

2014 papers of the year

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- Transcription factor influences codon choice and protein evolution
- Human stem cells reveal gene-environment interaction in Parkinson's disease
- New tool for assessing ovarian cancer
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- One strain of bioremediation bacteria uses novel metabolic pathway
- Endoplasmic reticulum stress triggers obesity-driven liver cancer
- Phthalate exposure linked to preterm birth
- Girls are reaching puberty earlier
- Developmental exposure to BPA increases prostate cancer risk

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- tssRNAs associated with paused Pol II serve as scaffold for transcription factors
- X-ray crystallography reveals previously unknown damage response pathway
- Human obesity increases colon cancer risk
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- GWAS meta-analysis reveals new DNA loci of lung function
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- DNA replication errors in yeast offer new insight into cancer research

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- NTP finds a better animal model to evaluate the effects of chemical exposure
- NTP research finds low doses of inorganic arsenic cause lung tumors in male mice
- NTP review framework addresses environmental health questions

Research funded by grants

AhR controls endotoxin tolerance pathway

Research by an NIEHS grantee and colleagues revealed new details regarding the mechanisms involved in endotoxin tolerance, a phenomenon in which prior exposure to endotoxin from gram-negative bacteria reduces the host's inflammatory response to subsequent exposure. The findings could lead to new approaches for treating infectious diseases, by controlling host-pathogen interactions.

The researchers used genetically modified mice to investigate the biological pathways involved in endotoxin tolerance. They found that primary exposure of mice to lipopolysaccharide activated the aryl hydrocarbon receptor (AhR) transcription factor and the liver enzyme tryptophan 2,3-dioxygenase. However, when the mice were again exposed to lipopolysaccharide, AhR engaged in long-term regulation of systemic inflammation only when indoleamine 2,3-dioxygenase 1 was present. The resulting endotoxin tolerance protected the mice against immune response damage to both gram-negative and gram-positive infections.

Citation: Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Bicciato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazia MA, Piobbico D, Zelante T, Funakoshi H, Nakamura T, Gilot D, Denison MS, Guillemin GJ, DuHadaway JB, Prendergast GC, Metz R, Geffard M, Boon L,

Pirro M, Iorio A, Veyret B, Romani L, Grohmann U, Fallarino F, Puccetti P.

(<http://www.ncbi.nlm.nih.gov/pubmed/24930766>)

2014. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature* 511(7508):184-190. [Synopsis]

Transcription factor influences codon choice and protein evolution

Research, partially supported by an NIEHS grant funded by the National Institutes of Health Common Fund, revealed that complex genomes simultaneously code for amino acids and regulatory information. The work adds a transcription factor binding code to the spectrum of other regulatory codes that are believed to influence protein evolution by influencing codon choice.

Scientists created a nucleotide resolution map showing where protein-coding regions of the human genome were occupied by a transcription factor. They looked at 81 diverse cell types, and found that approximately 15 percent of human codons simultaneously specify both proteins and transcription factor recognition sites. These dual-use codons, or duons, are highly conserved. They also found that more than 17 percent of single-nucleotide variants within duons directly altered transcription factor binding. The researchers concluded that widespread dual encoding of amino acid and regulatory information may be a fundamental feature of genome evolution.

Citation: Stergachis AB, Haugen E, Shafer A, Fu W, Vernot B, Reynolds A, Raubitschek A, Ziegler S, LeProust EM, Akey JM, Stamatoyannopoulos JA.

(<http://www.ncbi.nlm.nih.gov/pubmed/24337295>)

2013. Exonic transcription factor binding directs codon choice and affects protein evolution. *Science* 342(6164):1367-1372.

[Synopsis]

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

Researchers 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.

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.

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. [Synopsis]

New tool for assessing ovarian cancer

An NIEHS grantee and colleagues developed a new technique that may help predict ovarian cancer treatment response, cancer recurrence, and disease-free survival earlier and more effectively than current methods.

For many types of cancer, counting the number of tumor-attacking immune cells (TILs) that have migrated into the tumor offers a way to predict a patient's survival. The number of TILs indicates the body's immune response to cancer. The researchers developed a new approach called QuanTILfy, which uses droplet digital polymerase chain reaction technology to count TILs reliably, quickly, and cheaply.

