BLASTIC TRANSFORMATION IN CHRONIC MYELOID LEUKEMIA: THE BCR-ABL PROTEIN, TELOMERES AND TELOMERASE

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a high proliferation and massive accumulation of myeloid cells that retain their ability to differentiate. It is mainly caused by the fusion protein BCR-ABL which disrupts the normal cell cycle.

Telomeres are specialized structures which are found at the end of eukaryotic chromosomes. They are involved in the protection against genetic information loss, prevention of end-to-end fusions, senescence and apoptosis.

OBJECTIVES

CML, like many cancers, is characterized by a telomere shortening. The aim of this review is to discuss this shortening and how it affects cells that display it. On the other hand, due to the discordance among researchers, the relationship between the oncogenic protein and the telomerase is going to be discussed.

THE FUSION GENE

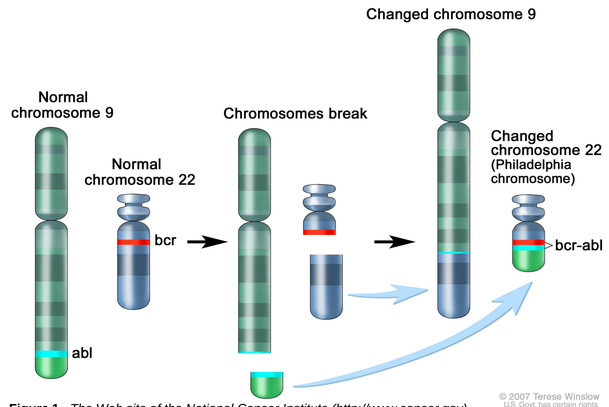


Figure 1. *The Web site of the National Cancer Institute (http://www.cancer.gov)*

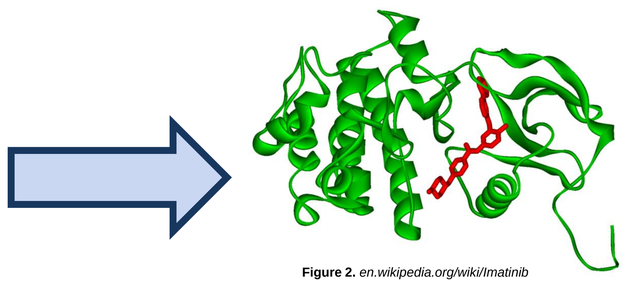


Figure 2. *en.wikipedia.org/wiki/Imatinib*

On the left side of the diagram there is the reciprocal translocation t(9;22)(q34;q11.2) which results in the formation of the Philadelphia chromosome. This chromosome carries the *BCR-Abl* gene, which codes for the BCR-ABL protein. On the right side of the diagram there is the gene product (green) with Imatinib, a tyrosine kinase inhibitor (TKI), in red.

BCR-ABL AND ITS EFFECTS ON CELL'S STABILITY

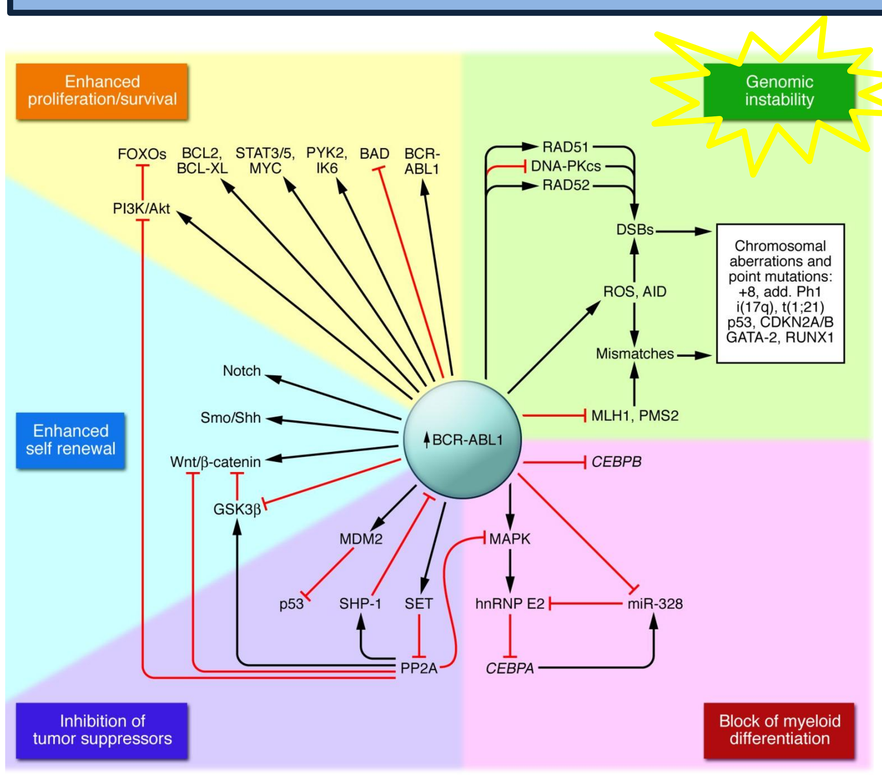


Figure 3. Modified from Danilo Perrotti, et al. (2010) . Chronic myeloid leukemia: mechanisms of blastic transformation. *Journal of Clinical Investigation*;120(7):2254-2264.

