DNA DAMAGE RESPONSE, CHECKPOINT ACTIVATION AND DYSFUNCTIONAL TELOMERES: FACE TO FACE BETWEEN MAMMALIAN CELLS AND *DROSOPHILA*

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Eukaryotic cells evolved telomeres, specialized nucleoproteic complexes, to protect and replicate chromosome ends. In most organisms, telomeres consist of short, repetitive G-rich sequences added to chromosome ends by a reverse transcriptase with an internal RNA template, called telomerase. Specific DNA-binding protein complexes associate with telomeric sequences allowing cells to distinguish chromosome ends from sites of DNA damage. When telomeres become dysfunctional, either through excessive shortening or due to defects in the proteins that form their structure, they trigger p53/pRb pathways that limits proliferative lifespan and eventually leads to chromosome instability. *Drosophila* lacks telomerase, telomeres are assembled in a sequence-independent fashion and their length is maintained by transposition of three specialized retroelements. Nevertheless, fly telomeres are maintained by a number of proteins involved in telomere metabolism as in other eukaryotic systems and that are required to prevent checkpoint activation and end-to-end fusion. Uncapped *Drosophila* telomeres induce a DNA damage response just as dysfunctional human telomeres. Most interestingly, uncapped *Drosophila* telomeres also activate the spindle assembly checkpoint (SAC) by recruiting the SAC kinase BubR1. Here we review parallelisms and variations between mammalian and *Drosophila* cells in the crosstalks between telomeres and cell cycle regulation.

Key words: telomeres, DNA damage response, cell cycle checkpoint, mammals, Drosophila.

The ends of eukaryotic chromosomes have evolved special chromatin architectures, the telomeres, which resolve two fundamental challenges: the end replication problem and the protection of chromosome termini from being improperly identified and repaired as DNA double-strand breaks (DSBs). This latter is achieved by the constitution of a protective nucleoprotein structure, the cap, that avoids inappropriate repair which would otherwise lead to aberrant end joining and recombinational events. Essential for the maintenance of a proper telomere function and configuration is a set of proteins that assemble on chromosome tips and, in most organisms, employ both double-stranded (ds)- or (single-stranded) ss-telomeric DNA repeats as anchor site. In mammals, chromosomes ends consist of tracts of the tandemly repeated G-rich sequence TTAGGG, whose length varies from approximately15 kb in humans to 20—60 kb in mice (reviewed in: Palm, de Lange, 2008). The G-rich strand forms a 3′ single-stranded (ss) overhang at the extreme terminus. This overhang is specifically elongated by a specialized reverse transcriptase, the telomerase, which contains a species-specific RNA template (Nugent, Lundblad, 1998). The double-stranded (ds) terminal region contains histones (Makarov et al., 1993; Wu, de Lange, 2008), but little is known about the contribution of nucleosomes to the protection of chromosome ends. Telomeric chromatin also includes RNA transcripts of telomeric and subtelomeric sequences, named TERRA, that associate with at least a subset of chromosome ends (Azzalin et al., 2007; Schoeftner, Blasco, 2008).

The mammalian telomere is hypothesized to be organized into a unique lariat-like structure (t-loop) (Griffith et al., 1999), formed by the invasion of the 3′ ss G-rich overhang (G-tail) into the ds region of the telomere, which prevents exposure of free DNA ends. Formation and maintenance of this t-loop structure is promoted by the shelterin complex that is itself telomere associated (Palm, de Lange, 2008). Shelterin is a multi-protein complex that is composed of six core components: TRF1, TRF2, RAP1, POT1, TPP1 and TIN2 (mice harbor two POT1 isoforms: POT1a and POT1b, while humans only one). In addition to maintaining the t-loop structure, shelterin also controls telomerase-mediated telomere elongation, aids semi-conservative replication of telomeres and suppresses the DNA damage response (DDR) (Palm, de Lange, 2008; Jain, Cooper, 2010). G-rich 3′ overhangs are also present at both fission and budding yeast telomeres, which contain G-rich ds tracts of approximately 300 bp. Remarkably, fission yeast harbors the TRF1/2 ortholog Taz1 and a POT1 ortholog that bind the ds telomeric repeats and the ss overhang, respectively. Consequently, the ss- and ds-binding proteins of fission yeast form a shelterin-like complex as mammalian telomeres (reviewed in: Jain, Cooper, 2010). However, unlike fission yeast, there is no TRF1/2 ortholog in budding yeast and telomeres are bound directly by Rap1, which recruits the additional factors Rif1 and Rif2, and the silent information regulator (SIR) proteins (reviewed in: Wellinger, Zakian, 2012). An additional factor, the CST complex composed of oligosaccharide/oligonucleotide binding (OB)-fold-contai-

