SIRT3-IDH2 axis is a target of dietary fructose: implication of IDH2 as a key player in dietary carcinogen toxicity in mice colon

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The potential roles of fructose in promoting colon cancer are of growing concern. In the present study, we aimed to investigate the molecular mechanisms by which fructose contributes to colon carcinogenesis, focusing on the role of mitochondrial NADP+-dependent isocitrate dehydrogenase (IDH2). Using an unbiased multi-omics approach (namely, transcriptomics and proteomics), liver and colon tissues from fructose-fed wild-type (WT) mice were analyzed to identify key genes implicated in cancer-related pathways. Following, IDH2 knockout (KO) mice were exposed to a dietary carcinogen, 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP), to validate the involvement of IDH2 in colon cancer development. In the WT mice, fructose suppressed Aryl Hydrocarbon Receptor signaling and induced oxidative stress, leading to mitochondrial dysfunction through the SIRT3-IDH2 axis. The IDH2 KO mice, on the other hand, exhibited increased DNA damage and colonic tumorigenesis in response to PhIP, with significant disruptions in mitochondrial function and GSH-mediated detoxification pathways. Our in vitro works confirmed that fructose reduced SIRT3 expression and IDH2 activity, further reinforcing the implications of fructose intake in colon carcinogenesis. Collectively, these findings suggest that fructose promotes colon carcinogenesis by disrupting mitochondrial function and impairing DNA damage response mechanisms, particularly through the suppression of the SIRT3-IDH2 axis.

Mitigating obesogen-induced lipid accumulation: anti-obesogenic effects of Cirsium setidens Nakai extracts in adipocyte differentiation and mouse models

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As industry develops, environmental pollution intensifies, creating an urgent need to assess environmental exposure and the associated risks of trace pollutants. Among these pollutants, certain endocrine-disrupting chemicals (EDCs), termed "obesogens," are known to contribute to obesity. Major sources of exposure through food include bisphenols (food packaging and can linings), phthalates (plasticizers in plastic food packaging), and parabens (preservatives). Given international restrictions on EDCs, alternatives have been developed; however, similar chemical structures and physical properties raise safety concerns about these substitutes. This study aimed to elucidate the mechanisms of lipid metabolism disruption induced by EDCs, specifically bisphenols, phthalates, and parabens, and to explore functional food ingredients capable of mitigating obesogenic effects. As a result, treatment with BPA, BPS, BPF, EtP, and DOTP during adipocyte differentiation (days 0–10) significantly induced lipid accumulation, with the bisphenol-treated group exhibiting the highest levels of lipid accumulation compared to other obesogens. Obesogens treatment markedly increased the protein expression levels of PPARγ and C/EBPα, with the effects most pronounced at 48 hours of differentiation time. Increased PPARγ expression was entirely inhibited by treatment with GW9662 after 48 hours, suggesting that obesogens induce PPARγ expression, thereby promoting obesity-related effects. Moreover, a standardized *Cirsium setidens* Nakai extracts (CNE), based on extraction solvents, time, production area, and harvest season, was evaluated for its anti-obesogenic effects in obesogen-induced 3T3-L1 adipocytes and C57BL/6J mice. CNE treatment effectively suppressed obesogen-induced increases in key adipogenic transcription factors (ATFs) and lipid accumulation during both early (48 hours) and terminal differentiation stages (10 days). In mice co-administered with obesogen and CNE, body weight, epididymal white adipose tissue (WAT) mass, adipocyte size, plasma triglyceride levels, and the expression of ATFs and lipogenesis-related enzymes in WAT were reduced compared to the obesogen-only group. These findings suggest that CNE could serve as a promising natural intervention to counteract obesogen-induced obesity and related metabolic disorders.

Matcha improves NAFLD through modulating inflammatory responses in cafeteria diet-fed rats

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Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases globally. The cafeteria diet is a well-established model of inducing NAFLD in rodents, which is characterized by adding junk food containing high levels of fat, sugar, salt, saturated fat, and cholesterol into animal-based foods. Matcha contains catechins and caffeine which are the main bioactive components that improve lipid accumulation, boost anti-inflammation, and promote gut health benefits. However, the effects of matcha based on NAFLD still need more research. In this study, we investigated the effect of matcha on NAFLD in rats under a 16-week Taiwanese cafeteria diet-feeding. Four-week-old male Wistar rats were divided into four groups (10 rats/group) : a control diet (C) group, C+0.2% matcha (C+0.2% M) group, Taiwanese cafeteria diet (CAF) group, and CAF+0.2% M group. Results indicated that the Taiwanese cafeteria diet induced obesity, abnormal lipid metabolism, insulin resistance, and liver injury which may relate to decreased intestinal barrier impairment as well as activation of the toll-like receptor 4 (TLR4) pathway. In contrast, the intervention with 0.2% matcha repaired the intestinal barrier which in turn improved hepatic inflammation and liver injury. We concluded that matcha has anti-inflammatory potential to improve Taiwanese cafeteria diet-induced NAFLD in rats which may associated with gut health.

