New insights into mechanisms of telomerase inactivation in ALT pathway of telomere maintenance

Maya Raghunandan, Eva Majerova and Anabelle Decottignies
Institut de Duve, Université catholique de Louvain, Brussels, Belgium

Telomeres are key chromosomal components that maintain genomic integrity in normal cells. Telomeres undergo progressive shortening with successive cell division serving as inducers of replicative senescence. Replicative immortality by overcoming senescence is a classic hallmak of cancers. Telomeres of tumor cells employ one of the two, mutually exclusive, Telomere Maintenance Mechanisms (TMM): either re-activation of telomerase or alternative lengthening of telomeres (ALT). To understand the genetic basis driving the choice of TMM pathway, we studied a set of comparable ALT positive (ALT+) and telomerase-positive (TEL+) human cell lines. To obtain these cells, we hybridized isogenic TEL+ and ALT+ cells, which subsequently choose one of the two TMM pathways for continued survival. This system allows us to delineate changes- genetic and proteomic – in the cells during the pathway choice. Using our hybrid cell system, we have identified a novel two-pronged mechanism of telomerase silencing in the ALT+ cells. On one hand, the protein subunit hTERT undergoes increased proteosome-mediated degradation while simultaneously the RNA subunit hTR is silenced via transcriptional regulation. We will present data elaborating on this new mode of hTR and hTERT regulation, different from the classically better-understood promoter hypermethylation or mutations.