The oncogenic protein BCR-ABL has many important roles in the progression through the three phases of the disease (chronic, advanced and blast crisis). These roles include the stimulation of signaling pathways that induce growth independently of the presence of growth factors, apoptosis inhibition, regulation of cell adhesion and tissue invasion, modulation of DNA damage responses and genomic instability, among others. *Red arrows indicate inhibition and black arrows indicate activation of cell factors.*

Probably, the most important factor involved in the chronic phase – blast crisis transition. It is mainly due to:

- **Reactive oxygen species (ROS)**
- **Unfaithful/inefficient DNA damage repair**
- **Telomere shortening**

High proliferation and disruption of shelterines

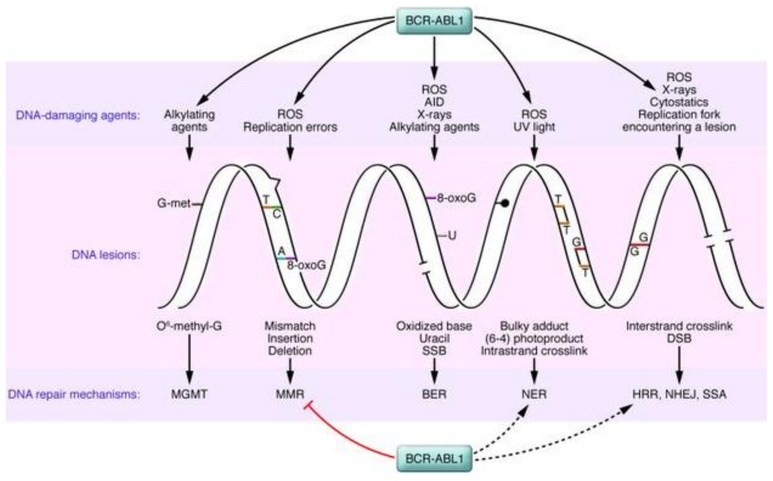


Figure 4. Danilo Perrotti, et al. (2010) . Chronic myeloid leukemia: mechanisms of blastic transformation. *Journal of Clinical Investigation*;120(7):2254-2264.

ROS may induce single and double strand breaks in DNA. These damages can be fixed by several DNA repair mechanisms such as BER, NER, HRR, MMR, etc. However, if damages are not properly repaired, because of the inefficiency of repair pathways, they can lead to genomic instability.

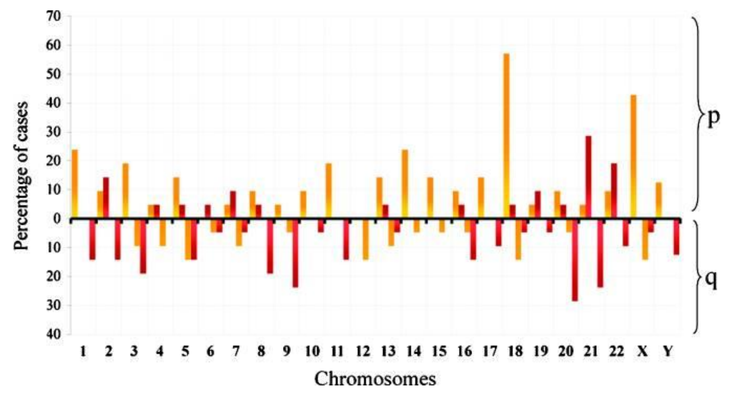


Figure 5. Samassekou, O., et al. (2009). Individual telomere lengths in chronic myeloid leukemia. *Neoplasia*, *11*(11), 1146–1154.

The overproduction of ROS, the high tax of cell proliferation and the disruption of shelterines may lead to telomere erosion. Despite there is a general telomere shortening, some chromosomes may show a telomere lengthening on specific arms. *Red bars indicate telomere shortening and yellow bars indicate telomere lengthening. The chromosome number is on the x-axis and the percentage of cases is on the y-axis.*

