How telomeres solve the end-protection problem

Dr. Titia de Lange  
Leon Hess Professor  
American Cancer Society Professor  
Head, Laboratory of Cell Biology and Genetics  
Director, Anderson Center for Cancer Research  
Rockefeller University  
New York, NY 10065-6399

The de Lange lab studies how telomeres protect chromosome ends from inadvertently activating DNA damage signaling and repair pathways. Protection of telomeres relies on the six-subunit shelterin complex that binds to the telomeric DNA. Shelterin protects telomeres by forming the t-loop in which the 3’ overhang at the telomere ends is strand-invaded into the duplex telomeric DNA. T-loops are thought to hide the telomere end from the ATM kinase and NHEJ pathways. As t-loop formation requires the presence of a 3’ overhang, we have studied how this ssDNA is recreated after DNA replication. We showed that newly-replicated telomeres initially undergo extensive 5’ resection by Exo1, leading to 3’ overhangs that are overly long. Subsequent fill-in synthesis by Polα/primase restores the 3’ overhang to the correct length. Polα/primase is brought to telomeres by the Polα-interacting factor CST (also called Polymeraseα-Associated Factor, AAF), which binds to the POT1b subunit of mouse shelterin. We have recently discovered an analogous role for CST/Polα in limiting resection of genome-wide DSBs. Rather than the POT1b recruitment mode seen at telomeres, CST is recruited to DSBs by the 53BP1 DNA damage factor. Although 53BP1 was long thought to block resection at DSBs, our data reveal a sophisticated mechanism by which 53BP1 uses CST and Polα to fill in resected ends. These findings are relevant to PARPi treatment of BCRA1 deficient breast and ovarian cancers.