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Journal of Cardiology & Current Research

Emerging Roles of Klotho in Cardiovascular Diseases

Abstract

Klotho is a putative anti-aging gene, which in recent years has emerged as an important factor in the etiologic and cure/prevention of varied pathologies. The expression of this protein in the vascular wall and its role in maintenance of vascular homeostasis indicates its importance in cardiovascular diseases (CVD) such as diabetes, hypertension, vascular calcification, cardiac hypertrophy, atherosclerosis, etc. It seems to be a panacea and as such holds a major influence on future medicine. This review attempts to provide an overview of the part played by Klotho in the various pathologies included in CVD.

Keywords: Diabetes; Hypertension; Preeclampsia; Cardiac hypertrophy

Mini Review

Volume 6 Issue 6 - 2016

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Received: October 22, 2016 | **Published:** October 28, 2016

Introduction

In 1997, mutation of a single gene in Chromosome 13q12 causing extensive aging phenotypes identified a new anti-aging factor. It was named after the Greek Goddess, Klotho, spinner of the thread of life. Genetic mutations in this gene were shown to cause multiple premature aging-like phenotypes and strikingly shorten lifespan. The aging phenotypes included arteriosclerosis, vascular calcifications, soft tissue calcifications, emphysema, hypo-activity, gonadal dysplasia, infertility, skin atrophy, ataxia, hypoglycaemia and severe hyperphosphatemia [1]. While, over expression of the Klotho gene in mice suppressed aging and was shown to extend lifespan via regulation of the insulin and insulin-like growth factor-1 (IGF-1) signalling, which is an evolutionarily conserved mechanism for extending life span [1,2]. The discovery of Klotho has a great impact on aging research.

The human Klotho gene, spanning over 50kb in length, encodes a single pass transmembrane protein *(α-Klotho)* and is expressed primarily in the kidney [3,4], the parathyroid gland [5,6], and the choroid plexus in brain [7]. The protein has a large extracellular amino-terminal domain and a small intracellular carboxy-terminal domain [1]. Circulating α-Klotho results either from direct secretion by the cell or from cleavage of the intracellular domain of the full length protein by secretases [1,8]. This *secreted α-Klothoprotein found in* blood circulation is also referred *to* as a peptide hormone due to its action on target sites other than the site of production [9]. It inhibits the actions of IGF-1 through binding to a specific cell membrane receptor which results in the suppression of tyrosine phosphorylation of the IGF-1 receptor as well as insulin receptor substrates (IRS), leading to disruption of IGF signals. This signalling activity in tissues shows close association with the extended life span and is known to regulate various metabolic processes [2]. It also influences other growth factor signalling pathways including p53/p21, cAMP, protein kinase C (PKC) and Wnt, [10-13]. Itacts as a sialidase that modifies glycans on the cell surface which may explain the ability of secreted Klotho protein to regulate activity of multiple ion channels [13]. It protects against endothelial dysfunction and regulates the production of nitric oxide. It inhibits the phosphorylation of transcription factors forkhead box O (FOXO) which then increase the expression of antioxidant enzymes, thereby protecting against oxidative stress [13,14]. The transmembrane form of α-Klotho protein, mainly expressed in kidney distal convoluted tubule*, is* widely studied. *It* functions as an obligatory co-receptor for a bone derived phosphaturic hormone, Fibroblast Growth Factor-23 (FGF-23). FGF-23 requires Klotho for its signalling: The Klotho protein binds to multiple FGF receptors and increases their affinity for FGF-23 and helps in excreting phosphorus from kidney [15]. Thus, α-Klotho regulates phosphate and vitamin D metabolism through FGF-23. The *Klotho gene* reportedly encodes two other Klotho proteins, β-Klotho and Klotho-related protein *(*Klrp). Klrp *is a transmembrane protein that binds to FGF receptor (FGFR)-1b, FGFR-1c and FGFR-2c but its function is unknown* [16-18]. *β-Klotho* is not found in secreted form and is predominantly expressed in liver and adipose tissue*. Its* main function involves metabolic regulation, glucose uptake, bile acid synthesis and fatty acid metabolism, independent of *β-Klotho* [9,17].

The α-Klotho gene is highly conserved in humans, mice, rats and Danio rerio and Caenorhabditis elegans [9]. Mouse Klotho cDNA shows 80% and Klotho protein shows 86% homology with that of human [19]. Klotho knock out mouse model (*kl-/-*) represents human progeroid syndrome and exhibits various phenotypes of aging in a wide range of organs including arteriosclerosis, neural degeneration, skin and gonadal atrophy, pulmonary emphysema, calcification of soft tissues, and cognition impairment [1,2]. Studies in this mouse model are expected to provide new insights into human aging as well as in diseases associated with aging. α-Klotho is involved in the protection of vasculature through various mechanisms, including prevention of endothelial dysfunction, anti-inflammatory effects, and reduction of vascular calcification or attenuation of cardiac hypertrophy [20]. On the other hand, it has also been demonstrated that Klotho mRNA is down regulated under sustained cardiovascular or metabolic stress, such as hypertension, diabetes mellitus, and hyperlipidemia [3]. This review attempts to provide an overview of the part played by Klotho in cardiovascular diseases (CVD) (Table 1).

