

## Department of Public Health and Environmental Medicine

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### General Summary

One of our major research projects in the 2019 academic year was involved in (1) a new incident of lung diseases in workers handling acrylic acid polymers. Other major research projects focused on (2) the effects of nanomaterials on chromosomal abnormality and extracellular vesicles, (3) the effects of zinc-deficiency on the thymus, (4) the role of phospholipase A<sub>2</sub> enzymes in the adverse effects induced by aromatic hydrocarbon receptor activation, (5) decompression stress in the hyperbaric work, (6) association between work/life-related factors and injuries among workers, (7) social independence of patients with neurofibromatosis type 2, (8) the effects of polaprezinc on pica and binge eating, (9) the legacy effect in patients with type 2 diabetes, and (10) the effect of postprandial hyperglycemia on the incidence of retinopathy in patients with type 2 diabetes.

### Research Activities

#### *Epidemiological and experimental studies on a new incident of lung diseases in Japanese workers handling cross-linked water-soluble acrylic acid polymer powders*

Lung diseases developed in many workers in a Japanese company who handled cross-linked water-soluble acrylic acid polymer powders. Because of a lack of supporting evidence for such pulmonary toxicity, we conducted epidemiological and experimental studies to verify whether occupational inhalation exposure to cross-linked water-soluble acrylic acid polymer powders causes lung diseases.

#### *Experimental medicine*

##### 1. Analyses of the biological effects of nanomaterials

To elucidate the effects of nanomaterials at the molecular level, we examined application of transmission electron microscope, scanning electron microscope, and energy dispersive X-ray spectroscopy on Chinese hamster lung cells exposed to poly(amidoamine) dendrimer ethylene diamine core, Al<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub>, or ZnO nanoparticles. Encapsulated elements were detected in cells exposed to Al<sub>2</sub>O<sub>3</sub> or CeO<sub>2</sub> but not in cells exposed to ZnO. Thus, subcellular localization may be a mechanism of ZnO cytotoxicity, such as oxidative stress. We have also investigated extracellular vesicles (EVs) secreted from human keratinocyte A549 cells exposed to ZnO nanoparticles (ZnONPs). We found several types of keratin derived from differentiated keratinocytes in EVs from cells treated with ZnONPs. We have developed a working hypothesis that ZnONPs may induce cell differentiation against the human keratinocytes and are testing this possibility.

## 2. Inhibitory effects of EVs derived from human colorectal cancer HT29 cells on migration of human keratinocyte HaCaT cells

EVs are thought to be involved in cell-to-cell signal transduction by changing the composition of EVs in response to environmental changes. We found the suppression of migration of human keratinocytes HaCaT cells treated with EVs released assay by human colorectal cancer HT29 cells. This effect was not seen in EVs derived from HT29 cells treated with etoposide. Furthermore, a comparative analysis of the components of each EV revealed that the clathrin heavy chain was increased in the EVs released from the etoposide-treated cells.

## 3. Mechanism of thymus atrophy in zinc deficiency

We investigated the potential association of immune dysfunctions and thymus atrophy induced by zinc deficiency. To this end, we examined interleukin (IL)-7, a T cell maturation factor, and peroxisomal proliferator-activated receptor (PPAR)- $\gamma$  in the thymus of rats fed a zinc-deficient diet. The number of PPAR- $\gamma$ -positive cells, PPAR- $\gamma$  messenger RNA expression, and thymic fat in zinc-deficient rats were increased, suggesting the positive association of PPAR- $\gamma$  to thymic fat. The expression of IL-7 in the thymus of zinc-deficient rats was decreased. The decrease in IL-7 messenger RNA expression may be due to thymic fat.