Biological and clinical significance of the AGE-RAGE axis in the aggressiveness and prognosis of prostate cancer

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Dietary patterns and chronic hyperglycemia are linked to the formation of advanced glycation end products (AGE) and prostate cancer (PCa) risk. The activation of the receptor for AGEs (RAGE) acts as a bridge between various RAGE ligands and certain malignancies. Our study showed that the interaction of AGEs and RAGE promoted PCa cell proliferation, invasion, and autophagy-mediated survival in response to chemotherapeutic agents. RAGE-overexpressed PCa cells underwent epithelial-mesenchymal transition and showed increased cancer stem cell-like properties. In mouse xenograft models, RAGE-overexpressed cells exhibited more substantial tumorigenic capacity than parental cells, whereas RAGE knockdown decreased tumorigenicity. Long-term consumption of the high-AGE diet caused prostate enlargement with precancerous high-grade prostatic intraepithelial neoplasia, abnormal glucose homeostasis, elevated oxidative stress, and AGE accumulation in mice. The clinical data validated a positive correlation between high AGE and RAGE expressions with poor clinical outcomes. Our findings suggest that the AGE-RAGE axis facilitates PCa progression and aggressiveness. Prostatic AGEs and RAGE expression levels are associated with PCa prognosis. Adherence to a reduced-AGE diet and targeting RAGE are potential approaches to complement and synergize with the current PCa therapies.

Keywords: advanced glycation end products, aggressiveness, glycative stress, prostate cancer, RAGE

The role of protein nutrition for pressure injury healing and prevention

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Protein malnutrition has been shown to inhibit pressure injury healing in elderly people and hospitalized patients. Understanding the molecular mechanisms that protein nutrition affects pressure injury is known to be important for optimal pressure injury healing and prevention. However, the molecular mechanism underlying the alteration of pressure injury healing and prevention by dietary protein sources is not well understood. In this session, I would like to talk about the relationship between pressure injuries and protein nutrition.

(1) A novel pressure injury mouse model
We developed a novel pressure injury mouse model that can be applied from the early stages of pressure injury. The reperfusion following ischemia has been shown to be a major etiology of pressure injuries. Dorsal mouse skin was pulled up and trapped between two magnetic plates, and then plates were removed after 24 hours. Gross observations revealed increased pressure injury development after ischemia-reperfusion (IR). To comprehensively characterize the transcriptome in response to IR, we next used bulk RNA-Sequencing. A total of 412 significant differential express genes were identified, of which 326 were upregulated and 86 were downregulated in the IR group. The upregulated genes were strikingly related to inflammatory response, neutrophil chemotaxis and immune response, revealed by Gene Ontology enrichment analysis.

(2) The role of dietary protein sources on pressure injury
We examined the effects of dietary protein sources (casein, gluten and rice protein) on pressure injury using the pressure injury mouse model. The wound areas were significantly smaller in the gluten and rice protein group than those in the casein group at 24 h after IR. The mRNA levels of pro-inflammatory cytokines, interleukin-1β and tumor necrosis factor-α, were significantly lower in skin tissue of the gluten and rice protein group than those in the casein group. Thus, it is likely that gluten and rice protein have positive effects on pressure injury prevention by the suppression of inflammation.

Novel physiological functions of intestinal microbes-derived soluble vitamin and hydrogen gas-mediated nondigestible saccharide

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Nondigestible saccharides have the effect of maintaining and promoting host health by improving the intestinal microflora. Nondigestible saccharides that are not digested in the small intestine by disaccharidases and reached the large intestine as intact saccharides are fermented by the intestinal microbes and produce a variety of metabolites. We have focused on intestinal microbes-derived soluble vitamins (IMDSV) and hydrogen gas (IMDH).

We have clarified that consecutive feeding of nondigestible saccharides increases IMDSV which are folate, vitamin B12 and vitamin B6, especially folate production being the most prominent. We have found that consecutive feeding of nondigestible saccharides can improve folate deficiency and insufficient by increasing folate via intestinal microbes in rat.

We have also shown that IMDH is transferred from the mother to the fetus via placenta in feeding of nondigestible saccharide in the pregnant mice. In addition, it has also been shown that the increased oxidative stress due to excessive folic acid in pregnant mice were suppressed by IMDH in mother and fetus.

It is possible that elucidating the effects of nondigestible oligosaccharide intake on host health will lead to the discovery of new functionalities in nondigestible oligosaccharides. We believe the progression of this research is the key not only to healthy aging, but also to maintaining and improving the health of young adult women, mothers and children.