

P029 Mre11 modulates the fidelity of telomere fusion events in human cells

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By capping the ends of linear chromosomes and preventing fusion, telomeres play a key role in upholding chromosomal integrity. The loss of telomere function can result in the fusion of telomeres with other telomeric loci, or non-telomeric double-stranded DNA breaks. These events can lead to genomic rearrangements, such as non-reciprocal translocations, that typify many types of cancer.

We have been characterising fusion events between short dysfunctional telomeres in human cells; we observe a specific threshold below which telomeres are capable of fusion, and that fusion is characterised by a distinct molecular signature, consisting of extensive deletions within the telomere-adjacent DNA, and microhomologies at the fusion points.

We are interested in the mechanism by which short telomeres undergo fusion. We have thus been examining the role that Mre11, a key protein involved in DNA end-joining, may play in this process. To do this we have analysed telomere fusion events in cells derived from ataxia-telangiectasia-like disorder (ATLD) patients that exhibit hypomorphic mutations in MRE11. Consistent with normal cells, fusion events in ATLD cells exhibit large deletions and microhomologies; but in addition we observe the insertion of apparently random DNA sequences at the fusion point.

The possible function of Mre11 in telomere fusion will be discussed.