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Rapid induction of skin and mammary tumors in human c-ha-ras proto-oncogene transgenic rats by treatment with 7,12-dimethylbenz[a] anthracene followed by 12-O-tetradecanoylphorbol 13-acetate

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It is reported that human c-Ha-ras proto-oncogene transgenic rat is highly sensitive to mammary, esophagus and bladder carcinogenesis. In the present study, male and female transgenic and wild-type littermates were topically treated with 2.5 mg of 7,12-dimethylbenz [a]anthracene(DMBA) dissolved in 1.0ml of acetone on the back skin at 50 days after birth. Starting 1 week thereafter, they were again topically treated with 100nm of TPA dissolved in 0.5ml of aceton 3 times weekly for the following 31 weeks. In males treated with DMBA and/or TPA, skin tumors, including both squamous cell papillomas and carcinomas, were preferentially induced at the DMBA-TPA painting sites; DMBA-TPA, 13/15(100%);DMBA, 6/8(75%);TPA,1/6(16/7%), Lesions were thus more frequent in the DMBA-TPA group than with DMBA or TPA alone. In females adenomas and adenocarcinomas of the mammary glands were preferentially induced; DMBA-TPA, 12/14(85.7%); DMBA,6/8(75%);TPA,3/6(50%), with only a few small skin papillomas at painting sites. Incidences and numbers of the mammary and skin tumors were much greater in c-Ha-ras transgenic rats than in their wild-type counterparts. PCR-RFLP analysis of the transgene indicated that percentage of the cell populations harboring a mutation in codons 12 and/or 61 ranged from 2% to 60% in individual tumors; skin tumors showed more mutations in codon 61 in the DMBA-treated groups. In contrast, no mutations were detected in the endogenous rat c-Ha-ras rat is highly susceptible to DMBA-TPA skin and mammary carcinogenesis, thus providing a unique painting model for skin as well as mammary gland carcinogenesis, that would be suitable for investigating the role of transgene mutations.

Keyword : carcinogenesis, c-ha-ras transgenic rat, skin tumor