

## Extramural papers of the month

By Nancy Lamontagne

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Superfund Research Program  
Research Brief. New issues  
are published on the first  
Wednesday of each month.

### DNA methylation maps of early embryo development

Researchers funded in part by NIEHS used high-throughput sequencing to produce genome-scale maps of DNA methylation at several developmental stages of early embryo development. This work is one step toward understanding the role of embryonic methylation patterns in normal development and disease.

Epigenetic modifications, including DNA methylation, affect gene expression without changing the genetic code. DNA methylation is drastically reprogrammed during early embryonic development in mice, but this reprogramming has not been well studied in humans. The new methylation maps confirm that global methylation patterns in human embryos closely resemble those of mice.

The researchers showed that there is considerable loss of methylation across most of the human genome just after fertilization and that methylation rapidly increases after implantation. One of the species differences researchers identified was that maternally contributed methylation is targeted to species-specific sets of CpG island promoters that extend beyond DNA regions known to control genes which are preferentially expressed from one parental chromosome.

*Citation:* [Smith ZD, Chan MM, Humm KC, Karnik R, Mekhoubad S, Regev A, Eggan K, Meissner A.](#)  
(<http://www.ncbi.nlm.nih.gov/pubmed/25079558>)  
2014. DNA methylation dynamics of the human preimplantation embryo. *Nature* 511(7511):611-615.

### Perinatal lead exposure linked to obesity

NIEHS grantees report that perinatal lead exposure is associated with obesity, even at low levels. The data support the hypothesis that toxicant exposures in the womb can contribute to higher risk for obesity later in life.

To assess the effects of prenatal and early-life exposure to multiple physiologically relevant levels of lead, groups of female mice were exposed to lead in drinking water for two weeks before mating, and then throughout pregnancy and nursing. Groups of mice were exposed to lead concentrations of 2.1 parts per million (ppm), 16 ppm, and 32 ppm. The control group was not exposed. For the exposed groups, maternal blood lead levels tested at weaning were 4.1 (+/-1.3) micrograms per deciliter, 25.1 (+/-7.3) micrograms per deciliter, and 32.1 (+/-11.4) micrograms per deciliter, respectively.

Both female and male offspring with perinatal lead exposure showed increased energy expenditure compared to controls ( $p < 0.0001$  for both), and exposed female offspring had higher average activity compared to controls throughout their lives. Overall, food consumption increased in exposed males and females ( $p < 0.0001$  and  $p < 0.0008$ , respectively), with significant linear trends at 6 months in males ( $p < 0.01$ ) and 9 months in females ( $p = 0.01$ ). The researchers also observed significant increases in body weight for males with medium and high exposures ( $p = 0.001$  and  $p = 0.006$ ), and significantly increased insulin response in males with medium levels of exposure ( $p < 0.05$ ).

The researchers conclude that perinatal lead exposure at maternal blood lead levels between 4.1 and 32 micrograms per deciliter is associated with increases in food consumption in offspring, bringing about increased body weight, as well as changes in energy expenditure, activity, glucose tolerance, and insulin response.

*Citation:* [Faulk C, Barks A, Sanchez BN, Zhang Z, Anderson OS, Peterson KE, Dolinoy DC.](#)  
(<http://www.ncbi.nlm.nih.gov/pubmed/25105421>)  
2014. Perinatal lead (Pb) exposure results in sex-specific effects on food intake, fat, weight, and insulin response across the murine life-course. *PLoS One* 9(8):e104273.

### Oxidative stress predicts hip fracture

An NIEHS grantee and colleagues report that biomarkers of oxidative stress are associated with hip fracture in postmenopausal women. If additional studies confirm these results, the biomarkers could help improve prediction of hip fracture, which is associated with substantial cost and a high risk of disability and death.

Oxidative stress occurs when the body insufficiently responds to reactive oxygen species. Environmental factors, such as radiation and pollutants, can add to the natural level of reactive oxygen species and overcome the body's defenses. Studies in people have suggested that oxidative stress might be a risk factor for osteoporosis, but its relationship with fracture risk was poorly understood. To find out more, the researchers prospectively assessed oxidative stress by measuring fluorescent oxidation products (FLOP) in 996 women from the Nurses' Health Study, who were 60 or older at baseline blood collection between 1989 and 1990. FLOPs are markers of global oxidation burden and can be measured using a fluorescent spectrophotometer.

The researchers measured plasma FLOPs at three excitation/emission wavelengths (360/420 nm, 320/420 nm, and 400/475 nm), reflecting products from different oxidative stress pathways. Women in the upper 30 percent of FLOP levels, measured at 320/420 nm, had 2.67 times the risk of hip fractures compared to those in the bottom 30 percent. No significant association was found between hip fracture and 360/420 nm or 400/475 nm FLOP measurements. Because FLOPs at 320/420 nm are generated when oxidative products react with DNA in the presence of metals, their strong association with hip fractures might reflect the coexisting effects of reactive oxygen species and heavy metals.

*Citation:* [Yang S, Feskanich D, Willett WC, Eliassen AH, Wu T.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24957524>)

2014. Association between global biomarkers of oxidative stress and hip fracture in postmenopausal women: a prospective study. *J Bone Miner Res*; doi:10.1002/jbmr.2302 [Online 23 Jun 2014].

## **AhR controls endotoxin tolerance pathway**

Research by an NIEHS grantee and colleagues reports 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.

Although endotoxin-induced inflammation is necessary for fighting gram-negative bacteria, too much inflammation can cause damage and lead to sepsis. Endotoxin tolerance helps reduce overexuberant inflammation, but its underlying mechanisms are not well understood. 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.

The AhR receptor is also known to regulate toxic and biological effects of exogenous chemicals, and these new results point to a role for the receptor in contributing to host fitness.

*Citation:* [Bessedé A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Biciato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazio 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.

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