

# Land of hope and dreams

## Selection of life science and translational medicine literature

by Marco Confalonieri

Epigenetics is the study of heritable changes in gene expression that occur without a change in the DNA sequence. Several epigenetic mechanisms, including DNA methylation, histone modifications and microRNA expression, can be triggered by environmental factors. Epigenetic changes may mediate specific mechanisms of toxicity and responses to certain chemicals. Furthermore, such modifications might persist even in the absence of the factors that established them. Epigenetic changes have been shown increasing the susceptibility to develop chronic diseases, such as COPD, asthma, cardiovascular disease, cancer, etc.

A recent experimental study published by the Skinner's Lab group on PLOSone reports that epigenetic changes promoted by methoxychlor, a pesticide introduced in 1948 and widely used in 1970s as a safer replacement for DDT, may be linked to three generation of disease. Researchers from the Washington State University found that the pesticide affected how genes are turned on and off in the progeny of an exposed animal, even though its DNA and gene sequences remain unchanged. This is called transgenerational epigenetic inheritance. The work is the first to show that a majority of transgenerational disease traits can be transmitted primarily through the female line. The epigenetic changes observed were specific to methoxychlor exposure and may prove to be valuable biomarkers for future research on transgenerational disease. Epigenetics study may be a key to understand the actual long-term effects on human health by chemical compounds.

### 1) Pesticide Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease through the Female Germline

Manikkam M, Haque MM, Guerrero-Bosagna C, Nilson EE, Skinner MK

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Environmental compounds including fungicides, plastics, pesticides, dioxin and hydrocarbons can promote the epigenetic transgenerational inheritance of adult-on-



set disease in future generation progeny following ancestral exposure during the critical period of fetal gonadal sex determination. This study examined the actions of the pesticide methoxychlor to promote the epigenetic transgenerational inheritance of adult-onset disease and associated differential DNA methylation regions (i.e. epimutations) in sperm. Gestating F0 generation female rats were transiently exposed to methoxychlor during fetal gonadal development (gestation days 8 to 14) and then adult-onset disease was evaluated in adult F1 and F3 (great-grand offspring) generation progeny for control (vehicle exposed) and methoxychlor lineage offspring. There were increases in the incidence of kidney disease, ovary disease, and obesity in the methoxychlor lineage animals. In females and males the incidence of disease increased in both the F1 and the F3 generations and the incidence of multiple disease increased in the F3 generation. There was increased disease incidence in F4 generation reverse outcross (female) offspring indicating disease transmission was primarily transmitted through the female germline. Analysis of the F3 generation sperm epigenome of the methoxychlor lineage males identified differentially DNA methylated regions (DMR) termed epimutations in a genome-wide gene promoters analysis. These epimutations were found to be methoxychlor exposure specific in comparison with other exposure specific sperm epimutation signatures. Observations indicate that the pesticide methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and the sperm epimutations appear to provide exposure specific epigenetic biomarkers for transgenerational disease and ancestral environmental exposures.