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General Summary

Our major research projects in the 2017 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) help-seeking intentions for mental illness; (8) impact of postprandial hyperglycemia on the incidence of cardiovascular events and all-cause mortality in type 2 diabetes patients; and (9) 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_2 or CeO_2 nanoparticles in both metabolic activation and inactivation on chinese hamster CHL/IU cells. We also isolated extracellular vesicles (EVs) secreted from human keratinocytes exposed to ZnO nano-particles to analyze molecular profiles of the EVs.

2. Mechanism of inflammatory response and the effect of IL-4 on Th2 lymphocytes derived from the spleen of Zn-deficient rats

The present study was designed to examine of Th2-lymphocyte transcription factor “GATA-3” and CD3⁺; CD4⁺ or CD3⁺; CD8⁺ cells population in the spleen of Zn control (ZnC) and Zn deficient (ZnD) rats. SD rats were pair-given 17 g/day of 0% or 0.01% Zn diets for 6 wks. After dietary manipulation, the measurements of CD3⁺; CD4⁺ or CD3⁺; CD8⁺ double positive cells were done using the flow cytometry. Also, CD4 positive cells from the spleen were extracted and GATA-3 was measured by the western blotting technique. CD3⁺; CD8⁺ double positive cells and GATA-3 protein levels were significantly lower in the ZnD group compared with the ZnC group. Zinc deficiency-induced aggravated inflammation is Th2-related, and is associated with the loss of GATA-3, IL-4, and anti-inflammatory M2 macrophages.

3. Mechanisms of dioxin toxicity

We investigated roles of cPLA₂ α in the development of dioxin toxicity. Using a cPLA₂ α -null mouse model, we revealed that the dioxin-induced increase in Oil Red O staining and Adipophilin protein abundance is mainly mediated by cPLA₂ α . In addition, we found that dioxin-induced fetal and neonatal hydronephrosis have distinct mechanisms in that

the latter requires cPLA₂ α but the former does not.

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 HepG2 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 PPAR 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. Development of persuasive messages encouraging help-seeking for depression

A cross-sectional web-based survey was conducted among Japanese adults aged 35–45 years to examine the effectiveness of persuasive messages encouraging help-seeking for depression among people with various depressive status. Depressed people are likely to be more susceptible to persuasive messages encouraging their help-seeking than non-depressed people. Message framing and formatting may have a significant effect on persuasive message effectiveness.

2. Predictive ability of visit-to-visit variability in HbA1c and systolic blood pressure (SBP) for the development of microalbuminuria and retinopathy in people with type 2 diabetes

Visit-to-visit variability in both HbA1c and SBP simultaneously predict the development of microalbuminuria. HbA1c variability may clearly predict the development of retinopathy when the mean SBP is normal (<130 mmHg).

3. Effects of polaprezinc on pica

Zinc deficiency has been associated with pica, although the role of zinc supplementation in the treatment of pica has not been well investigated. Polaprezinc is a complex of zinc and L-carnosine, both of which may participate in appetite regulation. We performed an open-label trial to evaluate the effects of polaprezinc on pica

4. Effects of polaprezinc on binge eating

We described 3 patients with binge-eating disorder or subthreshold binge-eating disorder who experienced considerable relief from binge eating with polaprezinc treatment. Based on the finding, 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.

5. Overwork-related mental disorders and suicide

We examined the state of occupational mental disorders and suicide among private business employees and local public employees in Japan using a database containing all cases involving compensation for mental disorders due to overwork and adverse work events over a 5-year period. The distribution of adverse work events differed by industry and job type among cases involving compensation for mental disorders. These differences should be taken into consideration when developing industry- and job type-specific preventive measures for mental disorders among workers.

6. Epidemiology of intractable rare diseases in Japan

We analyzed the characteristics of individuals suffering from neurofibromatosis type 1 (NF1) in Japan since 2000, using a national registry comprised of information regarding all cases of NF1 that claimed a medical expense subsidy and were registered in the system for the first time. Future work should follow up the prognosis of individuals suffering from NF1 using the registry.

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