Mammalian protein plays unexpected role in cell division, and perhaps cancer

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The French Nobel laureate Jacques Monod famously said, “What’s true for E.coli is true for an elephant.” With this in mind, researchers at Rockefeller University set out to determine the function of Tel2, a protein originally found in yeast where it maintains the length of chromosome tips called telomeres. But one experiment after another informed the group that Tel2 in humans plays an altogether different role.

Researchers led by Titia de Lange, head of the Laboratory of Cell Biology and Genetics, now reveal that mammalian Tel2 stabilizes a family of six proteins called PIKKs, enzymes that catalyze the “stop” or “go ahead” signals at certain checkpoints in the cell cycle. Without the coordinated activity of these proteins, cells either stop dividing and ultimately perish or accumulate mutations and form tumors. This research — and its surprising conclusion — appears in the December 28 issue of *Cell*.

When de Lange and Hiroyuki Takai, a postdoc in her lab, found that Tel2 had no obvious function in mammalian telomeres, they almost dropped the project. But then Takai noticed that cells without Tel2 were unable to detect damage in their DNA, a function carried out by two members of the PIKK family: ATM and ATR. “So Hiro decided to measure their levels in these Tel2 knockout mice and saw that within three or four days the two proteins were gone,” says de Lange, who is also Leon Hess Professor at Rockefeller. After measuring the four other PIKKs, de Lange and Takai found that only PIKKs disappeared in these

cells, suggesting that Tel2 specifically targets this family of signal transducers.

Takai and de Lange determined that Tel2 prevented the degradation of these proteins by using a laborious, “time-honored” technique called pulse-chase labeling. With this technique, they found that cells without Tel2 were able to synthesize the six proteins but were unable to keep them around. Tel2 doesn’t affect their synthesis but their stability. The group further showed that Tel2 stabilizes each of these six PIKKs by binding to a region common to all of them.

In addition to ATR and ATM, the PIKK family includes SMG1, TRRAP, DNA-PKcs and mTOR — “all kinases that regulate central pathways of enormous importance to human disease,” says de Lange. In particular, tumor cells depend on mTOR to survive and to a large extent ATR and ATM; for some time now, mTOR has been a target in clinical trials to combat cancer.

“We are excited about the possibility of using our findings to manipulate PIKKs in tumor cells and thereby kill them,” says de Lange. “As always with new approaches to cancer therapy, the challenge will be in figuring out how to avoid harming cells that are healthy.”

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