

S-7

Tumorigenicity of benzo(a)pyrene and benzo(a)pyrene diol epoxides in v-Ha-ras transgenic TG-AC mice

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Abstract

Tumorigenicity of benzo(a)pyrene (BP) and benzo(a)pyrene diol epoxides ((+)BPDE-I, (-)BPDE-I) was investigated in transgenic TG-AC mice carrying v-Ha-ras oncogene fused to the promoter of the mouse embryonic α -like, z-globin gene. Animals were topically treated twice per week for 25 weeks with BPDE (10 μ g/mouse) and BP (10, 20, 40 μ g/mouse). In addition, animals were treated with BPDE or BP (initiated) followed by TPA (2x2.5 μ g/week, for 4 weeks) for promotion study. In the continuous treatment of BPDE or BP, animals treated with 40 μ g BP showed 100% tumor response after 20 weeks, 40% of mice for 20 μ g BP, and 20% for (+)BPDE-I, but (-)BPDE-I and 10 μ g BP did not show any tumor response. After 25 weeks, most tumors turned out to be carcinomas in animals treated with 40 μ g BP. In BPDE or BP/TPA initiation-promotion study, papilloma response occurred earlier (6 weeks after TPA treatment) than in continuously treated animals with BPDE or BP.

RT-PCR assay for transgene expression showed that BP or BPDE was not transgene dependent in its tumorigenicity, but TPA was. Several Cytokine genes(TGF- α , TNF- α) and c-myc gene expressions were monitored in skin tissues during BP carcinogenesis. In early stage of BP treatment, the gene expressions were elevated(c-myc, TGF- α) or unchanged(TNF- α) compared to control, but the levels were gradually decreased during both middle and late stages of carcinogenesis. Gene expression levels of skin papillomas in acetone initiated-TPA promoted animals were close to those of middle stage or between middle and late stages. i-NOS was also highly expressed in carcinoma and papilloma. These data suggest that transgene expressions of TG-AC mice were not dependent on BP carcinogenesis and that TG-AC mice were more sensitive to TPA regardless of types of initiators. In addition, genes(TGF- α , c-myc, TNF- α , i-NOS) were modulated in the skin during BP carcinogenesis or TPA promotion.