Bone xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

Potential application of klotho in human chronic kidney disease

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ARTICLE INFO

Article history:
Received 1 June 2016
Revised 18 January 2017
Accepted 18 January 2017
Available online xxxx

Keywords:
AKI
CKD
Klotho
Phosphate
Uremic cardiomyopathy
Vascular calcification
Vitamin D

ABSTRACT

The extracellular domain of transmembrane alpha-Klotho (αKlotho, hereinafter simply called Klotho) is cleaved by secretases and released into the circulation as soluble Klotho. Soluble Klotho in the circulation starts to decline early in chronic kidney disease (CKD) stage 2 and urinary Klotho possibly even earlier in CKD stage 1. Therefore soluble Klotho could serve as an early and sensitive marker of kidney function decline. Moreover, preclinical animal data support Klotho deficiency is not just merely a biomarker, but a pathogenic factor for CKD progression and extrarenal CKD complications including cardiovascular disease and disturbed mineral metabolism. Prevention of Klotho decline, re-activation of endogenous Klotho production or supplementation of exogenous Klotho are all associated with attenuation of renal fibrosis, retardation of CKD progression, improvement of mineral metabolism, amelioration of cardiomyopathy, and alleviation of vascular calcification in CKD. Therefore Klotho is not only a diagnostic and/or prognostic marker for CKD, but the treatment of Klotho deficiency may be a promising strategy to prevent, retard, and decrease the burden of comorbidity in CKD.

Contents

1. Introduction

The *Klotho* gene was discovered in 1997 when mice with serendipitous silencing of this gene developed multiple organ dysfunction and failure with shortened life span [1]. Subsequently, two other paralogs βKlotho [2] and γKlotho [3] were identified, then Klotho was designated αKlotho [4]. For the sake of simplicity, αKlotho is referred hereinafter as Klotho throughout this manuscript.

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http://dx.doi.org/10.1016/j.bone.2017.01.017
8756-3282/

Klotho is highly expressed in the kidney, brain and to a lesser extent in other organs including parathyroid [1,5]. The extracellular domain of membrane Klotho consisting of two repeat sequences (Kl1 and Kl2) can be shed by secretases and released into the circulation as cleaved Klotho [6–9] (Fig. 1). Another form of Klotho protein in the circulation is Kl1 fragment which is generated by alternative transcript splicing called secreted Klotho (Fig. 1) [1,10–12]. In concert with cleaved Klotho, these are collectively termed soluble Klotho. But in this review, soluble Klotho is only strictly used for cleaved full length of extracellular domain of membrane Klotho. Soluble Klotho is a main functional form in the circulation [6,13–16] and is also present in cerebrospinal fluid [17] [16,18–21] and urine of mammals [15,22–24]. At physiologic condition, the kidney is a major contributor to maintaining soluble Klotho levels [6,25], but other organs may participate in maintaining soluble Klotho in chronic kidney disease (CKD) and end-stage renal disease (ESRD) [23]. Soluble Klotho functions as a circulating substance exerting multiple biological actions on distant organs [26–31].

CKD is characterized by progressive deterioration of renal function with high risk of ESRD. CKD risk increases with age, and about half of the CKD stage ≥ 3 cases occurs in subjects > 70 years old. CKD can be viewed as a state of accelerated aging [32,33]. The relative risk for cardiovascular mortality of a 25 to 34-year-old dialysis patient is similar to a non-CKD patient of >75 years of age [34]. Cardiovascular disease is the principal killer in CKD and ESRD patients. The fact that Klotho-deficient mice and CKD subjects have similar phenotypes also suggests a potential pathogenic role of Klotho deficiency in CKD development and progression [4,24,35–37].

Since the kidney is the main origin for circulating Klotho [6,25] [38,39], it is not surprising that CKD and ESRD patients have low renal Klotho expression and low levels of circulating Klotho. Renal Klotho deficiency in early stages of CKD may be attributed mainly to suppression of Klotho expression rather than loss of viable renal tubules. Several intermediates are shown to be involved in the reduction of Klotho expression: high serum phosphate [40], hypermethylation [41–45] and hyper-deacetylation [46] in Klotho gene promoter induced by inflammatory cytokines and the uremic toxin, indoxyl sulfate (Fig. 2). Furthermore, dialysis patients still have detectable circulating Klotho suggesting that renal Klotho expression is not completely suppressed, and Klotho may come from extra-renal source(s), although its origin is not clear to date (Fig. 1) [23]. Establishing extra-renal sources of Klotho and characterizing how this can be up-regulated when renal production fails is of paramount importance.

