Epigenetic alterations via mercury exposure

In this guide

119. Recent studies have indicated that epigenetic changes may be a key regulator of the mechanisms associated with Hg exposure and the development of a variety of human disorders (Bollati and Baccarelli, 2010). The human epigenome carries the inherited alterations to the genome that directly influences the regulation and expressions of genes. Epigenetic alterations are genetically

heritable modifications that do not affect the already existing DNA sequence, but rather result in changing the expression of the genes. The examples of epigenetic alterations are perturbations of the promoter methylation pattern, histone modifications and non-coding RNA dysregulations (Loscalzo and Handy, 2014).

120. Hanna et al. (2012) identified candidate methylation changes associated with exposure to mercury in women undergoing *in vitro* fertilisation (IVF). Methylation of the GSTM1/5 promoter was increased for women with higher mercury exposure ($p = 0.04$); however, no correlation was observed ($r = 0.17$, $p = 0.27$). These results were obtained from the blood samples of the women, where an elevated level of Hg was observed (exceeding 2.9 µg/L). Though, no statistical association was detected between different levels of Hg and the GSTM1 in the exposed individuals and the study did not establish the expression level of GSTM1.

121. Carazza-Kessler et al, (2024) evaluated the transgenerational effects of exposure to MeHg and/or vitamin A (VitA) on epigenetic and toxicological parameters in Wistar rats. They found persistent toxicological effects in generations F1 and F2 following low/mild doses of MeHg and/or VitA exposure during dams' (F0) gestation and breastfeeding. Toxicological effects observed in the F2 generation included chronic DNA damage, bone marrow toxicity, altered microglial content, reduced neuronal signal, and diminished male longevity. Additionally, the study demonstrated that MeHg and VitA affected histone methylation and caused consistent effects in the F2 generation. While MeHg exposure has been associated with transgenerational inheritance effects in other organisms, this study provides the first evidence of transgenerational inheritance of MeHg and VitA-induced toxicological effects in rodents.

122. Aung et al. (2020) tested whether metals are associated with concurrent differential maternal whole blood DNA methylation. In the Early Autism Risk Longitudinal Investigation (EARLI) cohort, first or second trimester maternal blood metals concentrations (cadmium, lead, mercury, manganese, and selenium) and DNA methylation were measured. A subset sample of 97 women had both measures available for analysis, all of whom did not report smoking during pregnancy. The authors observed exposure to mercury was associated with gene ontologies for organ morphogenesis, tube development (a precursor for neural tube development), and tissue development but no significant correlations in single-site results for Hg in EARLI were observed.

123. Kupsco et al. (2022) isolated extracellular vesicle (EV) RNA from 333 milk samples collected between 2 and 74 days postpartum from a Faroese birth

cohort born 1997–2000 and sequenced 2083 microRNA (miRNA) using a targeted library preparation method. The authors used negative binomial regressions to estimate associations between individual pollutants and 418 reliably expressed EV-miRNAs adjusted for potential confounders. They performed sparse principal components (PCs) analysis to derive the first four components of the EV-miRNA data and examined associations between pollutants and PCs using Bayesian kernel machine regression (BKMR). The authors observed no associations between pollutants and individual EV- miRNA expression; however, BKMR suggested that miRNA's: miR-200b-3p, miR-664a-3p, miR-6738-5p, miR-429, miR-1236-5p, miR-4464, and miR-30b- 5p may be related to mercury neurotoxicity.

124. Longo et al. (2022) measured the serum concentration of a suite of inorganic and organic pollutants and their association to serum miRNA-30b, miRNA-223 and Let-7a miRNA expression in 68 healthy pregnant women from the NEHO birth cohort sited in a highly industrialized area. The authors found Hg levels were associated with miRNA-30b and the higher tertile of Hg showed a positive association with miRNA-223 also. Statistical analysis also shows a driving effect of Hg on significant increased expression of Let-7a ($p = 0.045$) and significantly amplified expression of miRNA-30b ($p = 0.038$). The authors concluded modified expression of circulating miRNAs in the serum of pregnant women, exposed to low-medium dose contaminants offers innovative early-warning approaches to human health risk assessment.

125. Onishchenko et al. (2008) observed an elevated trimethylation of the histone H3K27, together with a declined H3 histone acetylation of the brain-derived neurotrophic factor gene in perinatal MeHg exposed mice. This study indicated that exposure to MeHg at the developmental levels, predisposed mice to depression and enhanced epigenetic suppression.

126. Maccani et al. (2015) investigated the methylation status of > 485,000 CG dinucleotides (CpGs) loci in 192 placental samples. Hg concentrations were analysed in toenail clippings from a subset of 41 infants. Neurobehavior was assessed using the NICU Network Neurobehavioral Scales (NNNS) in an independent subset of 151 infants. 339 loci were identified with an average methylation difference > 0.125 between any two toenail Hg tertiles. Variation among these loci was found to be associated with a high-risk NNNS profile. Ten loci had $p < 0.01$ for the association between methylation and the high- risk NNNS profile. Six of 10 loci reside in the EMID2 gene and were hypomethylated in the 16 high-risk profile infants' placentas. Methylation at these loci was moderately correlated (correlation coefficients range, –0.33 to –0.45) with EMID2

expression. EMID2 hypomethylation may represent a novel mechanism linking *in utero* Hg exposure and adverse infant neurobehavioral outcomes.

127. Sanders et al. (2015) assessed the association between miRNA expression in the cervix during pregnancy with lead and mercury levels. They obtained cervical swabs from 60 pregnant women and quantified cervical miRNA expression. Women's blood lead, bone lead and toenail mercury levels were analysed. Seventeen miRNAs were found to be negatively associated with toenail mercury levels, and tibial bone lead levels were associated with decreased expression of miR-575 and miR-4286. The authors concluded these findings highlight miRNAs in the human cervix as novel responders to maternal chemical exposure during pregnancy.