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Research resolves contradiction over protein's role at telomeres

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Mice and humans share a lot more than immediately meets the eye, and their commonalities include their telomeres, protective ends on chromosomes. But in recent years, the role of one particular protein at telomeres has puzzled scientists.

New work at Rockefeller University has solved the contradiction regarding the protein, Rap1, a component of the "shelterin" complex that binds to telomeres to help guard and maintain them, so they can perform their protective function. Previous studies of its role in mice versus humans had turned up contradictory results. In human cells, Rap1 appeared crucial, whereas mouse Rap1 seemed to only play a minor role. Given the close evolutionary relationship between mice and humans - both are mammals - this discrepancy was hard to explain.

New research in Leon Hess Professor Titia de Lange's Laboratory of Cell Biology and Genetics has led to an explanation: The previous studies were wrong. Rap1, it turns out, contributes next to nothing to the protection of human telomeres. The research, published today (November 6) in *Cell Reports*, contradicts a number of studies from the past decade.

"It seemed unlikely that Rap1's role would have changed so dramatically between mice and humans, and now we know that it didn't. Human Rap1 is in fact quite mouse-like," de Lange says. "But this raises another question, since Rap1's evolutionary lineage extends back to budding yeast. If Rap1 doesn't protect telomeres, why has evolution maintained it

in mice and humans?"

Telomeres are DNA-protein complexes formed when shelterin binds to specific repetitive DNA sequences that protect the integrity of chromosomes. Dysfunctional telomeres have been linked to cancer and aging, therefore, it is imperative that telomeres are properly maintained, which means maintaining their length. Shelterin helps regulate telomere length and also protects them from misguided cellular processes, including erroneous DNA repair efforts that can have disastrous repercussions.

Rap1 is one of six shelterin components in humans and mice, and one that evolution has maintained for a very long time, all the way back to yeast and single-celled parasites called trypanosomes. Beginning about a decade ago, research suggested that human Rap1 was important for telomere function. Rap1 was shown to be involved in controlling the length of telomeres, and also preventing a repair process that fuses telomeres together, which would ultimately result in cell death.

Meanwhile, studies in which Rap1 was inactivated in mice produced not only apparently normal cells but also apparently normal mice, so clearly erroneous DNA repair was not fusing chromosomes together. Furthermore, no changes in mouse telomere length were detected. However, because mice have much longer telomeres than humans, subtle changes are difficult to detect.

Studies from both sides of this human-mouse discrepancy included those from de Lange's lab. After working on experiments showing that Rap1 was not needed to prevent telomere fusion in mice, a graduate student in the lab, Shaheen Kabir, set out to investigate the conflicting reports by inactivating Rap1 in humans. To do so, she disrupted the gene encoding Rap1 by using a site-specific nuclease called TALEN, a special enzyme designed to cut DNA at a specific location, constructed by fellow author

Dirk Hockemeyer, then at MIT.

"We piled up a lot of negative data looking for effects of removing Rap1 from human telomeres. We observed no fusions, no significant changes in telomere length, no turning on of DNA damage signaling, the list goes on." Kabir says.

In considering what might account for the discrepancy between the current results and the previous studies, Kabir and de Lange think the techniques used may have produced results that were difficult to interpret for some studies, while others employed artificial systems that may not accurately represent the normal situation in a cell.

"While we cannot dismiss the possibility that Rap1 has a redundant function that overlaps with other shelterin components, it is most likely that Rap1 must fill some other, unrelated role. Otherwise, why would it be so strongly conserved?" Kabir says.

Evidence for that other function was already there: Rap1 was first identified not as a component of shelterin but as a protein that turns genes on or off. In fact, studies in mammalian cells have shown that it has a strong influence on genes related to body weight and metabolism. Using three different types of cells, Kabir then compared gene expression profiles between cells with and without Rap1 in those cell lines. She found large changes in the expression levels for a number of genes, whose identities varied depending on the cell line.

"Rap1 may only have a minor role in protecting telomeres in mammals, but it appears evolution has maintained it for an unrelated, but important reason: as a factor that regulates the expression of many genes," de Lange says.

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