TITL: Carcinogenic chromium(VI) induces cross-linking of vitamin C to DNA in vitro and in human lung A549 cells.

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ABST: Reductive activation of carcinogenic Cr(VI) is required for the induction of **DNA damage** and mutations. Here, we examined the formation of Cr-DNA adducts in the reactions of Cr(VI) with its dominant biological reducer, vitamin C (ascorbate). Reductive conversion of Cr(VI) to Cr(III) by ascorbate produced stable Cr-DNA adducts, of which approximately 25% constituted ascorbate-Cr(III)-DNA cross-links. No evidence was found for the involvement of Cr(V) or Cr(IV) intermediates in the formation of either binary or ternary adducts. The cross-linking reaction was consistent with the attack of DNA by transient Cr(III)-ascorbate complexes. The yield of Cr(III)-DNA adducts was similar on dsDNA and AGT, ACT, or CT oligonucleotides and was strongly inhibited by Mg(2+), suggesting predominant coordination of Cr(III) to DNA phosphate oxygens. We also detected cross-linking of ascorbate to DNA in Cr(VI)-exposed human lung A549 cells that were preincubated with dehydroascorbic acid to create normal levels of intracellular ascorbate. Ascorbate-Cr-DNA cross-links accounted for approximately 6% of the total Cr-DNA adducts in A549 cells. Shuttle-vector experiments showed that ascorbate-Cr-DNA cross-links were mutagenic in human cells. **Our results demonstrate that in addition to reduction of Cr(VI) to DNA-reactive Cr(III), vitamin C contributes to the genotoxicity of Cr(VI) via a direct chemical modification of DNA. The absence of Asc in A549 and other human cultured cells indicates that cells maintained under the usual in vitro conditions lack the most important reducing agent for Cr(VI) and would primarily display slow thiol-dependent activation of Cr(VI).**