H., Matsumoto, T., Yanagisawa, J., *Kato, S.*: The chromatin remodeling complex WINAC targets a nuclear receptor to promoters and is impaired in Williams Syndrome. *Cell*, 113, 905-917, 2003.

Suzawa, M., Takada, I., Yanagisawa, J., Ohtake, F., Ogawa, S., Yamauchi, T., Kadowaki, T., Takeuchi, Y., Shibuya, H., Gotoh, Y., Matsumoto, K., *Kato, S.*: Cytokines suppress adipogenesis and PPAR-gamma function through the TAK1/TAB1/NIK cascade. *Nature Cell Biol.*, 5, 224-230, 2003.

Kato, S., Takeyama, K.: Expression cloning of ligand biosynthetic enzymes. In Methods in enzymology, Vol. 364, Nuclear Receptors, ed. by D. W. Russel and D. J. Mangelsdorf, Elsevier, Inc., San Diego, CA, pp. 361-375, 2003

Taketani, Y., Nomoto, M., Yamamoto, H., Isshiki M., Morita, K., Arai, H., Miyamoto, K., Kato, S., Takeda E.: Increase in IP3 and intracellular Ca2+ induced by phosphate depletion in LLC-PK1 cells. *Biochem. Biophys. Res. Commun.*, 305, 287-291, 2003.

Fujishima, T., Kittaka, A., Yamaoka, K., Takeyama, K., Kato, S., Takayama, H.: Synthesis of 2, 2-dimethyl-1, 25-dihydroxyvitamin D3: A-ring structural motif that modulates interactions of vitamin D receptor with transcriptional coactivators. *Org. Biomol. Chem.*, 1, 1863-1869, 2003.

Masuyama, R., Nakaya, Y., Katsumata, S., Kajita, Y., Uehara, M., Tanaka, S., Sakai, A., Kato, S., Nakamura, T., Suzuki, K.: Dietary calcium and phosphorus ratio regulates bone mineralizaiton and turnover in vitamin D receptor knokckout mice by affecting intestinal calcium and phosphorus absorption. J. *Bone Miner. Res.*, 18, 1217-1226, 2003.

Endo, I., Inoue, D., Mitsui, T., Umaki, Y., Akaike, M., Yoshizawa, T., Kato, S., Matsumoto, T.: Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. *Endocrinology*, 144, 5138-5144, 2003.

Murayama, A., Kim, M., Yanagisawa, J., Takeyama, K., Kato, S.: Transrepression by a liganded nuclear receptor via a bHLH activator through co-regulator switching. *EMBO J.*, 23, 1598-1608, 2004.

Kato, S., Fujiki, R., Kitagawa, H.: Vitamin D receptor (VDR) promoter targeting through a novel chromatin remodeling complex. *J. Steroid Biochem. & Mol. Biol.*, 89-90, 173-178, 2004.

Aihara, K. I., Azuma, H., Akaike, M., Ikeda, Y., Yamashita, M., Sudo, T., Hayashi, H., Yamada, Y., Endoh, F., Fujimura, M., Yoshida, T., Yamaguchi, H., Hashizume, S., Kato, M., Yoshimura, K., Yamamoto, Y., Kato, S., Matsumoto, T.: Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. *J. Biol. Chem.*, 279, 35798-35802, 2004.

Segawa, H., Kaneko, I., Yamanaka, S., Ito, M., Kuwahata, M., Inoue, Y., Kato, S., Miyamoto K. : Intestinal Na-Pi cotransporter adaptation to dietary Pi content in vitamin D receptor null mice. *Am. J. Physiol. Renal. Physiol.*, 287, F39-F47, 2004.

Peters, J. M., Kato, S., Gonzalez, F : The United States-Japan workshop on : the role of nuclear receptors in carcinogenesis. *Mol. Carcinogenesis*, 41, 77-84, 2004.

Abe, M., Hiura, K., Wilde, J., Moriyama, K., Hashimoto, T., Ozaki, S., Wakatsuki, S., Kosaka, M., Kido, S., Inoue, D., Matsumoto, T. et al. 2002. Role for macrophage inflammatory protein (MIP)-1alpha and MIP-1beta in the development of osteolytic lesions in multiple myeloma. Blood 100 : 2195-2202.

Okazaki, R., Inoue, D., Shibata, M., Saika, M., Kido, S., Ooka, H., Tomiyama, H., Sakamoto, Y., and Matsumoto, T. 2002. Estrogen promotes early osteoblast differentiation and inhibits adipocyte differentiation in mouse bone marrow stromal cell lines that express estrogen receptor (ER) alpha or beta. Endocrinology 143 : 2349-2356.

Takeuchi, Y., Watanabe, S., Ishii, G., Takeda, S., Nakayama, K., Fukumoto, S., Kaneta, Y., Inoue, D., Matsumoto, T., Harigaya, K., et al. 2002. Interleukin-11 as a stimulatory factor for bone formation prevents bone loss with advancing age in mice. J Biol Chem 277 : 49011-49018.

Endo, I., Inoue, D., Mitsui, T., Umaki, Y., Akaike, M., Yoshizawa, T., Kato, S., and Matsumoto, T. 2003. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 144 : 5138-5144.

Iuchi, T., Akaike, M., Mitsui, T., Ohshima, Y., Shintani, Y., Azuma, H., and Matsumoto, T. 2003. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 92 : 81-87.

Kido, S., Inoue, D., Hiura, K., Javier, W., Ito, Y., and Matsumoto, T. 2003. Expression of RANK is dependent upon differentiation into the macrophage/osteoclast lineage: induction by 1alpha,25-dihydroxyvitamin D3 and TPA in a human myelomonocytic cell line, HL60. Bone 32 : 621-629.

Kitagawa, H., Fujiki, R., Yoshimura, K., Mezaki, Y., Uematsu, Y., Matsui, D., Ogawa, S., Unno, K., Okubo, M., Tokita, A., Matsumoto, T., Kato, S. et al. 2003. The Chromatin-Remodeling Complex WINAC Targets a Nuclear Receptor to Promoters and Is Impaired in Williams Syndrome. Cell 113 : 905-917.

Tohjima, E., Inoue, D., Yamamoto, N., Kido, S., Ito, Y., Kato, S., Takeuchi, Y., Fukumoto, S., and Matsumoto, T. 2003. Decreased AP-1 activity and interleukin-11 expression by bone marrow stromal cells may be associated with impaired bone formation in aged mice. J Bone Miner Res

18 : 1461-1470.

Abe, M., Hiura, K., Wilde, J., Shioyasono, A., Moriyama, K., Hashimoto, T., Kido, S., Oshima, T., Shibata, H., Ozaki, S., Inoue D., Matsumoto, T., et al. 2004. Osteoclasts enhance myeloma cell growth and survival via cell-cell contact : a vicious cycle between bone destruction and myeloma expansion. Blood 104 : 2484-2491.

