Ind J Clin Biochem (Apr-June 2019) 34(2):121–122
https://doi.org/10.1007/s12291-019-00829-w

EDITORIAL

Novel Direction in Mechanisms Underlying Lead Toxicity: Evidence and Prospective

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Published online: 10 April 2019

Lead, a toxic heavy metal, has harmful effects to almost all systems of human body. Although the molecular mechanisms of lead toxicity are still under investigation, the major contributor seems to be oxidative stress. As per Centre of Disease Control (CDC), blood lead level > 5 µg/dl indicates high risk for adults. Recently World Health Organisation has suggested that no lead level is safe. The susceptibility of an individual to the harmful effects of lead also depends on the genetic variations characterised by gene polymorphisms. Further, epigenetic regulation is also getting interest among researchers in the field of lead toxicity [1].

Single Nucleotide Polymorphisms (SNPs) in various genes are associated with the risk of lead poisoning. These genes include δ- Amino Levulinic Acid Dehydratase (ALAD), Metallothionein (MT's), Glutathione-S-Transferase (GST), Vitamin-D receptor (VDR), Transferrin (TF), Divalent Metal Transporter (DMT's) etc. [2]. A recent Korean study reported negative association between bone mineral density and blood lead levels among smokers. Further, Genome Wide Association Studies (GWAS)-based pathway analysis revealed significant upregulation of nuclear receptor and VEGF pathways by body lead burden, with regard to the prevalence of osteoporosis in smokers. Their study findings highlight the probable interactions that intracellular pathways of angiogenesis and nuclear hormone signalling may play between exposure to lead and genetic variation, especially in individuals with diminished bone mineral density [3].

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Epigenetic studies in the field of lead toxicity are newer areas of research. Epigenetic changes characterised by methylation changes, histone modification or miRNA regulation are potential candidates of mechanisms underlying lead poisoning. Among these epigenetic modifications, DNA methylation is most studied. Although few in vitro studies have established the potential role of histone modification in modulating lead toxicity, no human studies have evaluated the same. Thus, study of histone modifications pose a new area in lead toxicity research. MiRNA signatures have gained importance as possible diagnostic or therapeutic biomarker in several diseases. Few reports suggest the possible alteration of miRNA profile in individuals occupationally exposed to lead when compared to healthy non-exposed individuals. A study conducted among Chinese occupationally lead exposed workers suggested miR-520c-3p, miR-211, miR-148a, and miR-572 to be potential biomarkers for lead susceptibility [4].

Recent studies have investigated the plausible link of SNP in miRNA target regions of various genes, which may affect miRNA binding thereby dysregulating the gene regulation process and contributing towards lead susceptibility. These studies do have a holistic approach towards deciphering an epigenetic mechanism to explain the genetic associations that have been unravelled in the past. A study in a Chinese population evaluated the association of SNPs located in 3′-untranslated regions (3′-UTR) of ALAD gene with risk of lead toxicity and further their potential to alter ALAD expression via miRNA dysregulation. Findings from their study suggest that, rs818708 (T → C), a SNP located in 3′-UTR of ALAD gene is associated with risk of lead poisoning among occupationally exposed individuals [5]. In another Chinese study, the C allele of rs7079 (A → C), a SNP located in the 3′-UTR

of Angiotensinogen (AGT) gene, was found significantly associated to the risk of lead poisoning. The A allele of this SNP could alter the binding of miR-31-5p and miR-584-5p to the 3′-UTR of AGT, leading to increased AGT gene expression, thereby reducing risk of lead poisoning [6].

These studies featuring crosstalk between genetic variations and miRNA regulation pave the way for newer areas of future research in this field. The major limitations of these studies are small sample size and in some cases improper study design. Another issue is the absence of evaluation of dose specific alteration. Future studies planned in larger sample sets and broader ethnicities will provide a better idea of the underlying mechanisms. Identification of genetic variations linked to alteration in epigenetic regulation, which may finally contribute to the risk of lead toxicity will open up new avenues in personalised diagnostics and therapeutics.

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