English pages

Report from the 17th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2010)

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The 17th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT 2010) was held at Ohyama Memorial Hall of National Institute for Environmental Studies, Tsukuba during September 9-10, 2010. The theme of this meeting is "Immunotoxicology and Susceptibility".

On the first day, Invited Plenary Lecture "Mast cells and their regulation: Allergy, but so much more-innate to adaptive immunity" was given by Prof. A. D. Befus, (Univ. of Alberta, CANADA). In main symposium: "Immunotoxicity and chemical susceptibility", we have discussed determinants such as genetics, age, infection, nutrition and chronic diseases of increased susceptibility to chemicals. Dr. Gary R. Burleson (BRT-Burleson Research Technologies, Inc.) presented「Influenza viral disease: Dexamethasone and the role of age and genetics on viral disease severity」as the exchange speaker from SOT ImToxSS. Dr.Tetsurou Ishii (Tsukuba University) talked about「Responses of macrophages against oxidative stress-roles of transcription factor Nrf2 and the induced proteins」.Dr. Naoki Kunugita (National Institute of Public Health) presented「Effects of volatile organic compounds (VOCs) exposure on immunotoxicity in mice」.Dr. Takamichi Ichinose (Oita University of Nursing and Health Sciences) presented「Yellow sand and allergy」. Finally, Dr. Reiko Teshima (National Institute of Health Sciences) talked about「Effect of chemicals like brominated flame retardants (BFRs) on the development of the immune system in rodents」. As a Special lecture, Prof. Kensuke Miyake (The Institute of Medical Science, The University of Tokyo) presented "Molecular mechanisms underlying pathogen sensing in the innate immune system". From this symposium, we can learn the various factors play a role in susceptibility to chemicals, infection and environmental pollutants. In addition, from the Special lecture, we got knowledge about microbial product-related molecular signaling not only induces innate immune response but also triggers adaptive immune response.

The 18th Annual Meeting of JSIT 2011 (Japanese Society of Immunotoxicology)

September 8 - 9, 2011

KEYAKI-kaikan (University Hall), Chiba University (Nishi-Chiba campus)
1-33 Yayoi-cho, Inage-ku Chiba, 263-8522 Japan
Theme: "Crosstalk between clinical and experimental immunotoxicology"

- Invited Plenary Lecture:
  Dr. Robin L. Thurmond
  (J & J Pharm R & D, L.L.C. Research Fellow)
- Invited Special Lecture:
  Prof. Chisato Mori
  (Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University)
- Educational Lecture:
  Dr. Nahoko Kaniwa
  (Division of Medicinal Safety Science, NIHS)
- Symposium:
  Dr. Reiko Teshima
  (Division of Biochemistry and Immunochemistry, NIHS) and others
- Workshop:
  Oral / Poster presentation

Deadline for abstract submissions: June 27, 2011
Social gathering: September 8, 2011. 18:00 KEYAKI-kaikan (3rd floor, Banquet room)
President: Prof. Koichi Ueno
Department of Geriatric Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Chiba University
Secretariat: Assoc. Prof. Katsunori Yamaura
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http://jsit18.umin.ne.jp (Open Jan. 2011)

On the second day, in the first time Student session, four oral presentations were submitted by Seiko Takeda (Changes in expression pattern of human ß defensins in mouse tracheal epithelium induced by toluene exposure), Ning Ding (Enhancement of proliferation of splenocytes induced by fullerene nanoparticles instillation), Kazuyuki Okamura (Mechanism of the suppression of lymphocyte proliferation through an increase in p130 by inorganic arsenic), and Masashi Asao (The mechanism for regulating the interleukin-6 in exposure to manganese). As a Master' s Lecture Dr. Jun-ichi Sawada (President of JSIT) presented "Allergenicity testing: current and future issues" . In the Workshop, "The latest move in the immunotoxicity studies: in silico, in vitro and in vivo" was discussed by the chairmen, Dr. Eiji Maki (former Biosafety Research Center, Foods, Drugs and Pesticides) and Dr. Yasuhide Kouchi (Taiho Pharmaceutical Co. Ltd.) with six speakers and audience. 「In silico prediction of immunogenicity: sense and non-sense」 by Dr. Philippe Stas (Applied Protein Service, Lonza Biologics), 「Current situation of in vitro testing on skin sensitization assay」 by Dr. Hajime Kojima and (National Institute of Health Sciences), 「The inter-laboratory KLH-TDAR assay validation study (Study I)-investigation for the experimental conditions-」 by Dr. Kanako Mori (Takeda Pharmaceutical Company Limited) and Dr. Yasuhide Kouchi (Taiho Pharmaceutical Co. Ltd.), 「The inter-laboratory KLH-TDAR assay validation study II-investigation using an immunosuppressive agent-」 by Dr. Ryota Kawai (Daiichi Sankyo Co., Ltd.,) and Dr. Yuko Nagayama (Eisai Co., Ltd.,) were presented. From this Workshop, we can learn interesting topics about method of in vitro skin sensitization assay and parameters reflecting immunotoxicity from speakers.

