IN UTERO ORIGINS OF CANCER IN p53 KNOCKOUT MICE: MATERNAL DIETARY VITAMIN E, FETAL OXIDATIVE DNA DAMAGE AND POSTNATAL CARCINOGENESIS

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1. Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; 2. Dept. of Pharmacology, University of Toronto, Toronto, ON, Canada Reactive oxygen species (ROS), including hydroxyl radicals, can oxidatively damage cellular macromolecules such as lipids, proteins and DNA. ROS-mediated oxidative stress and macromolecular damage have been implicated in cancer initiation and promotion, and the embryo has limited protective antioxidative mechanisms, leaving it at potentially greater risk. We have previously shown that maternal supplementation with the antioxidant vitamin E (VE) alters levels of endogenous embryonic DNA oxidation. Here, to determine whether cancer can have in utero origins, we examined the effect of maternal dietary VE (dl-a-tocopherol-acetate) supplementation on spontaneous postnatal tumorigenesis, using high-dose VE and the cancer-prone p53 knockout mouse model. Virgin heterozygous (+/-) p53-deficient females were placed on either a normal or 10% [w/w] VE-supplemented diet for 4 weeks and mated with +/- p53-deficient males. VE supplementation was stopped on the day of birth. The offspring were p53-genotyped and observed for spontaneous tumor development. Compared to offspring from dams supplemented with control diet, in utero exposure to VE enhanced spontaneous tumor formation in both +/- and -/- p53-deficient offspring. At 40 weeks of age, VE-exposed -/- p53 pups had less than half the survival rate of -/- p53 control offspring (22% vs. 49%) ($p<0.02$). Among +/- p53 offspring, 78% of the VE offspring were still alive at 40 weeks of age, compared to 92% in the control group ($p<0.04$). This tumorigenic enhancement is consistent with a study in CD-1 mice in which high-dose VE failed to reduce endogenous fetal DNA oxidation, and shows that high-dose VE can exacerbate rather than block some ROS-mediated pathologies. These preliminary results indicate that some cancers originate in utero and can be substantially modified by altering embryonic redox status, suggesting novel carcinogenic mechanisms and potential therapeutic strategies.