Chair Food Life Sciences

2.7.3 Laboratory : Laboratory of Organic Chemistry in Life Science

Member :	Professor	Irie, Kazuhiro, D. Agric. Sci.
	Assistant Professor	Murakami, Akira, D. Agric. Sci. & Murakami, Kazuma, D. Agric. S
	Collaborative Laborator	Hirai, Nobuhiro, D. Agr. Sci. (comparative agricultural science)
	Doctor's program	3
	Master's Program	7
	Undergraduate	3
	Post-Doctoral fellow	1
	Researcher	1

A. Research Activities (2010.4-2011.3)

A-1. Main Subjects

a) Challenges to the development of bryostatin-type anticancer drugs

Protein kinase C (PKC) isozymes are widely recognized as targets for anti-cancer therapy. However, concerns exist about their therapeutic uses since most PKC activators are potent tumor-promoters. Bryostatin 1 (bryo-1) is a unique PKC activator with little tumor-promoting activities. Bryo-1 is currently undergoing clinical trials for the treatment of cancer. However, its limited availability from natural sources and difficulty in the synthesis hamper further studies on its mode of action and structural optimization. Recently, we reported that the simple and less lipophilic analogue of tumor-promoting aplysiatoxin could be a promising lead for bryo-1-like anti-cancer drugs. In order to enhance its anti-proliferative activity against cancer cells, aplog-1 was derivatized systematically. The results indicated the the hydrophobicity around the spiroketal moiety plays a critical role in the anti-proliferative activity and binding to PKC isozymes. In contrast, the phenol hydroxyl group in the side chain was not necessary for these activities.

b) Chemistry of amyloid β peptides

Aggregation of the 42-mer amyloid β protein (Aβ42) plays a critical role in the pathogenesis of Alzheimer's disease (AD). We have reported the importance of a turn at Glu-22 and Asp-23 of Aβ42 to induce its neurotoxicity through the formation of radicals. Recently, Mori and colleagues have found a novel deletion mutant at Glu-22 (E22D-Aβ42) to accelerate oligomerization and synaptotoxicity. To investigate this mechanism, the effects of the E22D mutation in Ab42 and Ab40 on b-sheet transformation, radical production, and neurotoxicity were examined. Both mutants promoted b-sheet transformation and radical production, but their neurotoxicity in PC12 cells and primary neuronal culture cells was negative. In contrast, E22P-Ab42 with a turn at Glu-22 and Asp-23 exhibited potent neurotoxicity along with the ability to form radicals and to induce potent synaptotoxicity. These data suggest that conformational change in E22D mutants of Ab42 and Ab40 is similar to that in E22P-Ab42, but not the same.

c) Physiological functions of food factors and their undelying molecular mechanisms

Zerumbone, a sesquiterpene found in subtropical ginger, covalently binds to the cysteine thiols of two key proteins for exerting its biological functions. We generated an antibody that recognizes zerumbone-adducted proteins to explore the roles of these non-specific bindings. Western blot analysis showed that zerumbone-treated hepa1c1c7 cell lysates displayed numerous bands from the adducted proteins. In addition, incubation of cells with zerumbone led to their global localization in both cytoplasmic and nuclear compartments. Furthermore, profound upregulation of expressions of a series of molecular chaperones such as HSPs was seen, which may have been an adaptive response to protein denaturing stress. Results of immunoprecipitation of zerumbone-treated cell lysates with the HSP90 antibody suggested that the adducted proteins were recognized, at least in part, by HSP90 for induction of HSPs. Interestingly, pretreatment of hepa1c1c7 cells with this agent also increased their heat resistance.

d) Molecular technology of a plant hormone, abscisic acid

Abscisic acid (ABA) is an important plant hormone that induces adaptative responses in plants upon water stress and low temperature. However, the effect of ABA does not last since ABA is quickly inactivated by the degradation enzyme, ABA 8'-hydroxylase. Inhibitors of the hydroxylase may delay the inactivation of ABA to increase resistance of plants to environmental stress. We have developed and improved hydroxylase inhibitors with the researchers at Shizuoka University and Chiba University. Phaseic acid is a metabolite of ABA having a moderate activity, and its reductase completely inactivates phaseic acid by conversion to dihydrophaseic acid. To develop inhibitors of the reductase, we purifyed the phaseic acid reductase and analyzed the amino acid sequence by MS. The result suggested that a known enzyme had high homology to the reductase.

e) Chemical ecology of ectomycorrhiza

Some ectomycorrhiza form a fairy ring which shows the circular formation of fruit body. The inside of the fairy ring of Tricholoma is a whitish mycelium-soil aggregated zone, and called “shiro”. The density of bacteria and fungi in the shiro is significantly lower than that of the outside of the shiro. The researchers of our University demonstrated in 1967 that the shiro had antimicrobial activity against bacteria. However, the antimicrobial compound(s) has been remained unclear. We identifyed an antimicrobial compound of the roots of Pinus densiflora growing at the Kamigamo research field of Kyoto University as totarol. In 2009, We have obtained ectomycorrhiza of P. densiflora growing at the Sakai research field of Kyoto Prefecture. The ectomycorrhiza contained a water-soluble antibacterial compound. The compound is heat-stable, and different from known antibitotics. Purifycation of this compoud is under progress.

