ORGANIZATION AND MAINTENANCE OF *DROSOPHILA* TELOMERES: THE ROLES OF TERMININ AND NON-TERMININ PROTEINS

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Drosophila telomeres are elongated by occasional transposition of specialized retroelements rather than telomerase activity, and are assembled independently of the sequence of the DNA termini. *Drosophila* telomeres are capped by terminin, a complex formed by the HOAP, Moi, Ver and HipHop proteins that localize exclusively at telomeres and protect them from fusion events. Other proteins required to prevent end-to-end fusion include HP1, Eff/UbcD1, ATM, the components of the Mre11-Rad50-Nbs (MRN) complex, and the Woc transcription factor. The terminin proteins are encoded by fast-evolving genes and are not evolutionarily conserved outside the *Drosophila* species. In contrast, the non-terminin telomere capping proteins are not fast-evolving, do not localize only at telomeres and are conserved from yeasts to mammals. We propose that following telomerase loss, *Drosophila* rapidly evolved terminin to bind chromosome ends in a sequence-independent manner, and that non-terminin proteins did not evolve as rapidly as terminin because of the functional constraints imposed by their involvement in diverse cellular processes. This hypothesis suggests that the *Drosophila* non-terminin proteins might correspond to ancestral telomere-associated proteins with homologues in other organisms including humans.

Key words: terminin, telomeres, telomere fusion, *Drosophila*.

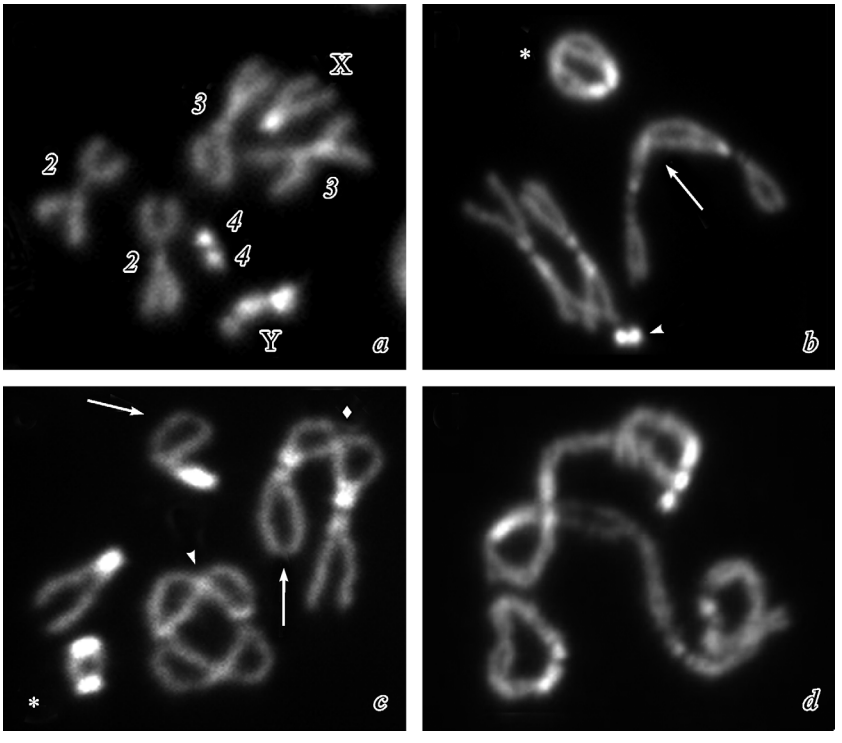
Telomeres of all eukaryotes are nucleoprotein complexes that protect the extremities of linear chromosomes from degradation and fusion, counterbalance incomplete replication of terminal DNA, and allow cells to distinguish natural chromosome termini from broken DNA ends (Jain, Cooper, 2010; O'Sullivan, Karlseder, 2010). In most organisms, the end replication problem is solved by the telomerase holoenzyme that mediates the addition of short GC-rich repeats to chromosome ends. In *Drosophila*, telomerase is absent, and telomeres are elongated by transposition of specialized retroelements to chromosome ends (Mason et al., 2008; Pardue, DeBaryshe, 2011; Zhang, Rong, 2012).

