The mechanism stopping DNA replication inspires cancer research

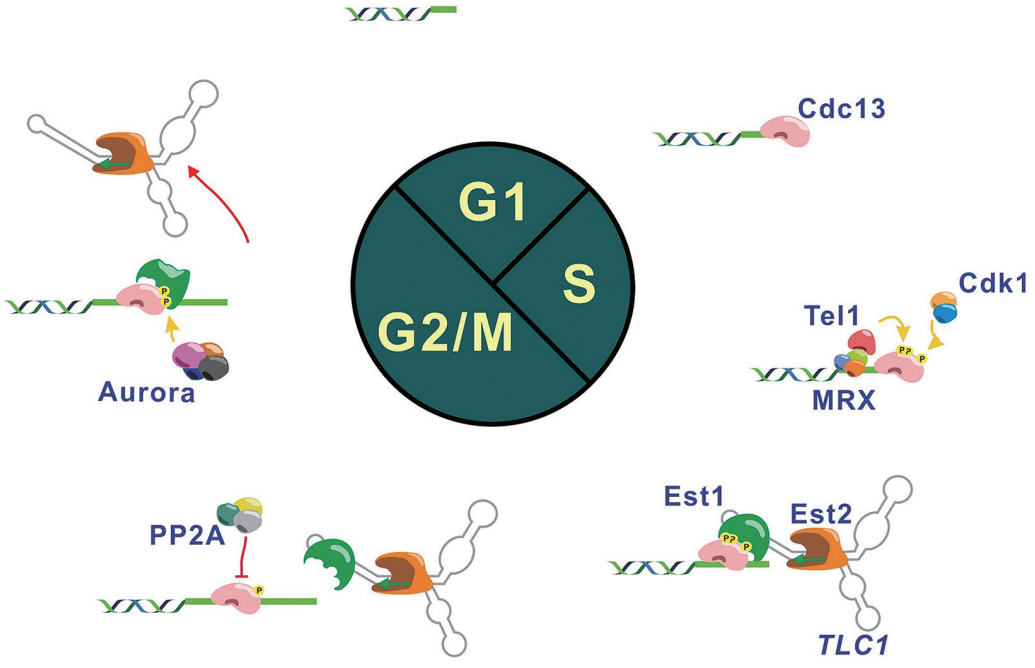
NTU discovers how cell stabilizes its division through terminating telomere replication, inspires cancer research

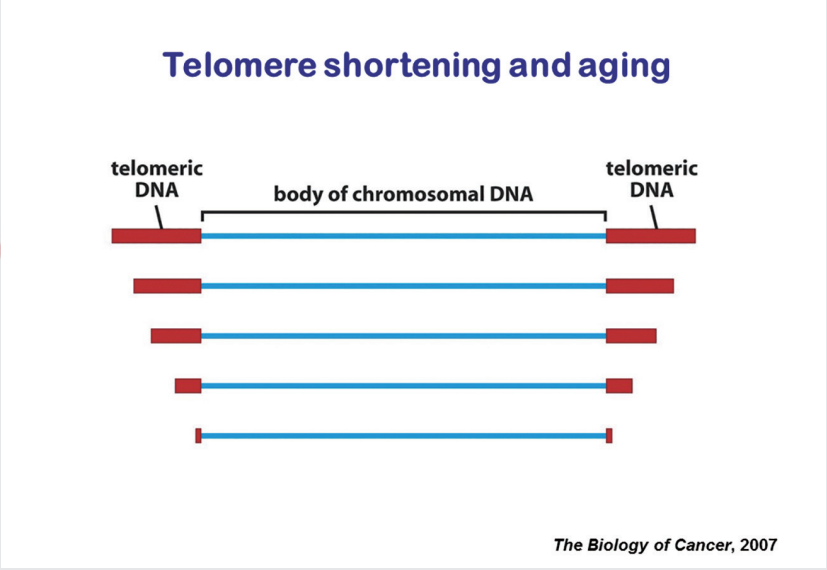
The National Taiwan University research team, which is led by Prof. Shu-Chun Teng from the Department of Microbiology, College of Medicine, has discovered a mechanism related to DNA replication and cellular stability. This discovery is very likely to have crucial implications for cancer research and treatment because understanding this mechanism might allow scientists to prevent harmful chromosome rearrangements and genomic instability in cancer. This research was accepted and published by the reputable journal Nature Communications in 2014.