ning proteins Cdc13, Stn1 and Ten1, binds the ss overhangs of budding yeast telomeres and modulates telomerase activity. Recently, CST complexes have been found to associate with a fraction of telomeres in different organisms, including mammals, fission yeast and plants. The members of this complex, which resemble Replication Protein A (RPA) factors, are mainly involved in telomere replication. However, recent findings revealed that mammalian CST is also implicated in telomere end protection (Miyake et al., 2009; Surovtseva et al., 2009) suggesting that mammalian CST and shelterin might have overlapping functions in telomere end protection.

In addition to the six shelterin components and the CST complex, other proteins are known to be associated with mammalian telomeres. Differently from shelterin components, these proteins do not exclusively interact with telomeres. Most of these factors are involved in DNA damage signaling, DNA repair, DNA replication or chromatin structure. Examples of such factors are the MRN complex, which is involved in the detection of double-strand breaks and in the homologous recombination pathway of DNA repair; the component of the nucleotide-excision repair pathway XPF/ERCC1; DNA-PKcs, a kinase required non homologous end-joining (NHEJ) pathway; Ku70/80, also involved in the NHEJ pathway; Apollo, a putative 5′ exonuclease; the helicases BLM and WRN RecQ, involved in the homologous recombination (HR) pathway; and Rad51D, also involved in the HR pathway.The interaction of these proteins with telomeres is mainly mediated by shelterin components TRF2, Rap1 and TRF1. However, TIN2 has been recently shown to recruit Heterochromatin Protein 1 (HP1)γ to ensure the maintenance of cohesion at telomeres (Canudas et al., 2011).

If compared to mammals, *Drosophila* telomeres are atypical. In fact, telomerase is absent and telomeric DNA is not formed by telomerase-generated simple repeats.Telomere length in *Drosophila* is maintained by transposition of three different but related non-long terminal repeat retrotransposons called HeT-A, TART and TAHRE (Mason et al., 2008). Interestingly, telomere elongation and capping are two uncoupled events, as chromosomes ends devoid of retrotransposons can still give rise to functional telomeres. Curiously, chromosomes carrying terminal deletions can assemble a normal telomere whatever sequence is found associated at the tip evoking for the fruit fly an epigenetic determination of telomeres. Despite the apparent and unusual telomere structure determination, *Drosophila* telomeres are maintained by a number of proteins involved in telomere metabolism as in other eukaryotic systems (for a review see: Cenci et al., 2005; Rong, 2008b; Raffa et al., 2011). The search for *Drosophila* telomere capping proteins has mainly relied on the isolation of mutants that exhibit frequent telomeric fusions (TFs) in larval brain cells. These mutants display three classes of TFs: single TFs (STFs), where a single telomere associates with either its sister (sister union, SU) or a non-sister telomere (non-sister union, NSU), and double TFs (DTFs), where a pair of sister telomeres joins with another pair. Genetic and molecular analyses have thus far identified 11 genes required to prevent TFs in *Drosophila*, which encode three classes of proteins: 1) the telomere-specific terminin components (HOAP, Moi, HipHop and Ver); 2) DNA repair/checkpoint proteins (ATM and the MRN complex) that are also required for terminin recruitment at telomeres; 3) non-terminin capping proteins (Woc, UbcD1, HP1) that protect telomeres independently of terminin (Cenci et al., 2005; Raffa et al., 2011). This suggests that multiple factors contribute to *Drosophila* telomere protection, and implies that multiple DNA end-joining pathways may be involved in recognition and processing of unprotected telomeres. This view is supported by the observation that loss of the *Drosophila* histone variant H2A.Z inhibits telomere fusion in cells lacking either ATM or MRN, but not in terminin-lacking cells (Rong, 2008a).

