

(様式1)

公益社団法人日本栄養・食糧学会研究業績

<学 会 賞>

1. 候補者

研究題目:(和)	糖・脂質代謝異常症の遺伝因子と食事因子に関する研究		
(英)	Studies on genetic and nutritional factors for disorders of glucose and lipid metabolism.		
氏 名:(和)	堀尾 文彦		
(英)	Fumihiko Horio		
所属機関:(和)	名古屋大学大学院生命農学研究科・教授		
(英)	Graduate School of Bioagricultural Sciences, Nagoya University, Professor		
学 位:	農学博士	最終学歴:	昭和 58 年 3 月、名古屋大学大学院農学研究科博士課程(後期)満了
専門分野	①栄養生理学、②栄養生化学、③分子栄養学、④公衆栄養学、⑤臨床・病態栄養学、⑥食生態学、⑦調理科学、⑧食品化学・食品分析学、⑨食品機能学、⑩食品工学、⑪食品加工・流通・貯蔵学、⑫食品衛生・安全学、⑬生理学、⑭生化学、⑮分子生物学、⑯臨床医学(内科系)、⑰臨床医学(外科系) ⑱その他		
履 歴	昭和 58 年 4 月 日本学術振興会特別研究員 昭和 58 年 6 月 名古屋大学農学部助手 昭和 63 年 3 月 米国コーネル大学(Div. Nutritional Sciences)客員研究員 (同年 12 月まで) 平成元年 1 月 米国ハーバード大学(Joslin Diabetes Center)博士研究員 (同年 12 月まで) 平成 7 年 1 月 名古屋大学農学部助教授 平成 16 年 4 月 中部大学応用生物学部教授 平成 18 年 4 月 名古屋大学大学院生命農学研究科教授 現在に至る。		
会員番号:		入会年度:	昭和 55 年

2. 研究業績要旨(1,000字以内)

候補者は、遺伝因子と食事因子との組み合わせによって発症する糖・脂質代謝異常症の予防と改善を目指し、本疾患を発症させる遺伝子の同定と、発症を抑制する食事因子の探求とを目的として研究を進めてきた。

遺伝因子に関しては、糖尿病を発症しない SM/J マウスと A/J マウスから作出された SMXA 組換え近交系統の中に 2 型糖尿病と脂肪肝を発症する系統 (SMXA5 マウス) を見出した。この現象は、正常な SM/J および A/J マウスそれぞれが有している潜在的な糖尿病遺伝子が組み合わさって糖尿病が発症することを示しており、ヒトの糖尿病の発症機構の解明に繋がる成果である (報文リスト論文 10)。さらに、SMXA5 マウスの 2 型糖尿病と脂肪肝は高脂肪食摂取により著明に重篤化することも見出した (9)。この SMXA5 マウスの原因遺伝子を同定するために高脂肪食摂取下での量的形質遺伝子座解析を行って、糖尿病遺伝子座は第 2 番染色体に、脂肪肝遺伝子座は第 12 番染色体に存在することを示した (6, 7, 8)。そして、これらの遺伝子座を含む SMXA5 の染色体断片を対照マウスに導入した染色体部分置換マウスを作出して原因遺伝子の染色体上の存在領域を狭めることに成功した。糖尿病遺伝子については SMXA5 で変異が見出された 4 つの候補遺伝子として *Itga6*, *Zak*, *Gpr155*, *Mtx2* を選抜している (3)。さらに、脂肪肝遺伝子については、エステラーゼに属する有力な候補遺伝子: *Iah1* が脂質代謝に関与することを見出し (2, 12)、本遺伝子の改変マウスを作製して脂肪肝発症作用の証明を進めている。

食事因子に関しては、コーヒー、植物性タンパク質、キノコ由来ペプチドなどの糖尿病発症抑制効果を見出した。中でも、コーヒー摂取は 2 型糖尿病モデルマウスにおいて骨格筋や肝臓でのインスリン感受性を亢進させて高血糖発症を抑制することと、脂肪肝を抑制することを見出し、その有効成分の 1 つがカフェインであることを明らかにした (4, 5, 24)。さらに、コーヒー摂取は膵臓 β 細胞の保護作用があり、薬剤誘発性 1 型糖尿病を発症抑制できることも明らかにした (1)。

