Asian Aging Core for Longevity Research (AACL) 2012 Seoul Conference

On Aging, Metabolism and Neurobiology

November 23-24, 2012
Natural Science Auditorium & International House Seminar room
University of Seoul

AACL 2006 at Ioujima Island, Nagasaki. June 17-19, 2006

- *The Regional Aging Connetion and the Future*
  Organized Mainly by Nozomu Mori

AACL 2008 at at Huis Ten Bosch, Nagasaki. Sep 4-6, 2008

- *Toward the establishment of Asian Aging Research and Education Center*
  Organized Mainly by Isao Shimokawa

AACL 2010 at Jeju Island, Jeju. Aug 22-24, 2010

- *Toward Friendship in Asian aging researches*
  Organized Mainly by Eun Seong Hwang

AACL 2011 at Nagasaki University, Nagasaki. Nov. 21-22, 2011

- *Brain Aging and Neurodegeneration: Molecular perspectives and Regional Bridging*
  Organized Mainly by Nozomu Mori

UNIVERSITY OF SEOUL

A brief introduction to University of Seoul

The University of Seoul was founded in 1918 and has since been providing higher education opportunities for the intelligent, motivated, and creative youths of Korea. As a public institution, the University of Seoul is committed to addressing the social, regional, technological, and creative issues of the urbanized world. It has thus dedicated itself to cultivating leaders who will shape the urban future of Korea and the world. The University of Seoul insists on quality and breadth, is committed to both theory and practice, and endorses an openness towards students, unique among Korea's elite institutions. With more than 10,000 students enrolled, the University of Seoul consists of seven undergraduate colleges and almost 90 fields of study in the Graduate School. It offers courses of study in eight schools and twenty seven departments.

Timeline : Ninety Years of UOS

The University of Seoul has its roots as an agricultural school first founded in 1918. In 1974, the school was re-established as a city university offering programs focused on disciplines that provide the knowledge-base of modern urban society. With the establishment of the College of Urban Sciences in 1996, its related programs and institutions have surged to the national and international forefront.

1918 Founded as Kyung Sung Public Agricultural College
1956 Upgraded to four-year college and renamed Seoul Agricultural College
1981 Renamed Seoul City University
1987 Upgraded to university status with 4 colleges and 22 departments
1996 Founded the College of Urban Sciences
1997 Renamed the University of Seoul

Faculty and Students

The student body consists of 7,500 undergraduate students and 2,500 graduate students. The faculty body consists of 350 full-time professors and 640 part-time lecturers and adjunct professors. The University of Seoul thus has one the best student-faculty ratios in Korea. The university is supported by an administrative staff body of 270 officials, most of whom are civil servants of the Seoul Metropolitan Government. For the fiscal year 2006, the University of Seoul commanded an annual budget of 100 million US$, of which 70 million US$ was provided by the Seoul Metropolitan Government. This amounts to one of the highest per-student educational investment ratios in Korea. The total annual budget amounts to 132.5million US$, which includes a UOS fund of 10.5million and a research budget of 22 million US$.

Asian Aging Core for Longevity Research (AACL)

2012 Seoul Conference

On Aging, Metabolism and Neurobiology

November 23-24, 2012
Natural Science Auditorium & International House Seminar room, University of Seoul

AACL-Seoul Symposium is organized by

Eun Seong Hwang, University of Seoul
Sang Chul Park, Gacheon University
Inhee Mook-Jung, Seoul National University
In Kwon Chung, Yonsei University
And, Nozomu Mori, Nagasaki University

And supported by

University of Seoul
Gachon University
WCU Integrated Omics for Biomedical Science at Yonsei University from NRF
WCU Neurocytomics program (R32-10084) at SNU from NRF, Rep of Korea,
Asian CORE Program of Japan Society for Promotion of Science 2010-2015

후원

서울시립대학교
가천대학교
WCU 융합오믹스의생명 사업단 (연세대학교)
뉴로사이토믹스 WCU 사업단 (서울대학교)
일본 JSPS Asian CORE 프로그램

Program

Nov 23 (Friday) **Natural Science Auditorium**

11:00	Academic activities of the Korean Society for Gerontology (KSG)
13:00	Joint Poster session I for KSG and AACL
14:20	Registration for AACL
14:30	Opening Remarks (EK Kim (president of KSG) and N Mori (Organizer, Japan))

Session I **Metabolism in aging** **Chair: Dr. ES Hwang**

14:40 **Yoichi Nabeshima** (Kobe Research Institute for Advanced Medicine)

α -Klotho in health and diseases

15:00 **Hee-Sook Jun** (Gachon University)

Aging and insulin sensitivity

15:20 **Toshiro Aigaki** (Tokyo Metropolitan University/ Molecular Genetics)

Genetic manipulation of fat metabolism and its impact on lifespan in *Drosophila*

15:40 **Hyo Bum Kwak** (Inha University)

Effects of aging and exercise training on apoptosis and remodeling in the rat heart

16:00 Coffee break

Session II **Metabolism and nutrition** **Chair: Dr. T Aigaki**

16:20 **Satoshi Inoue** (Tokyo University School of Medicine/ Geriatrics)

Vitamin K and Bone Metabolism

16:40 **Yoon Jung Park** (Ewha Womans University)

Molecular Targets of Rasgrf1 and epigenetic alteration in Metabolism and Aging

17:00 **Akiyoshi Fukamizu** (University of Tsukuba/Life Science Center)

Arginine methylation and lifespan control in *C. elegans*

17:20 **Soo Jin Yang** (Chonnam National University)

Hepatic metaflammation in aging

17:40 Poster session II

18:30 Reception and Dinner (21st Century Hall)

Nov 24 (Saturday) **International House Seminar room**

Special lecture **Chair: Dr. SC Park**

9:00 **Jung Jae Jung** (former director, Northeast Asian History Foundation)
한일교류의 역사 (韓日 交流の 歷史)

Session III **Aging and cell** **Chair: Dr. I Mook-Jung**

10:00 **Sung Young Kim** (Gacheon University)

Physiological antioxidative network of the bilirubin system in aging and age-related diseases

10:20 **Eun Seong Hwang** (University of Seoul)

Nicotinamide has multipotent effect on cellular function and longevity

Session IV **Neurogenesis and neuroimmunology** **Chair: Dr. N Mori**

10:40 **Minsoo Kim** (Seoul National University/Rochester University)

Leukocyte trafficking and vascular permeability during inflammation

11:00 **Shozo Jinno** (Kyusu University School of Medicine/ Neuroanatomy)

Decline in adult neurogenesis during aging follows a topographic pattern in the mouse hippocampus

11:20 **Ilo Jou** (Ajou University)

Multi-level regulation of inflammatory gene expression in brain glial cells

12:00 **Lunch**

Session V **Brain aging and neuroprotection** **Chair: Dr. A Takashima**

13:20 **Hoon Ryu** (Seoul National University/Boston University)

EWS deficiency deregulates CBP activity and leads to aberrant *c-Ret* expression and motor neuronal dysfunction

13:40 **Nozomu Mori** (Nagasaki University School of Medicine/ Neuroanatomy)

Novel regulators of dendritic spine morphology and cognitive decline in the aged brain

14:00 **Toru Nakazawa** (Tohoku University)

The molecular mechanism of glaucomatous optic neuropathy: learning from a mouse model of axonal damage-induced RGC death

14:20 Coffee break

Session VI	**Alzheimer disease pathogenesis**	**Chair: SJ Lee**
14:40	**Inhee Mook-Jung** (Seoul National University) Molecular Pathogenesis of Alzheimer's Disease : The effect of metabolism changes in Alzheimer's disease	
15:00	**Akihiko Takashima** (RIKEN/Nat'l Center for Gerontology and Geriatrics/AD Center) Granular tau oligomer: Intermediate of tau fibril is involved in neuronal loss	
15:20	**Seung Jae Lee** (Konkuk University) α-synuclein (mechanism of disease progress in age-related neurodegenerative diseases)	
15:40	**Toshiharu Suzuki** (Hokkaido University School of Pharmacy/ Biochemistry) Function and metabolism of Alcadein in the relation with Alzheimer's disease	
16:00	Coffee break	

Session VII	**Alzheimer disease therapy**	**Chair: Dr. H Ryu**
16:20	**Jae Sung Bae** (Kyung Buk University) Bone Marrow Stem cells in Alzheimer's Disease Pathogenesis	
16:40	**Shoichi Ishiura** (University of Tokyo) Transgenic rice expressing amyloid β peptide for oral vaccination	
17:00	**Masatoshi Hagiwara (**Kyoto University School of Medicine/ Anatomy) Novel DYRK1A inhibitor applicable for Alzheimer disease	
17:20	**Young Ho Koh** (Division of Brain Research/KNIH) Molecular mechanism of APP processing : SUMO1 as a new BACE1 interacting molecule	
17:40	Closing Remarks (Dr. SC Park, Dr. Y Nabeshima)	

Session I
Metabolism in aging

Chair: Dr. Eun Seong Hwang

Yo-ichi Nabeshima

Personal Information

Professor Emeritus of Kyoto University

President Institution: Institute of Biomedical Research and Innovation,

Foundation for Biomedical Research and Innovation

2-2 Minatojima-MInamimachi Chuo-ku, Kobe 650-0047 Japan

Phone: 81-78-306-0706,

FAX: 81-306-1708

E-mail: nabeshimayi@fbri.org,

Education

1972: M.S. Niigata University School of Medicine, Niigata, Japan

1976: M.D. & Ph. D. Niigata University, Niigata, Japan

Research and Professional Career

2010-present: President; Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation

1998-2010: Professor, Department of Pathology and Tumor Biology Graduate School of Medicine Kyoto University

1997-1998: Professor, Molecular and Cellular Biology Institute Osaka University

1988-1998: Head, Department of Molecular Genetic, National Institute of Neuroscience, National Center for Neurology and Psychiatry

1984-1987: Staff Scientist, Department of Biochemistry Japanese Foundation for Cancer Research, Cancer Research Institute

1976-1984: Assistant Professor, Department of Biochemistry School of Medicine Niigata University

Recent Publications

1. Tomiyama K. et al. Relevant use of Klotho in FGF19 subfamily signaling system *in vivo*. **Proc. Natl. Acad. Sci. USA** 107; 1666-1671 (2010)
2. Imura A. et. Al. a-Klotho as a regulator of Calcium homeostasis. **Science** 316, 1615-1618 (2007)
3. Tohyama O., et al. Klotho is a novel b-glucuronidase capable of hydrolyzing steroid b-glucuronides. **J. Biol Chem.** 279(11), 9777-9784 (2004)
4. Ito S. et al Impaired negative feedback suppression of bile acid synthesis in mice lacking bKlotho. **J. Clin. Invest.** 115, 2202-2208 (2005)
5. Manya H. et al Klotho protein deficiency leads to overactivation of (Mu)-calpain. **J.Biol. Chem.** 277 (38) 35503-35508 (2002)
6. Kuro-o M. et al. Mutation of the mouse *Klotho* gene leads to a syndrome resembling ageing. **Nature** 390, 45-51 (1997)

α-Klotho in health and diseases

Yo-ichi Nabeshima
Foundation for Biomedical Research and Innovation

α-klotho (*α-kl*) was first identified as an aging gene and later shown to be a regulator of mineral homeostasis. However, the precise molecular mechanisms and functional roles of α-Kl still remain to be solved.

The first topic is the novel role of glycoside chain in protein-protein interaction. We found that terminal glucuronidated N-glycan is attached on NaK b-subunit, FGFR1 and the other α-Kl binding proteins in common and plays a significant role for preferential and selective interactions between these proteins and α-Kl. When O-glycan consisted of sulfated-GlcA-GalNAc, attached on FGF23 is docked to α-Kl, the horo α-Kl becomes more thermodynamically stable, sifting α-Kl toward a high-affinity state for FGF23. Here, we propose that α-Kl acts as a novel glucuronide-binding lectin and the novel function of glycan that initiates conformational/allosteric-changes by docking to target proteins, leading to stabilized interaction.

The second topic is the therapeutic approach that ameliorates phenotypes of *α-kl-/-* mice such as vascular and heart-valve calcifications, pulmonary emphysema, lowered bone mineral density and senile atrophy of skin. We found that a protease is tremendously activated in *α-kl-/-* mice and that daily administration of an inhibitor of the enzyme strikingly improves the phenotypes of *α-kl-/-* mice, suggesting that the protease is the possible therapeutic target of aging associated diseases.

Hee-Sook Jun

Personal Information

Professor, College of Pharmacy and Lee Gil Ya Cancer and Diabetes Institute, Gachon University
Phone: 032-899-6056 Fax: 032-899-6057/ E-mail: hsjeon@gachon.ac.kr

Education

1980 BSc in pharmacy, Chosun University, Korea
1982 MSc in microbiology, Chosun University, Korea
1989 PhD in molecular biology, Chosun University, Korea

Professional Background

1999 – 2011 Adjunct professor, Department of Microbiology and Infectious Disease, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada
2003 – 2007 Associate Professor, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois, US
2004 – 2006 Associate Professor, College of Medicine, Chosun University, Gwangju, Korea
2007 – present Professor, Lee Gil Ya Cancer and Diabetes Institute, Gachon University, Korea
2010 – present Vice Director, Lee Gil Ya Cancer and Diabetes Institute, Gachon University
2011 – present Professor, College of Pharmacy, Gachon University

Recent Publications (2008 -)

Oh YS, Lee TS, Cheon GJ, Jang IS, Jun HS (co-corresponding author), Park SC. Modulation of insulin sensitivity and caveolon-1 expression by oechitectomy in a obese type 2 diabetes animal model. *Mol Med* 17(1-2):4-11, 2011.

Han JS, McLane B, Kim EH, Yoon JW, Jun HS. Remission of diabetes by insulin gene therapy using a hepatocyte-specific and glucose-responsive synthetic promoter. *Mol Ther* 19(3):470-8, 2011.

Oh YS, Lee YJ, Park EY, **Jun HS**. Interleukin-6 treatment induces beta cell apoptosis via STAT-3-mediated nitric oxide production. ***Diabetes Metab Res Rev*** 27: 813-819, 2011

Oh YS, Shin SJ, Lee YJ, Kim EH, **Jun HS**. Betacellulin-induced beta cell proliferation and regeneration is mediated by activation of ErbB-1 and ErbB-2 receptors. ***PLoS ONE*** e23894, 2011.

Lee YS, Park MS, Choung JS, Ha SY, **Jun HS**. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration in obese diabetic mice. ***Diabetologia*** 55 : 2456-2498, 2012.

Han J, Kim EH, Choi W, Jun HS. Insulin production in hepatocytes ameliorate hyperglycemia in obese diabetic mice *World J Gasteroenterol* (in press), 2012

Aging and insulin sensitivity

Hee-Sook Jun, PhD.
College of Pharmacy and Lee Gil Ya Cancer and Diabetes Institute, Gachon University

Type 2 diabetes is characterized by both insulin resistance and insulin deficiency. The prevalence of type 2 diabetes mellitus and insulin resistance is increasing in elderly population. However, how metabolic decline and hormonal changes during aging process affect the disease development remains poorly defined. We found that male offspring of non-diabetic C57BL/6 and DBA/2 mice developed type 2 diabetes when they grew old. Glucose and insulin tolerance were impaired, and hyperglycemia and hyperinsulinemia developed without obesity in these mice. Further studies showed that decreased expression levels of caveolin-1 were correlated with the development of age-dependent insulin resistance. The molecular mechanisms involved in the development of insulin resistance will be discussed. In addition, we will also discuss the diabetes-related hormonal changes and metabolic changes in aging in an animal model.

Toshiro Aigaki

Personal Information:

Professor, Department of Biological Sciences, Tokyo Metropolitan University
1-1 Minami-osawa, Hachioji, Tokyo 192-0397, Japan
Phone: +81-42-677-2560
Fax: +81-42-677-2559,
E-mail: aigaki-toshiro@tmu.ac.jp

Education

1986: Ph.D. in Biochemistry, Tokyo Metropolitan University, Japan

Research and Professional Career

1987 -1989: Postdoctoral fellow, University of Zurich, Switzerland
1989-1992: Research Associate, Tokyo Metropolitan Institute of Gerontology
1993-2005: Associate Professor, Department of Biology, Tokyo Metropolitan University
2005-Present: Professor, Department of Biological Sciences, Tokyo Metropolitan University

Recent Publications

1. Nakagawa-Yagi et al. (2012) Pharmacological modulation of histone demethylase activity by a small molecule isolated from subcritical water extracts of *Sasa senanensis* leaves prolongs the lifespan of *Drosophila melanogaster*. BMC Complement Altern Med. 12:101.
2. Trindade et al. (2012) Senemorphism: a novel perspective on aging patterns and its implication for diet-related biology. Biogerontology., 13:457-66.
3. Takeo et al. (2012) Shaggy/glycogen synthase kinase 3β and phosphorylation of Sarah/regulator of calcineurin are essential for completion of *Drosophila* female meiosis. Proc Natl Acad Sci U S A. 109: 6382-9.
4. Kishita et al. (2012) Impaired fatty acid oxidation in a *Drosophila* model of mitochondrial trifunctional protein (MTP) deficiency. Biochem Biophys Res Commun. 419:344-9.
5. Nakai et al. (2011) Calcineurin and its regulator sra/DSCR1 are essential for sleep in Drosophila. J Neurosci. 31:12759-66.