Maintenance of *Drosophila* telomere length

Drosophila telomeres are elongated by targeted transposition of three specialized non-long terminal repeat (LTR) retrotransposons called *HeT-A, TART* and *TAHRE* (collectively abbreviated as HTT). These transposable elements (TEs) target individual telomeres at rates ranging from 10^{-2} to 10^{-4} per fly generation. The HTT elements transpose independently of each other only onto the 5′ ends of both intact and truncated elements and onto broken chromosome ends that have lost all their TEs. As a result, *Drosophila* chromosomes terminate with HTT arrays of variable length in which transposable elements are always arranged head-to-tail with the 3′ end of the most proximal element attached to the end of the chromosome (Mason et al., 2008; Pardue, DeBaryshe, 2011; Zhang, Rong, 2012).

Transposition of telomeric TEs is regulated in several ways. Dominant mutations in the *E*(*tc*) and *Tel* genes cause dramatic elongations of the HTT array. Both mutations come from natural populations and map in the same region suggesting possible allelism. *E*(*tc*) enhances terminal gene conversion with no effect on HTT transposition; the mechanism of *Tel* action is currently unknown (Melnikova, Georgiev, 2002; Siriaco et al., 2002; Capkova Frydrychova et al., 2008). Mutations in the *Su*(*var*)*205* gene that encodes HP1 increase the rate of HeT-A transcription in somatic cells of about two orders of magnitude (Savitsky et al., 2002; Perrini et al., 2004). The expression of telomeric retroelements is also regulated by small RNAs. Piwi-interacting RNAs (piRNAs) target and silence telomeric transposons in the *Drosophila* germline, and mutations in genes that disrupt RNA interference machinery such as *spn-E* and *aub* results in a dramatic increase in the levels of Het-A and TART transcripts (Savitsky et al., 2006; Shpiz et al., 2011).

Although HeT-A, TART, and TAHRE transpose independently from each other, they collaborate to facilitate targeted transposition to chromosome ends. TART and TAHRE encode both a GAG protein and reverse transcriptase (RT). However, HeT-A does not contain an RT coding gene and must therefore rely on an RT encoded by another element. Nonetheless, Het-A is the most abundant element at *Drosophila* telomeres. The abundance of Het-A is probably due to the role of its GAG protein. The transcripts of the telomeric TEs associate with the 3 GAGs they encode, which in turn associate with interphase telomeres mediating targeted transposition. However, the TART and TAHRE GAGs require the



Example of telomeric fusions observed in *Drosophila* larval brains of mutants in terminin encoding genes.

a — wild type male metaphase. *b* — metaphase form a *ver* mutant containing 2-2 (arrow) and 4-4 (arrowhead) dicentric chromosomes, and a dicentric ring involving both X chromosomes (asterisk), all generated by double telomeric associations (DTAs). *c* — metaphase from a *moi* mutant showing a 4-4 DTA (asterisk), a 2-2 dicentric ring chromosome (arrowhead) and a 3-3 DTA (diamond); the XL and 3R telomeres exhibit single telomeric association (STAs) conjoining sister telomeres (arrows). *d* — late prophase/prometaphase from a *cav* mutant displaying multiple TFs.

HeT-A GAG for localization to telomeres, thus justifying the relative abundance of the Het-A element (Pardue, DeBaryshe, 2011).

Drosophila telomeres are sequence independent structures

In 1938 H. J. Muller observed that following X irradiation of males, terminal deletions could not be recovered. He thus postulated that chromosome ends are capped by special structures, he called telomeres, which are essential for chromosome transmission (Muller, 1938). Subsequent studies showed that terminal deletions (TDs) can be recovered by irradiating females carrying a mutation in the *mu2* gene. These TDs were transmitted for many generations without reacquiring HTT elements and were subject to progressive erosion of terminal DNA due to the end replication problem. It is now clear that TDs are capped by a functional neotelomere, which formed independently of the presence of HTT elements (Mason et al., 2008; Rong, 2008). TDs with neotelomeres have also been recovered from mutational events occurred in the male germline. These events include mobilization of P elements inserted near the telomere, breakage of dicentric chromosomes during anaphase, and induction of an enzymatic cut in P element construct inserted in the telomere region. Collectively, these results demonstrate that the HTT elements are not required for the assembly of a functional telomere. In addition, the fact that functional telomeres can form at the ends of different TD chromosomes strongly suggests that Drosophila telomeres are epigenetically determined structures that assemble in a sequence-independent fashion (Mason et al., 2008; Rong, 2008; Raffa et al., 2011).