## 4. Phospholipases as potential effectors of aryl hydrocarbon receptor activation

We had previously found the major role of cytosolic phospholipase A2 $\alpha$  (cPLA $_2\alpha$ ) in the adverse effects of aryl hydrocarbon receptor activation. This year, we found that *patatin-like phospholipase domain-containing (Pnpla) 7*, *Pnpla2*, and *phospholipase A2, group VII (Pla2g7)* have the same expression property as cPLA $_2\alpha$  and have the potential to mediate the effects of aryl hydrocarbon receptor activation. On the other hand, no phospholipase A2 exhibited a potential to compensate the action of cPLA $_2\alpha$ .

## 5. Decompression stress in hyperbaric work

Exposure to a hyperbaric environment and the subsequent decompression to the surface may cause the decompression stress. The level of decompression stress would be related to the risk of decompression sickness. However, there are no biomarkers for decompression sickness. Bubbles in the body after decompression and the number of human herpesvirus 6 cells in saliva may permit use of such biomarkers for the decompression stress.

### *Epidemiological studies*

#### 1. Longitudinal association between work/life-related factors and injuries among workers

We examined the longitudinal association between work/life-related variables and injuries by industry using 1-year follow-up data obtained from a nationally representative sample of Japanese workers. Whereas long working hours, near-misses, and depressive symptoms at baseline significantly predicted the occurrence of injuries during the follow-up period, these associations differed by industry.

#### 2. Social independence of patients with neurofibromatosis type 2

We examined the state of social independence and its contributing factors in patients with neurofibromatosis type 2 using data from a national registry in Japan. Approximately 80% of patients were socially independent. Socially dependent participants had more neurological features than did those who were socially independent.

### 3. Effects of polaprezinc on pica and binge eating

Polaprezinc is a complex of zinc and L-carnosine, both of which participate in the regulation of feeding behavior. Zinc deficiency has been known to be associated with pica, although the role of zinc supplementation in the treatment of pica has not been well investigated. We performed an open-label trial to evaluate the effects of polaprezinc on pica. In addition, we performed an open-label trial to evaluate the effects of polaprezinc on binge eating and its related psychopathology in patients with binge-eating disorder or bulimia nervosa.

### 4. Analysis of the duration and extent of the legacy effect in patients with type 2 diabetes

The legacy effect may continue for 14 to 19 years, with a greater effect for 10 years or less. The end of the legacy effect could be at 15 to 20 years. This effect may be the greatest for diabetic retinopathy, followed by diabetic kidney disease, and the smallest for cardiovascular disease.

### 5. Effect of postprandial hyperglycemia at clinic visits on the incidence of retinopathy in patients with type 2 diabetes

An analysis using real-world long-term follow-up data showed that postprandial hyperglycemia at clinic visits may predict the incidence of diabetic retinopathy, independent of HbA1c. The effect of postprandial hyperglycemia on diabetic retinopathy is obvious in patients with well-controlled HbA1c and in younger patients.

## Publications

**Takao T, Takahashi K, Yoshida Y, Kushiyama A, Onishi Y, Tahara T, Shimmei A, Kikuchi T, Suka M, Yanagisawa H, Iwamoto Y, Kasuga M.** Effect of postprandial hyperglycemia at clinic visits on the incidence of retinopathy in patients with type 2 diabetes: An analysis using real-world long-term follow-up data. *J Diabetes Investig.* 2019 Dec 7. doi: 10.1111/jdi.13194. [Epub ahead of print] PubMed PMID: 31811705.

**Suka M, Yamauchi T, Yanagisawa H.** Persuasive messages can be more effective when repeated: A comparative survey assessing a message to seek help for depression among Japanese adults. *Patient Educ Couns.* 2020 Apr; **103**(4): 811-818. doi: 10.1016/j.pec.2019.11.008. Epub 2019 Nov 13. PubMed PMID: 31761527.

**Takao T, Matsuyama Y, Suka M, Yanagisawa H, Kasuga M.** Analysis of the duration and extent of the legacy effect in patients with type 2 diabetes: A real-world longitudinal study. *J Diabetes Complications.* 2019 Aug; **33**(8): 516-522. doi: 10.1016/j.jdiacomp.2019.05.005. Epub 2019 May 10. PubMed PMID: 31186162.