The researchers tested QuanTILfy on tumor samples from 30 ovarian cancer patients who had survival times ranging from one to 22 months. The results showed an association between higher TIL counts and improved survival among women with ovarian cancer.

Citation: Robins HS, Ericson NG, Guenthoer J, O'Briant KC, Tewari M, Drescher CW, Bielas JH.

(<http://www.ncbi.nlm.nih.gov/pubmed/24307693>)

2013. Digital genomic quantification of tumor-infiltrating lymphocytes. *Sci Transl Med* 5(214):214ra169. [Synopsis]

Repairing UV-induced DNA damage

An NIEHS grantee and colleagues report new details on how cellular machinery detects and signals for repair DNA damage caused by ultraviolet (UV) light.

When DNA is damaged by UV light, a protein called human UV-damaged DNA-binding protein (UV-DDB) recognizes this damage and signals for repair. Experiments revealed that UV-DDB stops along the DNA strand and transiently attaches to it. If it comes to a spot damaged by UV radiation, two molecules of UV-DDB converge and stay bound to the site, signaling DNA repair machinery.

The researchers also examined a UV-DDB with a mutation associated with xeroderma pigmentosum, an inherited disease where the body is unable to sufficiently repair damage caused by UV light. The mutant UV-DDB could still bind to DNA, but continued to slide along the DNA, rather than remaining at the damaged site to signal for repair.

Citation: Ghodke H, Wang H, Hsieh CL, Woldemeskel S, Watkins SC, Ropic-Otrin V, Van Houten B.

(<http://www.ncbi.nlm.nih.gov/pubmed/24760829>)

2014. Single-molecule analysis reveals human UV-damaged DNA-binding protein (UV-DDB) dimerizes on DNA via multiple kinetic intermediates. *Proc Natl Acad Sci U S A* 111(18):E1862-E1871. [[Synopsis](#)]

One strain of bioremediation bacteria uses novel metabolic pathway

One strain of the organohalide-respiring bacterium, *Dehalococcoides mccartyi*, utilizes a novel strategy for generating compounds used in the bioremediation of chlorinated solvents, according to NIEHS grantees and their colleagues.

Anaerobes depend on the acetyl-CoA Wood-Ljungdahl pathway, which couples folate-mediated one-carbon metabolism to either carbon dioxide reduction or acetate oxidation through acetyl CoA to produce methyltetrahydrofolate (CH₃-THF) for methionine biosynthesis. However, *D. mccartyi* strain 195 lacks several Wood-Ljungdahl pathway enzymes, but still produces CH₃-THF by cleaving acetyl-CoA. Since this cleavage leads to a buildup of carbon monoxide (CO) and inhibits the growth of *D. mccartyi*, other anaerobes that metabolize CO coexist with the bacteria, thereby demonstrating an unusual syntrophic association. The authors also found that the pathway incorporates exogenous formate to support serine biosynthesis.

Citation: Zhuang WQ, Yi S, Bill M, Brisson VL, Feng X, Men Y, Conrad ME, Tang YJ, Alvarez-Cohen L.

(<http://www.ncbi.nlm.nih.gov/pubmed/24733917>)

2014. Incomplete Wood-Ljungdahl pathway facilitates one-carbon metabolism in organohalide-respiring *Dehalococcoides mccartyi*. *Proc Natl Acad Sci U S A* 111(17):6419-6424.

Endoplasmic reticulum stress triggers obesity-driven liver cancer

Research that was partially funded by NIEHS has determined that activation of endoplasmic reticulum (ER) stress signaling is instrumental in the development of nonalcoholic steatohepatitis (NASH), a disease caused by inflammation and fat accumulation in the liver. NASH is also a risk factor in hepatocellular carcinoma, or liver cancer.

The ER is a network of membranous tubes that move proteins throughout a eukaryotic cell. Previous research implicated the ER in NASH, so the authors fed a high-fat diet to both wild type mice and major urinary protein-urokinase plasminogen activator (MUP-uPA) transgenic mice. They noted that the MUP-uPA mice exhibited greater liver damage, immune infiltration, and increased production of fatty acids, all hallmarks of NASH. The researchers determined that in light of this stress on the ER, a proinflammatory protein produced by macrophages, known as tumor necrosis factor, spurs the development of liver cancer.

