexpression of Klotho has been shown to extend lifespan in mice, whereas loss-of-function mutations result in premature mortality; however, these effects have been demonstrated primarily in specific inbred genetic backgrounds under controlled housing and dietary conditions [51]. Evidence for cross-species translatability is provided by a study in aged rhesus macaques, in which a single low dose of recombinant Klotho enhanced working memory, with cognitive benefits persisting for approximately two weeks; while promising, these findings remain preliminary with respect to human applicability [52]. In humans, reported associations between circulating soluble Klotho and mortality or age-related diseases are heterogeneous; recent analyses have identified increased risk at both low and high concentrations, suggesting a U-shaped relationship, or context-specific associations in conditions such as chronic kidney disease and osteoporosis. Interpretation of these findings is further complicated by inter-assay variability, particularly between commercial ELISA kits and immunoprecipitation immunoblot methodologies [53]. Overall, the most robust evidence for longevity or cognitive benefits derives from Klotho overexpression models and acute recombinant protein administration in animals; however, translation to human lifespan remains unsubstantiated [52].

Molecular basis of Klotho

The human Klotho gene is located on chromosome 13q12, covering a region of about 50 kilobases. Its structure includes five exons separated by four introns [54]. The gene produces a type 1 transmembrane glycoprotein made up of 1,012 amino acids and has an approximate molecular weight of 135 kDa [55]. The full-length Klotho protein includes a predicted N-terminal signal sequence, followed by two internal repeats (KL1 and KL2) that form the extracellular domain, a single-pass transmembrane segment, and a short intracellular cytoplasmic tail of 10 amino acids at the C-terminal end [54]. Klotho exists in three distinct forms. The membrane-bound form (m-Klotho), mainly located in the kidney, brain, and parathyroid gland, functions as a co-receptor with FGF23 to regulate calcium and phosphate homeostasis [9]. The soluble form (s-Klotho) is generated through proteolytic cleavage and circulates in the blood, urine, and cerebrospinal fluid, acting like a hormone that influences ion transport, insulin/IGF-1 signaling, and oxidative stress. The third form, a secreted splice variant, results from alternative splicing and lacks the transmembrane region; it is less abundant and less understood in humans [56]. Klotho exists in the bloodstream in both soluble and secreted isoforms. Extracellular portion can be cleaved by membrane-bound proteases, especially ADAM10 and ADAM17 (α-secretases), leading to the release of the soluble α-Klotho (s-Klotho) for into various body fluids(4) as shown in Figure 2. Klotho protein characterized as single-pass transmembrane protein, including the α-, β-, and γ-Klotho isoforms [9]. These all isoforms are the single-pass transmembrane proteins that make up all klotho proteins. α-Klotho protein primarily produced in renal tubule part of Kidney, but its existence also found in choroid plexus part of brain, β-cell of pancreas, skin and blood vessel [57]. β form of-Klotho is predominantly present in the liver, with additional presence in the kidney, gut, and spleen. It contributes to regulating the actions of several fibroblast development factor (FGF) family members, particularly FGF-21and FGF-19 [9]. However, γ-Klotho is expressed in both the renal system and cutaneous tissues, even its precise biological roles are still unknown [9].

ROLES OF KLOTHO PROTEIN IN SIGNALING PATHWAYS

The Klotho protein plays a crucial role in modulating multiple signaling pathways that govern aging, mineral metabolism, oxidative stress, and inflammation as shown in Figure 3.

Wnt signaling pathway

Numerous biological processes, such as tissue homeostasis, stem-cell regulation, and embryonic development, are influenced by the Wnt signaling system. This system also promotes the increased expression of pro-fibrotic cytokines and molecule [58]. Klotho directly binds to molecules that activate the Wnt signaling system and this interaction prevents the pathway's activation thereby exerting a controlling influence over processes such as cell proliferation and fibrosis. Thereby exerting a controlling influence over processes such as cell proliferation and fibrosis. Calcium balance is crucial for cellular functions such as muscle contraction, nerve signaling, and enzyme activity [59]. The Klotho protein helps maintain this balance, preventing calcium overload, which can lead to cell damage and contribute to various diseases which may facilitate the

