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Mutation Research 577S (2005) e1–e256

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Fundamental and Molecular  
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**9<sup>th</sup> International Conference on  
Environmental Mutagens  
&  
36<sup>th</sup> Annual Meeting of the Environmental  
Mutagen Society**

# **Abstracts**

**September 3-9, 2005**

**Hyatt Regency at the Embarcadero Center  
San Francisco, California, USA**

(Abstracts are numbered according to their presentation order. For schedule information, please reference the final Program.)

The Abstracts of the 9th International Conference on Environmental Mutagens and 36th Annual Meeting Environmental Mutagen Society will also be published as an e-supplement to the September 2005 issue of *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis* and can be found at <http://www.sciencedirect.com/science/journal/00275107>

**17 THE POLQ FAMILY AND DNA DAMAGE TOLERANCE IN HUMAN CELLS.** Wood RD. University of Pittsburgh, Pittsburgh, PA, United States.

It is remarkable that about fourteen distinct nuclear DNA polymerases are encoded in the human genome. Many of these have functions in DNA repair and mutagenesis. POLQ (pol theta) is an A-family DNA polymerase in mammalian cells (Seki, M. 2003. *Nucleic Acids Res* 31:6117). There are no yeast homologs, but a POLQ homolog in *Drosophila* nuclei called Mus308 apparently functions in a pathway of DNA cross-link repair or tolerance. POLQ and Mus308 have a characteristic three-domain organization with a helicase-like domain in the N-terminal portion, a less conserved central domain which is largely derived from one large exon, and a C-terminal A-family polymerase domain. Mouse *Polq* is the gene defective in the *chaos1* mouse mutant, isolated by Schimenti and co-workers (Shima et al. *Mol Cell Biol* 24:10381). This presentation will discuss the properties of POLQ that allow it to bypass some types of DNA damage, and perhaps participate in other DNA damage processing (Seki et al. 2004. *EMBO J* 23:4484). The latest information on properties of two further human enzymes related to POLQ and Mus308, called HEL308 and POLN will also be discussed.

**18 ROLE OF THE FANCONI ANEMIA CORE COMPLEX IN RESPONSE TO DNA DAMAGE.** Meetej AR<sup>1</sup>, de Winter JP<sup>2</sup>, Medhurst AL<sup>2</sup>, Xue Y<sup>1</sup>, Ling C<sup>1</sup>, Levitus M<sup>1</sup>, Wallisch M<sup>3</sup>, Waisfisz Q<sup>2</sup>, Yan Z<sup>1</sup>, van de Vrugt HJ<sup>2</sup>, Bishop CE<sup>4</sup>, Hoatlin ME<sup>3</sup>, Joenje H<sup>4</sup>, Wang W<sup>1</sup>. <sup>1</sup>National Institute on Aging/NIH, Baltimore, MD, United States, <sup>2</sup>VU University Medical Center, Amsterdam, Netherlands, <sup>3</sup>Oregon Health and Science University, Portland, OR, United States, <sup>4</sup>Baylor University of Medicine, Houston, TX, United States.

Monoubiquitination of FANCD2 is a key step in a DNA damage response network involving Fanconi anemia (FA) proteins as well as the breast cancer susceptibility gene products, BRCA1 and BRCA2. We have previously purified a FA core complex containing 9 polypeptides. Five of them correspond to previously characterized FA proteins (FANCA, C, E, F and G) which are required for FANCD2 monoubiquitination. We have identified the four new components of the FA core complex by mass spectrometry. These proteins, termed FAAPs (for FANCA-associated polypeptides), were found to be integral components of the FA core complex by immunoprecipitation-coupled immunoblotting analyses. Depletion of any one of these proteins by siRNA drastically reduces monoubiquitination of FANCD2, suggesting that they are all required for the function of the FA core complex and thus considered to represent candidate-FA genes. One component, FAAP95, is the FA protein defective in complementation group B (FANCB) patients. A second component, FAAP43, represents a new FA complementation group gene product, FANCL (PHF9). Importantly, FANCL has an auto-ubiquitin ligase activity *in vitro* and is required for FANCD2 monoubiquitination *in vivo*, suggesting that the FA core complex is an E3 ubiquitin ligase complex necessary for FANCD2 monoubiquitination. The gene encoding the third protein, FAAP250, was also found to have biallelic mutations in FA patients of a new complementation group (FANCM). No patients have yet been identified with mutations in the gene encoding FAAP100. Our study has identified at least three new FA genes. The fact that all these proteins are required for FANCD2 monoubiquitination is consistent with a model that the entire FA core complex is a FANCD2 monoubiquitination machine with FANCL as its catalytic subunit. The biochemical function and interactions of these new subunits will be discussed. References: *Nature Genetics* 35 (2003)165; *Nature Genetics* 36 (2004) 1219.

