Telomeres, Aging, and Cancer

How telomeres influence cancerous cells and aging processes

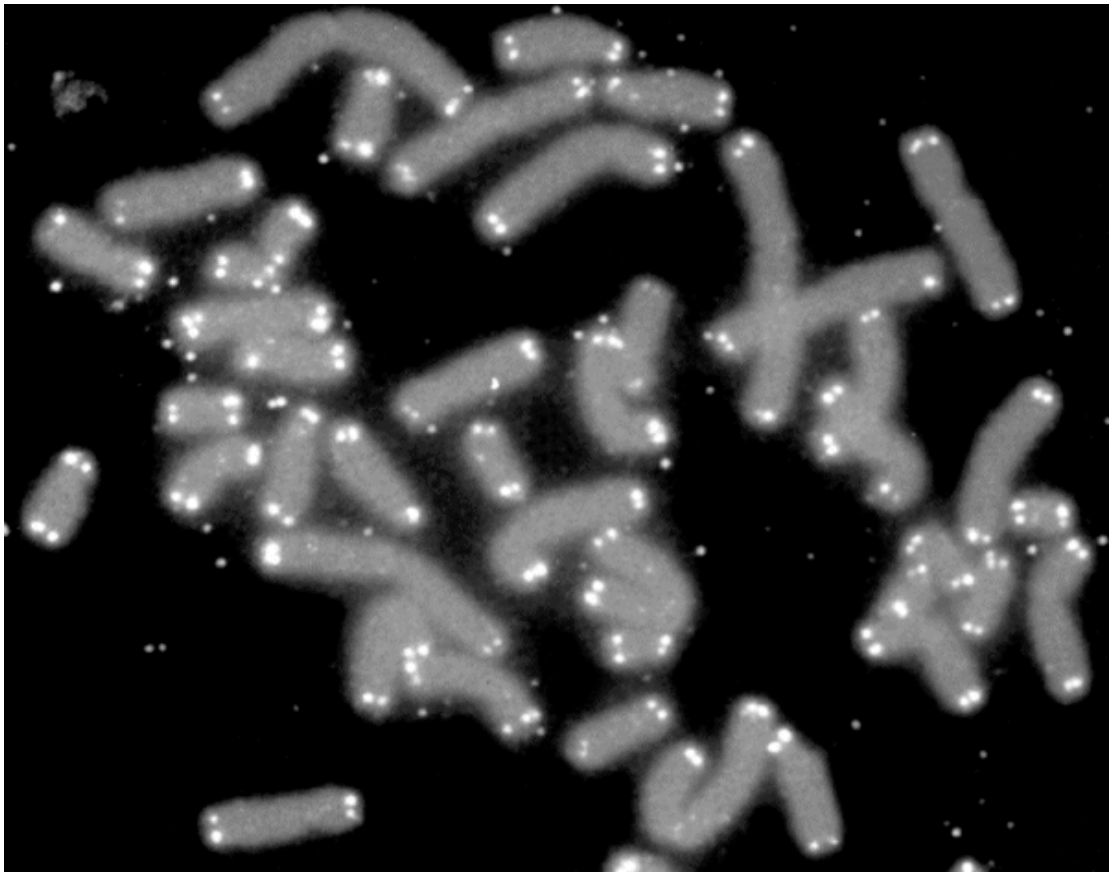

Figure 1: Telomeres appear as bright spots in chromosomes
(https://www.khanacademy.org/science/biology/dna-as-the-genetic-material/dna-replication/a/telomeres-telomerase, 24.03.18)

Gymnasium Kirschgarten, Biology 2017/2018
4e, Dr. P. Ruggle
Telomeres, Aging and Cancer
Term paper 2nd semester
David Tschan, Leo Amrein, Dominic Eichhorn

Table of Contents

1 Preface

In the fourth year of our biology class at Gymnasium Kirschgarten, we had been given the assignment to write a paper on the subject of molecular genetics or genetic engineering. We were to specify our precise choice of topic ourselves. After some research, we decided to write our paper on telomeres.

We had several reasons to choose this topic. Firstly, there is a connection of telomeres to the aging process of human cells, and also to cancerous cells. As cancer is still amongst the most severe diagnoses, research into this topic is of great importance, and cancer furthermore involves very interesting biophysiological processes. As the manipulation of telomeres possibly allows human beings to alter natural aging processes and would possibly also give them a powerful tool to fight cancer, the topic fuels the controversy on the question of to what extent science is to interfere with natural processes.