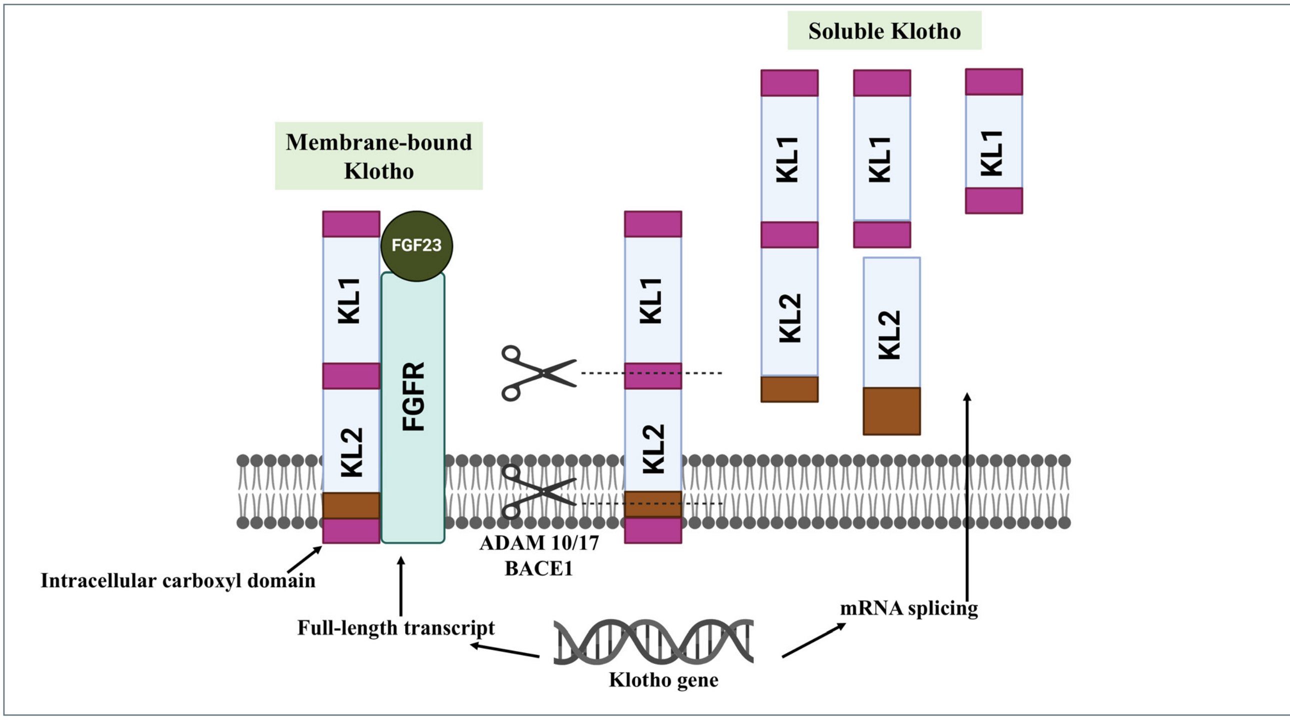

Figure 2. Membrane-bound and soluble forms of Klotho.
The Klotho gene produces a full-length transcript encoding membrane-bound Klotho, which complexes with fibroblast growth factor receptor (FGFR) to mediate FGF23 signaling. Ectodomain shedding by ADAM10/17 or BACE1 releases soluble Klotho (containing KL1 and/or KL2 domains) into circulation. Alternatively, mRNA splicing generates a secreted form lacking the transmembrane domain.

activation of μ-calpain, a calcium-dependent protease, ultimately resulting in the degradation of β-catenin [60]. Furthermore, diminished concentrations of Klotho in individuals afflicted with chronic kidney disease (CKD) may intensify the advancement of renal damage and fibrotic changes as a consequence of the impaired inhibition of the Wnt/β-catenin signaling cascade(58). Increased Wnt signaling has been linked to issues with stem and progenitor cell function, as well as cellular aging. As a result, Klotho's ability to reduce Wnt signaling could help alleviate these problems and support tissue regeneration [61].

NF-κB-mediated signaling cascade

The NF-κB signaling pathway serves as a central regulator of innate immunity and represents an evolutionarily conserved mechanism present in both insects and vertebrates. It functions as a critical hub, integrating signals from pathogens and cellular stress to coordinate appropriate defensive responses [62]. NF-κB is a principal regulator of the senescence-associated secretory phenotype (SASP) the pro-inflammatory array of cytokines, chemokines, proteases, and growth factors secreted by senescent cells. Its activation is triggered by DNA damage and oxidative stress (DAMPs, PAMPs), contributing to inflammaging and tissue degeneration [63]. Age-related degeneration is driven by accumulated cellular damage, including DNA breaks. NF-κB, activated by such stress, becomes increasingly active with age and in aging-related disorders [64]. Through NF-κB inhibition and inflammatory suppression, Klotho exerts anti-aging effects by decreasing SASP expression, promoting cellular resilience, and maintaining stem progenitor cell reserves [65]. The suppression appears to stem from increased Nrf2 activation, which antagonizes NF-κB activity [4].

