Localization of oxidative damage by a glutathione-gamma-glutamyl transpeptidase system in preneoplastic lesions in sections of liver from carcinogen-treated rats

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Previous studies from our laboratories have shown that catabolism of glutathione (GSH) by gamma-glutamyl transpeptidase (GGT) in the presence of transition metals leads to oxidative damage (OD). This damage is exemplified in vitro by GGT-dependent GSH mutagenesis which involves reactive oxygen species and by GGT-dependent accumulation of lipid peroxidation (LPO) products in systems containing polyunsaturated fatty acid and GSH. In order to test whether catabolism of GSH by membranal GGT in enzyme-altered preneoplastic hepatic lesions can induce oxidative damage in situ, and to test whether the OD is localized in these lesions, 21 day old Fischer rats were treated with 12 mg/kg diethylnitrosamine (DEN) followed by 0.1% or 0.25% Phenobarbital (PB) in the diet. Cryostat sections were examined histochemically for GGT-rich hepatic lesions. Adjacent section were incubated with GSH and iron and examined for areas staining for lipid peroxidation. Distinct LPO-positive areas were shown to corresponded well with the GGT-positive hepatic lesions. Promotion with 1.25% PB led to increasing proportions of LPO-positive lesions depended on the presence of GSH and iron, and was not observed following chelation of iron by diethyl triaminopentaacetic acid (DATPA), in the presence of acivicin, an inhibitor of GGT, or in the presence of the radical scavenger butylated hydroxytoluene affecting GSH-GGT-driven LPO in vitro, and were similar to those affecting oxidative GSH-mutagenesis catalyzed by GGT. The results indicate that metabolism of GSH by GGT in preneoplastic liver foci can initiate an oxidative process leading to a radical-rich environment and to oxidative damage. Such damage may contribute to the processes by which cells within such foci progress to malignancy.

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