The *Drosophila* terminin complex

Most of the proteins required for *Drosophila* telomere protection were identified by molecular cloning of genes specified by mutations causing telomeric fusions (TFs) in larval brain cells (Figure). Nine genes that prevent telomere fusions (TF genes) have been so far identified by this approach (Table). These are *effete* (*eff*) (or *UbcD1)* that specifies an E2 ubiquitin conjugating enzyme (Cenci et al., 1997); *Su*(*var*)*205* that encodes HP1 (Fanti et al., 1998); the *Drosophila* homologues of the *ATM, RAD50, MRE11* and *NBS1* DNA repair genes (Bi et al., 2004, 2005; Ciapponi et al., 2004, 2006; Oikemus et al., 2004, 2006; Silva et al., 2004; Song et al., 2004); *without children* (*woc*) that specifies a putative transcription factor (Raffa et al., 2005); *caravaggio* (*cav*) that encodes HOAP (HP1/ORC-associated protein (Cenci et al., 2003); *modigliani* (*moi*) that produces a protein that does not contain known functional motifs (Raffa et al., 2009); and *verrocchio* (*ver*) that specifies an OB-fold containing protein structurally homologous to STN1 (Raffa et al., 2010). An additional protein required to prevent telomere fusion, called HP1-HOAP interacting protein (or HipHop), was identified among the polypeptides that co-precipitate with HOAP (Gao et al., 2010).

Studies on both mitotic and polytene chromosomes indicate that HOAP, Ver, Moi and HipHop are exclusively enriched at telomeres, where they precisely co-localize. In addition, HOAP, Ver and Moi directly interact with each other both *in vitro* and *in vivo*; HOAP and Moi also bind HP1 but Ver does not. HipHop directly interacts with both HOAP and HP1, but it is currently unknown whether it also binds Moi and Ver. Collectively, these results strongly suggest that HOAP, Moi, Ver and HipHop form a complex, we call termi-

***Drosophila* genes required to prevent telomere fusion in larval brain cells**

Gene name	Protein name	Protein full name	Function outside of telomeres
cav	HOAP	HP1-ORC-Associated Protein	None known
hiphop	HiPHop	HP1-HOAP-interacting protein	The same
moi	Moi	Modigliani	» »
ver	Ver	Verrocchio	» »
Su(*var*)*205*	HP1	Heterochromatin Protein 1	Heterochromatin regulation; transcription factor
eff	UbcD1	Ubiquitin Conjugating Enzyme D1	E2 ubiquitin conjugating enzyme
woc	Woc	Without Children	Transcription factor
mre11	Mre11	Meiotic recombination 11	DNA repair; Component of the MRN complex
rad50	Rad50	Radiation sensitive 50	То же
nbs	Nbs	Nijmegen breakage syndrome	» »
tefu	ATM	Ataxia Telangiectasia Mutated	Kinase; DNA damage response
mei-41 (1)	ATR	Ataxia Telangiectasia Related	То же
mus-304 (1)	ATRIP	ATR Interacting Protein	DNA helicase; DNA damage response

N o t e. (1) Mutations in *mei-41* or *mus-304* do not cause TFs but enhance the TF frequency a in *tefu* mutant background so that *mei-41 tefu* and *mus-304 tefu* double mutants exhibit TF frequencies that are much higher than those seen in *tefu* single mutants.

nin, that accumulates only at telomeres (Raffa et al., 2009, 2010, 2011). The structural and functional characterization of the terminin complex is still incomplete and both the architecture and the individual roles of terminin subunits are poorly defined. Nonetheless, the extant data indicate that HOAP and HipHop are primarily bound to the telomeric DNA duplex while Ver and Moi are associated with the single stranded overhang (Raffa et al., 2011).

The roles of the *Drosophila* nonterminin proteins

To date, we know 7 non-terminin proteins required to prevent telomere fusion: HP1, Eff/UbcD1, Mre11, Rad50, Nbs, ATM and Woc. These proteins differ from the terminin components in two important characteristics: unlike the terminin subunits they do not localize and do not function only at telomeres. It should be noted that despite its direct interaction with HOAP, HipHop and Moi, HP1 should not be considered as a terminin component, because it does not localize exclusively at telomeres and has multiple telomere-unrelated functions (Fanti, Pimpinelli, 2008).