The signaling pathway of insulin-like Growth Factor 1 (IGF-1)

Insulin-like Growth Factor 1 (IGF-1) is a peptide hormone structurally related to insulin, predominantly synthesized in the liver in response to stimulation by growth hormone (GH). IGF-1 plays a pivotal role in regulating growth, development, cellular survival, and metabolic processes. This signaling pathway is highly conserved across species, from Caenorhabditis elegans to humans [66]. The insulin/IGF-1 receptor signaling pathway is closely associated with the aging process and is highly responsive to nutrient availability. Under nutrient-rich conditions, it activates a key downstream effector known as the mechanistic target of rapamycin (mTOR), a protein kinase that plays a central role

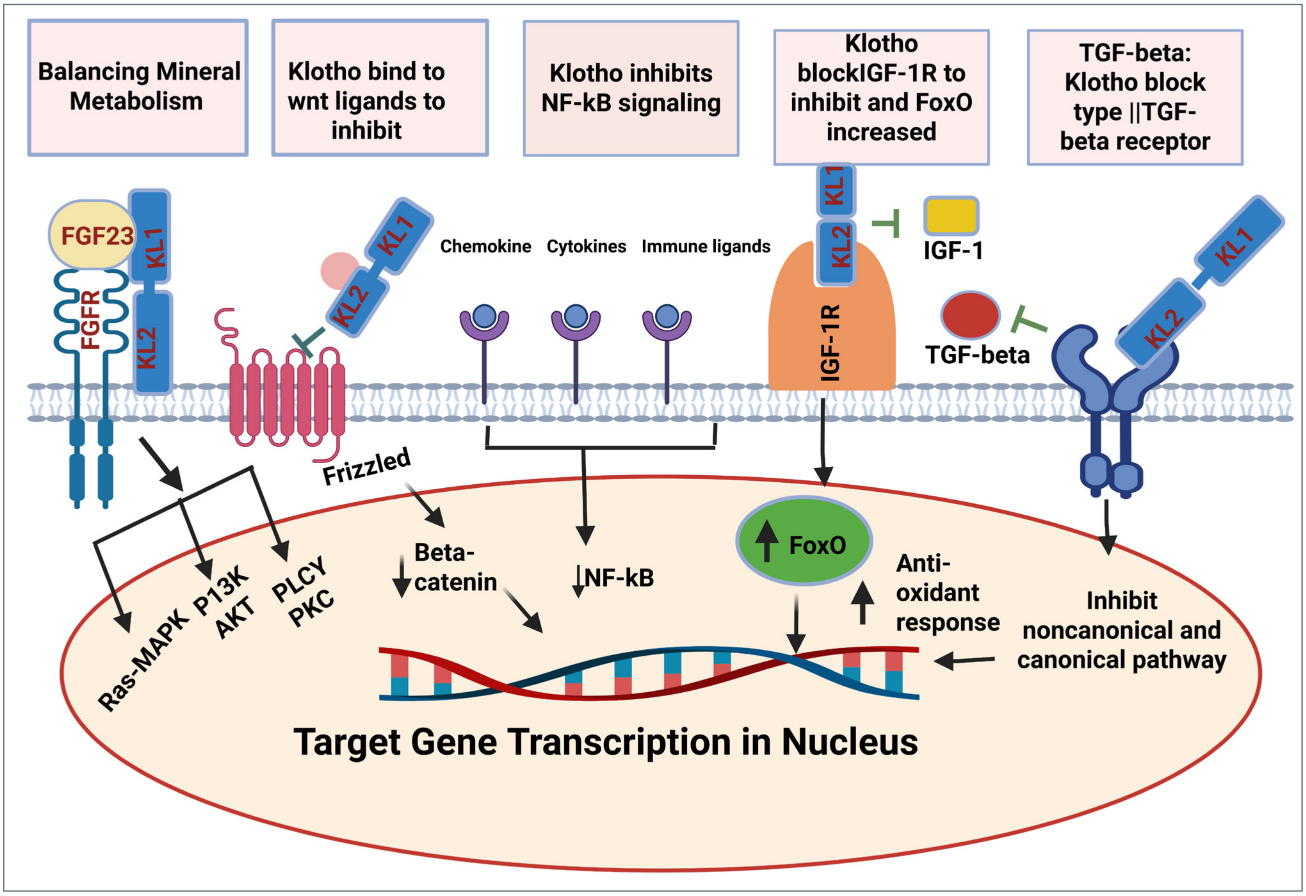

Figure 3. Regulatory roles of Klotho in cellular signaling.
Klotho modulates multiple pathways by facilitating FGF23-FGFR signaling, inhibiting Wnt/β-catenin and NF-κB pathways, blocking IGF-1R to activate FoxO antioxidant responses, and suppressing TGF-β receptor signaling. These actions regulate mineral metabolism, inflammation, oxidative stress, and fibrosis.