Aihara, K., Azuma, H., Akaike, M., Ikeda, Y., Yamashita, M., Sudo, T., Hayashi, H., Yamada, Y., Endoh, F., Fujimura, M., Kato, S., Matumoto, T., et al. 2004. Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem 279 : 35798-35802.

Inoue, D., Kido, S., and Matsumoto, T. 2004. Transcriptional induction of fosB/delta fosB gene by mechanical stress in osteoblasts. J Biol Chem 279 : 49795-49803, 2004.

Hashimoto, T., Abe, M., Oshima, T., Shibata, H., Ozaki, S., Inoue, D., and Matsumoto, T. 2004. Ability of myeloma cells to secrete macrophage inflammatory protein (MIP)-1alpha and MIP-1beta correlates with lytic bone lesions in patients with multiple myeloma. Br J Haematol 125 : 38-41.

Tanimoto, Y., Yokozeki, M., Hiura, K., Matsumoto, K., Nakanishi, H., Matsumoto, T., Marie, P.J., and Moriyama, K. 2004. A soluble form of fibroblast growth factor receptor 2 (FGFR2) with S252W mutation acts as an efficient inhibitor for the enhanced osteoblastic differentiation caused by FGFR2 activation In Apert syndrome. J Biol Chem 279 : 45926-45934.

Watanabe, Y., Ohshima, H., Mizuno, K., Sekiguchi, C., Fukunaga, M., Kohri, K., Rittweger, J., Felsenberg, D., Matsumoto, T., and Nakamura, T. 2004. Intravenous Pamidronate Prevents Femoral Bone Loss and Renal Stone Formation during 90-Day Bed Rest. J Bone Miner Res 19 : 1771-1779.

Kitagawa, H., Yanagisawa, J., Fuse, H., Ogawa, S., Yogiashi, Y., Okuno, A., Nagasawa, H., Nakajima, T., Matsumoto, T., and Kato, S. 2002. Ligand-selective potentiation of rat mineralocorticoid receptor activation function 1 by a CBP-containing histone acetyltransferase complex. Mol Cell Biol 22 : 3698-3706.

Inoue D and Matsumoto T. Reduced AP-1 Mediated Transcription of Interleukin-11 Gene in Marrow Stromal Cells As a Mechanism of Senile Osteoporosis : Lessons from SAMP6. Proceedings of the 2nd International conference on Senescence: The SAM Model. International Congress Series (Elsevier, Amsterdam) : 61-65 : 2004.

Watanabe S et al: Association between activating mutations of calcium-sensing receptor and Bartter' s syndrome. Lancet 360 : 692, 2002

Yamazaki Y et al: Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. J Clin Endocrinol

Metab 87 : 4957, 2002

Shimada T et al: Targeted ablation of *Fgf23* demonstrates an essential physiological role of FGF-23 in phosphate and vitamin D metabolism. J Clin Invest 113 : 561, 2004

Takeuchi Y et al: Venous sampling for fibroblast growth factor (FGF)-23 confirms preoperative diagnosis of tumor-induced osteomalacia. J Clin Endocrinol Metab 89 : 3979, 2004

Minagawa M, Yasuda T, Watanabe T, Minamitani K, Takahashi Y, Goltzman D, White JH, Hendy GN, Kohno Y. Functional significance of AAAG repeat polymorphism in the P3 promoter of the human parathyroid hormone(PTH)/PTH-related peptide receptor gene. J Clin Endocrinol Metab 87(4) : 1791-1796, 2002

Yamauchi M, Sugimoto T, Yamaguchi T, Yano S, Wang J, Bai M, Brown EM, Chihara K. Familial hypocalciuric hypercalcemia caused by an R648stop mutation in the calcium-sensing receptor gene. J Bone Miner Res. 17, 2174-2182, 2002.

Yano S, Sugimoto T, Tsukamoto T, Chihara K, Kobayashi A, Kitazawa S, Maeda S, Kitazawa S. Decrease in vitamin D receptor and calcium-sensing receptor in highly proliferative parathyroid adenomas. Eur J Endocrinol. 148, 403-411, 2003.

Makishima, M., Lu, T. T., Xie, W., Whitfield, G. K., Domoto, H., Evans, R. M., Haussler, M. R., and Mangelsdorf, D. J. Vitamin D receptor as an intestinal bile acid sensor. Science 296 : 1313-1316, 2002

Choi, M., Yamamoto, K., Itoh, T., Makishima, M., Mangelsdorf, D. J., Moras, D., DeLuca, H. F., and Yamada, S. Interaction between vitamin D receptor and vitamin D ligands: two-dimensional alanine scanning mutational analysis. Chemistry & Biology 10 : 261-270, 2003

Adachi, R., Shulman, A. I., Yamamoto, K., Shimomura, I., Yamada, S., Mangelsdorf, D. J., and Makishima, M. Structural determinants for vitamin D receptor response to endocrine and xenobiotic signals. Molecular Endocrinology 18 : 43-52, 2004

Hatakeyama Y, Mizunashi K, et al. Plasma levels of PTH(1-84) whole molecule and PTH(7-84)-like fragments in pseudohypoparathyroidism type I. J Clin Endocrinol Metab. 2003. 88 : 2250-5

Ihara-Watanabe M, Uchihashi T, Miyauchi Y, Sakai N, Yamagata M, Ozono K, Michigami T. Involvement of phosphoinositide 3-kinase signaling pathway in chondrocytic diffenetiation of ATDC5 cells: Application of a gene-trap mutagenesis. *J Cell Biochem* 93 : 418-426, 2004.

Santo Y, Hirai H, Shima M, Yamagata M, Michigami T, Nakajima S, Ozono K. Examination of megalin in the renal tubular epithelium in patients with Dent's disease. *Pediatr Nephrol* 19 : 612-615, 2004.

Izumi Y, Hidaka Y, Tada H, Takano T, Kashiwai T, Tatsumi K, Ichihara K, Amino N: Simple and practical parameters for differentiation between destruction-

induced thyrotoxicosis and Graves' thyrotoxicosis. Clin Endocrinol 57 : 51-58, 2002.

Kashiwai T, Hidaka Y, Takano T, Tatsumi K, Izumi Y, Shimaoka Y, Tada H, Takeoka K, Amino N: Practical treatment with minimum maintenance dose of antithyroid drugs for prediction of remission in Graves'disease. Endocr J 50 : 45-49, 2003.

Tada H, Mizuta I, Takano T, Tatsumi K,Izumi Y, Hidaka Y, Amino N: Blocking-type anti-TSH receptor antibodies and relation to responsiveness to antithyroid drug therapy and remission in Graves'disease. Clin Endocrinol 58 : 403-408, 2003.

