

## Department of Public Health and Environmental Medicine

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### General Summary

Our major research projects in the 2016 academic year focused on: (1) effects of nanomaterials on chromosomal abnormality; (2) effects of Zn-deficiency on the expression of interleukins associated with a decrease in anti-inflammatory M2 macrophages; (3) mechanisms of a developmental-stage specific toxicity of lithium carbonate; (4) molecular approaches toward cancer chemoprevention with food factors; (5) effects of arsenic on the cholesterol metabolism; (6) the decompression stress in the hyperbaric work; (7) menopause-specific health literacy; (8) help-seeking intentions for mental illness; (9) impact of postprandial hyperglycemia on the incidence of cardiovascular events and all-cause mortality in type 2 diabetes patients; and (10) effects of polaprezinc, a carnosine-zinc complex, on pica and polydipsia or binge eating.

### Research Activities

#### *Experimental Medicine*

#### 1. Effects of nanomaterials on chromosomal abnormality in CHL/IU cells

We examined induction of micronuclei by exposure of AlO<sub>2</sub> or CeO<sub>2</sub> nanoparticles in both metabolic activation and inactivation on chinese hamster CHL/IU cells.

#### 2. Mechanisms responsible for a decrease in anti-inflammatory M2 macrophages in the spleen and role of IL-4 in Zn-deficient rats

Zn deficiency causes growth retardation and the dysfunction of immune and reproductive systems. We found that IL-4 and IL-13 mRNA expression was significantly lower in the Zn deficient (ZnD) group compared with that in the standard diet (SD) group. The number of IL-4 and IL-13 positive lymphocytes in the spleen was reduced in the ZnD group compared to the SD group.

#### 3. Kidney damage induced by an overproduction of PGE2

Aberrant upregulation of PGE2 synthesis results in polyuria and hydronephrosis, which was demonstrated by us using dioxin-exposed mouse model. In this year, we found that lithium carbonate, which upregulates PGE2 synthesis system, induced polyuria and hydronephrosis in mouse neonates. Our findings suggest that those chemicals upregulating PGE2 synthesis system are hazardous to the mammalian kidney in the developing stage.

#### 4. Molecular approaches toward cancer chemoprevention with food factors

We have attempted to establish an evidence-based cancer prevention method using food factors. We elucidated that equol, an isoflavandiol metabolized from daidzein, a type of isoflavone, from bacterial flora in the intestines, enhanced the inhibitory effect of brassinin, a phytoalexin from *Brassica* vegetables, on the growth of cancer cells via cell-cycle

arrest at G1 phase with up-regulation of CDK inhibitors (p21 and p27) and induced caspase-dependent apoptosis accompanied with loss of mitochondrial membrane potential.

#### 5. The effect of arsenic on the cholesterol metabolism

Recent epidemiological studies suggest that arsenic exposure involved in atherosclerosis. In this study, we focused on the effect of arsenic in the cholesterol metabolism by using HepalC1c7 cells. Gene expression analysis showed that arsenic suppresses the expression of Abca1 transporter which involved in HDL efflux. To elucidate the mechanisms of inhibition of Abca1, we are now focusing on LXR pathway.

#### 6. A study of the decompression stress in the 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 (DCS). However, there are no biomarkers for DCS. Bubbles in the body after decompression and the number of HHV-6 in saliva may permit use of such biomarkers for the decompression stress.

### *Epidemiology, evidence-based medicine, investigation, and medical informatics*

#### 1. Menopause-specific health literacy

A web-based survey was conducted among Japanese women aged 30-59 years to assess menopause-specific health literacy. Participants were presented with a vignette describing a typical case of menopausal symptoms and were then asked a series of questions to assess their recognition of the disorder and intention, attitude, subjective norm, perceived behavioral control, and available information related to seeking medical care.

#### 2. Help-seeking intentions for mental illness

A web-based survey was conducted among Japanese adults aged 20-59 years to explore possible differences in help-seeking intentions for early signs of mental illness. Psychological problems (insomnia and depression) were significantly less likely to induce help-seeking intentions than physical problems (headache and vertigo).

#### 3. Impact of postprandial hyperglycemia at clinic visits on the incidence of cardiovascular events and all-cause mortality in patients with type 2 diabetes

Postprandial hyperglycemia represented by the mean level of 2-hour post-breakfast blood glucose at clinic visits is associated with the incidence of cardiovascular disease and all-cause mortality independently of the mean HbA1c level in type 2 diabetes patients.

#### 4. Effects of polaprezinc on pica and polydipsia

We performed an open-label trial to evaluate the effects of polaprezinc in pica patients with/without polydipsia and to also examine the changes in serum concentrations of brain-derived neurotrophic factor (BDNF) before and after polaprezinc treatment.

#### 5. Effects of polaprezinc on binge eating

We performed an open-label trial to evaluate the effects of polaprezinc on binge eating in patients with bulimia nervosa or binge-eating disorder. We also assessed the EDE-Q (Eating Disorder Examination Questionnaire), the QIDS-SR16 (Quick Inventory of Depressive Symptomatology-Self-report), body weight, blood biochemistry, and plasma concentrations of BDNF over the course of trial.

## Publications

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- NCD Risk Factor Collaboration.** A century of trends in adult human height. *Elife.* 2016; **5**.
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- NCD Risk Factor Collaboration.** Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet.* 2017; **389**: 37-55.
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