in multiple age-related diseases [4]. Insulin-like Growth Factor 1 (IGF-1) binds to its specific receptor, IGF-1 receptor (IGF-1R), inducing receptor autophosphorylation and initiating downstream signaling cascades, primarily the PI3K/Akt and MAPK/ERK pathways. These signaling events collectively regulate cellular processes such as growth, survival, and metabolic activity [67]. IGF-1 has been shown to downregulate the expression of POLD1, a critical DNA polymerase responsible for maintaining genomic integrity. This suppression contributes to the acceleration of cellular aging by compromising DNA replication fidelity and genome stability [68]. Calorie restriction (CR) has been shown to counteract this effect and extend lifespan in humans. Notably, Klotho suppresses the IGF-1/PI3K/Akt/mTOR signaling pathway, which is considered a key mechanism through which Klotho exerts its anti-aging effects and offers protection against various degenerative diseases [4]. Soluble Klotho (s-Klotho) inhibits the activation of insulin and IGF-1 receptors, thereby attenuating downstream signaling cascades, including the phosphorylation of insulin receptor substrates (IRS) and the subsequent activation of the PI3K/Akt/mTOR pathway [4].

Klotho demonstrates inhibitory effects on TGF-β

A multifunctional cytokine known as transforming growth factor-beta (TGF-β) has been implicated in the aging process by promoting cellular frailty, diminishing stem cell populations, inducing immunological dysfunction, contributing to fibrosis, and various other disorders associated with advanced age [69]. The type II TGF-β receptor (TβRII) is a cell surface receptor that binds to the cytokine TGF-β, initiating signaling processes that regulate cell growth, repair, and behavior. Klotho disrupts TGF-β's ability to bind to this receptor, preventing the activation of signaling pathway [4]. By blocking this pathway, Klotho may help reduce the harmful effects of excessive TGF-β signaling, such as tissue damage and age-related diseases. In the renal tissues of aged murine models, Klotho levels exhibit a marked reduction, in contrast to the elevated levels of TGF-β and its associated signaling intermediates [70]. The administration of soluble Klotho (s-Klotho) protein has been evidenced to inhibit TGF-β signaling cascades and provide protective effects against renal fibrosis. More specifically, a peptide derived from Klotho, comprising 30 amino acids and capable of inhibiting TGF-β via receptor interaction, has also demonstrated protective efficacy against renal fibrosis [4].

THE AGING PHOSPHATE AXIS: FGF23-KLOTHO PATHWAY DYNAMICS

Interaction between Klotho and FGF23

The Klotho protein is made up of two domains, KL1 and KL2, each featuring a core structure of an eight-stranded parallel α-barrel surrounded by eight β-helices. These two domains are linked by a rigid, proline-rich segment that includes structural elements such as the N-terminal of the β1 strand., the α7 helix of KL1, β5α5 and β6α6 loops, and the α7 helix of KL2. Additionally, zinc ions play a key role in forming a specific connection between the two domains, which helps stabilize the structure and enhances the function of the Klotho-FGFR co-receptor complex by reducing the flexibility between KL1 and KL2 [71]. The FGFR (fibroblast growth factor receptor) consists of three main parts: an extracellular domain that binds to ligands, a transmembrane helix that spans the cell membrane, and an intracellular region that contains tyrosine kinase activity responsible for initiating signaling inside the cell. The extracellular part of FGFR that binds to ligands is made up of three immunoglobulin-like domains, labeled D1 to D3. Klotho mainly attaches to FGFR through interactions between its KL2 domain and the D3 domain of FGFR [72]. The N-terminal region of FGF23 primarily interacts with the D2 and D3 domains of FGFR, but these interactions are relatively weak. Additionally, the connection between the D2 and D3 domains themselves is not very strong, leading to a naturally low binding affinity between FGF23 and FGFR [71]. Consequently, FGF23 serves as a connector between the D2 and D3 domains of FGFR. Klotho exists in two forms: membrane-bound and soluble. FGF23 primarily interacts with the membrane-bound form, rather than soluble Klotho. This is because soluble klotho consists only of the KL1 and KL2 domains and lacks the transmembrane region and the short intracellular domain. As a result, its ability to bind and support FGF23 signaling is significantly reduced compared to membrane bound Klotho but act as enzyme to affecting ion transport, oxidative stress and aging. Membrane-bound Klotho acting as a non-enzymatic scaffold, binds to both FGF23 and FGFR, positioning them close together and thereby strengthening the interaction between the two [72].

