ImmunoTox Letter Digest

June 2023

The 30th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2023)

1. Date

September 11-13th, 2023

2. Venues

Venue S: Shimadzu Tokyo Innovation Plaza
https://www.shimadzu.co.jp/aboutus/company/access/tonomachi.html
Venue L: Life Science & Environment research center (LiSE)
https://kawasaki-lise.jp/access.php
Venue R: TREX Kawasaki River Cafe
https://www.trex.style/

3. President

Ryosuke Nakamura, Ph.D.
(Division of Medicinal Safety Science, National Institute of Health Sciences, Kawasaki, Kanagawa, Japan)

4. Main theme of the meeting

New immunotoxicity study required by society.

5. Meeting secretariat

Division of Medicinal Safety Science, National Institute of Health Sciences.
E-mail: jsit2023@nihs.go.jp
URL: http://www.jsit2023.jp

6. Program (tentative)

30th Anniversary lecture

Immunotoxicology: Honor the Past and Build the Future

1) "The dawn of immunotoxicology – Immune system as target organ of toxicity and immuno-modulation by environmental factors –"
Takahiko Yoshida (4th Executive President)
2) "Significance of ICH S8 guideline and emerging issues thereafter"
Kazuichi Nakamura (5th Executive President)

Special lecture

1) "Vaccine R & D in Japan: SCARDA initiative"
Junichi Koga (Provost, Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response, Japan Agency for Medical Research and Development)
2) "Immunotoxicity Assessment Using Bone Marrow-Liver-Thymus (BLT) Immune Humanized Mice (TBD)"
Kristina E. Howard, DVM, PhD. (Research Veterinary Medical Officer, US Food and Drug Administration)

Symposium: Immunotoxicity in the R&D of New Modality Drugs and Vaccines

1) "Introduction"
kiko Ishii (Division of Biological Chemistry and Biologicals, National Institute of Health Sciences)
2) "Challenges in immunotoxicity evaluation for AAV vector products"
Shogo Matsumura (Non-Clinical Biomedical Science, Applied Research & Operations, Astellas Pharma Inc.)
3) "Non-clinical evaluation of CAR-T cell therapy, from the view of immunotoxicology"
Yukari Fujiwara (Preclinical Safety / Translational Medicine, Novartis Pharma K.K.)

4) “Immunotoxicity of oligonucleotide therapeutics”
Yuko Nagayama (Global Drug Safety, Biopharmaceutical Assessments Core Function Unit, Eisai Product Creation Systems, Eisai Co., Ltd.)
5) “Immunological studies for understanding new modality of vaccines”
Yoshimasa Takahashi (Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases)
6) Comprehensive discussion

Educational lecture
“Cell death mechanism in severe drug eruptions”
Riichiro Abe (Professor, Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences)

Special lecture of the recipient of the 13th JSIT award
“Establishment of a new concept “reproductive immunotoxicity” in immunotoxicology”
Kazuichi Nakamura (School of Veterinary Medicine, Kitasato University (Organization where the research was conducted))

Special lectures of the recipients of the 13th JSIT prize for encouragement
“Immunological mechanisms of metal allergy and its prevention and treatment”
Toshinobu Kuroishi (Division of Oral Immunology, Tohoku University Graduate School of Dentistry)

Workshop: Animal Models and the Alternatives Reflect Human Immune Responses: Current Status and Future Prospects

1) “Current status and prospect of drug toxicity assessment using HLA transgenic mice”
Shigeki Aoki (Laboratory of Biopharmaceutics, Faculty of Pharmaceutical Sciences & Graduate School of Pharmaceutical Sciences, Chiba University)
2) “Immunogenicity and toxicity evaluation system of vaccine adjuvant using genomics technology and humanized mouse model”
Eita Sasaki (Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases)
3) “Review: Trial to construct the human type immune tissues/organs and their possible application”
Takeshi Watanabe (Institute for Life and Medical Sciences, Kyoto University)
4) “Immunological characteristics related to age-associated pathogenesis in senescence-accelerated mouse (SAM): Significance as a model for evaluating immunotoxicity in elderly people”
Yasumitsu Nishimura (Department of Hygiene, Kawasaki Medical School)
5) Comprehensive discussion

