

Intramural papers of the month

By Aleksandra Adomas, Mallikarjuna Metukuri, Bailey Schug, and Ajeet Singh

- [Structurally similar endocrine-disrupting chemicals use same mechanism to activate estrogen receptors](#)
- [Mac-1 is a novel surface receptor of inflammatory response](#)
- [Consequences of ribonucleotide removal by topoisomerase 1](#)
- [Early-life exposures linked to early menarche in Sister Study](#)

Structurally similar endocrine-disrupting chemicals use same mechanism to activate estrogen receptors

In a recent study, NIEHS researchers demonstrated that endocrine-disrupting chemicals (EDCs) with similar structures tended to induce estrogen response element (ERE)-mediated activities using the same mechanism. These actions did not correlate with their known ligand binding affinities. Since EDCs interfere with the body's homeostatic control and alter normal development and reproduction, this finding helps scientists better understand how chemicals, such as bisphenol A, affect humans.

The authors used two estrogen receptor (ER) negative cell lines, HepG2 and HeLa, to analyze the effects of three groups of EDCs on the estrogenic ERE-mediated and AP1/Sp1-mediated responses of ERalpha and ERbeta. The EDCs were chosen based on the similarity of chemical structure and product class. Bisphenol compounds (Group 1) strongly activated the ERalpha ERE-mediated responses; Daidzein, Genistein, Kaempferol, and Coumestrol (Group 2) activated both the ERalpha and ERbeta ERE-mediated activities; and Endosulfan and Kepone (Group 3) weakly activated ERalpha. Using Ishikawa cells stably expressing ERalpha, the team determined that multiple EDCs can differentially induce endogenous ER target genes.

Apart from demonstrating the mechanistic importance of chemical structures, the data also raise the issue of whether multiple assays should be used to assess the potential activity of EDCs. **(MM)**

Citation: Li Y, Luh CJ, Burns KA, Arao Y, Jiang Z, Teng CT, Tice RR, Korach KS. (<http://www.ncbi.nlm.nih.gov/pubmed/23384675>) 2013. Endocrine-disrupting chemicals (EDCs): in vitro mechanism of estrogenic activation and differential effects on ER target genes. *Environ Health Perspect*; doi:10.1289/ehp.1205951 [Online 5 February 2013].

Mac-1 is a novel surface receptor of inflammatory response

In a new study, NIEHS researchers, for the first time, identified the immune cell receptor Mac-1 as a novel receptor for viruses. This study will help researchers better understand the molecular mechanisms that regulate innate immune responses that occur during a viral infection. Prior to this report, the role of Mac-1 had only been established in bacterial infection and tissue damage.

A host's inflammatory response may be triggered by double-stranded RNA (dsRNA), a byproduct of viral infection. The authors showed that Mac-1, which appears on the surface of macrophages, binds to dsRNA. The study also revealed two distinct signaling events following dsRNA recognition by Mac-1 in immune cells. Poly I:C, a synthetic dsRNA, activates inflammatory oxidative enzyme NOX2, a subunit of NADPH oxidase, to produce reactive oxygen species. Poly I:C additionally participates in the induction of proinflammatory cytokines in a Toll-like receptor 3-independent, but Mac-1-dependent, manner.

This research uncovers how macrophages recognize extracellular signals associated with virus infection and identify a potential therapeutic target for virus-related inflammatory diseases. It also offers a potential new direction in drug development. **(AS)**

Citation: Zhou H, Liao J, Aloor J, Nie H, Wilson BC, Fessler MB, Gao HM, Hong JS. (<http://www.ncbi.nlm.nih.gov/pubmed/23209319>) 2013. CD11b/CD18 (Mac-1) is a novel surface receptor for extracellular double-stranded RNA to mediate cellular inflammatory responses. *J Immunol* 190(1):115-125.

Consequences of ribonucleotide removal by topoisomerase 1

NIEHS researchers, together with collaborators at Umea University in Sweden, have determined that topoisomerase 1 (Top1), an enzyme important for uncoiling DNA during replication and transcription, can also remove ribonucleotides incorporated into DNA during replication. Because it happens when normal ribonucleotide excision repair (RER) mediated by the RNase H2 is defective, the research has implications for understanding Aicardi-Goutieres syndrome, a rare autoinflammatory disorder caused by mutations in RNase H2.

Using yeast as a model system, the scientists studied strains that were genetically engineered to incorporate a large number of ribonucleotides into DNA, and were defective in RER, Top1, or both. In the absence of RER, Top1 incised the DNA backbone where ribonucleotides were present, thereby initiating the removal of about 5,000 ribonucleotides from the genome.

However, these Top1 incisions generate dirty DNA ends that must be processed further to complete DNA repair. This process creates the opportunity for adverse consequences, demonstrated by the authors to include mutagenesis, replication stress, and genome instability. Because the enzymes involved in processing ribonucleotides in DNA are conserved, the authors suggest that the genome instability resulting from Top1 cleavage at ribonucleotides in DNA may be relevant to Aicardi-Goutieres syndrome, and possibly to other autoinflammatory disorders. **(AA)**

Citation: Williams JS, Smith DJ, Marjavaara L, Lujan SA, Chabes A, Kunkel TA. (<http://www.ncbi.nlm.nih.gov/pubmed/23375499>) 2013. Topoisomerase 1-mediated removal of ribonucleotides from nascent leading-strand DNA. Mol Cell 49(5):1010-1015.

Early-life exposures linked to early menarche in Sister Study

Sister Study researchers looked at factors associated with age at menarche, or first menstrual period, and found that several early-life exposures were associated with it starting at a younger age. This study provides additional evidence that early-life exposures may influence age at menarche and is the first to report an association with maternal pre-pregnancy diabetes.

The study included 33,501 women, aged 35-59 years when they enrolled in the Sister Study, a nationwide cohort of women with a family history of breast cancer. The research group estimated associations of self-reported exposures with menarche at age 10 or younger, 11, 14, and 15 or older, relative to menarche at 12-13 years. The group found that having low birth weight, having had a teenage mother, being firstborn, having ingested soy formula during infancy, and specific prenatal exposures — mother's smoking, diethylstilbestrol (DES), prepregnancy diabetes, or pregnancy-related hypertensive disorder — were associated with early menarche at 10-11 years. Soy formula was also associated with late menarche.

Animal studies have shown that early exposure to exogenous estrogens can alter pubertal timing, and this research corroborates those findings. The authors suggest that future studies should evaluate associations with other pubertal changes, as well as how these relationships contribute to observed associations between early menarche and disease, such as breast cancer later in life. **(BS)**

Citation: D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR, Sandler DP. (<http://www.ncbi.nlm.nih.gov/pubmed/23348069>) 2013. Prenatal and infant exposures and age at menarche. Epidemiology 24(2):277-284.

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