New explanation for the longevity of social insect reproductives: Transposable element activity

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The increasing frailty that accompanies old age deeply influences our lives and permeates our thoughts. As a result, studies tackling this topic naturally fascinate both specialists and the general public. However, despite a wealth of research, the fundamental mechanisms of aging remain undetermined. Damage to molecules, such as DNA and proteins that are essential for life and proper organismal function, is a prime candidate for explaining the degeneration that accompanies aging (1). Much of the research into age-related DNA damage has focused on the damage caused by oxidative stress (2), but this is by no means the only potential source of disruption that can occur to DNA. A ground-breaking study in PNAS by Elsner et al. (3) leverages the remarkable natural differences in longevity found among termite castes to identify transposable element (TE) activity as a potential source of DNA damage that is elevated in older workers compared with the reproductive kings and queens.

Transposable Elements and Social Insects

TEs are genetic elements capable of moving around the genome and inserting themselves into new locations (4). These insertions can cause significant damage when they interrupt crucial sequences of DNA, such as protein coding sequences or regulatory regions, and are thus associated with mutation-based diseases, such as cancer (5). Because of these deleterious effects, the expression of TEs (which is required for their transposition) is usually suppressed by the cell machinery. However, this suppression is not complete (6) and TE activity increases with age, leading to an accumulation of TE-related damage in a range of species (6–8).

While much research on aging focuses on humans and other mammals, important breakthroughs have come from model organisms, such as flies, worms, and yeast (9). Another, equally valuable line of research comes from organisms with more unusual patterns of aging, allowing us to detect features that underlie unique, and often extreme aging phenotypes. Foremost among these are the social insects, which have the longest adult lifespans of all insects and which display huge disparities in longevity between genetically identical reproductives (long-lived) and workers (short-lived). The largest differences are found in the highly social ants and termites, where reproductives can live up to 30 y (10), while workers typically have 10-fold shorter lifespans (11). For example, in the termite *Macrotermes bellicosus* [the species studied by Elsner et al. (3)], reproductives (queens and kings) can live up to 20 y, whereas minor and major workers do not live longer than a few months.

Because reproductives and workers do not differ genetically, their vastly different longevities must be due to differences in gene expression during development and adult life. Research into aging in social insects has therefore focused on studying differences in gene expression, especially in nutrient signaling or antioxidant pathways (12, 13), with only a few studies investigating the type of molecular damage that accompanies aging. In both honey bees and ants, there is evidence for higher expression of antioxidant enzymes in queens compared with workers (14, 15), and studies in honey bees have reported that a form of oxidative damage (lipofuscins) accumulates with age and does so more slowly in long-lived compared with short-lived workers (16). Whether oxidative damage accumulates faster in workers than in reproductives, however, remains unknown. In the black garden ant, queens show higher expression of DNA repair genes than workers (17), but this does not appear to be associated with increased rates of DNA damage (18). Without understanding the form of damage that limits lifespan, it is impossible to understand why reproductives live so much longer than workers.

Transposable Element Expression Increases with Age in Short-Lived Termite Workers

Elsner et al. (3) used RNA sequencing to study the global patterns of gene expression in young and old individuals of reproductives and workers in

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M. bellicosus. As previously described in other species (6, 7), they found that the expression of TEs increases with age in major workers. However, there was no change with age in reproductives or in minor workers. Elsner et al. (3) then investigated whether this increased TE activity can be explained by reduced activity of the PIWI-interacting RNA (piRNA) pathway, which is associated with TE silencing in fruit flies (19). The authors showed that the ping-pong amplification cycle, which acts in the germline to amplify piRNAs that are actively involved in TE silencing (19), is down-regulated with age in major workers, but not in reproductives or minor workers. These results suggest that the increased longevity of *M. bellicosus* reproductives may in part be due to the continued suppression of TEs throughout their life. What is remarkable is that ping-pong amplification generally occurs only in the germline (19), whereas Elsner et al. (3) were studying gene expression in the head. Termites therefore appear to employ a germline TE silencing pathway as a somatic maintenance mechanism.

The study by Elsner et al. (3) is particularly compelling because it reports on both the possible form of damage that is being accumulated (DNA damage resulting from the increased activity of TEs) and the underlying cause (down-regulation of TE suppression pathways). It draws attention to an aspect of aging that has so far been ignored in social insects, but which should receive more attention. The study also contributes to our understanding of aging more generally, showing that an age-related increase in TE activity is associated with differences in longevity of more than an order-of-magnitude. This study also benefits from its use of field-caught specimens, thus removing the effects of laboratory-rearing, which takes organisms out of their natural environment where normal aging occurs. Obtaining individuals of known age from the field is extremely challenging and rarely achieved.

Perspectives

This study raises many interesting questions and avenues for future research. First, as noted by Elsner et al. (3), it is interesting that the increase in TE activity is limited to major workers and not minor workers, whose longevity is similar to that of the major workers. The lack of TE differences between young and old minor workers suggests that increased TE activity may be an aspect of aging restricted to major workers, and that a different form of physiological damage may limit longevity in minor workers. Second, is the decreased repression of TE activity a cause or a symptom of aging? Aging caused by the accumulation of DNA damage might be best explained by the disposable soma theory, which predicts that aging is the result of a trade-off between reproduction and investment into processes that prevent and repair molecular damage in the soma (1). Under this model, the damage that causes aging should begin accumulating as soon as individuals reach maturity because there is a trade-off between investment into reproduction and somatic maintenance, and the optimal life-history strategy never favors investing fully into maintenance (1). Accordingly, if increased TE activity were the cause of aging in major workers, we would expect to see high TE activity not only in old but also in young individuals. The high levels of TE activity in old compared with young individuals may therefore indicate that reduced TE suppression is an effect of aging in major workers, and that the underlying cause of differential aging remains to be discovered. Third, does the increase in TE activity effectively translate into increased TE mobility in the genome? This could be tested by measuring the relative abundance of TE sequences using quantitative PCR of genomic DNA (7). Fourth, is the age-dependant increase in TE activity also higher in the longer-lived castes compared with the shorter-lived caste in other social insects? With the growing throughput and affordability of high-throughput sequencing studies, this question should be readily addressed in the near future.

Finally, an interesting experiment would be to investigate whether termite reproductives show lower disruption of somatic gene expression with age compared with major workers and shorter-lived insects. It is already known that increased repression of TE activity in fruit flies can extend lifespan (20), and it would thus be interesting to inhibit the TE-silencing pathway in termite reproductives to increase genome disruption and see whether this reduces longevity.

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