A-2.Publications and presentations

a) Publications

Books

- Murakami, A.: Cancer Preventive Phytochmicals from Southeast Asian Countries: In Vivo Activities and Underlying Molecular Mechanisms. In Bioactive Foods and Extracts, Watson, R.R, Preedy, VR (Eds), pp. 211-221, CRC Press, 2010

- Hirai, N. Abscisic acid. In Comprehensive Natural Products Chemistry II. Vol. 4: Chemical Ecology, ed. by Mori, K., pp. 53-67, Elsevier, 2010

Original Papers(including book-reviews)

- Nakagawa, Y., Kikumori, M., Yanagita, R. C., Murakami, A., Tokuda, H., Nagai, H. and Irie, K.: Synthesis and biological evaluation of the 12,12-dimethyl derivative of aplog-1, an anti-proliferative analogue of tumor-promoting aplysiatoxin. Biosci. Biotechnol. Biochem., in press, 2011

- Murakami, K., Murata, N., Ozawa, Y., Kinoshita, N., Irie, K., Shirasawa, T. and Shimizu, T.: Vitamin C restores behavioral deficits and Aβ oligomerization without affecting plaque formation in a mouse model of Alzheimer's disease. J. Alzheimers Dis., in press, 2011

- Yanagita, R. C., Kamachi, H., Tanaka, K., Murakami, A., Nakagawa, Y., Tokuda, H., Nagai, H. and Irie, K.: Role of the phenolic hydroxyl group in the biological activities of simplified analogue of aplysiatoxin with antiproliferative activity. Bioorg. Med. Chem. Lett., 20(20); 6064-6066, 2010

- Murakami, K., Horikoshi-Sakuraba, Y., Murata, N., Noda, Y., Masuda, Y., Kinoshita, N., Hatsuta, H., Murayama, S., Shirasawa, T., Shimizu, T. and Irie, K.: Monoclonal antibody against the turn of the 42-residue amyloid β-protein at positions 22 and 23. ACS Chem. Neurosci., 1(11); 747-756, 2010

- Murata, N., Murakami, K., Ozawa, Y., Kinoshita, N., Irie, K., Shirasawa, T. and Shimizu, T.: Silymarin attenuated the amyloid βplaque burden and improved behavioral abnormalities in an Alzheimer's disease mouse model. Biosci. Biotechnol. Biochem., 74(11); 2299-2306, 2010

- Suzuki, T., Murakami, K., Izuo, N., Kume, T., Akaike, A., Nagata, T., Nishizaki, T., Tomiyama, T., Mori, H. and Irie, K.: E22D Mutation in amyloid β-protein promotes β-sheet transformation, radical production and synaptotoxicity, but not neurotoxicity. Int. J. Alzheimers Dis., ID 431320 (8 pages), 2010

- Onuma, K., Suenaga, Y., Sakaki, R., Yoshitome, S., Sato, Y., Ogawara, S., Suzuki, S., Kuramitsu, M., Yokoyama, H., Murakami, A., Hamada, J., Nicolson, G.L., Kobayashi, M., Fujii, J. and Okada, F.: Development of a quantitative bioassay to assess preventive compounds against inflammation-based carcinogenesis. Nitric Oxide, in press, 2011

- Yamamoto, N., Kawabata, K., Sawada, K., Ueda, M., Fukuda, I., Kawasaki, K., Murakami, A. and Ashida, H.: Cardamonin stimulates glucose uptake through translocation of glucose transporter 4 in L6 myotubes. Phytother. Res., in press, 2011

- Sciullo, E.M., Vogel, C.F., Wu, D., Murakami, A., Ohigashi, H. and Matsumura, F.: Effects of selected food phytochemicals in reducing the toxic actions of TCDD and p,p'-DDT in U937 macrophages. Arch. Toxicol. 84(12); 957-966, 2010

- Yasuda, M.*, Schmid, T.*, Rubsamen, D., Colburn, N.H., Irie, K. and Murakami, A.: Down-regulation of programmed cell death 4 by inflammatory conditions contributes to the generation of the tumor promoting microenvironment. (*equally contributed). Mol. Carcinog. 49(9); 837-848, 2010

