Cell Cycle 9:19, 3840-3841; October 1, 2010; © 2010 Landes Bioscience

The genetic architecture of aging

Sexual antagonistic pleiotropy of *p53* and *foxo*

John Tower

Molecular and Computational Biology Program; Department of Biological Sciences; University of Southern California; Los Angeles, CA USA

Abbreviations: IIS, insulin/IGF1-like signaling; AP, antagonistic pleiotropy; SAP, sexual antagonistic pleiotropy

Current theories suggest that aging results from pleiotropy of gene function—that is, the ability of the same gene to be beneficial in one context but deleterious in another context.[1] The declining force of natural selection as a function of age is predicted to result in the accumulation of inherited alleles with late-acting deleterious effects ("mutation accumulation"). If these same alleles produce positive effects earlier in life they can be maintained by positive selection despite their late-acting deleterious effects ("antagonistic pleiotropy"; **Fig. 1A**). Because the sexes share most of the same genes, yet are under different selective pressures, alleles may accumulate that are relatively deleterious to one or both sexes, because they have been selected for sex-specific functions ("sexual antagonistic pleiotropy" SAP; **Fig. 1B**).[2] The prediction from these models is that genes affecting aging should tend to have developmental stage-specific and sex-specific effects, and so far the data appear to support this prediction. For example, quantitative trait loci (QTLs) affecting Drosophila life span have developmental stage-specific and age-specific effects that are often opposite in males and females.[3]

Recently Waskar et al. reported that Drosophila *p53* has developmental stage-specific and sex-specific effects on adult life span that are indicative of SAP.[4] For example, tissue-general overexpression of wild-type p53 (isoform A) in adult flies caused decreased life span in females and increased life span in males, and mutations of the endogenous *p53* gene also had sex-specific effects on life span. In addition to being sex-specific, the effects of *p53* on fly life span were also tissue-specific: overexpression of wild-type *p53* in nervous system caused increased life span in females and decreased life span in males —i.e., opposite of the pattern observed upon tissue-general expression.[5] The opposing effects on life span caused by *p53* overexpression in nervous tissue versus peripheral tissues suggests a model involving inter-tissue signaling, which is known to be important in regulating longevity[6,7] (**Fig. 1C**). Consistent with the observation of SAP of *p53* function in Drosophila, in humans *p53* mutations have sex-biased effects on cancer incidence, and certain *p53* alleles have been linked to human longevity.[8]

The Drosophila *foxo* gene has recently been found to interact with *p53* transgenes to affect life span in a sex-specific manner.[5] In females nervous-system-specific overexpression of *p53* increased life span in a *foxo* null background, demonstrating that *p53* can regulate life span independent of *foxo*. However, in males the *foxo* null mutation caused the tissue-specific effects of *p53* on life span to become reversed in sign, becoming like the pattern in females. This indicates that *foxo* acts in males to create the sexual-dimorphism in tissue-specific *p53* life span effects (**Fig. 1C**). Consistent with the idea of greater Foxo activity in males, the Foxo target genes *l(2)efl* and *4EBP* were expressed at higher levels in males than in females, in a *foxo*-dependent manner.[5] In general agreement with these observations, a recent study of 1,332 P-element induced mutations revealed that sexually antagonistic effects on life span are common, and identified a specific mutation of the *foxo* gene that increases life span in males but not females.[9]

IIS negatively regulates life span across several species, including *C. elegans*, Drosophila and mammals, and in *C. elegans* this has been shown to result from IIS repression of Foxo activity.[6] In Drosophila, mutation of the IIS pathway components *chico*[10] and *Insulin-like receptor* (*InR*)[11] caused greater increases in life span in females than in males, indicating that IIS limits life span to a greater extent in Drosophila females than in males. Moreover, tissue-specific overexpression of Foxo is reported to increase fly life span, with greater increases generally observed in females relative to males.[7] These results are consistent with a model involving greater levels of IIS activity and Foxo inactivation in Drosophila females, resulting in relatively greater Foxo activity in males (**Fig. 1C**). The greater Foxo activity in males then interacts with *p53* to cause the sexual dimorphism in *p53* life span effects in adult flies.

