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Klotho and endocrine FGFs: More than markers of CKD progression and cardiovascular complications

Klotho, the Greek goddess who spins the thread of life, has become popular among nephrologists, because the genes named after her encode receptors for hormones that play critical roles in the pathophysiology of chronic kidney disease (CKD). Namely, αKlotho and βKlotho function as receptors for two hormones, fibroblast growth factor-23 (FGF23) and FGF21, respectively. As Professor Makoto Kuro-o points out in his freshly published review in Nephrology, Dialysis, Transplantation (NDT), nephrologists may be able to develop new strategies for the diagnosis and treatment of chronic kidney disease (CKD) and its cardiovascular complications by viewing CKD progression as a process of adaptation and failure of the FGF-Klotho endocrine axes.

FGF23 is secreted from osteocytes in response to excess phosphate intake. When FGF23 binds to αKlotho expressed in renal tubules, it suppresses phosphate resorption and induces phosphaturia (i.e. increases phosphate excretion per nephron). At an early stage during CKD progression, serum FGF23 levels start increasing long before hyperphosphatemia ensues. This indicates that the rise in FGF23 compensates for a decrease in the number of nephrons by increasing phosphate excretion per nephron to maintain serum phosphate levels within normal range. FGF23 activity also lowers serum levels of 1,25-dihydroxyvitamin D3. Thus, the increase in FGF23 causes a reduction in 1,25-dihydroxyvitamin D3, which is followed by a rise in PTH, leading to the disorder called CKD-MBD (mineral-bone disorder), a major risk factor for cardiovascular complications.

FGF21 (fibroblast growth factor-21), when compared with FGF23, is less appreciated among nephrologists. FGF21 is secreted from hepatocytes in response to various kinds of stress, such as fasting and inflammation. When FGF21 binds to βKlotho expressed in adipocytes, it induces metabolic responses to fasting (i.e. lipolysis). Moreover, FGF21 crosses the blood-brain barrier and binds to βKlotho expressed in the suprachiasmatic nucleus (SCN) to induce responses to stress by activating the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system. Of note, FGF21 extends lifespan when overexpressed in mice, implying that FGF21 functions as an anti-aging hormone by enhancing the ability to cope with stress. Like FGF23, FGF21 starts to increase in early-stage CKD patients, and this may be regarded as a survival response to 'stress' caused by CKD. Consistent with this notion,

high FGF21 predicts high mortality in dialysis patients. Given the fact that the SCN is the center of circadian rhythm regulation, it is intriguing to speculate that high FGF21 may also contribute to disturbed circadian rhythm of blood pressure and sleep, which has been notorious as a risk factor for poor prognosis.

"Klotho is a fascinating compound which has been recently associated with increased survival in hemodialysis patients" underlines Professor Denis Fouque, editor- in-chief of NDT.

"If we view CKD progression as a process of adaptation and failure of the FGF-Klotho endocrine axes, we may be able to develop new strategies for the diagnosis and treatment of CKD and its cardiovascular complications. In only a few years, we might be able to target at the FGF-Klotho endocrine axes and reduce the high burden of cardiovascular events in CKD", concludes Professor Kuro-o.

[1] Kuro-o M et al. Klotho and endocrine FGFs: marker of CKD progression and cardiovascular complications? Nephrol Dial Transplant 2018.

About ERA-EDTA

With more than 7,500 members, the ERA-EDTA ("European Renal Association – European Dialysis and Transplant Association") is one of the biggest nephrology associations worldwide and one of the most important and prestigious European Medical Associations. It supports basic and clinical research in the fields of clinical nephrology, dialysis, renal transplantation and related subjects. It also supports a number of studies as well as research groups and has founded a special "Fellowship Programme" for young investigators as well as grant programmes. In order to involve young nephrologists in all its activities, ERA-EDTA has created the "Young Nephrologists' Platform" (YNP), a very active committee whose board includes members who are 40 years old or younger. In addition, it has established various working groups to promote the collaboration of nephrologists with other medical disciplines (e.g. cardiology, immunology). Furthermore, a "European Renal Best Practice" (ERBP) advisory board was established by the ERA-EDTA to draw up and publish guidelines and position statements. Another important goal of the ERA-EDTA is education: The series of CME courses combined with the annual congress offer an attractive scientific programme to cover the need for continuous medical education for doctors working in the fields of nephrology, dialysis and transplantation. The association's journals, NDT (Nephrology, Dialysis, Transplantation) and CKJ (Clinical Kidney Journal), are currently the leading nephrology journals in Europe; furthermore NDT-Educational is the online educational journal of the society, with free access for all users, as well as being a very important and useful feature of the NDT-Educational "Literature Review". The ERA-EDTA Registry is a large epidemiologic database comparing countries by assessing nephrology practices throughout Europe. ENP, the European Nephrology Portal, is the latest new initiative of ERA-EDTA, where all those interested in the activities of the Society can find everything that is happening, all in one place. Finally, ERA-EDTA is a member of the European Kidney Health Alliance (EKHA), a consortium of patients, nurses and foundations relating to renal issues that actively interacts with the European Parliament. For more information, please visit www.era-edta.org