Genetic manipulation of fat metabolism and its impact on lifespan in *Drosophila*

Toshiro Aigaki
Department of Biological Sciences, Tokyo Metropolitan University

The fruit fly, *Drosophila melanogaster* shares many genes with humans: approximately 75% of diseases-related genes in humans have orthologs in the fly, and it has been used as a model system to study molecular and genetic bases of human diseases. However, relatively little has been studied for mutations in genes involved in energy metabolism, whose defects may cause age-related metabolic disorders, such as diabetes, heart disease, fatty liver, and several cancers. Identification of *Drosophila* disease models should facilitate the understanding of molecular bases of these diseases. We search for such mutations among the collection of transposon insertion lines, or generate knockout mutants by gene-targeting. To characterize the mutants, we used liquid chromatography mass spectrometry (LC-MS), which is a powerful tool for metabolomics. I will present how mutations in genes involved in energy producing pathways affect energy metabolism, physiology and lifespan of flies.

Hyo Bum Kwak

Personal Information

Assistant Professor, Department of Kinesiology, Inha University, Incheon 402-751, South Korea.
032-860-8183 e-mail: kwakhb@inha.ac.kr

Education

2007 Ph.D. in Health and Kinesiology, Texas A&M University, TX, USA
2004 M.S. in Health and Kinesiology, Texas A&M University, TX, USA
1996 M.S. in Physical Education, Seoul National University, Seoul, South Korea
1994 B.S. in Physical Education, Seoul National University, Seoul, South Korea

Research and Professional Career

2012-present Assistant Professor in the Dept. of Kinesiology, Inha University, Incheon, South Korea
2010-2011 Research Assistant Professor in the Dept. of Physiology, East Carolina University School of Medicine, NC, USA

Recent pulications

1. Kwak HB, Thalacker-Mercer A, Anderson EJ, Lin CT, Kane DA, Lee NS, Cortright RN, Bamman MM, and Neufer PD. Simvastatin impairs ADP-stimulated respiration and increase mitochondrial oxidative stress in primary human skeletal myotubes. *Free Radic Biol Med* 52: 198-207, 2012.
2. Lawler JM, Kwak HB, Kim JH, Lee Y, Hord JM, and Martinez DA. Biphasic stress response in the soleus during reloading following hindlimb unloading. *Med Sci Sports Exerc* 44: 600-609, 2012.
3. Kane DA, Lin CT, Anderson EJ, Kwak HB, Cox JH, Brophy P, Hickner RC, Neufer PD, and Cortright RN. Progesterone increases skeletal muscle mitochondrial H_2O_2 emission in non-menopausal women. *Am J Physiol Endocrinol Metab* 300: E528-535, 2011.
4. Kwak HB, Kim JH, Joshi K, Yeh A, Martinez DA, and Lawler JM. Exercise training reduces fibrosis and matrix metalloproteinase dysregulation in the aging rat heart. *FASEB J* 25: 1106-1117, 2011.
5. Lawler JM, Kim JH, Kwak HB, and Barnes WS. Redox modulation of diaphragm contractility: Interaction between DHPR and RyR channels. *Free Radic Biol Med* 49: 1969-1977, 2010.
6. Lawler JM and Kwak HB. Potential exercise mitigation and regulation of age-induced apoptosis and remodeling in the heart. In: *Modern Insights into Disease from Molecules to Man: Apoptosis.* V. R. Preedy (Ed.). Enfield, NH: Science Publishers, p. 389-403, 2010.

Effects of aging and exercise training on apoptosis and remodeling in the rat heart

Hyo Bum Kwak, Ph.D.
Department of Kinesiology, Inha University, Incheon 402-751, South Korea

Aging induces a progressive impairment of cardiac function. The impairment of heart function with aging is a result of structural remodeling including 1) the loss of cardiac myocytes, 2) reactive hypertrophy of the remaining fibers, and 3) increased collagen connective tissue. Cardiac myocyte loss through apoptosis (i.e., programmed cell death) or necrosis increases exponentially with aging. Exercise training improves cardiovascular work capacity and reduces cardiovascular disease risk. However, the ability of exercise training to ameliorate apoptosis and remodeling in the aging heart has not been evaluated. We used 3-month and 24-month old Fischer-344 rats as our young and old groups, respectively. One-half of the rats in each group ran on a treadmill at 15 m/min up a 15° incline, one hour/day, 5 days/week for 12 weeks (n=10 in each group): young sedentary controls (YS), young exercise trained (YE), old sedentary controls (OS), and old exercise trained (OE). We observed dramatic remodeling (e.g., decrease in myocyte number/area, enlargement of remaining cardiomyocytes, and increased connective tissue) from OS compared with those from YS. However, 12 weeks exercise training provided significant protection against myocyte reduction and remodeling in the aging heart. Also, we found that aging significantly increased histone-associated DNA fragmentation (apoptosis marker) in the left ventricle in OS compared with YS. In contrast, exercise training attenuated DNA fragmentation in the left ventricle in OE compared with OS. Similarly, left ventricles from OS displayed a higher incidence (3.32%) of TUNEL+ nuclei (another apoptosis marker). However, exercise training greatly reduced TUNEL+ nuclei (1.62%) in OE, indicating that exercise training ameliorates apoptosis in the aging heart. In conclusion, exercise training provided protection against age-induced remodeling of the left ventricles. Furthermore, exercise training downregulated markers of apoptosis (DNA fragmentation and TUNEL+ nuclei) in the aging rat heart.

Keywords: aging, exercise, apoptosis, cardiac remodeling

Session II
Metabolism and nutrition

Chair: Dr. T Aigaki

Satoshi Inoue

Personal Information

Professor, [1]Department of Geriatric Medicine and [2]Department of Anti-Aging Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [3]Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical School, Saitama, Japan;

E-mail: sinoue07@gmail.com

Education

1985 M.D., University of Tokyo

Research and Professional Career

1985-1992 Physician, Department of Geriatrics, The University of Tokyo Hospital

1992 Ph.D., Graduate School of Medicine, The University of Tokyo

1993-1995 Assistant Professor, Department of Geriatrics, Graduate School of Medicine, The University of Tokyo

1995-1998 Research Associate, Gene Expression Laboratory, The Salk Institute for Biological Studies, California, USA

1998-2004 Assistant Professor, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo

2002- present Head and Visiting Professor, Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical University

2004- present Professor, Department of Anti-Aging Medicine, Graduate School of Medicine, The University of Tokyo

Recent Publications

1. Urano T, Shiraki M, Yagi H, Ito M, Sasaki N, Sato M, Ouchi Y, Inoue S. GPR98/Gpr98 gene is involved in the regulation of human and mouse bone mineral density. ***J Clin Endocrinol Metab*** 97: E565-74 (2012)

2. Takayama K, Tsutsumi S, Katayama S, Okayama T, Horie-Inoue K, Ikeda K, Urano T, Kawazu C, Hasegawa A, Ikeo K, Gojyobori T, Ouchi Y, Hayashizaki Y, Aburatani H, Inoue S. Integration of cap analysis of gene expression and chromatin immunoprecipitation analysis on array reveals genome-wide androgen receptor signaling in prostate cancer cells. ***Oncogene*** 30:619-630 (2011)

3. Gack MU, Shin YC, Joo CH, Urano T, Liang C, Sun L, Takeuchi O, Akira S, Chen Z, Inoue S, Jung JU. TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. ***Nature*** 446: 916-920 (2007)

4. Ichikawa T, Horie-Inoue K, Ikeda K, Blumberg B, Inoue S. Steroid and Xenobiotic Receptor SXR Mediates Vitamin K2-activated Transcription of Extracellular Matrix-related Genes and Collagen Accumulation in Osteoblastic Cells. ***J Bio Chem*** 281:16927-16934 (2006)

5. Urano T, Saito T, Tsukui T, Fujita M, Hosoi T, Muramatsu M, Ouchi Y, Inoue S. Efp targets 14-3-3σ for proteolysis and promotes breast tumour growth. ***Nature*** 417:871-875 (2002)

Vitamin K and Bone Metabolism

Satoshi Inoue[1,2,3*]

[1]Department of Geriatric Medicine and [2]Department of Anti-Aging Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [3]Division of Gene Regulation and Signal Transduction, Research Center for Genomic Medicine, Saitama Medical School, Saitama, Japan

Vitamin K is a fat-soluble vitamin, which is involved in blood coagulation mediated by maintaining the activity of coagulation factors in the liver. Vitamin K also been shown to prevent bone fractures in clinical studies. In addition, a lack of vitamin K is associated with several geriatric diseases, including osteoporosis, osteoarthritis, dementia, arteriosclerosis and some kinds of malignancies. Recently, we discovered a novel role for vitamin K as a ligand of the nuclear receptor, steroid and xenobiotic receptor (SXR), and its murine ortholog, pregnane X receptor (PXR). Besides its established roles as a cofactor of g-glutamyl carboxylase (GGCX) in mediating posttranscriptional modifications, vitamin K has a different mode of action mediated by transcriptional regulation of SXR/PXR target genes. Using PXR-deficient mice, we revealed that the bone protective effects of vitamin K are partially mediated by SXR/PXR-dependent signaling. The discoveries of extrahepatic actions of vitamin K and its novel mode of action, has opened up new possibilities that vitamin K is useful for prevention or treatment of a variety of diseases that affect the geriatric population.

Yoon Jung Park

Personal Information

Assistant Professor, Dept. of Nutritional Science and Food Management,College of Health Science, Ewha Womans University

Daehyundong 11-1, Seodaemoongu, Seoul 120-750, Rep. of Korea

+82 (0)2 3277 3093; park.yoonjung@ewha.ac.kr

Education

May 2008 Ph.D. Molecular Nutrition, Div. of Nutritional Science, Cornell University, *NY, USA*

Feb. 1998 M.S. Dept. of Food & Nutritional Science, Ewha Womans University, *Seoul, Korea*

Feb. 1996 B.S. Dept. of Food & Nutritional Science, Ewha Womans University, *Seoul, Korea*

Research and Professional Career

2011 -present Assistant Professor, Dept. of Nutritional Science and Food Management, , Ewha Womans University, *Seoul, Korea*

2004 -2006 Teaching assistant, Division of Nutritional Science, Cornell University, *NY, USA*

Recent Publications

1. Toenjes M, Barbus S, Park YJ, Wang W, Schlotter M, Lindroth AM, Pleier S, Bai HC, Karra D, Felsberg J, Lemke D, Hovestadt V, Rolli C, Kemkemer R, Schmidt K, Hull W, Hutson SM, Pfister S, Plass C, Okun JG, Reifenberger G, Lichter P, Radlwimmer B. Branched-chain amino acid transaminase 1 (BCAT1) is essential in IDH1 wild-type gliomas, *under revision in Nat Med*
2. Haas J*, Frese KS*, Park YJ*, Keller A, Vogel B, Franke J, Fischer S, Weichenhan D, Lindroth AM, Bauer A, Marquart S, Hassel S, Nietsch R, Ehlermann P, Dösch A, Schultz J, Mereles D, Hardt S, Backs J, Hoheisel JD, Plass C, Katus HA, Meder B. Alterations in cardiac DNA methylation suggest a role of epigenetic mechanisms in human dilated cardiomyopathy, *under revision in EMBO Mol Med* (*Co-first authorship)
3. Park YJ*, Herman H, Gao Y, Lindroth AM, Hu BY, Murphy PJ, Putnam JR, Soloway PD*. Sequences sufficient for reprogramming imprinted germline DNA methylation defined, PLoS One, 2012 Mar 5; 7(3):e33024 (*Co-corresponding authorship)
4. Park YJ, Claus R, Weichenhan D, Plass C. Genome-wide Epigenetic Modifications in Cancer, Prog Drug Res. 67:25-49, 2011; published as a book chapter in Epigenetics and Disease: Pharmaceutical Opportunities (Progress in Drug Research), ISBN-13: 978-3764389888 on Jan 28, 2010

Molecular Targets of Rasgrf1 and epigenetic alteration in Metabolism and Aging

Yoon Jung Park

Longevity is dictated by multi-factors including genetic variation, epigenetic alteration and environmental exposure. Calorie restriction (CR) has been demonstrated to extend lifespan in various organisms and to delay the onset of age-related diseases such as heart disease, diabetes, and cancer in the rhesus monkey. Its underlying molecular mechanisms involve evolutionary conserved nutrient signaling pathways including insulin/Igf1 as well as TOR. Recently, it has been shown by Borras et al that Rasgrf1 deficiency mimics CR-mediated anti-aging effect by increases lifespan by 20%. Rasgrf1 is a RAS GTP exchange factor that is activated by calmodulin-mediated $Ca2^{+}$ influx and G-protein coupled receptors. It is encoded by the paternally imprinted gene on mouse chromosome 9 and is tightly regulated by epigenetic mechanism through antagonistic DNA and histone methylation. It is mainly expressed in brain and pancreas, linking to its function in learning and memory as well as glucose homeostasis, respectively. In our previous report, we showed that Rasgrf1 knockdown in early development led to decrease in body weight and the reduced body weight sustained even after re-expression of Rasgrf1 in later development. Rasgrf1 deficient mice have repressed expression of Igf1 in liver and decreased Igf1 level in serum, followed by low transcriptional expression of Growth-hormone-releasing hormone (Ghrh) and the related transcriptional factors, although how Rasgrf1 affect Ghrh is not clear. Using cDNA microarray, we identified potential networks through hypothalamic LepR and NPY as molecular targets of Rasgrf1, which may explain the mechanism underlying Rasgrf1 deficiency-mediated longevity.

Akiyoshi Fukamizu

Personal Information

Professor and Vice Director
Life Science Center, Tsukuba Advanced Research Alliance, University of Tsukuba,
Tsukuba, Ibaraki 305-8577, Japan
Tel/Fax: 81-29-853-6070 e-mail: akif@tara.tsukuba.ac.jp

Education

1982-1983 Faculty of Agricultural and Forestry, University of Tsukuba: Awarded the B.S. degree.
1984-1986 Master, Environmental Sciences, University of Tsukuba: Awarded the M.S. degree.
1986-1987 Doctoral Degree Program in Agricultural Science, University of Tsukuba.
1989 Awarded the Ph.D. degree (University of Tsukuba).

Research and Professional Career

1987-1990 Research Associate at the Institute of Applied Biochemistry, Gene Experiment Center, University of Tsukuba.
1990-1994 Assistant Professor at the Institute of Applied Biochemistry, University of Tsukuba.
1994-1995 Research Associate at the Salk Institute for Biological Studies, USA
Associate Professor at the Institute of Applied Biochemistry, University of Tsukuba.
1999-present Professor and Aspect Director, Aspect of Functional Genomic Biology, Center for Tsukuba Advanced Research Alliance, University of Tsukuba
Program Leader in The 21st Century COE Program (Life Science), Graduate School of Life and Environmental Sciences, University of Tsukuba
2005-2006 Director of Research in the University of Tsukuba
2006-2011 Director, Center for Tsukuba Advanced Research Alliance, University of Tsukuba

Recent Publications

1. Takahashi Y, et al.: Asymmetric arginine dimethylation determines life span in *C. elegans* by regulating forkhead transcription factor DAF-16. ***Cell Metab.*** 13, 505-516 (2011)
2. Sakamaki JI, et al. Arginine methylation of BCL-2 antagonist of cell death (BAD) counteracts its phosphorylation and inactivation by Akt. ***Proic. Natl. Acad. Sci. USA*** 108, 6085-6090 (2011)
3. Daitoku H, Sakamaki J, and Fukamizu A: Regulation of FoxO transcription factors by acetylation and protein-protein interactions. ***Biochim. Biophys. Acta*** 1813, 1954-1960 (2011) [invited review]
4. Yamagata K, et al. Arginine methylation of FOXO transcription factors inhibits their phosphorylation by Akt. ***Mol. Cell*** 32, 221-231 (2008)

Arginine methylation and lifespan control in *C. elegans*

Akiyoshi Fukamizu
Life Science Center, Tsukuba Advanced Research Alliance, University of Tsukuba

Asymmetric arginine methylation catalyzed by protein arginine methyltransferase PRMT1 plays a variety of roles for cellular processes, including RNA processing, signal transduction, DNA repair and transcriptional regulation. We have recently shown that the *Caenorhabditis elegans* ortholog of mammalian PRMT1 regulates worm lifespan. In *C. elegans*, PRMT-1 is a dominant type I methyltransferase that catalyzes asymmetric dimethylation, in which the genetic loss of *prmt-1* shortens lifespan. The short lifespan phenotype was rescued by the extracromosomal array expressing wild-type *prmt-1*, but not an emzymatic mutant, suggesting PRMT-1 mediated-methylation controls worm lifespan. Moreover, overexpression of PRMT-1 significantly extends lifespan in a manner dependent on the forkhead transcriptional factor DAF-16, a key factor of longevity, which is negatively regulated by AKT-mediated phosphorylation through insulin/ IGF-like signaling pathway. PRMT-1 methylates DAF-16 at arginine residues within a consensus motif for AKT phosphorylation (RXRXXS/T) and directly blocks phosphorylation of DAF-16 in vivo and in vitro. In addition, the expression of DAF-16 target gene is reduced in *prmt-1*-deficent worms. Taken together, our findings suggest a role for arginine methylation in lifespan.

