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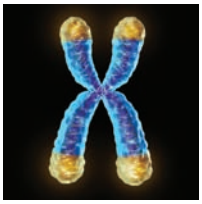
## Telomeres

**Major finding:** TERRA activates the DNA damage response at short telomeres to prevent premature senescence.

**Mechanism:** TERRA competes with ATRX for binding to telomeric DNA to promote telomere stability.

**Impact:** TERRA dysregulation may promote telomere instability and disrupt genomic integrity.

### THE TELOMERIC NONCODING RNA TERRA REGULATES TELOMERE STABILITY



Telomeric repeat–containing noncoding RNAs (TERRA) are long noncoding RNAs that contain the canonical telomeric repeat sequence UUAGGG and have been found to associate with telomere ends in mammals and have been linked to cancer, cellular senescence, and aging. TERRA have proposed roles in the protection of telomere ends, regulation of telomere length, recombination between telomere ends, and recruitment of chromatin factors, but the specific mechanisms by which TERRA contributes to these processes remains unclear. Chu and colleagues investigated the function of TERRA through integrated genomic and proteomic approaches. TERRA localized at telomeric ends at high density, but also associated with nontelomeric DNA, especially the pseudoautosomal regions (PAR) of sex chromosomes, and at introns within genes. TERRA depletion consistently downregulated subtelomeric TERRA-associated target genes and dysregulated expression of internal target genes (either up- or downregulation). Proteomic studies identified TERRA-interacting proteins including the RNA helicase ATRX. TERRA and ATRX co-occupied a number of chromatin sites and had opposing effects on target genes, with TERRA promoting gene expression and ATRX suppressing gene expression. Further, TERRA competed with ATRX for binding to telomeric DNA, and TERRA loss promoted telomere instability. In a related study, Graf, Bonetti, Lockhart, and colleagues found that TERRA preferentially accumulates at R-loops, RNA–DNA hybrids that promote double strand breaks and homology-directed repair (HDR), at short telomeres. Mechanistically, RIF2 recruited RNase H2 and RAT1 to long telomeres to promote degradation of TERRA and R-loops before telomere replication. Short telomeres were unable to associate with RAT1, allowing TERRA to activate the DNA damage response to promote HDR and prevent premature senescence. Taken together, these studies elucidate mechanisms by which TERRA maintains telomere stability and genomic integrity and functions as a transcriptional regulator. ■

*Chu HP, Cifuentes-Rojas C, Kesner B, Aeby E, Lee HG, Wei C, et al. TERRA RNA antagonizes ATRX and protects telomeres. Cell 2017;170:86–101.e16.*

*Graf M, Bonetti D, Lockhart A, Serhal K, Kellner V, Maicher A, et al. Telomere length determines TERRA and R-loop regulation through the cell cycle. Cell 2017;170:72–85.e14.*

## Translocations

**Major finding:** TOP2B induces double-strand breaks at CTCF-bound DNA loop anchors, increasing genomic rearrangements.

**Concept:** Breakpoint cluster regions associated with oncogenic translocations are enriched for loop anchors.

**Impact:** Loop anchors are susceptible to DNA breaks independent of transcription and replication.

### CHROMOSOME LOOP ANCHORS ARE SUSCEPTIBLE TO DNA DOUBLE-STRAND BREAKS

The type II topoisomerase TOP2B is expressed throughout the cell cycle and induces transient DNA double-strand breaks (DSB) to dissipate torsional stress especially at sites of transcription, but when these DSBs are not faithfully re-ligated, genomic rearrangements can occur. Further, treatment with the TOP2 inhibitor etoposide is associated with development of therapy-related acute myeloid leukemia (t-AML), which often harbors genomic rearrangements associated with translocations in breakpoint cluster regions (BCR). Thus, Canela, Maman, and colleagues sought to uncover the link between TOP2B and oncogenic translocations. Etoposide treatment induced DNA breaks at common BCRs, including *MLL*, *NUP98*, and *TMPRSS2*, and these sites showed DNase I hypersensitivity and were enriched for occupancy of TOP2B and CTCF, which binds to chromosome "loop anchors" in long-distance DNA loops. Moreover, spontaneous DSBs occurred at many of the same BCRs, albeit at a lower frequency than after etoposide treatment. TOP2B was required for etoposide-induced double-strand breaks, and its activity was higher at active promoters and enhancers and largely independent of transcription. DSBs were enriched at loop anchors, and TOP2B-associated DSBs were able to predict the positions of CTCF-anchored loops. Introduction of single-nucleotide variations in the CTCF binding sites disrupted DSBs and resulted in DSBs at different sites. Collectively, these findings demonstrate that CTCF-bound loop anchors are more susceptible to TOP2B-induced DSBs, thereby creating fragile sites that become hotspots for chromosomal translocations in cancer. Further, these findings shed light on the origin of etoposide-induced secondary cancers. ■

*Canela A, Maman Y, Jung S, Wong N, Callen E, Day A, et al. Genome organization drives chromosome fragility. Cell 2017;170:507–21.e18.*

AACR American Association for Cancer Research

CANCER DISCOVERY

# The Telomeric Noncoding RNA TERRA Regulates Telomere Stability

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