Elucidation of carcinogenic mechanisms induced by lifestyle diseases and search for novel biomarkers

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In recent years, many epidemiological studies showed the correlation between adult diseases and carcinogenesis. It has been thought that inflammatory cytokines induced by chronic inflammation in obese body are associated with the correlation. Meanwhile, DNA adducts are thought to contribute to gene mutation and carcinogenesis, and produced by reactive oxygen species (ROS), lipid peroxides (LPO) and so on. In this study, we investigated the DNA adduct formation in obese KK-A^y mice using LC-MS/MS method.

We determined the five kinds of DNA adducts (8-oxodG, etheno (ε)dA, heptanone etheno (Hε)dG, HεdA, HεdC) in obesity mice organs using the developed high-sensitive LC-MS/MS. Four LPO-derived DNA adducts, εdA, HεdG, HεA and HεdC, increased in the liver of KK-A^y (obesity model, 20 years old, female) mice compared to normal C57BL mice (normal, 20 years old, female). Also, these LPO-derived DNA adducts increased in the kidney of KK-A^y and these levels were higher compared to those of liver. Similarly, the levels of 8-oxodG, one of the oxidative stress marker, increased in KK-A^y. Furthermore, we measured the amounts of LPO in the liver of mice using TBARS method. The levels of LPO increased in KK-A^y compared with C57BL. On the other hand, since cyclooxygenase (COX)-2 induced by chronic inflammation contribute to generation of LPO, we examined the expression level of mRNA and protein of COX-2 in the liver. However, there was no change between KK-A^y and C57BL. These results suggest that ROS may contribute to the generation of LPO in the obese body with chronic inflammation. Moreover, DNA adduct levels of liver and kidney were similar between KK-A^y and C57BL mice, therefore increasing levels of ROS and LPO in obese body may be contributed by the development of obesity.

In conclusion, we demonstrated that the levels of ROS and/or LPO-related DNA adducts in liver and kidney of obese KK-A^y increased compared with lean C57BL mice. Therefore, these DNA adducts may contribute to obesity-related carcinogenesis.