Impact of Environment on the Epigenome

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Introduction

The risk of chronic diseases, like cancer, is mainly determined by genetic and environmental factors. Genome wide association studies (GWAS) have been able to attribute directly genetic risk factors to 10-20% of chronic diseases, which means that environment (including diet) plays a role in 80-90%. In order to elucidate the impact of external exposure it is important to characterize the total exposure of a subject from conception till death (exposome) and to understand the mechanisms involved in the development of chronic diseases like cancer. Carcinogenesis is a complex process driven by a continuous interaction between genes and environment. Besides DNA damage, environmental factors could induce cell transformation by epigenetic pathways affecting the gene expression. Epigenetic effects are heritable changes in genome function, without changes in the DNA sequence. The main epigenetic effects that are being studied are DNA methylation, histone modification and microRNAs. In environmental epigenetics the most studied endpoint is DNA methylation, which inhibits the interaction between gene and transcription factors resulting in a decreased gene expression. Despite DNA methylations take place directly on the DNA, it is not classified as a genetic effect because they do not change the genetic code. There is also evidence that altered DNA methylation is an important epigenetic mechanism in prenatal programming and that developmental periods are sensitive to environmental stressors.

Methods

We have set up several studies to investigate the impact of environmental factors (e.g. solvents, PAH, nanoparticles, GSM radiation) on global and gene specific DNA methylation alterations in several cell types e.g. TK6 (*in vitro*) and lymphocytes of workers and pregnant women (*in vivo*).

Results

In our *in vitro* studies benzene, hydroquinone, styrene, carbon tetrachloride and trichloroethylene induced global DNA hypomethylation in TK6 cells. In contrast, we did not observe epigenetic effects in human lymphocytes after mobile phone radiation.

Next, cross sectional *in vivo* studies have been set-up to validate these results. In a first study, DNA methylation in 128 solvent-workers was, after correction for age, negatively associated with total exposure time ($r = -0.198$, $p=0,025$) and the cumulative exposure index ($r = -0.244$, $p=0,006$). Age and smoking were associated with global DNA hypomethylation, while use of alcohol was associated with hypermethylation. In a second study with the ENVIRONAGE birth cohort, we observed a lower degree of global placental methylation in association with exposure to particulate air pollution in early pregnancy. Placental global DNA methylation was inversely associated with PM2.5 exposures during whole pregnancy and decreased by 1.94% for each 5 $\mu g/m^3$ increase in exposure to PM2.5.

Conclusion

These studies indicate that global DNA methylation can be affected by environmental exposure during different phases in life. Future studies are scheduled to elucidate genome-wide and gene-specific methylation.

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