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Transposon control mechanisms in telomere biology

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The ends of linear eukaryotic chromosomes, telomeres, are elongated by reverse transcriptase activity provided by the enzyme telomerase, or by specialized telomeric retrotransposons. Telomerase and telomeric retrotransposons represent unique examples of structurally different, but evolutionary and functionally related machineries that generate essential chromosome structures, namely telomeres. In fact, the telomere is an example of the taming of retroelements for the maintenance of essential genome function. Many features of telomere homeostasis are conserved between telomerase and retrotransposon maintained telomeres. The retrotransposon origin of telomeres suggests that mechanisms of transposon control could be adopted for telomere regulation. The discovery of the role of *Drosophila* telomeric piRNAs in telomere length control and the influence of LINE-1 retroelements on telomere regulation in human cells strongly support this idea and allow us to look at telomere regulation from a new angle.

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Introduction

The problem of incomplete replication of chromosome ends was originally raised by the Russian scientist Alexey Olovnikov [1,2]. The main function of telomeric DNA is to compensate for linear chromosome end degradation. In most organisms, short repeats of telomeric DNA are synthesized by a telomere-specific reverse transcriptase (RT), called telomerase, which utilizes RNA as a template [3]. The mechanism of telomere elongation by telomerase is very similar to process of retrotransposition of non-LTR (long terminal repeat) retrotransposons. Phylogenetic analysis of RT sequences strongly supports the idea that telomerase and retrotransposons have evolved from a common ancestral retroelement [4,5]. Endonuclease deficient *Penelope*-like retroelements (PLE) found in telomeres from representatives of four eukaryotic kingdoms (Table 1) were shown to be most closely related to telomerase [6]. Thus, telomerase ribonucleoprotein (RNP) complex may be considered as a specialized retroelement, that specifically targets the chromosome termini [7••]. Species of the *Drosophila* genus most likely, lost telomerase expression during evolution and therefore their telomeres are elongated exclusively by transpositions of telomeric retrotransposons [8]; a mechanism which is now considered as a primary evolutionary mode of protection for linear chromosome ends [9].

Dissection of the molecular mechanisms underlying telomere homeostasis is a hot topic in genome biology. Paradoxically, the majority of telomerase telomere research is performed using somatic cancer cells characterized by telomerase upregulation. Currently, it is well established that telomerase in mammals is highly active *in vivo* only in a few cell types such as germline, embryonic stem cells, zygote and early embryo [10–13]. However, little is known about telomere regulation in normal tissues and during development. Moreover, one of the major multicellular model organisms, *Drosophila melanogaster*, was for decades regarded by the telomerase community as an exception to the telomerase-based telomere system. At the same time, the input of the Piwi-interacting RNA (piRNA) pathway in telomere regulation in the female *Drosophila* germline suggests additional germline-specific functions for telomeres [14•,15–17]. One may speculate that the evolutionary relationship of telomerase and retrotransposons implies a similarity of telomerase and transposon regulation. Accordingly, the role of transposon control machinery in telomere function is likely to become a research focus in telomere biology.

Transposons in telomeres: alternative or ancestral mode of chromosome end protection?

Two types of telomere elongation, provided by telomerase or by retrotransposon attachments, were considered for a long time as alternative ways of telomeres maintenance (Figure 1). Indeed, a phylogenetic analysis of *Drosophila* telomeres demonstrated that multiple autonomous and non-autonomous telomere-specific retrotransposons were recruited to perform telomere maintenance [8]. The telomerase gene was not found in *Drosophila* genome, presumably due to its loss after replacement of dysfunctional telomerase with specialized telomeric retrotransposons [9,18]. Distribution of structural and

Table 1

Retrotransposons in telomeres.

