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2017

The 6th Japanese Society of
Immunotoxicology Prize for Encouragement

Effects of environmental chemicals on
immune response via nuclear receptors

Hiroyuki Kojima

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It is my great pleasure and honor to be awarded the JSIT prize for encouragement. I would like to sincerely thank all of the members of the awarding committee.

Nuclear receptors, including several hormone receptors, form a ligand-dependent transcription factor that regulates the genes involved in key physiological functions, such as cell growth and differentiation, development, homeostasis, and metabolism. Between 1998 and 1999, I studied the mechanisms underlying nuclear receptor-induced gene expression as a visiting researcher at the National Institute of Environmental Health Sciences (NIEHS/NIH, USA). After coming back to Hokkaido, Japan, I had shown that environmental chemicals, such as plasticizers, pesticides, and dioxins, can function as ligands of nuclear receptors. In particular, our findings using cell-based transactivation assays revealed that a number of environmental chemicals show estrogen receptor (ER) α , ER β and pregnane X receptor agonistic activity as well as androgen receptor antagonistic activity. These experiences provided me with my present research theme “the immunotoxicological effects of environmental chemicals via nuclear receptors”. However, although some nuclear receptors have been reported to have important roles in the immune systems, the immunotoxicological effects of environmental chemicals via nuclear receptors have not been fully understood. To date, we provided evidences that several

The 24th Annual Meeting of the Japanese
Society of Immunotoxicology

Date

September 4th - 5th, 2017 (Meeting)

September 3rd, 2017 (Lecture open to local citizens)

Venue

Lecture room at School of Veterinary Medicine, Kitasato
University

35-1 Higashi-23-bancho, Towada, Aomori 034-8628, Japan

President

Kazuichi Nakamura (Kitasato University)

Main theme of the meeting

New perspective of “immunoenhancement” and
“immunosuppression”

Aim of the meeting

Autoimmunity or allergy is not necessarily initiated by “immunoenhancement”, but can be caused by even immunosuppression or normal immunity recognizing altered-self antigen or MHC. Physiological immunosuppression during pregnancy may be impaired by xenobiotics. “Immunoenhancement” and “immunosuppression” as the phenotype of immunotoxicity need to be redefined. In this meeting, immunotoxicity will be discussed from new perspectives.

azole-type fungicides and isoflavones, such as biochanin A and genistein, can act as modulators of interleukin-17 gene expression via nuclear receptors, ROR α and ROR γ , in immune cells (Kojima et al., 2012; 2015; Takahashi et al., 2017). In the future, I want to clarify the effects of chemical mixtures on cytokine production via nuclear receptors.

Finally, I would like to give an appreciation to Dr. Ryuta Muromoto at Hokkaido University, and all my collaborators for their help.

Organizing Committee

Tetsuo Aida (Daiichi Sankyo Co., Ltd.)

Etsushi Kuroda (Osaka University)

Hayato Terayama (Tokai University)

Yasuo Yoshioka (Osaka University)

Lecture open to local citizens

Fujio Kayama (Jichi Medical University)

“Safety of rice as a staple food: Findings derived from nationwide epidemiological study in cadmium intake”

Special lectures

1. Danuta Herzyk (Merck Research Laboratories)
“Immunotoxicity assessment of biopharmaceuticals”
2. Tsuyoshi Yokoi (Nagoya University Graduate School of Medicine)
“Involvement of immune-related factors on idiosyncratic drug-induced liver injury”

Educational lecture

Takeharu Minamitani (National Institutes of Biomedical Innovation, Health and Nutrition)

“Autoimmune diseases induced by virus infection”

Symposium

“Reproductive immunotoxicology: Immunological mechanism of pregnancy and its breakdown”

1. Yosuke Maeda (Kitasato University)
“Immunological changes during pregnancy in cows”
2. Yoshie Kametani (Tokai University School of Medicine)
“Immune tolerance in placenta”
3. Tomoko Shima, Akitoshi Nakashima, Shigeru Saito (University of Toyama)
“Regulatory T cells are important for implantation and maintainance of pregnancy”