Hidaka Y, Kimura M, Izumi Y, Takano T, Tatsumi K, Amino N: Increased serum concentration of eosinophil-dereved neurotoxin in patients with Graves'disease. Thyroid 13 : 129-132, 2003.

Amino N, Hidaka Y, Takano T, Tatsumi K, Izumi Y, Nakata Y: Possible Induction of Graves'disease and painless thyroiditis by gonadotrophin-releasing hormone (GnRH) analogues. Thyroid 13 : 815-818, 2003.

Amino N, Hidaka Y, Takano T, Izumi Y, Tatsumi K, Nakata Y: Association of seasonal allergic rhinitis is high in Graves' disease and low in painless thyroiditis. Thyroid 13 : 811-814, 2003.

Takeoka K, Hidaka Y, Hanada H, Nomura T, Tanaka S, Takano T, Amino N: Increase in serum levels of autoantibodies after attack of seasonal allergic rhinitis in patients with Graves'disease. Int Arch Allergy Immunol 132 : 268-274, 2003.

Amino N, Izumi Y, Hidaka Y, Takeoka K, Nakata Y, Tatsumi K, Nagata A, Takano T: No increase of blocking type anti-TSH receptor antibodies during pregnancy in patients with Graves'disease. J Clin Endocr Metab 88 : 5871-5874, 2003.

Akamizu T, Ozaki S, Hiratani H, Uesugi H, Sobajima J, Hataya Y, Kanamoto N, Saijo M, Hattori Y, Moriyama K, Ohmori K, Nakao K. Drug-induced neutropenia associated with anti-neutrophil cytoplasmic antibodies (ANCA): possible involvement of complement in granulocyte cytotoxicity. Clin Exp Immunol. 2002 Jan ; 127(1) : 92-8.

Sellitti DF, Doi SQ, Akamizu T, Koshiyama H. Comments on "Thyrotropin Receptor Expression in Cardiac Muscle Tissue". J Clin Endorinol Metab, 87(2) : 946, 2002.

Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, Nakao K. Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab. 2002 Nov ; 87(11) : 5185-90.

Akamizu T, Hiratani H, Ikegami S, Rich SS, Bowden DW. Association study of autoimmune thyroid disease at 5q23-33 in Japanese patients. J HumGenet, 48 : 236-42, 2003

Saijo M, Akamizu T, Ikuta K, iida Y, Ohmori K, Matsubara K, Matsuda Y, Suzuki M, Matsuda F, Nakao K. Genaration of a transgenic animal model of hyperthyroid

graves'disease. Eur J Immunol, 33 : 2531-2538, 2003.

Akamizu T. Monoclonal Antibodies to Throid Specific Autontigens. Autoimmunity 36(6-7) : 361-366, 2003.

Moriyama K, Okuda J, Saijo M, Hattori Y, Kanamoto N, Hataya Y, Matsuda F, Mori T, Nakao K and Akamizu T: Recombinant monoclonal thyrotropin-stimulation blocking antibody (TSBAb) established from peripheral lymphocytes of a hypothroid patient with primary myxedema. J Endocrinol. Invest. 26 : 1076-1080, 2003.

Li YS, Kanamoto N, Hataya Y, Moriyama K, Hiratani H, Nakao K, Akamizu T. Transgenic Mice Producing MHC Class II Molecules on Thyroid Cells Do Not Develop Apparent Autoimmune Thyroid Diseases. Endocrinology. 2004,

MITSUYAMA H, KAMBE F, MURAKAMI R, CAO X, ISHIGURO N, SEO H: Calcium signaling pathway involving calcineurin regulates interleukin-8 gene expression through activation of NF-kappaB in human osteoblast-like cells. J. Bone. Miner. Res.h, 19(4) : 671-679, 2004.

MIZUNO Y, KANOU Y, ROGATCHEVA M, IMAI T, REFETOFF S, SEO H, MURATA Y: Genomic organization of mouse ZAKI-4 gene that encodes ZAKI-4 alpha and beta isoforms, endogenous calcineurin inhibitors, and changes in the expression of these isoforms by thyroid hormone in adult mouse brain and heart. Europ. J. Endocrinol., 150 : 371-380, 2004.

HIBI Y, NAGAYA T, KAMBE F, IMAI To, FUNAHASHI H, NAKAO A, SEO H: Is thyroid follicular cancer in japanese caused by a specific t(2;3)(q13;p25) translocation generating Paax-8-PPARgamma fusion mRNA? Endocr. J., 51(3) : 361-366, 2004.

WAKABAYASHI K, KAMBE F, CAO X, MURAKAMI R, MITSUYAMA H, NAGAYA T, SAITO K, YOSHIDA J, SEO H: Inhibitory effects of cyclosporin A on calcium mobilization-dependent interleukin-8 expression and invasive potential of human glioblastoma U251MG cells. Oncogene, 23(41) : 6924-6932, 2004.

KAMIJO T, HAYASHI Y, SEO H, YAMAMOTO M, OGAWA M, CHOSKI CS, SAWANT NJ, COLACO MP, DESAI MP: A nonsense mutation (E72X) in growth hormone releasing hormone receptor (*GHRHR*) gene is the major cause of familial isolated growth hormone deficiency in Western region of India: founder effect suggested by analysis of dinucleotide repeat polymorphism close to *GHRHR* gene. Growth Horm.IGF Res., 14(5) : 394-401, 2004.

HOSHINO S, TAKAGISHI Y, KANOU Y, HAYASAKA S, HATTORI K, KAMBE F, SEO H, MURATA Y: Spatial and intracellular distribution of the endogenous calcineurin-inhibitory proteins, ZAKI-4, in mouse brain. Acta Histochem. Cytochem., 37(4) : 247-257, 2004.

SADOW PM, KOO E, CHASSANDE O,

GAUTHIER K, SAMARUT J, XU J, O' Malley BW, SEO H, MURATA Y, WEISS RE: Thyroid hormone receptor-specific interactions with steroid receptor coactivator-1 in the pituitary. Molecular Endocrinology, 17(5) : 882-894, 2003.

CAO X, SEO H: Thyroid hormone-dependent regulation of ZAKI-4 α, an inhibitor of calcineurin, and its implication in brain development and function. Current Opinion in Endocrinol. Diabetes, 10 : 357-363, 2003.

MURAKAMI R, KAMBE F, MITSUYAMA H, OKUMURA K, MUROHARA T, NIWATA Satoru, YAMAMOTO R, SEO H: Cyclosporin A enhances interleukin-8 expression by inducing activator protein-1 in human aortic smooth muscle cells. Arteriosclerosis Thromb. Vasc. Biol., 23(11) : 2034-2040, 2003.