Teng's team specializes in studying the function of the 'telomere,' a region of sequences protecting the ends of chromosomes and stabilizing cells. How cells synthesize telomeres has long been a puzzle for biologists. Nevertheless, the answer to this question might help biologists understand why most cells remain unreplicated while cancer cells actively execute cell division. From previous studies in the field, it is known that three major regulatory molecules, CDKs, Aurora and Polo-like kinases, coordinate cell division. During this coordination, Cdc13, one of the CDK's substrates, plays a decisive role in telomere protection in live organisms. In addition, recent reports have suggested that 'phosphorylation,' a metabolic process in the cell cycle, may trigger the action of telomeres. However, this suggestion lacks empirical justification. Therefore, Teng's team aimed at addressing this research gap by investigating the effects of Cdc13 phosphorylation.

Through an experiment on yeast, Teng's team discovered

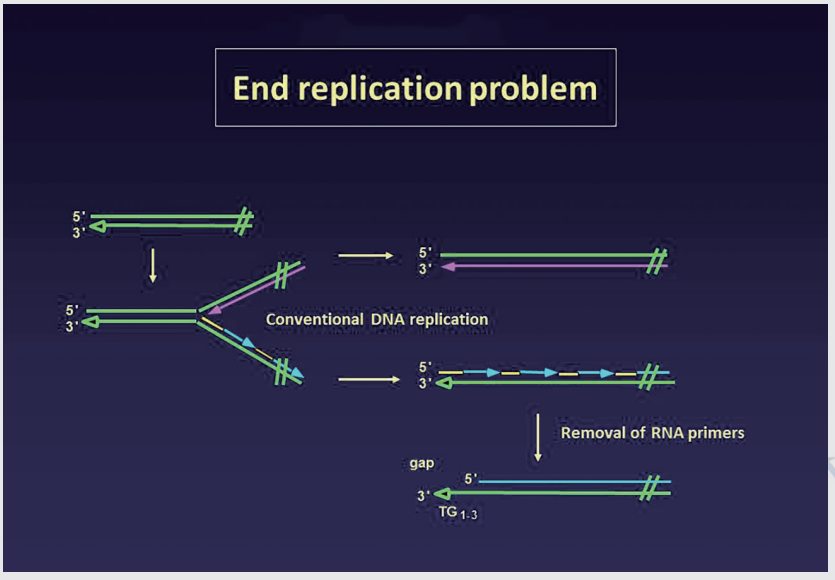
Start and end of the chromosome end replication





the importance of telomeres in stabilizing cells during the DNA replication process. In their experiment, they inactivated two regulatory molecules, Cdc13 and Aurora kinase, and found that this inactivation causes telomere elongation and a prolonged cell division phase. In addition, they also found a protein, 'protein phosphatase 2A (PP2A),' that functions in the de-phosphorylation process of Cdc13 substrates. This protein promotes telomerase release in the telomeres while opposing Cdc13's activation. In other words, in an independent but complementary manner, phosphatase and Aurora kinase use distinct mechanisms to release telomerase from telomeres. Thus, Teng's team has solved a puzzle for biologists around the world and has revealed the mechanism of how telomeres function in the cell cycle and stabilize cells.

Interestingly, cells use multiple pathways to release telomerase. Teng's team has discovered that not only the initiation but also the termination of telomerase recruitment plays important roles in telomere maintenance and cell cycle progression. Teng's team further predicts that in a single cell, PP2A phosphatase might facilitate telomerase release from some telomeres, whereas Aurora kinase might promote telomerase release from other telomeres. Their prediction also hints at directions for future research.



Reference

Zih-Jie Shen, Pang-Hung Hsu, Yu-Tai Su, Chia-Wei Yang, Li Kao, Shun-Fu Tseng, Ming-Daw Tsai & Shu-Chun Teng. PP2A and Aurora differentially modify Cdc13 to promote telomerase release from telomeres at G2/M phase. Nat. Commun. 5:5312 DOI:10.1038/ncomms6312 (2014).

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