4. Koumei Shirasuna¹, Nao Tanikawa¹, Ayae Ozeki¹, Akihide Ohkuchi², Masafumi Takahashi² (¹Tokyo University of Agriculture, ²Jichi Medical University)

“Mechanisms of pregnancy complications caused by nanoparticles: possible role of sterile inflammation (inflammasomes) during pregnancy”

Workshop

“The latest developments in the safety evaluation method of biopharmaceuticals (protein formulations)”

1. Akiko Ishii-Watabe (National Institute of Health Sciences)
“Outline and Points to Note on the Safety Evaluation Method of Biopharmaceuticals”
2. Kazushige Maki (Pharmaceuticals and Medical Devices Agency)
“Consideration for preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”
3. Chiyomi Kubo (Chugai Pharmaceutical Co., Ltd.)
“Characteristic test methods in biopharmaceutical nonclinical evaluation
- Evaluation methods using human cells -”
4. Tetsuo Aida (Daiichi Sankyo Co., Ltd.)
“Nonclinical safety assessment of antibody-drug conjugates”

Luncheon seminar

Day 1: Vanessa Peachee (Charles River Laboratories Ashland)

“Unraveling immunotoxicological assays for pharmaceutical and agrochemical industries”

Day 2: Asako Uchiyama

(Shin Nippon Biomedical Laboratories, Ltd.)

“Evaluation methods for cell and gene therapy products in SNBL”

Meeting Secretariat

Laboratory of Toxicology, School of Veterinary Medicine, Kitasato University

Ryo Kamata (Secretary General)

E-mail: secretariat@jsit2017.jp

Immunotoxicological Research

Analysis of the mechanism involved in the effect of environmental factors on living organisms through immunological research

Naoko Kumagai-Takei

(Department of Hygiene, Kawasaki Medical School)

I am studying the effects of asbestos exposure on the differentiation and function of cytotoxic T lymphocytes (CTLs) at the Department of Hygiene, Kawasaki Medical School. I have reported that exposure to chrysotile B asbestos suppressed the induction of human CTLs during mixed lymphocyte reactions, and was accompanied by decreased levels of IFN- γ and TNF- α , and the proliferation of immature CTLs (*Am J Respir Cell Mol Biol* 49: 28-36, 2013). Recently, I also reported that IL-2 insufficiency was not the main cause for the suppressed induction of CTLs by asbestos exposure, although the potential for an improvement of such suppressed CTL functions was suggested (*J Immunol Res* 2016: 7484872, 2016). Additionally, I found that patients with malignant mesothelioma showed decreased perforin levels in CD8⁺ lymphocytes following stimulation compared to patients with pleural plaque and healthy volunteers (*J Immuno Res* 2014: 670140, 2014).

In future, I would like to analyze the mechanisms involved in the immunological effects of environmental factors on living organisms at the organ, cellular and molecular levels. In particular, I wish to elucidate the mechanism of asbestos-caused suppression of the immune response in CTLs, as well as identifying molecules that can assist in the improvement of asbestos-caused suppressed CTL functions.

Real Voices of International Immunotoxicologists

What the other researchers think about? How can I do more exciting research in the future? Most of the young Japanese immunotoxicologists may hope to listen to some kind of comments from the experts in this field, in particular from the outside of Japan. This time, we interviewed Dr. Victor J. Johnson from Burleson Research Technologies, Inc., USA. Let's go to listen to his voice. What will you feel and learn?

Victor J. Johnson, Ph.D.

Director of Operations
Principal Investigator for Immunotoxicology for the
National Toxicology Program
Burleson Research Technologies, Inc.
Morrisville, North Carolina, USA



Q1. What was the most impressive event for you in your trip to Japan this time?

