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NOVEL ON-OFF KINETICS FOR HUMAN TELOMERASE HOLOENZYME

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Genome stability in human cells requires proper maintenance of telomere length at both ends of individual linear chromosomes. During cell division, telomerase activity adds telomeric repeats to telomeres. Past studies have revealed profound insights into the cellular functions of the telomerase holoenzyme. However, due to very low abundance of functional telomerase and limited accuracy in quantifying its activity, fundamental thermodynamic and kinetic properties of human telomerase remain uncharacterized. By using newly developed technologies to analyse both endogenous and recombinant telomerase holoenzymes, we demonstrate that each holoenzyme complex contains two different types of active sites. Surprisingly, both types of active sites turn inactive after each round of processive extension reaction, named single-run catalysis. The first type of active sites turns off ~40-fold quicker than the other and exhibits higher affinity to a typical substrate. When the first site is in action, the second site remains unoccupied. The two sites thus act in tandem with the faster site performing before the slower one. The inactive enzyme is reactivated by intracellular telomerase-activating factors (iTAFs) available in multiple different types of cells we have tested. Together, the single-run catalysis and the iTAFs serve as an intrinsic brake to ensure that each fully active dimeric holoenzyme is digitally controlled in the number of telomeres it can work on. Such exquisite kinetic control of telomerase activity is expected to play important roles in normal cell physiology and cancer biology.

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