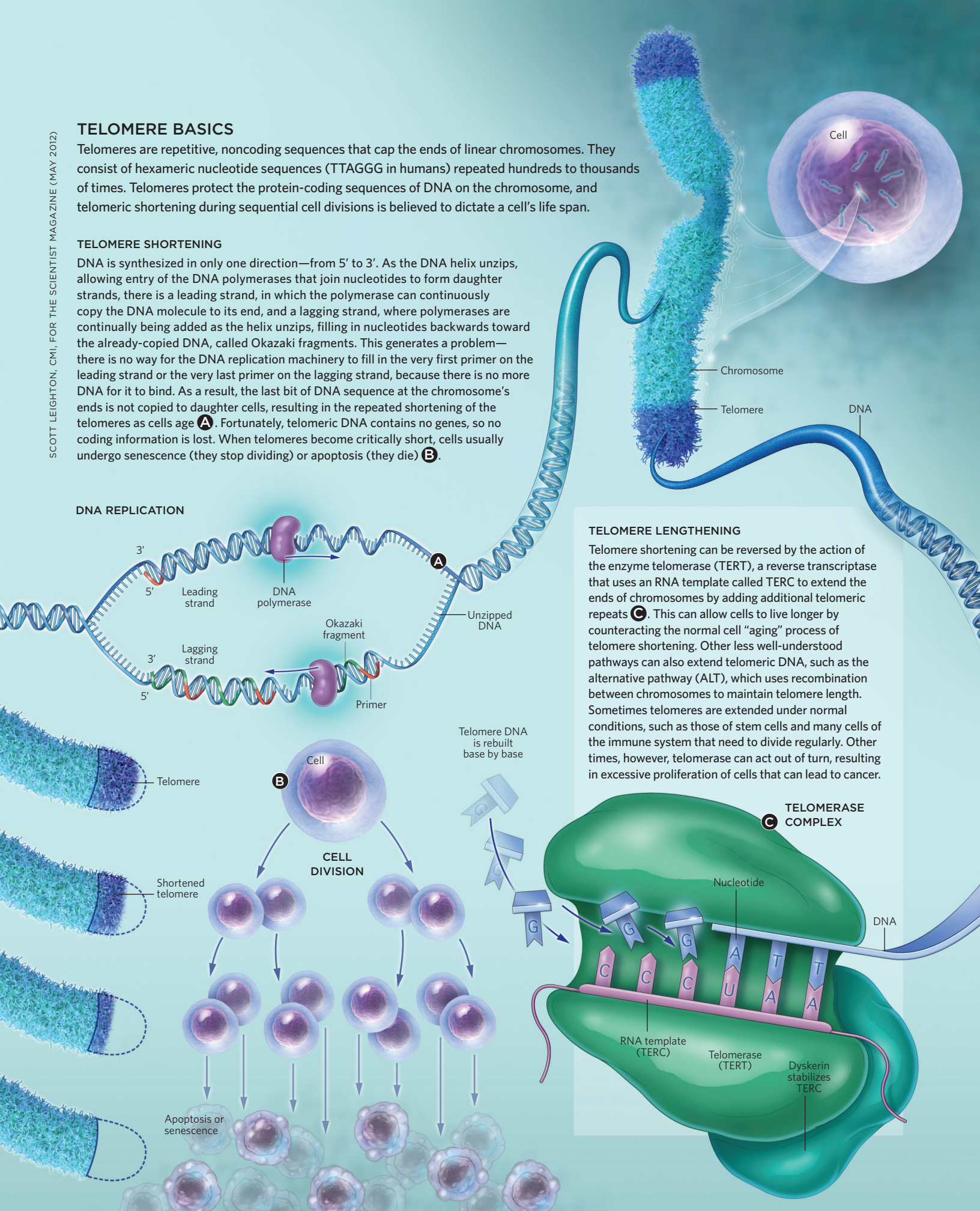
TELOMERE BASICS

Telomeres are repetitive, noncoding sequences that cap the ends of linear chromosomes. They consist of hexameric nucleotide sequences (TTAGGG in humans) repeated hundreds to thousands of times. Telomeres protect the protein-coding sequences of DNA on the chromosome, and telomeric shortening during sequential cell divisions is believed to dictate a cell's life span.

TELOMERE SHORTENING

DNA is synthesized in only one direction—from 5′ to 3′. As the DNA helix unzips, allowing entry of the DNA polymerases that join nucleotides to form daughter strands, there is a leading strand, in which the polymerase can continuously copy the DNA molecule to its end, and a lagging strand, where polymerases are continually being added as the helix unzips, filling in nucleotides backwards toward the already-copied DNA, called Okazaki fragments. This generates a problem—there is no way for the DNA replication machinery to fill in the very first primer on the leading strand or the very last primer on the lagging strand, because there is no more DNA for it to bind. As a result, the last bit of DNA sequence at the chromosome's ends is not copied to daughter cells, resulting in the repeated shortening of the telomeres as cells age (A). Fortunately, telomeric DNA contains no genes, so no coding information is lost. When telomeres become critically short, cells usually undergo senescence (they stop dividing) or apoptosis (they die) (B).



TELOMERE LENGTHENING

Telomere shortening can be reversed by the action of the enzyme telomerase (TERT), a reverse transcriptase that uses an RNA template called TERC to extend the ends of chromosomes by adding additional telomeric repeats (C). This can allow cells to live longer by counteracting the normal cell "aging" process of telomere shortening. Other less well-understood pathways can also extend telomeric DNA, such as the alternative pathway (ALT), which uses recombination between chromosomes to maintain telomere length. Sometimes telomeres are extended under normal conditions, such as those of stem cells and many cells of the immune system that need to divide regularly. Other times, however, telomerase can act out of turn, resulting in excessive proliferation of cells that can lead to cancer.