Review

Are *Drosophila* telomeres an exception or the rule?

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Abstract

At the ends of eukaryotic chromosomes are telomeres, specialized structures with unusual properties. The repetitive structure of telomere regions makes them difficult to deal with in general genome-sequencing projects. Specific efforts to compare sequences and properties of telomeres across species can reveal the generalities of telomere properties.

The concept of telomeres was first conceived in studies of irradiated *Drosophila*: Muller [1] found that X-ray-induced chromosomal rearrangements never resulted in loss of the terminal regions of the chromosomes. This observation, along with those of McClintock [2], led to the idea that the ends of chromosomes, or telomeres, must be different from the ends found at breaks in chromosomes, which are not protected from further detrimental rearrangements. Once the structure of DNA was determined and the properties of DNA replication were worked out, Olovnikov [3,4] and Watson [5] recognized that the normal replication machinery could not complete the replication of the ends of double-stranded DNA. We now know that most organisms replicate their chromosome ends using a special reverse transcriptase-like enzyme, called telomerase [6], which uses an RNA template. The repeated telomere sequences, templated by telomerase, perform two important roles in chromosome biology: they solve the end-protection problem, by 'capping' chromosome ends and they solve the end-replication problem, by adding templated sequence.

Drosophila telomeres are intriguing for a number of reasons because they appear to break the two cardinal rules of telomeres. First of all, telomere maintenance in *Drosophila* is not performed by the canonical telomerase but by a unique transposition mechanism. Two non-LTR (long terminal repeat) retrotransposable elements, HeT-A and TART telomere-associated retrotransposons, are attached specifically to the chromosome ends [7-10]. To date these are the only transposable elements that are known to perform a useful function for the host organism. Perhaps more important is that truncated *Drosophila* telomeres can be maintained and passed on both somatically and through the germ line, despite their progressive erosion over generations in the absence of HeT-A or TART elements [11-13]. This observation is in apparent contradiction to the primary end-protection or capping function of all telomeres, and together with other results led to the question of whether *Drosophila* provides an exception to the general properties of telomere biology. This review covers recent studies of telomere maintenance and end-protection in *Drosophila* and other organisms, demonstrating that rather than being an exception, the telomeres of *Drosophila* behave within the realms of known telomere properties and are providing new insights that may be applied to all telomeres.

The structure of telomeres

In most eukaryotic organisms, including protozoans, fungi, insects, higher plants and mammals, the chromosome termini are composed of short DNA-sequence repeats. These are generally G-rich and are maintained by telomerase (see [14,15] for reviews). There are many exceptions to this general rule, including *Drosophila* [7-10] and other insects, notably *Chironomus* (midge) species [16-18] and the mosquito *Anopheles gambiae* [19], as well as onion-related plants of the genus *Allium* [20]. Most of these exceptions have a complex tandem-repeat array at their ends [16-20]; the *Drosophila* non-LTR HeT-A and/or TART retrotransposable elements [7-10] may be unique in this respect. Virtually all eukaryotes, including *Drosophila* and the other

'exceptions' mentioned above, have complex repeats near the chromosome terminus called telomere-associated sequences (TASs) or subtelomeric repeat sequences (STRs) (see [21] for review). Many also have transposable elements near or even embedded within the telomerase-maintained repeats, making them somewhat similar to *Drosophila* (see Figure 1). The yeast *Saccharomyces cerevisiae* has a subtelomere specific LTR transposon, Ty5 [22], as well as a large open-reading frame containing an element called Y′ embedded in the telomere repeats [23,24]. The alga *Chlorella* has a telomeric element called Zepp [25,26]. The silk moth *Bombyx mori* has two telomeric non-LTR retrotransposable elements called SART and TRAS [27,28], which are not dissimilar to the HeT-A and TART elements of *Drosophila*. Recently, three transposon families in the protozoan intestinal parasite *Giardia lamblia* were described, two of which are telomere-specific [29]. *Drosophila melanogaster* and some of its relatives, such as *Drosophila yakuba* [30], may be unique in their use of telomeric retrotransposons at the terminus of the chromosomes but they are not alone in having telomeric elements. In addition, not all *Drosophila* species apparently have these retroelements: the more distantly related *Drosophila virilis* group apparently has a complex array of tandem repeats analogous to those found in *Chironomus* and *Allium* [31].

