ImmunoTox Letter Digest

June, 2018

The 25th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2018)

1. Date

September 18-19th, 2018

2. Venue

International Congress Center, 2-20-3 Takezono, Tsukuba, Ibaraki 305-0032, Japan.

3. President

Keiko Nohara
(National Institute for Environmental Studies, NIES)

4. Main theme of the meeting

Discussing and deepening our insight into the interaction between the immune system and the environment

5. Meeting Secretariat

Center for Health and Environmental Risk Research, NIES
Takehiro Suzuki (Secretary General)
E-mail: jsit25-office@nies.go.jp

6. Program (tentative)

September 18

Oral session

Luncheon seminar

Covance

Educational lecture

Akihiko Yoshimura (Keio University)

"Immune regulation by epigenetic modifications of T cells" (tentative)

Symposium

Gut microbiota and immune diseases

- A new perspective on immunotoxicology –

Rie Yanagisawa (NIES), Naoki Shimojo (Chiba University), Akira Shibuya (University of Tsukuba), Kiyoshi Takeda (Osaka University)

Poster and discussion session

September 19

Oral session

International session

Khaled Hossain (University of Rajshahi, Bangladesh), Myint Myint Nyein (University of Medicine (1), Myanmar)

Special lecture

B Paige Lawrence (University of Rochester, USA)

"Developmental exposure alters cellular processes critical for T cell functions, and affects some T cell properties across generations"

Luncheon seminar

Charles River Laboratories

Workshop

"Development of cancer immunotherapy and safety assessment of immune checkpoint inhibitors "

Organizer: Shigeru Hisada (Aska Pharmaceutical)

Hiroshi Shiku (Mie University), Kazuhiko Taguchi (Bristol-Myers Squibb), Minoru Satoh (University of Occupational and Environmental Health)

7. Social gathering

September 18, 18:30-20:30
Hotel Grand Shinonome: *www.hg-shinonome.co.jp/*

The 6th Japanese Society of Immunotoxicology Award
(The 2016 JSIT Award)

Immunotoxic effects of agro-chemicals.

Tadashi Kosaka
Study Management Division, the Institute of Environmental Toxicology

It is well known that agro-chemicals have a potential to cause the toxic effects on immunological functions. Then, we investigated the potential adverse effects of pesticides, organochlorine pesticide methoxychlor and organophosphorus pesticide parathion, on immune-suppression.

First, induction of apoptotic changes of the T cells treated with pesticides was investigated in the in-vitro and in-vivo studies. In order to detect the ability to induce the apoptosis of T cells, pesticides were incubated with mouse T cells and Jurkat cells in the RPMI 1640 medium containing 10% fetal calf serum. In this study, both of methoxychlor and parathion could cause apoptotic changes in both of mouse T cells and Jurkat cells. In-vivo study, TUNEL positive cells and/or AnexinV positive cells, which are indicative of apoptosis, were detected in rat pups in Utero pesticide exposure and in immature mice treated with repeated dosing of methoxychlor.

Secondly, to assess the immunosuppressive response to repeated exposure to some pesticides, ICR, Balb/c and C3H/He strain mice were treated with methoxychlor at 0, 150, 50, 1500 ppm in feed for 4 weeks. All mice were immunized with SRBC (Sheep red blood cell) by intraperitoneal injection (6×10^7/mice) 4 days before sacrifice, and their SRBC-IgM responses were subsequently assessed using ELISA method and PFC (Plaque-forming cell) assay. Repeated dosing with methoxychlor induced marked decreases in the production of SRBC-specific IgM antibodies in Balb/c and C3H/He mice.

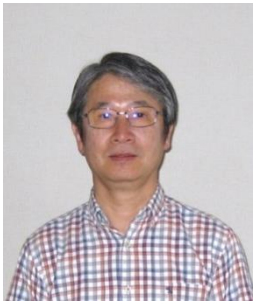
Third, we examined the relationship between dermal allergy and the immunosuppression induced by immunosuppressive pesticides. 1) The modulating potential of the organophosphorus pesticide (immunosuppressive chemicals) were studied for the skin sensitization of a contact allergen (phenoxyacetic acid herbicide; 2,4-d-butyl) using a local lymph node assay (LLNA). Four-week-old mice were orally administered parathion (0, 0.4, 1.2mg/kg) or methoxychlor (0, 100, 300 mg/kg). Four weeks after the last administration, an LLNA was conducted using 2,4-d-butyl. EC3 values of 2,4-d-butyl decreased markedly in parathion- and methoxychlor-pretreated groups. 2) The effects of the immunosuppressive pesticides on TNCB-induced atopic dermatitis (AD) were investigated in NC/Nga mice. Mice

were orally exposed to these chemicals (age, 4 weeks) and 4 weeks later received sensitization and challenge dosing (age, 8–12 weeks) with TNCB. Exposure to parathion and methoxychlor, immunosuppressive pesticides, markedly increased dermatitis severity including ear thickness and scored skin irritation. From there results, immunosuppressive pesticides can influence on the aggravation for the sensitizing response of some chemicals in LLNA assay or allergic responses in an atopic dermatitis model induced by TNCB.

