Extramural papers of the month

By Nancy Lamontagne

- Mouse study points to possible gene-environment interaction for schizophrenia
- Improving health for low-income workers
- Metabolomics reveals early changes in metabolic pathways for Alzheimer’s disease
- Brd4 insulates chromatin from DNA damage signaling

Mouse study points to possible gene-environment interaction for schizophrenia

An NIEHS grantee reports that mice engineered with a genetic risk factor for schizophrenia, and exposed to lead during early life, showed schizophrenia-like behaviors and structural changes in their brains. The findings suggest a gene-environment interaction is at work, and supports the hypothesis that environmental contaminants could contribute to the development of mental disorders in susceptible people.

Recent studies in people suggest a possible association between prenatal exposure to lead and increased likelihood of developing schizophrenia later. To find out more, the researchers looked at the consequences of lead exposure on mice with a mutant form of the human disrupted-in-schizophrenia-1 (mDISC1) gene, which is a risk factor for major psychiatric disorders. The mDISC1 mice that received lifelong exposure to lead showed schizophrenia-like behaviors and brain changes. These mice also had stronger responses to an N-methyl-D-aspartate receptor (NMDAR) antagonist. Some scientists hypothesize that NMDAR is an important factor in the pathophysiology of schizophrenia, and lead is a strong and selective antagonist of the NMDAR.


Improving health for low-income workers

An NIEHS grantee co-authored a paper that calls for improving the health of low-income workers, by integrating health protection and health promotion programs that can be delivered at worksites, state and local health departments, community health centers, and community-based organizations. Low-income workers experience overlapping occupational and nonoccupational risks that can be worsened by limited resources and societal racism.

The authors present a social ecological framework for creating programs that bring together health protection and promotion. This framework examines how various levels of influence - intrapersonal, interpersonal, institutional, community/society, and policy - can impact health. They provide six broad recommendations for reducing health inequities among low-income workers - improve access and quality of work-related data; integrate work environmental factors into care at community health centers; improve the exchange of information and ideas; increase the integration of health and occupational health education and training; test and evaluate new approaches; and improve worker and community engagement.

The authors emphasize the importance of integrated public health programs that control unhealthy exposures, promote healthy lifestyles, and encourage healthy decisions. They also stress that employers, workers, and advocates need to work with public health practitioners to deliver health protection and promotion programs at the workplace or in the community.


Metabolomics reveals early changes in metabolic pathways for Alzheimer's disease

With funding from NIEHS, researchers found changes in the metabolic pathways of Alzheimer’s patients that were detectable in blood plasma. The findings suggest that it might be possible to identify plasma biomarkers for early Alzheimer’s disease diagnosis, monitoring disease progression, and evaluating therapeutic approaches.
The researchers used a nontargeted metabolomics approach, based on liquid chromatography and mass spectrometry, to analyze cerebrospinal fluid (CSF) and plasma samples from 45 people enrolled in studies at the Mayo Clinic - 38 in the Study of Aging and 7 in the Alzheimer Disease Research Center. Study participants included 15 people with no cognitive decline, 15 with mild cognitive impairment, and 15 with Alzheimer's disease.

In total, the investigators found 342 metabolites in the plasma and 351 in the cerebrospinal fluid that were significantly altered. When looking at differences between the Alzheimer’s disease group and cognitively normal group, they found altered cholesterol and sphingolipids transport in both cerebrospinal fluid and plasma. Patients with mild cognitive impairment and Alzheimer’s disease showed significant impairment in energy metabolism, Krebs cycle, mitochondrial function, neurotransmitter and amino acid metabolism, and lipid biosynthesis pathways. As disease severity increased, so did the number of affected pathways for both fluids. Importantly, the changes observed in plasma accurately reflected the changes in cerebrospinal fluid (CSF), showing that the biomarkers in the plasma reflected the brain differences of the study participants. The researchers say that additional research using targeted metabolomics could identify specific panels of biomarkers.


Brd4 insulates chromatin from DNA damage signaling

Researchers supported in part by the NIEHS, report evidence that an isoform of the bromodomain protein Brd4 can modulate the signaling response to DNA damage by insulating chromatin.

When DNA damage occurs, a network of signals directs various responses, such as stopping the progression of the cell cycle, recruiting factors needed for DNA repair or prompting programmed cell death. Problems with the cell’s response to DNA damage can lead to tumor growth. The researchers studied the signaling and response of cells exposed to ionizing radiation damage, finding that Brd4 isoform B inhibited DNA damage response signaling. In cells with nonfunctioning Brd4 isoform B, the researchers observed a more relaxed chromatin structure and improved survival after irradiation.

Cells with functional Brd4 isoform B had more compact chromatin, lessened DNA damage response signaling, and enhanced radiation-induced lethality. From these findings, the researchers conclude that Brd4 facilitates structural changes in chromatin that lessen the DNA signaling response to ionizing radiation.


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