

Intramural papers of the month

By Aleksandra Adomas, Heather Franco, Mallikarjuna Metukuri, and Bailey Schug

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Ultraviolet radiation exposure associated with autoimmune diseases in juveniles

According to a new study conducted by the NIEHS Environmental Autoimmunity Group, ultraviolet radiation (UVR) from sunlight may be connected with the development of certain autoimmune diseases. The study examined whether there was a relationship between the level of ultraviolet exposure at illness onset, with the form of juvenile idiopathic inflammatory myopathies (IIMs), which are systematic autoimmune diseases characterized by muscle and skin inflammation.

To conduct the study, the researchers assessed the relationship between UVR exposure in the month before symptom onset and the prevalence of juvenile dermatomyositis (JDM), compared to juvenile polymyositis (JPM), in 298 juvenile IIM patients, and in JDM patients, the association between UVR and presence of myositis autoantibodies. They found an association between UVR and JDM, as well as an association between UVR and the anti-p155 myositis autoantibody, a subgroup with photosensitive skin rashes. Also, regions of the United States with higher UVR had an increased prevalence of JDM and the anti-p155 autoantibody. These data suggest photoprotective prevention measures should be implemented. They caution that more research on the role of UVR in the pathogenesis of juvenile myositis is needed.

While the causes of autoimmune diseases are not known, emerging research suggests they develop after one or more environmental exposures in genetically susceptible people. This study adds UVR to the growing list of environmental exposures that may be contributing factors in the development of autoimmune diseases. **(BS)**

Citation: [Shah M, Targoff IN, Rice MM, Miller FW, Rider LG, Childhood Myositis Heterogeneity Collaborative Study Group.](#)
(<http://www.ncbi.nlm.nih.gov/pubmed/23658122>)

2013. Brief report: ultraviolet radiation exposure is associated with clinical and autoantibody phenotypes in juvenile myositis. *Arthritis Rheum* 65(7):1934-1941.

Acrolein-induced adducts may cause mutations in mitochondria

NIEHS scientists, together with collaborators from the Oregon Health and Science University, demonstrated that, although the human DNA polymerase gamma can bypass lesions induced in mitochondrial DNA by acrolein, the subsequent replication process is inefficient and error prone. Since acrolein is a mutagenic aldehyde that is found in cigarette smoke, the research has implications for environmental exposures and human health.

Acrolein reacts with DNA bases to form lesions that, in the nucleus, are removed by repair mechanisms that do not exist in mitochondria. In fact, mammalian mitochondria contain a single polymerase, polymerase gamma, which handles both replication and repair processes.

The researchers used single nucleotide incorporation and primer extension assays to demonstrate that polymerase gamma was able to integrate correct nucleotide and process DNA extension, when acrolein-induced adduct was located in the major DNA groove. However, the enzyme was inefficient and error prone when the lesion was located in the minor groove. Polymerase gamma preferred to incorporate incorrect purine nucleotides and extension efficiency was negatively affected. The authors propose that acrolein produced internally by lipid peroxidation, or present in the environmental pollutants, can contribute to accumulation of somatic mutations in mitochondrial DNA and to age-dependent neurodegenerative disorders. **(AA)**

Citation: [Kasisviswanathan R, Minko IG, Lloyd RS, Copeland WC.](#)
(<http://www.ncbi.nlm.nih.gov/pubmed/23543747>)

2013. Translesion synthesis past acrolein-derived DNA adducts by human mitochondrial DNA polymerase gamma. *J Biol Chem* 288(20):14247-14255.

Interaction of Prox1 with RORs modulates circadian clock and metabolic regulatory networks in liver

Scientists from the NIEHS Cell Biology Group identified the coregulator Prospero-related homeobox 1 (Prox1) as a novel interacting partner and modulator of the retinoic acid-related orphan receptors (RORs), which play a critical role in the regulation of genes involved in liver metabolism and circadian rhythm. As RORs have been implicated in the regulation of embryonic development, obesity, inflammation, and diabetes, understanding the mechanism of action of these proteins is relevant to several major human health issues.

Using multiple biochemical approaches, the researchers demonstrated that the interaction between Prox1 and RORs promotes the nuclear localization of the complex to target gene promoters, where it affects chromatin structure and inhibits target gene transcription. The interaction occurs through specific domains of the proteins and is stabilized by ROR antagonists. While Prox1 regulates the expression and activity of ROR gamma, inversely ROR gamma regulates the circadian oscillation of Prox1 expression, indicating that each protein regulates the other. Thus, Prox1 appears to be part of a feedback loop that negatively modulates ROR transcriptional activity and, as such, the regulation of clock and metabolic networks by RORs.

Because disruption of the circadian clock and perturbation of metabolic pathways have been implicated in the etiology of several diseases, including metabolic syndrome, these studies not only provide new insights into the regulation of metabolic syndrome, but may also lead to new intervention strategies. **(HF)**

Citation: Takeda Y, Jetten AM.

(<http://www.ncbi.nlm.nih.gov/pubmed/23723244>)

2013. Prospero-related homeobox1 (Prox1) functions as a novel modulator of retinoic acid-related orphan receptors alpha- and gamma-mediated transactivation. *Nucleic Acids Res*; doi:10.1093/nar/gkt447 [Online 30 May 2013].

Mutations cause antagonist reversal activity of estrogen receptor alpha

In a recent study, NIEHS investigators have proposed a novel molecular mechanism by which estrogen receptor (ER) alpha antagonists modulate the ER alpha ligand binding domain (LBD) DNA binding activity and antagonist reversal activity.

ER alpha, a nuclear receptor ligand dependent nuclear transcription factor, has two transactivating functional domains (AF) - AF-1 and AF-2. AF-2 is distributed in the C-terminal LBD of the ER alpha protein. Helix 12 (H12) in the LBD is a component of the AF-2 and its configuration is ligand inducible to generate either an active or inactive form. H12 is needed for estradiol induced dimerization. Researchers have known that mutations that the ER alpha mutant, AF2ER, possessing L543A and L544A in H12 of ER alpha reverse antagonists, such as 4-hydroxytamoxifen, to agonists, but not the more effective antagonist fulvestrant/ICI182780 (ICI). In the present study, the authors analyzed the correlation between the ICI-dependent ER-mediated transcription activity of AF2ER, and AF2ER-LBD dimerization activity.

The results demonstrated that ICI-dependent AF2ER activation correlated with the activity of AF2ER-LBD homodimerization involving a unique and previously unrecognized region of the receptor protein involving the F-domain and not H12. Prevention of dimerization impaired the ICI-dependent estrogen-responsive element binding and transcription activity of AF2ER, supporting a mechanism that antagonist dependent LBD homodimerization results in antagonist reversal activity of ER alpha. The authors propose that this mechanism may be associated with the partial agonist activity of selective ER modulators, which depends on the F-domain for the dimerization. **(MM)**

Citation: Arao Y, Hamilton KJ, Coons LA, Korach KS.

(<http://www.ncbi.nlm.nih.gov/pubmed/23733188>)

2013. Estrogen receptor alpha L543A, L544A mutation changes antagonists to agonists, correlating with the ligand binding domain dimerization associated with DNA binding activity. *J Biol Chem* 288(29):21105-21116.

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