Effete/UbcD1 is a highly conserved E2 ubiquitin conjugating enzyme implicated in several *Drosophila* cellular processes. The Eff protein is a major constituent of *Drosophila* chromatin (Filion et al., 2010) with repressive properties and is enriched at many polytene chromosome bands (Cipressa, Cenci, unpublished observations). However, the telomere-associated target(s) of Eff remain to be identified. Given that inactivation of the proteasome does not cause TFs (our unpublished results), Eff-mediated ubiquitination is probably not aimed at protein degradation but is instead a post-translational modification that ensures proper capping function of one or more telomere-associated proteins. Polytene chromosomes from *eff* mutants exhibit normal amount of HOAP, suggesting that Eff function is not required for terminin recruitment and or maintenance at telomeres (Raffa et al., 2011).

Gene *without children (woc)* encodes a zinc finger protein that interacts with HP1c and functions both in transcriptional regulation and telomere capping (Raffa et al., 2005; Font-Burgada et al., 2008). Woc co-localizes with the initiating form of Pol II in many euchromatic bands and is also enriched at telomeres. Woc localization at telomeres is not affected by *cav* mutations and mutations in *woc* do not affect HOAP localization at chromosome ends (Raffa et al., 2005). These results indicate that the Woc function at telomeres is independent of that played by HOAP. It remains to be determined whether the Woc function is also independent of those played by Moi and Ver.

The non-terminin proteins required for telomere protection include several factors involved in DNA repair. Mutations in the *Drosophila mre11, rad50* and *nbs* genes, whose products form the conserved MRN complex, cause TFs in larval brain cells. TFs have been also observed in mutants in the *telomere fusion* (*tefu*) gene that encodes the *Drosophila* homologue of ATM (Ciapponi, Cenci, 2008; Rong, 2008). Mutations in the ATR-encoding *mei-41* gene or in the *mus-304* gene that encodes ATR-interacting protein (ATRIP) do not cause TFs, but interact with mutation in *tefu,* so that the *tefu mei-41* and *tefu mus-304* double mutants exhibit a dramatic increase in TFs compared with *tefu* single mutants (Bi et al., 2005; Ciapponi et al., 2006).

It is currently unknown whether the MRN complex, ATM, ATR or ATRIP interact with terminin. However, mutations in the *rad50*, *mre11* and *nbs* genes strongly reduce HOAP and Moi accumulation at telomeres. Mutations in *tefu*, *mei-41* or *mus-304* have little or no effect on HOAP localization at telomeres but *tefu mei-41* and *tefu mus-304* fail to recruit HOAP at chromosome ends (Raffa et al., 2011). Collectively, these results strongly suggest that terminin recruitment at telomeres requires the wild type function of the MRN complex and the function of either ATM or ATR. This implies that ATM and ATR/ATRIP have partially redundant roles in telomere protection and that failure to phosphorylate a common but as yet unknown target leads to deprotected telomeres. The mechanism by which the combined action of the MRN complex, ATM and ATR-ATRIP leads to terminin recruitment to telomeres is unclear. It has been suggested that interactions of the DNA ends with these DNA repair proteins result in conformational changes that facilitate terminin recruitment (Ciapponi, Cenci, 2008; Rong, 2008).

The telomere-capping proteins in organisms with telomerase

In organisms with telomerase, telomeres bind protein complexes that specifically interact with the DNA repeats generated by telomerase. In *S. cerevisiae,* telomeres are protected by the Rap1-Rif1-Rif2 complex that associates with the telomeric DNA duplex, and by the Cdc13-Stn1-Ten1 complex (CST) that interacts with the 3′ single stranded telomere overhang (Jain, Cooper, 2010). Human telomeres are protected by shelterin, a six-protein complex that specifically binds the telomeric TTAGGG repeats**.** Three of the shelterin subunits directly interact with these repeats; TRF1 and TRF2 bind the TTAGGG duplex, and POT1 binds the 3′ overhang. TRF1, TRF2 and POT1 are interconnected by TIN2 and TPP1, and TRF2 interacts with hRap1, a distant homologue of *S. cerevisiae* Rap1. The shelterin subunits share three properties that distinguish them from the nonshelterin telomere-associated proteins. They are specifically enriched at telomeres; they are present at telomeres throughout the cell cycle; and their functions are limited to telomere maintenance (Palm, de Lange, 2008).