候補者のこれらの研究により、同定された遺伝子の作用による糖尿病・脂肪肝の新規な発症機構の発見が期待でき、発症を抑制する食事因子はこれらの疾患を予防する食生活の構築に貢献できる。

3. 報文等リスト

- (1) この研究に直接関連するもの
- (2) の(10編以内)

- (1) * Kobayashi M., Kurata T., Hamana Y., Hiramitsu M., Inoue T., Murai A. and **Horio F.**: Coffee ingestion suppresses hyperglycemia in streptozotocin-induced diabetic mice. *J.Nutr.Sci.Vitaminol.*, 63,200-207(2017)
- (2) Kobayashi, M., Suzuki, M., Ohno, T., Tsuzuki, K., Taguchi, C., Tateishi, S., Kawada, T., Kim, Y., Murai, A. and **Horio, F.**: Detection of differentially expressed candidate genes for a fatty liver QTL on mouse chromosome 12. *BMC Genet.*, 17,73(2016)
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- (4) * Kobayashi, M., Matsuda, Y., Iwai, H., Hiramitsu, M., Inoue, T., Katagiri, T., Yamashita, Y., Ashida, H., Murai, A. and **Horio, F.** : Coffee improves insulin-stimulated Akt phosphorylation in liver and skeletal muscle in diabetic KK-*Ay* mice. *J.Nutr.Sci.Vitaminol.*, 58,408-414(2012)
- (5) Yamauchi, R., Kobayashi, M., Matsuda, Y., Ojika, M., Shigeoka, S., Yamamoto, Y., Tou, Y., Inoue, T., Katagiri, T., Murai, A. and **Horio, F.**: Coffee and caffeine ameliorate hyperglycemia, fatty liver, and inflammatory adipocytokine expression in spontaneously diabetic KK-*Ay* mice. *J.Agric.Food Chem.* , 58,5597-5603(2010)
- (6) Hada, N., Kobayashi, M., Fijiyoshi, M., Ishikawa, A., Kuga, M., Nishimura, M., Ebihara, S., Ohno, T. and **Horio, F.**: Quantitative trait loci for impaired glucose tolerance in nondiabetic SM/J and A/J mice. *Physiol. Genomics* , 35,65-74(2008).
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- (8) Kobayashi, M., Io, F., Kawai, T., Kumazawa, M., Ikegami, H., Nishimura, M., Ohno, T. and **Horio, F.**: Major quantitative trait locus on chromosome 2 for glucose tolerance in diabetic SMXA-5 mouse established from nondiabetic SM/J and A/J strains. *Diabetologia*, 49,486-495 (2006)
- (9) Kobayashi, M., Io, F., Kawai, T., Nishimura, M., Ohno, T. and **Horio, F.**: SMXA-5 mouse as a diabetic model susceptible to feeding a high-fat diet. *Biosci.Biotechnol.Biochem.*, 68,226-230 (2004)
- (10) Kobayashi, M., Ohno, T., Tsuji, A., Nishimura, M. and **Horio, F.**: Combinations non-diabetic parental genomes elicit impaired glucose tolerance in mouse SMXA RI strains. *Diabetes*, 52,180-186 (2003)

- (2) その他の論文(編数制限なし)

【原著論文】

- (11) Ohno T., Maegawa T., Kato H., Miyasaka Y., Suzuki M., Kobayashi M. and **Horio F.**: A new missense mutation in the paired domain of the mouse *Pax3* gene. *Exp.Anim.*, 66, 245-250 (2017)
- (12) Suzuki, M., Kobayashi, M., Ohno, T., Kanamori, S., Tateishi, S., Murai, A. and **Horio, F.**: Genetic dissection of the fatty liver QTL *F11sa* by using congenic mice and identification of candidate genes in the liver and epididymal fat. *BMC Genet.*, 17,145(2016)
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- (14) Murai, A., Kitahara, K., Okumura, S., Kobayashi, M. and **Horio, F.**: Oral antibiotics enhance antibody responses to keyhole limpet hemocyanin in orally but not muscularly immunized chickens. *Anim. Sci. J.*, 87, 257-265(2016)
- (15) Tokuda, Y., Miura, N., Kobayashi, M., Hoshinaga, Y., Murai, A., Aoyama, H., Ito, H., Morita, T. and **Horio, F.**: Ascorbic acid deficiency increases endotoxin influx to portal blood and liver

