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Real-time analysis of replicative senescence at single cell resolution

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Failure to maintain telomeres leads to their progressive erosion at each cell division and replicative senescence, a cell cycle arrest mediated by the DNA damage checkpoint signaling. To understand the flow of signaling events from telomeres to cell proliferation cessation, we set up a microfluidics-based live-cell imaging assay to investigate replicative senescence in individual *Saccharomyces cerevisiae* cell lineages following telomerase inactivation. Using this strategy, we found that most lineages experience an abrupt and irreversible transition consistent with a model where the first telomere reaching a critical short length triggers senescence onset. However, many lineages undergo frequent reversible DNA damage checkpoint cell-cycle arrests, beginning soon after telomerase inactivation (Xu et al, Nat Com, 2015). Here, we provide evidence that this novel phenotype stems from replicative stress at telomeres and gives rise to genomic instability, a hallmark of senescence escapers. First, we demonstrate that the DNA damage tolerance pathway is critical for viability immediately after telomerase inactivation. More specifically, Rad5 and Rad51 operate cooperatively and sequentially to bypass replication barriers at telomeres and the repair choice is modulated by Srs2 and orchestrated by PCNA modifications. Second, the long reversible arrests are suppressed in an adaptation defective mutant of the polo-like kinase Cdc5. This mutant strongly reduces the senescence-specific genome instability and alters the post-senescence survival patterns. Thus, replication stress at telomeres revealed by telomerase inactivation, initiates repair and adaptation pathways, leading to genomic instability and to potential post-senescence survival. Overall, our findings provide an essential mechanistic link between ageing and cancer emergence.

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