Citation: Nakagawa H, Umemura A, Taniguchi K, Font-Burgada J, Dhar D, Ogata H, Zhong Z, Valasek MA, Seki E, Hidalgo J, Koike K, Kaufman RJ, Karin M.

(<http://www.ncbi.nlm.nih.gov/pubmed/25132496>)

2014. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell* 26(3):331-343.

Phthalate exposure linked to preterm birth

NIEHS-supported research has found that, depending on the phthalate examined, women with the highest levels of exposure during pregnancy had 2-5 times the odds of preterm birth, compared to women with the lowest exposure. The findings point to phthalate exposure as a potentially preventable contributing factor to premature birth.

Using urine samples in a nested case control study design, the researchers examined associations between average levels of phthalate exposure during pregnancy and preterm birth in 130 mothers who had delivered prior to 37 weeks of completed gestation. The study also included 352 control mothers who delivered at or after 37 weeks.

They found that preterm birth showed the strongest dose-dependent associations with maternal levels of two di-2-ethylhexyl

phthalate (DEHP) metabolites — mono-(2-ethyl)-hexyl phthalate and mono-(2-ethyl-5-carboxypentyl) phthalate — and the summed levels of all the DEHP metabolites.

Citation: [Ferguson KK, McElrath TF, Meeker JD.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24247736>)

2014. Environmental phthalate exposure and preterm birth. *JAMA Pediatr* 168(1):61-67. [[Synopsis](#)] [[Story](#)]

Girls are reaching puberty earlier

In a study of more than 1,200 girls that was part of the NIEHS Breast Cancer and the Environment Research Program, scientists found that breast development is occurring at an earlier age, and that earlier development is strongly associated with greater body mass index (BMI).

Girls were 6-8 years old when enrolled in the study and were followed from 2004 to 2011. At regular intervals, staff used Tanner staging to assess sexual maturity. They found that the age at onset of breast development, or stage 2, varied by ethnicity, BMI at baseline, and geographical site. For African-American, Hispanic, white non-Hispanic, and Asian participants, the median age at onset of breast stage 2 was 8.8, 9.3, 9.7, and 9.7 years, respectively. Girls with BMIs greater than the 85th percentile reached breast stage 2 at younger ages.

Citation: [Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Dearthoff J, Herrick RL, Succop PA, Hiatt RA, Kushi LH, Wolff MS.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24190685>)

2013. Onset of breast development in a longitudinal cohort. *Pediatrics* 132(6):1019-1027. [[Synopsis](#)]

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.

Researchers implanted mice with epithelial stem-like cells cultured from prostates of young, disease-free men. The mice were fed 100 or 250 micrograms of BPA per kilogram body weight for two weeks during the period in which the cells produced humanized prostate tissue. The BPA that the mice ingested 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.

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* 155(3):805-817. [[Synopsis](#)]

In-house research

tssRNAs associated with paused Pol II serve as scaffold for transcription factors

Researchers from NIEHS have found that nascent transcription start site-associated (tss) RNAs, produced and stably bound by RNA polymerase II (Pol II) that has paused during early elongation, could provide a target for the recruitment of factors that modulate gene expression. Since transcription is a critical step in the creation of proteins from information within the genome, this work may provide insight into environmentally responsive gene expression and identify novel approaches for treating disease.

The scientists developed a highly sensitive method of characterizing the dynamics of promoter-associated Pol II and tssRNAs generated during early elongation in fruit fly, or *Drosophila*, cells. They found that paused Pol II and associated tssRNAs were very stable, long-lived species, remaining near gene promoters for tens of minutes before resuming transcription elongation.

Citation: [Henriques T, Gilchrist DA, Nechaev S, Bern M, Muse GW, Burkholder A, Fargo DC, Adelman K.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24184211>)

2013. Stable pausing by RNA polymerase II provides an opportunity to target and integrate regulatory signals. *Mol Cell* 52(4):517-528. [[Synopsis](#)]

X-ray crystallography reveals previously unknown damage response pathway

Lesions that result from the insertion of RNA into DNA are removed by the protein aprataxin, according to researchers at NIEHS. The scientists named the process RNA-DNA damage response and believe it is responsible for removing many potentially harmful DNA lesions. However, mutations in aprataxin impair efficient processing of RNA-DNA damage. The inability to remove RNA-DNA lesions may contribute to ataxia with oculomotor apraxia 1 (AOA1), a heritable cerebellar-wasting condition.