Modulation of phosphate balance in the body

The formation of FGF23-Klotho-FGFR complex is essential for regulating mineral metabolism in the body. It Regulate phosphate homeostasis by lowering the production of vitamin D, decreasing the reabsorption of phosphate by cells, promoting the excretion of phosphate through urine, and ultimately reducing the risk of vascular calcification [57] and this process occur when FGF23 bind to the FGFR1c-α-Klotho complex triggers the activation of the ERK1/2 signaling cascade in kidney cells. This cascade leads to the activation of SGK1 (serum/glucocorticoid-regulated kinase 1), which then phosphorylates NHERF-1 (Na^+/H^+ exchanger regulatory factor-1). Phosphorylated NHERF-1 causes the release of the NaPi2a (sodium-phosphate co-transporter) from the apical membrane of proximal tubular cells as shown in Figure 4. Once released, the NaPi2a transporter is internalized and subsequently degraded within the cell. As a result, the reabsorption of phosphate from the renal tubular fluid is significantly reduced, leading to increased phosphate excretion in urine, a process known as phosphaturia [73].

Homeostatic regulation of vitamin D levels

The FGF23/Klotho (KL) axis plays a key role in controlling the synthesis of 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D]. Activation of this signaling pathway leads to a reduction in circulating 1,25-$(OH)_2$D levels by downregulating Cyp27b1, the gene encoding 1-α-hydroxylase, which is responsible for converting 25-hydroxyvitamin D into its active form. Simultaneously, it upregulates Cyp24a1, which encodes 24-hydroxylase, promoting the breakdown and inactivation of 1,25-$(OH)_2$D. The presence of Klotho in the parathyroid gland appears to affect 1,25-$(OH)_2$D synthesis. Experimental studies in animals have demonstrated that activating the FGF23/Klotho axis in the parathyroid inhibits PTH production at both the transcriptional and secretion levels as shown in Figure 4. Thus, FGF23 may reduce 1,25-$(OH)_2$D synthesis in part by suppressing PTH production, since PTH is known to stimulate the expression of Cyp27b1 the enzyme responsible for activating vitamin D in the kidneys [74].

Klotho dependent and independent effects of FGF23 on cardiovascular system

FGF23 promoted hypertrophy in rat cardiomyocytes by activating the calcineurin-NFAT signaling pathway via FGFRs, independent of Klotho involvement. Klotho is absent in the heart and FGFR-4 is currently recognized as the primary receptor mediating FGF23's

Klotho-independent effects within the heart muscle. In cardiomyocytes, FGF23 specifically activates FGFR-4, which in turn initiates the PLC-γ-calcineurin–NFAT signaling cascade. Therefore, elevated levels of FGF23 in the blood can have harmful effects on the heart muscle through signaling pathways that do not require Klotho [75]. Elevated FGF23 reduces the renal expression of α-Klotho, which may contribute to the development of left ventricular hypertrophy (LVH) by diminishing the cardioprotective effects of circulating soluble Klotho [76]. Patients with advanced chronic kidney disease (CKD) experience elevated phosphate levels due to the kidneys' reduced ability to excrete phosphate effectively. Substantial evidence shows that vascular calcification is strongly linked to increased levels of calcium and phosphate in the bloodstream. Elevated phosphate, in particular, is regarded as a vascular toxin due to its damaging effects on blood vessels [75]. When phosphate levels are high, calcium-mediated mineralization is significantly accelerated. Hyperphosphatemia not only directly damages blood vessels but also promotes the transformation of vascular smooth muscle cells into bone-like cells by activating the type III sodium-dependent phosphate transporter (PiT-1) [75]. Therefore, mice lacking either FGF23 or Klotho exhibit characteristics of accelerated aging along with disrupted phosphate homeostasis [9] as demonstrated in Table I. FGF23 likely begins as a beneficial compensatory hormone to restrain phosphate load in early CKD, but chronic extreme elevations may exert off-target, klotho-independent cardiac effects that contribute to pathology. Until trials demonstrate that modifying FGF23 itself improves outcomes (without worsening phosphate balance), it is most defensible to present FGF23 as both adaptive and potentially maladaptive, depending on degree, duration, and tissue context and to emphasize standardized phosphate management while calling for causal, outcome-focused studies [77].

