

Department of Public Health and Environmental Medicine

Hiroyuki Yanagisawa, *Professor*
Shingo Yogosawa, *Assistant Professor*

Machi Suka, *Associate Professor*
Wataru Yoshioka, *Assistant Professor*

General Summary

Our major research projects in the 2015 academic year focused on: (1) effects of nanomaterials on chromosomal abnormality; (2) effects of Zn-deficiency on the expression of interleukins (ILs) associated with a decrease in anti-inflammatory M2 macrophages; (3) mechanisms responsible for tubulointerstitial nephropathy induced by fluoride; (4) mechanisms of a developmental stage-specific toxicity of dioxins; (5) molecular approaches toward cancer chemoprevention with food factors; (6) effects of arsenic on the cholesterol metabolism; (7) the decompression stress in the hyperbaric work; (8) menopause-specific health literacy; (9) help-seeking intentions for mental illness; (10) association between differences in blood pressure or HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes; and (11) 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 found that ZnO₂ and AlO₂ nanoparticles significantly induced micronuclei 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 of Zn-deficient rats: Roles of IL-4 and IL-13

A deficiency of Zn causes growth retardation and dysfunction of the immune and reproductive systems. We found that messenger RNA expression of IL-4 and IL-13, which induce differentiation into M2 macrophages, in splenic lymphocytes was significantly lower in rats with a Zn-deficient diet than in rats with a standard diet. Lymphocytes positive for IL-4 and IL-13 in the spleen were fewer in rats with a Zn-deficient diet than in rats with a standard diet.

3. Potential mechanisms responsible for tubulointerstitial nephropathy induced by fluoride in rats with unilateral ureteral obstruction

Fluoride, an environmental pollutant, is excreted from the kidney. The toxic effects of fluoride may deteriorate in animals with impaired renal function. In our previous animal experiments, ICR-derived glomerulonephritis mice, which have impaired renal function, were more severely affected by fluoride. In this study, we used the tubulointerstitial fibrosis model (unilateral ureteral obstruction) to examine whether fluoride deteriorates tubulointerstitial nephropathy in rats with unilateral ureteral obstruction.

4. Elucidation of the mechanism of a developmental stage-specific toxicity of dioxins

Dioxin-induced hydronephrosis develops only a few days after birth in rodents. The

molecular basis of this phenomenon has long been unknown. Aryl hydrocarbon receptor transactivation and prostaglandin E₂ overproduction are causes of dioxin-induced hydro-nephrosis, and only prostaglandin E₂ overproduction was found to be absent in dioxin-exposed adult mice. This finding indicates that the aberrant up-regulation of prostaglan-din E₂ synthesis is responsible for this developmental stage-specific toxicity of dioxins.

5. Molecular approaches toward cancer chemoprevention with food factors

Carcinogenesis is closely related to lifestyle, including eating habits. We have attempted to establish an evidence-based cancer prevention method using food factors, including phytochemicals and trace elements. We found 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 with up-regulation of p21 and induced apoptosis via an intrinsic pathway.

6. The effect of arsenic on cholesterol metabolism

Recent epidemiological studies suggest that arsenic exposure is involved in atherosclero-sis. In this study, we focused on the effect of arsenic on cholesterol metabolism by using Hepa1c1c7 cells. Gene expression analysis showed that arsenic suppresses the expression of ATP-binding cassette transporter A1, which is involved in high-density lipoprotein efflux. To elucidate the mechanisms of inhibition of this transporter, we are now focusing on the liver X receptor pathway.

7. A study of decompression stress in hyperbaric work

The decompression stress from hyperbaric work has been evaluated with the Doppler bubble detection technique. We attempted to evaluate the decompression stress by means of human herpes virus (HHV) 6 in saliva and the Doppler technique. The number of HHV-6 DNA in saliva was well correlated with the results of Doppler bubble detection. We were able to use HHV-6 in saliva as a marker to evaluate decompression stress.

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

1. Menopause-specific health literacy

An Internet-based survey was conducted among Japanese women aged 30 to 59 years. The majority (85%) of participants correctly labeled the vignette as menopausal symp-toms, and 60% expressed an intention to seek medical care if they had the presented symptoms.

2. Help-seeking intentions for mental illness

An Internet-based survey was conducted among Japanese adults aged 20 to 59 years. Those living in a communicative neighborhood were significantly more likely to express informal and formal help-seeking intentions.

3. Relationships between the risk of cardiovascular disease in patients with type 2 diabe-tes and both visit-to-visit variability and time-to-effect differences in blood pressure

Visit-to-visit variability in blood pressure is predictive of the incidence of cardiovascular disease independently of mean blood pressure in patients with type 2 diabetes. Increased systolic blood pressure over the preceding 3 to 5 years indicated a significant risk for car-diovascular disease.