The authors crystallized human aprataxin mutants in complex with RNA-DNA substrates, to visualize the aprataxin lesion processing reaction in high resolution. They determined that one of the AOA1 linked aprataxin mutations distorts the RNA-DNA damage recognition pocket in the protein and blocks its ability to efficiently recognize and process RNA-DNA lesions. Understanding these molecular mechanisms may aid in new therapies for neurological diseases and certain types of cancer.

Citation: [Tumbale P, Williams JS, Schellenberg MJ, Kunkel TA, Williams RS.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24362567>

2014. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. *Nature* 506(7486):111-115. [[Synopsis](#)] [[Story](#)]

Human obesity increases colon cancer risk

A research team led by NIEHS scientists determined that obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer.

The researchers fed two groups of mice a high-fat diet. The first contained a human version of the gene NAG-1, which protects against colon cancer, and the second lacked the gene. The NAG-1 group did not gain weight, while the second group grew plump and exhibited histone acetylation patterns in isolated colon cells that resembled patterns from mice with colorectal cancer. The additional weight carried by this group also activated genes that helped promote the rapid progression of cancer.

The findings suggest that preexisting colon lesions in obese individuals are more likely to rapidly evolve into malignant tumors. The results also provide further evidence that calorie control and frequent exercise may be keys to lowering risk.

Citation: [Li R, Grimm SA, Chrysovergis K, Kosak K, Wang X, Du Y, Burkholder A, Janardhan K, Mav D, Shah R, Eling TE, Wade PA.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24703701>

2014. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. *Cell Metab* 19(4):702-711. [[Synopsis](#)] [[Story](#)]

INO80 regulates embryonic stem cell fate and blastocyst development

NIEHS researchers and their collaborators discovered that the INO80 complex maintains the pluripotency of embryonic stem cells (ESCs), allowing them to remain undifferentiated. Their findings provide insights into how ESCs selectively activate pluripotency genes and repress differentiation genes.

Using a combination of molecular biology, biochemistry, and systems biology techniques, the scientists showed that INO80 occupies promoters of genes involved in ESC self-renewal and pluripotency. INO80 does so with help from transcription factor OCT4 and histone methyltransferase complex component WDR5 — two other key pluripotency proteins.

The researchers also observed an increase in INO80 expression during early embryonic development, reaching its peak at the blastocyst stage. INO80 expression in the blastocyst is required to establish pluripotency in the inner cell mass, which ultimately forms the embryo.

Citation: [Wang L, Du Y, Ward JM, Shimbo T, Lackford B, Zheng X, Miao YL, Zhou B, Han L, Fargo DC, Jothi R, Williams CJ, Wade PA, Hu G.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24792115>

2014. INO80 facilitates pluripotency gene activation in embryonic stem cell self-renewal, reprogramming, and blastocyst development. *Cell Stem Cell* 14(5):575-591. [[Synopsis](#)]

GWAS meta-analysis reveals new DNA loci of lung function

NIEHS researchers and their collaborators in a global consortium identified six new loci — specific regions of the genetic code — associated with individual variations in a widely used clinical measure of lung function. The genetic variants appear to influence an individual's forced vital capacity (FVC), a measure used to diagnose and monitor lung diseases. The new loci may shed light on mechanisms involved in lung development and the pathogenesis of lung diseases.

Using a large-scale meta-analysis approach, the scientists analyzed the results of genome-wide association studies (GWAS) in 52,253 individuals from 26 countries. They followed up the FVC associations in 32,917 additional individuals of European

descent. The study identified six new regions associated with FVC that had not been seen in previous GWAS lung function studies.

The newly implicated regions were also studied in samples from African-American, Korean, Chinese, and Hispanic individuals.