Soo Jin Yang

Personal Information

Assistant Professor, Department of Food and Nutrition, Chonnam National University
062-530-1331 (010-6397-2452) E-mail: sjyang89@chonnam.ac.kr

Education

1994-1998 B.S., . Food and Nutrition, Yonsei University
2002-2007 Ph.D. Nutritional Biology, University of California, Davis
2008-2009 Research Fellow, University of Michigan
2010-2011 Research Professor, Sungkyunkwan University
2011-current Assistant Professor, Chonnam National University

Recent Publications

1. Yang SJ, IglayReger HB, Kadouh HC, Bodary PF. Inhibition of the chemokine (C-C motif) ligand 2 /chemokine (C-C motif) receptor 2 pathway attenuates hyperglycaemia and inflammation in a mouse model of hepatic steatosis and lipoatrophy. Diabetologia 52(5): 972-981. 2009

2. Yang SJ, Choi JM, Chae SW, Kim WJ, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW, Kim SW, Park CY. Activation of peroxisome proliferator-activated receptor gamma by rosiglitazone increases Sirt6 expression and ameliorates hepatic steatosis in rats. PLoS ONE 6(2): e17057. doi: 10.1371/journal.pone.0017057. 2011

3. Yang SJ, Choi JM, Kim L, Kim BJ, Sohn JH, Kim WJ, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW, Kim SW, Park CY. Chronic administration of ezetimibe increases active glucagon-like peptide-1 and improves glycemic control and pancreatic beta cell mass in a rat model of type 2 diabetes. Biochem Biophys Res Commun 407(1): 153-157. 2011

4. Rhee M-Y, Yang SJ, Oh SW, Park Y, Kim C-I, Park H-K, Park SW, Park C-Y. Novel genetic variations associated with salt sensitivity in the Korean population. Hypertension research 34(5): 606-611. 2011

5. Yang SJ, Lee ST, Kim WJ, Park SE, Park SW, Kim JW, Park CY. Genetic Variation in *CYP17A1* Is Associated with Arterial Stiffness in Diabetic Subjects. Experimental Diabetes Research 2012: 827172. 2012

6. Yang SJ, Kim S, Park H, Kim SM, Choi KM, Lim Y. Lee M. Gender-dependent association between angiotensin converting enzyme insertion/deletion polymorphism and obesity relating to sodium intake in children. Nutrition. *In press*

Hepatic metaflammation in Aging

Soo Jin Yang
Chonnam National University

Niacin is a soluble vitamin which exists as nicotinic acid (NA) and nicotinamide (NAM). It involves in physiological processes (e.g. metabolism, stress response, and cell differentiation etc.) as its active form, nicotinamide adenine dinucleotide (NAD). NAD is a classic coenzyme and exerts their biological functions via redox and non-redox reactions (e.g. sirtuin pathway). NAD is synthesized from tryptophan and two major forms of niacin, NA, and NAM. In mammals, it is known that NAM is used predominantly for NAD synthesis, which consists of two enzymatic processes by nicotinamide phosphoribosyltransferase (Nampt) and NAM/NA mononucleotide adenylyltransferase. Nampt is a rate-limiting enzyme for the NAD synthesis from NAM and involves in the regulation of sirtuin1 (Sirt1)-mediated function by modulating NAD availability.

Sirtuins, NAD-dependent deacetylases, regulate glucose and lipid metabolism, and are implicated in the pathophysiology of aging, diabetes and hepatic steatosis. Previous studies have reported ambiguous findings regarding the metabolic regulation by NAD-sirtuin pathway, which reflects its complexity. For example, NAM acts as a favorable NAD donor as well as an effective inhibitor of Sirt1. It is speculated that the fate of NAM-mediated regulation is dependent on status of available NAD and type of metabolic stresses.

In addition to above-mentioned NAD donors, other NAD precursors have recently drawn attention by interesting findings. Especially, nicotinamide riboside (NR) present in milk profoundly involves in NAD biosynthesis and Sirt1 activation and contributes to the protection against high fat-diet induced obesity.

Metabolic regulation of NAD-sirtuin pathway may be mediated by several metaflammation-related mechanisms including inflammasome and autophagy. In this presentation, I will discuss 1) effects of several NAD donors (NA, NAM, resveratrol, and NR) on glucose control and hepatic NAD-sirtuin pathway, and 2) related mechanisms focused on hepatic metaflammation.

Special lecture

Chair: Dr. SC Park

한일교류의 역사 (韓日 交流の 歷史)

정재정 (Jung Jae Jung)

(former director, Northeast Asian History Foundation)

Jung Jae Jung

Personal Information

Professor, Department of History, University of Seoul

02-2210-2545 E-mail : chungjj@uos.ac.kr

Education

1974 Department of History Education, Seoul National University, BA

1982 Department of Humanities Science, University of Tokyo, MA

1992 Department of Korean History, Seoul National University, DA

Professional Career

1992 – 1993 日本放送教育開發センター 客員教授

1999 – 2000 日本東北大學 東北アジア研究センター客員教授

2005 – 2006 國際日本文化研究センター 客員教授

2010 – 2012 Director, Northeast Asian History Foundation

Session III
Aging and cell

Chair: Dr. Inhee Mook-Jung

Sung Young Kim

Personal Information

Assistant Professor, Department of Biochemistry
Gachon University of Medicine and Science.
Hambakmoeiro 191, Yeonsu-gu, Incheon city, 406-799, Korea
Tel. 032-820-4275 Fax. 032-820-4744
E-mail: palelamp@gachon.ac.kr

Education

♦ Ph.D., 2011, Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine, Seoul, Korea
♦ M.D., 2008, Kon kuk University College of Medicine, Seoul, Korea

Recent Publications

♦ **Kim SY**, Park SC, Physiological antioxidative network of the bilirubin system in aging and age-related diseases. Frontiers in Pharmacology. 2012 Mar. Volume 3, Article 45: 1-9.

♦ **Kim SY**, Ryu SJ, Kang HT, Choi HR, Park SC, Defective nuclear translocation of stress-activated signaling in senescent diploid human fibroblasts: a possible explanation for aging-associated apoptosis resistance. Apoptosis. 2011. 16:795-807.

♦ **Kim SY**, Kang HT, Choi HR, Park SC, Biliverdin reductase A in the prevention of cellular senescence against oxidative stress. Exp Mol Med. 2011. 43:15-23.

♦ **Kim SY**, Kang HT, Choi HR, Park SC, Reduction of Nup107 attenuates the growth factor signaling in the senescent cells. Biochemical and Biophysical Research Communications. 2010.401:131-6.

♦ **Kim SY**, Ryu SJ, An HJ, Choi HR, Kang HT, Park SC, Senescence-related functional nuclear barrier by down-regulation of nucleo-cytoplasmic trafficking gene expression. Biochemical and Biophysical Research Communications . 2010. 391: 28-32

♦ Hyun Tae Kang, Ki Baek Lee, Sung Young Kim, Hae Ri Choi and Sang Chul Park, Autophagy Impairment Induces Premature Senescence in Primary Human Fibroblasts 2011 Aug PLoS One 6(8): e23367

Physiological antioxidative network of the bilirubin system in aging and age-related diseases

Kim SY, Park SC.

Oxidative stress is detrimental to life process and is particularly responsible for aging and age-related diseases. Thus, most organisms are well equipped with a spectrum of biological defense mechanisms against oxidative stress. The major efficient antioxidative mechanism is the glutathione system, operating a redox cycling mechanism for glutathione utilization, which consists of glutathione and its peroxidase and reductase. However, this system is mainly effective for hydrophilic oxidants, while lipophilic oxidants require another scavenging system. Since many age-related pathological conditions are related to lipid peroxidation, especially in association with the aging process, the physiological role of the scavenging system for lipophilic oxidants should be considered. In this regard, the biliverdin to bilirubin conversion pathway, via biliverdin reductase (BVR), is suggested to be another major protective mechanism that scavenges lipophilic oxidants because of the lipophilic nature of bilirubin. The efficiency of this bilirubin system might be potentiated by operation of the intertwined bicyclic systems of the suggested redox metabolic cycle of biliverdin and bilirubin and the interactive control cycle of BVR and heme oxygenase. In order to combat oxidative stress, both antioxidative systems against hydrophilic and lipophilic oxidants are required to work cooperatively. In this regard, the roles of the bilirubin system in aging and age-related diseases are reassessed in this presentation, and their interacting networks are evaluated.

Eun Seong Hwang

Personal Information

Professor, Department of Life Science, University of Seoul
Dongdaemun-gu, Jeonnong-dong 90, Seoul, Republic of Korea 130-743
TEL: 82-2-2210-2608 FAX: 82-2-2210-2888 E-MAIL: eshwang@uos.ac.kr

Education

Ph.D. Department of Biochemistry, The Johns Hopkins University School of Hygiene. 1991
M.S. Department of Food Science, Seoul National University, Korea. 1984
B.A. Department of Food Science, Seoul National University, Korea. 1981

Research and Professional Career

Professor (Department of Life Science, University of Seoul) 2006. 9 - present
Associate Professor (Department of Life Science, University of Seoul) 2001-2006
Assistant Professor (Department of Life Science, University of Seoul) 1997- 2001
Research Associate (Samsung Biomedical Research Institute) 1994 - 1997
(Kangnamgu, Ilwondong 50, Seoul, Republic of Korea 135-230)
Postdoctoral Fellow (Department of Genetics, Yale University) 1991–1994

Recent Publications

1. Lee BY, et al. Senescence-associated β-galactosidase is lysosomal β-galactosidase. 2006. *Aging Cell* 5: 187-195.
2. Kang HT, et al. Nicotinamide extends replicative lifespan of human cells. 2006. *Aging Cell* 5:423-436.
3. Kang HT, Hwang ES. Nicotinamide enhances mitochondria quality through autophagy activation in human cells. 2009. *Aging Cell*. 8: 426–438.
4. Hwang ES, et al. A comparative analysis of the cell biology of senescence and aging. 2009. *Cellular and Molecular Life Sciences*. 66: 2503-2525.
5. Kang MR, et al. Reciprocal roles of SIRT1 and SKIP in the regulation of RAR activity: Implication in the retinoic acid-induced neuronal differentiation of P19 cells. 2010. *Nucleic Acids Res*. 38: 822-831.
6. Jang SY, et al. Nicotinamide-induced mitophagy: Event mediated by high NAD+/NADH ratio and SIRT1 protein activation. 2012. J Biol Chem. 287:19304-14
7. Byun HO, et al. GSK3 inactivation is involved in mitochondrial complex IV defect in transforming growth factor (TGF) β1-induced senescence. 2012. Exp Cell Res. 318(15): 1808-19.

Nicotinamide has multipotent effects on cellular function and longevity

So-Young Jang, Ho Jin Choi, Jung Soo Ock, and Eun Seong Hwang
Department of Life Science, University of Seoul

As a derivative of Vit B3, nicotinamide (NAM) provides cells with NAD^+, an essential component in cellular metabolism. In addition to the vital function at the micro-level, NAM, at higher doses, has recently been shown to exert positive effects on survival of various cell types *in vitro* and *in vivo*. Especially, we showed that NAM treatment extends doubling capacity and thereby increases replicative lifespan of normal human fibroblasts and keratinocytes. As for an underlying mechanism for these cell-beneficial effects, we proposed NAM-mediated improvement of mitochondria quality possibly through activation of autophagy and mitochondria structural dynamics. Autophagy activation appears to be mediated through an increase of the cellular NAD^+/NADH ratio and possibly an activation of SIRT1 since the treatment of NAD^+ or Asn, which also increase the NAD^+/NADH ratio, and SIRT1 activators commonly caused similar decrease in mitochondria content. We further examined the effect of NAM treatment on the functions of other cell types, and found that NAM treatment potentiates activation of primary human CD8+ T cells. When naïve T cells were activated in the presence of NAM, the cellular content of mitochondria and ROS, an increase of which are known to accompany T cell activation and be involved in T cell apoptosis which brings in population contraction for T cell homeostasis after activation, were diminished. More importantly, the population grew at higher rates and to higher extents during the expansion period, and this appeared to be due to a decrease in apoptotic cell death. Further, this occurred without a delay in the onset of contraction or an impairment in T cell effector function. This, if occurred in aged body, which suffers from a decline in the level of T cell activation, would exert a significant beneficial effect against immune senescence. NAM was also found to exert a positive effect on the stemness of mesenchymal stem cells suggesting a possible utilization of NAM in MSC expansion *ex vivo* for cell therapies in vivo.

Session IV

Neurogenesis and neuroimmunology

Chair: Dr. N Mori

Minsoo Kim

Personal Information

Address: Center for Vaccine Biology & Immunology, Department of Microbiology & Immunology, 601 Elmwood Ave. Box 609, Rochester, NY 14642
Telephone: 585-276-3917 (Office) E-Mail Address: Minsoo_Kim@urmc.rochester.edu

Education

1988 – 1993 B.S. Korea University Genetic Engineering
1997 – 2001 Ph.D. Ohio State University Pharmacology
2001 – 2004 Post-Doctoral Fellow Center for Blood Research, Harvard Medical School

Research and Professional Career

2007 – 2011 Assistant Professor University of Rochester, Department of Microbiology & Immunology, Center Vaccine Biology & Immunology
2011 – present Associate Professor (tenured)
2005 – 2007 Assistant Professor, Brown Medical School, Department of Surgery

Recent Publications

X. Hua, S. Kang, C. Lefort, M. Kim, and M.M. Jin. 2010. Combinatorial libraries against libraries for selecting neoepitope activation-specific antibodies. *PNAS* 107(14):6252-7
L. Ma, J.-s. Gao, Y. Guan, et al. 2010. Acetylation modulates prolactin receptor dimerization. *PNAS* Nov 9;107 (45): 19314-9.
Y.J. Guan, Z. Zhang, C Yu, et al. Phospho-SXXE/D Motif Mediated TNF Receptor 1-TRADD Death Domain Complex Formation for T Cell Activation and Migration. *J. Immunol.* Aug.1;187(3):1289-97.
C.T. Lefort, Y.M. Hyun, and M. Kim. 2011. Monitoring integrin activation by fluorescence resonance energy transfer. *Methods Mol. Biol.* 757: 205-14.
M. Sanchez-Lockhart, M. Kim, and J. Miller. 2011. Cutting Edge: A Role for Inside-Out Signaling in TCR Regulation of CD28 Ligand Binding. *J. Immunol.* Dec 1;187(11):5515-9.
X.M. O'Brien, K.E. Heflin, et al. 2012. Lectin site ligation of CR3 induces conformational changes and signaling. *J. Immunol.* Jan 27;287(5):3337-48-9.
P.P. Sarangi, Y.V. Lerman, Y. Hyun, A.P. Pietropaoli, M. Kim. 2012. Essential role of β1 Integrin in Tissue Homing of Neutrophils During Sepsis. *Shock. (in press).*
CM Baker, WA Comrie, Y-M Hyun, C Fedorchuk, C Brakebusch, J Miller, M Meier-Schellersheim, and Kim M. 2012. Opposing roles for RhoH GTPase during T cell migration and activation. *PNAS* Jun 26;109(26):10474-9.
Y-M Hyun, R Sumagin, P Sarangi, M Overstreet, C Baker, D Fowell, I Sarelius, and M. Kim. 2012. Uropod elongation is a common final step in leukocyte extravasation through inflamed vessels. *J. Ex. Med.* Jul 2;209(7):1349-62.

Leukocyte trafficking and vascular permeability during inflammation

Minsoo Kim, Ph.D.
Center for Vaccine Biology & Immunology, Department of Microbiology & Immunology, 601 Elmwood Ave. Box 609, Rochester, NY 14642

Efficient trafficking of immune cells into peripheral non-lymphoid tissues is key to enact their protective functions. Emerging evidence suggests that gaps between or openings through microvascular endothelial cells are actively controlled to minimize the loss of vascular barrier integrity during leukocyte extravasation from the blood to sites of tissue infection. However, the mechanisms by which leukocytes maintain vascular homeostasis remain unknown. The conventional multistep paradigm of leukocyte extravasation depends on CD18 integrin-mediated events, such as rapid arrest and crawling on the surface of the endothelium, and transmigration through the endothelial layer. With enhanced three-dimensional detection of fluorescent CD18 fusion protein in a newly developed knock-in mouse and extended *in vivo* z-series sections, we report that extravasating leukocytes (neutrophils, monocytes, and T lymphocytes) show delayed uropod detachment and become extremely elongated prior to complete transmigration across the endothelium. Additionally, these cells deposit CD18-enriched microparticles at the subendothelial layer before retracting the stretched uropod. Inhibition of such microparticle formation results in dramatically increased vascular permeability. Thus, we conclude that uropod elongation is a common final step in the extravasation cascade, during which leukocytes produce microparticles that function as a "vascular seal" to minimize the loss of endothelial barrier function.

Shozo Jinno

Personal Information

Professor, Department of Developmental Molecular Anatomy, Graduate School of Medical Sciences, Kyushu University
3-1-1, Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan
Tel: 81-92-642-6051
Fax 81-92-642-6202
Email: sjnno@med.kyushu-u.ac.jp

Education

1988-1994, Kyushu University, Department of Medicine, Medical Degree
1996-2000, Kyushu University, Graduate School of Medical Science, Doctor of Philosophy

Research and Professional Career

1994-1995: Resident, Department of Psychiatry, Dazaifu Hospital
1995-1996: Resident, Department of Psychiatry, Kyushu University Hospital
2000-2004: Assistant Professor, Department of Anatomy and Neurobiology, Graduate School of Medical Science, Kyushu University
2004-2006: Investigator Scientist, Medical Research Council, Anatomical Neuropharmacology Unit, Department of Pharmacology, University of Oxford
2008: Lecturer, Department of Anatomy and Neurobiology, Graduate School of Medical Science, Kyushu University
2009: Associate Professor, Department of Anatomy and Neurobiology, Graduate School of Medical Science, Kyushu University
2011-present: Professor, Department of Developmental Molecular Anatomy, Graduate School of Medical Science, Kyushu University

Recent Publications

1. A novel objective classification of reactive microglia following hypoglossal axotomy using hierarchical cluster analysis. Yamada J, Jinno S. J Comp Neurol (in press)
2. Decline in adult neurogenesis during aging follows a topographic pattern in the mouse hippocampus. (2011) Jinno S. J Comp Neurol. 519(3):451-66.
3. Regional and laminar differences in antigen profiles and spatial distributions of astrocytes in the mouse hippocampus, with reference to aging. (2011) Jinno S. Neuroscience 180:41-52.
4. Topographic differences in adult neurogenesis in the mouse hippocampus: a stereology-based study using endogenous markers. (2011) Jinno S. Hippocampus. 21(5):467-80.