IWATA H, ITOH T, SAKANO S, SUGIURA H, KAWAMURA M, MURATA Y, SEO H: Is bone matrix still important substitute for bone graft surgery-from point of view of heat and MBP activity. Bone, 32(5) : S120(Suppl.), 2003.

KOZAKI Y, KAMBE F, HAYASHI Y, OHMORI S, SEO H, KUMAZAWA T, MIZUMURA K: Cloning of cDNAs for prostaglandin EP3 receptor(EP3R) from canine dorsal root ganglia(DRG): Two different cDNAs encoding the isoforms with different C-termini and their inhibitory effects of cAMP accumulation. Neurosci. Res., 26 : S80(Suppl.), 2003.

TAKEUCHI Y, MURATA Y, SADOW PM, HAYASHI Y, SEO H, XU. J, O' MALLEY BW, WEISS RE, REFETOFF S: Steroid receptor coactivator-1 deficiency causes variable alterations in the modulation of T(3)-regulated transcription of genes in vivo. Endocrinology, 143(4) : 1346-1352, 2002.

KATO M, NAGAYA T, FUJIEDA M, SAITO K, YOSHIDA J, SEO H: Expression of PPAR γ and its ligand-dependent growth inhibition in human brain tumor cell lines. Japan J. Caner Res., 93(6) : 660-666, 2002.

SAKANO S, HASEGAWA Y, MURATA Y, ITO T, GENDA E, IWATA H, ISHIGURO N, SEO H: Inhibitory effect of βFGF on endochondral heterotopic ossification. Biochem. Biophys. Res. Commun., 293 : 680-685, 2002.

SHIBATA A, NAGAYA T, IMAI T, FUNAHASHI H, NAKAO A, SEO H: Inhibition of NF-kB activity decreases the VEGF mRNA expression in MDA-MB-231 breast cancer cells. Breast Cancer Res and Treatment, 73 : 237-243, 2002.

HAYASHI Y, KAMIJO T, OGAWA M, SEO H: Familial isolated growth hormone deficiency: genetics and pathophysiology. Endocr. J., (Review), 49(3) : 265-272, 2002.

CAO X, KAMBE F, MIYAZAKI T, SARKAR D, OHMORI S, SEO H: Novel human ZAKI-4 isoforms: Hormonal and tissue-specific regulation and function as calcineurin inhibitors. Biochem. J., 367 :

459-466, 2002.

CAO X, KAMBE F, OHMORI S, SEO H: Oxidoreductive modification of two cysteine residues in paired domain by Ref-1 regulates DNA-binding activity of Pax-8. Biochem. and Biophysi. Res. Commun., 297 : 288-293, 2002.

ROGATCHEVA M, HAYASHI Y, ODA S, SEO H, CUA K, REFETOFF S, MURAKAMI M, MORI M, MURATA Y: Type 1 iodothyronine deiodinase in the house musk shrew(Suncus murinus, Insectivora: Soricidae): cloning and characterization of commplementary DNA, unique tissue distribution and regulation by T3. General and Comparative Endocrinol., 127 : 48-58, 2002.

Nakano K, Matsushita A, Sasaki S, Misawa H, Nishiyama K, Kashiwabara Y, Nakamura H: Thyroid hormone-dependent negative regulation of thyrotropin beta gene by thyroid hormone receptors: STUDY WITH A NEW EXPERIMENTAL SYSTEM USING CV1 CELLS. Biochem J. 378 : 549-557, 2004

Kawai K, Sasaki S, Morita H, Ito T, Suzuki S, Misawa H, Nakamura H: Unliganded thyroid hormone receptor b1 represses liver X receptor a / oxysterol-dependent transactivation. Endocrinology 145 : 5515-5524, 2004

Nishiyama K, Baba S, Yamada T, Matsushita A, Natsume H, Nakano K, Sasaki S, Nakamura H: Embryonic lethal effect of expressing a dominant negative mutant human thyroid hormone receptor al in mice. Endocrine J. 50 : 561-570, 2003.

Natsume H, Sasaki S, Kitagawa M, Kashiwabara Y, Matsushita A, Nakano K, Nishiyama K, Nagayama K, Misawa H, Nakamura H: Beta-catenin/Tcf1-mediated transactivation of cyclin D1 promoter is negatively regulated by thyroid hormone. Biochem Biophys Res Commun 309 : 408-413, 2003

Yokomura K, Suda Y, Sasaki S, Inui N, Chida K, Nakamura H: Increased expression of the 25-hydroxyvitamin D3-1alfa-hydroxylase gene in alveolar macrophages of patients with lung cancer. J Clin Endcrinol Metab 88 : 5704-5709, 2003

Ishii S, Yamada M, Satoh T, Monden T, Hashimoto K, Shibusawa N, Onigata K, Morikawa A, Mori M. Aberrant dynamics of histone deacetylation at the thyrotropin-releasing hormone gene in resistance to thyroid hormone. Mol Endocrinol. 2004, 18 : 1708-20.

Monden T, Yamada M, Nihei Y, Kishi M, Tomaru T, Ishii S, Hashida T, Shibusawa N, Hashimoto K, Satoh T, Kasai N, Mori M. Unliganded RXR acts as an inhibitory factor on troglitazone-induced activation. Life Sci 2004, 76 : 731-741

Monden T, Yamada M, Ishii S, Hosoya T, Satoh T, Wondisford FE, Hollenberg AN, Mori M. Leucine at codon 428 in the ninth heptad of thyroid hormone receptor betal is necessary for interactions with the transcriptional cofactors and functions regardless of dimer formations. Thyroid.

2003 13(5) : 427-35.

Furuya F, Shimura H, Suzuki H, Haraguchi K, Onaya T, Endo T, Kobayashi T. Histone deacetylase inhibitors restore radioiodide uptake and retension in pooly differentiated and anaplastic thyroid cancer cells by expression of the sodium/iodide symporter, thyroidperoxidase and thyroglobulin. Endocrinology 145, 2865-2875, 2004

Furuya F, Shimura H, Miyazaki A, Taki K, Ohta K, Haraguchi K, Onaya T, Endo T, Kobayashi T. Adenovirus-mediated transfer of thyroid transcription factor-1 induced radioiodine organificatin and retention in thyroid cancer cells. Endocrinology 145, 5397-5405, 2004

Hiromatsu Y, et al.:Interleukin-13 gene polymorphisms confer the susceptibility of Japanese populations to Graves'disease. J Clin Endocrinol Metab. 2004 Oct 13; [Epub ahead of print]

Bednarczuk T, Hiromatsu Y, et al.: Association of tumor necrosis factor and human leukocyte antigen DRB1 alleles with Graves'ophthalmopathy. Hum Immunol. 2004 Jun;65(6) : 632-9.