With this wide range of possibilities to conduct research on this subject, we decided to focus on the impact that telomeres and the enzyme telomerase have on cancer, and how telomeres influence aging. One of the questions that we are most interested in is how telomeres and telomerase are linked to cancer. Another question that we asked ourselves is whether there are aspects of our lifestyle that influence the activity of telomeres on the human body, perhaps even in such a manner that cells become cancerous, and whether our lifestyle can affect how quickly our cells age.

2 Introduction

2.1 Biological background

DNA, or deoxyribonucleic acid, is the macromolecule that contains the genetic information. The structure of DNA is a double helix that consists of two antiparallel strands. Both strands have a 3'-end and a 5'-end (see figure Figure 2: DNA structure), a terminology that is based on the chemical functional groups at the end of the strands. The end caps of the strands are called telomeres. They protect the DNA from gene erosion in DNA replication. This erosion occurs because the mechanism of DNA replication cannot synthesize new DNA at the 5'-end of the strand. This means that after replication, the daughter DNA is shorter. The telomeres form a buffer zone of non-coding DNA that prevents genes from being cut off the DNA. In some cells, an enzyme called telomerase leads to the elongation of the shortened telomeres of replicated DNA. However, in most cells, telomerase activity can not quite keep up with the rate of telomere erosion, or telomerase is not present at all. This results in a net shortening of DNA after a number of replications. Cellular mechanisms prevent a cell to undergo mitosis once the telomeres of the cell's DNA reach a critical minimal length. This is a stress reaction of the cell which is also referred to as senescence. If the DNA of a cell is damaged to such an extent that repair mechanisms cannot sufficiently undo the damages, a cell can undergo cell death, also referred to as apoptosis.

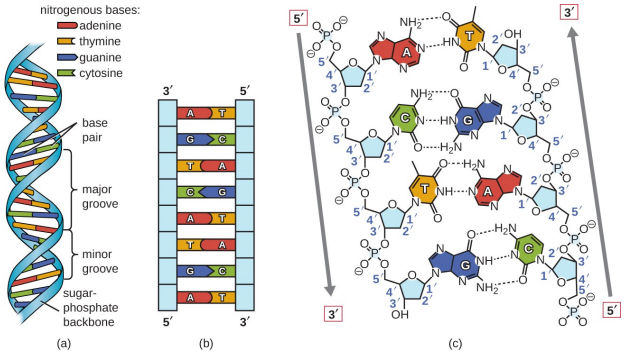

Figure 2: DNA structure
Antiparallel double-helix structure of DNA (a); complementary base pairs A-T and G-C (b); DNA structure in close-up with the pyrimidines C and T and the purines A and G, visible are also the hydroxyl group at the 3'-end of the strand and the phosphate group at the 5'-end of the strand (c). (https://courses.lumenlearning.com/microbiology/chapter/structure-and-function-of-dna/, 27.04.18)

2.2 Historical background

In the 1930s two different geneticists discovered telomeres for the first time at the end of chromosomes. Barbara McClintock and Hermann J. Muller worked separately and with different organisms, but both of them discovered that the ends of chromosomes had a particular function. Muller named them *telomeres*, a name derived from the Greek "*telos*", meaning "*end*" and "*meros*", meaning "*part*". McClintock realized that chromosomes without telomeres would stick to one another, which she thought to possibly cause deformations in the affected organism.
In 1978, Blackburn and Joseph Gall found that *Tetrahymena*[1] telomeres contained a particular simple sequence of nucleotides which repeated over and over (*TTGGGG*)[2]. Since then, scientists have tried to find this sequence for other creatures such as humans or mice. The nucleotide sequences of telomeres are the same in every organism of a species, e.g. for humans it's TTAGGG and for roundworms it's TTAGGC. However, all of them contain a lot of Thymine and Guanine (see section 9.1). In 1984, the enzyme telomerase was discovered and within the next years, scientists learned much about how telomerase works. Four years later, the

