Title:	Variable Mutations at the p53-R273 Oncogenic Hotspot Position Leads to Altered Properties
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Abstract:	Mutations in p53 protein, especially in the DNA-binding domain, is one of the major hallmarks of cancer. The R273 position is a DNA-contact position and has several oncogenic variants. Surprisingly, cancer patients carrying different mutant variants of R273 in p53 have different survival rates, indicating that the DNA-contact inhibition may not be the sole reason for reduced survival with R273 variants. Here, we probed the properties of three major oncogenic variants of the wild-type (WT) p53: [R273H]p53, [R273C]p53, and [R273L]p53. Using a series of biophysical, biochemical, and theoretical simulation studies, we observe that these oncogenic variants of the p53 not only suffer a loss in DNA binding, but they also show distinct structural stability, aggregation, and toxicity profiles. The WTp53 and the [R273H]p53 show the least destabilization and aggregation propensity. [R273C]p53 aggregation is disulfide mediated, leading to cross-β, thioflavin-T-positive aggregates, whereas hydrophobic interactions dominate self-assembly in [R273L]p53, leading to a mixture of amyloid and amorphous aggregates. Molecular dynamics simulations indicate different contact maps and secondary structures for the different variants along the course of the simulations. Our study indicates that each of the R273 variants has its own distinct property of stability and self-assembly, the molecular basis of which may lead to different types of cancer pathogenesis in vivo. These studies will aid the design of therapeutic strategies for cancer using residue-specific or process-specific protein aggregation as a target.
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