Fukutani T, Hiromatsu Y, et al.:A polymorphism of interferon-gamma gene associated with changes of anti-thyrotropin receptor antibodies induced by antithyroid drug treatment for Graves'disease in Japanese patients. Thyroid. 2004 Feb; 14(2) : 93-7.

学会発表

H. Tanaka, N. Inoue, K. Kinuta, S. Kato, Y. Seino VITAMIN D SUPPRESSES PERIOSTEAL BONE FORMATION THROUGH SUPPRESSING RUNX2 GENE EXPRESSION. the 1st Joint Meeting of the International Bone and Mineral Society (IBMS) and the Japanese Society for Bone and Mineral Research (JSBMR) Osaka 2003/June

N. Inoue, H. Tanaka, K. Hasegawa, M. inoue, S. Kato, Y. Seino VITAMIN D RECEPTOR NULL BONE SHOWS HIGHER PERIOSTEAL BONE FORMATION. the 1st Joint Meeting of the International Bone and Mineral Society (IBMS) and the Japanese Society for Bone and Mineral Research (JSBMR) Osaka 2003/June

Y. Yamanaka, H. Tanaka, K. Ueda, E. Yamagami, R. Nishimura, Y. Seino SPROUTY2 INDUCED BY CONSTITUTIVELY ACTIVE FGF RECEPTOR 3 SUPPRESSES THE CHONDROCYTE PROLIFERATION THROUGH INHIBITION OF IGF-1 SIGNALING. the 1st Joint Meeting of the International Bone and Mineral Society (IBMS) and the Japanese Society for Bone and Mineral Research (JSBMR) Osaka 2003/June

H. Tanaka, Y. Seino DIRECT ACTION OF 1,25-DIHYDROXYVITAMIN D ON BONE; VDRKO BONE SHOWS EXCESSIVE BONE FORMATION IN NORMAL MINERAL CONDITION. 12th Workshop on Vitamin D Maastricht, Netherland.

July/2003

K. Hasegawa, H. Tokumaru, H. Tanaka, Y. Seino 1,25-DIHYDROXYVITAMIN D3 SUPPRESSES RUNX2/ CBFA1 GENE PROMOTOR ACTIVITY, BUT NOT VIA VDRE. 12th Workshop on Vitamin D Maastricht, Netherland. July/2003

H. Tanaka. Normal bone growth and growth hormone. 2nd Ferring Pharmaceuticals International Paediatric Endocrinology Symposium, Rome, Italy, 2002 May

J Shimizu, H Tanaka, K Aya, S Itoh, Y Sado, and Y Seino A Missense Mutation in the Nephrin Gene Impairs Membrane Targeting. 8th Asian Congress of Pediatric Nephrology Jeju Island, Korea 2002 Sep

Y. Yamanaka, H. Tanaka, K. Ueda, E. Yamagami, R. Nishimura, Y. Seino. Sprouty2 induced by constitutively active FGF receptor 3 suppresses the chondrocyte proliferation through inhibition of IGF-I signaling. American Society for Bone and Mineral Research 24th Annual Meeting, San Antonio, TX, USA, 2002 Sep

Identification of oncogenic nucleoporin CAN/Nup214 as a regulator of vitamin D receptor-mediated transcription. Miyauchi Y、Michigami T、Ozono K. 20th Annual Meeting of American Society of Bone and Mineral Research. 2002.9;USA

NUS-IMCB-IMSUT Joint Symposium on Integrative Biotechnology Function of steroid hormone receptors in gene regulations S. Kato (2002)

ASBMR 26th Annual Meeting Genetic evidence of androgen receptor function in osteoclasts: Generation and characterization of osteoclast-specific androgen Receptor knockout miceT. Nakamura, T. Watanabe, Y. Nakamichi, T. Fukuda, T. Matsumoto, K. Yoshimura, J. Miyamoto, Y. Yamamoto, H. Shiina, S. Tanaka, M. Sakari, T. Sato, D. Metzger, P. Chambon, S. Kato (2004)

ASBMR 26th Annual Meeting A genetic evidence of direct VDR function in osteoblasts: generation and analysis of osteoblast-specific VDRKO mice Y. Yamamoto, T. Yoshizawa, T. Fukuda, H. Kawano,T. Nakamura, T. Yamada, G. Karsenty, S. Kato (2004)

ASBMR 26th Annual Meeting Modulation of VDR function by a novel vitamin D analogue, ED-71, is mediated through a novel serum proteinY. Shirode, K. Takeyama, S. Kato (2004)

ASBMR 26th Annual Meeting Keystone Symposia Co-regulator complexes for nuclear receptors and genetic analyses of AR function S. Kato (2004)

ASBMR 26th Annual Meeting TRAP240, as a component of the mediator complex, represses transactivation function of androgen receptor K. Takeyama, S. Ito, S. Sawatsubash, Y. Shirode, E. Suzuki, A. Maki, Y. Zhao, K. Yamagata, A. Kouzmenko, T. Tabata, S. Kato (2004)

ENDO 2004, the 86th Annual Meeting of the Endocrine Society Classes of nuclear receptor coregulatory complexes S. Kato (2004)

UT Forum 2004 in Sweden

Transcriptional controls by nuclear receptors S. Kato (2004)

Vitamin D Workshop Working Group

The Williams Syndrome and the Vitamin D Receptor. S. Kato (2004)

Ninth Workshop on Cell Biology of Bone and Cartilage in Health and Disease (Davos, Switzerland, 3/16-19/02) Interleukin-11 Is An Osteogenic Cytokine That Inhibits Osteoblast Apoptosis D. Inoue, S. Kido, S. Kato, Y. ito, and T. Matsumoto

24th Annual Meeting of the American Society for Bone and Mineral Research, 2002 Downregulation of Interleukin-11 may be involved in the pathogenesis of glucocorticoid-induced osteoporosis S. Kido, D. Inoue, S. Kato, Y. Ito, T. Matsumoto

24th Annual Meeting of the American Society for Bone and Mineral Research, 2002 Mechanism of mechanical stress-induced activation of AP-1/IL-11 transcriptional cascades D. Inoue, S. Kido, T. Matsumoto

1st Joint meeting of IBMS/JSBMR (Osaka, June 3-7, 2003) Transcriptional induction of fosB/deltafosB gene by fluid shear stress in osteoblasts. D. Inoue, S. Kido, Y. Ito, T. Matsumoto

1st Joint meeting of IBMS/JSBMR (Osaka, June 3-7, 2003) Interleukin-11 is an osteogenic cytokine that inhibits osteoblast apoptosis: upregulation of bcl-2 and synergism with estrogen S. Kido, D. Inoue, S. kato, K. Yoshida, T. Matsumoto.

