Computational Evaluations of Metal Replacement and Charge Transfer in Xeroderma Pigmentosum Group A (XPA)

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The Xeroderma Pigmentosum Group A (XPA) protein is part of the Nucleotide Excision Repair (NER) pathway, which is a series of steps involved in the removal of bulky DNA lesions. The zinc finger of XPA is the site that binds to DNA, triggering a series of reactions that involves several other proteins and eventually rids the DNA of its lesions. The mechanism used by XPA to identify damaged DNA is not well known, and it has even been suggested that XPA not only identifies damaged DNA that will subsequently be corrected by other proteins, but it may participate in the repair very directly by affecting charge transfer, either by absorption of electrons from damaged DNA or by blocking the transfer of charge down the DNA backbone.

Metal replacement studies in the zinc finger structure of XPA may elucidate XPA's role and catalytic mechanism. Cadmium in particular is a carcinogenic heavy metal that is known to inactivate the protein thereby leaving damaged DNA vulnerable to permanent mutations (this may be a significant reason why cadmium is carcinogenic). In this study, we examine the electron affinities of XPA complexes under varied conditions, in order to evaluate the likelihood that XPA is directly involved in charge transfer and to verify the effect of cadmium substitution in the zinc finger structure. Our calculations involving reduced models of the protein metal center suggest that XPA does not absorb electrons from DNA, which is not a surprising result. Additionally, those simulations are in agreement with experimental results that show a reversible reduction of the cadmium complex. Perhaps most interestingly, our results indicate that a significant structural change occurs in XPA concomitantly with the reduction of cadmium. This effect has been heretofore unreported by other groups.

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