

Extramural papers of the month

By Nancy Lamontagne

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Superfund Research Program
Research Brief. New issues
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New animal model reveals role of abnormal DNA repair in lupus

An NIEHS grantee and colleagues discovered that a genetic mutation involved in DNA repair leads to lupus in mice. Their new mouse model of lupus could provide insight into the environmental mechanisms of the disease and, potentially, other autoimmune diseases.

The lack of an animal model has hindered research of systemic lupus erythematosus (SLE), which causes widespread inflammation in internal organs, joints, and the nervous system. Genome-wide association studies have suggested that a mutation in the gene coding for DNA polymerase beta (Pol B) is involved in SLE. DNA Pol B is a key enzyme in the genome integrity process of base excision repair, which defends cells and organisms against direct insults to DNA.

To determine if decreased DNA Pol B activity results in SLE, the researchers genetically engineered mice to express lower amounts of the enzyme. The mutant mice developed lupus-like disease and shorter antibody heavy-chain junctions. They also showed dramatically increased levels of somatic hypermutation, a process by which the immune system adapts to new foreign elements. The researchers say their findings suggest that mutations in DNA repair genes, associated with immunological processes, could lead to the development of autoimmune disease, including SLE.

Citation: [Senejani AG, Liu Y, Kidane D, Maher SE, Zeiss CJ, Park HJ, Kashgarian M, McNiff JM, Zeltermann D, Bothwell AL, Sweasy JB.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24388753>)

2014. Mutation of POLB Causes Lupus in Mice. *Cell Rep* 6(1):1-8.

Developmental exposure to BPA increases prostate cancer risk

NIEHS grantees report that exposure to bisphenol A (BPA) during development increases the risk for cancer in human prostate tissue. The researchers believe that BPA reprograms prostate stem cells to be more sensitive to estrogen throughout life, leading to increased susceptibility to diseases, including cancer.

To investigate the effect of BPA on human cells, the researchers implanted mice with epithelial stem-like cells cultured from prostates of young, disease-free men. Prostate stem cells arise during early fetal development and produce and maintain a man's prostate tissue throughout his life. To mimic exposure to BPA during embryonic development, the mice were fed 100 or 250 micrograms of BPA per kilogram body weight for two weeks following implantation, the time during which the cells produced humanized prostate tissue. The BPA fed to the mice was equivalent to levels ingested by the average person.

The researchers found that 33 to 36 percent of tissue samples taken from the mice fed BPA had either precancerous lesions or prostate cancer, compared to only 13 percent for a control group of mice. For mice that received prostate stem cells exposed to BPA before implantation, and then were continuously exposed to BPA as the stem cells produced prostate tissue, 45 percent of the tissue samples had precancerous lesions or cancer.

Citation: [Prins GS, Hu WY, Shi GB, Hu DP, Majumdar S, Li G, Huang K, Nelles J, Ho SM, Walker CL, Kajdacsy-Balla A, van Breemen RB.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24424067>)

2014. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. *Endocrinology*; doi: <http://dx.doi.org/10.1210/en.2013-1955>

(<http://dx.doi.org/10.1210/en.2013-1955>)

[Online 1 January 2014].

Human stem cells reveal gene-environment interaction in Parkinson's disease

Researchers, supported in part by NIEHS, used human stem cells derived from Parkinson's disease patients to show that a gene mutation, combined with exposure to pesticides, produces free radicals in neurons, leading to nerve cell death. Prior to this work, the link between pesticides and Parkinson's disease was based mostly on animal studies and epidemiological research.

Parkinson's disease is characterized by loss of dopamine-containing neurons in the substantia nigra, a structure located in the midbrain that plays an important role in reward, addiction, and movement. Using the human stem cell model, researchers created two sets of dopamine-containing neurons that were genetically identical, except for an alpha-synuclein mutation in one set of neurons. The researchers exposed the cells to pesticides, including paraquat, maneb, and rotenone. In the cells with the mutation, they observed excessive free radicals, as well as damage to the dopamine-containing neurons, which led to cell death. The detrimental effects were observed even with short exposures to doses well below EPA-accepted levels.

The genetically matched neurons revealed that, in the cells with the mutation, exposure to pesticides disrupts a key mitochondrial pathway that normally protects dopamine-containing neurons. Using high-throughput screening, the researchers identified a molecule called isoxazole that protected mutant neurons from cell death induced by the tested pesticides. Since several FDA-approved drugs contain derivatives of isoxazole, these findings may have potential clinical implications for treating Parkinson's.

Citation: Ryan SD, Dolatabadi N, Chan SF, Zhang X, Akhtar MW, Parker J, Soldner F, Sunico CR, Nagar S, Talantova M, Lee B, Lopez K, Nutter A, Shan B, Molokanova E, Zhang Y, Han X, Nakamura T, Masliah E, Yates JR 3rd, Nakanishi N, Andreyev AY, Okamoto S, Jaenisch R, Ambasudhan R, Lipton SA.

(<http://www.ncbi.nlm.nih.gov/pubmed/24290359>)

2013. Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1alpha transcription. *Cell* 155(6):1351-1364.

Simulation helps prioritize housing interventions based on health outcomes and costs

An NIEHS grantee and colleagues used their pediatric asthma model to simulate the effects of environmental factors, medication compliance, seasonality, and medical history on indoor pollutant concentrations and asthma outcomes. The simulation provided information that can be used to prioritize individual and building interventions, based on how they affect health outcomes and costs.

The researchers applied their previously developed discrete event simulation model of pediatric asthma, to estimate the potential effect of multiple building interventions in low-income multifamily dwellings. They focused on comparing health care use with the estimated costs of implementing interventions. Interventions such as integrated pest management and repairing kitchen exhaust fans led to 7 to 12 percent reductions in serious asthma events, with payback periods of one to three years. Weatherization efforts aimed only at tightening the separation between the interior and the exterior environments of a building led to 20 percent more serious asthma events. However, combining this weatherization with repairing kitchen exhaust fans and eliminating indoor pollution sources mitigated this effect.

The researchers say that their findings increase physicians' understanding of the effect that home environmental changes have on asthma, thus bridging the gap between environmental health and clinical science.

Citation: Fabian MP, Adamkiewicz G, Stout NK, Sandel M, Levy JI.

(<http://www.ncbi.nlm.nih.gov/pubmed/23910689>)

2014. A simulation model of building intervention impacts on indoor environmental quality, pediatric asthma, and costs. *J Allergy Clin Immunol.* 2014 Jan. 133(1):77-84.

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