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Hepatocarcinogenesis by Diethylnitrosamine (DEN) in NADPH Oxidase Knock-Out Mice and Their Wild-Type Counterparts

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Nitrosamines occur in traces in food or may be generated endogenously. They are one chemical factor involved in hepatocarcinogenesis, a process mediated by genotoxic and cytotoxic events. Ethanol is a widely consumed hepatotoxic agent and has been shown to increase hepatocarcinogenesis in humans. Cytotoxic reactive oxygen species (ROS) and TNF-α production, and DNA damage increased after DEN treatment in wild-type (wt) mouse liver but not in p47-NADPH oxidase knockout (phox-ko) mice [Teufelhofer et al.: Carcinogenesis 2005; 26: 319–329]. Therefore we examined if phox-ko mice might be protected from hepatocarcinogenesis. Two models were employed: (1) treatment of neonatal mice with a single dose of DEN and later with three cytotoxic doses of DEN at 7 week intervals. (2) Initiation of carcinogenesis in 6 week old mice and subsequent promotion by either feeding a phenobarbital diet or providing ethanol in the drinking water. Here we present the macroscopic findings: (1) was a powerful regimen and produced tumors in almost all wt mice after 30 wks. However, some phox-ko mice also developed tumors. (2) Phenobarbital was a strong tumor-promoting agent producing more tumors in wt than in phox-ko. Ethanol proved to be much weaker but it enhanced tumorigenesis in wt and less so in phox-ko. Oxidative DNA lesions were higher in wt than in phox-ko liver DNA. Thus, ROS generation appears to be an important mechanism in DEN carcinogenesis but other factors seem to be involved, as exemplified by tumor development in phox-ko mice.

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