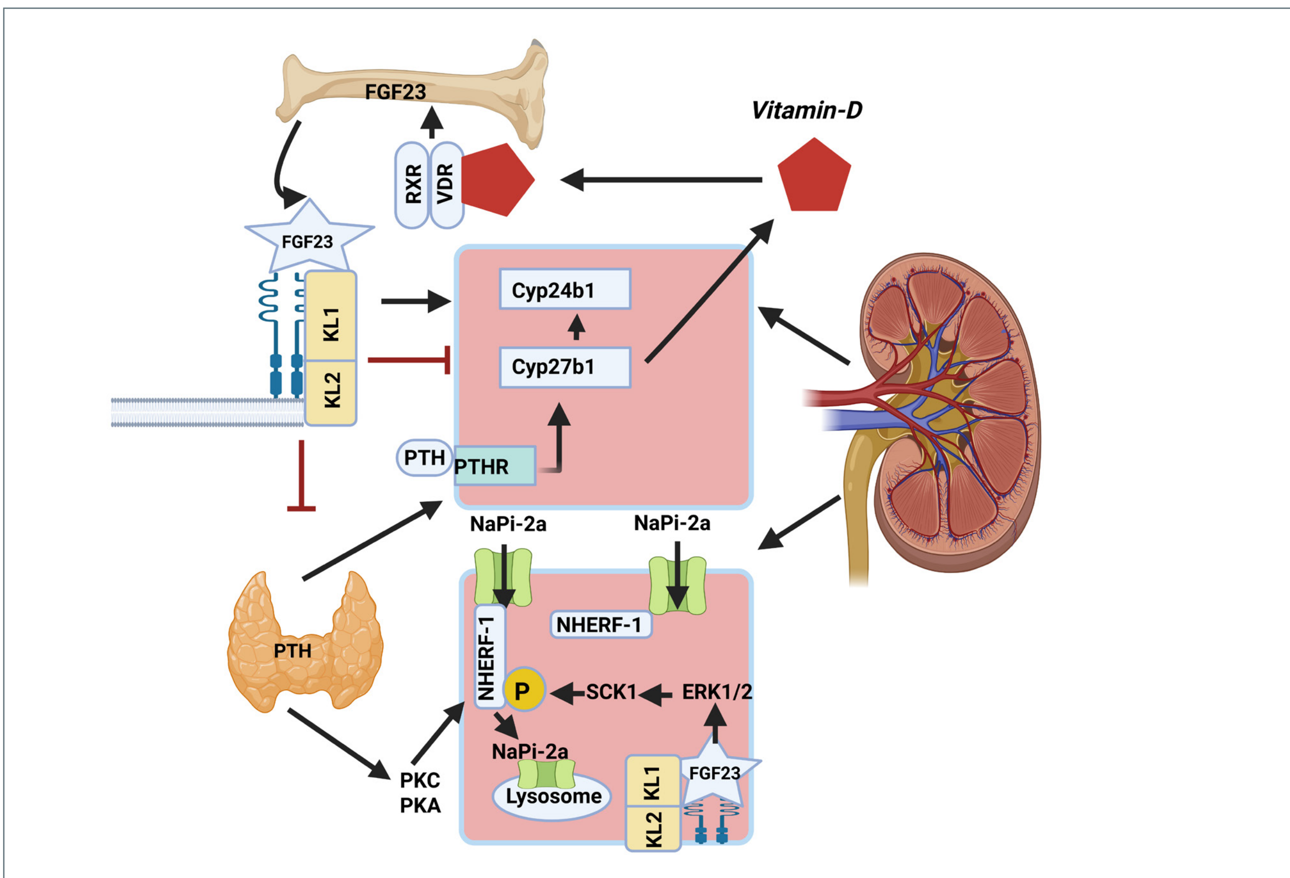

Figure 4.
Klotho-FGF23-PTH-vitamin D axis in phosphate homeostasis. FGF23, via Klotho-FGFR, suppresses renal Cyp27b1 and stimulates Cyp24b1, reducing active vitamin D, while downregulating NaPi-2a transporters. PTH promotes phosphate excretion by NHERF-1 phosphorylation and NaPi-2a internalization.