Citation: Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, Strachan DP, James AL, Huffman JE, Vitart V, Ramasamy A, Wareham NJ, Kaprio J, Wang XQ, Trochet H, Kahonen M, Flexeder C, Albrecht E, Lopez LM, de Jong K, Thyagarajan B, Alves AC, Enroth S, Omenaas E, Joshi PK, Fall T, Vinuela A, Launer LJ, Loehr LR, Fornage M, Li G, Wilk JB, Tang W, Manichaikul A, Lahousse L, Harris TB, North KE, Rudnicka AR, Hui J, Gu X, Lumley T, Wright AF, Hastie ND, Campbell S, Kumar R, Pin I, Scott RA, Pietilainen KH, Surakka I, Liu Y, Holliday EG, Schulz H, Heinrich J, Davies G, Vonk JM, Wojczynski M, Pouta A, Johansson A, Wild SH, Ingelsson E, Rivadeneira F, Volzke H, Hysi PG, Eiriksdottir G, Morrison AC, Rotter JI, Gao W, Postma DS, White WB, Rich SS, Hofman A, Aspelund T, Couper D, Smith LJ, Psaty BM, Lohman K, Burchard EG, Uitterlinden AG, Garcia M, Joubert BR, McArdle WL, Musk AB, Hansel N, Heckbert SR, Zgaga L, van Meurs JB, Navarro P, Rudan I, Oh YM, Redline S, Jarvis DL, Zhao JH, Rantanen T, O'Connor GT, Ripatti S, Scott RJ, Karrasch S, Grallert H, Gaddis NC, Starr JM, Wijmenga C, Minster RL, Lederer DJ, Pekkanen J, Gyllenstein U, Campbell H, Morris AP, Glaser S, Hammond CJ, Burkart KM, Beilby J, Kritchevsky SB, Gudnason V, Hancock DB, Williams OD, Polasek O, Zemunik T, Kolcic I, Petrini MF, Wjst M, Kim WJ, Porteous DJ, Scotland G, Smith BH, Viljanen A, Heliovaara M, Attia JR, Sayers I, Hampel R, Gieger C, Deary IJ, Boezen HM, Newman A, Jarvelin MR, Wilson JF, Lind L, Stricker BH, Teumer A, Spector TD, Melen E, Peters MJ, Lange LA, Barr RG, Bracke KR, Verhamme FM, Sung J, Hiemstra PS, Cassano PA, Sood A, Hayward C, Dupuis J, Hall IP, Brusselle GG, Tobin MD, London SJ.

(<http://www.ncbi.nlm.nih.gov/pubmed/24929828>)

2014. Genome-wide association analysis identifies six new loci associated with forced vital capacity. *Nat Genet* 46(7):669-677. [Synopsis] [Story]

Humans with APOE4 gene more prone to inflammation

NIEHS scientists and their colleagues are the first to report that people with a particular form of the lipid-regulating gene apolipoprotein E (APOE) — specifically the APOE4 allele — may be more prone to inflammation than others.

The researchers used the NIEHS [Environmental Polymorphisms Registry](#) to identify healthy volunteers, based on their APOE genotype. Using the NIEHS Clinical Research Unit to obtain and examine the samples, they found that whole blood from patients with at least one copy of APOE4 produced a more robust inflammatory response to lipopolysaccharide, a surface component of bacteria, than blood from patients who didn't express APOE4.

APOE4 has been previously associated with the development of inflammatory diseases, such as cardiovascular disease and Alzheimer's. These findings indicate that APOE4 may contribute to the inflammatory disease process through its regulation of the innate immune response.

Citation: Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB.

(<http://www.ncbi.nlm.nih.gov/pubmed/24655576>)

2014. APOepsilon4 is associated with enhanced in vivo innate immune responses in human subjects. *J Allergy Clin Immunol* 134(1):127-134. [Synopsis] [Story]

Control of histone expression by phosphorylation of an mRNA processing protein

By examining phosphorylation of the stem-loop-binding protein (SLBP), which has a role in processing histone mRNA, NIEHS scientists and their collaborators detailed a new method of histone expression regulation. This research is important because levels of histones, proteins that package DNA within the nucleus, have to be controlled throughout the cell cycle. During DNA replication, histone levels must increase to package new DNA, but following replication, extra histones are toxic to the cell.

Using biochemical assays, the scientists found that phosphorylation of SLBP at two different regions increases the ability of the protein to bind RNA. Interestingly, phosphorylation at the protein C-terminus increases RNA binding without actually coming into contact with the RNA. Further crystallography and nuclear magnetic resonance experiments showed that phosphorylation of this region caused a conformational change that increases RNA-binding abilities of the whole protein.

Citation: Zhang J, Tan D, DeRose EF, Perera L, Dominski Z, Marzluff WF, Tong L, Hall TM.