A basic function of telomeres is to escape the activation of the DNA damage response by the natural ends of chromosomes. Here we will discuss how mammals and *Drosophila* telomeres achieve this, highlighting similarities and differences between these two systems.

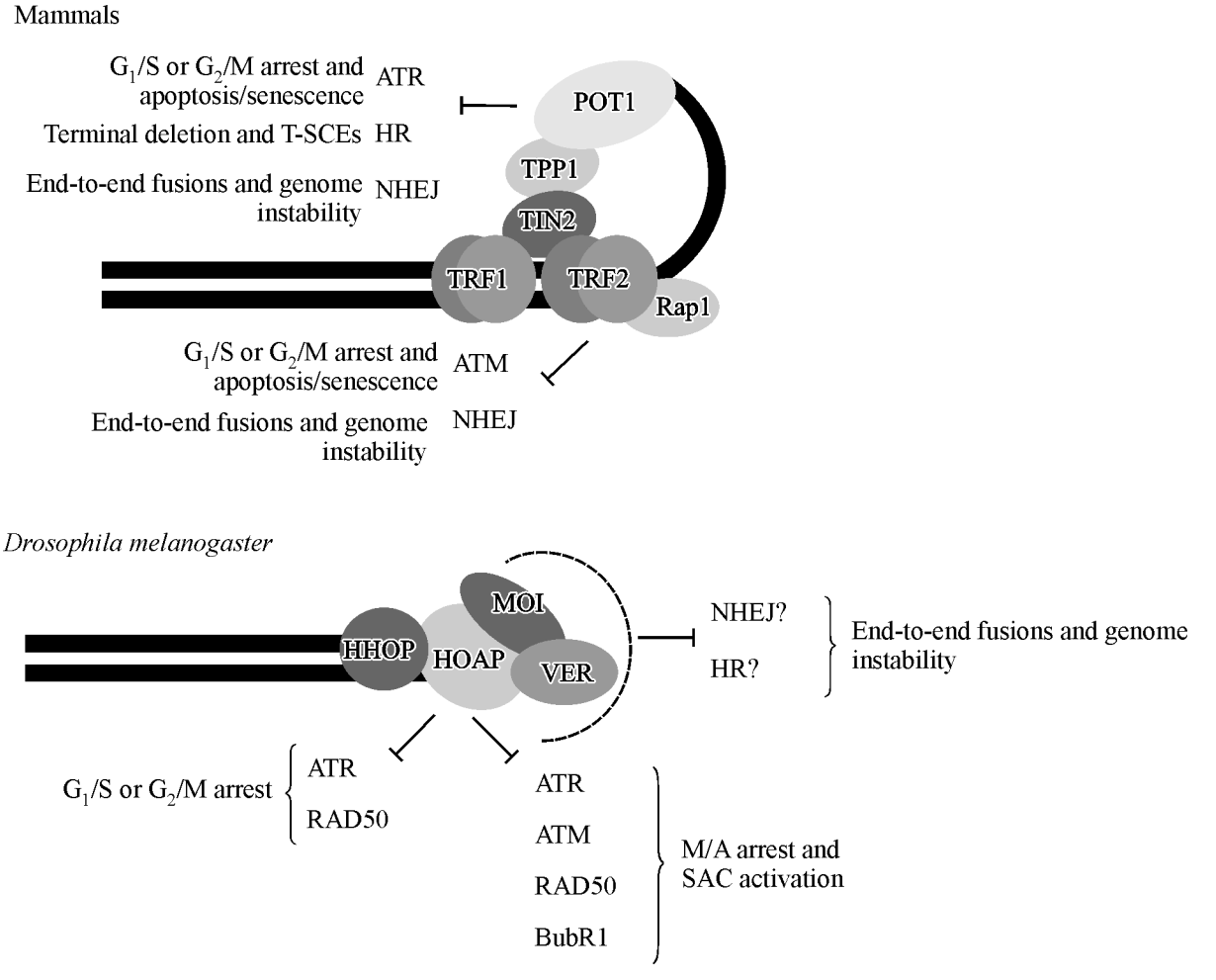
Suppression of DNA damage signaling at human telomeres