Klotho deficiency is not only an early biomarker of CKD (to be discussed in detail below), but also a pathogenic intermediate for CKD development and progression (Fig. 2), and extrarenal complications [24,47,48]. It has been shown that Klotho deficiency is associated with stem cell dysfunction and depletion which is part of normal aging [49]. Furthermore, Klotho deficiency in CKD could enhance renal tubular and vascular cell senescence induced by oxidative stress, uremic toxins such as indoxyl sulfate, and high phosphate (Fig. 2) [50–57]. In addition, Klotho deficiency promotes renal fibrosis in several kidney disease models [58–60]. Klotho deficiency also results in defective endothelial function and impaired vasculogenesis [61], and Klotho protein protects vascular endothelium by inhibition of endothelial inflammation [62]. Klotho deficiency directly and indirectly contributes to uremic cardiomyopathy which can be prevented or attenuated by supplementation of soluble Klotho [47,48,63,64]. Therefore, soluble Klotho protein may be a novel therapeutic agent for CKD patients. We will first discuss the recent literatures about Klotho deficiency as a biomarker for CKD and its role in CKD-mineral and bone disorder (MBD) development, then

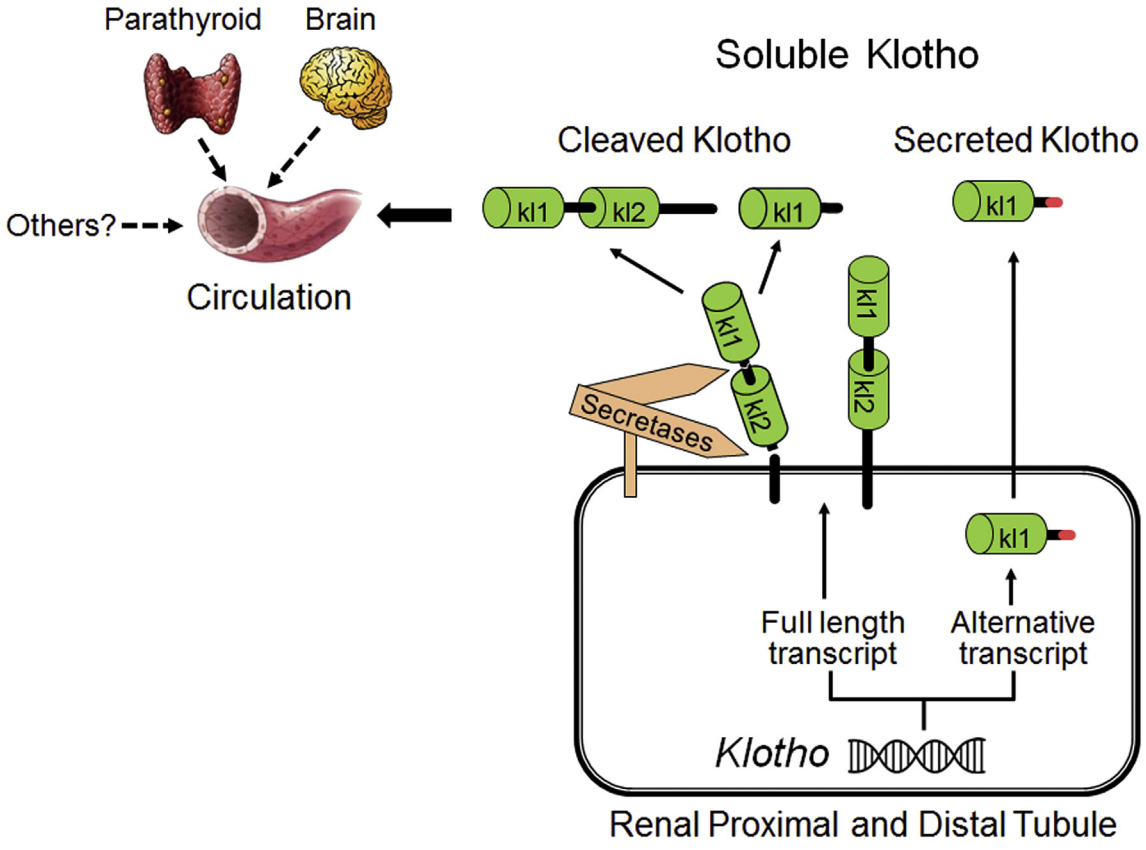

Fig. 1. Source of soluble Klotho. The kidney is the main source of circulating Klotho under physiological conditions. Both renal proximal and distal tubules express membrane Klotho protein and may also produce a secreted Klotho protein through alternative splicing. The secreted Klotho only contains Kl1 domain and is directly secreted into the blood circulation. But its biologic function is not clear yet. Extracellular domain of membrane Klotho containing Kl1 and Kl2 repeats is shed and cleaved by secretases into either full extracellular domain or Kl1 repeat. Both cleaved Klotho fragments are present in the circulation. A few extra-renal organs including parathyroid gland and brain express Klotho protein as well, but their contribution to circulating Klotho in CKD/ESRD (dash line) remains to be confirmed.

Please cite this article as: J.A. Neyra, M.C. Hu, Potential application of klotho in human chronic kidney disease, Bone (2017), http://dx.doi.org/10.1016/j.bone.2017.01.017