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Mini-Review

Genetics of aging in *Drosophila*

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Abstract

The genetics of aging in Drosophila are reviewed under the separate headings of population genetics, physiological genetics, and molecular genetics. However, connections between these sub-fields are brought forward for discussion.

Keywords: Drosophila; Population genetics; Physiology; Molecular genetics

1. Introduction

The genetics of aging in *Drosophila* have been studied since the work of Pearl's laboratory in the 1920s and Maynard Smith's laboratory in the 1950s and 1960s (e.g., Clarke and Maynard Smith, 1955). Indeed, many of the genetic theories of aging that were then current were tested first in *Drosophila* (Maynard Smith, 1966). Recent years have seen continued progress with the genetics of *Drosophila* aging. However, the field has somewhat fractured into subsidiary areas: population genetics, physiological genetics, and molecular genetics. Here, I will review these areas separately, while pointing out connections between them.

2. Population genetics

Population or evolutionary genetics is the area where *Drosophila* genetics have been most in advance of aging genetics as a whole. There are three ideas that have consumed the attention of work in this area. First is the decline with adult age in the force of natural selection acting on survival. This idea has been offered by evolutionary biologists as the fundamental explanation for aging (e.g., Medawar, 1952; Hamilton, 1966; Charlesworth,

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1980, 1994). The second idea is that of antagonistic pleiotropy, when alleles have opposed effects on life-history characters at different ages (Williams, 1957; Charlesworth, 1980, 1990; Rose, 1985). Antagonistic pleiotropy coupled with the declining force of natural selection is predicted to give rise to aging because of selection for benefits to early reproduction or survival, which are genetically associated with later reductions in reproduction or survival. The third idea is mutation accumulation, in which weak natural selection at late ages allows recurrent deleterious mutation to undermine later survival and reproduction (Medawar, 1952; Charlesworth, 1980). It should be noted that both antagonistic pleiotropy and mutation accumulation theories for the genetics of aging presume that the force of natural selection does indeed decline with adult age. In addition, antagonistic pleiotropy and mutation accumulation are not mutually exclusive; both may operate in the population genetics of a species. Thus, all of these evolutionary genetic theories can be valid at the same time, in the same species.

All three ideas have been tested in the *Drosophila* literature since 1980. *Drosophila* tests of the theory that the force of natural selection normally falls with age have been extensive. The key experiment involves the reinforcement of selection at later ages by preventing earlier reproduction. Theory predicts that this should lead to the evolution of increased lifespan, because the force of natural selection does not start to decline until the first individuals in a population have reproduced, in each generation. This delayed-reproduction experiment was first deliberately performed in the 1970s (Rose and Charlesworth, 1980), though the same procedures had been inadvertently used in earlier *Drosophila* experiments (e.g., Wattiaux, 1968). In the 1980s and early 1990s, several *Drosophila* laboratories took up this experimental system (e.g., Luckinbill et al., 1984; Rose, 1984; Luckinbill and Clare, 1985; Partridge and Fowler, 1992; Arking et al., 1993). All obtained a qualitatively uniform result: delayed reproduction resulted in the evolution of increased lifespan after ten or more generations. This work has essentially established the theory of a declining force of natural selection as the fundamental explanation for aging, albeit not the cellular or molecular explanation. No other experimental system has approached the importance of the *Drosophila* research in validating the concept of the force of natural selection.

The other two population genetic theories have also been tested frequently. There is evidence for both. Supporting antagonistic pleiotropy are the depressed early fecundities of flies with genetically postponed aging and negative genetic correlations between early fecundity and longevity (e.g., Rose and Charlesworth, 1981; Luckinbill and Clare, 1985; Rose, 1984; Partridge and Fowler, 1992). These results suggest that the genetics of aging may depend pleiotropically on the genetics of early reproduction. In particular, because natural selection will favor increased early reproduction, and there is evidence that alleles increasing early reproduction reduce longevity, *Drosophila* aging might be actively fostered by selection for early reproduction.

