How Inhibiting Telomerase Could Cure Cancer

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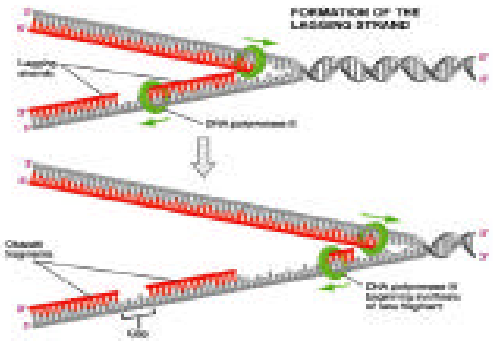
Cancer is one of the leading causes of death in the United States, claiming over half a million lives each year. The causes of cancer have remained somewhat unknown to scientists for decades, yet in recent years, several experiments and observations have corroborated its genetic basis. More importantly, however, is the elucidation of the specific mechanism that causes cells to become cancerous, namely the effect that telomerase has on the formation of tumors.

The process begins with chromosomal replication, during which the entire genetic code is copied and duplicated, thereby resulting in two identical blueprints. Each end of a chromosome has a 5' and a 3' end, a symbol dependent on the chemical constitution at either end.

New DNA is always polymerized in the 5' to 3' direction due to this anti-parallel structuring. This means that one strand can be synthesized continuously while the opposite strand forms sequential gaps, known as Okazaki fragments, because the polymerase has to repeatedly jump back.



These gaps are filled through the function of DNA ligase and polymerase III. Unfortunately, when the polymerization nears the tail end of the chromosome, the process has to be curtailed on the lagging strand side. As a result, a piece of genetic material is not coded for on the lagging side after each replication and would therefore be lost.

To compensate for this, eukariotic chromosomes contain telomeres, non-coding segments of DNA, at the end of each lagging strand. After several cell cycles, the telomeres will be depleted and the cell will either senesce or enter apoptosis.

If tumor suppressor genes have been inhibited, the exposed ends of a chromosome can be interpreted as double stranded breaks. To correct this, a dysfunctional cell will splice two different chromosomes together. During anaphase, this will result in splitting of the chromosomes at arbitrary locations, causing mutations and chromosomal abnormalities. The activation of telomerase can sometimes result from these mutations.

Telomerase is an enzyme that adds segments of DNA to the telomere region of a chromosome. When telomerase is expressed in this situation, it allows telomeres to be added to the end of the mutated chromosome. As a result of this, mutated, or cancerous cells can synthesize an unlimited number of telomeres and can divide indefinitely as a result causing tumors. Not surprisingly, telomerase has been observed in approximately 90% of cancerous tumors.

It would therefore seem logical that curtailing the function of telomerase would prove beneficial in promoting cellular senescence. Certain synthetic molecules, such as oligonucleotides and PNAs have been shown to do just that. By binding to the template region of the enzyme, telomerase activity is inhibited and the normal cell cycle is reestablished.

There have been many obstacles to the success of these molecules, especially since they do not easily permeate the cell membrane or localize in the nucleus. Additionally, telomerase is imperative to the functionality of stem and germ line cells; therefore, high concentrations would prove to be toxic.

The use of antisense molecules, specifically oligonucleotides, has shown great experimental success in vitro as well as in the tumors of mice. GERON is currently doing clinical trials using one of their newly synthesized drugs, GRN163. While the time for tumor senescence typically depends on the length of the telomeres at onset, one study depicts the cell cycle arrest in a lymphoma tumor the same day as the drug was introduced.

The use of telomerase inhibiting drugs is still a novel field in cancer research although it appears to show promise for the future. There are still many obstacles that these drugs face before they will be successful and commercially available.