Decline in adult neurogenesis during aging follows a topographic pattern in the mouse hippocampus

Shozo Jinno
Department of Developmental Molecular Anatomy, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan

In the rodent brain, diverse functions are topographically distributed within the hippocampus. For instance, the dorsal (septal) hippocampus is involved in spatial memory, while the ventral (temporal) hippocampus is related to emotion and anxiety. Accumulating evidence shows that age-dependent decline in hippocampal neurogenesis is associated with impairments of these functions. However, little is known whether the decline in dentate granule cell production during aging follows a topographic pattern. Here we quantitatively estimated specific populations of adult-born cells in young adult and middle-aged mice using endogenous markers, and determined whether age-dependent reductions in adult neurogenesis exhibited topographic differences. The numerical densities (NDs) of putative primary progenitors, intermediate neuronal progenitors, and neuronal lineages were higher in the dorsal dentate gyrus (DG) than in the ventral DG both in young adult and middle-aged mice, but the ratios of the NDs in the dorsal DG to the NDs in the ventral DG noticeably increased with age. The age-related reductions in the numbers of these populations were larger in the ventral DG than in the dorsal DG. By contrast, the NDs of glial lineages were higher in the ventral DG than in the dorsal DG during life, and the numbers of glial lineages showed no significant age-related changes. Our findings suggest that neurogenesis, but not gliogenesis, wanes faster in the ventral hippocampus than in the dorsal hippocampus during aging. Such age-related topographic changes in hippocampal neurogenesis might be implicated in memory and affective impairments in old people.

Ilo Jou

Personal Information

Professor, Dept. of Pharmacology, Ajou University School of Medicine
E-mail: jouilo@ajou.ac.kr

Education

1981-1987 Yonsei University Medical school, MD
1988-1990 Yonsei University Graduate School, MS (majored in Pharmacology)
1990-1993 Yonsei University Graduate School, PhD (majored in Pharmacology)

Research and Professional Career

1993 – present: assistant, associate and full professor, Dept. of Pharmacology, Ajou University School of Medicine
2003- present: director, Chronic Inflammtory Disease Research Center, Ajou University School of Medicine (MRC)

Recent Publications

Anti-inflammatory mechanisms of nuclear receptor ligands

1. Lee JH, Kim HM, Woo JH, Joe E-H, **Jou I**. 5,8,11,14-eicosatetraynoic acid suppresses CCL2/MCP-1 expression in IFN-γ-stimulated astrocytes by increasing MAPK phosphatase-1 mRNA stability. *J Neuroinflammation* 2012 Feb18, 9:34
2. Lee JH, Park SM, Kim OS, Lee CS, Woo JH, Park SJ, Joe E-h, **Jou I**. Differential SUMOylation of LXR**α** and LXR**β** mediates transrepression of STAT1 inflammatory signaling in IFN-**γ**-stimulated brain astrocytes. *Mol Cell* 2009 Sep 25, 35:806-817
3. Lee JH, Woo JH, Woo SW, Kim KS, Park SM, Joe EH, **Jou I**. 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 suppresses MCP-1 expression in IFN-γ-stimulated astrocytes through induction of MAPK phosphatase-1. *J Immunol* 2008 Dec 15, 181(12):8642-49

STAT signals in neuroinflammation and glioma

1. Park SJ, Lee JH, Kim HY, Choi YH, Park JS, Suh YH, Park SM, Joe E-H, **Jou I**. Astrocytes, but not microglia, rapidly sense H_2O_2 via STAT6 phosphorylation, resulting in cyclooxygenase-2 expression and prostaglandin release. *J Immunol* 2012 May 15, 188(10):5132-41
2. Park SJ, Kim HY, Kim H, Park SM, Joe EH, **Jou I**(Co CA), Choi YH. Oxidative stress induces lipid-raft-mediated activation of Src homology 2 domain-containing protein tyrosine phosphatase 2 in astrocytes. *Free Radic Biol Med* 2009 Jun 15, 46(12):1694-702
3. Kim HY, Park SJ, Joe EH, **Jou I**. Raft-mediated Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP-2) regulation in microglia. *J Biol Chem*. 2006 Apr 28, 281(17):11872-8.

Multi-level regulation of inflammatory gene expression in brain glial cells

JH Lee, JH Woo, HM Kim, Ilo Jou
Dept. of Pharmacology, Chronic Inflammatory Disease Research Center Ajou University School of Medicine, Suwon 442-721

Inflammatory gene expressions are regulated at multiple levels, including transcription, mRNA decay and translational processes and through post-translational modifications. In an effort to find a novel target to control inflammation, we have screened the effects and underlying mechanisms of several molecules which are known to have anti-inflammatory actions. Especially, we focused on the activators of nuclear receptors such as Liver X Receptors (LXRs), small heterodimer partner (SHP), and peroxisome proliferator-activated receptors (PPARs). Among them, oxysterols and synthetic LXR ligands transrepressed inflammatory gene expressions LXR receptor-dependently in IFN-γ-stimulated astrocytes and microglia. And the inhibitory action was mediated by the co-operation with another nuclear receptor, SHP in astrocytes, but independently in microglia. The anti-inflammatory actions of PPAR ligands and oxysterols on JNK MAPK appeared through induction of MAPK phosphatase(MKP)-1, an endogenous regulator of MAPK. And MKP-1 inductions by them were regulated post-trasncriptional levels, mRNA decay and processing. Altogether, our experiments demonstrate that known anti-inflammatory molecules could regulate different steps of inflammatory gene expression and not infrequently, of more than one step. Given the complexity and redundancy of inflammatory signaling pathways and resulting inevitable unwanted reaction, our present result that indicates specific regulation of inflammatory responses at different steps of inflammatory gene expression suggest that a novel target with efficient regulation of inflammation could be developed in the near future.

Session V

Brain aging and neuroprotection

Chair: Dr. A Takashima

Hoon Ryu

Personal Information

Department of Neurology, Boston University School of Medicine, Laboratory for Neuronal Gene Regulation and Epigenetics, VA Boston Healthcare System, Building 1A, Room 109, 150 S Huntington Avenue, Boston, MA 02130, USA, Tel: 857-364-5910

Department of Biomedical Sciences, Seoul National University College of Medicine, 105 Biomedical Research Bldg. 1st Fl. Rm106, 103 Daehak-ro, Jongno-gu, Seoul 110-799, South Korea, Tel: 82-2-740-8904

Education

1983 – 1986	Chonbuk National University	B.S.
1987 – 1992	Chonbuk National University	M.S.,Ph.D.
1997 – 1999	Harvard Medical School, USA	Post-Doc Neurology

Research and Professional Career

2003 – 2004 *Assistant Professor*, Department of Neurology, University of Massachusetts Medical School, USA

2004 – 2006 *Assistant Professor*, Department of Neurology, Boston University School of Medicine, USA

2007 – present *Associate Professor*, Department of Neurology, Boston University School of Medicine, USA

2009 – present *Associate Professor*, WCU Neurocytomics Group, Department of Biomedical Science, Seoul National University College of Medicine, South Korea

2010 – present *Investigator*, Boston University Alzheimer's Disease Center, Boston University

Recent Publications

1. Lee J, Hon YK, Jeon GS, et al. (2012) ATRX induction by mutant huntingtin via Cdx-2 modulates heterochromatin condensation and pathology in Huntington's disease. *Cell Death & Differ.* 19:1109-1116.
2. Lee ST, ChuK, Jung KH, et al. (2012) miR-206 regulates brain-derived neurotrophic factor in Alzheimer's disease model. *Ann Neurol.* published March 15, 2012
3. Song H, Boo JH, Kim KH et al.. (2012) PML expression is regulated by -secretase activity of presenilin under DNA damage condition. *Cell Death & Differ. revision*
4. Moon M, Song H, Hong HJ, et al. (2012) The direct interaction of vitamin D-binding protein with amyloid beta (Ab) suppresses Ab-related pathology *in vitro* and *in vivo. Cell Death & Differ. Under revision*
5. Jeon GS, Kim KY, Hwang YJ, et al. (2012) Deregulation of BRCA1 leads to impaired spatiotemporal dynamics of γ-H2AX and DNA damage responses in Huntington's disease. *Moleclular Neurobiology* 45:550-556.
6. Liu T, Roh SE, Woo JA, Ryu H, Kang D. (2012) Cooperative Role of RanBP9 and P73 in Mitochondria-Mediated Apoptosis. *Cell Death & Disease. Accepted.*
7. Jungh M-K, Lee NY, Kang YS, et al. (2012) Expression of taurine transporter (TauT) by heat shock factor1 (HSF1) is linked to the pathology of motor neurons in ALS. *Moleclular Neurobiology. Accepted.*

EWS deficiency deregulates CBP activity and leads to aberrant *c-Ret* expression and motor neuronal dysfunction

Hoon Ryu, Ph.D.
WCU Neurocytomics Group, Department of Biomedical Sciences,
Seoul National University Graduate School, Seoul, South Korea
Department of Neurology, Boston University School of Medicine and
VA Boston Healthcare System, Boston, MA 02130, USA

EWS, a putative RNA-binding protein and a FUS/TLS homologue protein, is found in neuronal system but its physiological role is not known. To determine the role of EWS expression in neuronal system, we characterized the murine model with knock out of *EWS* gene by homologous recombination. EWS null ($^{-/-}$) mice exhibited a severe defect in motor neuronal differentiation and impaired development in the ventral horn of spinal cord. We further found a mechanism how EWS deficiency leads to motor neuronal dysfunction. The direct interaction between EWS and CBP engaged in the expression of *c-Ret*. EWS is acetylated at K144 by CBP and, in turn, acetylated EWS stabilizes CBP and modulates CBP-dependent *c-Ret* transcription in EWS WT ($^{+/+}$) mice. In contrast, the loss of EWS function significantly reduced the stability of CBP protein and led to the aberrant c-Ret expression and GDNF signaling transduction in motor neurons. EWS null ($^{-/-}$) motor neurons and mouse embryonic fibroblasts were sensitive to neuronal stress induced by neurotoxins and oxidative stress, demonstrating a *bona fide* function of EWS in motor neuronal survival. Taken together, our findings indicate that EWS plays a role as a co-transcriptional factor for CBP-dependent induction of c-Ret and contributes to motor neuronal survival.

Nozomu Mori

Personal Information

Dept. of Anatomy and Neurobiology
Nagasaki University, School of Medicine
1-12-4 Sakamoto, Nagasaki 852-8523, Japan
Tel: +81-95-819-7017
Fax: +81-95-819-7017
E-MAIL: morinosm@nagasaki-u.ac.jp

Education

1976 B.S. University of Tokyo, School of Pharmacy
1984 Ph.D., University of Tokyo (Pharmaceutical Sciences)

Research and Professional Career

1979-1984 Assistant Professor, Toho University, School of Pharmacy
1984-1986 Postdoctoral Fellow, City of Hope Medical Institute, Duarte, CA, USA
1986-1990 Senior Research Fellow, California Institute of Technology, Howard Hughes Medical Institute, Pasadena, CA, USA
1990-1995 Assistant Professor, Andrus Gerontology Center, University of Southern California, Los Angeles, CA, USA
1995-1997 Researcher, Sakigake Project (Inheritance and Variation), JST, Keihanna Plaza, Kyoto, Japan
1997-2004 Director, Department of Molecular Genetics/Aging Intervention, National Institute for Longevity Sciences (NILS), Oobu, Japan
2004-present Professor, Department of Anatomy and Neurobiology, Nagasaki University School of Medicine, Nagasaki, Japan

Recent Publications

1. Kakizawa S, Shibazaki M, Mori N, Protein oxidation inhibits NO-mediated signaling pathway for synaptic plasticity, ***Neurobiol. Aging***, 33, 535-545 (2012)
2. Kakizawa S, Yamazawa T, Chen Y, Ito A, Murayama T, Oyamada H, Kurebayashi N, Sato O, Watanabe M, Mori N, Oguchi K, Sakurai T, Takeshima H, Saito N, and Iino M. Nitric oxide-induced calcium release via ryanodine receptors regulates neuronal function. ***EMBO J.*** 31, 417-428 (2012)
3. Mori N and Mori M, Neuronal Shc: A gene of longevity in the brain? ***Medical Hypotheses***, 77, 996-999 (2011)
4. Mori N, Mori M, Quest for a long life: Paradoxes and essentials of evolving longevity. ***Acta Med. Nagasaki*** 56, 73-80 (2011)

Novel regulators of dendritic spine morphology and cognitive decline in the aged brain

Nozomu Mori
Department of Anatomy and Neurobiology, Nagasaki University School of Medicine

It is well known that higher brain functions such as cognitive abilities decline with age. The age-related cognitive decline could be caused either by loss of synaptic plasticity and/or neurodegeneration. In pathological conditions such as in Alzheimer's disease (AD), neurodegeneration should be a main cause; however, in the stages of physiological aging, we assume the synaptic plasticity loss would be a major reason for such a functional decline in the learning and memory. Among a variety of molecules that are involved in synaptic plasticity, molecules involved in modulation of spine size and/or density are primarily important for further understanding of the molecular mechanisms of the age-related cognitive decline.

We previously showed that N-Shc/ShcC affects the learning and memory function via specific modulation of NMDA-receptor affecting long-term potentiation, LTP. We have further evidence that N-Shc/ShcC affects actin dynamics in neurons, leading to the modulation of dendritic spine morphology. To elucidate further mechanisms, we isolated a 250kD-Rho-GAP by yeast two-hybrid screen. The p250-GAP, also known as GRIT or RICS, was able to modulate dendritic morphology of hippocampal and cortical neurons. The dendritic spines of mature neurons are enriched with protein named Drebrin, a spine-enriched actin-binding protein. We screened several interacting proteins with Drebrin as a bait, and recently found that one such protein named Spikar also involved in dendritic spine modulation. While both the N-Shc-p250-GAP and Drebrin-Spikar complexes affect dendritic spine morphology in mature adult neurons, is it unclear whether the two machineries interact or affect each other or not. Further examination of these spine regulatory machineries in the adult and aged brain would facilitate further understanding of the molecular mechanisms of age-related cognitive decline at the levels of dendritic spine morphology.

The work was supported, in part, by the A-CORE Program from JSPS.

Toru Nakazawa

Personal Information

Professor, Department of Ophthalmology, Tohoku University Graduate School of Medicine
E-mail: ntoru@oph.med.tohoku.ac.jp

Education

1995 M.D., Tohoku University Graduate School of Medicine

Research, and Professional Career

2003-2006 Research Fellow, Harvard Medical School

2006 Assistant Professor, Department of Ophthalmology, Tohoku University Graduate School of Medicine

2009 Associate Professor, Advanced Ophthalmic Medicine, Tohoku University Graduate School of Medicine

2011-present Professor, Department of Ophthalmology, Tohoku University Graduate School of Medicine

Recent Publications

1. **Nakazawa T**, Shimura M, Ryu M,Himori N, Nitta F, Omodaka K,Doi H, Yasui T, Fuse N, Nishida K. Progression of visual field defects in eyes with different optic disc appearances in patients withnormal tension glaucoma, ***J Glaucoma.***2012 Feb 5. in press.

2. Ryu M, **Nakazawa T**, Akagi T,Tanaka T, Watanabe R, Yasuda M, Himori N, Maruyama K, Yamashita T, Abe T,Akashi M, Nishida K. Suppression of phagocytic cells in retinal disorders using amphiphilic poly(γ-glutamic acid) nanoparticles containing dexamethasone, ***J Control Release.*** 2011 Apr 10;151(1):65-73.

3. **Nakazawa T**, Hisatomi T, Nakazawa C, Noda K, Maruyama K, Miyahara S, Nakao S, She H, Matsubara A, Yin Y, Benowitz L, Hafezi-Moghadam A, Miller JW., Monocytes Chemoattractant Protein-1 mediates retinal detachment-induced photoreceptor loss. ***ProcNatlAcadSci U S A.*** 2007;104(7):2425-30.

4. **Nakazawa T,** Takahashi H, Nishijima.K, Shimura M, Fuse N, Tamai M, Hafezi-Moghadam A, Nishida K., Pitavastatin Prevents NMDA-Induced Retinal Ganglion Cell Death By Suppressing Leukocyte Recruitment, ***J Neurochem.***2007;100(4):1018-31.

5. **Nakazawa T,**Nakazawa C, Matsubara A, Noda K, Hisatomi T, She H, Michaud N, Hafezi-Moghadam A, Miller JW, Benowitz L, Tumor Necrosis Factor-α mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma, ***J Neurosci.*** 2006;26(49):12633-41.

The molecular mechanism of glaucomatous optic neuropathy: learning from a mouse model of axonal damage-induced RGC death

Toru Nakazawa
Department of Ophthalmology, Tohoku University Graduate School of Medicine

Glaucoma, which progresses with age, is the leading cause of blindness in Japan, and the increasing frequency of visual impairment is becoming a serious issue as the country's population aging. The best current treatment for glaucoma is reduction of intraocular pressure, and there is an urgent need for the development of new treatments.

