**Telomeres and their effect in cancer**

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**Abstract**

Cancer cells have two unique characteristics which make them stand out: a loss of contact inhibition and a gain of immortality. As it turns out there are many ways to achieve immortality. Senescence, polyploidy, self-renewal, and telomere length retention all seem to work together in the role of the longevity of Cancer cells (Cragg, 2013). Contact inhibition allows our cells to form layers, which in turn leads to the formation of tissue, muscle, and organs. So, with this loss of function the cells clump together in a large mass, and with immortality the cells have unlimited division/ replication potential (Chen, 2020). The main element at play in cancer is the over expression of telomerase which help retain the telomeres our cells would otherwise slowly lose (McNally,2019). Alternative pathways have been used by cancer cells to try and over come the dependance on telomerase for longevity. With this knowledge researcher have found anti-cancer therapies and vaccines (Mizukoshi, 2019) (Bajaj, 2020). These therapies target telomerase and its components to try and fight the cancer cells. There are also vaccines which aim to trigger an immune response to kill tumors (Mizukoshi, 2019). As Mizukoshi and Kaneko have found in their research, and with the normal methods of cancer treatments, it takes more than one type of therapy to combat the tumors/ cancers. My main concern is the side effects, what are they? How severe are they? Could these therapies have the same or similar body degrading effects of radiation and chemotherapies?

**Introduction**

It has become evident that cancer cells can develop a resistance to treatments. Cancer cells have traits that make them unique when compared to normal cells. Two traits that really stick out are 1) a loss of contact inhibition and 2) cancer cells are immortal. Contact inhibition allows our cells to form layer which leads to tissue, muscles, and organs. Without contact inhibition cells would grow into lumps called tumors, which can be benign or malignant (non-cancerous or cancerous). With immortality the cancer cells keep growing and growing (Mizukoshi, 2019) until either the individual dies or until it is removed. What Immortality means in this case is that without intervention by either anticancer therapies or cancer vaccines the cancer cells will just continuously grow. They have nothing stopping them from dividing an unlimited number of times. Cancer/ tumor cells can achieve this immortality in a multitude of ways: reversible senescence and polyploidy, self-renewal, and telomere retention (Cragg, 2013). Senescence is when a cell dies of old age, this is required for “cell rejuvenation” after anti-cancer treatments. It has been viewed that senescence, poly ploidy (more than two sets of chromosomes) and autophagy (removal of unnecessary or dysfunctional components) cooperate for self-renewal in cancer/ tumor cells, however, the exact mechanism is unknown at this time (Cragg, 2013). Another observation is that cancer cells behave/ adopt traits of pluripotent stem cells, this is seen in the resistance to treatments, DNA repair abilities, and the resistance to apoptosis (cellular suicide). In Cragg’s research, she found that irradiation caused a shift from specificity of a cell type back to its original pluripotency of stem cells, all cells start out as stem cells and become more specified over time and with signals from neighboring cells. It has also been viewed that immortality is gained during the final stages of depolyploidization (Cragg, 2013). The biggest contributor to cell immortality is telomere retention (Chen, 2020).