- Yasuda, M., Irie K. and Murakami, A.: Genistein inhibits lipopolysaccharide-induced down-regulation of programmed cell death 4 in RAW 264.7 mouse macrophages. Biosci. Biotechnol. Biochem. 74(5); 1095-1097, 2010

- Sekiguchi, H., Irie, K. and Murakami, A.: Auraptene suppresses Helicobacter pylori adhesion and IL-8 production via targeting ERK 1/2-dependent CD74 expression in NCI-N87 gastric carcinoma cells. Biosci. Biotechnol. Biochem. 74(5); 1018-1024, 2010

- Todoroki Y., Naiki, K., Aoyama, H., Shirakura, M., Ueno, K., Mizutani, M. and Hirai, N. Selectivity improvement of an azole inhibitor of CYP707A by replacing the monosubstituted azole with a disubstituted azole. Bioorg. Med. Chem. Lett., 20; 5506-5509, 2010

- Irie, K., Yanagita, R. C. and Nakagawa, Y.: Challenges to the development of bryostatin-type anticancer drugs based on the activation mechanism of protein kinase Cδ. Med. Res. Rev., in press.

- Murakami, K., Masuda, Y., Shirasawa, T., Shimizu, T. and Irie, K.: The turn formation at positions 22 and 23 in the 42-mer amyloid β peptide: the emerging role in the pathogenesis of Alzheimer's disease. Geriat. Geront. Int., 10; S169-S179, 2010

- Murakami, K., Shimizu, T. and Irie, K.: Formation of the 42-mer amyloid β radical and the therapeutic role of superoxide dismutase in Alzheimer's disease. J. Amino Acids, ID 654207 (10 pages), 2011

- Nishiumi, S.*, Miyamoto, S.*, Kawabata, K.*, Ohnishi, K., Mukai, R., Murakami, A., Ashida, H., Tera,o J.: Dietary flavonoids as cancer-preventive biofactors. Front Biosci, in press. *These authors equally contributed.

- Murakami, A: Functional components of zengiberaceous plants. Medical Herb, 14; 22-25, 2010

Reports,others

- Monbu-Kagakusho Research Grant. Scientific Research (A): Development of agents against Alzheimer's disease based on the structural analysis of amyloid beta oligomers (Irie, K., Head)

- Monbu-Kagakusho Research Grant. Scientific Research (C): Role of adipocytokines in colon carcinogenesis and identification of preventive food factors (Murakami, A., Head)

- Monbu-Kagakusho Research Grant. Scientific Research (C): Development of RNA aptamers against toxic oligomers of amyloid beta (Murakami, K., Head)

b) Conference and seminar papers presented

- The 2010 Annual Meeting of Japan Society for Bioscience, Biotechnology, and Agrochemistry (Kyoto): 13 Presentations, 1 Invited presentation

- The 33rd Annual Meeting of the Molecular Biology Society of Japan (Kobe): 1 Presentation

- The 14th Annual Meeting of Japanese Society for Food Factors (Sendai): 1 Presentation

- The 4th International Gastrointestinal Consensus Symposium (Kyoto): 1 Invited presentation

- The 6th International Conference on the Biology, Chemistry, and Therapeutic Applications of Nitric Oxide (Kyoto): 1 Presentation

- The 10th Annual Meeting of Anti-oxidant Biofactor Research (Kobe): 1 Presentation

- 2010 International Chemical Congress of Pacific Basin Societies (Honolulu): 5 Presentations, 1 Invited presentation

- The 5th Annual Meeting of The Chemical Biology: 1 presentation

- The 45th Annual Meeting of The Japanse Society for Chemical Regulation of Plants (Kobe): 5 Presentations

- The 2010 International Conference on Plant Growth Substances (Taragona): 1 Presentation

- The 49th Annual Meeting of the NMR Society of Japan (Tokyo): 1 Presentation

- 2010 Specialist Research Meeting on Abnormal Protein Aggregation and the Folding Diseases, and Their Protein and Repair System (Osaka): 1 Invited presentation

- The 29th Annual Meeting of Japan Society for Dementia Research (Nagoya): 1 Presentation

- 2010 Asia-Pacific EPR/ESR Symposium: 1 Invited presentation

- The 52nd Symposium on the Chemistry of Natural Products (Shizuoka): 1 Presentation

- The 45th Summer School on Natural Products Chemistry (Gamagohri): 1 Presentation

- The 51st Experimental Nuclear Magnetic Resonance Conference (Florida): 1 Presentation

