P067 Oxidative stress-induced tumorigenesis in the small intestine of Mutyh-deficient mice

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Oxygen radicals are produced through normal cellular metabolism, and the formation of such radicals is further enhanced by exposure to either ionizing radiation or various chemicals. The oxygen radicals attack DNA and its precursor nucleotides, and consequently induce various oxidized forms of bases in DNA within normally growing cells. Among such modified bases, 8-oxo-7, 8-dihydroguanine (8-oxoG) and 2-hydroxyadenine (2-OH-A) are highly mutagenic lesions, if not repaired. MUTYH is a DNA glycosylase that excises adenine or 2-OH-A incorporated opposite either 8-oxoG or guanine, respectively, thus considered to prevent G:C to T:A transversions in mammalian cells. The *Mutyh*-deficient mice showed a marked predisposition to spontaneous tumorigenesis in various tissues when examined at 18 months of age. The incidence of adenoma/carcinoma in the intestine significantly increased in *Mutyh*-deficient mice, as compared with wild-type mice. This high susceptibility of the mutant mice to intestinal tumor-development was well correlated with the condition observed in MAP (MUTYH-associated polyposis) patients. We performed mutation analysis of the tumor-associated genes amplified from the intestinal tumors developed in four mutant mice that had been treated with $KBrO_3$. Many tumors had G:C to T:A transversions in either *Apc* or *Ctnnb1*. No mutations were found in either *k-ras* (exon 2) or *Trp53* (exon 5-8). Our findings indicate that the abnormality in the Wnt signaling pathway is causatively associated with oxidative stress-induced tumorigenesis in the small intestines of the *Mutyh*-deficient mice.

Mutyh 遺伝子欠損マウスにおける酸化ストレス誘発消化管腫瘍の解析

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P068 Induction effect of coadministration of soybean isoflavones and sodium nitrite on the oxidative DNA damage in mouse gastric mucosa.

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We previously found that a reaction mixture of isoflavones (daidzein or genistein) and sodium nitrite produced free radicals under acidic condition like stomach in vitro.
In this study, we examined the induction potency of oxidative DNA damage in gastric mucosa of ICR male mice coadministrated with isoflavones (1mg/kg B.W.) and sodium nitrite (10mg/kg B.W.). After 3 hours of coadministration of with both compounds, mice were sacrificed immediately. We used two assays to measure the oxidative DNA damage of gastric mucosa. Comet assay combined with the repair enzyme formamidopyrimidine-*N*-glycosylase (Fpg) was applied to detect the Fpg-sensitive site. HPLC-ECD system was applied for determination of 8-oxo-2'-deoxyguanosine (8-oxodG), a useful marker of oxidative DNA damage to detect G:C-to-T:A transversion. In the Fpg-comet assay, the values of DNA tail moment in gastric mucosa were significantly increased by coadministration of either isoflavone and sodium nitrite, compared with control group. These data showed that coadministration of both compounds cause oxidative DNA damage in gastric mucosa. The determination of 8-OxodG is now under experiment.

大豆イソフラボンと亜硝酸ナトリウムの同時投与はマウス胃粘膜における酸化的DNA損傷を引き起こす.

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