It's all about balance: p53 and aging

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New studies assessing whether the p53 tumor suppressor influences lifespan in flies highlight the complexities inherent in modulating the activity of this potent and versatile transcriptional regulator.

Promoting efficient regeneration while preventing cancer is critical for tissue homeostasis. Genes and processes that influence the balance between regeneration and cancer are thus likely to affect lifespan of metazoans. Supporting this view, the tumor suppressor p53 has been found to strongly influence aging in mice. Interestingly, the lifespan consequences of increasing or decreasing p53 activity in mice are complex [1-5]. It is no surprise that loss of p53 leads to increased cancer incidence, and thus shorter lifespan [2]. Yet increasing p53 activity can have pleiotropic consequences: such interventions generally prevent cancer, increasing lifespan in some cases, but can also cause accelerated aging in others [6-11]. The discrepancy between lifespan shortening and lifespan extending consequences of p53 gain-of-function conditions has been attributed to differences in regulation of the corresponding transgenes, and highlights the complex and dose-dependent effects that such a versatile regulator of cell proliferation, repair and death can have on health span and aging [2]. The exact reasons for the pleiotropic effects of p53 on aging, however, remain elusive.

Aging studies in less complex model organisms might be expected to contribute important insights into this puzzle. New studies by the Tower and Helfand labs assess the consequences of modulating p53 activity for the lifespan of flies, and shed light on the complexities of p53 function in even such relatively simple organisms [12-15].

In an exhaustive analysis of the lifespan effects of p53 gain- and loss-of-function conditions, Waskar and colleagues find strikingly pleiotropic effects resulting from ubiquitous increase or decrease of wild type p53 function [12]. Importantly, the consequences of modulating p53 are found to be tissue-, stage- and sex-specific: ubiquitous over-expression of p53 in adults shortens lifespan in females but slightly increases lifespan in males [12], whereas neuronal expression of the same construct extends lifespan in females and decreases life span in males [13]. Over-expressing p53 in larval stages, on the other hand, is sufficient to extend adult lifespan in both sexes, but in a dose-dependent manner, where strong expression is deleterious for lifespan, while moderate to weak over-expression increases lifespan [12].

The authors further examine the lifespan of a battery of mutants in which the endogenous p53 gene is disrupted, and find robust increase of lifespan in females, but context-dependent effects in males [12]. Confirming earlier studies by the Helfand lab, which demonstrated lifespan extension when dominant-negative p53 is expressed in neurons [16-18], Waskar and colleagues

find that ubiquitous expression of a dominant negative form of p53 extends lifespan moderately in females [12].
The pleiotropic and sex-specific effects of modulating p53 activity in adults are likely caused by specific functions of this tumor suppressor in particular biological processes. It is tempting to speculate that p53 might act to compromise or maintain the function of various tissues and processes in specific ways, thus causing antagonistic effects on overall lifespan. For example, (i) p53 is expressed in the female germline [19, 20], and modulating p53 expression in this tissue is likely to affect its function. The ablation of germline stem cells has recently been shown to cause robust lifespan extension in *Drosophila* [21], suggesting that the effects of ubiquitous over-expression of p53 might in part be mediated by p53 function in this tissue.
(ii) expression of p53 in intestinal stem cells (ISCs) leads to cell loss and strongly impairs gut regeneration [22]. Interestingly, probably due to a higher nutrient demand, intestinal tissue turnover is faster in females than in males [22]. As a consequence, p53-induced loss of ISCs would negatively affect female lifespan preferentially, counteracting the beneficial effects of neuronal expression or reduced germline function.
(iii) the regulation of insulin-like peptide production by p53 (described by [16] is likely to influence tissue function systemically and thus further complicate the effects of p53 on lifespan. Accordingly, Foxo modulates the sex-specific lifespan consequences of p53 over-expression [13].
(iv) the lifespan extending effects of a dominant mutant p53 transgene were not additive with Sir2 over-expression or dietary restriction (DR) [14, 15], and the life span extension due to wild-type p53 over-expression was dependent upon Sir2 function [13], indicating that tissue-specific interactions between these proteins might control metabolic homeostasis, further complicating the lifespan effects of modulating p53 activity.

The fly offers unique tools to start testing these hypotheses, and it can thus be expected that the tissue-specific functions of p53, and the relative contribution of these functions to overall lifespan will be further explored in the near future. Such studies are expected to help obtaining a comprehensive view of the effects of p53 on tissue homeostasis, metabolic control, and other physiological processes that influence aging.

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CONFLICT OF INTERESTS STATEMENT

The authors of this manuscript have no conflict of interest to declare.

