ImmunoTox Letter Digest

December
2024

Report on the 31st Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2024)

Etsushi Kuroda
President of the 31st Annual Meeting of the JSIT
Hyogo Medical University, Japan

The 31st Annual meeting of the Japanese Society of Immunotoxicology was held on September 19 and 20, 2024, at the Heisei Memorial Hall of Hyogo Medical University. The meeting welcomed 132 participants and featured 10 oral presentations, 22 poster presentations, and 12 presentations of Young Researchers and Students. Additionally, nine companies participated in the exhibition, exceeding our initial expectations.

The theme of this meeting was “Scientific Exploration of Environment and Healthcare through Immunotoxicological Research.” This theme reflects my research on environmental chemicals and immunotoxicology as well as vaccine and adjuvant development. In addition, Hyogo Medical University has a notable history of addressing asbestos-related health issue and treats one of highest numbers of malignant pleural mesothelioma cases in Japan. These factors made our university an ideal venue for discussing the intricate relationship between environment and medicine.

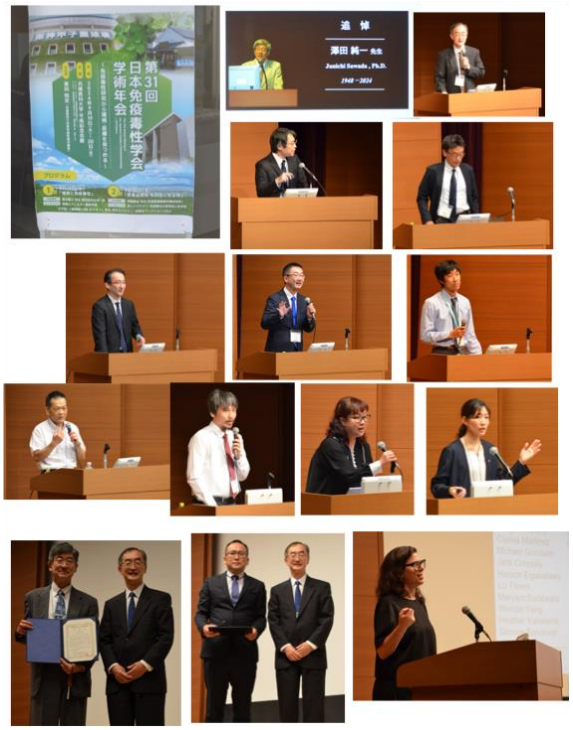
On the first day, under the theme “Environment and Immunotoxicology,” discussions primarily focused on allergies. In the special lecture, Dr. Takayuki Yoshimoto from Tokyo Medical University presented the latest insight into methods for assessing the sensitization potential of chemicals. During the symposium, Dr. Kitoshi Hirahara (Chiba University), Dr. Hideaki Morita (National Center for Child Health and Development), and Dr. Kazufumi Matsushita (Hyogo Medical University) shared valuable knowledge on environmental factors and allergies from their interesting talk. In the luncheon seminar, Dr. Toshiyuki Minami delivered and insightful talk titled “Asbestos-related Diseases and the Latest Treatment topics,” which highlighted the realities of medical practice and proved highly engaging for the participants. Additionally, Dr. Allison Ehrlich, invited from the Society of Toxicology (SOT), delivered a compelling lecture on the mechanisms of macrophages and CD4+ T cell differentiation in autoimmune diseases. This high-level presentation served as a fitting conclusion to the first day.

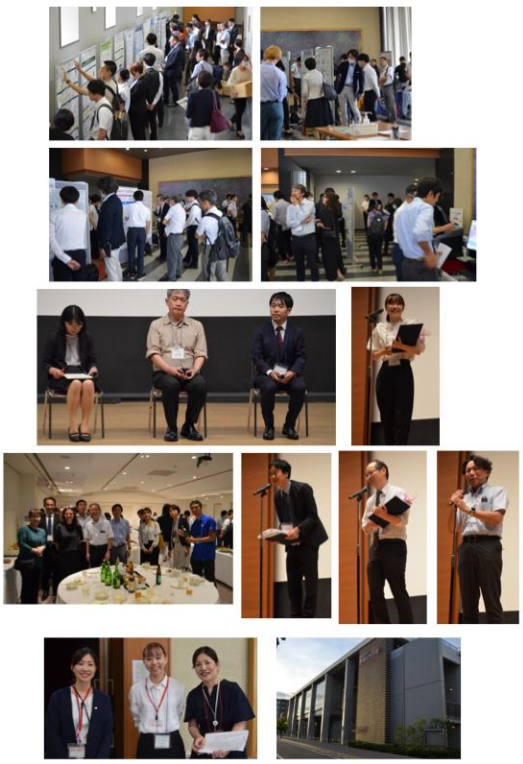
On the second day, the theme was “drug Development: Efficacy and safety.” In the special lecture, Dr. Yasuhiro Yasutomi (National Institutes of Biomedical Innovation,