A-3.Off-campus activities 1

Membership in academic societies

- Irie, Kazuhiro, D. Agric. Sci. : Japan Society for Bioscience, Biotechnology, and Agrochemistry (councilor), Japan Society for Bioscience, Biotechnology, and Agrochemistry in Kansai Branch (councilor), Japan Society for Dementia Research (councilar), Organizing committee of Symposium on The Chemistry of Natural Products (member), The Japanese Association for the Pursuit of New Bioactive Resources (councilor)

- Murakami, Akira, D. Agric. Sci. : Japanese Society for Oxidative Stress Research (councilor), Japanese Society for Food Factors (councilor), Japanese Association for Cancer Prevention (councilor)

- Murakami, Kazuma, D. Agric. Sci. : Organizing committee of Summer School on Natural Products Chemistry (member)

A-3.Off-campus activities 2

Research grants

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

- Scientific Research (A) : Irie, Kazuhiro, D. Agric.Sci : Development of agents against Alzheimer's disease based on the structural analysis of amyloid b oligomers

- Scientific Research (C) : Murakami, Akira, D. Agric.Sci : Role of adipocytokines in colon carcinogenesis and identification of preventive food factors

- Scientific Research (C) : Murakami, Kazuma, D. Agric.Sci : Development of RNA aptamers against toxic oligomers of amyloid β

2.Other Research Grants

- The Programme for Promotion of Basic and Applied Researches for Innovations in Bio-oriented Industry：Yamamoto-Maeda, Mari (Murakami, Akira, D. Agric.Sci, cooperator)：Cultivation of novel anthocyanin-rich tea cultivars with anti-fatigue activigty and development of their applied foods

A-4.International cooperation and overseas activities 1

Membership in academic societies

- Irie, Kazuhiro, D. Agric.Sci: American Chemical Society (member) , The Society for Neuroscience (member)

- Murakami, Akira, D. Agric. Sci.: American Association for Cancer Research (member)

- Murakami, Kazuma, D. Agric. Sci.: The Society for Neuroscience (member), American Chemical Society (member)

- Hirai, Nobuhiro, D. Agric. Sci.:

International meetings(country,roles)

- Irie, Kazuhiro, D. Agric. Sci.: The 51st Experimental Nuclear Magnetic Resonance Conference (Florida, USA, 1 presentation), 2010 International Chemical Congress of Pacific Basin Societies (PACIFICHEM 2010) (Hawaii, USA, 4 presentations)

- Murakami, Akira, D. Agric. Sci.: The 4th International Gastrointestinal Consensus Symposium (Japan, 1 invited presentation), The 6th International Conference on the Biology, Chemistry, and Therapeutic Applications of Nitric Oxide (Japan, 1 presentation), 2010 International Chemical Congress of Pacific Basin Societies (USA, 1 invited presentation)

- Murakami, Kazuma, D. Agric. Sci. : Asia-Pacific EPR/ESR symposium (Jeju, Republic of Korea, 1 invited presentation)

B.Educational Activities(2010.4-2011.3)

B-1.On-campus teaching

a) Courses given

- Undergraduate level: Organic Chemistry in Food Science I (Irie, K.), Organic Chemistry in Food Science II (Irie, K.), Organic Chemistry in Food Science III (Irie, K. and Murakami, K.), Organic Chemistry in Life Science (Irie, K.), Laboratory Course in Organic Chemistry (Irie, K., Murakami, A., Murakami, K. and Hirai, N.), Introduction and Practice in the Department of Food Science and Biotechnology (Irie, K., Murakami, A., Murakami, K. and Hirai, N., a partial charge)

- Graduate level: Organic Chemistry in Life Science, Advanced Course (Irie, K., Murakami, A., Murakami, K. and Hirai, N.), Seminar of Organic Chemistry in Life Science (Irie, K., Murakami, A., Murakami, K. and Hirai, N.), Experimental Course of Organic Chemistry in Life Science (Irie, K., Murakami, A., Murakami, K. and Hirai, N.)

B-2.Off-campus teaching etc.

Part-time lecturer

- Murakami, Akira, D. Agric.Sci.: Department of Pharmacy, Faculty of Pharmacy, Meijo University, Closely-packed series of lecture “Functional Food Sciences”

Open lectures, etc.

- Irie, Kazuhiro , D. Agric. Sci.: 2nd Symposium in Faculty of Agriculture, Kagawa University, "Reserch in life science from the standpoint of chemistry" (Lecturer), "Identification of the toxic conformer of amyloid b and development of new medicinal leads for Alzheimer's disease"

B-3.Overseas teaching 2

Lectures and seminars

- Kazuma Murakami

Alzheimer's Disease and Functional Foods(Lecturer) : Gwangju University(South Korea)

C.Other Remarks

- Murakami, Akira, D. Agric.Sci.：Review Committee of The Programme for Promotion of Basic and Applied Researches for Innovations in Bio-oriented Industry (member)