[1] *Tetrahymena*: A genus of unicellular ciliate organisms (https://en.wikipedia.org/wiki/Tetrahymena, 18.02.18)
[2] *Nucleotides*: **A**denine, **T**hymine, **C**ytosine, **G**uanine (see section 9.1)

enzyme was found in organisms other than *Tetrahymena*, such as in yeast, frogs, mice, and in 1989, Gregg B. Morin found telomerase in cancerous cells in humans for the first time. A year later, Guo-Liang Yu demonstrated that *Tetrahymena* needs telomerase in order to retain immortality. When the enzyme is not present, telomeres shrink and the cell dies. Then, in the late 1980s, some scientists discovered the lack of telomerase in many human cells. Eight years after this, another research group discovered that telomeres shortened over time and in 1994, Christopher M. Counter, Silvia Bacchetti, Harley and their group showed that telomerase was active not only in cancer-cell lines maintained in laboratories but in *ovarian tumors*[3] in the human body. (Greider & Blackburn, 2009)

3 Hypotheses

On the basis of the biological background, the following hypotheses are proposed:

I. The abundance of telomerase influences the life span of a cell. The shortening rate of telomeres is determined by telomerase. As short telomeres are a possible reason for death, telomerase concentration is therefore a factor determining cellular life span.
II. Human cancerous cells are characterized by significantly higher concentrations of telomerase to retain the full length of their telomeres than normal cells.
III. One of the reasons that cells age is the shortening of their telomeres. The rate of telomere erosion is also dependent on lifestyle.

These hypotheses will be discussed in section 7.1.

4 Literature research

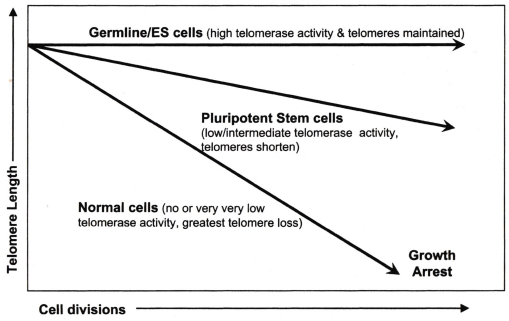

Figure 3: Telomere length
Telomere length with cell divisions in normal cells, cells with moderate telomerase activity and cells with high telomerase activity (Shay & Wright, Telomerase and Human Cancer, 2006)

4.1 Biochemistry of telomeres

It has been proposed that abnormal telomerase activity can lead to the development of cancer, and that the shortening of telomeres is a major factor in the aging of cells (Alberts, et al., 2015), and thus of human beings. The reason that telomeres shorten is the fact that genes that code for the synthesis of telomerase, an enzyme that catalyses telomere elongation after DNA replication, are switched off nearly completely in adult organisms (Shay & Wright, Telomerase and Human Cancer, 2006). As outlined in section 2.1, the continuous shortening of telomeres can trigger a cell to enter senescence. This is achieved by the initiation of a tumor suppressor protein – p53 – which inhibits cell division (Schmidt, Lang, & Heckmann, 2010). Therefore, telomeres, or their shortening to be more accurate, provide a cellular clock mechanism (Schmidt, Lang, & Heckmann, 2010) – if the telomeres of a cell become too short, something that endangers its functionality, it stops to undergo mitosis, thus protecting the organism from dysfunctionalities that stem from genome defects due to eroded genes. This is essential, as otherwise continuing cell division can cause apoptosis (Shay & Wright, Telomerase and Human Cancer, 2006).

[3] *Ovarian tumors*: Tumor in the ovary, the reproductive organ in females producing egg cells

On the other hand, experiments where telomerase genes were artificially expressed[4] in somatic cells have shown that through the resulting abundance of the enzyme telomerase, the erosion of telomeres ceases, telomere length become constant over time (Schmidt, Lang, & Heckmann, 2010) and the cell becomes immortal. Telomere length therefore is a very important factor in controlling cellular procreation. Furthermore, this shows that there is a link between telomere length, telomerase activity and tumors. Yet, the causal relationship between telomere length, influenced by telomerase concentration, and cell aging is contentious as the following quote shows: "*Multiple studies have demonstrated that telomere length predicts mortality and that telomeres shorten with age. Although rarely acknowledged these associations do not dictate causality. […] Inferring the causal involvement of telomeres in aging from current knowledge is therefore speculative and hinders scientific progress."* (Simons, 2015).

