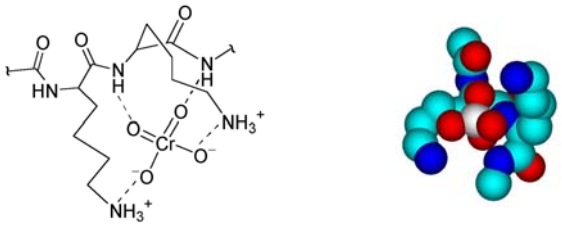
Binding of Chromium(VI) to Histones: Implications for Chromium(VI)-Induced Genotoxicity

Aviva Levina, Hugh H. Harris and Peter A. Lay

Centre for Heavy Metals Research, and Centre for Structural Biology and Structural Chemistry, School of Chemistry, University of Sydney, NSW, 2006, Australia

A generally-accepted mechanism of the cytotoxicity and genotoxicity of Cr(VI) includes its efficient uptake by cells, followed by the reactions with intracellular reductants, leading to the formation of highly stable DNA-Cr(III)-DNA and DNA-Cr(III)-protein crosslinks in the cell nucleus (probably via the reactive Cr(V/IV) intermediates). Until recently, it was unclear how Cr complexes penetrate the nucleus, since both $[CrO_4]^{2-}$ and Cr(III) complexes with biological ligands (which are likely to form during the reduction of Cr(VI) in the cytoplasm) are not taken up by the isolated nuclei at any significant rate.

The current work provides the first plausible explanation for the efficient Cr uptake by the nuclei of Cr(VI)-treated cells, based on the $[CrO_4]^{2-}$ binding to the newly synthesized histones and other nuclear proteins in the cytoplasm, followed by the active transport of the Cr(VI)-protein complexes into the nucleus. Inside the nucleus, $[CrO_4]^{2-}$ is likely to dissociate from histones during the formation of chromatin, followed by Cr(VI) reduction in the vicinity of DNA, leading to the formation of potentially genotoxic Cr(III)-DNA lesions. A model of Cr(VI) binding to H1 histones (rich in Lys-Lys fragments) has been proposed based on the electronic, vibrational and X-ray absorption (XANES and XAFS) spectroscopic studies of $[CrO_4]^{2-}$ binding to H1 histones and poly(Lys) in vitro, as well as on molecular mechanics calculations (see Figure).



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