25th Annual Meeting of the American Society for Bone and Mineral Research (Minneapolis, September 19-23, 2003) Transcriptional induction of FosB/DeltafosB gene by mechanical stress in osteoblasts. D. Inoue, S. Kido, S.Kato, T. Matsumoto

25th Annual Meeting of the American Society for Bone and Mineral Research (Minneapolis, September 19-23, 2003) Transcriptional induction of FosB/DeltafosB gene by mechanical stress in osteoblasts. D. Inoue, S. Kido, S.Kato, T. Matsumoto

25th Annual Meeting of the American Society for Bone and Mineral Research (Minneapolis, September 19-23, 2003) A novel mechanical stress-induced signaling pathway leading to Smad1/5/8 activation in osteoblasts. S. Kido, D. Inoue, T. Imamura, K. Miyazono, T. Matsumoto.

26th Annual Meeting of the American Society for Bone and Mineral Research (Seattle, October 1-5, 2004) Inhibition of interleukin-11 gene transcription by glucocorticoid. Ito Y, Kido S, Inoue D, Matsumoto, T.

Yamauchi M, Yamaguchi T, Sowa H, Yano S, Kaji H, Sugimoto T, Chihara K. The extracellular calcium-sensing receptor (CaR) is indispensable for expression of alkaline phosphatase (ALP) and osteocalcin (OC) as well as mineralization in mouse osteoblastic MC3T3-E1 cells. J Bone Miner Res. 18, S289, 2003. Twenty-fifth annual meeting of the American Society for Bone and Mineral Reseach (Minneapolis)

SugimotoT. Primaryhyperparathyroidism. 2002 Ist Conference of Young Human Society of Endocrinology and Metabolism (Gwangju, Korea)

Makishima, M. New function of vitamin D receptor as a bile acid sensor (Lunch Symposia: New aspects of vitamin D action). 1st Joint Meeting of International Bone and Mineral Society and Japanese Society of Bone and Mineral Research, Osaka, Japan, 2003.6

Yamada, S., Yamamoto, K., Shimizu, M., Choi, M., Abe, D., Mihori, M., Makishima, M., DeLuca, H. F., Garabedian, M., and Nguyen, T. N. Interaction between vitamin D receptor and ligands: two-dimensional alanine scanning mutational analysis. 12th Workshop on Vitamin D, Maastricht, The Netherlands, 2003.7

Makishima, M. Bile acid derivatives acting on VDR and their effects on leukemia. The US-Japan Workshop on: The Role of Nuclear Receptors in Carcinogenesis, Makena, Hawaii, 2004.3

Yamagata M, Ozono K, Hashimoto Y, Kondou H, Michigami T. Intraperitoneal administration of recombinant receptor-associated protein impairs megalin function and increases renal phosphate excretion. 26th annual meeting of the American Society for Bone and Mineral Research. 2004.10. Seattle, U.S.A.

Saijo M, Akamizu T, Ikuta K, Ohmori K, Iida Y, Matsubara K, Matsuda Y, Honjo T, Nakao K. Transgenic Mice Bearing Anti-TSH Receptor Autoantibody Genes Derived from a Graves' Patient. The 84th Annual Meeting of the Endocrine Society, (San Francisco, U.S.A.) 6.19-22, 2002

Akamizu T, Kangawa K. Central effects of Ghrelin and GHS. 2003 Hypopituitary Control and Complications Study Symposium and Investigators Meeting (Prague, Czech Republic) 3.11-15, 2003.

Saijo M, Akamizu T, Ikuta K, Ohmori K, Honjo T, Nakao K. Oral Administration of Lipopolysaccharides Induces hyperthyroidism in a Patients Derived Thyroid-Stimulating Anti-Thyrotropin Receptor Antibodies Trangenic Mouse. The 85th Annual Meeting of the Endocrine Society (Philadelphia, USA) 6.19-22, 2003.

Akamizu T, Saijo M: Transgenic Model of Graves'Disease. 7th Asia & Oceania Thyroid Association Congress 2003 (Raffles City Convention Center, Singapore), 2-4 December, 2003.

Li YS, Kanamoto N, Hataya Y, Moriyama K, Nakao K, Akamizu T: Preparation and Characterization of Transgenic Mice Expressing MHC Class II Molecules on Throid Cells. The 75th meeting of The American Throid Association, Palm Beach, Florida, #106 (p85), 2003.

Akamizu T. Transgenic models of Autoimmune thyroid disease. The 4th China-Japan-Korea Thyroid Conference. 2004. 5.23-26, Shanghai Worldfield Convention Hotel, Shanghai, China.

CAO X, KAMBE F, SEO H: Redox regulation of DNA-binding activity of Pax-8 paired domain by glutathionylation. 11th International Thyroid Association. 2004

SEO H, CAO X, KAMBE F, MOELLER LC, REFETOFF S: Novel Thyroid Hormone Action Activating PI3K/Akt/PKB-mTOR Signaling Cascade and Inhibiting Calcineurin. The 4th China-Japan-Korea Thyroid Conference, 2004.

SEO H, KAMBE F: Endocrine disruptors and thyroid function. 7th Asia and Oceania Thyroid Association Congress Abstract Book, p19, 2003.

KAMBE F, CAO X, SEO H: TSH modifies TNF-

α -dependent activation of NF-kB in rat thyroid FRTL-5 cells. 7th Asia and Oceania Thyroid Association Congress Abstract Book, p81, 2003.

CAO X, KAMBE F, MOELLER LC, REFETOFF S, SEO H: Thyroid hormone-dependent ZAKI-4 α induction requires activation of P13K-PKB-mTOR signaling cascade. 7th Asia and Oceania Thyroid Association Congress Abstract Book, p33, 2003.

MITSUYAMA H, KAMBE F, MURAKAMI R, CAO X, ISHIGURO N, SEO H: Calcium signaling pathway involving calcineurin regulates IL-8 gene expression through activation of NF-kappaB in human osteoblast-like cells. The Endocrine Society's 85th Annual Meeting Program & Abstruct, P2-3, 2003.

MURAKAMI R, KAMBE F, MITSUYAMA H, OKUMURA K, NIWATA S, YAMAMOTO R, SEO H: Cyclosporin A enhances IL-8 expression by inducing AP-1 in human aortic smooth muscle cells. The Endocrine Society's 85th Annual Meeting Program & Abstruct, P2-22, 2003.

WAKABAYASHI K, KAMBE F, MITSUYAMA H, MURAKAMI R, YOSHIDA J, SEO H: IL-8 gene expression in human glioma U251MG cells is regulated by calcium signaling pathway through activation of NF-KappaB. The Endocrine Society's 85th Annual Meeting Program & Abstruct, P2-24, 2003.

