Evidence of rapid evolution is found at the tips of chromosomes

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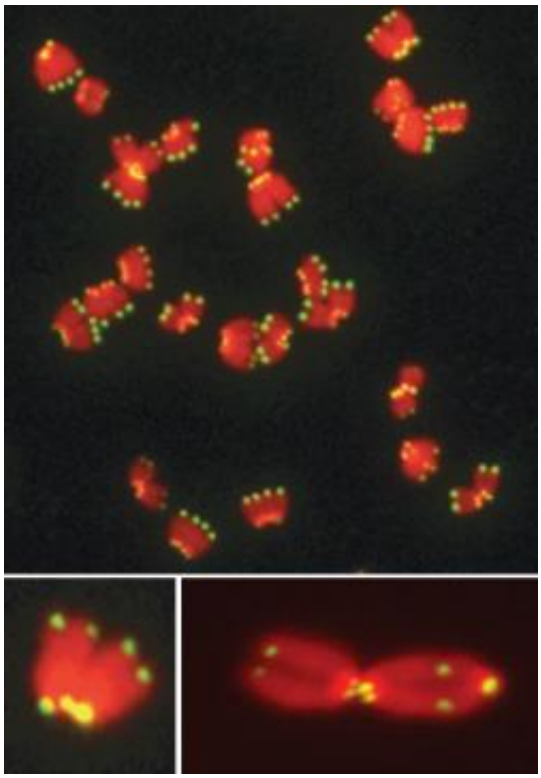

Chromosomes gone to POT. When the genes for the two POT proteins, POT1a and POT1b, are removed from mice, telomeres don't function properly, frequently resulting in endoreduplication, when chromosomes are doubled at inappropriate times (left), and, more rarely, chromosome fusions (right).

In terms of their telomeres, mice are more complicated than humans. That's the finding from a recent Rockefeller University study, which shows that mice have two proteins working together to do the job of a single protein in human cells. The findings, published recently in Cell, suggest that the protein complex that protects chromosome ends may have evolved far more rapidly than previously believed.

Acting as caps on the ends of each chromosome, telomeres are composed of repetitive DNA and shelterin, a protective protein complex. Titia de Lange's lab has identified many of the components of shelterin and studies how its components work together to ensure that chromosome ends are not recognized as DNA breaks.

Previous work from the de Lange lab showed that TRF2, a shelterin protein that binds to the duplex part of the telomere, is crucial for telomere protection. Without TRF2, telomeres activate a DNA damage signal and are repaired by the same pathways that act on DNA breaks. TRF2 brings a second shelterin protein, POT1, to the telomeres. Because POT1 binds to single-stranded telomeric DNA present at the very end of the chromosomes, the de Lange lab asked how POT1 contributes to the protection of telomeres.

"We had previously removed TRF2 from mouse cells and seen many dramatic phenotypes," says de Lange, "all of the telomeres ligate together; there is a massive DNA damage response and the cells basically die. We argued that if the function of TRF2 was to bring POT1 to the DNA, then we should observe the same phenotype if we removed POT1."

To determine if this was the case, graduate student Dirk Hockemeyer, the first author of the paper, decided to remove the POT1 gene from mice. Humans have one POT1 gene, so de Lange and Hockemeyer were more than a bit surprised when they found two POT1 genes in the mouse genome. "Both genes are ubiquitously expressed and both are at telomeres," says de Lange. "Nothing prepared us for the possibility that these two genes, which we called POT1a and POT1b, were doing different things at the telomere."

But the mice showed that POT1a and POT1b did indeed serve different functions. Without POT1a, the cells showed a massive DNA damage response, which did not happen in cells missing POT1b. In contrast, cells without POT1b had

strangely altered telomere structures, something that didn't occur when POT1a was removed. "Wherever we looked, the two phenotypes were different," de Lange says. "To make it more extreme, the POT1b knockout mouse was alive and well, but the POT1a knockout mouse was embryonic lethal at a very early stage."

The other surprise came from the POT1a/b double knockout mouse. While it had a very strong DNA damage response, similar to cells missing TRF2, there was hardly any chromosome end fusion. This result led de Lange and Hockemeyer to realize that while POT1a and b are required for the protection of the telomeres from the DNA damage response, TRF2 is what is needed to protect against the repair pathway.

But this leaves an interesting dilemma for human telomere biology, which only has one POT1 gene. Does the human POT1 gene serve the functions of both POT1a and POT1b? How does the presence of the second POT1 protein affect the rest of the complex? "I've gone through hundreds of genes involved in chromosome biology and the genes from mouse to human are always there one to one," says de Lange. "We know that the telomeric complex evolves rapidly, but I had no idea that it was this rapid, that even within the mammalian lineage you can see big changes in evolution. We will have to be very careful now how we use rodent systems, bearing in mind this difference and the possibility that there might be others."

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Source: Rockefeller University