

It's important what happens at the end. A story of PARN deficiency.

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The ends of large biological molecules are important places, they can have signals to attract other molecules, or can be subjected to attack or decay if left unguarded or neglected. Poly(A)-specific ribonuclease (PARN), is a protein machine inside human cells that modifies the end of ribonucleic acid (RNA) molecules.

One of the uses of RNA in cells is to copy DNA, it is then used by ribosomes, the protein making machines of the cell, with the RNA being used as the instructions for making the protein. RNA is composed of the four nucleotides, G, U, A, and C. When RNA is copied from DNA it gets a long tail of around 200 'A's and these remain for most of the working life of this RNA molecule. When the cell requires the removal of the RNA, PARN comes along and removes some of the 'A's, targeting the RNA for recycling.

In addition to copying the genetic code, some RNAs act as structural elements on which proteins can sit in close proximity to perform collective functions. For the structural RNA molecules, they need the 'A's removed completely to function properly. PARN is one enzyme that helps to mature these structural RNAs.

Some individuals have slightly different variations in the PARN enzyme and we wanted to look at how these differences affect how well PARN removes the 'A's from the end of the RNA. The mutations we look at come from a number of patients that have a range of diseases like dyskeratosis congenita, which causes malformed nails, poor hair growth and other growth defects. Another mutant is seen in a patient with pulmonary fibrosis, or scarring in the lungs. Other patients have aplastic anemia, a blood disorder. One common aspect to all of these diseases is an underlying problem with a particular structural RNA, called *TERC*, the telomerase RNA component. There are a number of proteins required to make telomerase work. If *TERC* doesn't have its 'A's trimmed it won't mature, and it gets recycled prematurely. Since there is no structure on which the telomerase proteins can associate, they don't get together to do their job taking care of the end of our chromosomes. The DNA in our cells is long, but as it gets copied for the next cell replication, the ends are not copied completely. Telomerase adds a filler sequence to the end of the DNA so that with continued copying the end of the chromosome doesn't keep getting smaller and smaller. This way our chromosomes stay at full length and the important sequences, like the ones that are the instructions for making proteins, stay protected. So PARN is important for trimming the ends of an RNA molecule, that is important in keeping the ends of our DNA properly maintained.

In our studies we've shown that different PARN mutants from people with telomere syndromes do not operate with the same efficiency as normal PARN, but that there is great variability between the different PARN mutants. This manifests as different severities of telomere disorders as different PARN mutants trim the ends of RNA molecules with varying degrees of efficiency.