Table 1: Klotho in CVD.

No	Study	Findings
1	Utsugi et al. [21]	Deceased insulin production in pancreas and increased insulin sensitivity in Klotho deficient mice
2	Zhao et al. [22], Kacso et al. [23]	Decreased serum α-Klotho levels in diabetic nephropathy
3	Wu et al. [24]	Decreased serum α-Klotho levels T2DM
4	Leahy [25]	β-cell failure occurs from early phase in T2DM
5	Lin and Sun [26]	Klotho gene and protein expressed in pancreatic islets
6	Lin and Sun [27]	β cell–specific expression preserved β-cell function
Klotho in Hypertension		
1	Su and Yang [31]	Systolic or elderly hypertension due to reduction in serum Klotho levels
2	Xiaoli et al. [32]	In mutant Klotho mice persistent elevation of SBP
3	Saito et al. [33]	Klotho gene deliveryin animal model of atherosclerotic disease reduced elevated BP and prevented medial hypertrophy
4	Wang and Sun et al. [34]	Klotho gene delivery in spontaneous hypertensive rats stopped further increase in BP
Klotho in Preeclampsia		
1	Cecati et al.[38] & Guannubilo et al. [39]	Significantly (80-83%) lower expression levels of placental Klotho
2	Loichinger et al [40]	AVM with reduced levels of α-Klotho
Klotho in Other CVD related Cardiac Pathologies:		
1	Semba et al. [41]	Higher plasma Klotho with lower likelihood of developing CVD
2	Navarro-González et al. [42]	Lower mRNA and soluble Klotho in vascular wall with CAD
3	Xie et al. [43]	Klotho deficient mice with atherosclerotic pathologies
		Over expression ameliorated cardiac pathologies

Discussion

Klotho in Diabetes

Physiologically, pancreatic β-cells constantly synthesize insulin, which is stored within vacuoles and released once triggered by an elevation in blood glucose level. Utsugi et al. [21] have demonstrated that Klotho mutant mice have deceased insulin production in the pancreas and increased insulin sensitivity. However they could not elucidate the precise mechanism involving Klotho. Subsequent studies by Zhao et al. [22], Kacso et al. [23] and Wu et al. [24] Have reported decreased serum α-Klotho levels in diabetic nephropathy and Type 2 Diabetes Mellitus (T2DM) respectively. T2DM is now recognized not only owing to insulin resistance, but also due to β-cell failure from early phase [25]. Thus, apart from the normal glucose control, one of the goals in the treatment of T2DM is to preserve functional β-cells in pancreatic islets. Lin and Sun in their study [26] have demonstrated that Klotho gene and protein are expressed in pancreatic islets. In their subsequent study[27], they further established that β cell–specific expression of Klotho decreased hyperglycemia, enhanced glucose tolerance, preserved β-cell function and protected against the development of T2DM in murine model of T2DM (*db/db*). In addition, β-cell-specific expression of Klotho decreased intracellular superoxide levels, oxidative damage, apoptosis, and DNAJC3 (a marker for endoplasmic reticulum stress) in pancreatic islets, increased expression levels of Pdx-1 (insulin transcription factor), PCNA (a marker of cell proliferation), and LC3 (a marker of autophagy) in pancreatic islets in *db/db* mice. Thus, these results reveal that β-cell-specific expression of Klotho improves β-cell function and attenuates the development of T2DM by suppressing oxidative stress, endoplasmic reticulum stress, apoptosis; increasing cell proliferation and normalizing autophagy in pancreatic islets. Therefore, in vivo expression of Klotho in pancreatic β-cells may offer a new and effective therapeutic strategy for overcoming β-cell dysfunction in T2DM and warrants further mechanistic investigation into the therapeutic role of Klotho in protecting β-cell function. However, Lin and Sun further documented that β-cell–specific expression of Klotho attenuates but does not

prevent the development of T2DM [27]. Therefore, simultaneous management of hyperglycemia and insulin resistance is also important for the protection of β-cells in T2DM.

Klotho Hypertension

Blood pressure usually refers to the arterial pressure in systemic circulation which when elevated leads to Hypertension. The pathophysiology associated with hypertension involves mechanical stretch on the vascular wall, increased systemic vascular resistance, increased vascular stiffness, activation of the renin-angiotensin system (RAS) responsible for increased Angiotensin II, which further activates NADPH/NADH oxidase of the vascular smooth muscle cells, resulting in release of Reactive Oxygen Species (ROS), which in turn trap Nitric Oxide (NO), an endothelium-derived relaxing factor [28,29].

