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Describing novel pathways involved in the onset of telomere-dependent replicative senescence in *S. cerevisiae*

Abstract:

Linear chromosomes end with special regions, the telomeres, which ensure the integrity and the stability of the genome. In eukaryotes, telomeres also determine cell proliferation potential by triggering replicative senescence. This occurs upon telomere shortening in the absence of telomerase. In *Saccharomyces cerevisiae*, it is likely mediated by the first telomere in the cell that reaches a critically short length. This shortened telomere subsequently activates a DNA-damage-like response. How the signalling is modulated in terms of telomeric structure and context is largely unknown. During my thesis, I aimed at understanding the influence of the chromatin environment on the senescence signal starting at the shortest telomere. By comparing two sets of strains in which the shortest telomere either harbours naturally occurring subtelomeric elements or lacks these elements altogether, we show that a subtelomeric region comprising an X element counteracts the establishment of senescence. This effect is likely not due to differential Rad51-mediated homology directed repair activities at both types of telomeres. Furthermore, TERRA transcription is induced at both types of critically short telomeres, although levels are elevated in the absence of natural subtelomeric elements. Together, our results demonstrate that transcription from a telomere-proximal region greatly increases when the shortest telomere reaches a critical length, regardless of the presence of a native subtelomere or a dedicated TERRA promoter. This transcription at short telomere is intriguingly reminiscent of the transcripts found at double-strand breaks in other organisms. Furthermore, senescence modulates chromatin leading to the gene expression of the subtelomeric genes that are involved in replicative senescence.