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Fruit fly p53, cell death and the cell cycle

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Abstract

A homolog of the tumor suppressor p53 regulates apoptosis in fruit flies.

Significance and context

The inactivation of p53 function in the majority of human tumors highlights the importance of this tumor suppressor protein and its critical ability to regulate cell proliferation and cell death. Mammalian p53 has several apparently independent functions related to its role as a transcription factor. First, p53-dependent growth arrest during the G1 phase of the cell cycle involves transactivation of the *p21/Cip1* gene, which encodes an inhibitor of cyclin-dependent kinases. Second, p53-dependent apoptosis may involve multiple transcriptional targets, including the pro-apoptotic genes *bax* and *fas*. The recent identification of related p63 and p73 family members has complicated our understanding of mammalian p53 function. Ollmann *et al.* describe the characterization of a *Drosophila* p53 homolog, Dmp53, which is capable of inducing apoptosis without affecting G1 cell-cycle arrest.

Key results

The authors identified a *Drosophila* expressed sequence tag similar to human p53 (Hp53) and localized the *Dmp53* gene to chromosome 3 band 94D. Dmp53 is the most evolutionarily distant member of the p53 family and significant sequence similarity was limited to the central DNA-binding domain. Secondary structure prediction models suggest that structural features of the carboxy-terminal region are also conserved, but amino-terminal residues critical for binding to the regulatory MDM2 protein are not conserved. Dmp53 bound to p53-binding sites from the human *p21* and *GADD45* genes in electrophoretic mobility shift assays, whereas mutants corresponding to tumor-derived mutations of Hp53 function as dominant-negatives. Overexpression of Dmp53 in eye imaginal disks in the larva produces small rough eyes and increased apoptosis. Surprisingly, Dmp53 had no effect on G1- to S-phase transition, but did affect the initiation or duration of M phase. Dominant-negative Dmp53 mutants could suppress the rough-eye phenotype, but had no effect on normal development. Dominant-negative Dmp53 suppressed X-irradiation-induced apoptosis in the posterior wing imaginal disk, without affecting the damage-induced cell-cycle arrest. High expression of the *Dmp53* gene in germ cells suggests that it may be important for germline development.

Links

More information on *Drosophila* genomics can be found at the Berkeley *Drosophila* genome project website and at 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):reports0053).

Conclusions

Ollmann *et al*. conclude that the Dmp53 protein is clearly a functional homolog of the Hp53 tumor suppressor. The regulation of apoptosis appears to be an ancient conserved function. However, regulation of the G1 checkpoint and the interaction with MDM2 are late evolutionary events. Whereas Dmp53 seems not to regulate the p21 homolog *dacapo*, the effect of Dmp53 mutants on the G2/M cell-cycle checkpoint merits further investigation.

Reporter's comments

The identification of a fruit fly p53 homolog and the recent sequencing of the *Drosophila* genome offer an exciting opportunity to use 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*

Genome ***Biology*** **1**(2):reports0053

References

1. Ollmann M, Young LM, Como CJ Di, Karim F, Belvin M, Robertson S, Whittaker K, Demsky M, Fisher WW, Buchman A, et al: *Drosophila p53* is a structural and functional homolog of the tumor suppressor *p53*. Cell. 2000, 101: 91-101. 0092-1903