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Editorial

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New Insights into the Molecular Mechanisms of Phthalate-Caused Hepatotoxicity: Novel Epigenetic Alterations

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Hepatocellular carcinoma (HCC) is one of the most frequent and life-threatening cancers and the most severe complication of chronic liver disease [1]. It represents approximately 85% of liver cancers. Its incidence is not only increasing worldwide in the past decade [2], but is also a leading cause of cancer-related deaths worldwide. Because most HCC cells display biochemical and morphological features of normal hepatocytes, it is assumed that HCC results from malignant transformation of normal hepatocytes, although a "stem cell" origin is also suspected [3]. Underlying liver injury, which leads to repeated cycles of inflammation, hepatocyte death (apoptotic/necrotic), and compensatory proliferation, is an ineluctable factor in the development of most HCCs. Therefore, determining mechanisms underlying the liver injury is a basic requirement for understanding molecular pathogenesis of hepatocarcinogenesis. The distinguishing epigenetic molecular feature of HCC is immensely reshaped epigenome that is characterized by global genomic hypomethylation, hyper- or hypo-methylation of gene-specific DNA, abnormal expression of DNA methyltransferases and histone modifying enzymes, altered histone modification patterns, and aberrant expression of microRNAs [4].

Peroxisome proliferators (PPs) are a structurally diverse group of chemicals, which act as epigenetic carcinogens in rodents [5]. In both male and female mice and rats, long-term exposure to these agents results in the development of liver tumors. The occurrence of liver cancer caused by these substances in rodents has a complex mode of action which involves activation of the peroxisome proliferator-activated receptor α (PPARα). This activation leads to changes in transcription of many genes that have roles in metabolism, increase in size and amount of peroxisomes in liver parenchymal cells, increased hepatocellular proliferation, suppression of apoptosis, and secondary oxidative stress that finally leads to DNA damage [6].

Phthalates are ubiquitous industrial plasticizers which are classified as PPs. Di-(2-ethylhexyl) phthalate (DEHP) is the most widely used phthalate ester, although it is banned from children products in several countries. Their potential public health risks include not only metabolic disorders, carcinogenesis, and reproductive toxicity but also endocrine disruption [6]. DEHP is being classified as a hepatocarcinogen in both sexes in rodents causing HCCs and adenomas. The incidence of liver tumors is known to be dependent both on dose of DEHP and duration of exposure. However, this mechanism was suggested to have low relevance to humans [7-9].

Although for several years these compounds have been classified as epigenetic hepatocarcinogens due to their ability to induce peroxisome proliferation, this phenomenon does not seem to be a sole causative factor in their toxicity. Research has shown that these chemicals can also cause genotoxicity as a consequence of primary or secondary oxidative stress and many other epigenetic effects through different mechanisms, some of them yet to be investigated mechanistically.

Interest is growing over the years on the new epigenetic mechanisms in phthalate-induced hepatotoxicity other than peroxisome proliferation. Treatment of human breast cancer MCF7 cells with butylbenzyl phthalate (BBP) led to the demethylation of estrogen receptor (ESR1) promoter-associated CpG islands, indicating that altered *ESR1* mRNA expression by BBP is related to aberrant DNA methylation in the promoter region of the receptor gene [10]. After phthalate exposure, the activated receptor PPAR triggers DNA transcription of genes regulating peroxisomal enzymes, cell proliferation and apoptosis that lead to selective clonal expansion of cells resulting in adenomas and carcinomas in rodents [11]. DEHP was shown to cause DNA hypermethylation in insulin-like hormone 3 (Insl3) gene in mouse testis, causing a reduction in Insl3 expression [12]. In addition, DEHP was shown to induce a potential relaxation of the monoallelic methylation pattern, in all or in 6 out 7 of the imprinted genes tested in the livers of C57BL/6 and FVB/N mice [13]. Moreover, a recent study showed that di-butyl phthalate (DBP) induced demethylation of the c-myc protooncogene and changes in this gene's methylation status, which is one of the so-called immediate early genes, associated with increased cell proliferation in the liver. Changes in the methylation status of the c-myc were correlated with alterations in DNA synthesis, DNA methyltransferase (DNMTs) activity and liver weight in rats [14]. This gene encodes a transcriptional factor that activates genes for cyclins and for cyclin-dependent kinases (CDKs), which initiate and participate in the progression of the cell cycle [15]. It has also recently been found that c-myc was also shown to regulate chromatin structure in a global fashion [16].

Molecular mechanisms that underlie the long-lasting effects of phthalates continue to be elucidated, and they likely involve disruption of epigenetic programming of gene expression. Such studies need to be performed on human cell and tissue lines to observe whether these substances are capable of exerting the same effects in humans. In this aspect, it is noteworthy that new mechanistic studies should investigate the interactions between phthalates and epigenome. The discrepancy between rodent and human liver's response to these chemicals necessitates more research to elucidate the difference in the mechanism of action of phthalate in rodent and human livers.

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