MECHANISMS OF TELOMERE MAINTENANCE

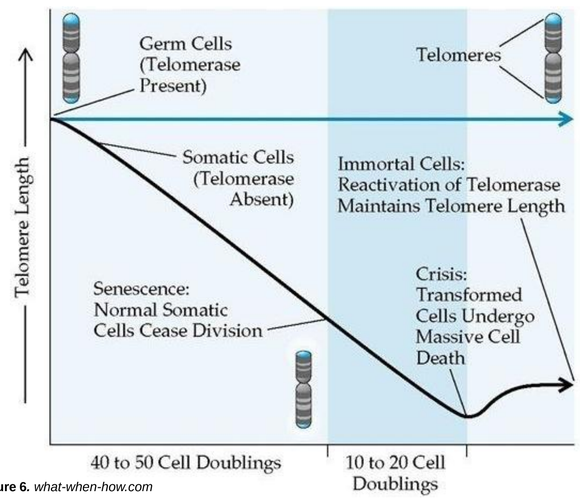
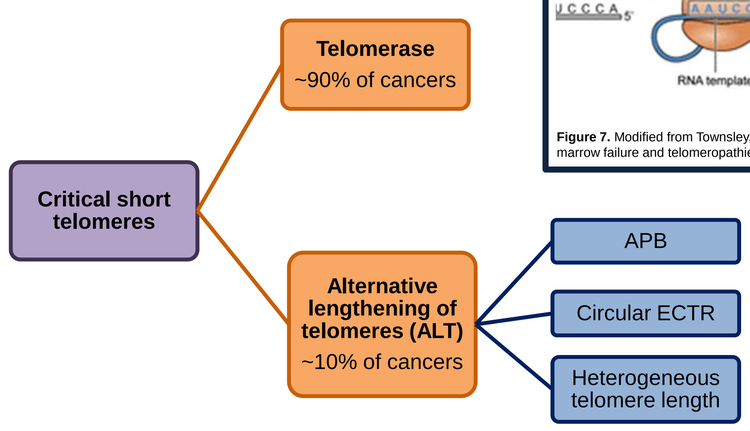


Figure 6. *what-when-how.com*

Cellular senescence, crisis and telomerase activation. Somatic cells display telomere shortening in each cell division until they reach senescence. However, some cells might develop mechanisms to avoid this. *Cell doublings are on the x-axis and telomere length is on the y-axis. The blue arrow shows the telomerase activity in germ cells. The black arrow shows the telomerase activity in the other cells.*



Several projects have aimed to shed light on the relationship between telomerase and the BCR-ABL protein. Some scientists have found that the oncoprotein upregulates *hTERT* gene expression. However, other researchers have found that the BCR-ABL protein downregulates telomerase activity by inhibiting *hTERT* gene expression. In addition, the possibility of an alternative lengthening of telomeres (ALT) has also been proposed.

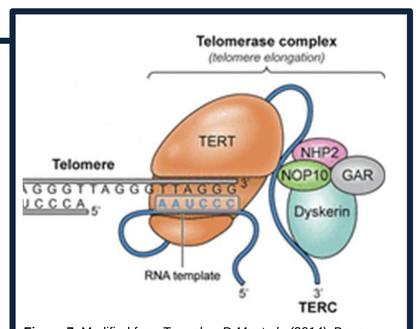


Figure 7. Modified from Townsley, D.*M. et al., (2014).* Bone marrow failure and telomeropathies. *Blood* ;124 (18) 2775-2783.

CONCLUDING REMARKS

- The causes of the BCR-ABL protein formation are still unknown, but the effects of the oncoprotein on cell's stability have been extensively studied.
- The deregulation of the protein produces high cell proliferation, telomere shortening, ROS, DNA damage and disruption of DNA repair mechanisms. Altogether, these factors might induce genomic instability.
- CML cells in their early stages may "activate" ALT as a telomere maintaining mechanism. Through the acquisition of additional chromosomal aberrations telomerase might be activated and become the predominant mechanism.
- Taking all these data together, an appropriate strategy of treatment could be the supply of TKIs and antioxidant drugs to CML patients in the early stages of the disease.

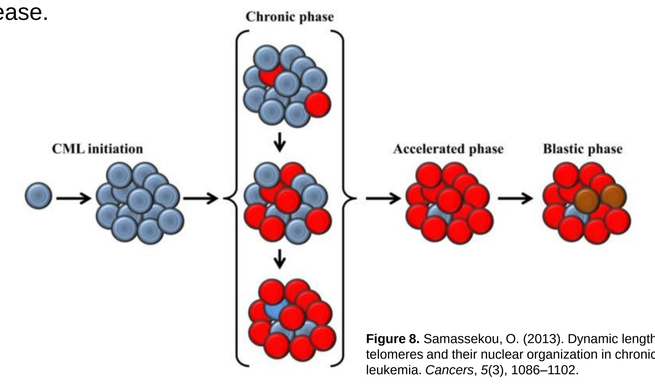


Figure 8. Samassekou, O. (2013). Dynamic length changes of telomeres and their nuclear organization in chronic myeloid leukemia. *Cancers*, *5*(3), 1086–1102.

Suggested model for telomere maintenance in CML. *Blue circles are cells using ALT. Red circles are cells using telomerase. Brown circles are cells expressing high telomerase activity and resistance to Imatinib.*

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