

Study of bioresponse system regulated by the Klotho/Na⁺, K⁺ATPase complex

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【Outline of survey】

A mouse mutant, *klotho*, exhibits multiple phenotypes resembling human aging, including decreased activity, shortened lifespan, infertility, arteriosclerosis, osteoporosis, skinatrophy and ectopic calcification. A single gene, termed *klotho*, has been described to be responsible for the phenotypes observed in the mutant mice. *klotho* is predominantly expressed in the choroid plexus, the parathyroid gland and the distal tubule of the kidney and has been suggested to be involved in the regulation of the serum electrode and calcium homeostasis. In an attempt to define the mechanisms underlying the molecular function of the Klotho we performed immunoprecipitation from mouse choroid plexus by anti-Klotho antibodies followed by mass spectrometry analysis and identified NaK-ATPase as a Klotho associating protein. The NaK-ATPase is one of the most well known apparatus that maintain electropotential of the plasma membrane. To study the biological roles and molecular function of Klotho / NaK-ATPase complex, the following subjects will be elucidated in this project. They are (1) elucidation of biological phenomenon regulated by Klotho / NaK-ATPase

complex, (2) identification of sensor molecules which recognize the extracellular circumstance changes, (3) study of signaling cascade from cell surface sensor molecule to Klotho / NaK-ATPase complex, (4) trafficking mechanism of Klotho / NaK-ATPase complex to cell surface membrane in response to the signal from cell surface sensor molecule, and (5) homeostasis maintenance by the action of the Klotho /NaK-ATPase complex.

【Expected results】

At the end of this project, the molecular mechanisms of newly found bio-response system required for the maintenance of homeostasis of individuals and new sensor system to recognize the extra-cellular circumstance changes will be clarified. In addition, we will reach to the understanding to explain how the functional deterioration of newly found bio-response system leads to aging related symptoms.

【References by the principal researcher】

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2) Ito S. Fujimori T., Satoh J., Nabeshima Y., Nabeshima Y.

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【Term of project】 FY 2005 - 2009

【Budget allocation】 87,200,000 yen

【Homepage address】 <http://www.lmls.med.kyoto-u.ac.jp>