(<http://www.ncbi.nlm.nih.gov/pubmed/25002523>)

2014. Molecular mechanisms for the regulation of histone mRNA stem-loop-binding protein by phosphorylation. *Proc Natl Acad Sci U S A* 111(29):E2937-E2946. [Synopsis]

Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification

NIEHS researchers have unearthed a novel function for NF-Y in promoting chromatin accessibility and specification of cell

identity. Histone-fold protein NF-Y, a ubiquitously expressed transcription factor, was previously known for its role in the regulation of cell cycle progression in proliferating cells.

The authors investigated NF-Y's function and mechanism of action using genome-wide occupancy and transcriptomic analyses in embryonic stem cells and neurons. They discovered that NF-Y uses distinct modes to regulate housekeeping and cell identity programs. While NF-Y regulates housekeeping genes through cell type-invariant promoter-proximal binding, the findings demonstrated that NF-Y regulates genes required for cell identity by binding to cell type-specific enhancers. At enhancers, NF-Y promotes the binding of master transcription factors by facilitating a permissive chromatin conformation. Based on these results, the authors propose a potential mechanism for NF-Y in recruiting pioneer transcription factors for cell specification.

Citation: [Oldfield AJ, Yang P, Conway AE, Cinghu S, Freudenberg JM, Yellaboina S, Jothi R.](#)
(<http://www.ncbi.nlm.nih.gov/pubmed/25132174>)

2014. Histone-fold domain protein NF-Y promotes chromatin accessibility for cell type-specific master transcription factors. *Mol Cell* 55(5):708-722. [[Synopsis](#)]

SIRT1 regulates retinoic acid signaling and stem cell differentiation

NIEHS researchers and their collaborators demonstrated that stem cell differentiation signals stemming from retinoic acid (RA), an active metabolite of vitamin A, involve the cellular metabolic sensor sirtuin 1 (SIRT1). SIRT1 is a protein deacetylase that coordinates the activation of transcription factors in response to cellular stress, which allows the cell to react to environmental cues.

In mice, deletion of SIRT1 results in embryonic lethality and severe developmental defects in surviving offspring. The authors show that loss of SIRT1 in mouse embryonic stem cells accelerates RA-induced differentiation. They also determined that hyperacetylation of cellular retinoic acid binding protein II (CRABP2) at amino acid K102 is partially responsible for the RA-mediated hyperdifferentiation of SIRT1-deficient embryonic stem cells. Understanding the signaling pathways that SIRT1 mediates will provide insight into how the environment affects mammalian development.

Citation: [Tang S, Huang G, Fan W, Chen Y, Ward JM, Xu X, Xu Q, Kang A, McBurney MW, Fargo DC, Hu G, Baumgart-Vogt E, Zhao Y, Li X.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/25155613>)

2014. SIRT1-mediated deacetylation of CRABP2 regulates cellular retinoic acid signaling and modulates embryonic stem cell differentiation. *Mol Cell* 55(6):843-855. [[Synopsis](#)]

Maternal smoking linked to altered DNA in newborns

New research demonstrates that mothers who choose to smoke during pregnancy may actually alter their offspring's epigenetic DNA profile. In one of the largest studies of its kind to date, researchers from NIEHS and Norway have identified specific modified regions in the genomes of children from mothers who smoked during pregnancy.

Examining DNA methylation marks in blood collected from 889 newborns, with 287 newborns from mothers with self-reported smoking during the first trimester, the scientists discovered altered methylation patterns in or near 110 genes. Some of these genes are related to the ability to quit smoking, nicotine addiction, and fetal development.

This work adds to a body of evidence that maternal exposure and behavior can modify DNA during fetal development. More research is needed to understand the persistence of these DNA alterations as children mature.

Citation: [Markunas CA, Xu Z, Harlid S, Wade PA, Lie RT, Taylor JA, Wilcox AJ.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24906187>)

2014. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. *Environ Health Perspect* 122(10):1147-1153. [[Synopsis](#)]

Duking it out? My CA2 made me do it

In collaboration with the National Institute of Mental Health, researchers at NIEHS have discovered that activation of the vasopressin 1b receptor (Avpr1b) in a certain part of the brain is necessary for social aggression. Within the brain, this receptor is expressed uniquely in the CA2 region of the hippocampus, a part of the brain more commonly associated with learning and memory.

