Y chromosome makes fruit flies die younger

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In most animal species, males and females display distinct survival prospect, a phenomenon known as sex gap in longevity (SGL, Marais et al. 2018). The study of SGLs is crucial not only for having a full picture of the causes underlying organisms’ health, aging and death but also to initiate the development of sex-specific anti-aging interventions in humans (Austad and Bartke 2015). Three non-mutually evolutionary causes have been proposed to underlie SGLs (Marais et al. 2018). First, SGLs could be the consequences of sex-differences in life history strategies. For example, evolving dimorphic traits (e.g. body size, ornaments or armaments) may imply unequal physiological costs (e.g. developmental, maintenance) between the sexes and this may result in differences in longevity and aging. Second, mitochondria are usually transmitted by the mother and thus selection is blind to mitochondrial deleterious mutations affecting only males. Such mutations can freely accumulate in the mitochondrial genome and may reduce male longevity, a phenomenon called the mother’s curse (Frank and Hurst 1996). Third, in species with sex chromosomes, all recessive deleterious mutations will be expressed on the single X chromosome in XY males and may reduce their longevity (the unguarded X effect). In addition, the numerous transposable elements (TEs) on the Y chromosome may affect aging. TE activity is normally repressed by epigenetic regulation (DNA methylation, histone modifications and small RNAs). However, it is known that this regulation is disrupted with increasing age. Because of the TE-rich Y chromosome, more TEs may become active in old males than in old females, generating more somatic mutations, accelerating aging and reducing longevity in males (the toxic Y effect, Marais et al. 2018).

The relative contributions of these different effects to SGLs remain unknown. Sex-differences in life history strategies have been considered as the most important cause of SGLs for long (Tidière et al. 2015) but this effect remain equivocal (Lemaître et al. 2020) and cannot explain alone the diversity of patterns observed across species (Marais et al. 2018). Similarly, while studies in Drosophila and humans have shown that the
mother’s curse contributes to SGLs in those organisms (e.g. Milot et al. 2007), its contribution may not be
strong. Recently, two large-scale comparative analyses have shown that in species with XY chromosomes
males show a shorter lifespan compared to females, while in species with ZW chromosomes (a system in
which the female are the heterogametic sex and are ZW, and the males ZZ) the opposite pattern is observed
(Pipoly et al. 2015; Xirocostas et al. 2020). Apart from these correlative studies, very little experimental
tests of the effect of sex chromosomes on longevity have been conducted. In Drosophila, the evidence
suggests that the unguarded X effect does not contribute to SGLs (Brengdahl et al. 2018). Whether a toxic Y
effect exists in this species was unknown.
In a very elegant study, Brown et al. (2020) provided strong evidence for such a toxic Y effect in Drosophila
melanogaster. First, they checked that in the D. melanogaster strain that they were studying (Canton-S),
males were indeed dying younger than females. They also confirmed that in this strain, as in others, the male
genomes include more repeats and heterochromatin than the female ones using cytometry. A careful
analysis of the heterochromatin (using H3K9me2, a repressive histone modification typical of
heterochromatin, as a proxy) in old flies revealed that heterochromatin loss was much more important in
males than in females, in particular on the Y chromosome (but also to a lesser extent at the pericentromeric
regions of the autosomes). This change in heterochromatin had two outputs, they found. First, the
expression of the genes in those regions was affected. They highlighted that many of such genes are involved
in immunity and regulation with a potential impact on longevity. Second, they found a striking TE
reactivation. These two effects were stronger in males. While females showed clear reactivation of 6 TEs,
with the total fraction of repeats in the transcriptome going from 2% (young females) to 4.6% (old females),
males experienced the reactivation of 32 TEs, with the total fraction of repeats in the transcriptome going
from 1.6% (young males) to 5.8% (old males). It appeared that most of these TEs are Y-linked. And when
focusing on Y-linked repeats, they found that 32 Y-linked TEs became upregulated during male aging and the
fraction of Y-linked TEs in the transcriptome increased ninefold.
All these observations clearly suggested that male longevity was decreased because of a toxic Y effect. To
really uncover a causal relationship between having a Y chromosome and shorter longevity, Brown et al. (2020)
artificially produced flies with atypical karyotypes: X0 males, XXY females and XYY males. This is
very interesting as they coulduncouple the effect of the phenotypical sex (being male or female) and having
a Y chromosome or not, as in fruit flies sex is determined not by the Y chromosome but by the X/autosome
ratio. Their results are striking. They found that longevity of the X0 males was the highest (higher than XX
females in fact), and that of the XYY males the lowest. Females XXY had intermediate longevities.
Importantly, this was found to be robust to genomic background as results were the same using crosses from
different strains. When analysing TEs of these flies, they found a particularly strong expression of the Y-linked
TEs in old XXY and XYY flies. Interestingly, in young XXY and XYY flies Y-linked TEs expression was also strong,
suggesting the chromatin regulation of the Y chromosome is disrupted in these flies.
This work points to the idea that SGLs in D. melanogaster are mainly explained by the toxic Y effect. The
molecular details however remain to be elucidated. The effect of the Y chromosome on aging might be more
complex than envisioned in the toxic Y model presented above. Brown et al. (2020) indeed found that
heterochromatin loss was globally faster in males, both at the Y chromosome and the autosomes. The
organisation of the nucleus, in particular of the nucleolus, which is involved in heterochromatin maintenance,
involves the sex chromosomes in D. melanogaster as discussed in the paper, and may explain this
observation. The epigenetic status of the Y chromosome is known to affect that of all the autosomes
in Drosophila (Lemos et al. 2008). Also, in Brown et al. (2020) most of the work (in particular the genomic
part) has been done on Canton-S. Only D. melanogaster was studied but limited data suggest
different Drosophila species may have different SGLs. The TE analysis is known to be tricky, different tools to
analyse TE expression exist (e.g. Lerat et al. 2017; Lanciano and Cristofari 2020). Future work should focus on
testing the toxic Y effect on other D. melanogaster strains and other Drosophila species, using different tools
to study TE expression, and on dissecting the molecular details of the toxic Y effect.

References


