Klotho Improves Renal Function in Autosomal Dominant Tubulo-Interstitial Kidney Disease (ADTKD-UMOD)

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Abstract
Klotho is a transmembrane protein highly expressed in the DCT and alleviates different forms of nephropathies. Klotho overexpression reduces interstitial fibrosis and tubular atrophy in mouse models. Does Klotho overexpression alleviate the progression of ADTKD-UMOD?

Introduction

ADTKD is the second most common genetic cause for end-stage renal disease (ESRD) (Gest C et al, BMC Nephrol 19: 31, 2018).

ADTKD is characterized by ESRD at the age of 40-50 years, hyperuricemia, gout, urinary concentration defect, and salt wasting.

This condition was previously also known as medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy, or gomlinicystic kidney disease (Ramakrishna L et al, Hum Mol Genet 12:3389, 2003).

Klotho is a transmembrane protein highly expressed in the distal convoluted tubule and functions as an anti-aging hormone.

Klotho functions as a co-receptor with FGF15 and reduces tubular phosphate absorption.

Klotho regulates different signaling pathways (e.g. insulin/IGF1, Wnt, TGF)

Klothos interferes with apoptosis, fibrosis, senescence, and stimulates autophagy.

Klotho is known to improve acute kidney injury, hypertension, chronic kidney disease, vascular calcification, proteinuria, glomerulopathy, and is also downregulated in renal fibrosis and better renal outcome in mice.

Results
Does Klotho overexpression decrease body weight in Umod−/− mice?

At 6 and 13 months TgKl/Umod mice had mildly higher body weight compared to Umod−/− mice. TgKl/Umod mice had lower weight than WT or TgKl mice. Klotho overexpression did not increase body weight of Umod−/− mice.

Does Klotho overexpression affect renal function and progression of kidney disease in Umod−/− mice?

At 6 and 13 months TgKl/Umod−/− mice had significantly lower BUN, creatinine, and cystatin C values compared to Umod−/− mice.

BUN, creatinine, and cystatin C were between 15-30% lower in the TgKl/Umod−/− group.

At 6 and 13 months TgKl/Umod−/− mice had significantly lower PTH values compared to Umod−/− mice.

At 13 months TgKl/Umod−/− mice had significantly lower FGF23 values compared to Umod−/− mice.

PTH and FGF23 were approximately 45% lower in the TgKl/Umod−/− group.

Consistent with cellular hypertrophy but not heart/body weight or heart weight/tibia ratio.

No effect of Klotho overexpression was seen on heart rate (Fig. 5C).

Umod−/− mice had significantly lower FGF23 values.

Umod−/− mice have approximately 40% lower in weight than WT or TgKl mice.

Urinary UMOD secretion was tested.

Klotho overexpression reduces interstitial fibrosis and tubular atrophy (W&T/AKI) compared to Umod−/− mice.

Urinary UMOD secretion was decreased in TgKl/Umod−/− mice compared to Umod−/− mice.

Klotho overexpression improves systolic and diastolic blood pressure and mRNA expression of genes involved in cardiac hypertrophy but not heart/body weight or heart weight/tibia ratio.

What is the mechanism that Klotho overexpression improves ADTKD-UMOD?

1) Applying an unbiased proteomics approach we identified downregulation of multiple proteins in TgKl/Umod−/− mice compared to Umod−/− mice.

2) Other downregulated proteins in TgKl/Umod−/− mice included interaction partners and modifiers of collagens such as transmembrane activator and STIMulator 1 and beta-induced protein (TGFβI).

3) We also confirmed downregulation of transforming growth factor-beta-induced protein (TGFβI) mRNA expression in TgKl/Umod−/− mice compared to Umod−/− mice.

4) Expression of mRNA biomarkers for cardiac hypertrophy (Nephran ANPI), (P), (Nephr Anpi BNP), (FGF23), (Mianin heavy chain 7) (H), were significantly downregulated in TgKl/Umod−/− compared to Umod−/− mice.

5) Applying qPCR we confirmed downregulation of Collagen 1, Collagen 12, and Collagen 14 mRNA expression in TgKl/Umod−/− mice compared to Umod−/− mice.

6) In contrast to TGFβI, TGFβI mRNA expression was not significantly downregulated in TgKl/Umod−/− mice.

Summary
1) Klotho overexpression improves progression of chronic kidney disease in TgKl/Umod−/− mice with improved creatinine, BUN, cystatin C, PTH, and FGF23 values.

2) Klotho overexpression reduces interstitial fibrosis and tubular atrophy in TgKl/Umod−/− mice.

3) Klotho overexpression increases urinary UMOD secretion.

4) Systolic and diastolic blood pressures are improved in TgKl/Umod−/− mice at 6 and 13 months.

5) Expression of proteins involved in cardiac hypertrophy such as ANP, BNP, and MYH1 are lower in TgKl/Umod−/− mice compared to Umod−/− mice.

6) An unbiased proteomics approach shows that TgKl/Umod−/− mice have a lower protein expression of multiple collagens and TGFβI but not TGFβI.

7) The lower TGFβI and collagen expression may explain the lower degree of renal fibrosis and better renal outcome in TgKl/Umod−/− mice.

Funded by NIADDK R41DK119631 and Children’s Clinical Research Advisory Committee (CORAC), Children’s Medical Center, Dallas.