Title:	Role of Internal and external stimuli towards modulation of P53 structure-function activity
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Abstract:	The tumour suppressor protein, p53, plays a very crucial role in our human physiology. p53 recognizes cellular stress and damage, and reacts to stop cell division or inducts cell death, hence preventing a damaged cell from reproducing. Mutation of this gene disrupts this equilibrium of cellular function leading to a major cause of oncogenesis. Mutations in p53 and its accumulation is a major hallmark of cancer. It has been observed that the majority of the oncogenic mutations occur in the DNA-binding domain of p53. These oncogenic mutations are broadly categorised as DNA-contact mutations and structural mutations. While DNA-contact mutations impair DNA binding function of p53, structural mutations affect both the structure and function of the protein. Perturbations in the structure of p53, eventually lead to p53 aggregation in cancer cells. Multiple variants of a single point mutant of p53 are found in different cancer cell lines. These variants have different gain of oncogenic functions and present different effect on cancer cell malignancies. However, the structural differences among the mutant variants are not well understood. The present thesis uses the R273 variants (p53 DNA-contact mutant) as a paradigm to understand the structural implications of the different variants of the R273 mutant. The rationale behind using R273 variants is that, different variants of R273 mutant pose different cancer cell malignancy. Using a series of biophysical, biochemical and theoretical studies, we probe the properties of three major oncogenic R273 variants of WTp53 i.e. [R273H]p53, [R273C]p53, and [R273L]p53. We observe that these oncogenic variants of the p53 not only suffer a loss in DNA binding, but also show distinct structural stability, aggregation and toxicity profiles. 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. Interestingly, the aggregates of only wild type p53 has also been reported in the tumour biopsy samples of the patients under cancer treatment. This suggests that beside mutations, there are other external factors that could trigger p53 aberrant self-assembly. Chemotherapy is the first line of treatment for the cancer patients. This raises the question if chemotherapeutic drugs could alter p53 structure leading to aggregation? To answer this question, doxorubicin has been used as a candidate drug to see the effect of the chemotherapeutic drugs on p53 aggregation. The selection of the drug molecule is based on the preliminary results which show accumulation of p53 post doxorubicin administration. Our study indicates that doxorubicin interacts with the p53 and induce aggregation which is mediated by phase separation event. Based on our observations, we put forward a new thought that p53 aggregation can be mediated by both mutations and chemotherapeutic drugs both of which induce structural perturbations leading to aggregation.
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