To understand the mechanism of Avpr1b action, scientists measured the synaptic strength in brain slices from rats and mice. They found that vasopressin caused synaptic potentiation, but only in the CA2. Further studies indicated this response was exactly the same as that induced by oxytocin, which is another social neuropeptide. This research could lead to exciting new treatments for patients with psychiatric disorders who have inappropriate social aggression.

Citation: Pagani JH, Zhao M, Cui Z, Williams Avram SK, Caruana DA, Dudek SM, Young WS.

(<http://www.ncbi.nlm.nih.gov/pubmed/24863146>)

2014. Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. *Mol Psychiatry*; doi:10.1038/mp.2014.47 [Online 27 May 2014]. [[Synopsis](#)] [[Story](#)]

DNA replication errors in yeast offer new insight into cancer research

NIEHS researchers have discovered new information regarding the DNA replication error rate of yeast, and the efficiency with which the mismatch repair system (MMR) can correct these errors. The findings could help scientists understand mutations in both evolutionary processes and human cancers and identify mutations that drive cancer formation.

By sequencing 70 nuclear genomes from eight yeast strains with a variety of MMR and polymerase defects, the researchers collected 40,000 mutations. From observed error rates, they concluded that MMR corrects more than 99 percent of all mismatches. They found that MMR efficiency and replication fidelity are influenced by mismatch type, the responsible polymerase, timing of replication, and replication origin proximity. Mutation rates also vary by replication fork direction, protein coding state, nucleosome proximity, and sequence context. Mutation patterns established in this work explain patterns in hypermutated endometrial cancers.

Citation: Lujan SA, Clausen AR, Clark AB, MacAlpine HK, MacAlpine DM, Malc EP, Mieczkowski PA, Burkholder AB, Fargo DC, Gordenin DA, Kunkel TA.

(<http://www.ncbi.nlm.nih.gov/pubmed/25217194>)

2014. Heterogeneous polymerase fidelity and mismatch repair bias genome variation and composition. *Genome Res* 24(11):1751-1764. [[Synopsis](#)]

National Toxicology Program research

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

Researchers from NTP have 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 estimates 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.

Since micronuclei are standard biomarkers of chromosomal damage, the scientists measured the frequency of micronucleated red blood cells in each genetically unique DO mouse before and after inhalation exposure to benzene. Using genetic mapping and linkage analysis, the authors 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.

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*; doi:10.1289/ehp.1408202 [Online 6 November 2014]. [[Synopsis](#)]

NTP research finds low doses of inorganic arsenic cause lung tumors in male mice

NTP researchers found that exposure to low doses of inorganic arsenic caused lung tumors in male mice. The researchers used a model that duplicated how humans are exposed to arsenic throughout their lifetime. Mice were given 50 parts per billion (ppb), 500 ppb, and 5,000 ppb of inorganic arsenic in their drinking water three weeks before breeding and throughout pregnancy and lactation. Arsenic was then given to offspring after weaning and throughout adulthood.

More than half of the male offspring developed significant increases in benign and malignant lung tumors at the two lower doses.

Citation: Waalkes MP, Qu W, Tokar EJ, Kissling GE, Dixon D.

(<http://www.ncbi.nlm.nih.gov/pubmed/25005685>)

2014. Lung tumors in mice induced by “whole-life” inorganic arsenic exposure at human-relevant doses. *Arch Toxicol* 88(8):1619-1629. [[Synopsis](#)] [[Story](#)]

NTP review framework addresses environmental health questions

Scientists in the NTP Office of Health Assessment and Translation (OHAT) published a flexible seven-step process to streamline the development of hazard identification conclusions. The principles of this systematic review process are intended to help

environmental health scientists integrate evidence from a variety of sources.

In 2011, OHAT began consulting technical experts, the NTP Board of Scientific Counselors, the public, and others to develop an efficient and standardized systematic review approach for literature-based environmental health science assessments. The resulting seven-step framework provides guidance on problem formulation and protocol development, searching and selecting studies for inclusion, extracting data from studies, assessing the quality of individual studies, rating confidence in the body of evidence, translating confidence ratings into evidence of health effects, and integrating evidence to develop hazard identification conclusions.

Citation: [Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24755067>)

2014. Systemic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122(7):711–718. [[Synopsis](#)]

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