Table I. Comparison across experimental model.

	FGF23 level	Klotho expression	Phenotype	Signaling	Reference
Wild-type (normal)	Normal	Normal	Normal phosphate and calcium balance; healthy aging	ERK1/2, Wnt inhibition, Nrf2 activation	(6)
Klotho knockout ($KL^{-/-}$)	High	Absent	Hyperphosphatemia, vascular calcification, premature aging	Loss of ERK, Wnt overactivation, NF-κB ↑	(6)
FGF23 knockout ($FGF23^{-/-}$)	Absent	Present	Similar to $KL^{-/-}$: hypervitaminosis D, hyperphosphatemia, calcification	ERK inactivated, excess vitamin D signaling	(86)
Klotho overexpression ($KL^{+/+}$)	Low/normal	High	Extended lifespan, enhanced oxidative stress resistance	Suppressed IGF-1/Akt, activated Nrf2	(87)
CKD model (5/6 nephrectomy)	High	Low	Vascular calcification, cardiac hypertrophy, FGF23 resistance	ERK overactivation (Klotho-independent), Wnt	(88)

THERAPEUTICS APPROACH TO MAINTAIN PHOSPHATE HOMEOSTASIS

Maintaining phosphate balance is a critical strategy for mitigating aging-related pathologies, particularly those linked to Klotho or FGF23 dysregulation. Therapeutic interventions can be broadly classified into dietary, pharmacologic, hormonal, and molecular strategies targeting systemic phosphate levels or their regulatory pathways. Dietary phosphate restriction remains a foundational approach, shown to reverse aging-like features in Klotho- and FGF23-deficient mice even in the presence of elevated vitamin D, highlighting phosphate toxicity as a central driver of premature aging phenotypes [78].

A key molecular target is FGF23, whose excess can lead to hypophosphatemia and associated bone disorders. The monoclonal antibody burosumab has shown efficacy in restoring phosphate levels and improving skeletal outcomes in disorders like XLH and tumor-induced osteomalacia [79]. In contrast, FGFR4 inhibition has been proposed to counteract the deleterious cardiac effects of elevated FGF23 in Klotho-deficient or CKD models [80]. At the upstream level, soluble Klotho supplementation and Klotho-enhancing therapies (e.g., statins, RAS inhibitors, senolytics) aim to restore phosphate excretion and modulate aging-associated pathways including oxidative stress and inflammation. A detailed summary of these interventions, including their mechanisms, evidence, and applications, is presented in Table II.

Barriers to clinical utilization of Klotho-FGF23-based therapies

Despite the growing enthusiasm for the Klotho–FGF23 axis as a target for aging-related interventions, there are significant barriers to clinical application that must be acknowledged. First, assays measuring circulating soluble

Table II. Therapeutic strategies targeting phosphate homeostasis through Klotho-based and FGF23-based mechanisms to alleviate aging-associated phenotypes.