**19 NOVEL MOUSE CHROMOSOME INSTABILITY MUTANTS ISOLATED BY FORWARD GENETIC MUTAGENESIS SCREENS.** Shima N, Hartford S, Schimenti J. Cornell University, Ithaca, NY, United States.

Genomic instability is a hallmark of cancer. To identify novel genes required for maintenance of genomic stability in mice, we conducted forward genetic mutagenesis screens for chromosome instability mutants. Deviants were identified using a flow cytometric peripheral blood micronucleus assay, and two of the mutations have now been cloned. *chaos1* (chromosome aberrations occurring spontaneously 1), which exhibits properties consistent with a defect in homologous recombination or interstrand crosslink repair, is an allele of *Polq*, which encodes the translesion synthesis DNA polymerase  $\theta$ . While mutant mice are not cancer prone, homozygosity for ATM and POLQ nulls results in a synthetic lethality. The second mutation, which causes extremely high levels of chromosome instability, has characteristics of a defect in replication rather than double strand break repair. Positional cloning led to the identification of a hypomorphic mutation in *Mcm4* (Minichromosome maintenance deficient 4), an essential eukaryotic gene required for licensing of replication origins, and which encodes a subunit of the presumptive replicative helicase. Homozygous females are highly susceptible to mammary adenocarcinomas. Details of the phenotypic and molecular characterization of these mouse models will be presented.

**20 CANCER-ASSOCIATED MUTANTS OF DNA POLYMERASE BETA.** Sweasy JB, Dalal S, Lang T, DiMaio D, Starcevic D. Yale University School of Medicine, New Haven, CT, United States.

Thirty percent of the 189 tumors studied to date express DNA polymerase beta variants. Some of these variants induce cellular transformation, as assessed by focus formation and anchorage independent growth, when expressed in mouse C127 cells. Expression of wild type DNA polymerase does not induce cellular transformation. Strikingly, cellular transformation does not require continuous expression of the polymerase beta variant proteins, implying that it has a mutational basis. The variants that induce cellular transformation do not appear to increase the overall mutation frequency. Instead, the tumor-associated polymerase beta variants induce different types of mutations than those normally induced by the wild-type enzyme. Examples include expansions of dinucleotide repeat sequences, frameshift mutations within dipyrimidine motifs, and a propensity to induce transversions. We suggest that in cells, the polymerase beta variants induce mutations that are not normally induced by the wild type protein. Mutations that occur in key growth control genes have the potential to lead to tumorigenesis or more aggressive disease. Because DNA polymerase beta functions in base excision repair, our results suggest that mutations that arise during this process can lead to the onset or progression of cancer.

**21 INCORPORATING HORMESIS INTO THE RISK-ASSESSMENT PARADIGM.** Paustenbach D. ChemRisk, Inc., San Francisco, CA, United States.

Hormesis is a phenomenon which has been recognized to exist within biological systems for many decades. Basically, contrary to the classic view that "dose makes the poison", hormesis illustrates that very low doses of some chemicals can often produce a lesser incidence of adverse responses than that observed in control groups (e.g., below the background rate). If this phenomenon were to be considered within regulatory policy in the United States and elsewhere, its impact on the degree to which chemicals are regulated could be substantial. For example, for the carcinogens, if hormesis were incorporated into the mathematical models for estimating the risk at low doses, then much higher "acceptable" or tolerable levels of exposure would be identified. A number of suggestions about how this phenomenon should be evaluated will be offered and the impediments to having it adopted by regulatory agencies will be discussed.