Role of Tel1 in promoting DNA end-tethering

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Abstract:
DNA double-strand breaks (DSBs) are particularly dangerous cytotoxic lesions having the potential to cause loss of genetic information, chromosomal rearrangements and cell death. Eukaryotic cells have evolved two major repair pathways: non-homologous end-joining (NHEJ) and homologous recombination (HR). In NHEJ, DSBs are directly ligated with no or limited processing at their ends, while in HR the two DNA broken ends are nucleolytically degraded to generate 3′ single-stranded DNA overhangs that pair with intact homologous DNA templates to restore the genetic information lost at the break site. Generation of DSBs also triggers the activation of the DNA damage checkpoint, in which Tel1 is one of the main apical kinases. A central aspect in both NHEJ and HR is the maintenance of DNA ends in close proximity to allow a correct and efficient DSB repair. In *Saccharomyces cerevisiae*, this function, known as end-tethering, involves the Mre11-Rad50-Xrs2 (MRX) complex and Sae2, which are among the first proteins to be recruited at DSB ends. We have identified a Tel1 mutant variant, carrying three amino acid substitutions in Tel1 C-terminus, which restores DNA damage resistance of cells lacking Sae2 by suppressing their end-tethering defect in a Rad9-dependent manner, suggesting a role of Tel1 and Rad9 in keeping the DSB ends tethered to each other. We present data regarding the role of these two proteins in this molecular mechanism.