Two distinct phosphatidylinositol 3-kinase-related protein kinases, the ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) kinases, play a central role in the response to DNA lesions (Shiloh, 2003). Double stranded breaks (DSBs) activate primarily ATM, whereas ATR activation requires the formation of ssDNA. Once activated, both kinases phosphorylate histone H2AX on Serine139 around the site of damage. This event then promotes the local accumulation of other DNA damage response factors (MDC1, 53BP1, the Mre11 complex, etc.), resulting in cytologically detectable foci that span hundreds of kb from the site of the lesion. As the activation of the ATM/ATR kinases is incompatible with cell proliferation, it stands to reason that telomeres must ensure that these signal transducers remain silent. Nevertheless, the finding that telomeres require a relatively limited activity of both kinases to become functional (reviewed in: Verdun et al., 2005; Verdun, Karlseder, 2006; Shore, Bianchi, 2009), indicates that the comprehension of checkpoint suppression mechanisms at chromosome termini is more complex than initially thought.

At mammalian telomeres, ATM and ATR are suppressed in a specific and independent manner (Figure). ATM suppression is mediated by TRF2. Deletion of TRF2 from mouse cells or expression of a dominant negative TRF2 allele in human cells specifically activates ATM (Karlseder et al., 1999; Takai et al., 2003; Celli, de Lange, 2005) and results in an ATM-dependent formation of DNA damage foci at telomeres (Denchi et al., 2006). These telomere dysfunction-induced foci (TIFs) contain the same factors detected at DNA damage foci induced by DSBs. The cellular response to ATM activation at telomeres is also similar, with Chk2 and p53 induction and consequently cell cycle arrest or, in some cell types, apoptosis (Karlseder et al., 1999; Smogorzewska, de Lange, 2002). The mechanisms enabling TRF2 to suppress ATM activation are yet objects of debate (reviewed in: Denchi, 2009).

Like TRF2, POT1 is required to prevent DNA damage activation at chromosome ends and loss of POT1 leads to the accumulation of TIFs at chromosome ends (Churikov et al., 2006; Hockemeyer et al., 2006). Yet, the induction of TIFs at telomeres lacking POT1 requires the ATR kinase and phosphorylation of the ATR target, Chk1 (Denchi, de Lange, 2007). The suppression of ATR signaling by Pot1 might rely on the capability of this shelterin factor to bind ssDNA (reviewed in: Denchi, 2009).

ATR is also activated during S phase at the telomeres of MEFs upon TRF1 deletion. However, this ATR activation does neither define a role of TRF1 in the inhibition of ATR nor imply a displacement of Pot1 from the telomeric overhang after TRF1 stripping. This loss of TRF1 is thought to



Roles of mammal shelterin and *Drosophila* terminin in the end-protection.

At mammalian telomeres, the presence of shelterin and the t-loop structure together ensure the repression of the four pathways that threaten telomeres and genome stability (*top*). At *Drosophila* telomeres, all terminin components prevent the formation of end-to-end fusions by suppressing very likely either NHEJ or HR. Loss of HOAP, but not of other terminin members, delays cell cycle progression and causes the recruitment of the SAC protein BubR1 in a ATR, ATRIP, CHK1, Rad50 and ATM dependent manner (*bottom*). Once accumulated at telomeres, BubR1 negatively regulates the activity of the APC/Cdc20 complex leading to a metaphase-to-anaphase transition block.

lead to the accumulation of ssDNA at telomeres as consequence of stalled replication forks which in turn would result in the ATR activation (Sfeir et al., 2009).