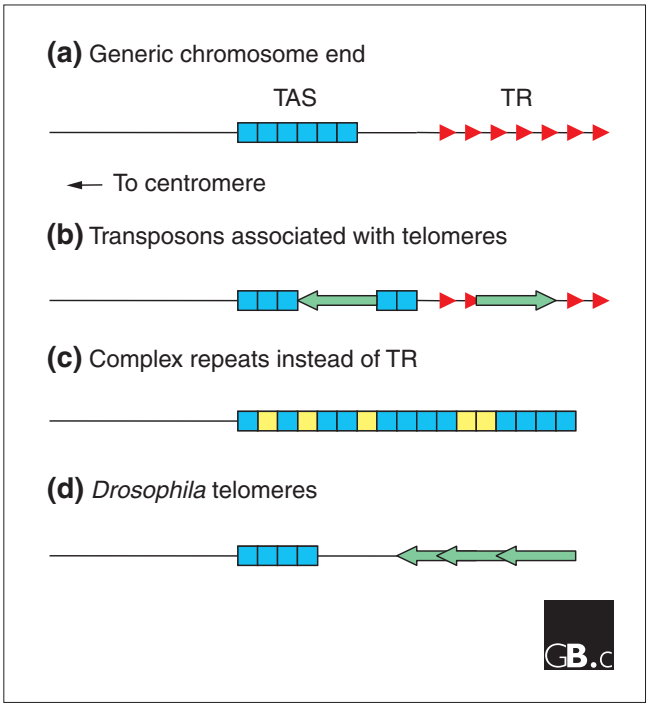

Figure 1
Telomere structures, illustrating the myriad mechanisms for maintaining chromosome ends. **(a)** Most organisms have the generic chromosome-end structure consisting of the G-rich telomere repeats (TRs) that are maintained by telomerase with adjacent telomere associated sequences (TASs), also called subtelomeric repeat sequences (STRs) (see [21,63] for review). **(b)** In some organisms, such as the yeast *S. cerevisiae* [23], the moth *Bombyx mori* [27,28], the alga *Chlorella* [25,26], and protozoan *Giardia lamblia* [29], there are retrotransposable elements (green arrows) embedded in or near the telomere repeats. **(c)** In some organisms, such as the mosquito *Anopheles gambiae* [19], the onion *Allium cepa* [20], the midge *Chironomus* [16-18,64], and the fruitfly *Drosophila virilis* [31], the chromosome ends consist of complex tandem repeats that are not maintained by telomerase. **(d)** *Drosophila melanogaster* and close relatives have only retrotransposable elements at their ends [7-10].

The function of telomeres

The primary function of telomeres is to prevent the end of the chromosome from being treated as a DNA double-strand break, which would be subject to fusions and rearrangements and would invoke cell-cycle arrest [14]. This concept of the telomere capping the chromosome end, first recognized by Muller [1] in his studies of X-ray-induced rearrangements in *Drosophila*, has driven much of the research in telomere biology to this day (see [14] for review).

In mammals, loss of telomeres results in cell-cycle arrest and eventual cell death via induction of apoptosis. Telomere fusions can be found in mitotic cells in such senescing cultures [32]. In yeast the analogous situation is seen in telomerase-negative cells: a culture of such cells eventually stops dividing and evidence of fusions can be recovered [33]. Even a single double-strand break near a telomere can induce cell-cycle arrest [34]. Genes have now been identified in mammals and yeast that are involved in preventing the end of the chromosome from inducing the DNA-damage response [35-38]. In *Drosophila* there also are mutants that result in telomeric fusions [39-41].

