Cell

# ALT Telomeres Borrow from Meiosis to Get Moving

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http://dx.doi.org/10.1016/j.cell.2014.09.013

**Telomere clustering is required for the homologous recombination events that maintain chromosome ends in cells relying on alternative lengthening of telomeres (ALT). New data demonstrate that damage signaling at telomeres, a likely step in activating maintenance mechanisms, induces directional movement and synapsis driven by the machinery responsible for recombination in meiosis.**

Telomeres in human somatic cells shorten with each replication cycle, while stem cells and the majority of cancer cells actively maintain their telomeres at a steady length by activating the reverse transcriptase telomerase. However, in the cancers where telomerase is inactive, the alternative lengthening of telomeres (ALT) mechanism counteracts telomere shortening. The ALT mechanism relies on the interaction between individual telomeres, where one telomere serves as a template for recombination-based elongation of another. The human genome consists of 3 billion base pairs of genetic information. Of this, telomeres all together represent approximately 0.03% of the genome, with each individual telomere contributing roughly 0.0003%. How likely is it that they meet randomly? It's about as likely as the serendipitous meeting between individuals, if the whole island of Manhattan had only 100 inhabitants. In this issue of *Cell*, Cho et al. suggest that telomeres take advantage of the machinery that drives homologous chromosome synapsis during meiosis to perform directional movement across great distances to enable the recombination events required for telomere length maintenance in ALT (Cho et al., 2014).

The authors hypothesized that a DNA damage response at a subset of telomeres could represent an event that initiates spatial coalescence of telomeres. Indeed, it has been shown previously that many telomeres associate with DNA damage markers in ALT cells independently of telomere length, and that such telomeres tend to cluster (Cesare et al., 2009). Even in ALT negative cells, deprotected telomeres bound by the DNA damage marker 53BP1, are mobile and scan large territories of the nucleus (Dimitrova et al., 2008), supporting the authors hypothesis that a damage response might stimulate telomere movement.

To test the link between damage and movement directly, Cho et al. used a Fok1 endonuclease fused to the telomeric protein TRF1 to induce damage at telomeres. The damage response at ALT telomeres led to a strong increase in telomere clustering in ALT-associated promyelocytic leukemia (PML) bodies (APB) and resulted in greater telomere length heterogeneity. When telomeres were visually tracked in the endonuclease-expressing cells, it became obvious that they exhibited directed movement in which telomeric foci initially separated by up to 5 μm were capable of clustering, thereby migrating a distance equivalent to half the nuclear diameter. Clustering occurred between an incoming (migrating) telomere and a recipient (static) telomere that was in most cases associated with PML (Figure 1). After a phase of diffuse mobility, the incoming telomere displayed a striking long-range directional movement, homing in on the recipient telomere thereby forming an APB, or homing to an existing APB. Once the incoming and recipient telomeres associated, movement almost stopped, consistent with conclusion of the search process for recombination partners. This directional homology search was also carried out by a limited number of telomeres in ALT cells without exogenous induction of damage.

The search for factors controlling the directional movement led the authors to draw parallels to double-strand break movement that occurs during homology searches in yeast during damage repair by homologous recombination. Indeed, suppression of Rad51, a repair factor required for the homology search, strongly diminished telomere movement and clustering. Strikingly, Rad51 staining picked out the path that telomeres took on the way to their clusters, pointing out similarities in the mechanism for telomere clustering in ALT and the initiation of homologous recombination-based repair.

Another system that requires programmed double-stranded breaks and the Rad51 family of proteins is the recombination between homologous chromosomes during meiosis where the Hop2-Mnd1 heterodimer is required for Rad51 dependent recombination during gametogenesis (Bugreev et al., 2014). When Cho et al. tested the requirement for Hop2-Mnd1 for telomere movement and clustering, they observed a strong dependency on these meiotic factors, which were broadly expressed in all ALT cells tested. Suppression of Hop2-Mnd1 also diminished clustering of telomeres and telomeric recombination in ALT cells that did not express the damage-inducing enodonuclease, confirming the requirement of directional movement for telomeric clustering in ALT.