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- (16) Kobayashi, M., Hoshinaga, Y., Miura, N., Tokuda, Y., Shigeoka, S., Murai, A. and **Horio, F.**: Ascorbic acid deficiency decreases hepatic cytochrome P-450, especially CYP2B1/2B2, and simultaneously induces heme oxygenase-1 gene expression in scurvy-prone ODS rats. *Biosci.Biotechnol.Biochem.*, 78(6),1060-1066(2014)
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- (21) Ohno, T., Hata, K., Baba, T., Io, F., Kobayashi, M., **Horio, F.** and Nishimura, M. : Establishment of consomic strains derived from A/J and SM/J mice for genetic analysis of complex traits. *Mamm.Genome*, 23,764-769(2012)
- (22) Kobayashi, M., Kawashima, H., Takemori, K., Ito, H., Murai, A., Masuda, S. , Yamada, K., Uemura, D. and **Horio, F.** : Ternatin, a cyclic peptide isolated from mushroom, and its derivative suppress hyperglycemia and hepatic fatty acid synthesis in spontaneously diabetic KK- A^y mice. *Biochem.Biophys.Res.Commun.*, 427,299-304(2012)
- (23) Minakata, K., Yamagishi, I., Nozawa, H., Gonmori, K., Hasegawa, K., Suzuki, M., **Horio, F.**, Watanabe, K. and Suzuki, O.: Simultaneous determination of coinage metals, copper, silver, and gold in tissues using electrospray ionization tandem mass spectrometry. *Forensic Toxicol.*, 30, 149-155(2012)
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- (27) Kitaguchi, K., Bae, H.-D., Sasanami, T., Kobayashi, M., **Horio, F.** and Murai, A.: Microscopic detection of IgY-Fc binding signal in the inner layers of ovarian follicular tissue in quail. *Anim.Sci.J.*, 81,580-585(2010)
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- (33) Tanaka, S., Mizorogi, T., Nishijima, K., Kuwahara, S., Tsujio, M., Aoyama, H., Taguchi, C., Kobayashi, M., **Horio, F.** and Ohno, T.: Body and major organ weights of A/J-Chr 11(SM) consomic mice. *Exp.Anim.*, 58,357-361(2009)
- (34) Murai, A., Furuse, M., Kitaguchi, K., Kusumoto, K., Nakanishi, Y., Kobayashi, M. and **Horio, F.**: Characterization of critical factors influencing gene expression of two types of fatty acid-binding proteins (L-FABP and Lb-FABP) in the liver of birds. *Comp.Biochem.Physiol.(A)* 154,216-223(2009)
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(3) 過去 5 年間の本学会での活動状況

<学会役員・各種委員・支部役員>

平成 24 年～現在 代議員 (平成 12 年～23 年は評議員・参与)

平成 23 年～現在 J.Nutr.Sci.Vitaminol. 編集委員

平成 26 年～27 年 理事

平成 26 年～27 年 学会活動強化委員会委員

平成 24 年～25 年 日本栄養・食糧学会中部支部 支部長

<大会・支部大会での座長等>

平成 28 年 第 71 回日本栄養・食糧学会支部大会一般講演座長

平成 27 年 第 69 回日本栄養・食糧学会支部大会一般講演座長

平成 25 年 第 67 回日本栄養・食糧学会大会シンポジウム・オーガナイザーおよび座長

(4) 特記事項

平成 27 年 日本ビタミン学会 学会賞

平成 4 年 日本栄養・食糧学会 奨励賞