Ind J Clin Biochem (Apr-June 2021) 36(2):129–130
https://doi.org/10.1007/s12291-021-00969-y

EDITORIAL

Epigenetics in Lead Toxicity: New Avenues for Future Research

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Published online: 18 March 2021

Lead (Pb), a potentially toxic heavy metal, is ubiquitously present in the environment and has a broad industrial usage. Apart from being a carcinogen as per the International Agency for Research on Cancer (IARC), Pb is also known to have several adverse effects on different body systems. As per the Centre for Disease Prevention and Control (CDC) guidelines, a blood lead level > 5 µg/dL represents a high risk in adults. On the other hand, the World Health Organisation (WHO) has recommended not considering any blood Pb level to be safe. To date, oxidative stress remains the principal mechanism by which this heavy metal exerts its toxicity. However, the individual susceptibility to Pb's adverse effects depends on genetic constituency and epigenetic alterations. Although the molecular studies on Pb toxicity are ongoing for quite some time, studies that have evaluated Pb exposure relationships with epigenetic alterations are rare [1].

Epigenetics involves studying all those mechanisms that impact gene regulation without altering the DNA sequence. These mechanisms include DNA methylation, histone modification and regulation by non-coding RNAs. Among them, DNA methylation has been evaluated in a few studies. A small number of studies on cell lines have provided preliminary evidence of a plausible role of histone modification in modulating the harmful effects of Pb. There is no study on human subjects examining the relationship of Pb exposure with histone levels or Histone de-acetylases (HDACs), a group of enzymes that modify histones, thereby regulating gene expression, making it a novel area for future studies on Pb toxicity [2].

Non-coding RNAs are comprised of several types of RNAs that play various roles in regulating gene expression. Among them, miRNAs, which are short, single-stranded RNA molecules of about 22 nucleotides in length, have been extensively studied concerning their regulatory roles in several diseases like cancer, metabolic disease and others. Few studies provide evidence regarding possible alteration of miRNA profile in occupationally Pb-exposed individuals. A study in occupationally Pb-exposed workers from China reported miR-520c-3p, miR-211, miR-148a, and miR-572 as potential biomarkers of Pb toxicity [3]. A recent study explored the circulating levels of selected miRNAs (miR-20b, 221, and 155) in occupationally Pb-exposed workers and studied their relationship with blood lead levels. The mean levels of blood Pb were significantly higher in Pb-exposed subjects (6.94 ± 11.96 µg/dL) compared to individuals without occupational Pb exposure (2.39 ± 4.66 µg/dL) ($p < 0.001$). Among the three miRNAs, the authors reported a significant upregulation of miR-155 and miR-221 without any significant change in miR-20b. Functional analysis of these miRNAs unravelled predictive targets comprising genes involved in various cellular pathways, including cell differentiation, development, and apoptosis [4].

In another study on 190 Pb-exposed Mexican women, the expression changes of selected miRNAs (miR-155, miR-126, miR-145) were evaluated. The mean levels of blood Pb were 10.5 ± 4.50 µg/dL. While miR-155 was upregulated, miR-126 was downregulated in women with higher Pb levels. A significant positive relationship between blood Pb and miR-155 levels and a significant

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inverse relationship between blood Pb and miR-126 levels was also reported [5].

There are certain limitations in the present studies, like inappropriate sample size and improper study design, which need to be addressed in future studies. Further, the effect of dose-dependent alteration also needs evaluation. Thus, epigenetics in Pb toxicity is still in its infancy and has strong research potential. Exploring histone modifications and the expression of HDACs in Pb exposure may aid in the knowledge of newer mechanisms. In miRNA studies, screening for identification of differentially expressed miRNAs with subsequent validation is essential to establish biomarkers of Pb exposure. Moreover, validation of findings obtained from functional analysis of altered miRNAs may provide a holistic picture of the molecular mechanisms underlying Pb toxicity.

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