# 2.7.5 Laboratory: Molecular Function of Food

Member:	Professor	Kawada, Teruo, Dr. Agric. Sci.
	Associate Professor	Urade, Reiko, Dr. Agric. Sci.
	Assistant Professor	Takahashi, Nobuyuki, Dr. Med. Sci
	Doctor's program	5
	Master's Program	15
	Undergraduate	4
	Other	1
	Post-Doctoral fellow	1

### A. Research Activities (2009.4-2010.3)

#### A-1. Main Subjects

a) Genomic regulatory science on lipid metabolism and obesity

Overweight is superfluous formation of the fat, which constitutes an adipose tissue. It has been pointed out that the factor secreted from a fat cell as a key factor of a lifestyle-related diseases of recent years. Multiplication of a fat cell, specialization, and secretion of the various factor further related to development of symptoms are strongly influenced by the food ingredient to daily take. As a result of analyzing the transcriptional regulation mechanism over the target gene of PPARs (peroxisome proliferator-activated receptors), which are the master regulator of specialization of a fat cell differentiation. And then we found out that CREB-binding protein (CBP) was the indispensable factor of fat cell specialization. Furthermore, the activation factor of PPARs which promotes carbohydrate metabolism and lipid metabolism using this system was found out to natural occurring materials, especially a medicinal herb, or plants.

b) Basic and applied studies on energy and lipid metabolism aimed at prevention of the life-style related disease and metabolic syndrome

Initiation and progression of the life-style related disease are involved in the lipid metabolism in the various organs including gastrointestinal tract, liver and adipose tissue. For understanding and prevention of these diseases, we are performing the basic studies about lipid metabolism and adipocyte function, and applied studies about food factors regulating lipid metabolism properly. Our current research topics are 1) the screening of natural products for normalizing lipid metabolism, 2) basic and applied studies about lipoproteins in liver and small intestine, and 3) analysis of molecular mechanisms that monitor hypertrophy of adipocytes.

c) Molecular food function on the regulation of obesity-related inflammatory pathologies
Arteriosclerosis and the allergy are the familiar living body inflammations caused by food and the genetic background. The importance of the cytokines and chemokines such as tumor necrosis factor (TNF)-a, adiponectin, and monocyte chemoattractant protein-1 (MCP-1) in the lifestyle disease is clarified inside and outside the country in recent years. The chemokine is a super-family of the cytokine of cell migration (chemoattractant), and it is known as inflammatory mediator. In addition, the function has been found receiving the modification by various nutrients and the food factors. This research theme clarifies the realities of a chemical factor that it develops metabolic syndrome from the aspect of the cytokine and chemokine.
d) Studies on signaling network of lipid metabolism among organs/tissues.

Communication among organs/tissues is indispensable for the homeostasis. For example, nutrients derived from foods are recognized on the gastrointestinal epithelial cells so that gastrointestinal hormones are released from specific endocrine cells. The gastrointestinal hormones regulate metabolism and/or functions in other organs and tissues like the liver and adipose tissues. Disruption in such network may induce various diseases of metabolism. We are elucidating mechanism of the network composed by the liver, intestine, and adipose tissues, which are significant for systemic regulation of lipid metabolism. Our final purpose is to clarify relationship between regulation of the network and development of lipid metabolism abnormalities.

e) Studies on folding and quality control of protein in endoplasmic reticulum.

The endoplasmic reticulum (ER) is the site of synthesis and posttranslational modifications of secretary and membrane proteins. The ER also plays an important role in folding and quality control of nascent polypeptides. The nascent polypeptides translocated into the ER are folded with assistance of molecular chaperones and many enzymes, which are localized in the ER. The unfoled and misfolded proteins are removed from the transport pathway to the Golgi and then degraded by ER-associated degradation systems. Our primary research goal of this project is to clarify the interactions between nascent polypeptide, molecular chaperones and enzymes during folding of proteins and its regulatory mechanism. We are also studying the roles of ER chaperones and enzymes on the regulation of VLDL secretion from liver, which is an important factor affecting serum triacylglycerol level. In addition, we are interested in the folding mechanism of soybean storage proteins. We are actively studying the characteristics and expression profiles of soybean ER-resident chaperons and their interactions with storage proteins during maturing of cotyledon.

f) Basic and applied studies on dietary lipids and health.

