Exploring the function of the CST complex at DNA double-strand breaks

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Abstract:
DNA double-strand breaks (DSBs) are cytotoxic lesions that must be repaired to preserve genomic integrity. The two main mechanisms devoted to DSBs repair are homologous recombination (HR), which uses intact homologous DNA as a template to restore the genetic information lost at the break site, and non-homologous end-joining (NHEJ), which catalyzes the direct religation of the DSB ends. The key process in determining which pathway is used to repair DSBs is the initial processing of the DSB ends. While NHEJ requires little or no DNA end processing, HR is initiated by nucleolytic degradation of the 5′ terminated strands at both DNA ends by a concerted action of nucleases such as the MRX complex, Exo1 and Dna2/Sgs1. The preferential degradation of the 5′-terminated strands results in formation of 3′-ended single-stranded DNA ends that are first coated by the Replication Protein A (RPA) complex.

Following DSBs, cells also activate a signal transduction pathway, known as DNA damage checkpoint, whose apical checkpoint kinases are Tel1 and Mec1 (ATM and ATR in humans, respectively). In *Saccharomyces cerevisiae*, these checkpoint kinases, once activated, promote DNA damage repair and support DNA replication under stress conditions[1].

The Cdc13-Stn1-Ten1 (CST) complex is known to be involved in telomere maintenance[2]. Interestingly, we found that the lack of Stn1 C terminus exacerbates the DNA damage sensitivity of *mec1* and *tel1* mutant cells, whereas a *stn1* missense mutation suppresses it, suggesting a role for this protein in supporting the functions of these kinases in DNA damage repair and DNA replication. We will investigate the molecular mechanisms of these genetic interactions.

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