Open symposium: Registration required, free admission: Immunotoxicity Risk Assessment for Chemicals in the Environment
1) “Health risk assessment of chemical substances contaminated in the environment”
Yasunobu Aoki (Research Center for Environmental Risk, Health Risk Assessment Section, National Institute for Environmental Studies)
2) “Risk assessment of quasi-drugs and chemical substances in food”
Reiko Teshima (Faculty of Veterinary Medicine, Okayama University of Science)

3) “Chemical exposures and allergic diseases from epidemiological studies”
Kiwako Yamamoto (Allergy Center, and Medical Support Center of Japan Environment and Children’s Study, National Center for Child Health and Development)
4) “Health hazards and risk assessment of chemicals based on immunotoxicity”
Eiko Koike (Health and Environmental Risk Division, National Institute for Environmental Studies)
5) Comprehensive discussion

Oral sessions of young scientist
Oral presentations
Poster presentations
Luncheon seminars

7. Social gathering
TREX Kawasaki River Cafe
September 11, 18:00-20:00 (tentative)
https://www.trex.style/

The 12th Japanese Society of Immunotoxicology Award
(The 2022 JSIT Award)

Immunological disturbance in arsenic-induced health effects

Seiichiro Himeno
Showa University, School of Pharmacy

Arsenic is an environmental pollutant that contaminates groundwater in many countries. Exposure to arsenic causes skin disorders and cancers. Extensive studies have demonstrated that exposure to arsenic also causes elevated mortality of cardiovascular diseases and increased incidence of hypertension and diabetes. Since 2009, I have been collaborating with Dr. Hossain of Rajshahi University, Bangladesh, to examine the health effects of arsenic among the residents in Bangladesh, focusing on common diseases such as hypertension, atherosclerosis, and diabetes. We also investigated the effects of arsenic exposure on asthma and its relation to immunological responses. Determination of respiratory functions such as FEV1 and FEV6 using a Hi-Checker, a compact device that can measure respiratory functions, revealed that about 100 villagers among over 800 study participants showed airway obstruction, with 70% of them showing reversible airway obstruction (RAO). RAO is a feature suggestive of asthma rather than COPD. The frequency of RAO increased dose-dependently with increasing arsenic exposure markers, such as water, hair, and nail arsenic concentrations. The frequency of the four major asthma symptoms, such as cough, wheezing, chest tightness, and shortness of breath, also increased by arsenic exposure dose-dependently. Since the RAO patients showed two times higher levels of serum IgE than non-symptom residents, it is suggested that arsenic exposure enhanced the risk of allergic asthma. To test the involvement of immunological disturbance in developing asthma, we determined serum levels of Th1/Th2 cytokines. Serum levels of IL-4, IL-5, and IL-13 were significantly higher among arsenic-exposed residents, whereas those of IFN-ɤ or TNF-α were not elevated, suggesting the Th2 dominant shift of cytokines. Serum levels of eotaxin and periostin were also enhanced by arsenic exposure, with significant correlations with Th2 cytokine levels. We also found arsenic-induced elevation of IL-33, which is involved in innate immune responses. Periostin is a clinical marker for asthma but is also involved in other allergic symptoms such as atopic dermatitis. We found that serum levels of periostin were higher among the residents with advanced-stage skin lesions than those

with initial-stage skin lesions caused by arsenic exposure. Thus, the immunological disturbance is important in various symptoms of arsenic-induced diseases, such as asthma and skin lesions. In addition, disturbances in tumor immunity may be involved in arsenic-induced carcinogenesis in multiple organs, and decreased infection immunity by arsenic exposure may lead to enhanced incidences of infectious diseases in children. Further research on the mechanism of arsenic-induced dysregulation of immune responses is required in the field of immunotoxicology.

Hossain Laboratory, Rajshahi University, Bangladesh

The 12th Japanese Society of Immunotoxicology Prize for Encouragement

Study on immunotoxicity through mRNA stability control mechanism

Ryuta Muromoto
Department of Immunology,
Faculty of Pharmaceutical Sciences,
Hokkaido University

I am deeply honored to have received the JSIT Prize for Encouragement for the year 2022. I would like to express my sincere gratitude to the selection committee, Dr. Hiroyuki Kojima of Health Sciences University of Hokkaido, who recommended me for the award, as well as my mentors and advisors. My research has focused on the analysis of regulatory mechanisms of cytokine signaling, particularly the function and regulation of Tyk2, a JAK family kinase, and STAT3, a transcription factor. Tyk2 deficiency impairs signaling pathways involved in IL-23 and IL-17 production, leading to attenuated T cell-mediated inflammation. Tyk2 has emerged as an important therapeutic target for immune diseases, including psoriasis, and selective Tyk2 inhibitors have been developed.