The observation that terminal deletions can be recovered and maintained in *Drosophila* [12,13] appears to contradict our understanding of the prime function of telomeres. These truncated ends do not contain any HeT-A or TART sequences and continuously erode with each generation. They can be 'healed' by the addition of HeT-A or TART [10,12], but the ability to propagate the truncated end without inducing cell-cycle arrest or resulting in end-to-end fusions means that end protection is sequence-independent and can be acquired by the truncated ends. In studies designed to induce a break in a non-essential chromosome fragment, initial findings indicated a lack of DNA-damage response [13]. Subsequently, a cell-cycle-arrest response was found [42], indicating that *Drosophila* telomeres do fulfill the primary role of end protection. One solution to the apparent contradiction is that the end-protection function, mediated through the heterochromatin protein HP1 [40] and other proteins [39], is sequence-independent. This would be analogous to the current understanding of centromere function being epigenetically determined by chromatin state [43]. The sequence-independence of the end-protection function may be unique to *Drosophila*, and perhaps *Anopheles* [19], as it seems that telomeric repeat sequences are specifically required in other systems [14]. Alternatively, this property may be more general (see [36] for discussion).

The maintenance of telomeres

The inability of the normal replication machinery to maintain the sequences at the ends of chromosomes was recognized in the early 1970s [3-5]. The solution to this problem was elegantly found in ciliated protozoa where short repeats are added onto the 3′-protruding end of the chromosome by a reverse-transcriptase-like reaction using an RNA template with a complement to the short repeat [6]. This telomerase mechanism has since been found in many organisms and is thought to be the major and ancestral evolutionary solution to the end-replication problem. In the last decade a few exceptions have been found. We now know that a wide range of organisms from plants to insects can have complex tandem repeats at their ends rather than short repeats maintained by telomerase (see Figure 1). Although it is difficult to measure directly in these organisms, a homologous recombination mechanism is proposed for the continued maintenance of such chromosomes.

In the yeasts *S. cerevisiae*, *Schizosaccharomyces pombe* and *Kluyveromyces lactis* as well as in mammalian cells, the telomeres can be maintained without telomerase [44-49]. When telomerase is absent, as in normal somatic mammalian cells and in mutant yeast, the telomeres erode until the cell-cycle checkpoint is induced, resulting in loss of population and culture growth. If the checkpoint is bypassed or overcome then further erosion occurs, resulting in loss of capping or end-protection and the cultures 'crash' due to the genomic instability that arises from free DNA ends. In higher organisms this leads to apoptosis. A few rare cells appear to arise out of these cultures and they use mechanisms for alternative lengthening of telomeres (ALT) [44-49]. These survivors are generally quite healthy, and have recovered their end-protection. In all cases so far, the mechanism(s) of ALT are based on (or thought to be based on) homologous recombination. In most cases of ALT there is telomere-repeat elongation, to lengths much longer than in telomerase-maintained telomeres. In some cases there is amplification of larger repeated elements embedded in the telomere repeats. The general structure of these ALT ends derived from telomerase-based systems is very similar to the long tandem repeats found naturally at telomere ends in some of the non-telomerase-based systems. The only real difference is that the repeats in the ALT cells are composed of the original telomere repeats while those of *Chironomus*, *Anopheles* and *Allium* are not the same as the presumed ancestral telomere repeat.

The maintenance of *Drosophila* telomeres is different from all other maintenance mechanisms [50-53]. In this case, as telomeres erode there is an occasional transposition event mediated by reverse transcription. A cDNA copy of an RNA template located at the eroding end is made, resulting in the elongation of the telomere. It is not clear how this mechanism is regulated, but there are mutations that result in very long telomeres [54,55].