4. The combined effect of visit-to-visit variability in HbA1c and systolic blood pressure on the incidence of cardiovascular events in patients with type 2 diabetes

Long-term visit-to-visit variability in HbA1c and systolic blood pressure simultaneously represented a combined and additive risk for the incidence of cardiovascular disease in patients with type 2 diabetes. In addition, a synergistic effect was suggested to exist between HbA1c variability and mean systolic blood pressure levels for the incidence of cardiovascular disease.

5. Effects of polaprezinc on pica and polydipsia

We performed an open-label trial to evaluate the effects of polaprezinc in patients who had pica with or without polydipsia and to examine the changes in serum concentrations of brain-derived neurotrophic factor before and after polaprezinc treatment. The trial is in progress.

6. 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 a binge-eating disorder. We also assessed the Eating Disorder Examination Questionnaire, the 16 Item Quick Inventory of Depressive Symptomatology Self-Report Version, body weight, blood biochemistry, and plasma concentrations of brain-derived neurotrophic factor over the course of the trial. The trial is in progress.

Publications

Sakae K, Yanagisawa H. Continuous follow-up with polaprezinc (zinc-L-carnosine complex) after oral treatment with L-carnosine for pressure ulcers. *Biomedical Research on Trace Elements*. 2015; **26**: 174-80.

Yanagisawa H, Kido T, Yogosawa S, Satoh O, Sakae K, Suka M. Inadequate intake of zinc exacerbates blood pressure and renal function via superoxide radical-induced oxidative stress. *Biomedical Research on Trace Elements*. 2015; **26**: 117-23.

Yanagisawa H. Role of Zn in blood pressure and renal function. *Aen Eiyō Chiryō*. 2015; **6**: 12-7.

Suka M, Yamauchi T (Natl Ctr Neurol Psychiatry), Sugimori H(Daito Bunka Univ). Relationship between individual characteristics, neighborhood contexts, and help-seeking intentions for mental illness. *BMJ Open*. 2015; **5**: e008261.

Takao T¹, Matsuyama Y², Suka M, Yanagisawa H, Iwamoto Y¹ (Asahi Life Fnd, ²Univ Tokyo). The combined effect of visit-to-visit variability in HbA1c and systolic blood pressure on the incidence of cardiovascular events in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2015; **3**: e000129.

Takao T¹, Kimura K¹, Suka M, Yanagisawa H, Kikuchi M¹, Kawazu S¹, Matsuyama Y² (Asahi Life Fnd, ²Univ Tokyo). Relationships between the risk of cardiovascular disease in type 2 diabetes patients and both visit-to-visit variability and time-to-effect in blood pressure. *J Diabetes Complications*. 2015; **29**: 699-706.

NCD Risk Factor Collaboration. Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331, 288 participants. *Lancet Diabetes Endocrinol*. 2015; **3**: 624-37.

Suka M, Odajima T¹, Okamoto M², Sumitani M², Igarashi A, Ishikawa H, Kusama M, Yamamoto M, Nakayama T, Sugimori H³ (Jpn Red Cross Kanto-Koshinetsu Block Blood Ctr, ²Univ Tokyo, ³Daito Bunka Univ). Relationship between health literacy, health information access, health behavior, and health status in Japanese people. *Patient Educ Couns*. 2015; **98**: 660-8.

Yamamoto M, Kubota K, Okazaki M, Dobashi A, Hashiguchi M, Doi H, Suka M, Mochizuki M. Patients views and experiences in online reporting adverse drug reactions: findings of a national pilot study in Japan. *Patient Prefer Adherence*. 2015; **9**: 173-84.

Maeda E, Sugimori H(Daito Bunka Univ), Nakamura F, Kobayashi Y, Green J, Suka M, Okamoto M (Univ Tokyo), Boivin J, Saito H. A cross sectional study on fertility knowledge in Japan, measured with the Japanese version of Cardiff Fertility Knowledge Scale (CFKS-J). *Reprod Health*. 2015; **12**: 10.

Benner S, Takeyama M, Endo T, Yoshioka W, Tohyama C. Application of NeuroTrace staining in the fresh frozen brain samples to laser microdissection combined with quantitative RT-PCR analysis. *BMC Res Notes*. 2015; **8**: 252.

Miyajima E, Tsunoda M¹, Sugiura Y¹, Hoshi K, Kido T, Sakamoto Y, Sakabe K, Aizawa Y¹ (Kitasato Univ). The diagnosis of sick house

syndrome: the contribution of diagnostic criteria and determination of chemicals in an indoor environment. *Tokai J Exp Clin Med.* 2015; **40**: 69-75.