Cell cycle alteration and telomeric DNA damage

Unlike proliferating progenitor germ cells and some stem cells in which telomerase is expressed, somatic cells do not exhibit telomerase activity and therefore their telomeres undergo progressive shortening. The subsequent telomere erosion induces replicative senescence and cells with critically short telomeres activate a DNA damage response, accumulate the DNA damage factors 53BP1, γ-H2AX, MDC1 and NBS1 at telomeres, and activate both DNA damage kinases, ATM and ATR (d'Adda di Fagagna et al., 2003). The activation of ATM and ATR triggers a checkpoint through the effectors kinases Chk1 and Chk2, and through p53 activation. Replicative senescence is also induced when telomeres cannot recruit sufficient TRF2 and POT1 to suppress the DNA damage response thus activating both the ATM and the ATR pathways. Loss of shelterin components gives rise to the same cellular responses that are induced by critically short telomeres, including TIFs (Takai et al., 2003), activation of ATM and its downstream effector proteins (Smogorzewska, de Lange, 2002; Takai et al., 2003), and ultimately to cell death through apoptosis or permanent withdrawal from the cell cycle (Smogorzewska, de Lange, 2002; Takai et al., 2003). However, whereas human cells with dysfunctional telomeres arrest cell cycle through the induction of p53 and pRB inhibition (Smogorzewska, de Lange, 2002; Jacobs, de Lange, 2004), in mouse cells the cell cycle block is achieved only by suppression of p53 (Smogorzewska, de Lange, 2002).

Telomeres are rendered dysfunctional also as result of a prolonged mitotic arrest induced by either chemical factors or gene silencing (Hayashi et al., 2012). These unprotected telomeres elicit dissociation of TRF2, telomeric 3′-overhang degradation and lead to ATM activation. Normal cells that escape from prolonged mitotic arrest halt in the following G_1 phase, whereas cells lacking p53 continue to cycle and become aneuploid (Hayashi et al., 2012). These findings suggest the existence of a telomere-dependent mitotic-duration monitoring system that reacts to improper progression through mitotis. Interestingly, a persistent telomere dysfunction can determine a prolonged DNA damage signal that can lead to tetraploidization of cells in which p53 is absent. These cells extend

the G2 phase as result of ATM/ATR- and Chk1/Chk2-mediated inhibition of Cdk1/CyclinB and eventually by-pass mitosis. Despite their lack of mitosis, the cells show degradation of the replication inhibitor geminin and accumulation of Cdt1, which is required for origin licensing. They eventually enter a second S phase resulting in whole-genome reduplication and tetraploidy. However, upon restoration of telomere protection, these tetraploid cells resume cell division cycles and proliferated leading to a dramatic genome instability (Davoli et al., 2010). This finding can explain the occurrence of tetraploidization in the early stages of tumorigenesis when telomere dysfunction can result from excessive telomere shortening.