**Recent Progress**

Telomeres retention has led to many new discoveries in the field of cancer and its treatment, specifically telomere length. Telomeres have a normal range of length in humans and animals (McNally, 2019). Depending on the length it can have different effects on the individual. For example, shorter telomeres are associated with diseases rather than cancer. McNally hypothesized that long telomeres are associated with melanoma and leukemia. These two are a skin cancer and a bone cancer. When a cell divides/ replicates, it cuts away at the ends of the genetic sequence (this is where the telomere is located). It is estimated that about 50 to 200 bases (Lloyd, 2005) are cut off with each replication (McNally,2019). Telomerase is the enzyme that adds bases to a telomere. This enzyme has two components to it 1) Telomere reverse transcriptase which uses a template within the telomerase and 2) TR or TERC which is the specific protein that adds the bases to the telomere. This process is regulated Shelterin. This protein prevents the chromosome ends from fusing (McNally, 2019). Another function of Shelterin is that it regulates telomerases access the telomere. Interestingly, telomerase has four limits: 1) it is very limiting because the ratio of telomere to telomerase is in favor of the telomeres. So only a few telomeres can be added to during the replication process. 2) TERT (gene that encodes telomerase) and TR (telomerase RNA) are expressed in low concentrations 3) its expression is highly regulated by shelterin (as stated above) 4) The additions to the telomeres can only be done during the s phase of cell replication. As I stated previously, telomere length has an effect in certain cancers and diseases, it has also been seen that there is a time in the individual’s life that the effects of the length are seen. Short telomere syndrome is expressed in either childhood or adulthood. In children, immunodeficiency and bone marrow failure have been reported (McNally, 2019). For adults, idiopathic pulmonary fibrosis, and other lung diseases are seen. Long telomeres aid in cancer more than short telomeres because they aid in the longevity of the cancer cell. McNally pointed out that it will not aid in the longevity of the individual, just the cells. Evidence has been found that supports this theory of cancer being associated with long telomeres over short. A Danish study with 95,000 individuals, and animal model data help in providing the evidence for said theory. With the now known knowledge of telomeres, along with their enzymes and proteins which are expressed, scientist have been able to come up with possible treatments and vaccines. A vaccine made by Geron (Durant, 2012) was designed to trigger T cell responses, but this may not have an effect on telomerase deficient tumors. Another anti-cancer therapy has been theorized, this therapy would target telomerase components in two ways 1) targeting hTERT or RNA TR 2) the telomerase itself. This would be easy since telomerase is over expressed in cancerous cells and not normal cells (Durant, 2012). BRACO19 has been shown to have anti-tumor effects in about seven days. BRACO19 is a telomerase inhibitor. An important thing to note is that there are alternative mechanisms to lengthening telomeres that do not use telomerase. An example of how this is done is through homologous recombination (Durant, 2012). CAR-T therapy has been successful in clinical trials. This therapy/ vaccine targets T cells to activate the immune system (Mizukoshi,2019). CAR stands for chimeric antigen receptor. T cells have the capability to recognize antigens located on tumor cells. Like previous therapies, it will target the hTERT expressed by telomerase. However, the vaccine only targets tumors with MHC 1 & 2 in their DNA sequences. MHC stands for major histocompatibility complex. Mizukoshi reports that a vaccine using dendritic cells have also been effective as they are also capable of targeting hTERT. One therapy in particular would use telomerase inhibitors (Bajaj, 2020). Just like our typical cancer treatments researchers have found that it takes multiple treatments at a time to eradicate a solid tumor (Mizukoshi, 2019).

**Discussion**

Even though there is data supporting this telomerase targeting therapy, there seem to be as many drawbacks as there are advantages. I believe that these therapeutic options are viable, but as Durant stated in his research there is a possibility that a resistance could be built against the therapies in the cells. The resistance could come in time, or a lot quicker that the developer thought. I also feel that the possible side effects of these therapies have yet to be fully understood. What are the possible long term side effects of these vaccines? Will these side effects be as deteriorating as the radiation and chemotherapy treatments? Chemotherapy can seriously deteriorate a person’s body. A youtuber has self-reported their experience and their side effects. The biggest issue at the moment is that their jawbone has slowly disintegrated over time and now they will have to have major surgery to repair it. These are the possible side effects of chemotherapy radiation, and as I stated above, will these new therapies have these types serious side effects?

**References**

Erenpreisa, J., Cragg, M.S. Three steps to the immortality of cancer cells: senescence, polyploidy and self-renewal. *Cancer Cell Int* **13,**92 (2013). <https://doi.org/10.1186/1475-2867-13-92>

Lloyd R. Kelland, Overcoming the immortality of tumour cells by telomere and telomerase based cancer therapeutics – current status and future prospects, European Journal of Cancer, Volume 41, Issue 7, 2005, Pages 971-979, ISSN 0959-8049, <https://doi.org/10.1016/j.ejca.2004.11.024>. (<https://www.sciencedirect.com/science/article/pii/S095980490500153X>)

Durant S. T. (2012). Telomerase-independent paths to immortality in predictable cancer subtypes. *Journal of Cancer*, *3*, 67–82. <https://doi.org/10.7150/jca.3965>

McNally E. J (2019). Long telomeres and cancer risk: the price of cellular immortality. The Journal of Clinical Investigation. Vol 129. Issue 9. <https://www.jci.org/articles/view/120851>

Mizukoshi, Eishiro; Kaneko, Shuichi. 2019. "Telomerase-Targeted Cancer Immunotherapy" Int. J. Mol. Sci. 20, no. 8: 1823. <https://doi.org/10.3390/ijms20081823>

Bajaj, S, Kumar, MS, Peters, G, Mayur, Y. Targeting telomerase for its advent in cancer therapeutics. *Med Res https://onlinelibrary.wiley.com/doi/abs/10.1002/med.21674Rev*. 2020; 40: 1871– 1919. <https://doi.org/10.1002/med.21674>

Chen, X, Tang, W‐J, Shi, JB, Liu, MM, Liu, X‐H. Therapeutic strategies for targeting telomerase in cancer. *Med Res Rev*. 2020; 40: 532‐ 585. <https://doi.org/10.1002/med.21626>