Klotho: Unclothing the mysteries in chronic kidney disease

Sir,

Chronic kidney disease (CKD) is the most potent accelerator of vascular senescence that amplifies the risk for cardiovascular diseases. The expression of Klotho (a single-pass transmembrane protein of 135 kDa belonging to family 1 glycosidase) in renal tubular epithelial cells is documented to be decreased in CKD. Named after a Greek goddess spinning the thread of life, Klotho was linked initially to premature aging syndrome and later to shortened life span, growth retardation, hypogonadism, accelerated thymic involution, skin atrophy, muscle atrophy, vascular calcification, osteopenia, pulmonary emphysema, cognition impairment, hearing loss, and motor neuron degeneration.[1] The secretory Klotho, a circulating factor produced by extracellular domain shedding, binds to the type II transforming growth factor-beta (TGF-β) receptor and inhibits TGF-β1 signaling. Klotho has shown to suppress TGF-β1-induced epithelial-to-mesenchymal transition (EMT) response. There was also a decrease in epithelial marker expression, increase in mesenchymal marker expression, and/or increase in cell migration. Inhibition of Wnt gene and Insulin like growth factor (IGF)-1 signaling is also hypothesized to contribute to the promotion of EMT.[2]

Deficiency of the protein fibroblast growth factor (FGF) 23 has shown multiple aging-like phenotypes (such as hyperphosphatemia, hypercalcemia, and hypervitaminosis D) similar to those due to a dysfunctional Klotho. Experimental studies showed that Klotho operates as an obligatory coreceptor for FGF23 and significantly increases the affinity of FGF23 to the FGF receptors. Various observations such as Klotho defects leading to extremely high serum FGF23 levels and Klotho deficiency phenotypes being identical to FGF23 deficiency reiterate the indispensable nature of Klotho's association with FGF23. Also, Klotho has a kidney-specific expression that enumerates the specificity of FGF23 to kidney as its target organ among many other tissues expressing multiple FGF receptor isoforms. The resistance to FGF23, probably mediated by Klotho suppression, might result in the increase of serum FGF23 levels before serum phosphate during the progression of CKD.

When reduction in renal expression of Klotho was induced, promotion of cell senescence with expression of senescence-related proteins, such as p16INK4a, p21WAF1/CIP1, p53, and retinoblastoma protein, was noticed, ultimately accompanied by renal fibrosis.[3] A graded reduction in urinary Klotho has been noted, starting at an early stage of CKD that progressed with a loss of renal function; conversely, overexpression of Klotho has been shown to alleviate progressive renal injury in glomerulonephritis and acute kidney injury. The severity of vascular calcification also correlated with the Klotho deficiency. Klotho suppressed the Na^+-dependent uptake of phosphate and mineralization induced by high phosphate and preserved the differentiation in vascular smooth muscle cells. The benefits of Klotho on vascular calcification could be from the direct effect on the vascular wall[4] rather than its renoprotective effects such as preserving glomerular filtration and enhancing phosphaturia.

Reduced insulin/IGF-1 signaling and activation of Forkhead box O and increased expression of manganese superoxide dismutase are also postulated to explain the inherent resistance to oxidative stress that Klotho transgenics sport.[5]

Apart from being an early biomarker for CKD, Klotho, along with FGF23, is an important part of the bone–kidney–parathyroid endocrine axis that new therapeutic interventions need to target in the future.

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Website: http://www.cysonline.org	Quick Response Code
DOI: 10.4103/2229-5186.90898	