The Stn1 and Ten1 subunits of the CST complex are conserved in *S. pombe*, plants and humans, while shelterin-like elements are found in *S. pombe* and plants but not in *S. cerevisiae*. *S. pombe* and plants have both a shelterin-like and a CST-like complex, which are both required for telomere protection. The two complexes are present also in humans. However, the human CST complex does not share the shelterin properties and appears to have a relatively minor role in telomere capping (Jain, Cooper, 2010).

In addition to the shelterin and CST components, human telomeres contain several conserved polypeptides required for telomere function. These polypeptides, often called shelterin accessory factors, include many proteins involved in DNA repair such as the ATM and Chk2 kinases, the Ku70/80 heterodimer, the MRN complex, Rad51, the ERCC1-XPF and MUS81 endonucleases, the Apollo exonuclease and the RecQ family members WRN and BLM, In addition human telomeres are enriched in proteins that are homologous to *Drosophila* HP1. All these shelterin accessory factors do not function only at telomeres but are involved in several cellular processes that are not related with telomeres (Palm, de Lange, 2008; Jain, Cooper, 2010; O'Sullivan, Karlseder, 2010).

The evolution of *Drosophila* telomeres

With the possible exception of Ver, whose OB fold domain exhibits a structural homology with *S. pombe* STN1, none of the terminin proteins has homologues in yeasts, mammals or plants (Raffa et al., 2010, 2011). In addition, all terminin proteins exhibit a very high rate of nonsynonymous substitution per nonsynonymous site, and are therefore fast-evolving proteins. In contrast, all *Drosophila* non-terminin proteins are not fast-evolving, are evolutionarily conserved and have human homologues. Based on these results, we hypothesized that following telomerase loss, *Drosophila* lost the shelterin and the CST homologues that bind DNA in a sequence-specific fashion, and evolved terminin to bind chromosome ends independently of the DNA sequence. It is indeed conceivable that the transition from a telomerase-driven to a transposon-driven telomere elongation mechanism resulted in a divergence of terminal DNA sequences, accompanied by a strong selective pressure towards the evolution of sequence-independent telomere-binding factors. We also hypothesized that the non-terminin proteins did not evolve as rapidly as terminin because of the functional constraints imposed by their involvement in diverse cellular processes (Raffa et al., 2009, 2010, 2011).

Shelterin and terminin share the property of localizing and functioning only at telomeres throughout the cell cycle. Thus even if these complexes contain very different proteins, our hypothesis on terminin evolution suggests that terminin is the functional analog of shelterin. The *Drosophila* non-terminin proteins should instead correspond to ancestral telomere-associated proteins. Indeed, 5 (HP1, Mre11, Rad50, Nbs, Tefu/ATM) out of the 7 non-terminin proteins so far identified have been implicated in human telomere maintenance. Thus, it appears that the main difference between *Drosophila* and human telomeres is in the protective complexes that specifically associate with the DNA termini, and that the two types of telomeres, despite the different mechanism of elongation, share many proteins. It has been estimated that the *Drosophila* genome contains at least 40 genes required to prevent telomere fusion (Cenci et al., 2005). We believe that the identification of additional *Drosophila* genes encoding non-terminin factors required for telomere protection will lead to the discovery of novel components of human telomeres.

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References

Bi X., Srikanta D., Fanti L., Pimpinelli S., Badugu R., Kellum R., Rong Y. S. 2005. Drosophila ATM and ATR checkpoint kinases control partially redundant pathways for telomere maintenance. Proc. Nat. Acad. Sci. USA. 102 : 15 167—15 172.

Bi X., Wei S. D., Rong Y. S. 2004. Telomere protection without a telomerase: the role of ATM and Mre11 in *Drosophila* telomere maintenance. Curr. Biol. 14 : 1348—1353.

Capkova Frydrychova R., Biessmann H., Mason J. M. 2008. Regulation of telomere length in *Drosophila*. Cytogenet. Genome Res. 122 : 356—364.

Cenci G., Ciapponi L., Gatti M. 2005. The mechanism of telomere protection: a comparison between *Drosophila* and humans. Chromosoma. 114 : 135—145.

Cenci G., Rawson R. B., Belloni G., Castrillon D. H., Tudor M., Petrucci R, Goldberg M. L , Wasserman S. A., Gatti M. 1997. UbcD1, a *Drosophila* ubiquitin-conjugating enzyme required for proper telomere behavior. Genes Develop. 11 : 863—875.

