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Computational alanine scanning to probe DNA-wild type and mutant P53 interactions

Sabrina Pricl[1], Marco Ferrone[1], Maurizio Fermeglia[1], Laetitia Laurent[1], Elena Tamborini[2], Domenico Delia[3], Marco A. Pierotti[3], and Silvana Pilotti[2]. (1) Department of Chemical Engineering, University of Trieste, Piazzale Europa 1, Trieste, 34127, Italy, (2) Pathology and Cytopathology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Via Venezian 1, Milan, 20133, Italy, (3) Department of Experimental Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Via Venezian 1, Milan, 20133, Italy

TP53 encodes p53, a nuclear phosphoprotein with cancer-inhibiting properties. Mutations in the p53 are associated with more than 50% human cancers, and 90% of these affect p53-DNA interactions, resulting in a partial or complete loss of transactivation functions. 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 a limited understanding of the structural and functional characteristics of the p53 mutants. Accordingly, we applied the computational alanine scanning approach to study the noncovalent interactions between p53 and DNA. This methodology could prove to be a useful general design tool for molecules optimized for interactions or stability, since we can qualitatively estimate the free energy consequences of many mutations from a singular molecular dynamics trajectory.

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