DNA repair at dysfunctional telomeres

Shelterin not only suppresses the activation of a DNA damage response, but is also essential to repress inappropriate repair reactions at chromosome ends. Like DSBs, telomeres are in fact subjected to all events of processing and repair, including non-homologous-end-joining (NHEJ) and homologous recombination (HR) (Figure). One of the most deleterious outcomes of non-homologous endjoining (NHEJ) at telomeres is the generation of end-to-end chromosome fusions. Fused chromosomes cannot be properly segregated in mitosis and can lead to aneuploidy and severe genome instability through the so-called breakage-fusion-bridge cycle originally described by McClintock (1939). Depletion of TRF2 in MEFs and human cells results in end-to-end fusions with telomeric sequences retained at the site of fusions (Van Steensel et al., 1998; Celli, de Lange, 2005). These telomeric fusions are suppressed by deletion of Ligase IV, demonstrating that are dependent on the classical NHEJ pathway and that TRF2 inhibits NHEJ (Smogorzewska et al., 2002; Celli, de Lange, 2005; Celli et al., 2006). Efficient NHEJ of TRF2 depleted telomeres requires a functional ATM pathway, since loss of ATM, H2AX or MDC1 prevents telomere fusions (Dimitrova, de Lange, 2006; Denchi, de Lange, 2007). In contrast, loss of POT1 does not result in high levels of NHEJ at chromosome ends (Hockemeyer et al., 2005, 2006; Denchi, de Lange, 2007). Interestingly, depletion of POT1 leads to fusions between sister chromatids (Hockemeyer et al., 2006) suggesting that they occur preferentially following replication whereas fusions resulting after stripping of TRF2 occur preferentially in the G_1 phase of the cell cycle (Konishi, de Lange, 2008). The mechanism of POT1-mediated NHEJ repression may be therefore distinct from TRF2 and may involve protection of the terminal overhang. TRF2, POT1 and Rap1 also play crucial roles in the suppression of the HR pathway at telomeres. In cells lacking Ku70 and either TRF2 or POT1, telomeres undergo numerous telomeric sister-chromatid exchanges (T-SCEs) as consequence of severe HR (Celli et al., 2006). Particularly, Ku70 null cells exhibit increased rates of recombination at chromosome ends only when either TRF2 or POT1 is missing indicating that both shelterin factors and Ku70 act in a redundant manner to prevent recombination at telomeres.

Repression of T-SCEs can be achieved also by the WRN helicase. In particular, telomerase deficient mouse cells with severely shortened telomeres exhibit increased levels of T-SCEs when WRN is absent (Laud et al., 2005). WRN could promote branch migration and, therefore, suppress recombination by simply moving the Holliday Junction towards the telomere terminus. Interestingly, HR can also exert beneficial effects at telomeres. After replication, exposed telomere ends are recognized as DSBs and processed (Verdun et al., 2005). The DNA damage signaling triggered by ATM/ATR in G_2 recruits DNA repair proteins, such as the HR machinery, to restore the DNA lesion at telomeres. These proteins have been proven to be essential for generation of a D loop with telomeric sequences *in vitro*, implicating HR in the formation of the t loop structure *in vivo* (Verdun, Karlseder, 2006).

In addition to NHEJ and HR, other DNA damage response pathways are activated upon deletion of shelterin proteins. A very recent work has revealed that the end-protection problem is specified by six pathways namely the ATM and ATR signaling, classical-NHEJ, alt-NHEJ, homologous recombination and resection (Sfeir, de Lange, 2012). The accuracy of how shelterin acts with general DNA damage response factors guarantees telomere defense from inappropriate repair.

Telomeres and DNA damage response in Drosophila

How *Drosophila* telomeres suppress either NHEJ, HR or both is still a broad open-ended question. With the exception of Ligase IV, whose depletion only slightly lowers TFs' frequency upon loss of either HOAP or Woc (Bi et al., 2004; Raffa et al., 2005), the effects of DNA repair genes on telomere fusion are still poorly defined. Moreover, a direct evidence of the presence of telomeric ssDNA overhangs at telomeres is still missing thus making the understanding of DNA repair at telomeres even more challenging.

The loss of a single telomere from only one chromosome produced during development of *D. melanogaster* by breakage of an induced dicentric chromosome leads to levels of apoptosis that are similar to those seen after ionizing radiation. Telomere-loss-induced cell death is mediated by the activation of p53 via Chk2 and Chk1 and represents a robust example of defense against the proliferation of cells with damaged genomes. However, a small fraction of cells that have lost a telomere escape apoptosis, divides repeatedly, and accumulates karyotypic abnormalites, including end-to-end chromosome fusions, anaphase bridges, aneuploidy, and polyploidy. Thus, consistent with observation in yeast and mammalian cells, a single dysfunctional telomere is sufficient to induce instability also in *Drosophila* (Titen, Golic, 2008). Chk2 can also act independently of p53 to eliminate cells that have lost a telomere. Mutant analysis has also revealed the genes encoding Chk2 and p53 are haplo-insufficient in *Drosophila*, as they are in humans demonstrating that the response to DNA damage, in the form of telomere loss, has an unexpectedly high degree of functional conservation from *Drosophila* to humans (Kurzhals et al., 2011).