4.2 Cancer

At this point it is important to differentiate between cancer and tumor. A tumor is simply the increase in tissue volume, and as such, it is not a very clear term. Tumor can be either benign or malignant, the latter of which is referred to as cancer. They differ in that benign tumors do neither invade neighboring tissues nor form metastases, while cancers do (Wikipedia, 2018). There had been some contention in the past on whether telomerase activity in cancers is simply a by-product of the growth process, or an essential carcinogenic mechanism that destabilizes the genome (Shay & Wright, Telomerase and Human Cancer, 2006). The fact that nearly all cancerous cells retain stable telomere length (Shay & Wright, Telomerase and Human Cancer, 2006) advocates that telomerase abundance is essential for cancerous cells, but it does not clarify the question of whether telomerase activity induces cancer, or whether cancer results in telomerase activity as a by-product. The status quo in the scientific community advocates that telomerase is not oncogenic, meaning that telomerase activity by itself does not induce cancer.

4.3 Possible applications of telomere research

In spite of the causality problem, it has been suggested that telomerase might provide an alternative path of therapy when fighting cancer (Kipling, 1995), next to chemotherapy or similarly stressful therapies for humans. The underlying idea is that a drug inhibiting telomerase should suffice to bring cancerous cells to senescence, or even apoptosis. This will be further discussed in section 6.2. It shows, however, that understanding the biochemistry of telomeres and telomerase is essential when seeking to apply them in i.e. medicine.

4.4 Lifestyle factors

Factors which may influence telomere shortening are obesity, a sedentary lifestyle, smoking, chronic stress and a low socioeconomic status. These factors may also lead to chronical, preventable diseases including depression, hypertension and osteoporosis. Recent studies have also shown that by giving birth, the telomere length of a woman will decline on average by 4.2% (Dockrill, 2018). Other research suggests that high levels of air pollution (i.e. smog) may also shorten telomeres in newborns (Columbia University's Mailman School of Public Health, 2018).

[4] Refers to *gene expression*, the mechanism by which a gene is first transcribed into RNA and then into protein consisting of a sequence of amino acids

On the other hand, there are a number of factors which may help decelerate the aging process or to maintain telomere length as high as possible, respectively: A high level of vegetable and fruit consumption, fiber intake, vitamin and mineral adequacy. Regular exercise will also lead to a healthier aging process (Fuhrmann, 2018).

5 Interview

Dr. Claus M. Azzalin currently is the leader of a research group at the iMM ("Instituto de Medicina Molecular") in Lisbon. In this research group, he investigates how dysfunctional telomeres affect chromosome stability. Instable chromosomes can ultimately lead to cellular response reactions that are typical symptoms for diseases, such as cancer or premature aging. He has also been affiliated with the ETH Zürich, and has been honored with several prices.

Figure 4: Dr. Claus Maria Azzalin (https://imm.medicina.ulisboa.pt/en/investigacao/labs/azzalin-claus-m-lab/, 25.04.18)

David, Leo, Dominic: How come that in *somatic*[5] cells, telomerase is not active to such an extent that mitosis can proceed indefinitely, which has the effect that eventually mitosis will stop and the somatic cell will become senescent?

There had been some confusion regarding this question, and after having clarified it with Dr. Azzalin, his answer was the following:

Dr. Claus M. Azzalin: Now, living forever is not what living animals are there for. This would not allow *speciation*[6] and positive natural selection. Indeed, biologically, we are here just to maintain the species (i.e. procreating) and after that, we are not useful anymore, which means that when we go past our fertile age, we can be 'discarded'. Also, one has to consider that senescence is not only induced by telomere shortening, but also by other insults that are normally associated with cell aging, for example *mitochondria*[7] dysfunctionality and reactive oxygen species, oncogene activation, and so on. For example, mouse expresses telomerase in all tissues, thus including somatic cells. Yet, mouse cells, despite having telomerase, enter senescence when old through other mechanisms. All in all, what we have to learn and accept is that we need to be mortal to allow species survival and amelioration. Telomere shortening is one way that has been developed throughout evolution to set a limited lifespan to our cells.

Telomeres play a major part in the cellular aging process, and we have learned that cancerous cells do occur, amongst other reasons, also because of abnormal telomerase activity.
Here you need to be careful, as telomerase is not an oncogene. You can over-express telomerase in primary human fibroblasts, for example, and make them immortal. Yet, this is not enough to make them transformed, cancerous cells.

What do you think are the ethical ramifications of researching the biochemical relevance of telomeres? Is it ethically correct to conduct research on something that influences very natural processes, such as aging and ultimately dying, or does this somehow break a boundary, such as cloning or "designing" babies may do it?

