OXIDATIVE DAMAGE, DNA REPAIR AND SIGNAL TRANSDUCTION IN CHEMICAL TERATOGENESIS.

Peter G Wells[1,2], Yadvinder Bhuller[1], Connie S Chen[1], Jeffrey T Henderson[1], Winnie Jeng[1], Sonja Kasapinovic[1], Julia C Kennedy[1], Rebecca R Laposa[1], Christopher J Nicol[2], Toufan Parman[1], Michael J Wiley[3], Louise M Winn[1] and Andrea W Wong[1]. [1]Faculty of Pharmacy and Depts. of [2]Pharmacology and [3]Surgery, University of Toronto, Toronto, Ontario, Canada.

Embryonic prostaglandin H synthases (PHSs) and lipoxygenases bioactivate xenobiotics (phenytoin, thalidomide, benzo[a]pyrene) to free radical intermediates that initiate reactive oxygen species (ROS) formation, which oxidatively damage cellular macromolecules and/or alter signal transduction. Embryonic DNA oxidation is repaired within 24 hr. Oxidative DNA damage and embryopathies are reduced in PHS knockout mice, and in mice treated with PHS inhibiters, antioxidative enzymes, antioxidants and free radical trapping agents. Thalidomide causes embryonic DNA oxidation in susceptible (rabbit) but not resistant (mice) species. Embryopathies are increased in mutant mice deficient in the antioxidative enzyme glucose-6-phosphate dehydrogenase (G6PD), or by glutathione (GSH) depletion, or inhibition of GSH peroxidase or GSH reductase. Inducible nitric oxide synthase knockout mice are partially protected. Inhibition of Ras or NF-kB pathways reduces embryopathies, implicating ROS-mediated signal transduction. Atm and p53 knockout mice deficient in DNA damage response/repair are more susceptible to xenobiotic or radiation embryopathies, implicating a teratological role for DNA damage. Even endogenous embryonic oxidative stress carries a risk, since untreated G6PD- or ATM-deficient mice have increased embryopathies. Thus, embryonic processes regulating the balance of ROS signaling, oxidative DNA damage and repair may be important determinants of teratologic risk.
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