Cenci G., Siriaco G., Raffa G. D., Kellum R., Gatti M. 2003. The *Drosophila* HOAP protein is required for telomere capping. Nat. Cell Biol. 5 : 82—84.

Ciapponi L., Cenci G. 2008. Telomere capping and cellular checkpoints: clues from fruit flies. Cytogenet. Genome Res. 122 : 365—373.

Ciapponi L., Cenci G., Ducau J., Flores C., Johnson-Schlitz D., Gorski M. M., Engels W. R., Gatti M. 2004. The *Drosophila* Mre11/Rad50 complex is required to prevent both telomeric fusion and chromosome breakage. Curr. Biol. 14 : 1360—1366.

Ciapponi L., Cenci G., Gatti M. 2006. The *Drosophila* Nbs protein functions in multiple pathways for the maintenance of genome stability. Genetics. 173 : 1447—1454.

Fanti L., Giovinazzo G., Berloco M., Pimpinelli S. 1998. The heterochromatin protein 1 prevents telomere fusions in *Drosophila*. Mol. Cell. 2 : 527—538.

Fanti L., Pimpinelli S. 2008. HP1: a functionally multifaceted protein. Curr. Opin. Genet. Develop. 18 : 169—174.

Filion G. J., van Bemmel J. G., Braunschweig U., Talhout W., Kind J., Ward L. D., Brugman W., de Castro I. J., Kerkhoven R. M.,

Bussemaker H. J., van Steensel B. 2010. Systematic protein location mapping reveals five principal chromatin types in *Drosophila* cells. Cell. 143 : 212—224.

Font-Burgada J., Rossell D., Auer H., Azorin F. 2008. Drosophila HP1c isoform interacts with the zinc-finger proteins WOC and Relative-of-WOC to regulate gene expression. Genes Develop. 22 : 3007—3023.

Gao G., Walser J. C., Beaucher M. L., Morciano P., Wesolowska N., Chen J., Rong Y. S. 2010. HipHop interacts with HOAP and HP1 to protect *Drosophila* telomeres in a sequence-independent manner. EMBO J. 29 : 819—829.

Jain D., Cooper J. P. 2010. Telomeric strategies: means to an end. Annu. Rev. Genet. 44 : 243—269.

Mason J. M., Frydrychova R. C., Biessmann H. 2008. Drosophila telomeres: an exception providing new insights. Bioessays. 30 : 25—37.

Melnikova L., Georgiev P. 2002. Enhancer of terminal gene conversion, a new mutation in *Drosophila melanogaster* that induces telomere elongation by gene conversion. Genetics. 162 : 1301—1312.

Muller H. J. 1938. The remaking of chromosomes. Collecting Net. 8 : 182—195.

Oikemus S. R., McGinnis N., Queiroz-Machado J., Tukachinsky H., Takada S., Sunkel C. E., Brodsky M. H. 2004. Drosophila atm/telomere fusion is required for telomeric localization of HP1 and telomere position effect. Genes Develop. 18 : 1850—1861.

Oikemus S. R., Queiroz-Machado J., Lai K., McGinnis N., Sunkel C., Brodsky M. H. 2006. Epigenetic telomere protection by Drosophila DNA damage response pathways. PLoS Genet. 2 : e71.

O'Sullivan R. J., Karlseder J. 2010. Telomeres: protecting chromosomes against genome instability. Nat. Rev. Mol. Cell. Biol. 11 : 171—181.

Palm W., de Lange T. 2008. How shelterin protects mammalian telomeres. Annu. Rev. Genet. 42 : 301—334.

Pardue M. L., DeBaryshe P. G. 2011. Retrotransposons that maintain chromosome ends. Proc. Nat. Acad. Sci. USA. 108 : 20 317—20 324.

Perrini B., Piacentini L., Fanti L., Altieri F., Chichiarelli S., Berloco M., Turano C., Ferraro A., Pimpinelli S. 2004. HP1 controls telomere capping, telomere elongation, and telomere silencing by two different mechanisms in *Drosophila*. Mol. Cell. 15 : 467—476.

Raffa G. D., Cenci G., Siriaco G., Goldberg M. L., Gatti M. 2005. The putative *Drosophila* transcription factor woc is required to prevent telomeric fusions. Mol. Cell. 20 : 821—831.

Raffa G. D., Ciapponi L., Cenci G., Gatti M. 2011. Terminin: a protein complex that mediates epigenetic maintenance of *Drosophila* telomeres. Nucleus. 2 : 383—391.