Intensive studies using bacteria, plant and animal culture cells, rat heart and platelets have been performed focusing how dietary lipids consisting of various fatty acids influence on the structure and function of biological membrane. Previously, the toxic effects of saturated fatty acids, erucic acid and trans-fatty acids on animal cells have been revealed. We also have demonstrated that linoleic acid is an essential component for respiratory enzyme, cytochrome c oxidase in heart mitochondria. Moreover, arachidonoyl molecular species of phosphatidylinositol was shown to plays a primary role on the signal transduction for activation of platelets by using methods for phospholipid molecular species analysis, which was progressed by our laboratory. Based on those studies on the physiological roles of dietary lipids at the molecular levels, a reasonable way to intake fatty acids for health is being designed.

#### **A-2.Publications and presentations**

a) Publications

Books

- 後藤剛、李周容、寺南亜紀、高橋信之、河田照雄:肥満症:栄養素によるエネルギ 一代謝調節 『脂肪細胞での代謝調節』日本臨床 増刊号 印刷中

- 高橋信之、大山夏奈、千田真里、西村加奈子、河田照雄:カロテノイドの科学と最 新応用技術 第11章「カンキツ由来カロテノイドの機能性」シーエムシー出版 2009.

- Takahashi, N., Goto, T., Hirai, S., Uemura, T. and Kawada, T. Genome science of lipid metabolism and obesity. in "FOOD FACTORS for HEALTH PROMOTION" (Editor: Dr. T. Yoshikawa, Kyoto, Japan), Forum Nutri., 61, 25-38, 2009

- Teruo Kawada, Tsuyoshi Goto, Shizuka Hirai, Rina Yu, and Nobuyuki Takahashi. Obesity and Nuclear Receptors : Effective Genomic Strategies in Functional Foods. in : NUTRIGENOMICS AND PROTEOMICS IN HEALTH AND DISEASE (Yoshinori Mine, Kazuo Miyashita and Fereidoon Shahidi,Eds), pp. 47-58. WILEY-BLACK WELL, 2009.

- Tsuyoshi Goto, Nobuyuki Takahashi, Shizuka Hirai, and Teruo Kawada. Isoprenols : Effective Genomic Strategies in Functional Foods. in : NUTRIGENOMICS AND PROTEOMICS IN HEALTH AND DISEASE (Yoshinori Mine, Kazuo Miyashita and Fereidoon Shahidi,Eds), pp. 301-310. WILEY-BLACK WELL, 2009.

- Kamiya Y, Kamiya D, Urade R, Suzuki T, Kato K : Sophisticated Modes of Sugar Recognition by Intracellular Lectins Involved in Quality Control of Glycoproteins in Book "Glycobiology Research Trends" Edited by Powell G and McCabe O, 27-40, Nova Science Publishers, Inc. 2009.

## **Original Papers**

- Takahashi, N.\*, Goto, T.\*, Taimatsu, A., Egawa, K., Katoh, S., Kusudo, T., Sakamoto, T., Ohyane, C., Lee, J.Y., Kim, Y.I., Uemura, T., Hirai, S. and Kawada, T. Bixin regulates gene expression involved in adipogenesis and enhances insulin sensitivity in 3T3-L1 adipocytes through PPAR-gamma activation. Biochem. Biophys. Res. Commun., 390:1372-1376, 2009 (\* equal contributions).

- Ando, C.\*, Takahashi, N.\*, Hirai, S.\*, Lee, J.Y., Goto, T., Yu, R. and Kawada, T. Luteolin, a food-derived flavonoid, inhibits adipocyte-dependent activation of macrophages in adipose tissues. FEBS Lett. 583:3649-3654, 2009 (\* equal contributions).

- Kang, M.S., Hirai, S., Goto, T., Kuroyanagi, K., Kim, I.Y., Ohyama, K., Uemura, T., Lee, J.Y., Sakamoto, T., Ezaki, Y., Yu, R., Takahashi, N. and Kawada, T. Dehydroabietic acid, a phytochemical, acts as ligand for PPARs in macrophages and adipocytes to regulate inflammation of mouse adipose tissues. BioFactors, 35, 442-448, 2009.

- Kang J-H, Goto T, Han I-S, Kim C-S, Kawada T, Kim Y-M, Yu R. Dietary Capsaicin reduces Obesity-induced Insulin Resistance and Hepatic Steatosis in Obese Mice fed a High-fat Diet. Obesity, in press, 2009

- Iwasaki,K. ,Kamauchi, S., Wadahama, H., Ishimoto, M., Kawada, T. and Urade, R. Molecular cloning and characterization of soybean protein disulfide isomerases family proteins with nonclassic active center motifs. FEBS J. 276: 4130-4141, 2009.

