Live long and prosper: Germline stem cell maintenance revisited (retrospective on DOI: 10.1002/bies.201000085)

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In many animals there is an apparent trade-off between reproduction and lifespan. Reproductive capacity is often determined by germ line stem cell (GLSC) function. These cells undergo self-renewing divisions to give rise to a gametogenic daughter cell that differentiates into one or more gametes, and a stem cell daughter that remains in the stem cell niche. If GLSC aging is slow or their mitoses are biased towards self-renewing conditions, then they may last longer and enable animals to undergo late-life reproduction, associated with increased longevity. In contrast, if GLSC aging is rapid or their divisions tend to produce gametogenic daughters, then they may limit animals with such cells to early-life reproduction and shortened lifespan. Kazmarczyk and Kopp recently suggested that variation in GLSC maintenance may mediate this trade-off. Their hypothesis predicts that allelic variation in GLSC genes in short-lived strains would show bias towards "short term alleles" driving high, early-life expression of GLSC maintenance genes; in long-lived strains, "long term alleles" driving high, late-life expression of stem cell maintenance genes would predominate [1].

However, female flies from a long-lived lineage show little change over their lifespan in expression levels of genes associated with oogenesis and stem cell division: they do not downregulate these genes with age, in contrast to shorter-lived control females [2]. Moreover, there was no clear overlap between the results of this next generation sequencing study and an independent microarray-based study of gene expression in males of long-lived and control strains [3]. None of the genes identified in these studies were those suggested by Kazmarczyk and Kopp as specific candidates for the local molecular mechanisms regulating GLSC maintenance with respect to reproductive strategy.

However, another study supported one of their specific molecular mechanistic predictions: given that overexpression of the oxidative stress resistance enzyme *manganese superoxide dismutase* (*sod*) can slow GLSC aging in *Drosophila*, *sod* should be expressed at higher levels in long-lived lines. *sod2* is indeed expressed at higher levels in males of long-lived butterfly lines under both optimal nutrition and starvation regimes [4]. High *sod2* expression may be a response to selection for starvation resistance because of a general role for *sod2* in combating the oxidative stress caused by poor nutrition, and its specific GLSC role could allow late life reproduction, thus prolonging lifespan.

Forward genetics has identified multiple *Drosophila* genes that regulate lifespan, but these genes have largely sex-specific effects and lack clear roles in GLSC function [5]. It is therefore unclear to what extent these genes contribute to the reproduction-lifespan trade-off via a role in GLSC maintenance or function.

Importantly, the reproduction-lifespan trade-off is not inevitable. Long-lived strains have been experimentally evolved that are not always less fecund and may even be more so than unselected control lines [6]. This highlights the importance of performing experiments addressing the genetic basis of the reproduction-lifespan trade-off with multiple replicate lines that are generated using the same selective regimes. This should be done under tightly controlled laboratory conditions that are comparable from study to study. Specifically, for differential gene expression studies, comparable chronological and/or physiological ages should be used; these should be controlled for potential sex-specific differences in longevity, fecundity and related trade-offs, and gene expression.

In summary, the Kazmarczyk and Kopp hypothesis appears to be supported to some extent by recent genetic studies, but that support is confounded by the poorly understood interplay of reproduction, lifespan, and fecundity.

References

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