KAMBE F, CAO X, OHMORI S, SEO H: Oxidoreductive modification of two cysteine residues in paired domain of Pax-8 regulates its DNA-binding activity. The Endocrine Society's 85th Annual Meeting Program & Abstruct, P3-239, 2003.

CAO X, LEE JK, MOELLER LC, KAMBE F, HAYASHI Y, REFETOFF S, SEO H: Thyroid hormone receptor-mediated regulation of ZAKI-4 α expression involves the activation of P13K and mammalian target of rapamycin (mTOR). The Endocrine Society's 85th Annual Meeting Program & Abstruct, P3-245, 2003.

CAO X, KAMBE F, SARKAR D, OHMORI S, SEO H: Involvement of cyclosporin A(CsA)- and rapamycin-sensitive pathway for the thyroid hormone-mediated induction of ZAKI-4 α expression. 84th Anuual Meeting of the Endocrine Society, Program and Abstracts, P3, 2002.

KAMBE F, SARKAR D, SEO H: Search for dioxin-responsive gene. International Symposium for Environmental Medicine, Program and Abstracts, P9, 2002.

Sasaki S, Nakamura H et al.: The negative regulation of thyroid stimulating hormone (TSH) beta gene is mediated through the interaction between DNA binding domain of thyroid hormone receptor and the zinc finger region of transcription factor, GATA2. 第76回米国甲状腺学会（Vancouver, Canada）2003年9月

Nishiyama K, Nakamura H et al.: Hypothyroidism of transgenic mice expressing a dominant negative mutant thyroid hormone receptor in thyroid. 第76回米国甲状腺学会（Vancouver, Canada）2003年9月

Nakamura H et al.: Analysis of transgenic mice expressing a dominant negative mutant thyroid hormone receptor in thyroid. 第26回欧州甲状腺学会（Edinburgh, UK）Topic highlights 2003

年10月

Sasaki S, Nakamura H et al.: GATA2 is Essential to mediate the negative regulation of TSH alpha subunit gene by T3 and T3 receptor. 第75回米国甲状腺学会（Palm Beach, FL, USA）2003年9月

Nakamura H et al.: Thyroid hormone dependent negative regulation of thyrotropin gene promoters by thyroid hormone receptor in CV1 cells. 第25回欧州甲状腺学（Gothenburg, Sweden）Topic highlights 2002年9月

Sasaki S, Nakamura H et al.: The negative regulation of the thyrotropin promoters by thyroid hormone and its receptors. Keystone Symposia（Nuclear Receptor Superfamily）2002年4月（Snowbird, Utah, USA）

Sasaki S, Nakamura H et al.: Involvement of GATA2 in the T3 dependent negative regulation of the thyrotropin beta and alpha gene promoters by thyroid hormone receptor. 第74回米国甲状腺学会. 2002年10月（Los Angels, CA, USA）

Mori M. Management of hyperthyroidism. 12th International Congress of Endocrinology.

Satoh T, Tomaru T, Ishizuka T, Ishii S, Hashimoto K, Monden T, Yamada M, Mori M. Negative regulation of the thyrotropin-releasing hormone gene by thyroid hormone requires direct interaction between Leader binding protein-1c and the DNA-binding domain of thyroid hormone receptor. 12th International Congress of Endocrinology.

Tomaru T, Satoh T, Ishizuka T, Hashida T, Shibusawa N, Hashimoto K, Monden T, Yamada M, Mori M. Isolation of a novel DNA binding cofactor that binds the DNA-binding domain of peroxisome proliferator-activated receptor γ 12th International Congress of Endocrinology.

Shibusawa N, Hashimoto K, Yamada M, Wondisfort FE, Mori M. DNA-binding function of thyroid hormone receptor-b in mice. 10th International Symposium on Molecular Thyroidology.

Satoh T, Tomaru T, Ishizuka T, Hashimoto K, Nihei Y, Ishii S, Monden T, Yamada M, Mori M. Negative regulation of the mouse TRH gene by thyroid hormone requires direct interaction between leader binding protein-1 and the DNA-binding domain of thyroid hormone receptor 85TH Annual Meeting of the Endocrine Society.

Hashimoto K, Yamada M, Satoh T, Monden T, Hashida T, Ishii S, Tomaru T, Nihei Y, Mori M, Wondisfort FE. The role of the unliganded thyroid hormone receptor in cholesterol metabolism. 85TH Annual Meeting of the Endocrine Society.

Tomaru T, Satoh T, Ishizuka T, Nihei Y, Ishii S, Ozawa A, Hashimoto K, Hashida T, Monden T, Yamada M, Mori M. Regulation by retinoids of the expression of the hypotharamic TRH and pituitary TSH β gene in mouse. 9th International Symposium on Molecular Thyroidology.

Tomaru T, Satoh T, Ishizuka T, Ishii S, Ozawa A, Hashimoto K, Monden T, Yamada M, Mori M. Regulation by retinoids of the expression of the Hypothalamic TRH and pituitary TSH β gene in mouse. 84TH Annual Meeting of the Endocrine Society.

Hashimoto K, Yamada M, Satoh T, Monden T, Wondisfort FE, Mori M. Thyrotropin-Releasing Hormone (TRH) Modulates Phenotypes of Resistance ti Thyroid Hormone. 84TH Annual Meeting of the Endocrine Society.

S.Ishii, M.Yamada, T.Satoh, T.Monden,

K.Hashimoto, Y.Nihei, K.Onigata, A.Morikawa, M.Mori Involvement of Coactivators in the Dominant Negative Potency of the Mutant TRs in RTH: Analysis of a Novel Nutant,F455S. 74th Annual Meeting of the American Thyroid Association

Nihei Y, Monden T, Ishii S, Hashimoto K, Satoh T, Yamada M, Mori M. Down-Regulation of Thyroid Hormone Receptor Expressions by Thyroid Hormone in Human Neuroblastome SH-SY5Y Cells and Medulloblastoma HTB-185 Cells. 74th Annual Meeting of the American Thyroid Association

Onigata K, et al. High Prevalence of R450H Thyrotropin Receptor Gene Inactivating Mutation in Japanese Cases with Resistance to Thyrotropin. The Endocrine Society's 85th Annual Meeting, Philadelphia, 19-22 June, 2003.

Onigata K, et al. The R450H mutation of the thyrotropin receptor gene is common in Japanese patients with resistance to thyrotropin. 75th Annual Meeting of the America Thyroid Association. West Palm Beach, 16-20 September, 2003.