It is important to elucidate the mechanism of the process of glaucomatous optic neuropathy (GON) to develop a neuroprotective treatment for patients with normal tension glaucoma (NTG). In patients with glaucoma, sampling neuronal tissue is difficult, and human studies have been limited and unable to explore the details of molecular pathogenesis. To overcome this problem, we set up a mouse model of axonal damage-induced RGC death, and found that growth factor shortage, oxidative stress, and calpain activation were all involved.

NF-E2 related factor2 (Nrf2) is a transcription factor that plays a pivotal role against oxidative stress. Calpastatin is an endogenous inhibitory protein for the activation of calpain. We performed retrograde labeling of RGCs and crushed the optic nerve in Nrf2- or calpastatin-deficient mice. Seven days after nerve crush, we estimated the density of surviving RGCs in the mice. The number of surviving RGCs was significantly decreased compared to wild-type mice, and the mice were significantly susceptible to axonal damage. Nrf2 activators or calpain inhibitors prevented the degeneration of RGCs with axonal damage. These data suggest that oxidative stress and calpain activation are involved in the process of axonal damage-induced RGC death.

I would like to discuss future drug targets for neuroprotective treatment in patients with NTG.

Session VI

Alzheimer disease pathogenesis

Chair: SJ Lee

Inhee Mook-Jung

Education

1986 B.S., Seoul National University

1995 Ph.D., University of Arizona, U.S.A.

Research and Professional Career

1987~1991 Researcher, UC Irvine

1995~1996 Post-doc, UC San Diego

1996~2003 Assistant/Associate Professor, Ajou University School of Medicine

2004~Present Professor, Dept. Biochemistry & Biomedical Sciences, Seoul National University College of Medicine

2011-present Editor, Journal of Alzheimer's disease

2012-present Editorial Board member, Experimental Molecular Medicine

Recent Publication (year of 2012)

1. Jung ES, An K, Hong HS, Kim J, **Mook-Jung I.** (2012) Astrocyte-originated ATP protects Abeta1-42-induced impairment of synaptic plasticity. Journal of Neurosciecne. 32(9):3081-7.

2. Kim C, Nam DW, Park SY, Song H, Hong HS, Boo JH, Jung ES, Kim Y, Baek JY, Kim KS, Cho JW, **Mook-Jung I.** (2012) O-GlcNAcase inhibitor attenuates Abeta plauqe and rescues memory impairment in a mouse model of Alzheimer's disease. Neurobiology of Aging. In press.

3. Son SM, Song H, Byun J, Park KS, Jang HC, Park YJ, **Mook-Jung I.** (2012) Altered APP processing in the diabetic condition is mediated by autophagosome accumulation. Diabetes. 61:1-13.

4. Kook SY, Hong HS, Moon MH, Ha CM, Chang S, **Mook-Jung I.** (2012) Abeta1-42-RAGE interaction disrupts tight junctions of the blood brain barrier via Ca2+-calcineurin signaling. Journal of Neuroscience. 32(26):8845-8854.

5. Cha MY, Han SH, Son SM, Hong HS, Choi YS, Byun J, **Mook-Jung I.** (2012) Mitochondria-specific accumulation of amyloid beta induces mitochondrial dysfunction leading to apoptotic cell death. PLoS One. 7(4):e34929.

6. Kim C, Choi H, Jung ES, Lee W, Oh S, Jeon NL, **Mook-Jung I.** (2012) Histone deacetylase 6 inhibitor recovers amyloid beeta-induced impairment of mitochondrial transport. PLoS One, 7(8):e42983..

7. Son SM, Jung ES, Shin HJ, Byun J and **Mook-Jung I**. (2012) Abeta-induced formation of autophagosomes is mediated by RAGE-CaMKKb-AMPK signaling. Neurobiol Aging. 33(5):1006.e11-23.

8. Son SM, Song H, Byun J, Park KS, Jang HC, Park YJ, **Mook-Jung I.** (2012) Accumulation of autophagosomes contributes to enhanced amyloidogenic APP processing under insulin-resistant conditions. Autophagy, 8(12) Epub ahead of print.

Molecular Pathogenesis of Alzheimer's Disease
: The effect of metabolism changes in Alzheimer's disease

Inhee Mook-Jung
Department of Biochemistry & Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

Alzheimer's disease (AD) is an age related neurological disorder, which is the most prominent form of dementia. One of major causes of AD pathogenesis is beta amyloid (Aβ) accumulation due to increase of generation and decrease of degradation. Also, disruption of glucose metabolism and mitochondrial function is well documented in AD patients. However, how these metabolism failures are associated with beta amyloid generation and accumulation in the brain is not known. In the present talk, we will discuss 1) how this disturbed glucose metabolism in AD brain contributes the production or processing of Aβ focused on post-translational modification, 2) What is a functional role of mitochondria in AD, specially identifying proteins that directly interacted with Aβ in mitochondria. This research will identify the reciprocal relationship between disturbed glucose metabolism and AD idiopathy related to specially diabetes. In addition, we will elucidate new mechanism of Aβ production, processing and clearance related to glucose metabolism. More importantly, since there is no specific medicine to cure AD completely until now, this research will provide new drug target mechanism based on relationship between disturbed glucose metabolism and Aβ.

Akihiko Takashima

Personal Information

Dr. Takashima (kenneth@brain.riken.go.jp) is Drector of Department of Aging Neurobiology at the Center for Geriatrics and Gerontology, the RIKEN Brain Science Institute, Wako, Japan. He is an internationally renowned neurobiologist on Alzheimer's disease and an expert of tau pathology. He is a board member of Directors in Dementia Japan and a council member of Neurochemistry Japan, and served in the Scientific Advisory Board for the Alzheimer Research Forum (USA). He also serves in the editorial boards of many scientific journals including Journal of Biological Chemistry, Journal of Alzheimer's Disease and Neurobiology of Aging.

Recent Publications

1. Kimura T, Fukuda T, Sahara N, Yamashita S, Murayama M, Mizoroki T, Yoshiike Y, Lee B, Sotiropoulos I, Maeda S, Takashima A., Aggregation of detergent-insoluble tau is involved in neuronal loss but not in synaptic loss. J. Biol Chem. **2010;** 285(49):38692-9.

2. Takashima A. Tau Aggregation is a Therapeutic Target for Alzheimer's Disease. Curr Alzheimer Res. **2010;** 7(8):665-9.

3. Kimura, T., Yamashita, S., Fukuda, T., Park, J-M., Murayama, M., Mizoroki, T., Yoshiike, Y., Sahara, N., and Takashima, A. Hyperphosphorylated tau in parahippocampal cortex impairs place learning in aged mice expressing wild-type human tau: Analysis of brain function in a novel neurodegenerative disease model using Mn-enhanced MRI. EMBO. J. **2007;** 26, 5143-5152.

4. Planel, E., Tatebayashi, Y., Miyasaka, T., Liu, L., Wang, L., Herman, M., Yu, W.H., Luchsinger, J.A., Wadzinski, B., Duff, K.E., and Takashima, A. Insulin dysfunction induces in vivo tau hyperphosphorylation through distinct mechanisms. J. Neurosci. **2007;** 27,13635-13648.

5. Maeda, S., Sahara, N., Kim, H., Saito, Y., Akagi, T., Miyasaka, T., Hashikawa, T., Murayama, S., Ikai, A., and Takashima, A. Granular tau oligomers as intermediates of tau filaments. Biochemistry. **2007;** 46, 3856-3861.

Granular tau oligomer: Intermediate of tau fibril is involved in neuronal loss

Akihiko Takashima
Department of Aging Neurobiology, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka, Oobu-shi, 474-0031 Aichi, Japan

Neurofibrillarly tangles (NFTs) are a pathological hallmark of Alzheimer's Disease (AD), and is thought to form under control of Ab deposition. Based on Braak study (Braak and Braak, 1996), NFTs are first observed in entorhinal cortex, and then spread to limbic and neocortex after Ab deposition. This expanding distribution of NFTs seems to explain clinical progression of AD, suggesting the process of NFT formation or NFT itself may be a cause of neuronal dysfunction. In vitro tau aggregation was analyzed using SDS-PAGE gels, and monitoring ThioflavinT fluorescence and AFM observation. Role of tau aggregates in neurodegeneration was investigated by using two different human tau expressing mouse lines. Analysis of tau fibril formation in vitro shows that tau first bind together and form oligomers, which is soluble in solution. When tau oligomer consist of approximately 40 tau molecules, and have b-pleated sheet, tau oligomer precipitates in solution, and form granular form oligomers. Granular tau oligomer stick together, and finally form tau fibrils (Maeda et.al., 2007). Analysis of wild human tau Tg mouse, which shows memory impairment at old age without exhibiting neuronal loss and NFTs, suggest that hyperphosphorylated tau or oligomer tau formation associate with synapse loss (Kimura et.al., 2007). P301L tau Tg mouse exhibits sarcosyl insoluble tau, and neuronal loss (Kimura et.al., 2010), and EGCG, which blocks tau fibril formation, but increase the amount of granular tau oligomer, enhances tau –induced cell death. Taken together, granular tau oligomer may be involved in neuronal loss. This was supported by a result that an inhibitor for granular tau oligomer formation block neuronal loss, and alleviate neuronal dysfunction in P301L tau Tg mouse. In conclusion, Granular tau oligomer is a toxic tau species, and inhibition of granular tau formation block tau aggregation induced neuronal loss. Thus, inhibition of granular tau formation may be a potential therapy for AD and tauopathy.

Seung-Jae Lee

Personal Information

Department of Biomedical Science and Technology, Institute of Biomedical Science and Technology, Konkuk University, 1 Hwayang-Dong, Gwangjin-Gu, Seoul 143-701, Korea
Tel: +82-2-450-4166, Email: sjlee@konkuk.ac.kr

Education

1992-1995 PhD Department of Life Science, Pohang University of Science and Technology, Pohang, Korea

1990-1992 M.S. Department of Life Science, Pohang University of Science and Technology, Pohang, Korea

1985-1989 B.S. Department of Biology Education, Seoul National University, Seoul, Korea

Research and Professional Career

2011-present Professor, Department of Biomedical Science and Technology, Konkuk University, Seoul, Korea

2006-2011 Associate Professor, Department of Biomedical Science and Technology, Konkuk University, Seoul, Korea

2000-2006 Assistant Professor, The Parkinson's Institute, Sunnyvale, CA

1998-2000 Instructor in Neurology, Center for Neurologic Diseases, Harvard Medical School and Brigham and Women's Hospital, Boston, MA

1996-1998 Postdoctoral Fellow, Center for Neurologic Diseases, Harvard Medical School and Brigham and Women's Hospital, Boston, MA

Recent Publications

1. Eun-Jin Bae, et al. (2012) Antibody-aided clearance of extracellular α-synuclein prevents cell-to-cell aggregate transmission. J. Neurosci. In press

2. Eun-Jin Bae, et al. (2012) Lipid peroxidation product, 4-hydroxy-2-nonenal, promotes seeding-capable oligomer formation and cell-to-cell transfer of α-synuclein. Antioxidant & Redox Signaling, in press

3. **Lee S-J**, et al. (2012) Cell-to-cell transmission of alpha-synuclein aggregates. Met. Mol. Biol. 849, 347-359

4. Lee H-J, et al. (2011) Transmission of synucleinopathies in the enteric nervous system of A53T alpha-synuclein transgenic mice. Exp. Neurobiol. 20, 181-188

5. Lee H-J*, et al. (2011) Enzyme-linked immunosorbent assays for alpha-synuclein with species and multimeric state specificities. J. Neurosci. Methods, 199, 249-257

6. **Lee S-J**, et al. (2011) Protein aggregate spreading in neurodegenerative diseases: problems and perspectives. Neurosci. Res. 70, 339-348

7. **Lee S-J**, et al. (2010) Cell-Cell Transmission of Non-Prion Protein Aggregates, Nature Review Neurology, 6, 702-706

8. Lee H-J, et al. (2010) Alpha-synuclein stimulation of astrocytes: Potential role for neuroinflammation and neuroprotection. Oxid Med & Cel Longev, 3, 283-287

Mechanism of Disease Progression in Age-Related Neurodegenerative Diseases

Seung-Jae Lee
Department of Biomedical Science and Technology, SMART-IABS, Konkuk University, Seoul 143-701, Korea

Neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease (PD), fronto-temporal dementia, Huntington's Disease and Creutzfeldt-Jakob Disease (CJD) are characterized by progressive accumulation of protein aggregates in selected brain regions. Protein misfolding and templated assembly into aggregates might result from an imbalance between protein synthesis, aggregation and clearance. In this talk, I will present the data showing that a small amount of α-synuclein, a protein implicated in PD, is released from neurons via unconventional exocytosis and that the secreted α-synuclein aggregates are transmitted to the neighboring neurons and glia forming Lewy body-like inclusions. This intercellular transfer and deposition of α-synuclein aggregates is associated with cell death in neurons and pro-inflammatory responses in astrocytes and microglia. Our studies suggest a novel mechanism leading to the formation and spread of neuronal and glial α-synuclein aggregates, emphasizing the importance of effective clearance of extracellular α-synuclein in therapy.

Toshiharu Suzuki

Personal Information

Professor and Head, Laboratory of Neuroscience, Graduate School of Pharmaceutical Sciences, Hokkaido University, E-mail: tsuzuki@pharm.hokudai.ac.jp

Education

1985: Ph. D. Nagoya University, Graduate School of Science, Biology (Nagoya, Japan) with a major in Biochemistry and Molecular Biology.

Research and Professional Career

2001-present: Professor and Head, Laboratory of Neuroscience, Graduate School of Pharmaceutical Sciences, Hokkaido University (Sapporo, Japan)

1994-2001: Associate Professor, Laboratory of Neurobiophysics, Graduate School of Pharmaceutical Sciences, The University of Tokyo (Tokyo, Japan)

1992-1994: Visiting Assistant Professor, Molecular and Cellular Neuroscience, The Rockefeller University (New York, USA)

1990-1992: Post-doctoral Research Associate, Molecular and Cellular Neuroscience, The Rockefeller University (New York, USA)

1985-1990: Research Associate, Department of Cell Differentiation, National Institute for Basic Biology (Okazaki, Japan)

Recent Publications

1. Matsushima, T., Saito, Y., Eliott, J. E., Iijima-Ando, K., Nishimura, M., Kimura, N., Hata, S., Yamamoto, T., Nakaya, T. and **Suzuki, T**. (2012) Membrane-microdomain localization of amyloid b-precyrsor protein (APP) C-terminal fragments is regulated by phosphorylation of cytoplasmic Thr668 residue.***J. Biol. Chem.*** 287, 19715-19724

2. Kawano, T., Araseki, M., Araki, Y., Kinjo, M., Yamamoto, T. and **Suzuki, T.** (2012) A small peptide sequence is sufficient for initiating kinesin-1 activation through part of TPR region of KLC1.***Traffic*** 13, 834-848.

3 Hata, S., Fujishige, S., Araki, Y., Taniguchi, M., Urakami, K., Peskind E., Akatsu, H., Araseki, M., Yamamoto, K., Martins, N. R., Maeda, M., Nishimura, M., Levey, A., Chung, K. A., Montine, T., Leverenz, J., Fagan, A., Goate, A., Bateman, R., Holtzman, D. M., Yamamoto, T., Nakaya, T., Gandy, S. and **Suzuki, T.** (2011) Alternative g-secretase processing of g-secretase substrates in common forms of mild cognitive impairment and Alzheimer disease: Evidence for g-secretase dysfunction. ***Ann. Neurol.*** 69, 1026-1031.

4. Hata, S., Fujishige, S., Araki, Y, Kato, N., Araseki, M., Nishimura, M., Hartmann, D., Saftig, P., Fahrenholz, F., Taniguchi, M., Urakami, K., Akatsu, H., Martins, R. N., Yamamoto, K., Maeda, M., Yamamoto, T., Nakaya, T., Gandy, S. and **Suzuki, T.** (2009) Alcadein cleavages by APP a- and g-secretases generate small peptides p3-Alcs indicating Alzheimer disease-related g-secretase dysfunction. ***J. Biol. Chem.*** 284, 36024-36033.

5. Saito, Y., Sano, Y., Vassar, R., Gandy, S., Nakaya, T., Yamamoto, T., and **Suzuki, T.** (2008) X11 proteins regulate the translocation of APP into detergent resistant membrane and suppress the amyloidogenic cleavage of APP by BACE in brain. ***J. Biol. Chem.*** 283 35763-35771.

Function and metabolism of Alcadein in the relation with Alzheimer's disease.

Toshiharu Suzuki
Laboratory of Neuroscience, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan.

Alcadeins (Alcs) represent a family of neural type I membrane proteins, designated as Alca, Alcb, and Alcg) that are encoded by independent genes. In neurons, Alc forms a complex with Alzheimer's amyloid b-protein precursor (APP) via the mediation of the neural adaptor protein X11-like (X11L), thereby Alc and APP largely colocalize in neurons. In the absence of X11L, both Alc and APP are subjected to coordinated proteolytic cleavage [1, 2]. Alc are cleaved by APP a-secretase to leave C-terminal cell membrane associated CTF (Alc-CTF) which are also cleaved by g-secretase complex to secreat small p3-Alc peptide. The p3-Alc are non-aggregatable, while amyloid b-peptides (Aβ) derived from the b- and g-cleavages of APP are aggregatable. Soluble p3-Alc peptide is detectable in CSF and blood. Alteration of p3-Alc species can reflects in aberrancy of substrate cleavage by g-secretase, by which the generation of aggregatable and neurotoxic minor Aβ specie Aβ42 increases, along with the altered production of minor p3-Alc specie [3-7]. In contrast to the fact that the quantification of net Aβ 42 generation is difficult by its aggregatable nature, the quantification of soluble p3-Alc can contribute for the development of convenient, reliable, and sensitive procedure to detect g-cleavage alteration. Furthermore, Alc functions as a cargo-receptor for the kinesin-1 motor that mediates anterograde transport of APP [8, 9]. Taken together with similarity and/or identities in their structure, cellular distribution, and neural function, the physiological and pathophysiological metabolic fate of Alc would be predicted to parallel that of APP.