[5] *Somatic cell*: A normal cell in the body, to be differentiated from i.e. stem cells or gametes
[6] *Speciation*: Evolutionary process creating new species
[7] *Mitochondria*: Cell organelle in which sugars, fatty acids and amino acids are synthesized into ATP, thereby producing the energy required in most processes in the body (Schmidt, Lang, & Heckmann, 2010)

I believe that deciphering how telomerase works is essential. Here we are not talking about genome manipulation (for example using CRIPR/Cas9) to correct genetic defects or alter genetic features. Here we are talking about blocking telomerase in cancer cells [as] therapy or promoting telomerase action in individuals with defects in telomerase activity (for example in *Diskeratosis congenita*[8] patients). Also, short telomeres should not be considered a trigger of premature aging necessarily, but rather a good marker for predisposition towards worsening of age-associated diseases (diabetes, stroke, etc.). Thus, elongating telomeres is not a way to make people live longer, rather a way to get people to age better, disease-free.

What methods are generally applied in researching telomeres and telomerase, more specifically with regard to cancerous cells (i.e. do you use animals in your experiments, are you investigating with microscopes, etc., are there perhaps specific analysis procedures)?
We have not received an answer to this question.

How can the knowledge that you obtain through your research be applied (i.e. medicine, pharmacology, etc.)?
We have not received an answer to this question.

6 Means of research

We have found hardly any literature on this topic. As can be seen in section 5, we asked Dr. Claus Azzalin for information on this, but have not received any.
The research on telomeres and telomerase is practiced in a laboratory. The methods used require microscopes, some chemicals to stabilize DNA and chromosomes (such as ethanol). Also, some more advanced techniques such as *PCR*[9] are used.

6.1 Ongoing research

Recently scientists found out that *interstitial telomere loops*[10] (ITLs), that are formed by telomeres, interact with *interstitial telomere sequences*[11] (ITSs) and thus modify gene expression. Furthermore, ITLs may also change and have functional roles in normal pathophysiological processes (Shay, Telomeres and Aging, 2017). Other work shows that there is a critical telomere length at which senescence is induced. This means the assumption that telomerase is somehow causally linked to aging is not proven (Simons, 2015). Additionally, research has been done which explains the link between telomere shortening and diverse effects of aging on *oocyte*[12] function (Keefe, 2017). Moreover, zebrafish has recently emerged as an advanced and useful model system to study telomere biology. Their telomeres are similar to those of humans and likewise they progressively decline with age (Carneiro, de Castro, & Ferreira, 2016). Other work shows new information on the telomere-tumor-suppressor-pathway and has revealed that telomere cellular stress reactions due to telomere shortening can induce

[8] *Diskeratosis congenita*: A genetic disease affecting the telomerase RNA gene. Symptoms are abnormal pigmentation, abnormal growth of toe/finger nails and others. Individuals affected have prematurely shortened telomeres (Alberts, et al., 2015)
[9] *PCR*: Polymerase chain reaction; a process that allows for the production of many copies of a particular gene (Campbell, et al., 2015)
[10] *Interstitial telomere loops*: Loops in the telomeric DNA
[11] *Interstitial telomere sequences*: Sequences of telomeric DNA somewhere on the chromosome
[12] *Oocyte*: Egg cell

numerous cancer-relevant changes, including *chromothripsis*[13] and others (Maciejowski & de Lange, 2017). A study published in March 2018 suggests that there is a different telomerase *substrate*[14], called 6-thio-dG, which inhibits telomerase activity by leading to a dysfunctionality of telomeres. They showed that 6-thio-dG induced cell death in some skin cancer cells carrying mutations on a particular gene without affecting the viability of normal skin cells. In such cancers, focusing to amend the abnormal telomerase activity may provide a promising therapeutic approach, capable of achieving long-term control over the cancer. In this study, the substrate has been tested in mice (The Wistar Institute, 2018). Furthermore, scientists in Spain have achieved to create "supermice". These mice were genetically altered so that they more easily activated tumor suppressor genes. They exhibited a much higher life expectancy than mice of the control group. This goes to show that it is possible to artificially elongate the life span of living beings without inducing a higher risk of cancer (was-ist-antiaging, 2016). Ongoing research is also considering how telomerase is actually expressed in cancerous cells – the mechanisms behind this are still not known in detail.