Evolution of *Drosophila* telomeres

The structure and expression of HeT-A and TART elements has led to the idea that the *Drosophila* telomere uses an adaptation of the telomerase-based mechanism of telomere maintenance [50-52] that may have arisen very early in the evolution of Diptera, the order that includes flies, midges and mosquitoes. An alternative to a direct connection between HeT-A, TART and telomerase is that the current telomere-maintenance system in *Drosophila* evolved through several steps (Figure 2). Perhaps the first step was the loss of sequence-dependence of capping, which must have occurred at some stage during *Drosophila* evolution [14]. Followed by loss of telomerase, this could have resulted in an ALT maintenance mechanism, as is seen in some other insects. Eventually the transposable elements - which were perhaps already present - were upregulated sufficiently to take over the maintenance function.

This hypothesis is supported by many observations, including the clear epigenetic transcriptional silencing phenomena at telomeres in many organisms, such as *Drosophila* [56]. The repression of gene expression at telomeres could be a manifestation of some other function, as is thought to be the case for centromeres [43]. Perhaps this function is part of end-protection or capping, which in some cases does not have to be dependent on a specific sequence. ALT mechanisms based on homologous recombination appear to have arisen frequently in evolution, as have cellular systems in which telomerase function is lost [18-20,44-49]. At least two diverse insects, *Chironomus* and *Anopheles*, have dispensed with telomerase and canonical telomere repeats, and in the case of *Anopheles* the capping function appears to be sequence-independent and telomere-maintenance-independent [57]. In the close relatives of the *D. virilis* subgroup (more distant from *D. melanogaster* than *D. yakuba*) the telomeres appear to be complex tandem arrays of a non-canonical repeat [31] and are therefore likely to be ALT-like in their maintenance. Finally, many organisms have transposable elements embedded in or near the telomere repeats and these could easily spread by ALT mechanisms in the absence of telomerase. Indeed in yeast the Y′ element, not known to be a transposable element, is spread to all ends in some ALT survivors [46], and in addition its expression increases many fold in the absence of telomerase [58]. Perhaps *D. melanogaster* and close relatives were primed for HeT-A and TART retrotransposition during the evolution of telomerase loss. Indeed, evidence of homologous recombination, in the maintenance of *Drosophila* telomeres is sometimes seen in rescues of eroding telomeres by addition of HeT-A elements [59]. In many such events there is clear evidence of recombinational capture of the retroelement from another telomere rather than the retrotransposition resulting in a *de novo* HeT-A addition.

Bombyx mori telomeres are interesting as they have two sets of retrotransposable elements embedded in the telomere