It is well known that with increase in age, systolic blood pressure (SBP) increases [30] and recent findings demonstrate decrease in α-Klotho protein with age [13]. Su & Yang [31] have demonstrated that Systolic or elderly hypertension may be partially attributed to reduction in serum Klotho levels. In mutant Klotho mice, Xiaoli et al. [32] showed that, Klotho is essential for the maintenance of normal BP and its deficiency caused significant and persistent elevation of SBP. Saito et al. [33] observed that in Otsuka Long-Evans Tokushima Fatty (OLETF) rat, animal model of atherosclerotic disease, adenovirus-mediated Klotho gene delivery ameliorated vascular endothelial dysfunction, increased nitric oxide production, reduced elevated blood pressure, prevented medial hypertrophy and perivascular fibrosis. In a similar study by Wang & Sun [34], Klotho gene delivery via an adeno-associated virus (AAV) in spontaneous hypertensive rats stopped further increase in BP but did not decrease the BP levels to that of controls. Additionally, Klotho gene delivery resulted in prolonged up-regulation of Klotho gene expression. Thus, AAV delivery of Klotho may be a new approach for long term control of hypertension.

Klotho in Preeclampsia

Preeclampsia is the most common pregnancy hypertensive disorder characterized by a peripheral vasoconstriction and decreased arterial compliance that induce various clinical manifestations including failure of several maternal organs as liver, kidney and brain which complicates about 5–7% of pregnancies, depending on the populations studied [35]. Preeclampsia and cardiovascular disease share many risk factors, including endothelial dysfunction, obesity, hyperglycemia, insulin resistance, diabetes mellitus, hypertension, and dyslipidemia. Women who develop preeclampsia are exposed to an increased risk of coronary heart disease, stroke, and cardiovascular disease in general [36]. The relative risk of future cardiovascular events after a pregnancy complicated by preeclampsia has been reported varying from 1.3 to 3.3, with a range of 2.7–8.1 in more severe preeclampsia states [37].

To date, for preeclampsia, there are no reliable predictors, specific preventive measures, or treatments other than delivery. Klotho may be involved in the pathogenesis of preeclampsia. Cecati et al. [39] & Guannubilo et al. [39] found that the expression levels of placental Klotho were significantly (80-83%) lower in preeclampsia group as compared with controls. Prolonged oxidative damage in the placenta gives rise to characteristic placental histology, defined as accelerated villous maturation (AVM) which within the preeclampsia group, were associated with reduced levels of α-Klotho [40]. Thus, α-Klotho is a potentially important protein in preeclampsia.

Klotho in Other CVD related Cardiac Pathologies

Coronary artery disease (CAD) and its clinical manifestations including vascular stiffening, peripheral arterial disease, left ventricular hypertrophy and myocardial infarction are further complications of CVD [20]. The disruption in the homeostasis of Klotho seems to be a key element in the development of these diseases. Semba et al. [41] found that individuals with higher plasma Klotho concentrations were independently associated with lower likelihood of developing CVD. Correspondingly, lower concentrations of soluble Klotho as well as reduced mRNA expression of Klotho in vascular wall were associated independently of established CVD risk factors in CAD patients as reported by Navarro-González et al. [42]. Xie et al. [43] showed that Klotho deficient mice developed an exaggerated pathological cardiac hypertrophy and remodelling in response to stress. They further demonstrated that, Klotho over expression ameliorated cardiac pathologies in these mice and improved their long-term survival. The cardiac protection bestowed by Klotho was via down-regulation of TRPC6 channels which are Ca^{2+}- permeable cations channels expressed in the cardiac membrane, which function as an important modulator of cardiac hypertrophy and are responsible for aberrant cardiac development and premature death. The central role of Klotho in the pathogenesis of CVD makes its use possible as a diagnostic biomarker or as a therapeutic factor for treatment of vascular diseases. However, further studies are needed to clarify the relationship between this factor and promotion of vascular health [20].

Conclusion

Since its discovery, Klotho has been hailed as the novel anti-aging gene. There are strong evidences suggesting an important role for Klotho in the etiology of CVD and its clinical manifestations such as diabetes, hypertension, cardiac hypertrophy etc. Various *in-vitro* and animal studies have demonstrated that Klotho over expression ameliorates cardiac pathologies and ensures vascular health. Though its mechanism of action remains elusive, research conducted worldwide postulates that Klotho may be the elixir that mankind has been in search of. Identifying the specific pathways linking to its known actions or novel functions will enhance our understanding of the exact role of this anti-aging protein.

Acknowledgement

Sir H. N. Medical Research Society for financial help in initiating Klotho related projects.

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Citation: Pathare G, Shah VK, Shalia K (2016) Emerging Roles of Klotho in Cardiovascular Diseases. J Cardiol Curr Res 6(6): 00228.
DOI: 10.15406/jccr.2016.06.00228

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Citation: Pathare G, Shah VK, Shalia K (2016) Emerging Roles of Klotho in Cardiovascular Diseases. J Cardiol Curr Res 6(6): 00228.
DOI: 10.15406/jccr.2016.06.00228