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Klotho in Kidney Transplantation: A New and Important Target?

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Commentary

On July 10th, 2019, the presidential Executive Order on Advancing American Kidney Health (AAKH) catalyzed a radical reconfiguration in the delivery of care for patients with kidney disease.[1] This historic initiative establishes the first national strategy for addressing a specific disease state, elevating kidney for transplant by 2030.[2] The superiority of kidney transplantation over dialysis as the optimal renal replacement modality is well established. Kidney transplantation is associated with improved quality of life, cardiovascular morbidity and survival.[3] Despite this, unfortunately ~20% of procured kidneys are currently not utilized for transplant and this is exceedingly worrying given the already long wait-list for available organs. The availability of organs has therefore been a critical obstacle to transplant procedures. Therefore, strategies to fill the growing gap between demand and supply for kidney transplants has led to a growing interest in the use of expanded criteria donor (ECD) kidneys to increase the donor pool. This involves utilizing donor organs that previously would not have been considered at higher risk, involving donors who are older and requiring tailored immunosuppressive regimens. Because of the rising demand for kidneys and increased risk of poor graft function with ECDs, there has therefore been a greater need for novel pharmacologic strategies to reduce the risk of allograft rejection, complications associated with immunosuppression and to optimize medical management. Additionally, the use of aging kidneys increases susceptibility to acute kidney injury (AKI) and reduces tissue regenerative capability. Therefore, new strategies such as the potential for a novel α-Klotho-based therapeutic to improve renal allograft outcomes with the use of aging kidneys from ECDs is therefore a current research priority.

The identification of α-Klotho (herein, called Klotho), a remarkable protein that confers powerful anti-aging properties is of particular relevance in patients undergoing kidney transplantation. Total Klotho protein levels decline in serum as kidney dysfunction ensues and with advancing age.[4] Moreover, Klotho deficiency has now been linked with a variety of important clinical outcomes, including increased risk of cardiovascular disease, progression of AKI and Chronic Kidney Disease (CKD) and more recently, allograft

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KL drafted the manuscript. All other authors read the manuscript and provided important intellectual guidance.

function after kidney transplantation.[5,6] Significantly, Klotho knockout mice develop a premature aging phenotype that resemble patients with CKD and exhibit shortened life span.[7] However, restoration of Klotho in Klotho-deficient mice ameliorated these changes and these mice live 30% longer than wild-type.[7–9] These striking discoveries have therefore provided fundamental rationale for the development of potential Klotho-based therapeutic interventions that could target the kidneys. Furthermore, with the increasing acceptance of aging kidneys from ECDs, the anti-aging properties of Klotho is of particular interest and suggests that aging of the kidneys is an active, tightly regulated cell-mediated process that could be potentially modifiable.

In this issue of Transplantation, Donate-Correa, et al. present a comprehensive review of our current understanding of Klotho in kidney transplantation. The article highlights important variations in serum Klotho levels in kidney transplant recipients. Circulating Klotho levels are generally low in the short-term postoperatively and exhibit gradual restoration over time with improving allograft function, though only partially recovering to levels observed in healthy controls (see table 3 in Donate-Correa, et al).[10] These findings are reflective of the kidneys being the major source of endocrine Klotho and suggests that therapeutic administration of Klotho may be needed to restore physiologic levels. Although circulating Klotho levels decline with progressive reductions of estimated glomerular filtration rate (eGFR), emerging data suggests that several other factors could potentially modulate Klotho levels in the post-transplant population, these include age of donor organ, cold ischemia time and the selection of immunosuppressive protocols.[10] Significantly, there is evidence that the calcineurin inhibitors (CNIs), Cyclosporin suppress renal Klotho expression while mammalian target of rapamycin (mTOR) inhibitors could upregulate its expression. The use of renal-protective medications such as angiotensin converting enzyme (ACE) inhibitors and vitamin D agonists could potentially counteract Klotho deficiency.[10] Given that reversible Klotho deficiency has been observed in donor kidneys with ischemic reperfusion injury and kidneys with delayed graft function, these results suggests that the assessment of Klotho may also have prognostic value. Moreover, a growing body of literature has now demonstrated that soluble Klotho administration in preclinical models of AKI and CKD exert therapeutic effects.[5,11] Taken together, these data provide strong rationale for experimental studies exploring the therapeutic benefits of exogenous Klotho supplementation following kidney transplantation.

Despite these promising biological discoveries, we must first overcome several substantial challenges and knowledge gaps before Klotho could be translated into a potential therapy for the kidney transplant community (table 1). Firstly, the Klotho field is hampered by methodologic challenges including the lack of a reliable Klotho assay, in fact studies have shown a striking 1000-fold difference between various commercially based assays.[5] Secondly, the natural history of circulating Klotho, its tissue expression, their alterations perioperatively, post-transplantation, in response to graft function, immunosuppressant regimens and their clinical relevance is still largely undefined. Additionally, Klotho exists in several different isoforms and the precise functional role of the various isoforms in health and disease, as well as their mechanisms of actions and the identity of the Klotho receptor still remain elusive.[5] Moreover, full-length Klotho is a very large globular pleiotropic protein and therefore the identification of the precise active site of Klotho that harness therapeutic

effects at the kidney would be critical from a drug development perspective. Additionally, given the well-established role of Klotho as a co-receptor for fibroblast growth factor (FGF)-23, identifying the fragment of Klotho that could exert FGF23 independent renal protective effects could help reduce off-target effects.

In summary, the central thesis of this commentary is that accumulating evidence now provides fundamental rationale that Klotho could have therapeutic and prognostic relevance in kidney transplantation. The growing burden for organ transplantation calls for significant concerted strategies to help overcome current challenges in Klotho research with balanced optimism. Additionally, many patients that are not currently wait-listed would likely pursue and benefit from transplantation if it were more readily available.[2] Novel therapeutics such as a Klotho-based therapeutic that harness anti-aging properties could potentially help transform the use of aging kidneys that would not have otherwise been considered for transplantation. In order to achieve the high targets laid out by the AAKH, greater collaborative efforts and research funding is needed to stimulate research advancement of potentially promising new targets such as Klotho.

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Table 1:

Challenges to translating Klotho into a therapy

Challenges	Description
Methodologic challenges	• Large variations between commercially available Klotho assays. • No current commercial assay that can distinguish between various Klotho isoforms.
Critical knowledge gaps	• Identify of Klotho receptor(s) is still unclear. • The role of various Klotho isoforms is largely unknown. • Natural history of endogenous and circulating Klotho and its isoforms in health, disease and after transplantation is still largely undefined.
Therapeutic administration	• Klotho is a large globular protein, potentially unstable which poses challenges with administration. • ;Klotho has a large volume of distribution (Vd). • Pleiotropic properties may lead to off-target effects.