Molecular mechanism involved in Chromium (VI) toxicity

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Chromium exists in many different oxidation states in the environment, Cr(VI) and Cr(III) being the most stable forms. Chromium has been known for over 100 years to be a human carcinogen. The greatest risk of cancer from chromium exposure is associated with Cr(VI). Cr(VI) enters cells via the sulfate anion transporter system and is reduced to intermediate oxidation states, such as Cr(V) and Cr(IV), in the process of forming stable Cr(III) forms. It is known that Cr(VI) affects expression of various genes. Metal responsive element-binding transcription factor-1 (MTF-1) is involved in sensing heavy metal load and the induced transcription of several protective genes, including metallothionein (MT)-I, MT-II, zinc transporter-1, and glutamate-cysteine ligase catalytic subunit. Cr(VI) inhibits zinc-induced MT transcription via modifying transactivation potential of MTF-1. However, the molecular mechanism for the Cr(VI)-mediated inhibition of MTF-1 has not been fully elucidated. In order to address the molecular mechanism, we identified a transcription cofactor for zinc-mediated transactivation. Immunoprecipitation analysis indicated that zinc induced the binding of MTF-1 to p300 transcription cofactor. Cr(VI) blocked the complex formation of MTF-1–p300. On a mouse model of gamma-ray-induced thymic lymphomas, linkage analysis and haplotype mapping indicates MTF-1 as a candidate lymphoma susceptibility gene. I will discuss the relationship between the Cr(VI) toxicity and the Cr(VI)-mediated inhibition of MTF-1.