We have studied a various aspects of basic immunology and immunotoxicology from all delegates with their excellent presentation and discussion. Finally, we bid a warm welcome to delegates not only from Japan, but also from foreign countries to participate in this kind of Conference to exchange our knowledge concerning immunotoxicology globally. Then, we hope to meet again in next JSIT 2011 at Chiba.

A prize for annual convention

Particulates activate innate immune systems and regulate type 2 immunity

Etsushi Kuroda[1] and Yasuo Morimoto[2]

([1]Department of Immunology and Parasitology, and [2]Department of Occupational Pneumology, University of Occupational and Environmental Health, Japan.)

Introduction

Some particulates can stimulate the innate immune system to induce inflammatory responses. In particular, aluminum salts (referred to as alum) and silica crystals can induce type 2 inflammatory responses, which are characterized by the elevation of antigen-specific serum IgE and IgG1 levels in vivo. However, mechanism involved in the induction of type 2 immunity has not been elucidated. Several reports have shown that some particulates such as silica, asbestos and alum activate NALP3 inflammasome, which is one of intracellular PPRs, and promote the secretion of the pro-inflammatory cytokines IL-1β and IL-18 by the action of caspase-1 (reference 1-3). In this study, we found that some particulates induce macrophages (Mϕs) to produce the lipid mediator prostaglandin (PG) via NALP3 inflammasome-independent mechanisms and that the induction of PGE_2 by particulates controls immune response in vivo.

Methods

We used 7~10 weeks old C57BL/6, BALB/c and several knock-out (mPGES-1, NALP3, ASC, caspase-1) mice. Thioglycollate-induced peritoneal Mϕs and M-CSF-induced bone-marrow derived Mϕs were used as Mϕs in this study. For in vitro study, Mϕs were treated with 1 ng/ml LPS for 2 hrs (priming) and then stimulated with crystalline silica, alum, nickel oxide, titanium dioxide or amorphous silica (20~50 μg/cm^2) for 2~18 hrs. After stimulation, cell-free supernatants were collected and used for IL-1β and PGE_2 ELISA. For in vivo study, mice were immunized twice (day 0 and 7) i.p. with 100 μg OVA plus 2 mg alum or 100 μg OVA plus 0.5 mg silica. Ten days after the last immunization, sera were collected and analyzed for the OVA-specific IgE by ELISA.

Results

1. Silica induce IL-1β and PGE_2 production in LPS-primed Mφs

Many reports have shown that alum, silica and asbestos stimulate Mφs to produce the caspase-1-dependent cytokines IL-1β and IL-18 by activating the NALP3 inflammasome (reference 1~3). We also found that silica and alum induced LPS-primed Mφs to produce IL-1β and IL-18, which is in agreement with previous reports. Interestingly, we found that these inflammasome activators also induced LPS-primed Mφs to produce PGE_2. Titanium dioxide (TiO_2), which does not cause severe inflammation on inhalational exposure, does not activate the NALP3 inflammasome (reference 3). Worthy of note was that TiO_2 did not induce IL-1β or PGE_2 production in LPS-primed Mφs.

2. The inflammasome is not involved in silica-induced PGE_2 production in Mφs

To investigate whether the inflammasome is involved in silica-induced PGE_2 production, we performed similar experiments using NALP3-/-, ASC-/- and caspase-1-/- Mφs. Unexpectedly, the levels of PGE_2 were comparable between WT and inflammasome-deficient Mφs in response to silica and alum. These results indicate that silica and alum induce Mφs to produce PGE_2 through inflammasome–independent mechanisms.