Turning to the second population genetic mechanism for aging, there is support for mutation accumulation in the experiments that detect increasing genetic variance at later ages (e.g., Kosuda, 1985; Hughes and Charlesworth, 1994). Evidently, genetic variance should increase with age if recurrent deleterious mutations are not eliminated, or reduced to low frequencies, because of the weakness of natural selection at later ages. Another result supporting mutation accumulation is the existence of hybrid superiority for late fecundity in hybrids of fruit flies from lines long denied opportunities for later reproduction (Mueller, 1987). This fits mutation accumulation because the late-acting deleterious mutations that are expected to rise to high frequencies will usually be both recessive and

line-specific. Other breeding systems, in which selection is weakened by inbreeding or small population size, also exhibit hybrid vigor when lines are crossed. Thus, like antagonistic pleiotropy, there are qualitatively different lines of experimental evidence that favor mutation accumulation as a population genetic process underlying aging, at least in *Drosophila*.

There is also *Drosophila* evidence against both population genetic theories of aging. Opposing antagonistic pleiotropy are dominance patterns that do not fit theoretical expectations, age-specificity of genetic effects, and a lack of evidence for genetic correlations between fecundity and survival in some studies (e.g., Hutchinson and Rose, 1991; Promislow et al., 1996; Tatar et al., 1996; Pletcher et al., 1998). Specifically, it is hard to find evidence for the maintenance of variant alleles in which early fecundity or survival is genetically opposed to long-term survival. The required genetic patterns of dominance and genetic correlation do not appear to be common. However, these experiments do not address the possibility of alleles having antagonistic pleiotropy that become fixed by natural selection, rather than continuing to segregate. They also do not address the possibility that antagonistic pleiotropy might involve only a few loci, yet have extensive effects on aging. That is, antagonistic pleiotropy might be rare in general, and especially among segregating loci, but still have great importance for the evolution of aging.

Mutation accumulation also faces experimental difficulties. One result opposing mutation accumulation is a lack of increase in age-specific genetic variance for female fecundity (e.g., Rose and Charlesworth, 1981). However, that same study provided evidence for alleles affecting early fecundity and later survival pleiotropically. Under such conditions, the genetic variance for early fecundity will not necessarily show a predictable increase. Thus, the study of Rose and Charlesworth (1981) may not have been a valid test of mutation accumulation.

Given these varied and sometimes seemingly conflicting results, perhaps the most judicious conclusion that can be offered at this time is that both antagonistic pleiotropy and mutation accumulation *intermittently* affect the population genetics of aging in *Drosophila*, with neither apparently dominant or consistent. In other words, the population genetics of aging, even within *Drosophila*, do not appear to be determined by a single evolutionary mechanism. They could still, however, be determined by some combination of antagonistic pleiotropy and mutation accumulation.

3. Physiological genetics

A refreshing feature of recent *Drosophila* aging research has been a sustained effort to unravel the physiological controls involved. A key step in the development of this research approach has been the realization that organisms that die sooner may do so because of mechanisms that do not normally determine aging patterns (Maynard Smith, 1966). For this reason, such technically excellent work as Trout and Kaplan's (1970) demonstration of an inverse correlation between *Drosophila* metabolic rate and lifespan in short-lived *shaker* mutants has given way to studies of *Drosophila* with postponed aging. Such flies have fortunately been widely available, thanks to the aforementioned experiments in which the force of natural selection was increased at later ages. Physiological studies of flies with selectively postponed aging may not be as elegant as studies of mutant stocks, because they are outbred. But they allow more straightforward interpretation, because organisms that live longer must have undergone some abrogation or slowing of normal

aging mechanisms. This is not to deny, however, that studies of life-shortening mutants can be illuminating, especially when they are combined with other experiments.

One of the earlier functional studies measured gross morphology in *Drosophila* with selectively postponed aging (Rose et al., 1984). Those flies appeared to have smaller ovaries when they were young, relative to normal flies. This result corresponded to the depression in early fecundity that has frequently been found in studies of postponed aging in *Drosophila*. But further work has shown an abundance of complications where ovary size is concerned (Chippindale et al., 1997).

A central thread of physiological genetic research on aging in *Drosophila* has been resistance to acute, abiotic, environmental stressors. *Drosophila* was the first genetic system in which enhanced stress resistance was linked to increased lifespan (Service et al., 1985), a result that has since been found widely in yeast, nematodes, and mice (cf. Jazwinski, 1996). The *Drosophila* system was also the first in which selection on stress resistance was used as a surrogate for selection on longevity (Rose et al., 1992), a procedure that is now used with other genetic systems (e.g., Kennedy et al., 1996).

