P69

***DUN1*-Mediated Pathway That Controls Ribonucleotide Reductase Induction is Required for Both Aflatoxin B1 (AFB1)-Associated Sister Chromatid Exchange (SCE) and Mutation in *Saccharomyces cerevisiae* (Yeast).** Fasullo MT[1,3], Sun M[3], Egner P[2]. [1]State University of New York at Albany, Albany, NY, United States, [2]Johns Hopkins University, Baltimore, MD, United States, [3]Ordway Research Institute, Abany, NY, United States.

Introduction: The mycotoxin aflatoxin B1 (AFB1) is an extremely potent liver carcinogen produced by *Aspergillus flavus* that contaminates food supplies in tropical regions. Epidemiological data indicate that the p53 Ser249 mutation present in hepatocellular carcinoma correlates with AFB1 exposure. The genetic control of AFB1-induced mutation and genomic instability phenotypes is not well understood. However, AFB1-associated mutation frequencies in yeast are enhanced in *rad51* mutants, defective in homologous recombination, suggesting that a common AFB1-associated DNA adduct could stimulate either recombination or mutation. We asked whether there are particular checkpoint genes that channel DNA damage tolerance pathways towards recombination vs. mutation. Methods: We have designed yeast strains that can detect AFB1-associated SCE and mutation events. These yeast strains contain plasmids expressing human cytochrome P450 genes (CYP1A1 or CYP1A2) and the corresponding human oxido-reductase (hOR). Results: Microarray experiments have revealed that 15 DNA repair genes, including *RAD51, MLH1,* and *SRS2,* are induced in following AFB1 exposure in concentrated diploid cells (Keller-Seitz et al., 2004). Interestingly, in log phase cells, genes encoding ribonucleotide reductase (RNR) subunits are also induced (Guo et al., 2006). In yeast, RNR induction is controlled by the *MEC1* (ATR)-dependent signaling pathway, which includes Rad53 and Dun1. Activation of Rad53 (CHK2) requires *MEC1*. *MEC1*, *RAD53*, and *DUN1* are all required for AFB1-associated mutation and SCE. Interestingly, *DUN1* is not required for UV-associated AFB1-associated mutation or SCE. Discussion: We speculate that the AFB1-associated foramidopyrimidine (FAPY) and N7-guanine may impede DNA replication and subsequently stimulate SCE or mutation. After yeast were exposed to 50 μM AFB1 for four hours, we detected N7-guanine AFB1 DNA adducts and FAPY derivatives in both the wild type and *rad53* mutant strains, using mass spectroscopy (LC/ESI/MS). Thus, the genetic requirements of AFB1-associated mutagenesis and recombination involve checkpoint genes that induce dNTP levels, which are not required for UV-associated mutation.

P70

Gene Expression Profiles in Normal Human Mammary Epithelial Cells (NHMECs) Exposed to Benzo(a)pyrene (BP) in the Presence or Absence of Chlorophyllin. John K[1,2], Keshava C[3], Richardson DL[2], Weston A[1,2], Nath J[1]. [1]West Virginia University, Morgantown, WV, United States, [2]National Institute for Occupational Safety and Health, CDC, Morgantown, WV, United States, [3]National Center for Environment Assessment, USEPA, Washington, DC, United States.

A panel of six NHMEC strains developed from breast tissue discarded at reduction mammoplasty was exposed to the ubiquitous carcinogen BP, both in the presence or absence of the chemopreventive agent chlorophyllin. Three exposure regimens were used: T1- solvent control (24h), T2- BP alone (24h), T3- 24h pretreatment with chlorophyllin followed by BP and chlorophyllin together (24h). Hu-Gene 133A arrays (Affymetrix, Santa Clara, CA) were used for expression analysis and the data analyzed using Microarray Suite 5.0 and Cluster and Tree View software. Genes altered by three fold or greater were considered for pathway analysis. Cross-talk among immune response genes were determined using Pathway Studio (Ariadne Genomics, Rockville, MD) and ArrayXPath software. A total of 49 genes were altered in T2 of which 43 were up-regulated and six down-regulated. A total of 125 genes were altered in T3 of which 103 were up-regulated and 22 down-regulated. The only gene up-regulated by more than three fold in all six cell strains was *CYP1B1*. Five immune response genes altered in T2 exhibited 2248 interactions involving a total of 1485 other genes. Twenty-four immune response genes altered in T3 exhibited 5782 interactions involving a total of 2299 other genes. Various immune response genes altered in T2 and T3 shared statistically significant associations ($p < 0.05$) with various pathways including: Biocarta, GenMAPP, PharmGKB and KEGG. These studies begin to define a role for carcinogen-induced immune response genes in human chemical carcinogenesis, and further suggest that the modulatory role of chlorophyllin in PAH mediated carcinogenesis may be mediated in part by interactions involving genes and pathways altered by BP exposure.