**Yamauchi T, Sasaki T, Takahashi K, Umezaki S, Takahashi M, Yoshikawa T, Suka M, Yanagisawa H.** Long working hours, sleep-related problems, and near-misses/injuries in industrial settings using a nationally representative sample of workers in Japan. *PLoS One.* 2019 Jul 15; **14**(7): e0219657. doi: 10.1371/journal.pone.0219657. eCollection 2019. PubMed PMID: 31306462; PubMed Central PMCID: PMC6629083.

**Kobayashi N, Nishiyama T, Yamauchi T, Shimada K, Suka M, Kondo K, Yanagisawa H.** Attenuation of human herpesvirus 6B reactivation by aging. *J Med Virol.* 2019 Jul; **91**(7): 1335-1341. doi: 10.1002/jmv.25434. Epub 2019 Feb 27. PubMed PMID: 30788852.

**Futagawa Y, Yanaga K, Kosuge T, Suka M, Isaji S, Hirano S, Murakami Y, Yamamoto M, Yamaue H.** Outcomes of pancreaticoduodenectomy in patients with chronic hepatic dysfunction including liver cirrhosis: results of a retrospective multicenter study by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci.* 2019 Jul; **26**(7): 310-324. doi: 10.1002/jhbp.630. Epub 2019 Jun 19. PubMed PMID: 31017730.

**Yamauchi T, Suka M, Nishigori C, Yanagisawa H.** Evaluation of neurofibromatosis type 1 progression using a nationwide registry of patients who submitted claims for medical expense subsidies in Japan between 2008 and 2012. *Orphanet J Rare Dis.* 2019 Jul 5; **14**(1): 166. doi: 10.1186/s13023-019-1148-8. PubMed PMID: 31277677; PubMed Central PMCID: PMC6612089.

**Yamauchi T, Suka M, Yanagisawa H.** Help-seeking behavior and psychological distress by age in a nationally representative sample of Japanese employees. *J Epidemiol.* 2019 May 18. doi: 10.2188/jea.JE20190042. [Epub ahead of print] PubMed PMID: 31105090.

**Suka M, Yamauchi T, Yanagisawa H.** Responses to persuasive messages encouraging professional help

seeking for depression: comparison between individuals with and without psychological distress. *Environ Health Prev Med.* 2019 May 8; **24**(1): 29. doi: 10.1186/s12199-019-0786-8. PubMed PMID: 31068125; PubMed Central PMCID: PMC6507167.

**Kido T, Ishiwata K, Suka M, Yanagisawa H.** Inflammatory response under zinc deficiency is exacerbated by dysfunction of the T helper type 2 lymphocyte-M2 macrophage pathway. *Immunology.* 2019 Apr; **156**(4): 356-372. doi: 10.1111/imm.13033. Epub 2019 Jan 21. PubMed PMID: 30552817; PubMed Central PMCID: PMC6418430.

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**NCD Risk Factor Collaboration (NCD-RisC).** Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature.* 2019 May; **569**(7755): 260-264. doi: 10.1038/s41586-019-1171-x. Epub 2019 May 8. PubMed PMID: 31068725; PubMed Central PMCID: PMC6784868.

### Reviews and Books

**Nomura K, Karita K, Araki A, Nishioka E, Muto G, Iwai-Shimada M, Nishikitani M, Inoue M, Tsurugano S, Kitano N, Tsuji M, Iijima S, Ueda K, Kamijima M, Yamagata Z, Sakata K, Iki M, Yanagisawa H, Kato M, Inadera H, Kokubo Y, Yokoyama K, Koizumi A, Otsuki T.** For making a declaration of countermeasures against the falling birth rate from the Japanese Society for Hygiene: summary of discussion in the working group on academic research strategy against an aging society with low birth rate. *Environ Health Prev Med.* 2019 Mar 5; **24**(1): 14. doi: 10.1186/s12199-019-0768-x. PubMed PMID: 30836940; PubMed Central PMCID: PMC6402135.