Impact of Arg175His mutation on the dynamical patterns of full-length human p53 protein

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Abstract

p53, a tumor suppressor protein, is essential for preventing cancer development. Although individual domains of the human p53 have been well analyzed, no study has experimentally revealed a full-length structure of human wild-type p53 protein at atomistic level. The presence of all human p53 domains in one structure will help in showing the correlated interactions among these domains, thus, leading to enhance our understanding about the dynamics of this protein and its mutant forms. In this study we have modeled five human p53 forms, namely, inactive, distal-active, proximal-active, distal-mutant, and proximal-mutant forms. These forms have been investigated in this study by gaussian accelerated molecular dynamics simulations in OPC water model at physiological temperature and pH. On the basis of the observed dynamical patterns, all wild-type forms can achieve better conformational stability through dimerization or tetramerization process. The dynamical patterns and free-energy profiles of the wild-type forms highlight the most vulnerable sites to mutations; that is, p53–DNA and p53–p53 interfaces. On the other hand, principal component and clustering analysis methods on Arg175His mutant forms reveal two distinct conformational states (clusters); extended and compact clusters. The two clusters of each mutant form reveal negative cavities near the mutation site, which can be used for drug screening studies. The observed compact structures in the conformations of Arg175His mutant forms may indicate formation of aggregation.

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