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The Klotho proteins in health and disease

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Affiliations expand

PMID: 30455427 DOI: 10.1038/s41581-018-0078-3

Abstract

The Klotho proteins, αKlotho and βKlotho, are essential components of endocrine fibroblast growth factor (FGF) receptor complexes, as they are required for the high-affinity binding of FGF19, FGF21 and FGF23 to their cognate FGF receptors (FGFRs). Collectively, these proteins form a unique endocrine system that governs multiple metabolic processes in mammals. FGF19 is a satiety hormone that is secreted from the intestine on ingestion of food and binds the βKlotho-FGFR4 complex in hepatocytes to promote metabolic responses to feeding. By contrast, under fasting conditions, the liver secretes the starvation hormone FGF21, which induces metabolic responses to fasting and stress responses through the activation of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system following binding to the βKlotho-FGFR1c complex in adipocytes and the suprachiasmatic nucleus, respectively. Finally, FGF23 is secreted by osteocytes in response to phosphate intake and binds to αKlotho-FGFR complexes, which are expressed most abundantly in renal tubules, to regulate mineral metabolism. Growing evidence suggests that the FGF-Klotho endocrine system also has a crucial role in the pathophysiology of ageing-related disorders, including diabetes, cancer, arteriosclerosis and chronic kidney disease. Therefore, targeting the FGF-Klotho endocrine axes might have therapeutic benefit in multiple systems; investigation of the crystal structures of FGF-Klotho-FGFR complexes is paving the way for the development of drugs that can regulate these axes.

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