[MS5-P15] Multi-way Restoration of the Function of p53 Oncogenic Mutants by Suppressor Mutations.

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In response to cellular stress, the tumor suppressor protein p53 acts as a transcription factor by binding to DNA targets, leading to the expression of several genes that participate in a variety of biological processes including DNA repair, cell cycle arrest or apoptosis; Thus, p53 "protects" the integrity of the genome. Human p53 binds as a tetramer to specific response elements made of two decameric half-sites separated by a linker of variable size. About 50% of all invasive cancer cases show mutations in p53 and 97% of these mutations occur within the DNA binding domain (DBD), among them, six "hot spots" mutations account for more than 30% of cancer cases. It was shown that several oncogenic mutants can be rescued by second-site suppressor mutations, resulting in wild-type-like activity in terms of DNA binding and transcriptional activation. To understand the structural effects caused by such mutations and the mechanisms of their rescue by suppressor mutations, we determined several high-resolution crystal structures of human p53DBD incorporating hot-spot mutations as well as the rescued proteins and their complexes with DNA. These included DNA contact mutations, R273H and R273C, structural mutation G245S, and the corresponding double mutants incorporating the suppressor mutations. Our crystal structures elucidate the structural basis of loss of activity of the mutated p53. The crystal structures of the rescued proteins bound to DNA show different mechanisms by which the DNA binding activity is restored: formation of alternative H-bond interactions for the DNA-contact mutants, and for the structural mutant, both intra- and intermolecular stabilizing interactions which compensate for the loss of stability caused by the oncogenic mutation. Understanding of the mechanisms of mutant p53 loss of function and its rescue by suppressor mutations may help in the design of drugs for treating cancer.