Title
Levels of Kras Codon 12 Mutations in Mouse Ovary Measured by ACB-PCR Were Not Increased by Transplacental Exposure to benzo[a]pyrene or Impacted by Gclm Genotype

Permalink
https://escholarship.org/uc/item/13f2136w

Journal
ENVIRONMENTAL AND MOLECULAR MUTAGENESIS, 56

ISSN
0893-6692

Authors
Parsons, BL
Banda, M
Myers, MB
et al.

Publication Date
2015-08-01

Peer reviewed
Levels of *Kras* Codon 12 Mutations in Mouse Ovary Measured by ACB-PCR Were Not Increased by Transplacental Exposure to benzo[a]pyrene or Impacted by *Gclm* Genotype. Parsons BL\(^1\), Banda M\(^1\), Myers MB\(^1\), McKim KL\(^1\), Ortiz L\(^2\), Luderer U\(^2\). \(^1\)National Center for Toxicological Research, US FDA, Jefferson, AR, United States, \(^2\)University of California, Irvine, Irvine, CA, United States.

ACB-PCR, a sensitive DNA-based method for quantifying cancer-driver mutations, has been used to demonstrate: 1) relatively high levels of *KRAS* mutations are frequently present in normal rodent and human tissues, 2) human tumors frequently carry *KRAS* mutant subpopulations, thus *KRAS* mutation contributes to a greater fraction of human cancers than is recognized, and 3) increased levels of *Kras* mutation may occur following short-term exposure to carcinogens. *KRAS* is the fourth most frequently mutated gene in ovarian cancer, with two specific mutations accounting for 73% of those reported (G12D, 41%; G12V, 32%). This study investigated the utility of ACB-PCR in evaluating the transplacental mutagenesis of benzo[a]pyrene, in the presence and absence of Gclm-deficiency. Our prior study showed *Gclm*−/− mice have increased sensitivity to ovarian tumorigenesis induced by prenatal benzo[a]pyrene exposure. Gclm is the modifier subunit of glutamate cysteine ligase, which catalyzes the rate limiting step in glutathione biosynthesis. C57Bl/6J (*Gclm* heterozygous) dams were gavaged with 2 mg/kg/day benzo[a]pyrene or the sesame oil vehicle on gestational days 6.5-15.5. Ovaries of female offspring (*Gclm*+/+, *Gclm* +/−, and *Gclm*−/−) were harvested at first vaginal estrus (postnatal day 34-46) and *Kras* codon 12 GAT and GTT mutations (G12D and G12V, respectively) were quantified. Measureable levels of *Kras* mutation were present in all ovarian DNA samples, with geometric mean mutant fractions (MFs) of 6.11 x 10\(^{−5}\) and 1.07 x 10\(^{−4}\) for G12D and G12V in *Gclm*+/+ vehicle control mice, respectively. No significant changes in *Kras* MF were observed due to benzo[a]pyrene-treatment, *Gclm* genotype, or their interaction.