- Lee HS, Park JH, Kang JH, Kawada T, Yu R, Han IS Chemokine and chemokine receptor gene expression in the mesenteric adipose tissue of KKAy mice. Cytokine. 46: 160-165, 2009.

- Mochizuki Y, Maebuchi M, Kohno M, Hirotsuka M, Wadahama H, Moriyama T, Kawada T, Urade R. Changes in lipid metabolism by soy beta-conglycinin-derived peptides in HepG2 cells. J Agric Food Chem. 57:1473-1480, 2009.

#### Reviews

- Urade R. The endoplasmic reticulum stress signaling pathways in plants. BioFactors 35: 326-331, 2009.

#### Patents

- Kawada T., Takahashi N., Hirai S., Kim YI, Takahashi H., Shibata D., Aoki K., Iijima Y., Tsugane T., Inai S., Fujii T., Konishi C., "anti-metabolic syndrome medicine containing tomato extracts". 2010-053886

b) Conference and seminar papers presented

- The 2010 Annual Meeting of Japan Society for Bioscience, Biotechnology and Biochemistry (1)

- The 63th Annual Meeting of Japan Society for Nutrition and Food Science (7)
- The 2009 Annual Meeting of Japan Society for the Study of Obesity (6)
- The 2009 Annual Meeting of Biochemistry (1)
- The 34rd FEBS Congress (1)
- The 14th International Congress of Endocrinology (3)

#### A-3.Off-campus activities

#### Membership in academic societies

- Kawada, Teruo, Dr. Agric. Sci. : Japan Society for the Study of Obesity (General affairs & publicity committee), Japan Society for Bioscience, Biotechnology, and Agrochemistry (Kansai Branch general affairs), The Japan Endocrine Society (General affairs), Study Group on Adiposcience (General affairs)

- Takahashi, Nobuyuki, Dr. Med. Sci : Japan Society for the Study of Obesity (Councilor), The Physiological Society of Japan (Councilor), The Molecular Biology Society of Japan

# Research grants

1. Grants-in-aid for Scientific Research(KAKENHI)

- Scientific Research (B) : Kawada, Teruo, Dr. Agric. Sci. : The signal transduction of Dietary fat and energy metabolism via nuclear receptors

- Scientific Research (B) : Urade, Reiko, Dr. Agric. Sci. : Gene targeting analysis of a folding enzyme ER-60 localized in the endoplasmic reticulum

2. Other Research Grants

- Research and Development Program for New Bio-industry Initiatives: Kawada, Teruo, Dr. Agric. Sci.: Development of functional food for the prevention hay fever and life-style related disease

- The Iijima Memorial Foundation For The Promotion Of Food Science And Technology: Research Grant: Urade, Reiko, Dr. Agric. Sci.: Improvement of dough quality and loaf volume of bread by reduced and oxidized glutathione

- Fiji Foundation For Protein Research: Research Grant: Urade, Reiko, Dr. Agric. Sci.: Physiological Function of Highly Purified Soy Proteins

## A-4.International cooperation and overseas activities

International joint research, overseas research surveys

- Studies on cytokine and chemokine from adipose tissue and obesity related diseases, Kawada and University of Ulsan, South Korea

- Studies on differentiation and proliferation of adipose stem cells, Kawada and INSERM, France

- Studies on the roles of ER-60 on regulatory degradation of ApoB-100, Urade and Toronto University, Canada

## **B.Educational Activities**(2009.4-2010.3)

## **B-1.On-campus teaching**

a) Courses given

- Undergraduate level :	Molecular Function of Food (Kawada and Urade), Introduction and
	practice in the department of food science and biotechnology I
	(Kawada and Urade), Food biochemistry II (Kawada), Food
	biochemistry I (Urade), Food Safety II (Kawada), Laboratory
	Course in Enzyme Chemistry and Biochemistry (Urade and
	Takahashi)
- Graduate level:	Advanced Course in Food and Health Science (Kawada), Seminar
	on Molecular Function of Food Constituents (Kawada, Urade, and
	Takahashi), Experimental Course in Molecular Function of Food
	Constituents (Kawada, Urade, and Takahashi)

## **B-2.Off-campus teaching etc.**

Part-time lecturer

- Kawada, Teruo: Dosisha women's University, Faculty of Human Life and Science(Enzyme Science), Saga University (Bioresource chemisrty )

# **B-3.**Overseas teaching

International students

- International students : Master 2 (Taiwan 1, China 1) Doctral 1 (Korea) Research Students 1 (Korea)