## REACTIVE OXYGEN SPECIES (ROS) AND OXIDATIVE DAMAGE IN TERATOGENESIS.

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Using xenobiotics (phenytoin, thalidomide, BENZO(A)PYRENE (B[a]P)) and gamma irradiation, we examined the teratologic relevance of embryonic bioactivation by prostaglandin H synthases (PHSs), ROS-mediated oxidative macromolecular target damage and signal transduction, and putative DNA repair in mouse, rat and rabbit models. The xenobiotics were bioactivated by purified PHS to free radical intermediates. PHS-2 expression was high in mouse embryos during organogenesis, xenobiotic embryopathy was reduced by PHS inhibitors and in PHS-1 and PHS-2 knockout mice. Xenobiotic bioactivation, DNA/protein oxidation and embryotoxicity occurred in embryo culture. in vivo embryonic DNA oxidation was reduced to baseline within 24 hr, indicating active DNA repair. Treatment with antioxidative enzymes increased embryonic antioxidative activity, blocked DNA oxidation and inhibited teratogenicity, as did free radical trapping agents and antioxidants. Thalidomide embryonic DNA damage occurred only in susceptible (rabbit) but not resistant (rodents) species. Hydroxyl radicals were formed in vivo, and teratogenicity increased either with mutant mice deficient in the antioxidative enzyme glucose-6-phosphate dehydrogenase, GSH depletion, or inhibition of GSH peroxidase or GSH reductase. Nitric oxide synthases (NOSs) likely contribute to ROS-mediated teratogenesis, since iNOS knockout mice were partially protected. Inhibition of Ras reduced embryotoxicity, implicating ROS-mediated signal transduction. DNA may be a teratologically important target for oxidative lesions, since Atm and p53 knockout mice were more susceptible to teratogenesis, in some cases independent of apoptosis. These studies suggest that embryonic processes regulating the balance of ROS signaling, oxidative DNA damage and repair may be important determinants of teratologic risk.