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General Summary

Our major research projects in the 2018 academic year focused on: (1) the effects of nanomaterials on chromosomal abnormality, (2) the effects of zinc-deficiency on the expression of interleukins associated with a decrease in anti-inflammatory M2 macrophages, (3) the disruption of prostaglandin synthesis pathway by environmental chemicals and related kidney abnormality, (4) molecular approaches toward cancer chemoprevention with food factors, (5) decompression stress in the hyperbaric work, (6) help-seeking intentions for mental illness, (7) postprandial hyperglycemia on the incidence of cardiovascular events and all-cause mortality in patients with type 2 diabetes, (8) job-related stress and health, and (9) the effects of polaprezinc, a carnosine-zinc complex, on pica and polydipsia or binge eating.

Research Activities

Experimental medicine

1. Mechanism of renal prostaglandin production via aryl hydrocarbon receptor

Aryl hydrocarbon receptor (AhR), a sensor protein activated by exogenous ligands, causes overproduction of prostaglandin E_2 and the onset of hydronephrosis in neonatal mammals. The activation of AhR elicits nuclear translocation, transcription enhancement, and activation of cytosolic signaling molecules, such as cytosolic phospholipase $A_2\alpha$. Using a mutant AhR lacking a nuclear translocation signal, we found that AhR nuclear translocation is required for transcription enhancement, cytosolic phospholipase $A_2\alpha$ activation, and prostaglandin E_2 production. These findings suggest a hitherto unknown cross-talk of transactivation activity in the nucleus and cytoplasmic signaling upon AhR activation.

2. Decompression stress in hyperbaric work

Exposure to a hyperbaric environment and the subsequent decompression of the surface might cause decompression stress. The level of decompression stress would be related to the risk of decompression sickness. Bubbles in the body after decompression and the level of human herpesvirus 6 in saliva might permit use of such biomarkers for research on decompression stress.

3. Role of macrophage subtypes in thymus atrophy of zinc-deficient rats and effects of interleukin 4 administration

Zinc deficiency causes growth retardation and dysfunction of the immune and reproductive systems. In this study, a relationship between thymus atrophy and zinc-deficiency was examined by the administration of interleukin 4 or by a change from a zinc-deficient diet to a zinc-standard diet. We found that the number of CD4 and CD8 double-positive

cells was significantly lower in rats fed the zinc-deficient diet than that in rats fed the zinc-standard diet. In contrast, the numbers of CD4 and CD8 double-negative cells, apoptotic cells, and macrophage subtypes (M1 and M2) were significantly higher in rats fed the zinc-deficient diet group than in rats fed the zinc-standard diet. These findings suggest that interleukin 4 administration results in a decreased inflammatory response and, therefore, in a decrease in M1 macrophages. The M2 macrophages remain elevated in this scenario, and we propose that they mediate a repair function.

4. Effects of nanomaterials on chromosomal abnormality in Chinese hamster lung cells

We examined the induction of micronuclei by exposure of AlO_2 or CeO_2 nanoparticles in both metabolic activation and inactivation in Chinese hamster lung cells. We also studied extracellular vesicles (EVs) secreted from human keratinocytes exposed to ZnO nanoparticles. The EVs were isolated from a culturing supernatant by means of ultracentrifugation. Dynamic light scattering analysis showed that the particle size of EVs was smaller from cells exposed to ZnO nanoparticles than from control cells. Sodium dodecylsulfate-polyacrylamide gel electrophoresis showed that several specific bands were contained in preparations of EVs from cells treated with ZnO nanoparticles. Subsequently, several types of keratin (such as keratin 1/2/5/6B/9/10) were detected with mass spectrometry.

5. Molecular approaches toward cancer chemoprevention with food factors

We have attempted to establish an evidence-based cancer prevention method with food factors. We reported that instant coffee powders inhibit the growth of human colon cancer HT-29 cells via cell-cycle arrest at the G2/M phase with up-regulation of cyclin-dependent kinase inhibitor p21.

Epidemiological studies

1. Development of persuasive messages encouraging help-seeking for depression

A cross-sectional Internet-based survey was conducted among Japanese adults to compare the responses to differently framed and formatted persuasive messages to encourage help-seeking for depression. Message framing and formatting might affect emotional responses to the message, the willingness to read the message, and the intention to seek help for depression. The application of loss framing and formatting to depression help-seeking messages would be recommendable.

2. Long working hours, sleep-related problems, and near-misses/injuries

We examined, in a nationally representative sample of workers, the association of long working hours/sleep-related problems and near-misses/injuries in industrial settings. Protective measures for workers, such as reducing the total hours of service/job-related fatigue, might effectively prevent near-misses/injuries in industrial settings.

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 participate in the regulation of feeding behavior. We performed an open-label trial to evaluate the effects of polaprezinc on pica.

4. Effects of polaprezinc on binge eating

We performed an open-label trial to evaluate the effects of polaprezinc on binge eating and its related psychopathology in patients with a binge-eating disorder or bulimia ner-

vosa.

5. Optimal cutoff values of fasting plasma glucose variability for detecting retinopathy in type 2 diabetes

Our longitudinal study of 27 years provides new cutoff values for fasting plasma glucose variability. The threshold of fasting plasma glucose levels (6.9 mmol/L) is proposed to predict the incidence of retinopathy during the subsequent 25 years.

Publications

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