

## Novel Targets for Metal Compounds Inducing Carcinogenesis

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### Editorial

Since long, in fact from the beginning of life organisms have confronted various environmental toxicants. The growing literature has provided enormous epidemiological studies regarding metal-induced carcinogenicity. Among these principally considered cancer-inducing metals are arsenic, chromium, cadmium and nickel. Our intension over here is to focus on contemporary and novel targets for metal causing cancer, since a comprehensive and broad understanding of these targets may help researches develop combinatorial modalities against metal-induced carcinogenesis.

Through various studies that were either conducted on animals and/or humans, we have observed that metal exposure surely exerts certain degree of toxic and carcinogenic affects. These effects may depend upon the type of metal, its concentration and exposure time. Above all, the foremost factor that determines the exertion and intensity of the carcinogenic effects are the mechanisms of action for carcinogenesis induced by these metals. Over the past decades, different pathways have been investigated for the induction and progression of cancer via these metals; however, from these studies and our own observations, we more or less assertively may state that metal-induced reactive oxygen stress (ROS) can be a major determinant of metal-induced carcinogenicity. Further, as a consequence ROS may or may not influence different pathways including cellular redox regulation, DNA repair inhibition and/or deregulation of cell proliferation. These events may lead to stimulation/inhibition of signaling cascades [1], genomic instability, mutation, alteration in protein responses effecting cell cycle and tumor suppressor genes [2]. Besides ROS generation, different signaling pathways including transcription pathways like NF- $\kappa$ B has been also considered to be involved in progression of carcinogenesis, but interestingly, NF- $\kappa$ B has been also observed to be activated by an unknown mechanism independent of ROS involvement via different heavy metals [3].

Similarly, in past recent years, the emerging field of metal toxicity has suggested the promising role played by epigenetic mechanisms which means transmissible alterations in gene expression devoid of DNA sequence mutation. These include DNA methylation, RNA (non-coding) expression and/or chromatin/histone alterations by metal-induced carcinogenesis. Interestingly, some researchers have suggested that epigenetic mechanisms may affect the gene expression as well making this field of more interest. Various studies have verified that these metals can probably perturb normal DNA methylation induce and histone alteration along with or without ncRNA expression [4]. Though, the cause, induction and progression of epigenetic changes induced by metals still need to be elucidated.

Moreover, emerging transcription factors like hypoxia inducible factor-1 (HIF-1) has been recently identified as one of the major targets for metal toxicity where increase level of HIF-1 can lead to adaptation to low oxygen tension (hypoxia) and cell damage [5]. More recently, HIF-1 has been related to carcinogenesis by regulating expression of various genes encoding cancer-related proteins modifying important functions like angiogenesis [6]. Furthermore, a new field toxicogenomics, which studies the effect of toxicants including metals on genome responses,

has revealed many unanswered queries defining gene responses and toxicity related pathways as well as individual sensitivity towards specific metals. Among these genes, cell cycle regulatory genes can be perceived as different an unusual target for metals inducing carcinogenesis. For instance, even at low concentration metals have been found to increase expression of cell proliferating and tumor formation proteins like cyclinD1 in human fibroblasts [7] as well as other cell cycle genes including CCNB1, MNAT1, CLK1, RAD9 have been also over-expressed after metal (arsenic) exposure [8]. Similarly cell-cell adhesion is another unique mechanism for metal (cadmium) that can deregulate cell proliferation [2].

Conversely, with the growing researches on metal-induced carcinogenesis, more contradictory questions have been arising regarding the interference of particular metal on specific carcinogenic pathway. Thereby, there is a need for a thorough understanding and clarification of various factors prior to make any succinct conclusion relating to their carcinogenic effects, these factors include biotransformation of metal, their metabolites [9] and pathways involve in carcinogenesis [10]. In short from here, we would like to say that it is rather difficult to make precise conclusion regarding the targets for carcinogenesis induced by different metals as by recent studies, it has been made evident that metals can cause cancer by acting on unusual pathways other than the conventional targets known for induction of carcinogenesis which need to be elucidated thoroughly.

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