6.2 Application in cancer treatment

As outlined in section 4.3, it has been proposed that drugs inhibiting telomerase could be used as an alternative treatment for cancer (Kipling, 1995). This would provide an alternative to the rather aggressive chemotherapy that is in practice today. There are, however, several aspects that need to be taken into account when considering anti-telomerase drugs as cancer treatments:

Advantages	Disadvantages
– There is ongoing research into this topic. Scientists are already trying to find a substance which suppresses telomerase – It is being argued that the combination of an anti-telomerase-drug and an anti-cancer-drug already existing (i.e. Avastin©, a drug by Roche) could be very potent in fighting cancer – Depending on the substance used, it would not cause severe adverse effects as can be seen in i.e. chemotherapy	– There is telomerase in gametes. A drug that inhibits telomerase would also cause the shortening of telomeres in gametes, endangering offspring – It is very costly to produce such drugs – There is no guarantee that such a drug would work for every patient because due to individual physiology, not every drug works for everyone

It appears as though the possible application of telomerase in cancer medicine seems one of the most realistic applications that research on telomeres creates. Apart from giving insight into the processes in cancerous cells, telomere and telomerase research, the research on telomeres could therefore prove to be very attractive for pharmaceutical companies.

[13] *Chromothripsis*: A genetic phenomenon where sections of chromosomes are relocated. Observed especially in cancer patients (https://de.wikipedia.org/wiki/Chromothripsis, 24.04.2018)

[14] *Substrate*: Reactant in a chemical reaction catalysed by an enzyme

7 Discussion

7.1 Hypotheses

At this point, the hypotheses as listed in section 3 shall be discussed.

I. This hypothesis seems to hold true. It is the case that telomerase concentration influences the life span of a cell. The lack of telomerase in somatic cells of humans leads to the shortening of telomeres. This eventually triggers response mechanisms that prevent the cell from further mitosis – it enters senescence. It has been shown, however, that in mice, organisms whose cells exhibit telomerase, and whose cells should therefore be immortal, senescence occurs in spite of telomerase abundance. This suggests that there are other cellular mechanisms that influence the onset of senescence – possible mechanisms could be the dysfunctionality of mitochondria or the activation of oncogenes – genes that foster cell proliferation.

II. This hypothesis is closely linked to the first one. It is not wrong that cancerous cells are characterized by higher telomerase concentrations than normal cells. However, it needs to be emphasized that in spite of this, there is no proven causality between telomerase activity and cancer. Since the causality is not given, the most plausible conclusion is that telomerase activity is amongst the determining factors that transform a cell into a cancerous cell. Keeping in mind, for instance, the fact that UV-radiation can cause skin cancer, or smoking can cause lung cancer, it becomes clear that external influences also impact the cellular process of transformation into cancerous cells. Telomerase is a factor that plays into this. Furthermore, it seems much more plausible to argue that telomerase, while not being involved causally in cancers, must be present in sufficient abundancy for cancer cells to persist.

III. If understanding aging to be the cells decreasing ability to undergo mitosis, then the telomere length is to be considered a major factor. As outlined in section 4.1, cells can enter senescence if their telomeres become too short. Through this stress reaction, the cell loses its capability to undergo mitosis. As the shortening of telomeres is a continuous process with time, their length functions as a “biological clock” (see section 4.1). However, it seems that telomere length is not only determined by the rate of cell divisions. As outlined in section 4.4, lifestyle factors such as smoking, chronic stress or low socioeconomic status also influence the rate at which telomeres shorten. Interestingly, lifestyle aspects generally associated with healthy living, such as exercise and adequate nutrition seem to lead to a deceleration of telomere shortening. This suggests that cellular aging is not merely a process determined by mitosis rate, but which is also influenced by other factors. This also links to cancer: it has been proposed that short telomeres can induce cancer. Short telomeres reduce chromosome stability, therefore making the cell more prone to genetic malfunctions, a possible cause of cancer, but also to other diseases such as diabetes. Shorter telomeres therefore increase the risk of disease, and also of cancer. This goes to show that cancer is also linked to lifestyle.

When assessing the research on telomeres and telomerase, ethical aspects need to be taken into account as well, especially when considering possible applications of the research. This should be assessed using the possible application of anti-telomerase drugs as cancer therapy outlined in section 6.2.