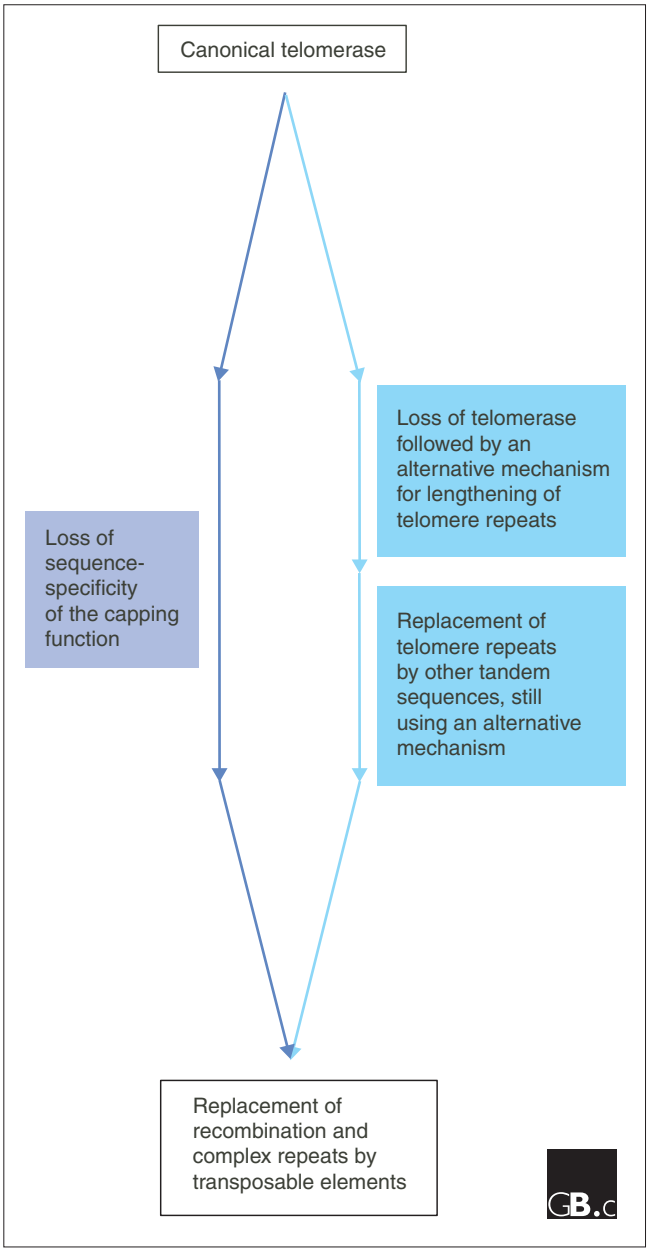

Figure 2
Potential steps in the evolution of *Drosophila* telomeres. Several steps were probably involved in the evolution of the HeT-A and TART system of telomere maintenance. Two steps could have occurred sequentially or in parallel: these are the loss of sequence specificity for the capping function of telomeres, and the recombinational maintenance of telomeres after loss of telomerase. After loss of telomerase and acquisition of an ALT mechanism, the telomere repeats, if still present, may be replaced by other tandem repeats. Finally, retrotransposable elements that may already be present take over the end-maintenance function.

repeats [27,28], making them similar in structure to the Type I ALT survivors of *S. cerevisiae* in which tandem arrays of the Y′ elements embedded in the TG1-3 repeats maintain the ends via homologous recombination. Interestingly, telomerase has yet to be found in *Bombyx* [60], despite the fact that it has long tracts of the insect telomere repeat [61]. Telomerase may be present in undetectably low levels or there may be the beginnings of an ALT mechanism of telomere maintenance. The resolution of this issue will be interesting as *Bombyx* is in the insect order of Lepidoptera (moths and butterflies), which is close to Diptera, and most lepidopteran species that have been tested have both the insect telomere repeat as well as telomerase activity [60]. Perhaps experiments in which telomerase function is knocked out in *Bombyx* could address the question.

The telomeres of *Drosophila* are unique and of interest to biologists for a number of reasons. Despite the apparent differences from most other organisms, there are lessons to be learned that are applicable to all. The primary function of telomeres - end-protection or capping - has generally been functionally linked with telomere maintenance and the G-rich repeats added by telomerase. *Drosophila* telomeres tell us that these functions can be separated and that end-protection may not require the telomerase-maintained telomere repeats found in most eukaryotic organisms. The heterochromatin-dependent nature of the function of capping has been pointed out before [40] and has been hypothesized to account for capping in the long tandem arrays found in ALT maintained telomeres [36]. *Drosophila* telomeres also highlight the myriad ways of maintaining the ends of chromosomes. There are now several known mechanisms of telomere maintenance - from telomerase to homologous recombination extending canonical telomere repeats, to homologous recombination extending tandem arrays of larger and/or more complex repeats, and finally to those complex repeats achieving addition by their own expression.

Drosophila is merely at one extreme of the spectrum of possibilities for telomere structure. The current genome-sequencing projects may not themselves reveal much about telomeres, but specific studies can elucidate the evolution and biology of telomeres. The continued evolution of the *Drosophila* telomere-maintenance mechanism is a case in point, with recent comparisons between *D. yakuba* and *D. melanogaster* [62]. We can expect new insights over coming months as projects focused on telomeres come to fruition alongside the more acclaimed 'complete' genome sequences.

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