ImmunoTox Letter Digest

June, 2020

The 27th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2020)

1. Date

September 26-27th, 2020

2. Venue

The meeting will be held on the web site "http://procomu.jp/jsit2020/index.html".

3. President

Masashi Tsunoda, MD, PhD
(Professor, Department of Preventive Medicine and Public Health, National Defense Medical College, Tokorozawa, Saitama, Japan)

4. Main theme of the meeting

Immnotoxicology, its past, present and future

5. Meeting Secretariat

Akemi Shimada,
Department of Preventive Medicine and Public Health, National Defense Medical College
E-mail: jsit27@procom-i.jp
URL: http://procomu.jp/jsit2020/index.html

6. Program (tentative)

Symposium: Immnotoxicology, its past, present and future

1) Ikuo Tsunoda (Department of Microbiology, Kinki University of Faculty Medicine) and Shigemitsu Toriyama (Former-Faculty of Agriculture, the University of Tokyo)
"Role of gut microbiota in Theiler's virus model for multiple sclerosis: Max Theiler and Hideyo Noguchi"

2) Yasuo Yoshioka (Research Institute of Microbial Diseases, Osaka University)
"The development of vaccine from the standpoint of immunotoxicology: the development of vaccine for Corona virus disease 2019"

3) Masashi Takano (Department of Obstetrics and Gynecology, National Defense Medical College)
"Carcinogenesis of ovarian clear cell carcinoma through toxic metabolism"

Special lecture of the recipient of the 10th JSIT award

Tomoaki Inoue (Former-Chugai Pharmaceutical)
"Investigation of novel in vitro evaluation methods for prediction on in vivo immunotoxicity"

Special lectures of the recipients of the 10th JSIT prize for encouragement

1) Shigeki Aoki (Laboratory of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Chiba University)
"Investigation of idiosyncratic drug toxicity using HLA transgenic mice"

2) Takamasa Kido (Department of Public Health and Environmental Medicine, The Jikei University School of Medicine)
"Immune dysfunction derived from zinc deficiency exacerbates the Th2 cell – M2 macrophage pathway"

Workshop

Organizer: Kiyoshi Kushima (Astellas)
Presenters:
Yoshitaka Shirasaki (Graduate School of Pharmaceutical Sciences, The University of Tokyo)
Etsushi Kuroda (Department of Immunology, Hyogo College of Medicine)
Youichi Tagawa (School of Life Science and Technology, Tokyo Institute of Technology)
Chiyomi Kubo (Research Division, Chugai Pharmaceutical)

Oral session of young scientist

Poster presentation

The 9th Japanese Society of Immunotoxicology Award
(The 2019 JSIT Award)

An immunotoxicological study in the drug development

Koichi Ueno
Center for Preventive Medical Sciences,
Chiba University, Japan

I have been conducting research on immunotoxicological evaluations of drug development from both basic and applied aspects for forty years. I have been focusing on the following two topics: (1) exogenously-induced, natural killer cell-mediated neuronal killing: a novel pathogenetic mechanism, and (2) expression and function of the histamine receptors in dermal and articular tissues.

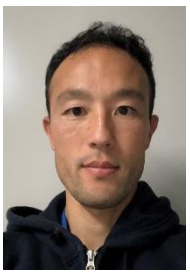
Regarding the first topic, many human neurodegenerative diseases are characterized by the idiopathic death of cells narrowly restricted to a subset of neurons in a specific functional neuroanatomic system. Few in vivo models exist for the analysis of these types of degeneration. This report documents the death of sympathetic neurons resident in the superior cervical ganglia of rats after exposure to an exogenous chemical agent, the drug guanethidine, as being mediated by natural killer (NK) cells. This is the first in vivo model of a disorder of the nervous system in which NK cells appear to be the principal effector cell, and thus could serve a central role in dissecting the normal and pathological function of NK cells. In addition, this pathogenetic mechanism appears to represent a novel type of autoimmune reaction that could have a direct bearing on a number of human illnesses.

Regarding the second topic, histamine was first identified in 1910 as a physiologically active amine. It is now recognized for its multiple regulatory activities in the digestive, neuronal, and immune systems, and new roles are still being elucidated. Histamine exerts its effects through four distinct receptor subtypes. Histamine H_4 receptor was identified in 2000 and is the most recently identified of the four histamine receptors. It is expressed primarily in immune cells and is involved in physiologic functions related to inflammation and allergy. Recently, the histamine H_4 receptor was highlighted as a promising therapeutic target in atopic dermatitis, asthma, and chronic arthritis. In fact, some histamine H_4 receptor antagonists have reached clinical trials for the treatment of asthma, atopic dermatitis, and allergic rhinitis. Based on an

initial assessment of distribution, the histamine H_4 receptor has been referred to as the histamine receptor of the hematopoietic system. However, the histamine H_4 receptor has also been implicated in the regulation of other non-hematopoietic systems. In articular tissue, histamine H_4 receptor expression has been detected in synovial cells. Chondrocytes, a major cell sources for cartilage tissue engineering, also express the histamine H_4 receptor. In skin, the histamine H_4 receptor is expressed in both the epidermis and dermis, with stronger receptor expression in the epidermis. Further understanding of the functions of histamine H_4 receptors in non-hematopoietic cells might lead to novel treatments for diseases with unmet medical needs.