Taken together the data support a model in which IIS favors aging, at least in part, by promoting sexual differentiation and the SAP of *p53* and *foxo*.[2,4,5] In the future it will be of interest to determine if asymmetry in IIS between the sexes might underlie the SAP of genes in addition to *p53* and *foxo*, and whether other pathways known to promote aging, such as TOR, RAS, oxidative stress, etc., might also act to promote sexual differentiation and the SAP of *p53* and *foxo* and/or other genes.

Correspondence to: John Tower; Email: jtower@usc.edu
Submitted: 08/18/10; Accepted: 08/27/10
Previously published online: www.landesbioscience.com/journals/cc/article/13464
DOI: 10.4161/cc.9.19.13464

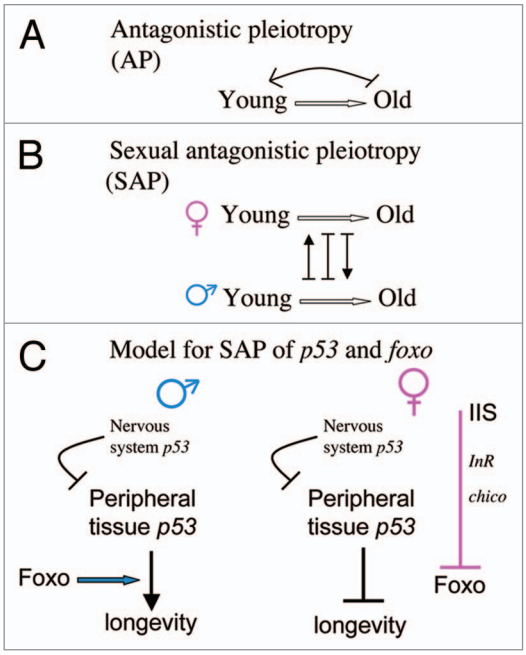

Figure 1. Gene pleiotropy in aging. (A) Antagonistic pleiotropy refers to genes that have a beneficial and selectively advantageous effect in young animals, but that contribute to aging in old animals. (B) Sexual antagonistic pleiotropy refers to genes that respond to sex-specific selective pressures, resulting in a benefit to one sex and a detrimental effect in the other sex, or a detriment to both sexes. (C) Model for SAP of *p53* and *foxo* in adult flies. The black arrows and bars summarize the effects of wild-type *p53* overexpression on life span in males and females. The opposite effects on longevity of *p53* overexpression in nervous system relative to tissue-general overexpression suggest that signals from nervous system may act to repress the effects on longevity caused by the peripheral tissues. In females, relatively greater levels of IIS act through *InR* and *chico* to repress Foxo activity. In males, the relatively greater Foxo activity interacts with *p53* to alter the effect of *p53* in peripheral tissues from a negative effect on longevity to a positive effect on longevity. Therefore, in a *foxo* null background, the effects of *p53* overexpression on life span become reversed in males, becoming like the pattern in females.

Acknowledgements

Work in the author's laboratory is supported by a grant from the Department of Health and Human Services (AG011833).

References

1. Hughes KA, et al. Annu Rev Entomol 2005; 50:421-45.
2. Tower J. Sex-specific regulation of aging and apoptosis. Mech Ageing Dev 2006; 127:705-18.
3. Nuzhdin SV, et al. Proc Natl Acad Sci USA 1997; 94:9734-9.
4. Waskar M, et al. Aging 2009; 1:903-36.
5. Shen J, et al. Exp Gerontol 2010; 45:97-105.
6. Kenyon CJ. Nature 2010; 464:504-12.
7. Toivonen JM, et al. Mol Cell Endocrinol 2009; 299:39-50.
8. Salvioli S, et al. Cancer Immunol Immunother 2009; 58:1909-17.
9. Magwire MM, et al. PLoS Genet 2010; 6:1001037.
10. Clancy DJ, et al. Science 2001; 292:104-6.
11. Tatar M, et al. Science 2001; 292:107-10.