3. Silica-induced production of PGE_2 by Mφs regulates antigen-specific IgE production in vivo

Membrane-bound PGE synthase-1 (mPGES-1) plays important role for PGE2 production in Mφs, because mPGES-1-/- Mφs cannot produce PGE_2 in response to silica and alum. Next we examined whether silica- and alum-induced PGE_2 production plays a role in regulating the immune responses in vivo. To this end, we immunized mPGES-1+/+ and -/- mice with alum plus OVA or silica plus OVA, and then analyzed for the levels of OVA-specific IgE antibodies. Interestingly, mPGES-1-/- mice displayed reduced levels of OVA-specific IgE.

Discussion

We found that particulates such as silica and alum stimulated innate cells to produce PGE_2 via the inflammasome independent pathway and regulated type 2 immune responses in vivo. The studies presented herein suggest that manipulating particulates-induced cytokines and PGE_2 production could open new possibilities for treating allergic inflammation, infectious diseases and cancer.

Acknowledgement

We feel honored to be awarded a prize for annual convention. We also thank Dr. Ishii (National Institute of Biomedical Innovation), Dr. Akira and Dr. Uematsu (WPI Immunology Frontier Research Center, Osaka University) for their helpful collaboration.

References

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2. Hornung, V. et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 9, 847-856 (2008).
3. Cassel, S. et al. The Nalp3 inflammasome is essential for the development of silicosis. Proc Natl Acad Sci U S A 105, 9035-9040 (2008).

A prize for encouragement

Effects of pesticides on IL-17 gene expression via retinoid-related orphan receptor α and γ

Hiroyuki Kojima[1], Shinji Takeuchi[1], Miki Takahashi[2], Ryuta Muromoto[2]

([1]Hokkaido Institute of Public Health, Sapporo, Japan, [2]Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan)

Retinoid-related orphan receptor (ROR) is a key regulator of Th17 cell differentiation in immune response. In this study, we characterized RORα / γ agonistic/inverse agonistic activity of a large number of 200 pesticides, and investigated the effects of several pesticides showing ROR activity on *IL-17* expression in mouse T lymphoma EL4 cells. For detecting ROR activity among 200 pesticides, the reporter gene assay using Chinese hamster ovary cells, transiently transfected

with ROR expression plasmid as well as RORE-reporter plasmid was performed. As a result, we found that eight pesticides acted as ROR α / γ inversed agonists at concentrations in the order of 10^{-6}-10^{-5} M. In addition, these pesticides were found to suppress IL-17 mRNA expression in EL4 cells treated with phorbor myristate acetate and ionomycin. Taken together, these results suggest that several pesticides possess inhibitory effect of *IL-17* expression via ROR α / γ. This study also indicates that our ROR-reporter gene assay is very suitable for identifying effects of IL-17 production via ROR α / γ in immune cells from a large number of chemicals.

A prize for excellent student

Mechanism of the suppression of lymphocyte proliferation through an increase in p130 by inorganic arsenic

Kazuyuki Okamura

(Graduate School of Life and Environmental Sciences, University of Tsukuba)

(Environmental Health Sciences Division, National Institute for Environmental Studies)

One of the three molecules in the pocket protein family is p130. It is known to have an important role in restraining the G1-S transition or G0 exit through the regulation of E2F-responsive genes. We investigated the mechanism of an arsenic-induced increase in p130 in the mouse A20 lymphoid cell line. We focused on the cyclin dependent kinase inhibitors (CDKIs) and protein phosphatases (PP1 and PP2A). The results of our studies suggest that the activity of PP1 is involved in the increase of p130 by arsenic, however PP2A and CDKIs are not.

Young power for immunotoxicological research

Dysregulation of neuroimmune function by environmental pollutants

Tin Tin Win Shwe

(National Institute for Environmental Studies)

In my mother land Myanmar, as I am a Medical doctor and teaching staff in Medical University, I have experiences to teach and guide Medical, Dental and Pharmacy students while doing clinical practice. Fortunately, I have an opportunity to study my Ph. D course in Department of Physiology, Yokohama City University Graduate School of Medicine. After the completion of my Ph. D course, in 2003, I joined to Project studying the health effects of nanoparticles exposure as a Post-doctor Fellow in Environmental Health Sciences Division, National Institute for Environmental Studies (NIES), Tsukuba. In 2006~2008, I was selected as a Foreign researcher for JSPS Post-doctor Fellowship and from 2008, I serve as a NIES Research Fellow in the same Institute.

