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Research Finds Novel Roles for AHR in Development

By Brian Chorley
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In the study's conclusion, Puga, above, and colleagues called for interdisciplinary approaches to the epigenetic implications of their findings. "Understanding adult environmental disease may require the synergistic interaction of toxicology and developmental biology." (Photo courtesy of Alvaro Puga)





Lead author Sartor earned her doctorate at the University of Cincinnati before joining the computational medicine biology faculty at the University of Michigan School of Public Health. (Photo courtesy of Maureen Sartor)

A recent study reports on novel roles for the cellular environmental sensor aryl hydrocarbon receptor (AHR). Using a combination of sophisticated molecular and bioinformatic techniques, an NIEHS-funded research group demonstrated that AHR

mediates several biological pathways involved in development and growth in the absence of pollutant stimulation. The study appeared in press online in *Environmental Health Perspectives*.

The findings of this study add to the mounting evidence supporting the idea that pollutant exposure during embryonic development may have serious developmental consequences. "Exposure to AHR ligands during embryonic life may derail the concerted expression of developmental genes," the researchers concluded, "and in addition alter the normal patterns of epigenetic modifications of these genes, an effect that might persist throughout the life-time of the organism and possibly be a determinant of disease susceptibility in the adult."

Alvaro Puga, Ph.D. (<http://www.med.uc.edu/cellbio/CVs/puga.shtm>) , professor of environmental health and deputy director of the Center for Environmental Genetics at the University of Cincinnati, was principal investigator on the study. (<http://www.ehponline.org/docs/2009/0800485/abstract.html>) Maureen Sartor, Ph.D. (<http://www.sph.umich.edu/isr/faculty/profile.cfm?uniqname=sartorma>) , who is now a University of Michigan School of Public Health research assistant professor, was lead author on the study.

AHR is a well-studied transcription factor known to respond to environmental pollutants, such as dioxins and polychlorinated biphenyls (PCBs), and mediate expression of genes involved in metabolism and detoxification of these compounds. Additionally, many natural ligands for AHR activation are known, including dietary carotenoids found in fruits and vegetables.

AHR is generally considered an inactive, yet poised, state in the absence of its ligands. However, there is both evolutionary and genetic evidence that AHR is involved in biological mechanisms beyond the breakdown of exogenous chemicals. According to the study, mice with targeted loss of AHR exhibit metabolism-independent, age-related problems with the cardiovascular system, eye and liver. Also, invertebrate forms of AHR have known roles in development, such as neuron formation in *C. elegans* and appendage morphogenesis in *Drosophila*. Direct environmental response by AHR is only known to exist in vertebrates, but some scientists believe that developmental roles seen in invertebrates may have been conserved through evolution.

In this study, the authors examined gene expression and AHR genomic binding patterns in cultured mouse liver cancer cells that were both exposed and unexposed to chemical pollutants. To assess the genome-wide binding patterns of AHR, a technique known as ChIP-chip was utilized. As anticipated, the analysis revealed AHR binding to several regulatory regions of genes involved in chemical metabolism and detoxification after exposure, although several unrelated regions were bound in unexposed cells. These regions were associated with genes that direct nervous system, eye and blood vessel development, among other developmental and growth processes.

To corroborate the binding data, global gene expression patterns were examined using microarray gene expression analysis. The results revealed AHR mediation of many genes involved in developmental processes whose regulatory genomic regions were also bound by AHR in the unexposed state.

The study proposed an important distinction between AHR-mediated regulation between the exposed and unexposed state. Specifically, when AHR was "activated" by pollutant exposure, the enriched binding and expression of genes involved in development waned,

as genes involved in metabolism were enriched. This highlights a dual, seemingly mutually exclusive role for AHR.

The research team found that AHR-mediated gene patterns significantly shift from roles of homeostasis to exogenous chemical response after pollutant exposure. The investigators hope to broaden their study to other tissues and organs, where they expect to find both overlapping and unique gene networks governed by steady-state and activated AHR.

Citation: Sartor MA, Schnekenburger M, Marlow JL, Reichard JF, Wang Y, Fan Y, Ma C, Karyala S, Halbleib D, Liu X, Medvedovic M, Puga A (<http://www.ehponline.org/docs/2009/0800485/abstract.html>). 2009. Genome-wide analysis of aryl hydrocarbon receptor binding targets reveals an extensive array of gene clusters that control morphogenetic and developmental programs. *Environ Health Perspect* doi:10.1289/ehp.0800485

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