【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project：Study of the metabolic regulation based on the elucidation of molecular function of Klotho family

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Research Area：Medicine, dentistry, and pharmacy
Keyword：Biomolecular medicine, Aging medicine, Molecular pathogenesis, Klotho, FGF19 subfamily

【Purpose and Background of the Research】

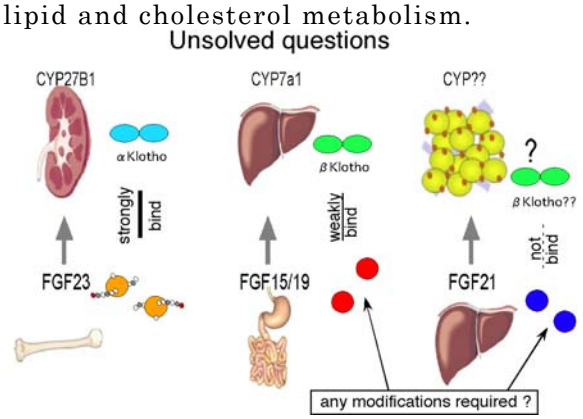
The discovery of α-Klotho, β-Klotho and FGF19 subfamily has brought a new system that covers regulations of mineral, lipid, glucose and energy metabolisms. In this project, we will analyze molecular functions and physiological roles of above members asfollows.

Project 1：Study the molecular mechanism required for the tissue specific signal transduction of FGF23 and FGF19 by analyzing how α-Klotho and β-Klotho specifically and distinctly recognize FGF23 and FGF19, respectively.

Project 2: Identification of third molecules required for the tissue specific signaling of FGF21 and the analyses of biological roles of the new factor and FGF21 complex.

Project 3: Study the mechanism that controls α-Klotho・Na+,K+ATPas complex formation.

Project 4: Study the molecular roles of β-Klotho complexes in the regulation of lipid and cholesterol metabolism.



【Research Methods】

Project 1：We will analyze the sugar chain structures of FGF23 and FGF19 which contribute to the formations of α-Klotho/FGF23 and β-Klotho/FGF19 complexes. We will also determine three-dimensional structures of putative enzyme active centers of α-Klotho and β–Klotho, and next study how α-Klotho and β-Klotho specifically recognize sugar chains of FGF23 and FGF19, respectively.

Project 2: We will analyze the fully active and functional form of FGF21 and next identify the new factor by analyzing the molecular components of active FGF21/FGFR/ unknown factor complex required for the FGF21 signaling. Then, we analyze the roles of post-translational modifications of FGF21 in complex formation and the roles of new factor in FGF21 signaling and metabolic regulation.

Project 3: We will characterize structures required for the complex formation of α-Klotho Na+,K+ATPase to clarify α-Klotho dependent recycling mechanism of Na+,K+ATPase.

Project4: We have identified β–Klotho binding proteins. Next, we analyze the effects of administrations of amino acids, insulin, fatty acid, bile acids and high fat diet, and fasting on the functions of β–Klotho complexes. By using genetic modifications of newly identified binding factors, we will discuss the roles of β–Klotho complexes in lipid and cholesterol metabolism.

【Expected Research Achievements and Scientific Significance】

The regulations of mineral, lipid, glucose and energy metabolisms are essential for the maintenance and survival of animals and closely involved in the occurrence of life-style related disease and aging mechanism. This study will contribute to establish new insights into this field and thus is tremendously important for basic life science and biomedical applications and innovations.

【Publications Relevant to the Project】

1. Tomiyama K. Maeda R. Imura A. Nabeshima Y. et al. Relevant use of Klotho in FGF19 subfamily signaling system *in vivo*. **Proc. Natl. Acad. Sci. USA** 107; 1666-1671 (2010)

2. Imura A. Tsuji J. Murata M. Nabeshima Y. et al. α-Klotho as a regulator of Calcium homeostasis. **Science** 316, 1615-1618 (2007)

3.Ito S. Fujimori T. Nabeshima Y. et al. Impaired negative feedback suppression of bile acid synthesis in mice lacking β-Klotho. **J. Clin. Invest.** 115, 2202-2208 (2005)

4. Kuro-o M.Mutation of the mouse *Klotho* gene leads to a syndrome resembling ageing. **Nature** 390, 45-51 (1997)

【Term of Project】 FY2010-2014

【Budget Allocation】 167,300 Thousand Yen

【Homepage Address and Other Contact Information】 http://www.ibri-kobe.org