Before anti-telomerase drugs are implemented in medicine and pharmaceutics, it needs to be assured that the effects that such a drug has on the human body upon intake of the drug are very clearly known. If it were not clear what effects such a drug has, not only in terms of how it affects telomerase, but also in terms of adverse effects, then the production of such a drug can ethically not be supported. As has been seen with previous drugs, profit-orientated-production, neglecting undesired yet significant adverse effects of the drug, can have severe consequences. An example is the pain killer Vioxx© by the company Merck. In spite of knowing about the severe adverse effects of Vioxx©, and in spite of many experts advising against it, the drug was produced to offer an alternative to Aspirin©, a pain killer that can cause harm to the stomach lining (Caspar, 2004). The problem is that many pharmaceutical companies produce drugs that are not researched sufficiently, or whose adverse effects are disregarded, in order to have enough profit to fund more research on more drugs to produce them to make profit. This creates a viscous cycle. Only if a drug is sufficiently research upon, and the function of the product is exactly what is required, is it ethically justifiable to produce an anti-telomerase drug.

Another question, and a more fundamental one perhaps, is whether research should be allowed into domains of genome and gene functionality – this inevitably needs to be done when seeking to find an anti-telomere drug. Again, if it can be assured that the adverse effects of a substance that affects the genome are minimized, and the substance is sufficiently researched upon and that it has the desired effect, it is ethically correct to produce such a substance. However, if it cannot be guaranteed that research on DNA – including on telomeres – is applied in such a manner that the patients profit, without having to suffer from unforeseen effects of the drug, then it is ethically incorrect to produce such a drug.

8 Summary

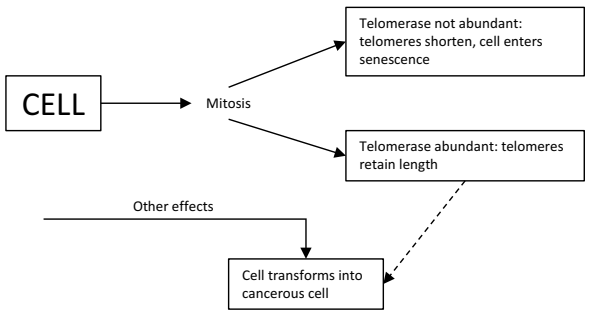

Figure 5: Summary
A cell undergoes mitosis. If telomerase in not abundant, the cell will eventually enter senescence. If telomerase is abundant, telomere length is retained. Cancer cells exhibit high abundancy of telomerase, suggesting a link. However, telomerase is not a causal factor for cells to become cancerous – other effects play into this as well.

Telomeres are sections of DNA that protect genes from erosion. They shorten continuously with every cell division. Some cells contain an enzyme – telomerase – that elongates telomeres again after cell division. In many cancerous cells, the enzyme telomerase is highly abundant, therefore retaining telomeres at a stable length with ongoing cell divisions. However, telomerase abundance itself is not the cause of cells to become cancerous. Such a transformation requires many factors, some of them also linked to the lifestyle of the affected person. Telomere length in normal cell is a good indication of the cells' age, and it also indicates the risk of being affected by age-associated diseases. The rate at which telomeres shorten is again influenced by lifestyle factors. The research on telomeres and telomerase can possibly be applied in cancer therapy. This, however, requires in-depth-research of telomerase and the possible drug to fight cancer.

9 Appendix

9.1 Glossary

Apoptosis	A cellular self-destruction mechanism that ends the life of a cell if damage to DNA exceeds the capacity of cellular repair mechanisms
Cancer	Malignant tumor; abnormally voluminous tissue that invades neighboring tissue and that builds metastases, harming the organism
Chromosome	DNA tightly coiled around proteins; structural array of the DNA before mitosis
DNA	Deoxyribonucleic acid; Double-helix polymeric macromolecule consisting of two antiparallel strands which contain genetic information, consisting of sequences of the four nucleotides adenine (A), thymine (T), guanine (G) and cytosine (C)
Gametes	Reproductive cells including oocytes (egg cells) and sperms
Gene	A section of DNA that codes for the synthesis of a protein
Gene expression	The process of translation and transcription of genetic information from the DNA into a protein
Meiosis	The process of genome distribution to and formation of reproductive cells
Mitosis	The process of cell division, including the copying of genetic information to a daughter cell which results in a net shortening of the copied DNA in comparison to the mother DNA
Nucleotide	An organic ring molecule consisting of a nitrogenous base and a sugar (ribose or deoxyribose) (this is also referred to as nucleoside) to which a phosphate group is attached. Single-ringed pyrimidines are Thymine and Cytosine, double-ringed purines are Adenine and Guanine
Oncogene	Through mutation or virally changed gene of a cell that foster cell proliferation. Oncogenes are very abundant in tumor tissue and cancerous cells
RNA	Ribonucleic acid; single-stranded-polymeric macromolecule that is important in the synthesis of proteins
Senescence	A state in which the cell has lost its capability to undergo mitosis
Telomerase	Enzyme that catalyzes the elongation of copied DNA after mitosis
Telomere	End section of DNA consisting of repeats of a particular nucleotide sequence not coding for genes but protecting genes from erosion caused by mitosis
Tumor	The increase in tissue volume, either of benign source (referred to as benign tumor) or of malignant source (referred to as cancer)