Interest in the role of stress resistance in aging has thus become intense (see also Khazaeli et al., 1997; Luckinbill, 1998), with a search for lower-level physiological mechanisms that might link stress resistance with longevity. The most popular candidate mechanism for increasing longevity is improved resistance to oxidative stress. Dudas and Arking (1995) have made a case for the up-regulation of the superoxide dismutase (SOD)-catalase pathway in longer lived *Drosophila*. This conclusion fits with some transgenic work, to be discussed below. It also fits a study of Cu,Zn SOD population genetics, which showed an increased frequency of an allele coding for a more active form of the SOD enzyme in longer-lived *Drosophila* stocks (Tyler et al., 1993), although other findings from that study were equivocal. More recent molecular genetic research, discussed below, has given results of greater clarity, however.

More specifically, physiological studies have been made of genetically increased starvation resistance and desiccation resistance in flies with postponed aging. Starvation resistance appears to be physiological determined by one variable—total stored calories. Total stored calories is in turn determined by the sum of calories supplied by lipid and glycogen. Longer-lived *Drosophila* are fatter adults. This is true under genetic manipulation (Service, 1987; Djawdan et al., 1998) and under nutritional manipulation (Chippindale et al., 1993). The genetics of this may depend in part on phosphoglucomutase, an enzyme that controls the utilization of glucose, because the frequency of alleles at this locus track longevity closely (Deckert–Cruz et al., 1997). An interesting point, with respect to population genetics, is that starvation resistance appears to be negatively genetically correlated with fecundity (Service and Rose, 1985; Leroi et al., 1994), a result that fits antagonistic pleiotropy. Another recent metabolic study of fruit fly aging (Riha and Luckinbill, 1996) found pronounced effects of larval nutrition on adult longevity. The whole story is not yet unraveled, but it is already clear that energetic metabolism and aging are intimately connected in *Drosophila*.

Desiccation resistance is also a complicated story. At least two major factors appear to determine the genetics of desiccation resistance: water content and water loss rate (Gibbs et al., 1997). Other factors, such as glycogen and epicuticular composition may play an additional secondary role (Graves et al., 1992; Gibbs et al., 1997). Unlike starvation resistance, desiccation resistance does not appear to exhibit antagonistic pleiotropy with early reproduction (Service et al., 1988). This supports the involvement of mutation accumulation in the determination of longevity by desiccation resistance.

At this point, the theory that stress resistance is a key limiting factor in aging may be the most general mechanistic theory of aging that we now possess. However, it should be noted that there is little evidence indicating that the various stress resistance characters are physiologically unified. For example, the hypothesis that metabolic rate underlies all forms of stress resistance (e.g., Hoffmann and Parsons, 1991) and aging (e.g., Parsons, 1995) has been refuted both physiologically (e.g., Djawdan et al., 1996; Djawdan et al., 1997) and in selection experiments in which aging-related stress resistance characters respond differently from each other (Service et al., 1985; Graves et al., 1992). If stress resistance is indeed a unifying mechanism in the physiology of aging, it is not unifying because disparate forms of stress resistance are united at the level of underlying cellular mechanisms.

4. Molecular genetics

Though molecular genetic research might seem like the obvious strategy in the study of *Drosophila* aging, it has only recently attracted much attention. Perhaps one factor limiting interest is that the virtual absence of adult somatic cell turnover makes *Drosophila* a poor model system for the study of such vertebrate cell "aging" phenomena as the Hayflick limit, apoptosis, and telomerase. On the other hand, more animal species are insects than belong to any other comparable taxonomic group, which recommends them for study even if they are not useful models for mammalian cells *in vitro*.

Early results on the *Drosophila* molecular front were limited by the lack of mutant stocks with postponed aging. Mutants with shortened lifespans have been known since the 1920s; *vestigial* for example. But many of these mutants were obviously dying of pathologies that had little to do with normal senescence in adult flies. An important exception were mutants with reduced ovaries, such as *ovariless* (Maynard Smith, 1958), in which absence of female reproductive structures leads to greatly increased lifespan. These stocks effectively embody the principle of antagonistic pleiotropy, particularly between reproduction and survival. However, they have not been generally pursued.

