

意味を有すると考えられる。

$\beta$ Klothoによる重層的かつ統合的な代謝制御システムの全貌が明らかになれば、脂質代謝・エネルギー代謝の理解に新しい展開をもたらすものと期待される。

#### 文 献

- 1) Kuro-o, M., Matsumura, Y., Aizawa, H. et al. : Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997, **390** : 45-51
- 2) Takeshita, K., Fujimori, T., Kurotaki, Y. et al. : Sinatrial node dysfunction and early unexpected death of mice with a defect of klotho gene expression. *Circulation* 2004, **109** : 1776-1782
- 3) Tohyama, O., Imura, A., Iwano, A. et al. : Klotho is a novel beta-glucuronidase capable of hydrolyzing steroid beta-glucuronides. *J Biol Chem* 2004, **279** : 9777-9784
- 4) Blagosklonny, M.V. : Aging and immortality : quasi-programmed senescence and its pharmacologic inhibition. *Cell Cycle* 2006, **5** : 2087-2102
- 5) Guarente, L. : Sirtuins in aging and disease. *Cold Spring Harb Symp Quant Biol* 2007, **72** : 483-488
- 6) Tanaka, T., Nabeshima, Y. : Nampt/PBEF/Visfatin : A new player in beta cell physiology and in metabolic diseases? *Cell Metab* 2007, **6** : 341-343
- 7) Greenstock, C.L. : Radiation and aging : free radical damage, biological response and possible antioxidant intervention. *Med Hypotheses* 1993, **41** : 473-482
- 8) Yoshida, T., Fujimori, T., Nabeshima, Y. : Mediation of unusually high concentration of 1,25-dihydroxyvitamin D in homozygous klotho mutant mice by increased expression of renal 1 alpha-hydroxylase gene. *Endocrinology* 2002, **143** : 683-689
- 9) Tsujikawa, H., Kurotaki, Y., Fujimori, T. et al. : Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. *Mol Endocrinol* 2003, **17** : 2393-2403
- 10) Shimada, T., Kakitani, M., Yamazaki, Y. et al. : Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest* 2004, **113** : 561-568
- 11) Urakawa, I., Yamazaki, Y., Shimada, T. et al. : Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature* 2006, **444** : 770-774
- 12) Kurosu, H., Ogawa, Y., Miyoshi, M. et al. : Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem* 2006, **281** : 6120-6123
- 13) Tomiyama, K., Maeda, R., Urakawa, I. et al. : Relevant use of Klotho in FGF19 subfamily signaling system in vivo. *Proc Natl Acad Sci USA* 2010, **107** : 1666-1671
- 14) Ito, S., Kinoshita, S., Shiraiishi, N. et al. : Molecular cloning and expression analysis of mouse betaklotho, which encodes a novel klotho family protein. *Mech Dev* 2000, **98** : 115-119
- 15) Ito, S., Fujimori, T., Furuya, A. et al. : Impaired negative feedback suppression of bile acid synthesis in mice lacking betaKlotho. *J Clin Invest* 2005, **115** : 2202-2208
- 16) Itoh, N., Ornitz, D.M. : Functional evolutionary history of the mouse Fgf gene family. *Dev Dyn* 2008, **237** : 18-27
- 17) Yu, C., Wang, F., Kan, M. et al. : Elevated cholesterol metabolism and bile acid synthesis in mice lacking membrane tyrosine kinase receptor FGFR4. *J Biol Chem* 2000, **275** : 15482-15489
- 18) Inagaki, T., Choi, M., Moschetta, A. et al. : Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab* 2005, **2** : 217-225
- 19) Lin, B.C., Wang, M., Blackmore, C. et al. : Liver-specific activities of FGF19 require Klotho beta. *J Biol Chem* 2007, **282** : 27277-27284
- 20) Imura, A., Tsuji, Y., Murata, M. et al. : Alpha-klotho as a regulator of calcium homeostasis. *Science* 2007, **316** : 1615-1618
- 21) Brown, E.M., Watson, E.J., Thatcher, J.G. et al. : Ouabain and low extracellular potassium inhibit PTH secretion from bovine parathyroid cells by a mechanism that does not involve increases in the cytosolic calcium concentration. *Metabolism* 1987, **36** : 36-42
- 22) Joshi, R. : Hypercalcemia due to hypervitaminosis D : Report of seven patients. *J Trop Pediatr* 2009, **55** : 396-398
- 23) Selby, P.L., Davies, M., Marks, J.S. et al. : Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. *Clin Endocrinol* 1995, **43** : 531-536
- 24) Nakatani, T., Sarraj, B., Ohnishi, M. et al. : In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (Fgf23) -mediated regulation of systemic phosphate homeostasis. *FASEB J* 2009, **23** : 433-441
- 25) Many, H., Inomata, M., Fujimori, T. et al. : Klotho protein deficiency leads to overactivation of  $\mu$ -calpain. *J Biol Chem* 2002, **277** : 35503-35508