Health and Nutrition) delivered an insightful presentation on the development of HIV vaccine using primate models. In the subsequent symposium, Dr. Kouji Kobiyama (the University of Tokyo), Dr. Katsuyo Ohashi-Doi (Torii Pharmaceutical Co Ltd), and Dr. Shiori Egashira (Daiichi Sankyo Co Ltd) provided comprehensive insight into drug development, covering topics ranging from fundamental research to practical applications from their respective perspectives. During the Workshop, Dr. Akiko Ishii (National institute of Health science), Dr. Tetsuo Aida (Daiichi Sankyo Co Ltd) and Dr. Eiichi Hashimoto (Chugai Pharmaceutical Co Ltd) engaged in highly valuable discussions on the evaluation of immunogenicity, incorporating case studies from their organizations. These sessions provided participants with an invaluable opportunity to gain a deeper understanding of the entire process, from drug development to safety assessment.

As annual events of this meeting, Award lectures were delivered on the afternoon of second day by Dr. Takahiko Yoshida (Asahikawa Medical University), recipient of the JSIT Award, and Dr. Izumi Sasaki (Wakayama Medical University), recipient of the JSIT Young Investigator Award. In addition, Dr. Tomoya Sagawa (Kyoto Prefectural University of Medicine) and Dr. Koubun Yasuda (Hyogo Medical University) received the Annual Meeting Award, and Ms. Nao Terakoshi (Chiba University) received the best Student and Young Scientist Presentation Award. We extend our congratulations to the awardees and look forward to their continued success in the future.

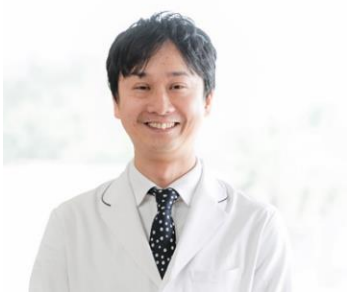
This meeting was particularly significant as it marked a return to vibrant in-parson discussions and interactions after the COVID-19 pandemic. We deeply appreciate the active participation and engagement of all attendees, which contributed to the event's success. Our heartful thanks go to everyone who participated and to all those who supported the organizations on this event. We wish you all continued success and look forward to seeing you at the next meeting in Gifu.


第31回日本免疫毒性学会学術年会
追悼
澤田 純一 先生
Junichi Sawada , Ph.D.
1948 – 2024



The Best Presentation Award

Study on the mechanism of acute lung inflammation caused by Asian sand dust particles



Tomoya Sagawa
Kyoto Prefectural University of Medicine

It is my great pleasure and honor to receive The Best Presentation Award at the 31th Annual Meeting of the Japanese Society of Immunotoxicology in 2024. I would like to sincerely express my appreciation to Dr. Etsushi Kuroda, President of the Annual Meeting of the Japanese Society of Immunotoxicology, and the selection committee members.

In this study, we investigated the process by which Asian sand dust (ASD) particles cause inflammatory responses in the lungs. ASD serves as a major air pollution source affecting countries in East Asia, including Japan, during spring and early summer. Epidemiologically, ASD is known to increase the risk of respiratory and cardiovascular diseases. In animal models, intratracheal administration of ASD has been shown to exacerbate the pathogenesis of bronchial asthma and bacterial pneumonia. Moreover, ASD induces acute neutrophilic lung inflammation even in healthy mice. However, the detailed mechanism by which ASD causes inflammatory reactions in the lungs has not been clarified to date, and we conducted this study with the aim of establishing measures to prevent and treat health problems caused by ASD.