Kingdom, Phylum, *Order*	Telomeric retrotransposon	Telomerase or telomeric repeats
Protozoa, Metamonada [56]	Non-LTR	+
Chromista, Heterokonta [6]	PLE	+
Plantae, Chlorophyta [57]	Non-LTR	+
Tracheophyta [6]	PLE	+
Fungi, Ascomycota [58]	Non-LTR	+
Basidiomycota [6]	Non-LTR, PLE	+
Animalia, Arthropoda,		
Diptera [8,18,59]	Non-LTR	–
Lepidoptera [19]	Non-LTR	+
Hemiptera [60]	Non-LTR	+
Chelicerata (subphylum) [9]	Non-LTR	+
Rotifera [6]	PLE	+
Chordata, *Primates* [20]	Non-LTR	+

enzymatic functions between different telomeric retroelements in *Drosophila* (*HeT-A*, *TART* and *TAHRE*) as well as between telomerase components (telomerase RT and RNA components) seems to be important for fine regulation of telomere length. The key feature of retrotransposon telomeres is that the RNA template for telomere elongation and RT activity are encoded by the telomeric sequences themselves, in contrast to the telomerase subunit genes which are located at different genomic loci.

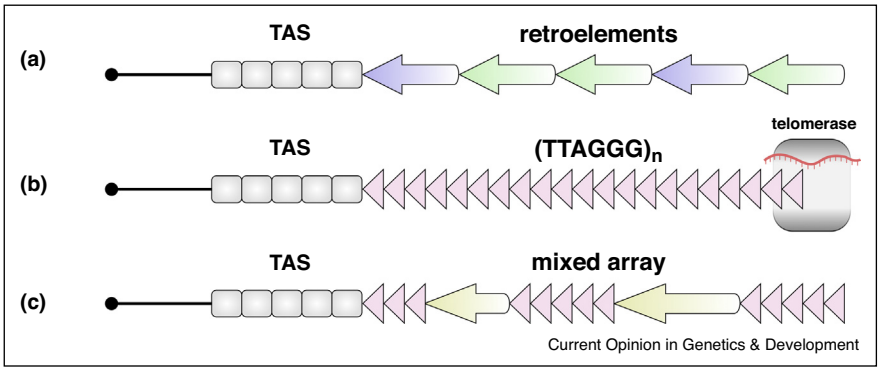
However, the subdivision of species into those that use telomerase or retrotransposons in telomeres is not strict. Indeed, retrotransposon insertions in telomerase-generated sequences were found during recent years in diverse present-day species (Figure 1, Table 1). Given that telomerase activity is extremely low in the silkworm and some other insects, it was proposed that non-LTR retrotransposons have been co-opted for telomere maintenance [9,19]. Moreover, endonuclease-independent retrotranspositions of *LINE-1* (*L1*, long interspersed nuclear element-1) at dysfunctional telomeres were detected in mammals [20]. This is not surprising, taking into account the intrinsic ability of retrotransposons to repair broken chromosomes by targeting DNA lesions using the 3′ hydroxyl to initiate endonuclease-independent reverse transcription [21]. It is believed that the attachments of non-LTR retrotransposons at the ends of DNA double-strand breaks have eventually given rise to 'proto-telomeres' of the primary linear chromosomes [9].

These data suggest that retroelements are not only the ancestors of telomerase, but also can provide a bypass for telomere repair in case of lost or decreased telomerase activity [7••].

Similarities and differences in the structure of the telomeric complex in telomerase and retrotransposon telomeres

The telomere is a complex structure containing, besides telomeric DNA itself, telomeric proteins, long telomeric transcripts and small telomeric RNAs (Figure 2). All these components are involved in the regulation of telomere homeostasis. Studies of telomere function in different organisms revealed a striking conservation of the basic principles of telomere regulation independent of their DNA sequence [8,22,23•]. The primary role in telomere protection belongs to the telomere capping complex. This protein structure differentiates chromosome ends from DNA breaks in order to prevent activation of DNA repair system leading to chromosome fusions. Assembly of the telomere protection complex is mediated by the temporal interaction of its components with the DNA repair system proteins [24]. A crucial component of the telomere capping complex is a single-strand DNA binding protein which protects exposed 3′ overhangs of telomeres. Such proteins were revealed in telomerase

Figure 1



Different modes of telomere elongation. **(a)** *Drosophila* telomeres are formed exclusively as a result of the retrotransposition of specialized telomeric retrotransposons. **(b)** Whereas in mammals and most other species telomeres are maintained by telomerase, which synthesizes short 6–9 nucleotide repeats using RNA as a template. The human-specific telomeric repeat is shown. **(c)** A mixed type of telomere elongation: telomeric retrotransposons are inserted into the telomerase generated repeats. Telomere-associated sequences (TAS) revealed in a broad spectrum of species and composed of various repeated elements are indicated.