[1] *J. Biol. Chem.* (2003) 278, 49448-49458. [2] *J. Biol. Chem.* (2004) 279,24343-24354. [3] *J. Biol. Chem.* (2009) 284, 36024-36033. [4] *Ann. Neurol.* (2011) 69, 1026-1031. [5] *Mol. Neurodegener.* (2011]) 6: 76. [6] *J. Alzheimers Dis.* (2012) 31, 421-428. [7] *Mol. Neurodegener.* (2012) 7:16. [8] *EMBO J.* (2007) 26, 1475-1486. [9] *Traffic* (2012) 13, 834-848.

Session VII
Alzheimer disease therapy

Chair: Dr. H Ryu

Jae-sung Bae

Personal Information

Department of Physiology, School of Medicine, Kyungpook National University
101 Dongin-dong 2 Ga, Jung-gu, Daegu, 700-422, South Korea
Email**:** jsbae@knu.ac.kr

Professional experience & Education

2007 – Present **Assistant Professor**, Department of Physiology, School of Medicine, Kyungpook National University, Korea

2005 -2007 **Postdoctoral fellow.** Royal Free and University College Medical School, University College London, United Kingdom

2003 – 2005 **Ph.D.** Graduate School of Veterinary Medicine, Kyungpook National University, Daegu, Korea

1994 – 2003 **B.S. & M.S.** College of Veterinary Medicine, Kyungpook National University, Daegu, Korea.

Publications (Correspondence, Recent 3 Years)

MH Park, et al. (2012) Recombinant soluble neprilysin reduces amyloid-beta accumulation and improves memory impairment in Alzheimer's disease mice. *Journal of Neuroscience*. *Under Revision*

H Lee, et al. (2012) Bone marrow-derived mesenchymal stem cells promote proliferation and neuronal differentiation of Niemann-Pick type C mouse neural stem cells by upregulation and secretion of CCL2. *Experimental Neurology*. *In Press*

J. S. Bae, et al. (2012) Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-beta deposits and the improvement of synaptic transmission in a mouse model of pre-dementia Alzheimer's disease. *Current Alzheimer Research*. *In press*

JH Choi, et al. (2012) Micropatterning of neural stem cells and purkinje neurons using a polydimethylsiloxane (PDMS) stencil. *Lab on a Chip*. *In press*

JK Lee, et al. (2012) Specific labeling of neurogenic, endothelial, and myogenic differentiated cells derived from human amniotic fluid stem cells with silica-coated magnetic nanoparticles. *The Journal of Veterinary Medical Science.* 74(8):969-975.

JK Lee**,** et al. (2012) Soluble CCL5 derived from bone marrow-derived mesenchymal stem cells and activated by amyloid-beta ameliorates Alzheimer's disease in mice by recruiting bone marrow-induced microglia immune responses. *Stem Cells*. 30(7):1544-1555.

HJ Lee, et al. (2012) Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. *Neurobiology of Aging*. 33(3):588-602.

Bone Marrow Stem cells in Alzheimer's Disease Pathogenesis

Jae-sung Bae
Department of Physiology, World Class University Program, School of Medicine,
Kyungpook National University, Daegu, Korea

Alzheimer's disease (AD) is the most common form of dementia. With increased life expectancy, this number is expected to rise in the future. Transplantation of bone marrow stem cells (BMSCs) has been suggested as a potential therapeutic approach to prevent neurodegenerative diseases including AD. However, the actual therapeutic impact of BMSCs and their mechanism of action in AD have not yet been ascertained. The aim of this study was therefore to examine the effects of BMSCs therapy in AD. The one strategy of BMSC therapy is pharmacological-induced recruitment of endogenous BMSCs into an injured site by systemic administration of growth factors or chemokines. To examine the effects of endogenous BMSC therapy, we injected granulocyte colony stimulating factor (G-CSF)/AMD3100 (CXCR4 antagonist) and stromal cell-derived factor-1α (SDF-1α) on endogenous BM-hematopoietic progenitor cell (BM-HPC) recruitment into the brain of an AD mouse model. To mobilize BM-HPCs, G-CSF was injected intraperitoneally, and boosted by AMD3100. Simultaneously, these mice received an intracerebral injection with SDF-1α to induce migration of mobilized BM-HPCs into brain. We found that the memory deficit in the AD mice was significantly improved by these treatments, but amyloid β (Aβ) deposition was unchanged. Interestingly, microglial activation was increased with alternative activation of microglia to a neuroprotective phenotype. Furthermore, by generating an APP/PS1-GFP chimeric mouse we ascertained that the GFP positive microglia identified in the brain were BM-derived. Additionally, increased hippocampal neurogenesis and improved memory was observed in mice receiving combined G-CSF/AMD3100 and SDF-1α, but not in controls or animals receiving each treatment alone. These results suggest that SDF-1α is an effective adjuvant in inducing migration into brain of the endogenous BM-HPCs, mobilized by G-CSF/AMD3100, and that the two can act synergistically to produce a therapeutic effect. Another strategy for stem cell therapy in AD is direct transplantation into the injured site, such as brain. The aim of the second study was therefore to evaluate the therapeutic effect of direct BMSCs transplantation on AD mice. Here we showed that intracerebral transplantation of BMSCs into AD mice significantly reduced A deposition. Interestingly, these effects were associated with restoration of defective microglial function, as evidenced by increased A -degrading factors, decreased inflammatory responses, and elevation of alternatively activated microglial markers. We also observed that CCL5 was increased when BMSCs were transplanted into the brains of A -deposited AD mice, but not normal mice. Interestingly, alternative activation of microglia in AD mice was associated with elevated CCL5 expression following intracerebral BM-MSC transplantation. Furthermore, by generating an AD-GFP chimeric mouse, we ascertained that endogenous BM cells, recruited into the brain by CCL5, induced microglial activation. Additionally, we observed that neprilysin (NEP) and IL-4 derived from the alternative microglia were associated with a reduction in A deposition and memory impairment in AD mice. These results suggest that the beneficial effects observed in AD mice after intracerebral BMSC transplantation may be explained by alternative microglia activation. The recruitment of the alternative microglia into the brain is driven by CCL5 secretion from the transplanted BMSCs, which itself is induced by A deposition in the AD brain. Our results demonstrate that BMSCs are a potential new therapeutic agent for AD. Our approach warrants further investigation as a potential therapeutic option for the treatment of AD patients in the future .

Shoichi Ishiura

Personal Information

4-24-23 Inokashira, Mitaka, Tokyo 181-0001
Tel: 0422-72-0109
E-mail: cishiura@mail.ecc.u-tokyo.ac.jp

Education

4/1976-3/1979 The University of Tokyo Ph.D.
4/1974-3/1976 The University of Tokyo M.Sc.
4/1971-3/1974 The University of Tokyo B.Sc.

Research and Professional Career

1/1998-present The University of Tokyo, Graduate School of Arts and Sciences, Professor
3/1992-12/1997 The University of Tokyo, Inst. of Mol.Cell.Biosci., Associate Professor
4/1979-2/1992 National Institute of Neurosciences, Researcher

Recent Publications

Nojima, J., Maeda, A., Aoki, S., Suo, S., Yanagihara, D., Watanabe, Y., Yoshida, T. & Ishiura, S. (2011) Effect of rice-expressed amyloid b in the Tg2576 Alzheimer's disease transgenic mouse model. *Vaccine* 29, 6252-6258

Yonemura, Y., Futai. E., Yagishita, S., Suo, S., Tomita, T., Iwatsubo, T. & Ishiura, S. (2011) Comparison of presenilin 1 and presenilin 2 gamma-secretase activities using a yeast reconstitution system. *J.Biol.Chem.* 286, 44569-44575

Yamakawa, H., Yagishita, S., Futai, E. & Ishiura S. (2010) b-Secretase inhibitor potency is decreased by aberrant b–cleavage location of "Swedish mutant" amyloid precursor protein. *J.Biol.Chem.* 285, 1634-1642

Transgenic rice expressing amyloid β peptide for oral vaccination

Shoichi Ishiura, Jun Nojima, Dai Yanagihara, Yuichiro Watanabe and Taiji Yoshida*
Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8902, Japan
*Local Crop Research Team, National Agricultural Research Center for the Tohoku Region, 4 Akahira, Shimo-kuriyagawa, Morioka, Iwate 020-0198, Japan

One of the main hallmark of Alzheimer's disease (AD) is senile plaques composed of amyloid β (Aβ). We developed a new edible vaccine: rice expressing GFP-Aβ42. In a previous report, we described the production of anti-Aβ antibodies in B6 mice fed Aβ rice mixed with cholera toxin B subunit (CTB). In this report, we investigated whether Aβ rice had therapeutic effects in the Tg2576 AD model mice. The anti-Aβ antibody titer was increased and levels of intracerebral Aβ (soluble and insoluble) and serum Aβ decreased. Because the value of IgG1/IgG2a in the Aβ feeding group was > 1, immunization via Aβ rice may induce a non-inflammatory Th2 reaction. We also found that the Aβ vaccine improved memory, as assessed in a Y-maze test. The number of arm entries in the Y-maze test was lower in the Aβ feeding group than in the control group. These results suggest that the new edible vaccine Aβ rice may have therapeutic effects in AD.

Masatoshi Hagiwara

Personal Information

Professor, Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University

Education

Dr. Masatoshi Hagiwara was born in 1958, and graduated Medical School of Mie University in 1984.

Research and Professional Career

In 1984, he got a research associate position in Medical School of Nagoya University when he finished PhD course (Pharmacology) in Mie University and went to Montminy Lab in the Salk Institute (San Diego) as a postdoctoral fellow in 1990. After returning Japan, he started his own laboratory in Nagoya University in 1993. He was promoted to a full professor of Medical Research Institute of Tokyo Medical and Dental University in 1997. He moved from Tokyo to Kyoto University in 2010. He interested in splicing code of pre-mRNA and developed chemical compounds for new therapeutics of congenital diseases.

Recent publications

1. Ninomiya K, Kataoka N, and **Hagiwara M.** (2011) Stress-responsive maturation of Clk1/4 pre-mRNAs promotes phosphorylation of SR splicing factor. ***J Cell Biol*.** 195(1):27-40.

2. Amin EM, Hua J, Cheung MK, Ni L, Kase S, Ren-nel ES, Gammons M, Nowak DG, Saleem MA, Hagiwara M, Schumacher VA, Harper SJ, Hinton D, Bates DO, Ladomery MR (2011) WT1 mutants reveal SRPK1 to be a downstream angiogenesis target by altering VEGF splicing. ***Cancer Cell*** 20(6):768-780

3. Nishida A, Kataoka N, Takeshima Y, Yagi M, Awano, H, Ota, M, Itoh K, **Hagiwara M**, and Matsuo M (2011) Chemical treatment enhances skipping of a mutated exon in the *dystrophin* gene. ***Nature Commun*** 2, 308.

4. Ogawa Y, Nonaka Y, Goto T, Ohnishi E, Hiramatsu T, Kii I, Yoshida M , Ikura T , Onogi H , Shibuya H , Hosoya T, Ito N, and **Hagiwara M** (2010) ***Nature Commun.*** 1, 86, doi:10.1038/ncomms1090

Novel DYRK1A inhibitor applicable for Alzheimer disease.

Isao Kii and Masatoshi Hagiwara
Graduate School of Medicine, Kyoto University, Japan.

Patients of congenital diseases such as Down syndrome (DS) have abnormalities in their chromosomes and/or genes. Therefore, it has been considered that drug treatments can serve to do little for these patients more than to patch over each symptom temporarily when it arises. Although we cannot normalize their chromosomes and genes with chemical drugs, we may be able to manipulate the amounts and patterns of mRNAs transcribed from patients DNAs with small chemicals. Based on this simple idea, we have looked for chemical compounds which can be applicable for congenital diseases and found INDY as the inhibitor of DYRKs (dual-specificity tyrosine phosphorylation regulated kinases) (Ogawa *et al.* Nature Commun. 2010)
DYRK1A is a serine/threonine kinase essential for brain development and function, and its excessive activity is considered a pathogenic factor in Down syndrome. Autophosphorylation of the critical residues is an essential maturation event required for the activation of DYRKs. Presence of chemical inhibitors that selectively affect the folding intermediate was predicted, but has been missed in conventional drug screens. To find out the hypothetical inhibitor, we designed a cell based assay that enables us to detect the inhibition of DYRK1A just at the transitional folding state. Through the screening of our chemical library, we found a folding intermediate-selective inhibitor of DYRK1A, referred to as FINDY. This suppressed intramolecular autophosphorylation of Ser97 in DYRK1A and destabilized the folding intermediate, but did not inhibit the substrate phosphorylation by the mature kinase. FINDY selectively suppressed the DYRK1A-induced abnormal development of *Xenopus laevis* embryos, indicating that targeting the intermediate states of protein kinases may open the way to develop a new type of therapeutic drugs.

Young Ho Koh

Personal Information

Deputy Scientific Director, Division of Brain Disease, Center for Biomedical Sciences, Korea National Institute of Health, Osong, Republic of Korea,

Email: kohyoungho122@gmail.com

Education

1989 - 1995 BA Department of Biochemistry, Kyungpook National University

1995 - 1997 MS Department of Biochemistry, Kyungpook National University

1997 - 2001 Ph.D. Department of Biochemistry, Osaka University Medical School

Research and Professional Career

2001- 2002 post-doc Division of Experimental Medicine, Beth Israel Medical Center, Harvard Institute of Medicine, Boston

2002 – 2005 post-doc Genetics and Aging Research Unit, Department of Neurology Massachusetts General Hospital/Harvard Medical School

2005- present Deputy Scientific Director, Division of Brain Disease, Center for Biomedical Sciences, Korea National Institute of Health,

Recent Publications

Yun SM, et al. (2012) SUMO1 modulates A generation via BACE1 accumulation. Neurobiology of Aging, in press

Jang BG, et al. (2010) Plasma carbonic anhydrase II protein is elevated in Alzheimer's disease. J. Alzheimer's disease

Chae SC, et al. (2010) Caspases-2 and -8 are Involved in the Presenilin1 -Secretase-Dependent Cleavage of Amyloid Precursor Protein after the Induction of Apoptosis. J. Neurosci. Res. 88; 1926-33

Tesco G, Koh YH, Kang EL, et al. (2007) Depletion of GGA3 stabilizes BACE and enhances beta-secretase activity. Neuron. 54(5):721-37.

Koh YH, von Arnim CAF, et al. (2005) BACE is degraded via the lysosomal pathway. J. Biol. Chem. 280; 32499-504

Molecular mechanism of APP processing : SUMO1 as a new BACE1 interacting molecule

Sang-Moon Yun, Sun-Jung Cho and Young Ho Koh

Division of Brain Diseases, Center for Biomedical Sciences, Korea National Institute of Health

Alzheimer's diseases (AD) is the most common cause of dementia in the elderly and is associated with cognitive and memory dysfunction. This progressive diseases is neuropathologically characterized by the presence of senile plaques and neurofibrillary tangles. Senile plaques result from the extracellular accumulation of aggregated amyloid-beta peptides, which are generated by BACE and gamma-secretase cleavage of the amyloid precursor protein. Accumulation of proteins is recurring event in AD. Evidence has suggest that protein accumulation may result from dysfunction in the ubiquitin proteasome system. Small ubiquitin-like modifiers (SUMO1) are proteins homologous to ubiquitin that possibly regulate intranuclear protein localization and ubiquitination. Understanding the mechanisms behind the SUMO contribution to neurodegenerative diseases would offer new perspectives for the diseases progression. We examine the major facts and hypotheses of the contribution of SUMO to AD.

Poster Sessions

I. 13:00-13:30

II. 17:40-18:30

<P1>

Ablation of Peroxiredoxin 3 Results in Abnormal Mitochondrial Membrane Potential and Decreased Contractile Function of Skeletal Muscle

Kwang-Pyo Lee[1], Sung Chun Cho [2], Hyun Ae Woo[3], Sue Goo Rhee[3], and Ki-Sun Kwon[1]

[1]Laboratory of Cell Signaling, Aging Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon 305-806, Korea, [2]Institute on Aging, Seoul National University College of Medicine, Seoul 110-799, Korea, [3]Division of Life and Pharmaceutical Sciences, Ewha Womans University, Seoul 120-750, Korea.

Sarcopenia is the gradual loss of skeletal muscle mass and function associated with aging. Reactive oxygen species (ROS) are known to be accumulated by a dysfunction of the respiratory chain complex and an insufficient function of the antioxidant protein during the aging process, a mechanism hypothesized to cause sarcopenia but remains unclear. Here, we examined whether peroxiredoxin 3 (PRX3), the major mitochondrial antioxidant protein, plays a critical role in muscle aging. Interestingly, PRX3 knockout mice showed less dynamic behavior than wild type mice. Isometric force measurements revealed that soleus muscle isolated from the knockout mice showed less force production than that of wild type mice after repeated electric stimuli, resulting in severe fatigue phenotype. Moreover, mitochondrial membrane potential was significantly reduced in flexor digitorum brevis (FDB) fibers isolated from PRX3 knockout mice. These results suggest that PRX3 has a crucial role in maintenance of mitochondrial membrane potential and thereby controls homeostasis of skeletal muscle function. We also propose PRX3 knockout mice as a novel mouse model for sarcopenia.

