

Fig. 1 Telomeres serve many functions.

apart when the cell is ready to divide, and the telomeres separate in a timely fashion. On the right is what happens if telomeres are not doing their job. These telomeres on the right are mutant telomeres. We have various ways of mutating telomeres, as I will describe below. With mutant telomeres, the chromosome starts to separate, but then the mutant telomeres become stuck together, although the chromosomes try to pull apart. With a particular mutant telomere, with the help of John Sedat and his group at the University of California, San Francisco, we were able to show that the chromosomes were unable to separate their telomeres. We used high resolution light microscopy to see the chromosomes trying to pull themselves apart.<sup>1</sup>

This is seen at the bottom right of Fig. 2, which shows a chromosome with two centromeres, which get into a fight. Think of the analogy with the shoelace. It is as though somebody took the shoelace on your left

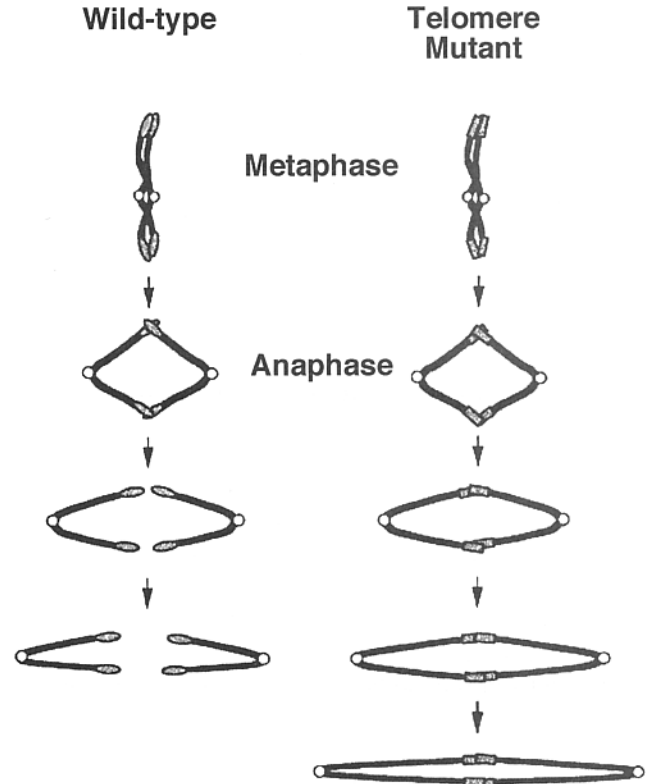


Fig. 2 Failure of mutant telomeres to separate.

foot, and tied it to the shoelace on your right foot. And you know the consequences of that. You trip up. This is the same sort of thing, where this telomere is not functioning, or is uncapped.

Before telomeres reach this very dangerous state of fusing because the telomere is not working, an uncapped telomere in danger of becoming like this one sends a signal to the cell and says: "Stop dividing; there is a problem here." Usually the cell tries to fix the uncapped telomere. But if it fails, telomere fusion is one of the drastic consequences that can ensue.

We can summarize the roles of telomeres as follows: A telomere has to cap the end of the chromosome. I have just shown you one consequence of failure to cap. The telomere also has to allow the complete replication of all the genetic material including that at the chromosome ends. I will get into that in a little more detail in a moment.

How do we look experimentally at the molecular characteristics of telomeres, and in particular, make conclusions about how the chromosome fulfills the function of allowing full replication of the ends? We originally used a pond organism that lives in pond scum called *Tetrahymena*. The *Tetrahymena* cell is covered with cilia that look like little hairs as seen under high