Nature Reviews Cancer | AOP, published online 19 March 2015; doi:10.1038/nrc3933

GENOMIC INSTABILITY

Building bridges

Dysfunctional telomeres are known to induce genomic instability through a breakage–fusion–bridge cycle. Marzec *et al.* have described a different telomere-dependent mechanism by which genomic instability can be induced in cancer cells that use alternative lengthening of telomeres (ALT) for telomere maintenance.

Previous data indicated that nuclear hormone receptor transcription factors of the NR2C and NR2F families (NR2C/F) are associated with telomeres in ALT$^+$ cells but not those in ALT$^-$ cells. To understand the biological relevance of this, the authors first analysed how these factors are recruited to telomeres. NR2C/F DNA binding sites, which occur throughout the genome, are very similar to a known variant telomere repeat motif, and this telomere motif was enriched in NR2C/F chromatin immunoprecipitation followed by sequencing (ChIP–seq) assays. This motif is present in both ALT$^-$ telomeres (as a monomer) and ALT$^+$ telomeres (as a multimer), but only the multimer in ALT$^+$ telomeres can recruit NR2C/F.

Genome-wide binding profiles of the NR2C/F proteins NR2C2 and NR2F2, and telomeric repeat binding factor 2 (TRF2) showed substantial overlap, both at telomeric and non-telomeric regions, and the proteins were colocalized in ALT$^+$ osteosarcoma cells, but not ALT$^-$ cells. Furthermore, many NR2C/F sites in ALT$^+$ cells did not contain TRF2, and NR2C/F and TRF2 did not bind by co-immunoprecipitation, suggesting a more complex mechanism underlying the interactions of these proteins. The authors hypothesized that NR2C/F proteins act as bridges between ALT telomeric sequences and non-telomeric NR2C/F binding sites, and several lines of evidence supported this.

Cancer cells that are ALT$^+$ typically have complex karyotypes with extensive genome rearrangement. The authors investigated whether the bridging of telomeric and non-telomeric NR2C/F binding sites resulted in genomic instability at the non-telomeric loci. Indeed, they found telomeric DNA insertions at a small portion (~4%) of NR2C/F binding sites specifically in ALT$^+$ cells, and termed these targeted telomeric insertions (TTIs). These TTIs create interstitial telomeric sequences, which have been identified as common fragile sites and can promote chromosomal rearrangement. Induction of DNA double-strand breaks in ALT$^+$ cells (but not in ALT$^-$ cells) increased the number of TTIs in an NR2C/F-dependent manner, suggesting that TTI is an active process. Induction of TTIs also led to an increased number of chromosomal translocations in these cells, 33% (29 out of 88) of which contained detectable telomeric sequences.

> “Induction of TTIs also led to an increased number of chromosomal translocations”

Neil Webb / Alamy

ALT is common in sarcoma, and 54.4% of 180 primary sarcomas were scored as ALT$^+$. NR2C/F was present at telomeres in ~79% of these, and the extent of NR2C/F binding correlated with higher tumour grade. As higher grade tumours typically have increased genomic complexity, the authors suggest that NR2C/F and TTI are involved in generating this phenotype, although the involvement of other mechanisms cannot be excluded.

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ORIGINAL RESEARCH PAPER Marzec, P. *et al.* Nuclear-receptor-mediated telomere insertion leads to genome instability in ALT cancers. *Cell* **160**, 913–927 (2015)