Key words: Sarcopenia, Peroxiredoxin3, aging, ROS, skeletal muscle

<P2>

A novel Peroxisome Proliferator-Activated receptor α/γ dual agonist MHY 908 alleviates insulin resistance and dyslipidemia in db/db mice.

Park MH[a,], Park JY[a], Lee HJ[a], Kim DH[a,], Park CH, Song YM[a], Choi YJ[a,], Chung KW[a,], Bae HR, Kim SR, Jung YR, Chun P[b], Moon HR[a], Chung HY[a]

[a] *Molecular Inflammation Research Center for Aging Intervention (MRCA), College of Pharmacy, Pusan National University, Busan 609-735, Republic of Korea*

[b] *College of Pharmacy, Inje University, Gimhae, Gyeongnam 621-749, republic of Korea*

Peroxisome proliferator-activated receptor α/γ (PPAR α/γ) dual agonists have the potential to be used as therapeutic agents for the treatment of type 2 diabetes and simultaneously prevent dyslipidemia that contributes to the high risk of cardiovascular disease in diabetics. However, PPAR α/γ dual agonists such as muraglitazar, tesaglitazar, and ragaglitazar have some side effect profile, including weight gain, hepatotoxicity, cardiovascular risks, potential carcinogenicity, and edema. Therefore, PPAR α/γ dual agonists are under development to prevent type Ⅱ diabetes complications. The purpose of this study was to characterize a novel PPAR α/γ dual agonist, 2-[4-(5-Chlorobenzothiazo thiazol-2-yl)phenoxy]-2-methyl-propionic acid (MHY 908), exhibiting the improvement in insulin sensitivity and type Ⅱ diabetes via both *in vitro* and *in vivo* approaches. In docking simulation binding affinity of MHY 908 is higher than fenofibrate and rosiglitazone, known as PPAR α and γ agonist, respectively. MHY 908 stimulated transcriptional activities of PPAR α and γ. High level of PPAR α/γ localization in nucleus was identified upon treatment with MHY 908. Next, after treated with MHY 908 (orally 1 or 3 mg/kg/day) for 30 days in obese diabetic (db/db) mouse, nuclear PPAR α/γ level in liver was assessed by Western blot analysis. MHY 908 stimulated activated PPAR α and PPAR γ activities in dose dependent manner. MHY 908 modulated the triglyceride, insulin, and glucose levels in db/db mice. MHY 908 also modulates serum leptin to adiponectin ratio, as an index of insulin resistance and diabetes. These results suggest that MHY is a novel PPAR 908 α/γ dual agonist with potency to improve type Ⅱ diabetes.

<P3>

APE1, XRCC4, and XPC are transcriptional target genes of FOXO to mediate DNA damage-dependant-activation of DNA repair

Jeong-Hyeon Kim[1,2], Jee-In Heo[1,2], Seong-Hoon Park[1], Hong-Jun Kang[1], Seung-Min Lee[1], Jeong-Min Lee[1], Jae-Bong Park[1], Jaebong Kim[1], Sung-Chan Kim[1] and Jae-Yong Lee[1,2]

[1]Department of Biochemistry,[2]Institute of Natural Medicine, Hallym University Medical School, 1 Okchon-dong, Chuncheon, Gangwon-do 200-702

DNA damage is known to activate DNA repair and also reported to increase FOXO3a, implying that FOXO3a is related with DNA repair. Since the detailed function of FOXO3a in DNA damage and DNA repair has not been elucidated yet, the role of FOXO3a in DNA damage-mediated activation of DNA repair HEF (human embryonic fibroblast) was examined. When HEF cells were treated with doxorubicin, a DNA intercalating agent the protein level of FOXO3a was increased. APE1 level and BER activity were also increased. Promoter activity of APE1 was increased by increased FOXO3a. Deletion and point mutants in FOXO3a binding sites of APE1 promoter showed decrease of promoter activity. CHIP (Chromatin Immunoprecipitation) assay showed that APE1 binding to FOXO3a binding sites of APE1 promoter was increased in doxorubicin treated-HEF cells, indicating that APE1 is a transcriptional target gene of FOXO3a. Deacetylation and dephosphorylation mutants of FOXO3a (activation of FOXO3a) resulted in up-regulation of APE1 and activation of BER as expected. Additional data also showed that XRCC4, a factor of non-homologous end-joining (NHEJ) and XPC, a component of nucleotide excision repair (NER) are transcriptional target genes of FOXO3a to mediate the increase of NHEJ and NER activities in doxorubicin-treated HEF cells.

<P4>

Development of DNA Cleavage Assay for XPG Endonuclease Activity of Endogenous Proteins in Human Cells and Rat Tissues via Radioactive-and Non-Radioactive Labeling of Specific Oligonucleotide

Preeyaporn Koedrith, Hye Lim Kim, and Young Rok Seo

Department of Life Science, Dongguk University, Institute of Environmental Medicine for Green Chemistry, Dongguk University, 30 Pildong-ro 1-gil (26 Pildong 3-ga), Jung-gu, Seoul 100-715, Korea

XPG, a structure-specific DNA endonuclease responsible for the 3' incision of DNA lesions during nucleotide excision repair (NER), is associated with high risk of skin cancer as well as skeletal, neurological, and developmental abnormalities when functional defective. These observations have led to the model in which the endonuclease activity of XPG is important for NER. Here, we firstly demonstrate a sensitive assay of XPG cleavage activity using direct protein extract as a XPG source. This method provided semi-quantitative evaluation of endogenous XPG endonuclease derived from either cells or tissues with high reproducibility. Our new assay takes advantage of 3'-end oligolabeling of the bubble-shaped substrate via 32P- or biotin-DNA labeling systems. Our results demonstrate efficient cleavage of the model substrate in both XPG wild-type cell lines (human fibroblasts and colon cancer RKO cells) and rat tissues (liver and kidney) in a time- and dose-dependent manner. In addition, XPG-deficient cells manifested lower cleavage relative to normal XPG cells, indicating that the incision activity of XPG was intrinsic in our methodology. It also found that 7 mM MgCl2 and buffer pH 6.8 resulted in optimal endonucleolytic activity. Our modified methodology might be adopted for quantitative monitoring of XPG cleavage activity in any cell type or tissue of interest. The usefulness of the assay for screening of human populations with NER defects might be proposed (412-112-011).

Key words: Xeroderma pigmentosum (XP), XPG endonuclease, ERCC1-XPF, DNA lesion, Nucleotide excision repair (NER)

<P5>

Developmental over-expression of malic enzyme in the fat body extends Drosophila life span.

Young-Eun Lee, Gye-Hyeong Kim, Yeogil Jang,Young-Nam Lee, Donggi Paik, Joong-Jean Park*

Department of Physiology, College of Medicine, Korea University
73 Inchon-ro, Seongbuk-gu, Seoul 136-705, Republic of Korea

Malic enzyme, linked to tricarboxylic acid (TCA) cycle, converts malate to pyruvate and produces CO_2 and NADPH. Recently function of malic enzyme that regulates lipid metabolism has been recognized. Pyruvate produced by malic enzyme is transported to mitochondria and changed to acetyl-CoA, the fuel of the TCA cycle. Then the acetyl-CoA is converted to citrate, which is transported to the cytoplasm for lipid biosynthesis. Thus, malic enzyme provides a component not only for the TCA cycle, but for fatty acid synthesis. In *Drosophila,* Men (CG10120) is homologous to human cytosolic $NADP^+$-dependent ME1 (EC 1.1.1.40) and is expressed highly in the fat body during larval period. Recently we reported Men overexpression extended fly lifespan. In the present studies, we investigated how Men overexpression made such lifespan extension. Transgenic flies expressing specifically Men transgene were generated and crossed with fat body-specific gene-switch (GS) Gal4 driver flies. The lifespan of these flies was measured with feeding RU486, the inducer of GS in various conditions. Men overexpression in the fat body limited to the larval period was sufficient to extend adult lifespan. In addition, such a condition reduced the body weight, the levels of triglyceride and expression of several genes related lipogenesis, such as acetyl-CoA carboxylase, fatty acid synthase, and carbohydrate-responsive element-binding protein (ChREBP).Together, Our results suggest that developmental Men in Drosophila plays an important role in the Drosophila fatty acid synthesis and life span extension.

<P6>

Esculetin promotes type I procollagen expression in human dermal fibroblasts through MAPK and PI3K/Akt pathways

Jung Hae Park, So Ra Kim, Hyun Ju An, Jeong A. Han*

Department of Biochemistry and Molecular Biology, Kangwon National University School of Medicine, Chuncheon 200-701, South Korea

Type I collagen is the major constituent of the skin and the reduction of dermal type I collagen content is closely associated with the intrinsic skin aging. We here found that esculetin, 6,7-dihydroxycoumarin, strongly induces type I procollagen expression in human dermal fibroblasts (HDFs). Esculetin not only increased protein levels of type I procollagen but also increased mRNA levels of *COL1A1* but not *COL1A2*. Esculetin activated the MAPKs (ERK1/2, p38, JNK) and PI3K/Akt pathways, through which it promoted the type I procollagen expression. We also demonstrated that the binding motifs for transcription factor Sp1 occur with the highest frequency in the *COL1A1* promoter and that esculetin increases the Sp1 expression through the MAPK and PI3K/Akt pathways. These results suggest that esculetin promotes type I procollagen expression through the MAPK and PI3K/Akt pathways and that Sp1 might be involved in the esculetin-induced type I procollagen expression via activation of the *COL1A1* transcription.

Key words: esculetin, type I procollagen, MAPK, PI3K/Akt, Sp1

<P7>

Genomic Profiling of Cadmium-and Nickel-Responsive Genes in Human Cells and Experimental Mice Models

Sang Min Lee, Young Rok Seo

Department of Life Science, Institute of Environmental Medicine for Green Chemistry, Dongguk University-Seoul, 26 Pil-dong 3-ga, Jung-gu, Seoul 100-715, Korea

Cadmium (Cd) and nickel (Ni) are used in industrial sectors for electroplating as well as manufacturing of batteries, plastics, paints, alloys and fertilizers. Long-term exposures to Cd and Ni cause detrimental health effects to human, including various cancers and cardiovascular diseases. At cellular level, Cd and Ni are known to damage to DNA molecules and impair DNA repair activity, giving rise to persistent accumulation of DNA damage. However, molecular mechanisms underlying toxicity of both metal individuals remain to be elucidated. DNA microarray technology is thus applied as powerful tool by which comprehensively provides global analysis of gene expression profiles, particularly in toxicological studies. In this study, we identified gene expression profiles of human cell line and mice in response to chronic exposure to Cd or Ni using 4K DNA microarray-based technology. Total 650 genes with1.5-fold change were altered in human cells while 1414 genes with 1.5-fold change in expression levels were observed in mice upon chronic exposure of Cd and Ni. Using pathway studio software 8.0, we found 123 genes whose functions are associated with DNA repair process. Our findings support the adverse biological effects of Cd and Ni with emphasis of DNA repair interference. Furthermore, the subset of genes discovered might be considered as biomarkers panel regarding to carcinogenicity of both carcinogenic metals Cd and Ni. [412-112-011]

Key words: Cadmium, Nickel, DNA microarray, DNA repair

<P8>

Mechanism of anti-melanogenic activity of 4-(Thiazolidin-2-yl) benzene-1,2-diol with effective *in vivo* skin lighting potency

Ki Wung Chung, Dae Hyun Kim, Min Hi Park, Kyung Kyun Noh, Eun Ji Jang, Hye Jin An, Hyung Ryoung Moon, Hae Young Chung
MRCA, Department of Pharmacy, Pusan National University, Busan 609-735, Republic of Korea

Tyrosinase inhibitors have become increasingly important due to their inhibitory effects of melanin biosynthesis causing pigmentation. Many approaches have been made to develop new kinds of tyrosinase inhibitor with various aspects including modulating intracellular signal transduction pathway. In search of new agents with a tyrosinase inhibitory effect, we synthesized a new kind of tyrosinase inhibitor, 4-(Thiazolidin-2-yl) benzene-1,2-diol (MHY-794). The novel compound, MHY-794 revealed the direct inhibitory effect on mushroom tyrosinase. MHY-794 also showed great efficacy in scavenging nitric oxide (NO), which serves as important modulator in melanogenesis signaling pathway. The inhibitory effect of MHY-794 on tyrosinase activity and melanin production were examined in murine melanoma B16F10 cells. When NO donor (SNP) was used as melanogenesis stimulator, MHY-794 showed great efficacy to decrease tyrosinase activity and melanin contents. MHY-794 effectively scavenged NO effectively and also diminished NO-mediated melanogenesis signaling. The anti-melanogenic effect of MHY-794 was further verified in HRM2 hairless mice. Repeated irradiation with UVB induced melanin synthesis in HRM2 hairless mice. The skin-whitening index (L value) of HRM2 hairless mice treated with MHY-794 before irradiation with UVB was greater than that of UVB-irradiated mice that were not treated with MHY-794. MHY-794-treated animal also showed the decreased stained melanin spots when detected with Fontana-masson staining.

Through these investigations, it was concluded that a newly synthesized tyrosinase inhibitor MHY-794, which also showed great efficacy to decrease NO-mediated melanogenesis by direct NO scavenging, might be utilized for the development of a new candidate for the hyper-pigmentation disorders.

<P9>

Hazardous effects of nano TiO_2 in *in vivo* mimic 3-dimensional (3D) skin culture system

Ji Su Shon, Preeyaporn Koedrith and Young Rok Seo
Department of Life Science, Institute of Environmental Medicine for Green Chemistry, Dongguk University, Seoul, South Korea

Not only acute but also chronic UV light exposure induces skin damage, including photo-aging and cancer. Therefore, sunscreen products become necessary for daily protecting skin from UV light. Most of sunscreens contain titanium dioxide (TiO_2) nanoparticles, so called nanoTiO_2, which are capable of protecting against UV light. However, photo-damage in combination with nano TiO_2 has not been clarified yet. Here, we investigated adverse effects of combinatorial exposure to nanoTiO_2+UV irradiation on DNA damage and repair using *in vivo* mimic 3-dimensional (3D) skin culture model which is successfully applied for the testing of cosmetic ingredients. In order to avoid forming of aggregated nano TiO_2, poly acrylic acid (PAA) was alternatively used as a non-cytotoxic dispersant throughout experiments. After the established 3D skin culture was confirmed by optical microscopic and histological methods, it was subjected to MTT assay for selection of sub-lethal dose of nano TiO_2. Using slot-blot assay, level of 6-4 photoproduct as UV-mediated DNA damage was increased in UV-irradiated group compared to control whereas no significant difference was observed between UV-exposed group and nano TiO_2+UV exposed group. Accordingly, level of p53 protein detected by Western blotting was induced after exposure to the sub-lethal nanoTiO_2, suggesting that nano TiO_2 stimulates the p53-mediated response. Our result of XPG cleavage assay showed that activity of XPG enzyme, which is involved in nucleotide excision repair (NER) of UV-damaged DNA, was dose-dependently impaired in the nano TiO_2-treated group relative to control. Of critical concern, this data might be meaningful information regarding to studies on potential toxicity as well as health hazard of nanoparticles, particularly nano TiO_2, using *in vitro* 3D skin culture system.

<P10>

Resveratrol ameliorates hepatic metaflammation By modulating inflammasome

So Young Lim, Woo-Mi Park, Hee Jae Lee and Soo Jin Yang
Department of Food and Nutrition, Chonnam National University, Gwangju, Korea

Resveratrol is known to regulate NAD bioavailability and sirtuin-related metabolism, which relates to aging, metabolic syndrome, and non-alcoholic fatty liver disease. The purpose of this study was to investigate the effects of resveratrol on hepatic metaflammation in a rodent model of high-fat diet induced obesity. After 6 weeks of high fat diet treatment, C57BL/6 mice were divided into four groups: 1) lean control with standard diet, 2) standard diet + resveratrol, 3) high fat diet-induced obese control, 4) high fat diet + resveratrol. Resveratrol (8 mg/kg/day) was delivered via osmotic pump for four weeks. After four weeks of each treatment, blood and liver tissues were collected and indices of inflammation and inflammasome were analyzed. Body weight and food intake were not altered by resveratrol administration. With HF diet, systemic and hepatic inflammation was aggravated shown as increased levels of pro-inflammatory markers interleukin-1, interleukin-6 and tumor necrosis factor alpha in blood and livers. However, resveratrol administration significantly reduced the levels of these pro-inflammatory markers. These improvements were accompanied by alteration of inflammasome complex proteins (NOD-like receptor family, pryin domain containing 3; apoptosis- associated speck-like protein; caspase 1). These results demonstrate that resveratrol ameliorates hepatic metaflammation by modulating inflammasome.

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A1004861).