Raffa G. D., Raimondo D., Sorino C., Cugusi S., Cenci G., Cacchione S., Gatti M., Ciapponi L. 2010. Verrocchio, a *Drosophila* OB fold-containing protein, is a component of the terminin telomere-capping complex. Genes Develop. 24 : 1596—1601.

Raffa G. D., Siriaco G., Cugusi S., Ciapponi L., Cenci G., Wojcik E., Gatti M. 2009. The Drosophila modigliani (moi) gene encodes a HOAP-interacting protein required for telomere protection. Proc. Nat. Acad. Sci. USA. 106 : 2271—2276.

Rong Y. S. 2008. Telomere capping in *Drosophila*: dealing with chromosome ends that most resemble DNA breaks. Chromosoma. 117 : 235—242.

Savitsky M., Kravchuk O., Melnikova L., Georgiev P. 2002. Heterochromatin protein 1 is involved in control of telomere elongation in *Drosophila melanogaster*. Mol. Cell. Biol. 22 : 3204—3218.

Savitsky M., Kwon D., Georgiev P., Kalmykova A., Gvozdev V. 2006. Telomere elongation is under the control of the RNAi-based mechanism in the *Drosophila* germline. Genes Develop. 20 : 345—354.

Shpiz S., Olovnikov I., Sergeeva A., Lavrov S., Abramov Y., Savitsky M., Kalmykova A. 2011. Mechanism of the piRNA-mediated silencing of *Drosophila* telomeric retrotransposons. Nucleic Acids Res. 39 : 8703—8711.

Silva E., Tiong S., Pedersen M., Homola E. M., Royou A., Fasulo B., Siriaco G., Campbell S. D. 2004. ATM is required for telomere maintenance and chromosome stability during *Drosophila* development. Curr. Biol. 14 : 1341—1347.

Siriaco G. M., Cenci G., Haoudi A., Champion L. E., Zhou C., Gatti M., Mason J. M. 2002. Telomere elongator (*Tel*) a new mutation in *Drosophila melanogaster* that produces long telomeres. Genetics. 160 : 235—245.

Song Y. H., Mirey G., Betson M., Haber D. A., Settleman J. 2004. The *Drosophila* ATM ortholog, dATM, mediates the response to ionizing radiation and to spontaneous DNA damage during development. Curr. Biol. 14 : 1354—1359.

Zhang L., Rong Y. S. 2012. Retrotransposons at *Drosophila* telomeres: Host domestication of a selfish element for the maintenance of genome integrity. Biochim. biophys. acta. 1819 : 771—775.

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ОРГАНИЗАЦИЯ И СТРУКТУРА ТЕЛОМЕР ДРОЗОФИЛЫ: РОЛИ БЕЛКОВ КОМПЛЕКСА ТЕРМИНИН И БЕЛКОВ, НЕ ОТНОСЯЩИХСЯ К ТЕРМИНИНУ

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Теломеры дрозофилы организованы под влиянием транспозиции специализированных ретроэлементов, а не активности теломеразы, и группируются независимо от сиквенса концов ДНК. Теломеры дрозофилы ограничены белковым комплексом terminin, который формируют белки HOAP, Moi, Ver и HipHop, локализующиеся исключительно на теломерах и защищающие их от слияния. Другие белки, необходимые для предотвращения слияния конец-в-конец, включают в себя HP1, Eff/UbcD1, ATM, компоненты Mre11-Rad50-NBS и фактора транскрипции Woc. Terminin-белки кодируются быстро эволюционирующими генами и не являются эволюционно консервативными за пределами вида *Drosophila*. В отличие от них не terminin-белки, ограничивающие теломеры, не являются быстро эволюционирующими и локализуются не только в теломерах. Они консервативны у разных организмов от дрожжей до млекопитающих. Мы полагаем, что после потери теломеразы у дрозофилы быстро развился комплекс terminin для формирования концов хромосом независимо от последовательности, а другие белки не развивались так быстро, как terminin, из-за функциональных ограничений, обусловленных их участием в различных клеточных процессах. Эта гипотеза предполагает, что terminin-белки дрозофилы могут соответствовать исходной субтеломерной ДНК с гомологами в других организмах, включая человека.

Ключевые слова: terminin, теломеры, слияние теломер, *Drosophila*.