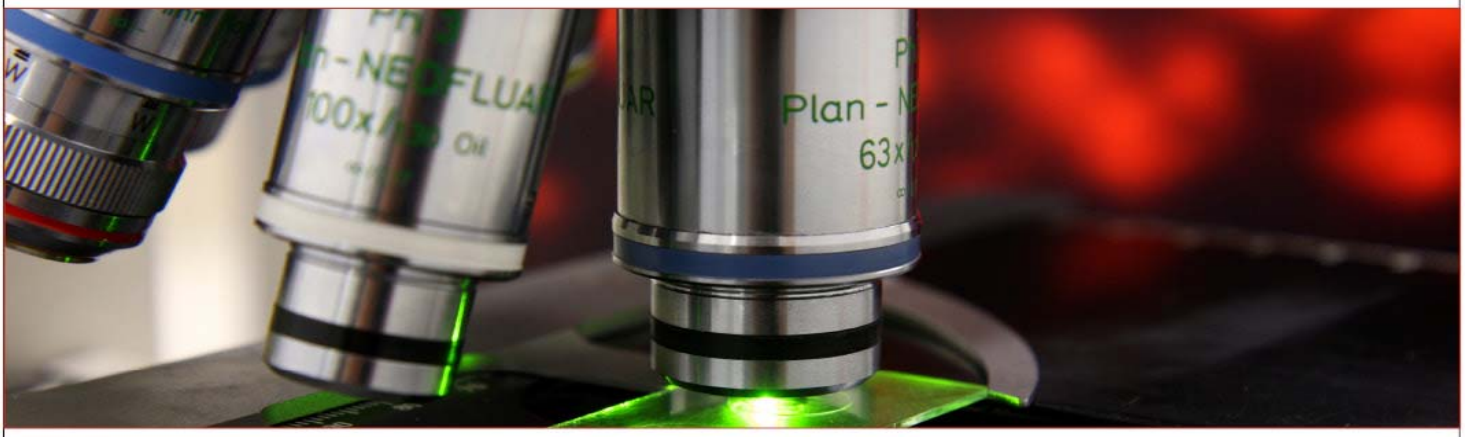
SÉMINAIRES ET CONFÉRENCES



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« Telomeres and the control of proliferation potential »

Replication of the ends of linear chromosomes of eukaryotes results in progressive sequence loss at each cell division, a process counteracted by telomerase. In its absence, telomeres reach a short length and induce replicative senescence to control organ homeostasis. This equilibrium is disrupted in cancer cells, as well as in patients suffering from a wide spectrum of degenerative syndromes. Still, progress in understanding telomere replication and its relationship to senescence has been hampered by intrinsic variations in telomeres and the stochastic nature of senescence onset. Work in our lab builds on our ability to experimentally circumvent and dissect the causes of such heterogeneity. Our strategy is to manipulate and track single telomeres in individual cells and evaluate the effects on the proliferation potential of single cell lineages. We set up a microfluidics-based live-cell imaging assay to investigate replicative senescence in individual *Saccharomyces cerevisiae* cell lineages following telomerase inactivation. We found that most lineages experience an abrupt and irreversible transition consistent with a mathematical 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. This novel phenotype likely stems from replicative stress at telomeres and gives rise to genomic instability. First, we identify factors involved in the response to replication stress acting at telomeres. More specifically, the helicase Rad5 and the recombinase Rad51 operate cooperatively to bypass replication barriers at telomeres and the repair choice is modulated by Srs2 and orchestrated by PCNA modifications. Second, we found that cells relied on a pathway called adaptation to DNA damage to bypass the frequent reversible DNA damage checkpoint cell-cycle arrests, by allowing cell division despite the presence of unrepaired DNA damage. We further demonstrate that adaptation is a major contributor to the genome instability induced in replicative senescence. Taken altogether, our results suggest that senescence dynamics and might constitute an essential mechanistic link between aging and increase in cancer incidence.

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