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Effect of protein interactions on DNA; understanding tumourigenic mutations with applications to p53 tumour suppressor

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P53 protein is a tumour suppressor encoded by a gene whose largely responsible for protecting cells from cancer causing DNA damaging agents. Functional p53 is thought to provide a protective effect against tumorigenesis, and indeed, mutations of p53 have been found in nearly all tumour types and are estimated to contribute to around 50% of all cancers. Focus of this investigation is to study the effect of protein interactions on DNA in understanding tumorigenic mutations. In this work, self-consistence field molecular orbital calculations were used to evaluate gas phase ionization potential of the isolated mononucleotides of the sequence (5'$_1$A-T-A-A-T$_5$-T-G-G-G-C$_{10}$-A-A-G-T-C$_{15}$-T-A-G-G-A$_{20}$-A3') 5'-dGMP$^-$(7,8,9,13,10'), 5'-dCMP$^-$(9'), 5'-dTMP$^-$(11') and dinucleotides 5'-pGpCp(10' and 9') and 5'-pTpGp(11' and 10'). To explore the impact of p53 loss on tumorigenesis in a mammalian model , most frequently mutated residues Arg^{248}, Arg^{273}, and their contacts with DNA were studied. Arg^{273} hot spot site was studied by considering 5'-dTMP$^-$(11')-Arg^{273}, 5'-dGMP$^-$(10')-Arg^{280}, and the large bridge 5'-dTMP$^-$(11')- Arg^{273}-Asp^{281}- Arg^{280}-5'-dGMP$^-$(10'). The Arg^{248} hot spot site was studied by considering 5'-dGMP$^-$(13) , 5'-dTMP$^-$(14), 5'-pGpTp (13 and 14), and the small bridge 5'-dGMP$^-$(13)-H_2O-Arg^{248}. Ionization potentials(IP) were obtained by employing Koopmans' theorem to results obtained from *ab-initio* Hartree-Fock level of calculations with a 3-21G basis set. The results guide that in the GGG sequence, the lowest ionization potential is obtained by middle Guanine among other G containing XGY sequences, indicating that the GGG triplet is most easily oxidized in DNA. The results obtained for the large bridge 5'-dTMP$^-$(11')-Arg^{273}-Asp^{281}-Arg^{280}-5'-dGMP$^-$(10') indicate that of the two base components, lowest IP is on Thymine base of 5'-dTMP$^-$(11'). Thymine (11') bridges to Arg^{273}, one of the frequently mutated residues of p53 in human cancer and results to obtain the lowest ionization potential. In the small bridge interaction (5'-dGMP$^-$(13)-H_2O-Arg^{248}), Guanine (13) nucleotide was found to have the lowest ionization potential. Hence substitutions at this position cause changes in the stability of the bridge thus making Arg^{248} more prone to mutations.

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