RESEARCH REPORT - No. 1604 FY 2016-2017

Title of research project	Elucidation of carcinogenic mechanisms of organic arsenicals
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【Abstract】

Accumulating experimental evidence indicates that dimethylarsinic acid (DMA^V) which is a major organic metabolite of inorganic arsenic and organic arsenic compounds contained in food is involved in the carcinogenicity of inorganic arsenic. However, the carcinogenic mechanisms of DMA^V remain unclear. In this project, we compared the altered profiles of mRNA and microRNA expression between the early proliferative lesion in urothelium and the DMA^V-induced bladder tumors in rats. Our findings suggested that mir-199a-mediated activation of Wnt/beta-catenin and Aryl hydrocarbon receptor signaling pathway play important roles in the DMA^V-induced rat bladder carcinogenesis. Furthermore, in the study aiming to evaluate the carcinogenic effects of prenatal DMA^V exposure in CD1 mice, we showed that exposure of pregnant CD1 mice to DMA^V through the drinking water induce lung and hepatocarcinogenesis in male offspring and indicated that abnormal histone methylation may responsible for the prenatal DMA^V carcinogenicity in the lung. We also showed that tumor suppressor genes Ink4a/Arf are unlikely involved in the carcinogenicity of arsenic in mice evidenced by the findings that no increased tumors were observed in the Ink4a/Arf knockout mice treated with sodium arsenite or DMA^V. In addition, we demonstrated that organic arsenic compound arsenosugar in the Hijiki and Nori powder were not decomposed by digestive juice or intestinal bacteria, and the glycerol arsenosugar is much less toxic compared with sodium arsenite *in vitro*. Our findings indicated the important role of epigenetic mechanism in the DMA^V-induced carcinogenesis in experimental animals.