REFERENCES

1. Ferbeyre G and Lowe SW. The price of tumour suppression? Nature. 2002; 415: 26-27.
2. Donehower LA and Lozano G. 20 years studying p53 functions in genetically engineered mice. Nat Rev Cancer. 2009; 9: 831-841.
3. Donehower LA. p53: guardian AND suppressor of longevity? Exp Gerontol. 2005; 40: 7-9.
4. Donehower LA. Does p53 affect organismal aging? J Cell Physiol. 2002; 192: 23-33.
5. Serrano M and Blasco MA. Cancer and ageing: convergent and divergent mechanisms. Nat Rev Mol Cell Biol. 2007; 8: 715-722.
6. Mendrysa SM, O'Leary KA, McElwee MK, Michalowski J, Eisenman RN, Powell DA, and Perry ME. Tumor suppression and normal aging in mice with constitutively high p53 activity. Genes Dev. 2006; 20: 16-21.
7. Matheu A, Maraver A, Klatt P, Flores I, Garcia-Cao I, Borras C, Flores JM, Vina J, Blasco MA, and Serrano M. Delayed ageing through damage protection by the Arf/p53 pathway. Nature. 2007; 448: 375-379.
8. Garcia-Cao I, Garcia-Cao M, Martin-Caballero J, Criado LM, Klatt P, Flores JM, Weill JC, Blasco MA, and Serrano M. "Super p53" mice exhibit enhanced DNA damage response, are tumor resistant and age normally. EMBO J. 2002; 21: 6225-6235.
9. Tomas-Loba A, Flores I, Fernandez-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borras C, Matheu A, Klatt P, Flores JM, Vina J, Serrano M, and Blasco MA. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell. 2008; 135: 609-622.
10. Maier B, Gluba W, Bernier B, Turner T, Mohammad K, Guise T, Sutherland A, Thorner M, and Scrable H. Modulation of mammalian life span by the short isoform of p53. Genes Dev. 2004; 18: 306-319.
11. Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, Lu X, Soron G, Cooper B, Brayton C, Hee Park S, Thompson T, Karsenty G, et al. p53 mutant mice that display early ageing-associated phenotypes. Nature. 2002; 415: 45-53.
12. Waskar M, Landis GN, Shen J, Curtis C, Tozer K, Abdueva D, Skvortsov D, Tavare S,Tower J. Drosophila melanogaster p53 has Developmental Stage-Specific and Sex-Specific Effects on Adult Life Span Indicative of Sexual Antagonistic Pleiotropy. Aging. 2009; 1: in this issue
13. Shen J and Tower J. Drosophila foxo acts in males to cause sexual-dimorphism in tissue-specific p53 life span effects. Exp Gerontol. 2009; doi:10.1016/j.exger.2009.10.009
14. Bauer JH, Morris SN, Chang C, Flatt T, Wood JG, and Helfand SL. dSir2 and Dmp53 interact to mediate aspects of CR-dependent life span extension in D. melanogaster. Aging. 2009; 1: 38-48.
15. Bauer JH and Helfand SL. Sir2 and longevity: the p53 connection. Cell Cycle. 2009; 8: 1821.
16. Bauer JH, Chang C, Morris SN, Hozier S, Andersen S, Waitzman JS, and Helfand SL. Expression of dominant-negative Dmp53 in the adult fly brain inhibits insulin signaling. Proc Natl Acad Sci U S A. 2007; 104: 13355-13360.

17. Bauer JH and Helfand SL. New tricks of an old molecule: lifespan regulation by p53. Aging Cell. 2006; 5: 437-440.

18. Bauer JH, Poon PC, Glatt-Deeley H, Abrams JM, and Helfand SL. Neuronal expression of p53 dominant-negative proteins in adult Drosophila melanogaster extends life span. Curr Biol. 2005; 15: 2063-2068.

19. Jin S, Martinek S, Joo WS, Wortman JR, Mirkovic N, Sali A, Yandell MD, Pavletich NP, Young MW, and Levine AJ. Identification and characterization of a p53 homologue in Drosophila melanogaster. Proc Natl Acad Sci U S A. 2000; 97: 7301-7306.

20. Chintapalli VR, Wang J, and Dow JA. Using FlyAtlas to identify better Drosophila melanogaster models of human disease. Nat Genet. 2007; 39: 715-720.

21. Flatt T, Min KJ, D'Alterio C, Villa-Cuesta E, Cumbers J, Lehmann R, Jones DL, and Tatar M. Drosophila germ-line modulation of insulin signaling and lifespan. Proc Natl Acad Sci U S A. 2008; 105: 6368-6373.

22. Jiang H, Patel PH, Kohlmaier A, Grenley MO, McEwen DG, and Edgar BA. Cytokine/Jak/Stat signaling mediates regeneration and homeostasis in the Drosophila midgut. Cell. 2009; 137: 1343-1355.