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Alpha-Klotho in health and diseases

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Aging societies are a major issue in the 21st century, and thus identification of potential drug targets to treat diseases associated with aging is desirable. α-klotho (α-kl) was first identified as an aging gene, since α-kl-/- displayed multiple phenotypes resembling human aging-related syndromes, including atherosclerosis, calcifications in various soft tissues, reduced bone mineral density, pulmonary emphysema, senile atrophy of skin, generalized tissue atrophy and short life span. However, α-Kl was later shown to be a regulator of mineral homeostasis, because synthesis of vitamin D, secretion of PTH, and absorption of calcium and phosphate ions in kidney are all controlled by α-Kl dependent machineries. In this meeting, I will focus on two topics of α-Kl. The first topic is how α-Kl selectively recognizes several distinct binding partners. We found that terminal glucuronidated N-glycan is attached on NaK β-subunit, FGFR1 and the other α-Kl binding proteins in common and plays a significant role for preferential and selective interactions between these proteins and α-Kl. When terminal glucuronidated O-glycan attached on FGF23 is docked to α-Kl, the horo α-Kl becomes more thermodynamically stable, sifting α-Kl toward a high-affinity state for FGF23. Based on the crystal structural analyses of α-Kl, here, we propose that α-Kl acts as a novel glucuronide-binding lectin and that terminal glucuronidated glycan initiates conformational/allosteric-changes by docking to target proteins, leading to stabilized interaction. The second topic is the therapeutic approach that ameliorates aging-related phenotypes of α-kl-/- mice such as vascular and heart-valve calcifications, pulmonary emphysema, lowered bone mineral density and senile atrophy of skin. We found that calpain-1 is greatly activated in α-kl-/- mice and that daily administration of its inhibitor strikingly improves the phenotypes of α-kl-/- mice. We also discovered that expressions of FGF23 and osteogenesis-related genes were ectopically induced in calcified arteries in parallel with the progression of cardiovascular calcification. This might account for the clinically observed association of increased FGF23 level with increased risk of cardiovascular mortality, particularly in patients with chronic kidney disease (CKD). Of interest, complications that develop in CKD patients are very similar to aging-related symptoms seen in α-kl-/- mice. These findings support our proposal that modulation of calpain-1 activity is a potential therapeutic target for intervention to prevent or delay the course of ageing-related syndromes and complications in CKD patients.

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