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Fruit fly p53 and cell death

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Jonathan Weitzman

Abstract

A homolog of the tumor suppressor p53 causes damage-induced apoptosis in fruit flies.

Significance and context

The human p53 protein is the most studied tumor suppressor protein and yet many questions still remain regarding its regulation and function. The activity of p53 is induced by DNA damage and genotoxic stress, initiating two potential outcomes - apoptosis or reversible cell-cycle arrest. These functions are thought to account for its tumor suppressor properties. The p53 protein is a transcription factor, containing an acidic transactivation domain, a sequence-specific DNA-binding domain and a tetramerization domain. Cancer-associated mutations frequently map to the DNA-binding region, creating effective dominant-negative polypeptides. p53 regulates the expression of many target genes, some of which partially explain its role in apoptosis and growth arrest. Examples include the p21/Cip1 cyclin-dependent kinase inhibitor that leads to G1/S arrest, and apoptosis-inducing genes such as *fas* and *bax*. Brodsky *et al*. describe the characterization of a *Drosophila* p53 homolog which regulates the expression of *reaper* (*rpr*), one of several fly genes associated with caspase-dependent apoptosis.

Key results

The authors used information generated by the *Drosophila* genome sequencing project to identify both genomic and cDNA clones and expressed sequence tags representing a *Drosophila p53* homolog (*Dmp53*). Dmp53 is the most divergent p53 family member to be characterized, with the highest similarities in the DNA-binding region. Comparison with the human Hp53 protein revealed that residues critical for DNA binding are conserved and the most frequent tumor-associated mutation hotspots were identical or similar in fly and human sequences. The authors demonstrate functional conservation by showing that Dmp53 can bind to human p53 consensus binding sites and can activate transcription. Point mutants of Dmp53 corresponding to cancer mutational hotspots in Hp53 abolished DNA binding and inhibited transactivation. The authors used these dominant-negative forms *in vivo* (using the elegant *GAL4-UAS* overexpression system) to test their effect during wing development. Dominant-negative *Dmp53* mutants had no effect on developmental apoptosis, but dramatically reduced apoptosis in the posterior wing imaginal disk following X-irradiation. Surprisingly, Dmp53 appears not to be involved in radiation-induced cell-cycle arrest. The authors identified a 20 bp p53-response element (p53RE) within

the upstream region of the pro-apoptotic *rpr* gene. This enhancer region was shown to be p53-responsive in yeast and multimers of the p53RE were sufficient to direct radiation-responsive transactivation in transgenic flies *in vivo*.

Links

Information on *Drosophila* genomics can be obtained from the Berkeley *Drosophila* genome project website and GadFly: genome annotation database of *Drosophila*. A related paper describing *Drosophila* p53 appeared in the same issue of *Cell* (see related report - *Genome* ***Biology*** **1**(2):reports0052).

Conclusions

Brodsky *et al*. conclude that Dmp53 is clearly a functional homolog of the Hp53 tumor suppressor. Like its mammalian counterpart, Dmp53 is important for the cellular stress response, but is not essential for normal development. Unlike the mammalian protein, Dmp53 regulates radiation-induced apoptosis but not radiation-induced cell-cycle arrest. The isolation of null mutants for the *Dmp53* gene will provide further insights into p53 function and the identification of other pro-apoptotic target genes.

Reporter's comments

The identification of a fruit fly p53 homolog and the recent sequencing of the *Drosophila* genome offer an exciting opportunity for using the fly as a model organism to understand p53 regulation and function. The application of powerful fly genetics together with whole-genome expression analysis will undoubtedly lead to the identification of novel upstream regulators and downstream target genes. These insights may give new clues to therapeutic strategies to treat p53-associated malignancies.

Table of links

Cell

Berkeley *Drosophila* genome project

GadFly: genome annotation database of *Drosophila*

References

1. Brodsky MH, Nordstrom W, Tsang G, Kwan E, Rubin GM, Abrams JM: *Drosophila p53* binds a damage response element at the *reaper* locus. Cell. 2000, 101: 103-113. 0092-1903