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Modulation of activity of the tumor suppressor p53 by small molecules and damaged DNA

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The p53 is a potent tumor suppressor, which becomes activated in response to stress. The activated p53 triggers a cell cyle arrest in G1 or apoptosis, ensuring a suppression of a tumor development by the elimination of cells carrying potentially tumorigenic lesions. In this study we addressed the question of the molecular mechanisms of p53 activation by DNA damage.

We characterized the ability of the p53 C-terminus to bind different types of DNA lesions and the effect of C-terminal interaction with DNA on the core domain DNA binding. We showed that one unpaired nucleotide within a double-stranded (ds) DNA is sufficient for recognition by the p53 C-terminus, either as a protruding end or as an internal gap in dsDNA. The C-terminal interaction with DNA ends facilitated the core domain binding to DNA, whereas interaction with gaps prevented the core domain-DNA complexing, implying that p53 might adopt distinct conformations upon binding to different DNA lesions. These observations suggest that both single-strand and double-strand breaks can serve as a target for p53 C-terminal recognition in vivo and indicate that p53 might recruit different repair factors to the sites of damaged DNA depending on the type of the lesion.

Next we addressed the question of the molecular mechanisms of p53 activation and stabilization after DNA damage in cells. Our data suggests that tetrametric p53 bound to DNA ends dissociates to monomers in vitro. Notably, we found that monomeric p53 has an alternative folding in its N-terminus, which is specifically recognized by newly characterized LSP16 anti-p53 antibody. We showed that LSP16 recognizes a cryptic N-terminal epitope exposed specifically in p53 monomer.

Using LSP16, we showed that in response to ionizing radiation, p53 rapidly re-localizes to DNA damage sites that also contain γH2AX and MRE11 complex. Furthermore, we showed that LSP16-positive p53 is localized in a close vicinity to DNA strand breaks independently of phosphorylation by P13 kinases and of MRE11 repair complex. We propose a model implying that localization of p53 to DNA damage sites serves to initiate p53 activation via induction of the alternative folding of the p53 N-terminus, which prevents Mdm2 binding and thus disrupts the p53/Mdm2 negative feedback loop. This may be viewed as a mechanism that regulates the level of active p53 in an orderly fashion dictated by the extent of DNA damage and repair, thereby coordinating the p53 response with ongoing DNA repair. In addition, alternative folding in the N-terminus upon binding to damaged DNA might create a binding site for a novel protein partner. We hypothesized that the direct interaction of p53 with DNA strand breaks can play a role in p53 activation in vivo.

Inactivation of p53 has always been considered as an unwanted event. However, under certain conditions, p53 activity might be harmful to normal tissues. Using the *p53*-null mice, it was shown that p53 expression is required for induction of cell death in the model of seizure activity. Recent studies have demonstrated the direct involvement of p53 in deaths of neurons, which occur during a pathogenic process in Alzheimer's disease, stroke and traumatic brain injury. Side effects of chemo- and radiotherapy have been shown to be p53-dependent. Taken together, these findings raise the possibility that pharmacological down-regulation of p53 functions might decrease the extent of tissue injury. In order to find a small molecule, the p53-inhibitor, we have screened a series of synthetic peptides and identified peptide 14, derived from p53 itself, which can inhibit p53 specific DNA binding and the transactivation function. Our data demonstrates that peptide 14 can bind p53 in vitro and prevent p53-dependent apoptosis in cells. Peptide14 can serve as a prototype for the development of the p53-specific inhibitor molecule.

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