Key words: hepatic inflammation, inflammasome, resveratrol

<P11>

Role of ARC, apoptosis repressor with caspase recruitment domain, in cellular senescence of human diploid fibroblast

Yun-Yeong Lee and In Kyoung Lim

Department of Biochemistry and Molecular Biology, Ajou University School of Medicine, Suwon, 443-721, Korea. E.mail: seven260@naver.com

Cellular senescence plays a key role in the biology of aging and carcinogenesis. Hayflick and Moorhead earlier described the replicative senescence revealing a limited proliferative capacity, and postulated cellular senescence as an in vitro manifestation of human aging. Apoptosis repressor with caspase recruitment domain (ARC) has been known as a highly potent and multifunctional inhibitor of apoptosis that is physiologically expressed mainly in the post-mitotic cells such as cardiomyocytes, skeletal muscle cells and neurons. It is also found to be upregulated in various forms of malignant tumors, and impairs the cellular apoptotic responsiveness to a wide range of stresses and insults, including extrinsic apoptosis initiation via death receptor ligands, dysregulation of cellular Ca2+ homeostasis and endoplasmatic reticulum (ER) stress, genotoxic drugs, ionizing radiation, oxidative stress and hypoxia. ARC is subject to both transcriptional and post-translational regulation and exhibits its function through a multitude of molecular interactions with upstream transducers of apoptosis signals. In the present work, we have observed that ARC expression was upregulated in senescent HDF compared with young cells. Also, during the pre-mature senescence ARC expression was upregulated. By employing lentiviral infection to maintain constitutive knockdown of ARC lead to cell death during pre-mature senescence compare with vector control via various apoptosis phenotype. We therefore, hypothesized that ARC may be one of the important factor for survival or stress resistance during the pre-mature senescence and maintenance of senescent cells.

Key words: senescence, ARC

<P12>

Sestrin2 modulates ROS-dependent cellular senescence through the NADPH oxidase 4 activation

Chae Young Hwang[a §], Ying-Hao Han[b §], Sang-Mi Cho[b], Dae-Yeul Yu[b]*, and Ki-Sun Kwon[a]*
[a]Laboratory of Cell Signaling, [b]Disease Model Research Laboratory, Aging Research Center, Korea Research Institute of Bioscience and Biotechnology, Yuseong-gu, Daejeon, Korea

Sestrin2 (Sesn2) is known to be involved in the maintenance of metabolic homeostasis and in aging through modulation of the AMPK-mTOR pathway. Here we show that Sesn2 plays a role in protecting the cellular senescence of mouse embryonic fibroblasts (MEFs). Loss of Sesn2 increased senescence associated (SA)- β -galactosidase activity, reactive oxygen species (ROS), the level of NADPH oxidases 4 (NOX4), and activity of AMP-activated protein kinase (AMPK). Additionally, pretreatment of Sesn2$^{-/-}$ MEFs with an antioxidant N-acetyl-cysteine (NAC) reduced SA-β-galactosidase activity and inhibited AMPK activation. Therefore we suggest that the induction of NOX4, which causes ROS generation and subsequent AMPK activation, is a likely mechanism of cellular senescence resulted from the loss of Sesn2.

Keywords: AMPK, NOX4, ROS, **senescence, sestrin2**

<P13>

The C-terminal region of Rad2p is important for cell cycle regulation and lifespan in the presence of DNA damage

Mi-Sun Kang[1,2], Sung-Lim Yu[3], Choco Michael Gorospe[4], and Sung-Keun Lee[1,2]

[1]Department of Pharmacology, Inha Research Institute for Medical Sciences and [2]Center for Advanced Medical Education, [3]Inha Research Institute for Medical Sciences, [4]Department of Molecular Biomedicine, Inha University College of Medicine by BK-21 Project, Incheon 400-712, Republic of Korea.

Yeast *RAD2* is a homolog of the human xeroderma pigmentosum group G gene (*XPG*). Rad2 and XPG proteins, endonucleases that function in nucleotide excision repair, are highly conserved in their structures and functions. The C-terminal truncation of *XPG* is known to cause a human hereditary disorder, Cockayne syndrome (CS) that is characterized by growth retardation, impaired neurological development, mental retardation and premature aging. In addition to its endonuclease function, Rad2p was shown to have a function in transcription. However, defects in endonuclease activity and transcription are not sufficient to explain the symptoms of CS. Recently, *RAD2* over-expression was shown to evoke mitotic catastrophe implying its involvement in cell cycle regulation. In this study, we show that the C-terminal region of Rad2p is important for maintaining cell growth after UV damage. We also show that the Rad2p C-terminal region is pivotal for replicative lifespan in the presence of DNA damage. These results indicate that the Rad2p C-terminal region may have an unidentified function or mechanism, beside its well known endonuclease activity, in its growth regulatory role upon UV irradiation that might be the underlying cause of CS.

[연구비과제번호: 20090071325〕

Key words: Yeast, *RAD2*, DNA Repair

<P14>

The effects of AMPK and AMP biosynthesis on lifespan extension in *Drosophila melanogaster.*

Jong-Seok Kim[1], Kyu-Sun Lee[2], Kweon Yu[2,] Kyung-Jin Min[1]

[1]*Department of Biological Sciences, Inha University, Incheon Korea 402-751*
[2]*Aging Research Center, Korean Research Institute of Bioscience and Biotechnology, 305-806, Korea.*

Dietary restriction(DR) is restriction of nutrient without deficiency and is known for extending lifespan of yeast to mammal. In *C.elegans* the extension of ligespan by DR has been well characterized by the increase of AMP/ATP ratio and the activation of AMP-activated protein kinase(AMPK). In addition, AMPK activation can extend lifespan of *C.elegans.* Here, to examine the effects of AMPK and AMP biosynthesis on lifespan extension, we use the fruit fly, *Drosophila melanogaster.* The overexpression of AMPK and LKB1, the activator of AMPK, in whole body did not affect the lifespan of *Drosophila*. The regulation of AMPK in the muscle and fatbody significantly increased the lifespan, but not in neuron. In addition lifespan of flies expressing dominant-negative form of AMPK in whole body was still affected by DR, suggesting that AMPK is unnecessary to lifespan extension by DR. Furthermore, we found that adenine supplementation restricted the effects of DR lifespan extension, indicating that AMP/ATP ratio is more effective than AMPK on lifespan extension of DR in *Drosophila melanogaster.*

Keywords : AMPK, dietary restriction, lifespan,

<P15>

The retinoic acid-induced up-regulation of insulin-like growth factor 1 and 2 is associated with prolidase-dependent collagne synthesis in uva-irradiated human dermal equivalents

Joong Hyun Shim[1*], Dong Wook Shin[1,*], Tae Ryong Lee[1], Hak Hee Kang[1], and Minsoo Noh[2]

[1]Bioscience Research Institute, AmorePacific Corporation R&D Center, Yongin, 446-729, Republic of Korea; [2]College of Pharmacy, Ajou University, Suwon, 443-749, Republic of Korea

Ultraviolet (UV) A irradiation causes disrupted collagen homeostasis, resulting in the photo-aging of human skin. All-trans retinoic acid (ATRA) increases collagen synthesis and inhibits matrix metalloproteinase (MMP) expression in UVA-irradiated human skin. Although the effects of ATRA on collagen synthesis and MMP regulation are well known, the effects of ATRA on other collagen homeostasis-associated genes have not been elucidated. Here, the gene transcription profile of collagen homeostasis-associated genes was systematically evaluated in three-dimensional human dermal equivalents (HDEs) following UVA-irradiation and/or ATRA treatment. In addition to the expected changes in MMPs and collagen synthesis in HDEs, prolidase, an important enzyme in the recycling of proline and hydroxyproline from degraded collagen molecules, was significantly decreased by UVA irradiation, and its down-regulation was antagonized by ATRA. In the present study, we demonstrate that ATRA regulates prolidase activity in HDEs by a specific mechanism, suggesting one of the pharmacological mechanisms by which improves photo-aged human skin.

Keywords: Prolidase; Collagen; All trans-retinoic acid; Ultraviolet A irradiation

<P16>

Transcriptional autoregulation of FOXO3a

Jeong-Min Lee[1], Min-Ju Kim[1], Jeong-Hyun Kim[1], Jee-In Heo[1,2], Seong-Hoon Park[1], Hong-Jun Kang[1], Sung-Chan Kim[1], Jaebong Kim[1], Jae-Bong Park[1] and Jae-Yong Lee[1,2]

[1]Department of Biochemistry, [2]Institute of Natural Medicine, Hallym University Medical School , 1Okchon-dong, Chuncheon, Gangwon-do 200-702

FOXO3a is down-regulated during cellular aging and up-regulated by treatment of hydrogen peroxide even though their molecular mechanism remains still unknown. In order to investigate how FOXO3a is up-regulated by treatment of hydrogen peroxide, we tested mRNA and protein levels of FOXO3a. Both mRNA and protein levels of FOXO3a were increased by H_2O_2 treatment in concentration-dependent manner, indicating that FOXO3a is mainly regulated at transcriptional level. The promoter assay using a reporter construct containing FOXO3a promoter and luciferase gene showed same up-regulation by H_2O_2 treatment. Promoter assay with serial deletions of FOXO3a promoter showed that FOXO3a binding sites of FOXO3a promoter are important, indicating that FOXO3a is transcriptionally autoregulated through FOXO3a binding site in its own promoter. Only FOXO3a overexpression increased FOXO3a promoter activity while overexpression of FOXO1 or FOXO4 could not activate, indicating that FOXO binding sites of FOXO3a promoter interact specifically only with FOXO3a. Serial deletion mutants of promoter and point mutants of FOXO binding sites showed the decrease of promoter rctivity. CHIP (chromatin-immunoprecipitation) assay in FOXO binding sites also confirmed that FOXO3a is a its own transcriptional target gene of FOXO3a. Overall, the results suggest that FOXO3a is up-regulated through FOXO binding site in its own promoter by H_2O_2 treatment.

Kyoji Ohyama

Personal Information

Department of Anatomy and Neurobiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8523, Japan

Education

1993 Ph.D. Department of Microbiology, Keio University, School of Medicine, Japan
1989 M.S. Applied Chemistry, Faculty of Science and Technology, Keio University, Japan
1987 B.S. Applied Chemistry, Faculty of Science and Technology, Keio University, Japan

Research and Professional Career

2012-present Associate Professor, Department of Anatomy and Neurobiology, Nagasaki University Graduate School of Biomedical Sciences
2010-2011 Assistant Professor, Department of Anatomy and Neurobiology, Nagasaki University Graduate School of Biomedical Sciences
1999-2010 MRC Postdoctoral Research Associate Instructor, Department of Anatomy, Keio University, School of Medicine

Recent publications

1. *Ohyama K, Yasuda K, Onga K, Kakizuka A, *Mori N, Spatio-temporal expression pattern of the NatB complex, Nat5/Mdm20 in the developing mouse brain: Implications for co-operative *versus* non-co-operative actions of Mdm20 and Nat5. ***Gene Expression Patterns,*** 12, 36-45 (2012). (*Co-corresponding author)

2. Pearson C, Ohyama K, Manning E, Aghamohammadzadeh SE, Sang H, Placzek M, FGF-dependent midline-derived progenitor cells in hypothalamic infundibular development. ***Development*** 138, 2613-24 **(**2011).

3. Xenaki D, Martin IB, Yoshida L, Ohyama K, Gennarini G, Grumet M, Sakurai T, Furley AJW, F3/contactin and TAG1 play antagonistic roles in the regulation of sonic hedgehog-induced cerebellar granule neuron progenitor proliferation. ***Development*** 138:519-29 (2011).

4. Ohyama K, Das R, Placzek M, Temporal progression of hypothalamic patterning by a dual action of BMP. ***Development*** 135, 3325-31 (2008).

5. Manning E, Ohyama K, Soubes S, Hatano O, Wilson S, Logan M, Placzek M, Regional morphogenesis in the hypothalamus: A BMP-Tbx2 pathway coordinates fate and proliferation through Shh downregulation. ***Dev Cell*** 11, 873-85 (2006).

<P17>

TGFβ1 signal protects primary hippocampal neurons during *in vitro* ageing via a p38 MAPK-dependent pathway

Kyoji Ohyama, Kunihiko Yasuda, Kazuko Onga, Nozomu Mori

Department of Anatomy and Neurobiology, Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

Ageing is a risk factor for neurodegenerative diseases. Many previous studies focused on uncovering cell signalling of ageing-related declines in brain functions such as memory deficits. As yet, it remains unclear whether a self-defense mechanism of the brain may operate in an ageing-dependent manner and prevent neuronal degeneration. Emerging evidence suggested that TGFβ1 expression is upregulated after brain injury and ischemia. TGFβ1 signaling also prevents the accumulation of amyloid beta polypeptides, thereby preventing Alzheimer disease. These studies led us to hypothesise that TGFβ1 may act as a self-defense signal to prevent neurodegeneration induced by brain insults such as oxidative stresses during ageing. To monitor the expression of downstream components of TGFβ1 signaling during neuronal ageing, we deployed long term culture of primary hippocampal neurons (starting with E18.5 and continuing for over 6 months). Intriguingly we found that pSmad2 expression decreased during the ageing of hippocamapal neurons, whereas pp38MAPK is upregulated. To test whether TGFβ1 can act as a neuroprotective signal, hippocampal neurons were exposed to H_2O_2 either in the presence or absence of TGFβ1. Consistent with the notion that neuronal ageing process generates reactive oxygen species (ROS), resulting in neuronal degeneration, a H_2O_2 treatment of primary cultured hippocampal neurons caused their dendritic degeneration. In contrast, a TGFβ1 treatment prevented the H_2O_2-induced dendritic degeneration of hippocampal neurons. Further, TGFβ1 via a pp38MAPK pathway led to the accumulation of Nrf2, a transcriptional regulator of an anti-oxidant responsive gene, in the cell nucleus. These data suggest that TGFβ1-pp38MAPK-Nrf2 cascade may operate as an ageing-dependent self-defense signal against oxidative stresses.

Kunihiko Yasuda

Personal Information

Department of Anatomy and Neurobiology, Nagasaki University School of Medicine, Nagasaki 852-8523, Japan

Education

2002 Ph.D. Department of Molecular and Cellular Biology, Institute fo FrontierMedicalSciences, Kyoto University, Kyoto, Japan

1995 M.S. Department of Biochemistry, Kyoto Pharmaceutical University, Kyoto, Japan

1992 B.S. Department of Biochemistry, Kyoto Pharmaceutical University, Kyoto, Japan

Research and Professional Career

2010-2011 Department of Anatomy and Neurobiology, Nagasaki University School of Medicine (Assistant professor)

2002-2010 Laboratory of Functional Biology, Kyoto University Graduate School of Biostudies(Postdoctoral researcher)

1995-1997 Department of Biochemistry, Kyoto Pharmaceutical University, Kyoto, Japan (Assistant professor)

Recent Publications

1. Spatio-temporal expression pattern of the NatB complex, Nat5/Mdm20 in the developing mouse brain: Implications for co-operative versus non-co-operative actions of Mdm20 and Nat5. Ohyama K, Yasuda K, Onga K, Kakizuka A, Mori N. ***Gene Expr. Patterns*** 2012 Jan-Feb; 12(1-2): 36-45.

2. Characterization of stress sensitivity and chaperone activity of Hsp105 in mammalian cells. Yamagishi N, Yokota M, Yasuda K, Saito Y, Nagata K, Hatayama T. ***Biochem. Biophys. Res. Commun.*** 2011 May 27; 409 (1): 90-95

3. p97/valosin-containing protein (VCP) is highly modulated by phosphorylation and acetylation. Mori-Konya C, Kato N, Maeda R, Yasuda K, Higashimae N, Noguchi M, Koike M, Kimura Y, Ohizumi H, Hori S, Kakizuka A. *Genes Cells.* 2009 Apr; 14(4): 483-97.

4. Targeted Hsp110/105 Gene Knockout Decreases Infarct Volume After Focal cerebral Ischemia in Mice. Nakamura J, Fujimoto M, Yasuda K, Takeda K, Akira S, Hatayama T, Takagi Y, Nozaki K, Hosokawa N, Nagata K. *Stroke*. 2008 Oct; 39(10): 2853-9.

<P18>

The effect of HDAC6 on the polyQ aggregates formation in primary cultured neurons: HDAC6 is a key regulator of mTOR signaling

Kunihiko Yasuda, Kyoji Ohyama and Nozomu Mori

Department of Anatomy and Neurobiology, Nagasaki University School of Medicine, Nagasaki 852-8523, Japan

In most of neurodegenerative disorders, such as Huntington's disease and Alzheimer's disease, protein aggregates accumulate in neuronal cell bodies, causing their degeneration. Neuronal cells are expected to have more protein aggregates in amount, since neuronal cells do not divide after fetal development and thus have a long life.

Protein quality control (PQC) is important to extend the life span of cells and maintain a cellular homeostasis. Three major protein clearance pathways have been identified in the PQC: 1) molecular chaperones 2) ubiquitin-proteasome system (UPS), and 3) macroautophagy system (APS). HDAC6, a deacetylase of a-tubulin, is also well known as a key regulator of PQC. Furthermore, given the recent finding that HDAC6 controls a quality control autophagy through autophagosome maturation independent of nutrient deficiency (Lee JY *et al*.: 2010). We hypothesize that HDAC6 may play a key role in neuronal homeostasis, thereby especially autophagy among the PQC. Using polyQ-expressed hippocampal neurons as a model system of polyQ diseases, we examined the effect of HDAC6 on the polyQ aggregates formation. In HDAC6 over-expressed neurons, the number of polyQ aggregates positive neurons was increased and conversely reduced with HDAC6 inhibitor treatment. For the reason, the inhibition of deacetyltransferase activity of HDAC6 induced autophagy by reduced the phosphorylation level of Akt, an one of key component for IGF-PI3K-Akt-mTOR signaling regulates autophagy induction under the nutrient deficient condition. We discuss a role for HDAC6 in IGF-PI3K-Akt-mTOR signaling to maintain the neuronal homeostasis.

Keywords: HDAC6, Protein aggregate, Poly-glutamine, Autophagy, Akt, mTOR