Strategy	Mechanism/approach	Evidence & aging related benefits
Soluble(s)Klotho supplementation	Direct administration of recombinant soluble Klotho enhances phosphate excretion, suppresses TGFβ signaling, and reduces cellular senescence	Mouse study: Intraperitoneal sKlotho (0.02 mg/kg every other day) extended lifespan by ~17%, improved growth, reversed thymic involution, reduced vascular calcification, and boosted urinary phosphate excretion (89)
Klothooverexpression (transgenic)	Genetic upregulation of Klotho acts antiaging via suppression of agingpathway signaling (IGF1, TGFβ, Wnt, NFκB), reducing oxidative stress and fibrosis	Klotho-overexpressing mice lived 20-30% longer, with improved systemic resilience (90)
Dietary phosphate restriction	Lowering dietary phosphate reverses hyperphosphatemia linked to premature aging in Klotho or FGF23-deficient models	In Klotho or FGF23-knockout mice, low-phosphate diets reversed aging-like features despite elevated vitamin D levels (90)
Genetic/pharmacologic suppression of vitamin D signaling or phosphate transport	Disruption of vitamin D activation (e.g., VDR or Cyp27b1 knockout) or NaPi2a transporter reduces phosphate burden	These interventions rescued aged phenotypes in Klotho/FGF23deficient mice by normalizing phosphate, even without affecting vitamin D levels (90)
AntiFGF23 (Burosumab) in FGF23 excess or imbalance	Neutralizes excessive FGF23 to restore phosphate and vitamin D homeostasis – relevant in conditions like XLH – and may indirectly affect aging pathways	While not directly studied in aging, Burosumab effectively corrects hypophosphatemia and improves bone health in XLH models (79) which leads to hypophosphatemia and consequently rickets, osteomalacia, and skeletal deformities. We investigated burosumab, a monoclonal antibody that targets FGF-23, in patients with X-linked hypophosphatemia. METHODS In an open-label, phase 2 trial, we randomly assigned 52 children with X-linked hypophosphatemia, in a 1:1 ratio, to receive subcutaneous burosumab either every 2 weeks or every 4 weeks; the dose was adjusted to achieve a serum phosphorus level at the low end of the normal range. The primary end point was the change from baseline to weeks 40 and 64 in the Thacher rickets severity total score (ranging from 0 to 10, with higher scores indicating greater disease severity)
FGFR4 inhibition in Klotho deficiency	Blocking maladaptive FGF23 signaling via FGFR4 prevents FGF23 – driven cardiac hypertrophy – a common agingrelated cardiovascular issue	In CKD models, FGFR4-blocking antibodies attenuated left ventricular hypertrophy linked to Klotho deficiency (80)
Senolytic therapies (via Klotho restoration)	Clearing senescent cells elevates endogenous Klotho levels, restoring phosphate regulation and potentially mitigating aging effects	In mice and humans, senolytics restored αKlotho in tissues and urine; higher Klotho is linked to delayed aging phenotypes (91)
Lifestyle & pharmacologic Klotho enhancers	Agents like RAS inhibitors (e.g., losartan), statins (fluvastatin), mTOR inhibitors, vitamin D, certain nutraceuticals, exercise, and antidiabetic drugs elevate Klotho levels	Numerous preclinical and clinical findings show that these raise circulating Klotho and offer protective, antiinflammatory, and metabolic benefits (4) as first observed in mice homozygous for a hypomorphic Klotho gene (kl/kl

Klotho (sKlotho) suffer from poor standardization and assay-dependent variability. For instance, a comparative study revealed substantial within-run variability (4-32%) across different commercial ELISA kits, with inconsistent correlations to renal function, whereas time-resolved fluorescence (TRF) or immunoprecipitation–immunoblot (IP-IB) methods displayed superior and more reliable performance though the latter remains labor-intensive and impractical for large-scale studies [81]. Additionally, sKlotho levels may not accurately reflect renal tissue expression [82] and are influenced by sample handling, freeze-thaw cycles, and processing conditions, further undermining their reliability as a biomarker [83]. The interpretation of sKlotho concentrations is confounded by a variety of biological and physiological modulators. These include residual kidney function, systemic inflammatory states particularly those associated with enhanced proteolytic shedding of Klotho, as observed in conditions like diabetes and potential diurnal fluctuations. Such variability undermines the specificity of sKlotho as a reliable biomarker across diverse populations [84]. The bulk of preclinical evidence supporting Klotho or FGF23 as anti-aging targets is derived from knockout mouse models, which display pronounced aging-like phenotypes. However, these models often do not fully recapitulate the multifactorial nature of human aging. For instance, phenotypic severity and lifespan reduction in Klotho-deficient mice vary substantially depending on the genetic background, with certain strains (e.g., C57BL/6) showing attenuated or absent aging features. These discrepancies highlight the importance of genetic context and raise concerns regarding the translational fidelity of such models to human physiology [85].

CONCLUSIONS

The Klotho-FGF23 axis represents a critical regulatory network at the intersection of mineral metabolism, systemic aging, and age-related diseases. As demonstrated by both animal models and emerging human studies, Klotho deficiency contributes to phosphate toxicity, oxidative stress, inflammation, and tissue degeneration hallmarks of aging that are partially reversible through restoration of Klotho signaling. While preclinical findings are compelling, several limitations must be addressed before clinical translation can be realized. Key among these are the variability and lack of standardization in soluble Klotho assays, the absence of longitudinal human studies linking Klotho dynamics to health span, and the limited fidelity of mouse models in capturing human aging complexity. Future research should prioritize the development of reliable, standardized assays for measuring Klotho across different biological compartments and populations. In parallel, longitudinal human studies are needed to validate Klotho as a predictive biomarker for age-related diseases. Finally, innovative therapeutic strategies including gene therapy, small-molecule Klotho enhancers, and combinatorial interventions targeting both Klotho and FGF23 related phosphate metabolism hold promise for extending health span and delaying the onset of aging-related pathologies. Bridging these gaps will be essential to translating the promise of Klotho biology into tangible interventions for human aging.

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