How the Angstrøm modifies the nano: effect of point mutations on the nanodimensional structure of human TP53 point mutations

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The p53 tumor suppressor helps maintain the genome integrity of the cell as it coordinates the cellular response to DNA damage by inducing cell cycle arrest or apoptosis. Accordingly, inactivation of p53 is one of the most common events in neoplastic transformation. In about one half of all cancer cases, p53 is inactivated by point, i.e., single aminoacid, mutations. p53 can bind to specific DNA sequences, giving rise to nanosized protein-DNA assembly, and activate gene expression, and this activity of p53 is likely to be central to its growth and suppressing effects because tumor-derived mutants are defective in DNA binding.
In theory, it should be possible to restore at least some functional activity of p53 mutants by enhancing the stability of the protein in its folded state, and/or providing additional DNA contacts. However, so far, the exploitation of the available clinical data has been hampered by our limited understanding of the structural and functional characteristics of the individual p53 mutants.
The work presented here is an attempt to exploit the knowledge available on p53 protein structure and the power of sophisticated molecular modeling techniques to classify the various types of mutants into specific categories. Accordingly, the following 20 cancer-associated mutants that are distributed throughout the core domain and are representative of the p53 mutation database have been considered and modeled: R175H M237I C238Y C242S R248Q R273H F134L G245S R249S R282W R282G V143A L145Q P151S V157F I195T Y220C I232T I255F F270C.
The results obtained so far revealed that, in agreement with the experimental findings, all mutants are destabilized with respect to the WT, and allowed us to rationalize the data set of mutations considered into 4 different classes, characterized by well-defined patterns of energy-structure relationship.