Beginning about a decade ago, various laboratories attempted to increase *Drosophila* lifespan using P-element mediated transgenesis. The story of EF-1α is instructive in this regard. When first published, the paper of Shephard et al. (1989) appeared to show that the provision of additional EF-1α substantially increased lifespan. However, this initial publication involved relatively few transgenic or control lines, raising issues of reproducibility. The Stearns laboratory proceeded to study EF-1α transgenic lines extensively, replicating genetic background and specific insertions. Their findings were that EF-1α inserts enhanced lifespan in a manner that was dependent on background and mode of insertion; there was no general beneficial effect (Stearns and Kaiser, 1993; Kaiser et al., 1997).

Similar confusion arose with another type of transgenic, those involving the free-radical scavenging pathway defined by Cu,Zn SOD and catalase. Early transgenic experiments showed inconsistent results, with some cases of beneficial effects, but others without (Seto et al., 1990; Reveillaud et al., 1991; Orr and Sohal, 1992, 1993). This situation seemed to be resolved when Orr and Sohal (1994) assembled stocks with both SOD and catalase transgenic inserts, giving increased lifespan, but their experiment was compromised by possible hybrid effects, because they crossed independent transgenic

lines to make their "double" transgenic stock, which had both SOD and catalase insertions.

The problems facing all of these transgenic experiments are genetic background and variation in site of insertion. Though it is relatively easy to construct a transgenic fly, it is extremely hard to create its appropriate control at the same time. However, a resolution of these problems may have been achieved in the study of Sun and Tower (1999). In this study, SOD and catalase DNA were inserted with an *hsp70* promoter driving an FLP recombinase system. This system requires a brief heat pulse before the transgenic insert is transcribed, which makes it possible to compare the effects of additional transcripts with an unpulsed control that is virtually identical in genetic background. With this somewhat elaborate system, it was possible for Sun and Tower to demonstrate a significant benefit of increased Cu,Zn SOD expression; catalase augmentation had no detectable effect. Background effects remained, however, even though they did not affect the ability of this system to detect the main effect of the insert. But this additional result helps to underscore why earlier transgenic experiments had proven confusing.

An exciting recent development has been the use of transgenics with tissue-specific gene expression. Parkes et al. (1998) constructed flies with Cu,Zn SOD overexpression in motorneurons. Some of these lines exhibited dramatic increases in lifespan. Although it remains to be seen how consistent their results will prove to be over multiple backgrounds, the specificity of this manipulation makes it an attractive experimental system.

Finally, a profoundly synthetic result has been obtained in the Benzer laboratory. Lin et al. (1998) have produced a mutant—*methuselah*—in which lifespan is increased by about 35% on average. The cunning thing about their mutagenesis strategy was the use of single P-factor mutagenesis, because such mutagenesis is likely to generate many more relatively benign mutations than EMS and like procedures. They have cloned and sequenced the gene, which appears to code for a novel transmembrane protein. Of greater interest, they have shown that this gene also gives enhanced resistance to a variety of stressors, including starvation, high temperature, and paraquat. Paraquat generates abundant free radicals; resistance to it is an indicator of defenses against reactive oxidizing agents. Thus, this single locus ties together many of the findings of physiological and molecular genetics, supporting the importance of stress resistance and free-radical defenses. What remains to be characterized in detail, in this system, is its population genetics. In particular, it would be interesting to know if the lifespan enhancement of the mutant allele is associated with any reduction in early reproduction.

5. Conclusion

The field of *Drosophila* aging genetics is vigorous and diversified. There are certainly problems. The population genetic mechanisms of aging in the genus have not been completely sorted out, perhaps because they are not in fact simple. Technical problems have bedeviled molecular work in this field, particularly issues of genetic background. But there are signs that these problems of genetic background are being resolved by the use of more powerful techniques. Physiological insights have been coming in with great speed, unlike most work on aging genetics, which tends to be lacking in *causally* significant physiological results. Perhaps one general strategy of promise might be the careful integration of population, physiological, and molecular research strategies. In part,

this approach has been recently embodied in the work of Lin et al. (1998) who discovered and characterized the first interesting *Drosophila* aging mutant.

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