Up to now, using brain *in vivo* microdialysis technique, molecular gene expression assay and learning performance test in a mouse model with different immunogenetic background, allergy, infection and inflammation, I have reported the effects of exposure to toxic chemical toluene, carbon black nanoparticles and diesel exhaust particles on brain neurotransmitter level, memory function-related gene expression, proinflammatory cytokine expression and cognitive functions of mice in many Domestic and International Conferences and International peer-review journals. Currently, I have been studying the effect of organophosphate pesticide (diazinon) exposure during developmental period on neuro-immune biomarkers and novel object recognition in adult mice.

Recently, it has been increasing health problems concerning with immuno-allergic system, metabolic-endocrine system and nervous system inside and outside Japan. The etiology of these life-style diseases may be due to exposure of environmental pollutants. I strongly suggest that it is important to establish techniques for early detection of abnormality in lung function, immune balance, learning behavior and enzyme and hormone

levels to prevent environmental pollution induced these life style diseases in next generation. It is also necessary to search biomarkers for susceptibility to environmental pollutants for early diagnosis and to understand the mechanism of action of these pollutants for development of drug for appropriate treatment.

Finally, I would like to request to give opinion, guidance and comments from senior and junior colleagues because my study and the experience are still dissatisfied with field of Immunotoxicology. Then, I wish all of you for good health, happiness and the research success at the New Year.

Interview with Imunotoxicologists in the world

Dr A. Dean Befus
Professor, Pulmonary Research Group, School of Internal Medicine, University of Alberta, Canada

Q1: How was your trip to Japan this time?

As with each of my previous trips, the latest trip was most enjoyable and provided many fond memories of your beautiful country and its people.I was able to bring my son along for his first visit to Japan. On the night we arrived, there was a typhoon. It was raining heavily, very windy and for us quite humid. Thereafter, the weather turned lovely and I had an opportunity to see many friends, previous trainees and scientific colleagues in Tsukuba and Tokyo.Everyone was generous and most hospitable. My son has fond memories of our trip and the wonderful people.

Q2: Is there a society of Immunotoxicology in Canada?

To the best of my knowledge, there is not a society of immunotoxicology in Canada. However, there is a Society of Toxicology (*http://www.stcweb.ca*). The society' s web page contains information on the activities of the Society with links to its documents, training programs and other societies of toxicology. The webpage states that "The majority of toxicology training programs in Canada currently exist within departments of pharmacology and toxicology or schools of veterinary medicine, but there are some notable exceptions."

In addition, Health Canada conducts research in many areas of toxicology, especially as they relate to foods and nutrition. Immunotoxicology is an important component of this research. Similarly, Environment Canada also supports research on the immunotoxicity of environmental contaminants. In my home province, Alberta, the environmental impacts and toxicology of oil and gas exploration and exploitation are an important concern.

Q3: Hottest topics in my field?

My major field of interest is allergic diseases. A hot topic in this field is the need to understand why there has been an epidemic of increasing prevalence of various allergic and other immune diseases, such as asthma. An important focus of research to understand the basis of this epidemic is on early life events and the maternal-fetal-infant relationship. There is exciting new information on how different environmental exposures, both physical and psychologic, early in life can have profound influences on development of allergy and many other chronic diseases. There appear to be windows of susceptibility early in life that can have long-term impacts. Scientists are beginning to understand how gene-environment interactions especially early in life influence health and disease.

Q4: Happiest and toughest things in my career?

These are hard questions. I am happiest when I see my trainees and mentees enthusiastic about their research and their personal growth as professionals and individuals. It is great to see the spark of discovery and the joy in having a long series of experimental insights published. The toughest times have been when bright young scientists struggle with difficult experimental models and become frustrated with challenging protocols or inadequate or immature experimental systems.

Q5: Advice to young researchers starting a career?