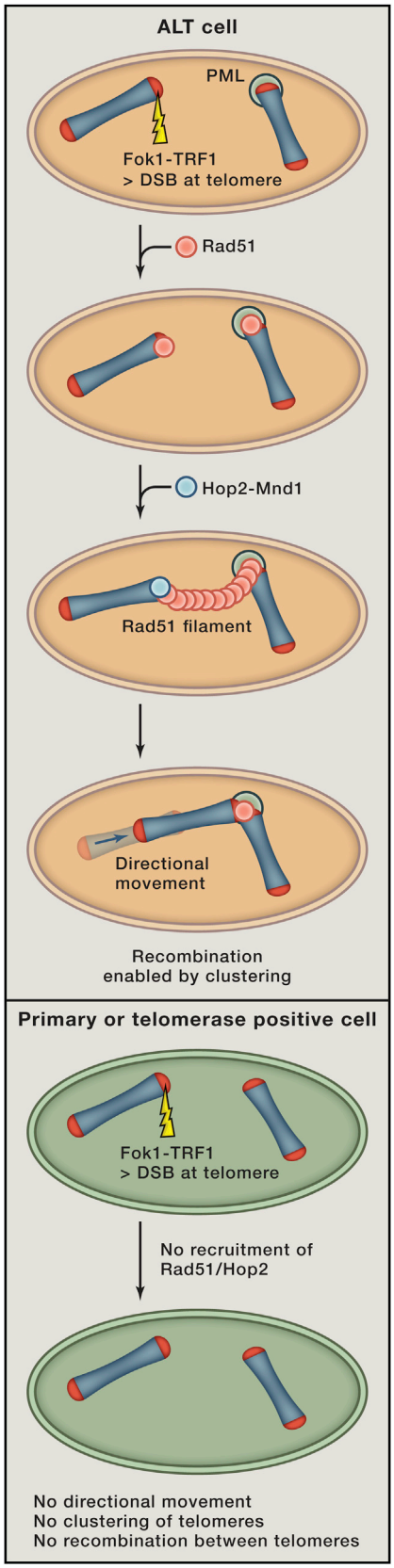


**Figure 1. Clustering of Telomeres in ALT Cells**

During alternative lengthening of telomeres (ALT), telomeres are maintained through a recombinogenic mechanism relying on a direct, long distance homology search facilitated by factors more typically linked to meiosis. Induction of damage at telomeres in ALT cells by Fok1-TRF1 expression leads to Rad51 recruitment. Subsequent association of Hop2-Mnd1 modifies Rad51 to promote the homology search. Rad51 filaments provide a backbone for directional movement and telomere clustering, thereby allowing recombination. Non-ALT cells lack this capacity.

A previous study established that clustering of telomeres promotes elongation by homologous recombination (Draskovic et al., 2009). The discoveries reported by Cho et al. provide the mechanistic basis for this observation, offering support for the idea that homology search and recombination-based telomere elongation in ALT cells is closely related to information exchange by homologous recombination during meiosis.

The data also raise many questions. The most obvious one is why ALT cell telomeres have this remarkable capacity for directional movement, clustering and homology search, which appears suppressed in both telomerase-positive cells and primary cells that lack telomere maintenance mechanisms. Recruitment of Rad51 and Hop2, which are primary events in the homology searches, were induced by endonuclease expression in ALT cells only.

So what allows homology search and synapsis in ALT cells? It is possible that telomeric chromatin has features that allow the interaction between Rad51, Hop2, and Mnd1 in ALT cells, but not in other cells. What might specify differences in chromatin is unclear, but it could be the tendency of ALT telomeres to be recognized as damage independently of telomere length (Cesare et al., 2009), or somatic mutations in the histone variant H3.3 and the ATRX-DAXX chromatin-remodeling complex (Heaphy et al., 2011; Schwartzentruber et al., 2012). Similarly, suppression of the histone chaperone ASF1 has been demonstrated to induce all hallmarks of ALT, suggesting that replication fork stalling at telomeres could represent the signal that induces ALT (O'Sullivan et al., 2014).

Homologous recombination is an error free mechanism of repair, usually restricted to cells in S/G2 of the cell cycle when a sister chromatid is present, and then favored over toxic nonhomologous end joining. The choice of repair pathway is tightly regulated, and HR is inhibited in G1. Damage at ALT telomeres, however, resulted in DNA synthesis in non-S-phase cells, suggesting that homologous recombination occurred during G1 (Cho et al., 2014). It will therefore be exciting to decipher the cell-cycle dependency of Rad51/Hop2-mediated directional movement of ALT telomeres and to determine whether repair pathway choice is altered in these cells. Finally, it remains unclear whether nuclear motors and cytoskeletal filaments are required for the homology search and how the search machinery locates other telomeres in the nucleus. Imagine how the 100 inhabitants of Manhattan would ever find each other without some form of communication technology.

## ACKNOWLEDGMENTS

N.A. thanks the Human Frontiers Science Program (LT000284/2013-L) and J.K. the NIH for funding (GM087476, CA174942).

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