Mutations in genes encoding the MRN complex, ATR, ATRIP and ATM all affect telomere homeostasis in *Drosophila* suggesting that, like mammals, these repair proteins, despite representing a continous threat for chromosome end integrity, play also beneficial role at telomeres. In particular, loss of *Drosophila mre11*, *rad50*, *nbs* and ATM-encoding *tefu* genes causes telomeric fusions (reviewed in: Rong, 2008b; Ciapponi, Cenci, 2009; Raffa et al., 2011). Interestingly, mutations in both *mei-41* or *mus-304* genes, which encode ATR and ATR-interacting protein ATRIP, respectively, do not give rise to TFs, but their inhibition in ATM depleted cells dramatically increases the frequency of TFs observed when only ATM is missing (Bi et al., 2005). Moreover, inhibition of MRN reduces terminin accumulation at telomeres, while loss

of either ATR or ATM does not. Surprisingly, HOAP is completely stripped off chromosome ends in ATM mutant cells that are also devoid of either ATR or ATRIP thus indicating that ATM and ATR/ATRIP have partially redundant roles in telomere protection (reviewed in:Rong, 2008b; Ciapponi, Cenci, 2009; Raffa et al., 2011).

Loss of telomere capping induces a DNA damage response also in *Drosophila* (Ciapponi, Cenci, 2008; Musarò et al., 2008; Cenci, 2009) (Figure). HOAP provides the most remarkable example of such an activation. Depletion of HOAP as consequence of mutation in HOAP-encoding gene *caravaggio* (*cav*), leads to a cell cycle delay in interphase that does not depend on the presence of TFs. Interestingly, mutations in genes encoding the ATR, ATRIP, CHK1 (*grapes*) and Rad50, but not in the ATM, alleviate the *cav*-induced cell cycle block suggesting that HOAP limits mainly the activity of the ATR-dependent pathway. Whether the *Drosophila* checkpoint activated by HOAP-depleted telomeres arrests cell cycle at G_1/S transition, during S phase or at the G_2/M transition remains still an open issue. Intriguingly, the absence of HOAP from telomeres leads to a block in the metaphase-to-anaphase transition, which is not due to perturbation of spindle structures as mitotic spindles in *cav* mutant brains are morphologically normal (Musarò et al., 2008). This *cav*-induced metaphase-to-anaphase block, but not the interphase block, is partially suppressed by mutations in spindle assembly checkpoint (SAC) genes such as *zw10* and *bubR1* (Karess, 2005), suggesting that unprotected telomeres activate the SAC which normally monitors the kinetochore-microtubule (MT) interaction and inhibits anaphase onset until all the chromosomes are properly aligned in a metaphase plate. Surprisingly, of all SAC proteins that are normally enriched at centromeres BubR1 concentrates also at telomeres in almost all *cav* mutant cells and this accumulation on unprotected telomeres is likely the key signal for the activation of this peculiar SAC response.

Moreover, BubR1 accumulation at telomeres was found to be specifically dependent on HOAP loss, as other mutants with TFs have a limited ability to recruit BubR1 at telomeres and elicit only a mild delay during the metaphase-to-anaphase transition. As such, the significant negative correlation between the frequencies of anaphases and the frequencies of BubR1-labeled telomeres indicates that the SAC response is triggered by telomeric accumulation of BubR1. Both ATR and ATM pathways are required for BubR1 localization at unprotected telomeres and therefore for the activation of the metaphase-to-anaphase block (Musarò et al., 2008) (Figure). However, since ATM is not involved in the interphase arrest, the telomere-induced DDR is independent of BubR1 recruiting. The reason why strong DDR and SAC responses are seen after HOAP loss and not after inhibition of other telomere-capping factors is puzzling. HOAP may have a key role in the organization of telomere structure and acts as a platform for recruiting the terminin complexes required for telomere stability (Cenci, 2009; Raffa et al., 2013). Thus, loss of HOAP would cause the most drastic and detrimental scenario of genome instability, which must be inhibited by the activation of cell cycle checkpoints. It is also conceivable that HOAP is involved in telomere replication. As HOAP interacts with several subunits of the Origin Replication Complex (ORC) (Pak et al., 1997; Shareef et al., 2001; Badugu et al., 2003), it is possible that the telomeres of *cav*mutants contain damaged replication forks, which would activate cell cycle checkpoints (Cenci, 2009).