知的所有権の出願・取得状況（予定を含む）

1）特許取得

発明の名称：　皮膚病関連遺伝子の用途
発　明　者：　妹尾　久雄、村田　善晴
出　願　日：　平成16年5月31日
出 願 番 号：　特願2004-160953

2）実用新案登録

3）その他

Ⅲ．分担研究報告

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

偽性副甲状腺機能低下症におけるPTH分子の存在様式に関する検討

研究協力者　水梨一利　東北大学医学研究科腎高血圧内分泌内科　助手

A．研究目的

最近PTH（1-84）whole molecule（Bio-PTH）に特異的な測定系が開発され、これまで用いられてきたいわゆるintact PTH assay系では、Bio-PTHの他にHPLCでPTH（7-84）と同じ分画に溶出されるfragmentsがcrossreactすることが明らかにされた。偽性副甲状腺機能低下症（PHP）では、PTHに対する標的器官の反応性の低下によって続発性に副甲状腺機能が亢進している。そこで、PHPにおいて、Bio-PTHとPTH（7-84）様fragmentsを測定することにより、本症における血中PTH分子の存在様式およびPTH分泌とその代謝について検討した。

B．研究方法

PHPにおける血中PTH濃度を血中PTHをBio-PTHに特異的な測定法と従来のintact PTH 測定法（iPTH）により測定し、両者の差からPTH（7-84）様fragments濃度を決定した。

C．研究結果及び考察

Bio-PTH濃度は、正常者22.3±7.1pg/mlに比べ、PHP 252.5±124.8 pg/mlと増加していた（P<0.01）。更に、BioPTH/iPTH比は、正常者0.77±0.06、PHP 0.64±0.03であった（P<0.01）。PTH（7-84）様 fragmentsの濃度も、正常者7.2±4.1pg/mlに対し、、PHP 142.5±76.9 pg/mlと増加していた（P<0.01）。PTH（7-84）/Bio-PTH比は、正常者0.30±0.11、PHP 0.56±0.07であった（P<0.01）。

PHP患者では、血中Bio-PTH値とPTH（7-84）様fragmentsがいずれも増加していることが明かとなった。また、PTH（7-84）様fragmentsの割合が正常者に比べ増加していることも明らかとなった。従って、PHPではPTHの合成分泌と分解のいずれもが亢進していると考えられた。

D．評　価

1）達成度について

血中PTH分子の存在様式の検討は、計画を達成することができた。

2）研究成果の学術的国際的社会的意義について

Bio-PTHに特異的な測定系を用いてのPHPにおける血中PTH分子の存在様式の最初の検討であり、PHPの新たな診断基準の基礎となるデータが得られた。

3）今後の展望について

BioPTHを用いてのPHPの新たな診断基準を確定する必要があると考えられる。

4）研究内容の効率性について

BioPTHに特異的な測定系が確立されたため、PHPの病態解明とその診断技術の向上は更に進むと考えられる。

E．結　論

Bio-PTHに特異的な測定系を用いた検討によ

って、PHPにおいてはPTHの分泌代謝動態がいずれも亢進していることが明らかとなった。Bio-PTHの測定は、副甲状腺機能の正確な評価のために重要と考えられるが、従来のintact PTHassayによる測定値との比較は、PHPにおけるPTH代謝異常を検討する上に有用と考えられた。

F．研究発表

論文発表

Hatakeyama Y, Mizunashi K, et al. Plasma levels of PTH (1-84) whole molecule and PTH (7-84) -like fragments in pseudohypoparathyroidism type I. J Clin Endocrinol Metab. 2003. 88 : 2250-5

G．知的所有権の出願取得状況

なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

高Ca尿症を呈した偽性副甲状腺機能低下症Ib症例における Ca受容体変異に関する研究

研究協力者　水梨一利　東北大学医学研究科腎高血圧内分泌内科　助手

A　研究目的

胸椎後靱帯骨化症を契機に偽性副甲状腺機能低下症Ib型と診断された症例において、低Ca血症にも関わらずCaの尿中排泄量の増加が認められた。本症例における高Ca尿症の発症機序を解明するとともに、有効でかつ安全な治療法の確立を目的として、vitaminD_3投与後の尿中Ca排泄量の推移を検討した。

B．研究方法

Ca受容体（CaR）のcoding region（exon2-7）をPCRにて増幅し、direct sequenceした。下に示すようなmissense mutationが認められたので、mutant CaRをHEK293細胞に発現し機能解析を行った。

C．研究結果及び考察

CaRのcodon592にheterozygousなmissense mutation（Asn→Ser）が認められた。CaRのmissense mutationは、主にcodon 1-300とcodon 520-881に認められているが、本症例の変異は、後者のclusterに存在していた。

mutant CaRの細胞外Ca濃度の変化に対する反応性は亢進していた（EC50：mutant CaR3.2mM,wild-type 2.4mM）。したがって、CaRのactive mutationが高Ca尿症の原因と考えられた。

1αOHD_3（1μg/day）投与後、尿中Caは一過性に増加したが、1αOHD_3の投与を継続したところ、血清Caの正常化とともに尿中Caも正常化した。血清PTH値は、1αOHD_3投与前640-755pg/ml、投与後382-685pg/mlであった。CaRのactive mutationによるhypoparathyroidismにPTH（1-34）を皮下注することにより、尿中および血清Caを正常化することが報告されている。我々の症例では、少量の1αOHD_3投与により血清PTHを高値に保つことで、血清および尿中Caを正常化できたと考えられる。

D．評　価

1）達成度について

高Ca尿症を伴ったPHPIb型症例の発症機序の解明と治療法の確立は、計画を達成することができた。

2）研究成果の学術的国際的社会的意義について

CaRのactive mutationを伴ったPHPは極めて稀な症例で、尿中Caを増加させずに治療する方法を見出すことができた。

3）今後の展望について

CaRのactive mutationを伴ったPHPの治療を継続中であるが、腎機能と骨量の長期予後と現在の治療法の安全性を検討する必要がある。

4）研究内容の効率性について

PHPは稀な疾患ではあるが、その病態解明は着実に進んでいる。Protein chipが実用化されたため、病態解明と診断技術の向上は更に進むと考えられる。

E．結　論

Caの尿中排泄量の増加を伴ったPHPIbの症例にCaRのactive mutationが認められ、これが高Ca尿症の原因と考えられた。さらに少量の1αOHD$_3$投与により血清PTHを高値に保つことで、血清および尿中Caを正常化できた。高Ca尿症を伴ったPHPIbの症例において、その発症機序を解明し、安全な治療法を確立することができた。

F．研究発表

論文発表

Mizunashi K et al. Low dose 1α-hydroxylated vitamin D3 normalized calcium excretion in a patient with activating mutation of calcium-sensing receptor and pseudohypoparathyroidism type Ib. J Am Soc Nephrol（on revision）.

G．知的所有権の出願取得状況

なし