My trip to Japan was amazing and it is very difficult for me to identify the single most impressive event or experience. I enjoyed every aspect of my journey in Japan. If I had to narrow it down, I would need to share two experiences to be fair to my trip. First, I was very impressed by the talent and enthusiasm of the immunotoxicologists in Japan and the breadth of the research that they are exploring. The majority of the meeting was in Japanese, however, I felt that I was able to understand and keep up to the presentations; a testament to the quality of the science. My lecture was given in English and was well received by the audience, making me feel accepted among the Japanese Immunotoxicology community. Equally impressive as the science was my experiences of the people, culture, and places of Japan. The hospitality provided to me was paralleled by none other. I was given the privilege of a grand tour of Japan and I owe a special thanks to many people including Dr. Yasuo Morimoto, and his team of organizers for the meeting, I met many great scientists. I was treated to the great food culture of Japan with many members of JSIT. I would like to send a big thanks to Alice Kayama for hosting me on a tour of the highlights of Fukuoka Prefecture including my first visit to a Japanese Castle, Kokura Castle. I also express sincere gratitude to my longtime friend and colleague, Dr. Masashi Tsunoda. Masashi and I set off on an ambitious tour of Japan, including people, culture, and architecture. Our journey started in Kokura, travel by rail (including my first ride on a bullet train!) and foot (some days reached over 40,000 steps!!!) to many great cities to see famous castles, temples, and heritage sites. Thanks for the great fun! Masashi and I split ways in Tokyo where I met another great friend and colleague, Dr. Fujio Kayama. Fujio and I shared some great food and conversation, oh,

and great beer and sake too. As you can see from my long-winded response, and I could go on, I enjoyed every aspect of my journey in Japan, memories for a lifetime. Thanks so much!

Q2. What is the most exciting thing in your career to date?

I have been studying Immunotoxicology for the past 20 years have had many exciting moments in my career ranging from research findings, networking with respected immunotoxicologists, to teaching the science of immunotoxicology to budding young immunotoxicologists. I started my career in immunotoxicology reading the works of Dr. Michael Luster and was fortunate enough to meet him at an annual meeting of the Society of Immunotoxicology. Eventually, I was blessed to be able to join his laboratory at the National Institute for Occupational Safety and Health, where we worked on mechanisms and susceptibility to occupational asthma and rhinitis. Many years of hard work lead to being recruited to my current position at Bureson Research Technologies (BRT), an immunotoxicology CRO, and the opportunity to compete for a premiere contract in the field. The most exciting development in my career to date was being awarded the Immunotoxicology Contract for the National Toxicology Program, NIEHS, NIH, and cherish all the hard work and perseverance that was required to get to this point. Achieve your goals, it is very rewarding.

Q3. What are the things you are doing energetically, right now?

My career focus is on immunotoxicology safety assessment and generation of quality data for human health risk assessment. Working at BRT allows me to study the effects of novel drugs on the immune system and contribute to safety evaluation for drug candidates prior to their entry into the public domain. Being the Principal Investigator for Immunotoxicology for the National Toxicology Program provides me the opportunity to conduct similar research on environmental and occupational chemicals of public concern. This type of research is critical to a comprehensive approach to human health risk assessment and is my passion and the mission of our research programs at BRT.

Q4. What is required for breakthrough in immunotoxicology research in the future, do you think?

Presenting your discoveries, responding to constructive criticism, networking, and keeping up with the cutting edge of immunology and toxicology are key to prospering in the field of immunotoxicology. Immunotoxicology is an applied discipline, taking concepts from immunology and toxicology and applying them to protection of the immune system is our charge. Breakthroughs for new immunotoxicologists will come from hard work and the willingness to venture outside of your comfort zone. Meet as many people as you can as they are the ones that can stimulate your next great idea and provide you the intellectual and financial support to work towards the next breakthrough. Share ideas and critical thinking, it will help make strides in your career. An area of research that is gaining popularity in toxicology and immunotoxicology is addressing the role of the microbiome in our science. The microbiome is the collection of microorganisms that live on and within us and are critical to health. These microorganisms are at all portals of entry to the body and can participate in xenobiotic metabolism ultimately influencing absorption and distribution of xenobiotics and their potential for immunotoxicity. Recent research indicates that the microbiome influences development of the immune system and can play a driving role or can mitigate immunotoxicity. Many breakthroughs are on the horizon through incorporation of the microbiome into the fields of immunotoxicology and toxicology.