The 9th Japanese Society of Immunotoxicology Prize for Encouragement

Interaction between allergy development and exposure to environmental chemicals including pesticide



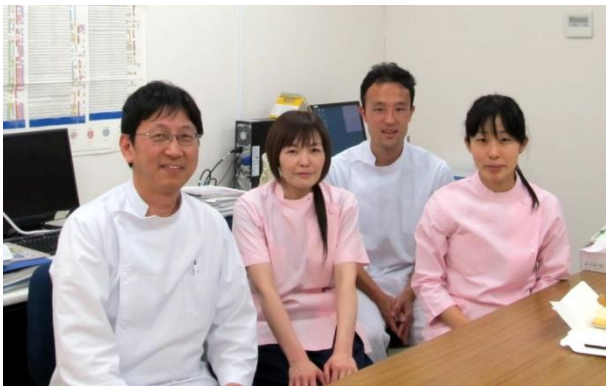
Tomoki Fukuyama
Azabu University Faculty of Veterinary Medicine,
Pharmacology Laboratory

It is great honor to be awarded the JSIT prize for encouragement. I would also like to express my sincere thanks to all the JSIT committee members and all colleagues of the Institute of Environmental Toxicology (IET) who worked together in my research project.

Approximately for 15 years since entering IET in 2004, I have followed the research entitled “Interaction between allergy development and exposure to environmental chemicals including pesticide”. When I started the immunotoxicology research at IET, local lymph node assay (LLNA) had just been launched by OECD as a new detection method for chemical skin sensitizers. LLNA drew attention as a growing sense of animal welfare against experimental animals since it can alternate and upgrade the existing guinea pig skin sensitization test. However, there was almost no background data for LLNA with pesticides. Therefore, my first project in IET was to develop the LLNA for evaluating pesticides. At that moment, I did not

have any experiences to perform the biological and immunological experiments, thus developing LLNA was a good training session for me to learn a skill for biological research. Through focusing on LLNA, I realized that although a detection method for chemical skin sensitizer was developed, there was no official test method being fully capable of assessment of respiratory sensitizers due to difficulties of inhalation exposure. Therefore, we attempt to develop the novel detection method for respiratory chemical sensitizers with modifications of LLNA and could introduce the newly developed detection method of environmental-chemical–related respiratory hypersensitivity in mice.

Recently, our group also focused on the direct interaction between exposure to environmental chemicals and the aggravation of chronic allergic diseases. Several epidemiological studies have suggested that there is possible intervention of exposure to environmental chemicals including endocrine disruptors and aromatic hydrocarbons with immune modulations, however, obvious evidences that demonstrate the direct association of these chemicals and allergy development. Therefore, we have investigated and demonstrated the direct involvement of these chemicals and several allergies development in vivo mice model and *in vitro* experiments.



Immunotoxicological Research

IL-17-induced mRNA stabilization and immunotoxicological research

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

Interleukin-17A (IL-17) is an immune cell-derived cytokine that acts on various types of cells, including epidermal keratinocytes. The signaling elicited by IL-17 is important for antimicrobial defense responses, whereas excessive IL-17 production leads to autoimmune diseases such as psoriasis and multiple sclerosis. IL-17-induced stabilization of mRNAs has been recognized as a unique and important feature of IL-17 signaling. Previously, we demonstrated that IL-17 signaling protein ACT1 is required to counteract constitutive IκBζ mRNA degradation by the ribonuclease Regnase-1. However, the mechanism of mRNA stabilization in IL-17-stimulated cells remains unclear. We recently conducted study to clarify the mechanism in more detail and identify an agent that can inhibit IL-17-induced mRNA stabilization. Intriguingly, TANK-binding kinase 1 (TBK1)-mediated phosphorylation of Regnase-1 was suppressed by the addition of dimethyl fumarate (DMF), an electrophilic small molecule that has been used to treat IL-17-related autoimmune diseases. Confocal microscopic observation of the cellular localization of ACT1 revealed that DMF treatment resulted in the disappearance of ACT1 nuclear dots and perinuclear accumulation of ACT1. These results suggested that DMF is a small molecule that perturbs IL-17-induced activation of the ACT1-TBK1 pathway, thereby inhibiting IL-17-induced mRNA stabilization. These findings would improve our understanding of the molecular mechanisms of IL-17 action in immunity and chronic inflammation. Also, IL-17-induced mRNA stabilization can be used to evaluate the potential immunotoxicity of environmental chemicals.

Reference: Ohgakiuchi Y et al. Biochem Biophys Res Commun. 2020 Jan 22;521(4):957-963.