Forth, male and female rat pups were obtained from dams receiving methoxychlor at dietary levels of 0, 30, 100, 300, and 1,000 ppm during the gestation and lactation period. They were fed a normal diet after weaning and kept up to 52 weeks of age. At 52 weeks of age, chronic nephropathy having enlarged glomeruli with increased IgM deposits in females at 1,000 ppm treatment group.

Thus, our investigation can exhibited the potential adverse effects of the pesticide on immune mechanisms that can lead to harmful changes in host responses such as; increased susceptibility to infectious diseases; the induction of hypersensitivity reactions; or an increased incidence of autoimmune disease. And, it is concluded that our short-term exposure protocol may be useful for detecting environmental chemicals having immunosuppressive potential.

The 7th Japanese Society of Immunotoxicology Award
(The 2017 JSIT Award)



Differential immunologic alteration in a mouse model exposed to low levels of volatile organic compounds

Hidekazu Fujimaki
National Institute for Environmental Studies

An increasing trend in the prevalence of allergic diseases, including asthma, rhinitis and eczema, has been reported from many industrialized countries. Toxic air pollutants such as volatile organic compounds (VOCs) can occur at relatively high concentrations in homes and buildings. The studies of unexplained symptoms observed in chemically sensitive subjects have been increased. However, there have been no studies on the effects of low-level inhalation of VOCs on the modulation of allergic and neurogenic inflammation in relation to the indoor air quality.

(1) Short-term formaldehyde (FA) exposure may directly produce dysfunction and inflammation in airways and aggravate allergic inflammatory reactions. However, nothing is yet known about the long-term effects of low-level FA exposure on allergic inflammation. We exposed C3H mice to low levels of FA and measured immunological parameters. Our results indicate that low levels of FA did not induce serious respiratory allergic inflammation, but modulated the production of nerve growth factor (NGF) in mice.

(2) The effect of low-level exposure to toluene on the airway inflammation in mice was studied and showed that toluene exposure aggravated the airway inflammatory responses in ovalbumin-immunized mice. Moreover, low-level exposure of immunized mice to toluene can modulate NGF signaling pathways in allergic airway inflammation and may disturb neuroimmune crosstalk between neurotrophins and allergic inflammation processes. The expression of neurotrophins and their receptors in adult mouse hippocampus was up-regulated by the exposure to low levels of toluene in a strain-dependent manner.

(3) The developing immune system may be more sensitive to toxicant-induced alterations than that of adults. We investigated the window of susceptibility to toluene exposure on immunological biomarkers during different developmental stages in infant mice and indicated that the late postnatal period which corresponds with neonatal period in human might represent a window of greatest susceptibility to toluene exposure, eliciting developmental toxicity. Dose-specific changes in neuroimmune markes in infant mice were also observed following toluene exposure.

The 7th Japanese Society of Immunotoxicology Prize for Encouragement

Long-term topical glucocorticoids induce pruritus in a mouse model of chronic dermatitis by affecting skin immunity.

Katsunori Yamaura

Faculty of Pharmacy, Keio University

It is my infinite honor and great pleasure to win the JSIT encouragement prize. I would like to express my sincere thanks and gratitude to all of the members of the awarding committee.

Topical glucocorticoids are commonly applied for treatment of chronic, inflammatory, pruritic skin disease such as atopic dermatitis, and are often administered over a long period. I reported that long-term topical dexamethasone exacerbates pruritus in a mouse model of allergic contact dermatitis (ACD). BALB/c mice with ACD induced by 5 weeks of repeated application of 2,4,6-trinitro-1-chlorobenzene (TNCB) were treated topically with dexamethasone for 3 weeks from 2 weeks after the elicitation of dermatitis. Significant enhancement of pruritus was confirmed after chronic application of dexamethasone. This increased frequency of scratching behavior was reduced by withdrawal of dexamethasone. On the other hand, ear-swelling was markedly ameliorated by dexamethasone treatment, but rapidly relapsed after dexamethasone withdrawal. I investigated the cause of augmentation of pruritus with a focus on the production of prostaglandin (PG) D_2. The scratching behavior induced by TNCB was augmented by topical application of dexamethasone, but dexamethasone did not have any effect on scratching bouts in mice that had not been treated with TNCB. Topical dexamethasone reduced the PGD_2 level, which increase in TNCB-treated mice, to the baseline level. Moreover, dexamethasone significantly decreased the PGD_2 production in IgE/antigen-stimulated RBL-2H3 mast cells; however, the same concentration of dexamethasone did not have any effect on the degranulation of stimulated mast cells. I concluded that topical glucocorticoids may exacerbate pruritus in a mouse model of ACD via inhibition of PGD_2 production in antigen-mediated activated mast cells in the skin. Furthermore, I elucidated the involvement of PGD_2 and its receptor (DP1) in augmentation of pruritus induced by dexamethasone, prednisolone, or betamethasone valerate.

Finally, I would like to express my deepest appreciation to Prof. K. Ueno, Dr. H. Satoh, Dr. RL. Thurmond and my students for their encouragement, support, comments, and suggestions.