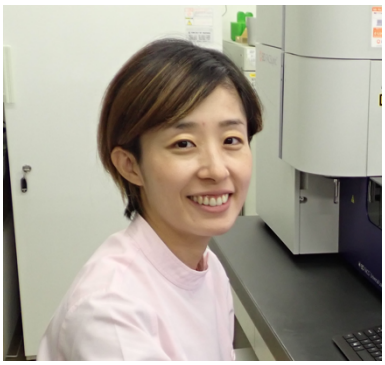
My awarded project, "Study on immunotoxicity through mRNA stability control mechanism," is related to the IL-17 response. I have studied IL-17 signaling in keratinocytes, which play a role in psoriasis. Through microarray analysis, I identified IκBζ as a protein specifically induced by IL-17. IκBζ was found to be involved in the IL-17 response and the pathogenesis of psoriasis. I also investigated the mechanism of rapid IκBζ induction and discovered the mRNA stabilizing activity of IL-17, which is distinct from other cytokines. Inhibition of this activity could potentially suppress IL-17-induced inflammation. Dimethyl fumarate, an approved compound for multiple sclerosis treatment, was found to inhibit IL-17 signaling by suppressing Regnase-1 phosphorylation. This suggests a partial explanation for its pharmacological effects. Furthermore, I have explored the effects of environmental chemicals on the IL-17 signaling pathway, considering their role in chemical-induced immunotoxicity.

I am grateful to the JSIT for recognizing my research with the Encouragement Award. This inspires me to further investigate cytokine signaling and its interactions with the

environment, aiming to contribute to the prevention and treatment of immune-related diseases. I will continue my research in immunotoxicology and greatly appreciate the guidance and encouragement from the society.

Immunotoxicological Research

Development of detection method in chemical-induced respiratory allergy and the effect of allergic response exposed estrogenic compound



Risako Tajiki
Laboratory of Short-term Toxicology,
Toxicology Division
The Institute of Environmental Toxicology (IET)

As we known, the patients of occupational asthma have been increased in the world. But, there is no generalized detectable method for chemical induced respiratory allergic disease. Therefore, we would like to propose the experimental protocols of respiratory allergic mouse model which detect some chemical having potential to respiratory sensitizer. First, we selected two strains of mice such as BALB/c mice and NC/Nga mice for suitable strain for the respiratory allergic model in the preliminary study. We validated the detection method of Trimellitic Anhydride (TMA)-induced respiratory allergy combined dermal sensitization and inhalation challenge. Several allergic responses (IgE level in serum, inflammatory cells and cytokine/chemokine levels in BALF) were significantly increased in TMA exposure groups. While, mice exposed negative control talc were not increased cytokine/chemokine levels. When comparing strain difference between BALB/c mice and NC/Nga mice, severe symptom in respiratory endpoints, the higher amount of mast cells population in BALF and increased histamine level in serum were only exhibited in NC/Nga mice. This experimental protocol and these differences of NC/Nga mice and BALB/c mice was considered to be useful to detect the respiratory allergic compound.

Recently, it is suggested that environmental chemicals aggravate several allergic responses in some epidemiologic study. In this view point, whether bisphenol A (BPA), chemicals having estrogenic potential, involved in the exacerbation of allergic inflammation in second study. Then, we have conducted the allergic dermatitis and/or allergic airway inflammation model using tolylene diisocyanate (TDI) to detect the BPA

on immune disrupting effects by oral exposure before the challenge of TDI. In the allergic dermatitis model, the thickness of challenge site (ear), cytokine levels were decreased in BPA exposure group. Conversely, eosinophil and cytokine levels in lung were significantly increased in BPA exposure group. These results suggest that BPA directly affects allergies, but that the effects differ depending on the target organ.