Science can be challenging, but also intellectually both stimulating and rewarding. It is essential to get an outstanding training. You must work hard and seek out excellent people for teamwork and mentorship. I continuously try to seek mentorship advice from senior as well as younger colleagues, and especially from trainees who often have insightful comments and suggestions.

Although career opportunities may appear to be a bit limited in our current global economy, high quality science and intellectual capital are the basis for future progress and global health. It is your task as a young researcher to strive for excellence and to work with honesty and integrity. The benefits of a career in science are many fold and well-worth the hard work and commitment needed to be successful.My network of colleagues and good friends in Japan is strong evidence of the benefits that I have received as a scientist.

Arigato gozaimus and sayonara

Dr. Gary R Burleson
President & CEO, Burleson Research Technologies, Inc.

Q1: How was my first trip to Japan?

The trip to Japan was a wonderful experience. I was fortunate to visit Japan as a representative of the SOT ImTox SS in the ongoing cooperation and scientific interchange between the ImTox SS and the Japanese Society of Immunotoxicology (JSIT), and to attend the 2010 Annual Meeting of the JSIT in the Ohyama Memorial Hall of the National Institute for Environmental Studies in Tsukuba. This was my first trip to Japan and I was very excited about the opportunity to visit this country and meet new Japanese colleagues. Dr. Hidekazu Fujimaki of the National Institute for Environmental Studies in Tsukuba, serving as Organizer of the meeting, and Dr. Kazuichi Nakamura of Shionogi and Co Ltd, tirelessly answered the many e-mails and questions that I had prior to my trip and were wonderful hosts.I was accompanied on this trip by my wife Florence and daughter Stefanie. We arrived in Tokyo on Friday

3rd of September and familiarized ourselves with the trains and subways in Tokyo. On Saturday night, we met Dr. Kazuichi Nakamura, who took us to a traditional Japanese pub and introduced us to Japanese cuisine. It was a wonderful evening. During the weekend, we toured Tokyo and enjoyed many sights, including the Imperial Palace gardens, the Tokyo Edo Museum, and the Senso-ji temple in Asakusa, before taking the Shinkansen to Kyoto on Monday. We had two days of sightseeing in Kyoto where we visited beautiful temples and shrines, including the Sanjusangendo shrine with its 1001 statues of Kannon.During out trip, we were very thankful for the many helpful strangers who prevented us from getting lost and gave us directions. On Wednesday, we once again took advantage of the excellent and extremely punctual Japanese transportation system to whisk us to Tsukuba for the JSIT meeting.That evening we were invited to the Executive Committee Meeting and were served a traditional Japanese dinner. It was a truly magnificent feast where we met the organizers of the meeting and the officers of the JSIT.The following evening reception at the Chateau Kamiya was an opportunity to have further discussions with many of the scientists attending the meeting, enjoy more wonderful food, and listen to Professor Takemi Otsuki' s rendering of the theme song for the 17th JSIT meeting. Our visit to Japan was truly memorable as we visited old friends, made new friends, enjoyed interesting scientific discussions, and were introduced to a new culture and excellent food.

Q2: What are the hottest topics in my field, or what are the topics I am interested in most right now?

Hot topics in immunotoxicology and my current interest include: (a) biologics – testing in non-human primates (NHP) and in rodents to evaluate innate, cell-mediated and humoral-mediated immune function; (b) assessment of risk for EBV-related lymphomas in humans; (c) developmental immunotoxicity; (d) immunotoxicity in the elderly; (d) incorporating the infectious disease paradigm (Environmental Health Perspectives (2010); (e) testing strategies for unintended immune responses and autoimmunity; and (e) research to better understand the role of environmentally- influenced immune dysfunction in disease.

Q3: What are the happiest thing and the toughest thing in my career?

The toughest thing in my career was graduate school, as only 10% of the incoming students were successful in obtaining the Ph.D. degree.The happiest thing in my career was starting BRT-Burleson Research Technologies, Inc. 14 years ago with my wife, Florence G. Burleson, Ph.D.

Q4: Could you offer some advice for young researchers who would like to start their career?

There are many opportunities in the field of immunotoxicology research.Utilize new cutting-edge immunological techniques in order to advance the science and to obtain data useful for human safety assessment.

Q5: Other comments?

I look forward to the opportunity of a return visit to Japan.