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Abstract

An ON-OFF control of human telomerase holoenzyme

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Abstract:

Elevated activity of telomerase holoenzyme is important for a majority of human cancer cells because they need it to maintain length equilibrium of the telomere sequences at the ends of their linear chromosomes and thus their genome stability. Telomerase activity is equally important for most of normal dividing cells and stem cells. Gradual loss of telomeres is a hallmark for cellular aging (senescence), which endows telomerase activators with the potentialof anti-aging therapeutics. Elevated telomerase activity has been reported in 85-90% of human cancer, suggesting that its suppression be a generic anti-cancer treatment. Throughout the cell cycle, telomerase activity varies in different phases, and appears the highest in late Sphase as expected. How telomerase is regulated during cell division is thus a critically important question, but remains incompletely understood. Recently we uncovered a surprising ON-OFF control mechanism for human telomerase holoenzymes isolated directly from cancer cells. We found that a telomerase active site turns off after its processive extension of a DNA substrate, and the inactive catalytic site of the enzyme can be re-activated by intracellular telomerase-activating factors (iTAFs). We identified fast- and slow-acting active sitesin the native telomerase holoenzyme, and elucidated that both types of active sites are under the same ON-OFF control, suggesting that it is a fundamental property of the native telomerase. Our data further suggested that a dimeric telomerase holoenzyme contains one fast and one slow active site, and these two sites function in tandem, instead of in parallel. I will discuss the experimental studies that lead to these new findings and the possible contributions of the ON-OFF control to telomere length maintenance in normal and cancerous cells.

Biography:

Qiu-Xing Jiang is a membrane biophysicist and is interested in the molecular physiology of different membrane proteins and RNA-binding molecular complexes that are closely pertaining to human health. His research group is working on three directions –– lipid-dependent gating of voltage-gated K channels, ion channels in the regulated secretory pathway, and tight ON-OFF control of human telomerase holoenzyme. He has also been involved in developing new technologies for both membrane biophysics and cryo-EM structure determination.The goal of

these studies is to reveal new insights on the fundamental mechanisms that might suggest new strategies to treat specific human diseases.

Recent Publications:

1. Gaya Yadav and Qiu-Xing Jiang (2020) Reconstituted membrane systems for assaying membrane proteins in controlled lipid environments. Chapter 6, pages 93-122. In: "New techniques for studying biomembranes" ed. By Qiu-Xing Jiang. CRC Press, Taylor & Francis Group, LLC. Boca Raton, London & New York

2. Mohammed Sayed, Ao Cheng, Andrew Ludlow, Jerry Shay, Woodring Wright and Qiu-Xing Jiang. Catalysis-dependent inactivation of human telomerase and its reactivation by intracellular telomerase-activating factors (iTAFs). J. Bio. Chem. 2019. pii: jbc.RA118.007234. doi: 10.1074/jbc.RA118.007234.

3. Qiu-Xing Jiang. Cholesterol-dependent gating effects on ion channels.Adv Exp Med Biol. 2019; 1115:167-190.

4. Gaya Yadav, Hui Zheng, Qing Yang, Lauren Douma, Linda Bloom, and Qiu-Xing Jiang. Secretory granule protein chromogranin B forms an anion channel in membrane. Life Science Alliance. 24 September 2018. DOI: 10.26508/lsa.201800139.

5. Hui Zheng*, Sungsoo Lee*, Marc C. Llaguno, and Qiu-Xing Jiang. bSUM: a bead-supported unilamellar membrane system enabling unidirectional insertion of membrane proteins into giant vesicles. (2016) Journal of General Physiology. 147(1):77-93.

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