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“I am fascinated by the complex DNA transactions that chromosomes undergo—particularly the types of events that occur at telomeres, the very tips of chromosomes. When these telomere-associated DNA processes start to run out of steam, or conversely, become overly active, this can lead to either premature aging or cancer predisposition.”

Whether cells have a finite or infinite ability to proliferate is determined by the ends of the chromosomes, called telomeres, which are tended to by a dedicated enzyme called telomerase. In cells where telomerase is inactive, telomeres shorten with each cell division until they become so whittled away that they signal the cell to stop dividing; cells that retain telomerase are able to continue dividing indefinitely.

Although our knowledge of how telomerase is regulated in human cells remains incomplete, researchers do know that there is a telomerase complex, which was first identified in simple single-celled organisms. Lundblad's group discovered the key protein subunit of telomerase in budding yeast, providing the tools to identify its human counterpart. In budding yeast, telomerase consists of three proteins, called Est (for ever shorter telomeres). The Est2 protein, together with a telomerase-dedicated RNA, does the heavy lifting in terms of telomere reconstruction, while Est1 and Est3 help orchestrate the process.

Lundblad's lab is now looking for the proteins that tell telomerase when and how to act, again using budding yeast as the starting point. Earlier, her group found a clue when they showed that a small area on the surface of Est1 acted like molecular Velcro, by attaching Est1 (and thus the rest of the telomerase complex) to a telomere-bound protein, thereby ensuring that yeast cells continuously divide. Simply changing a single amino acid on this site prevented telomerase from reaching the ends of chromosomes, and the telomeres shortened.

Lundblad's group postulates that there must be multiple docking points on the surfaces of the three Est proteins, each performing a distinct regulatory activity. To test this, they are surveying the entire surface of the telomerase complex. So far, her group has identified two additional molecular tethering points, on Est1 and Est3, and they are hot on the trail of the proteins that interact with these two sites.

For more information, please visit
salk.edu/faculty/lundblad.html

Left to right:

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