Intratracheal administration of ASD particles to mice resulted in an increase in the number of cells and the concentration of various inflammatory cytokines and chemokines in bronchoalveolar lavage (BAL) fluid, with peaks occurring 4-6 hours after administration.

By combining immunohistochemical staining, dark-field microscopy, Raman microscopy, and flow cytometry, it was found that alveolar macrophages (AMs) phagocytose ASD particles.

Based on these results, we observed time-lapse images of primary cultured AMs exposed to ASD particles using holotomography microscopy, and found that AMs

phagocytosed ASD particles immediately after exposure, and that some of them underwent cell death. Then, we measured the concentration of IL-1α, one of the alarmins, in BAL fluid and determined that it increased with a peak at 4 hours after exposure to ASD particles. Furthermore, the administration of neutralizing antibodies against IL-1α significantly suppressed the increase in neutrophils and the release of CXCL-1 in BAL fluid, confirming that IL-1α is an important mediator of acute neutrophilic inflammation caused by ASD particles.

Following confirmation that IL-1α originates from AMs by double immunohistochemical staining and in vitro experiments, administration of a RIPK3 inhibitor was found to suppress the release of IL-1α from primary cultured AMs, indicating that IL-1α is released through the necroptosis of AMs exposed to ASD particles.

To identify specific components of ASD that affect IL-1α release, we exposed heated ASD (h-ASD) particles, and compared to ASD particles, the number of neutrophils and IL-1α concentration in BAL fluid, as well as the IL-1α concentration in the culture supernatant of primary cultured AMs, were significantly reduced. Endotoxin levels in h-ASD particles were extremely low compared to those in ASD particles, and the addition of polymyxin B significantly suppressed the release of IL-1α from primary cultured AMs by ASD particles. Based on the above, the endotoxin contained in ASD particles was found to be an important component involved in the series of inflammatory reactions.

The composition of desert dust varies depending on the location and time of collection, however, the results of this research are expected to provide basic knowledge for understanding the biological effects by desert sand dust.

The Student and Young Scientists Award

Uncovering the role of nucleic acid sensors in innate immune responses triggered by DNA strand breaks

Nao Terakoshi
Graduate School of Science, Chiba University

I am deeply honored to receive the Student and Young Science Award at the 31st Annual Meeting of the Japanese Society of Immunotoxicology. I would like to express my sincere gratitude to the meeting chair, Professor Kuroda, as well as all those involved in organizing the event. I also extend my heartfelt thanks to Dr. Sassa and the members of my laboratory for their continued guidance and support. Since my third year as an undergraduate, I have been conducting research under the supervision of Dr. Sassa in the Laboratory of Chromatin Metabolism and Epigenetics, Chiba University. The research that led to this award focuses on uncovering the mechanism by which dysfunction of DNA repair enzymes induces immunotoxicity, with particular emphasis on the involvement of nucleic acid sensors.

Genomic DNA is continuously damaged by both exogenous and endogenous factors. One of the most frequent damage is the incorporation of ribonucleoside triphosphates, i.e., RNA precursors, during DNA replication. A DNA repair enzyme RNase H2 plays a critical role in genome integrity by removing incorporated ribonucleotides. Mutations in the gene encoding RNase H2 lead to a hereditary autoinflammatory disorder Aicardi-Goutières syndrome (AGS). Despite the absence of viral or bacterial infections, elevated interferon levels are observed in AGS patient-derived cells, though the underlying mechanisms remain unclear. To investigate the mechanism of interferon responses caused by RNase H2 deficiency, we established RNASEH2A-knockdown (KD) cells using human lymphoblastoid TK6 cells and examined the molecular basis of aberrant immune responses. Our findings revealed a significant accumulation of ribonucleotides and an increase in DNA strand breaks in KD cells compared to wild-type cells. Additionally, RNA sequencing technique revealed the upregulation of cytokines and nucleic acid sensors due to RNASEH2A deficiency. Furthermore, we demonstrated that the nucleic

acid sensors cGAS and IFI16 have distinct yet crucial roles in driving interferon responses associated with RNase H2 dysfunction. This award serves as a great motivation for me to further advance my research and make meaningful contributions to the development of the field. I am deeply appreciative of Professor Sassa's invaluable mentorship and guidance, and I sincerely look forward to your continued support.