9.2 List of figures

10 Bibliography

Alberts, B., Johnson, A., Lewis, J., Morgan, D., Raff, M., Roberts, K., & Walter, P. (2015). Molecular Biology of the cell (6 ed., Vol. 1). New York: Garland Science.

Campbell, N., Reece, J., Urry, L., Cain, M., Wassermann, S., Minorsky, P., & Jackson, R. (2015). Biology (10th Edition ed.). Harlow: Pearson Education Limited.

Carneiro, M., de Castro, I., & Ferreira, M. (2016). Telomeres in aging and disease: lessons from zebrafish. Retrieved from Diseases Models & Mechanisms: http://dmm.biologists.org/content/9/7/737

Caspar, L. (2004). Merck hat neue Probleme mit Vioxx. Basler Zeitung.

Columbia University's Mailman School of Public Health. (2018). Air pollution may shorten telomeres in newborns -- a sign of increased health risks. Retrieved April 2018, from Science Daily: https://www.sciencedaily.com/releases/2018/01/180124085540.htm

Dockrill, P. (2018). Motherhood Can Make a Woman's Cells 'Older' by as Much as 11 Years. Retrieved April 24, 2018, from Science Alert: https://www.sciencealert.com/having-children-makes-women-s-dna-age-equivalent-11-years-telomeres-mother-birth

Fuhrmann, J. (2018). Your DNA's 'age' depends on what you eat. Retrieved April 24, 2018, from Valley Courier: https://alamosanews.com/article/your-dnas-age-depends-on-what-you-eat

Greider, C., & Blackburn, E. (2009, October 5). Scientific American. Retrieved March 9, 2018, from Telomeres, Telomerase and Cancer: https://www.scientificamerican.com/article/telomeres-telomerase-and/

Keefe, D. (2017). Telomeres, Reproductive Aging, and Genomic Instability During Early Development.

Kipling, D. (1995). The Telomere. New York: Oxford University Press.

Maciejowski, J., & de Lange, T. (2017). Telomeres in cancer: tumour suppression and genome instability. Retrieved from Nature Reviews: https://www.nature.com/articles/nrm.2016.171

Schmidt, R. R., Lang, F., & Heckmann, M. (2010). Physiologie des Menschen (31 ed.). Heidelberg: Springer Medizin Verlag.

Shay, J. (2017). Telomeres and Aging. Retrieved April 24, 2018, from ScienceDirect: https://www.sciencedirect.com/science/article/pii/S0955067417300509

Shay, J., & Wright, W. (2006). Telomerase and Human Cancer. In T. de Lange, V. Lundblad, & E. Blackburn, Telomeres (2nd Edition ed., pp. 81-101). New York: Cold Spring Harbor Laboratory Press.

Simons, M. (2015, August 21). Questioning causal involvements of telomeres in aging. Ageing Research Reviews, 191-196.

The Wistar Institute. (2018). Targeting telomeres to overcome therapy resistance in advanced melanoma. Retrieved April 24, 2018, from Science Daily: https://www.sciencedaily.com/releases/2018/03/180321130904.htm

was-ist-antiaging. (2016, November 7). Telomerase und Krebs: ein Lebenselixier mit Risikofaktor. Retrieved April 24, 2018, from was-ist-antiaging: https://www.was-ist-

antiaging.de/telomerase-jungbrunnen-oder-krankmacher/
Wikipedia. (2018). Benign tumor. Retrieved April 24, 2018, from https://en.wikipedia.org/wiki/Benign_tumor