

Intramural papers of the month

By Simone Otto, Jacqueline Powell, Deepa Singh, Shannon Whirlledge, and Qing Xu

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NTP finds a better animal model to evaluate the effects of chemical exposure

Researchers from the National Toxicology Program used a genetically diverse mouse model to predict the range of toxicity that might be observed in humans after exposure to benzene, a common air pollutant and known human carcinogen. Using Diversity Outbred (DO) mice, the study estimated a benzene exposure threshold of 0.205 parts per million, which is consistent with observations of response in humans but is well below the value previously obtained using inbred mice. This study demonstrates the value of using a model, such as DO mice, that better reflects the genetic variability and range of response seen in human populations.

To evaluate the response to benzene, the scientists measured the frequency of micronucleated red blood cells in each genetically unique DO mouse, before and after inhalation exposure to benzene. Micronuclei are standard biomarkers of chromosomal damage. At the end of the 28-day exposure period, a reproducible, dose-dependent increase in benzene-induced chromosomal damage was observed. Importantly, a marked variation in response was seen among the mice, with some mice showing no increase in micronuclei and others showing large increases. Using genetic mapping and linkage analysis, the researchers identified a locus associated with resistance to benzene-induced genotoxicity on mouse chromosome 10. Sulfotransferases located in this region are likely candidate genes for benzene resistance. **(DS)**

Citation: French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA.

(<http://www.ncbi.nlm.nih.gov/pubmed/25376053>)

2014. Diversity outbred mice identify population-based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ Health Perspect* 122:711–718. [[Story](#)]

Time-lapse crystallography reveals link between oxidative stress and disease

NIEHS researchers and their collaborators have discovered how oxidative stress can lead to blocked DNA repair, which is implicated in many human diseases. For the first time, researchers were able to visualize how oxidized DNA nucleotides are incorporated during replication, and how a cell discriminates between damaged and undamaged substrates. These findings could lead to a better understanding of how DNA damage, stemming from environmental exposures, leads to diseases such as cancer.

Environmental chemicals, including air pollution, flame retardants, and phthalates, induce oxidative stress, which reflects an imbalance between damage and the body's ability to repair the damage. Oxidative stress can result in an accumulation of damaged DNA substrates that, when incorporated into DNA, results in DNA breaks, genomic instability, and disease.

Utilizing time-lapse crystallography, a method that allows the visualization of DNA synthesis over time, the researchers found that the incorporation of oxidized DNA substrates confounds later stages of DNA repair, which ultimately may lead to breaks in the DNA and cell death. Interestingly, cancerous cells are able to escape cell death in an environment with more oxidative stress by removing oxidized DNA substrates. Targeting the way cancer cells handle oxidative stress may lead to more effective treatments. **(SW)**

Citation: Freudenthal BD, Beard WA, Perera L, Shock DD, Kim T, Schlick T, Wilson SH.

(<http://www.ncbi.nlm.nih.gov/pubmed/25409153>)

2014. Uncovering the polymerase-induced cytotoxicity of an oxidized nucleotide. *Nature*; doi:10.1038/nature13886 [Online 17 November 2014]. [[Story](#)]

MED25 mediates epigenetic regulation of human drug metabolism gene CYP2C9

NIEHS researchers revealed that Mediator subunit MED25 dictates the status of histone H3K27 to regulate the expression of

CYP2C9, which is one of the cytochrome P450 (CYP) enzymes that clear pharmaceutical compounds and other chemicals in the liver. The study delineates epigenetic mechanisms underlying regulation of CYP2C9 and other CYP genes.

MED25 is a component of Mediator complex that interacts with transcription factors and RNA polymerase II to initiate the transcription of target genes. Previous studies from the same group of scientists showed that transactivation of CYP2C9 involves association of MED25 with nuclear receptor HNF4alpha at corresponding promoter binding sites. In this paper, the researchers further dissected the role of MED25 in epigenetic regulation of CYP2C9 expression.

After overexpressing or silencing MED25 in HepG2 cells, the researchers found a MED25-dependent change in H3K27 modifications. In the presence of MED25, the HNF4alpha binding region of the CYP2C9 promoter was enriched with the activating marker H3K27ac and other coactivators that acetylate histone. MED25 also induced a permissive chromatin conformation that allowed increased gene expression. In contrast, absence of MED25 led to accumulation of the repressing marker H3K27me3 and recruitment of PRC2, which trimethylated H3K27 and suppressed expression. These results suggest an essential role of MED25 in activation of a number of HNF4alpha inducible genes. **(QX)**

Citation: [Englert NA, Luo G, Goldstein JA, Surapureddi S.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/25391650>

2014. Epigenetic modification of histone 3 lysine 27: Mediator subunit MED25 is required for the dissociation of Polycomb repressive complex 2 from the promoter of cytochrome P450 2C9. *J Biol Chem*; doi:10.1074/jbc.M114.579474 [Online 12 November 2014].

Researchers find protein involved in glucocorticoid-resistant asthma

In an article published in *Mucosal Immunology*, NIEHS researchers revealed a novel mechanism that gives rise to a form of asthma dominated by neutrophilic inflammation. Neutrophilic asthma, unlike eosinophilic asthma, is resistant to standard treatment with inhaled glucocorticoids. It stems from lung dendritic cells expressing TIR-domain-containing adapter-inducing interferon-beta (TRIF) protein.

The scientists sensitized TRIF knockout mice to ovalbumin by allowing them to inhale this protein after mixing it with extracts of common house dust that contain lipopolysaccharide, a component of bacteria known to increase T helper 17 (Th17) cells. When subsequently challenged with aerosolized ovalbumin, the TRIF knockout mice had fewer Th17 cells, fewer neutrophils, and less airway constriction compared with similarly treated wild-type mice. Furthermore, dendritic cells from lungs of the TRIF knockout mice expressed very little CD40 and poorly stimulated Th17 cell differentiation in cell culture.

The researchers' demonstration that the CD40-TRIF-Th17 pathway leads to neutrophilic asthma suggests that small molecules that inhibit this pathway might be effective for treating neutrophilic asthma, without adversely affecting other immune functions in the lungs. **(SO)**

Citation: [Hsia BJ, Whitehead GS, Thomas SY, Nakano K, Gowdy KM, Aloor JJ, Nakano H, Cook DN.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24985082>

2014. Trif-dependent induction of Th17 immunity by lung dendritic cells. *Mucosal Immunol* 8(1):186-197.

Ambient air pollution increases the risk of asthma and wheeze in adult women

NIEHS researchers and collaborators reported that long-term exposure to particulate matter less than 2.5 micrometers in diameter (PM 2.5) increases the risk of developing asthma and wheeze in adult women. Previous research was done primarily in children and demonstrated an association between air pollution and the development of childhood asthma. No studies in adults have examined exposure to PM 2.5.

Using PM 2.5 and nitrogen dioxide (NO₂) concentrations estimated in the Sister Study, a nationwide cohort study of more than 50,000 U.S. women, researchers examined how ambient air pollution was related to follow-up self-reports of wheeze, chronic cough, and doctor diagnosed asthma in women without baseline symptoms. PM 2.5 and NO₂ concentrations were estimated at participants' primary addresses at the time of study enrollment, and annual averages were then derived from a national network of air pollution monitoring stations. In addition to the associations with PM_{2.5}, there was evidence for an association of NO₂ with wheeze.

Because the maximum estimated participant exposure in this analysis was less than the current Environmental Protection Agency's National Ambient Air Quality Standard, these results suggest that respiratory effects can be seen at levels well below the current national standards. **(JP)**

Citation: [Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/25172226>

2014. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 190(8):914-921.

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