Activation of the SAC by dysfunctional telomeres has been observed in both budding and fission yeast, although it is unclear how uncapped yeast telomeres are sensed by the SAC (Maringele, Lydall, 2002; Miller, Cooper, 2003). HOAP-depleted telomeres recruit BubR1 similarly to kinetochores that are unconnected to spindle microtubules and plausibly the anaphase inhibition occurs through the same mechanisms that govern SAC function at the kinetochore (Musarò et al., 2008). This SAC activation might embody a second surveillance system to prevent genomic instability by stopping cells that have escaped the DNA damage checkpoint with dysfunctional telomeres. Interestingly BubR1 and Mad2 have been found to localize at the telomeres of mouse epithelial cells that overexpress TRF1 (Munoz et al., 2009). Yet, if this localization activates the SAC as observed in Drosophila *cav* mutants, seeks further investigation.

Concluding remarks

Our comprehension of how telomeres suppress DNA damage response increaseas as more roles of proteins involved in telomere metabolism are unraveled. Understanding the complexity of chromosome end protection and its relationships with the DNA repair machinery may eventually allow to develop strategies for alleviating the consequences of telomere perturbation on aging and disease. Although *Drosophila* has evolved non-canonical telomeres, there is growing evidence that most proteins involved in *Drosophila* telomere metabolism are conserved also in human. Thus it is conceivable that the analysis of telomeres in this organism with a sophisticated genetics and the favorable cytology, can provide important information on how dysfunctional telomeres affect cell cycle progression.

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ОТВЕТ НА ПОВРЕЖДЕНИЕ ДНК, АКТИВАЦИЯ КОНТРОЛЬНОЙ ТОЧКИ И ДИСФУНКЦИОНАЛЬНЫЕ ТЕЛОМЕРЫ: КЛЕТКИ МЛЕКОПИТАЮЩИХ И ДРОЗОФИЛЫ ЛИЦОМ К ЛИЦУ

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Эукариотические клетки развили теломеры — специализированные нуклеопротеиновые комплексы — для защиты и репликации концов хромосом. У большинства организмов теломеры состоят из коротких повторяющихся G-богатых последовательностей, добавляемых к концам хромосом обратной транскриптазой с внутренней матричной РНК, называемой теломеразой. Специальные ДНК-связывающие белковые комплексы соединены с теломерными последовательностями, что позволяет клеткам различать концы хромосом от мест повреждения ДНК. Когда теломеры становятся дисфункциональными либо в результате чрезмерного сокращения или из-за дефектов в белках образующих их структуру, происходит запуск p53/pRb-пути, который ограничивает пролиферативный срок жизни и в конечном итоге приводит к хромосомной нестабильности. У *Drosophila* нет теломеразы, и теломеры собираются независимым от последовательностей путем, а их длина поддерживается переносом трех специализированных ретроэлементов. Тем не менее теломеры мух поддерживаются целым рядом белков, участвующих в метаболизме теломер и в других эукариотических системах, которые необходимы для предотвращения активации в контрольной точке и слияния конец-в-конец. Неприкрытые дисфункциональные теломеры у дрозофилы вызывают ответ на повреждение ДНК так же, как дисфункциональные теломеры человека. Самое интересное состоит в том, что неприкрытые теломеры у дрозофилы также активируют контрольную точку сборки веретена (SAC), привлекая SAC киназы BubR1. Здесь мы рассмотрим параллелизм и различия между клетками млекопитающих и дрозофилы в перекрестных помехах между теломерами и регуляцией клеточного цикла.

Ключевые слова: теломеры, ответ на повреждение ДНК, контрольная точка клеточного цикла, млекопитающие, дрозофила.