Telomeres and telomerase in ovarian cancer

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Ovarian cancer is the 6th most frequent and the most lethal of the gynaecological cancers; it its oestrogen dependent and it is associated with mutations in BRCA1 and BRCA2 genes. Both oestrogens and progesterone, and BRCA1 gene have important roles in the regulation of telomerase and telomeres, key structures in development and in progress in every epithelial cancer.

Introduction and objectives

Ovarian cancer is one of the most frequent and the most lethal of gynaecological cancers, it is hormone dependent and it is associated with mutations in BRCA1 and BRCA2 genes. It is known that oestrogens and BRCA1 have an important paper in the regulation of telomeres and telomerase, a structure and an enzyme that are deregulated in almost every epithelial cancer.

There is not an effective diagnostic, prognostic or treatment for this disease, so, the aim of these review is to improve this thanks to the knowledge of the importance, the implication and the regulation of telomeres and telomerase in this cancer.

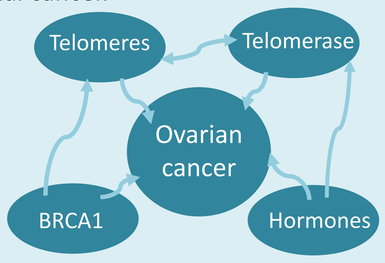

Figure. 1 Relationship of telomeres, telomerase, BRCA1, hormones and ovarian cancer

Methodology

Bibliography research in PubMed and summary of all the information collected.

Writing a memory that relates all the items and briefly represent them here.

Figure 2. PubMed logo. Taken from: http://www.ncbi.nlm.nih.gov/pubmed

Telomeric regulation by BRCA1

BRCA1 plays an important role in the regulation of the length and the stability of telomeres

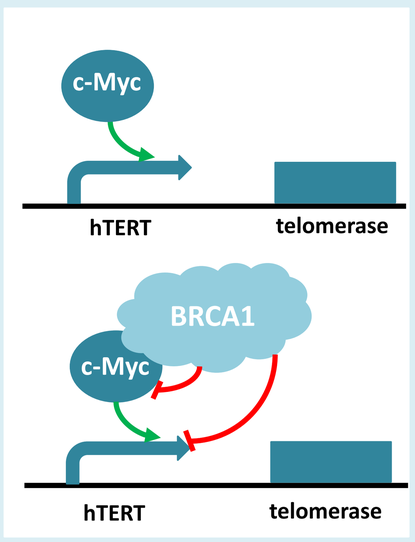

Figure 7. c-Myc induces the hTERT promoter to express telomerase, but when BRCA1 is expressed it inhibits its activity. That way BRCA1 is able to inhibit hTERT and to regulate the length of telomeres.

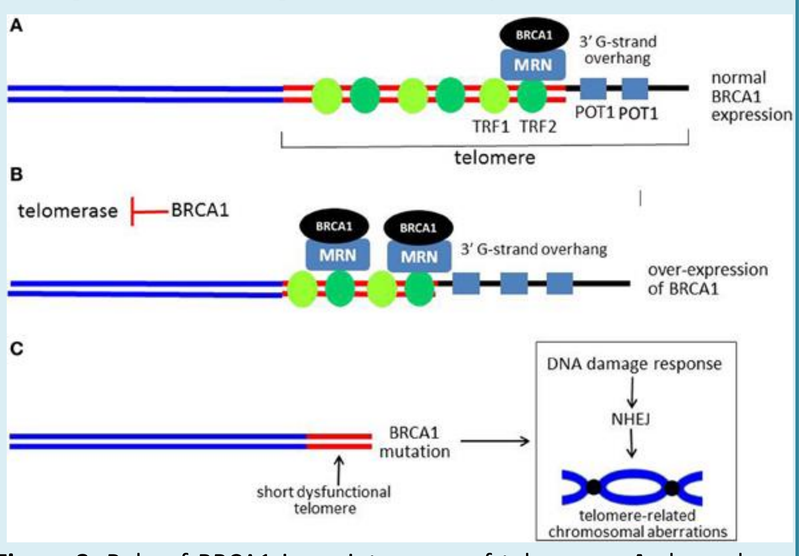

Figure 8. Role of BRCA1 in maintenance of telomeres. **A** shows how BRCA1 is recruited to telomeres by RAD50, a component of MRNA. **B** shows a sobreexpression of BRCA1, that causes telomeric lengthening and an inhibition of telomerase. **C** shows that when BRCA1 is mutated chromosomal aberrations are formed as a consequence of the telomeric dysfunction. Taken from: Rosen, M. E. (2013).

Ovarian cancer

Principal features

Ovarian cancer is the most lethal of gynaecological cancers and the 6th most frequent. It normally does not present symptoms and for that there is not any diagnostic. In addition, it usually develops early metastasis, contributing to a high mortality.

It is related to hormones: having no child, an onset menopause or an early menstruation favour the development of the disease.

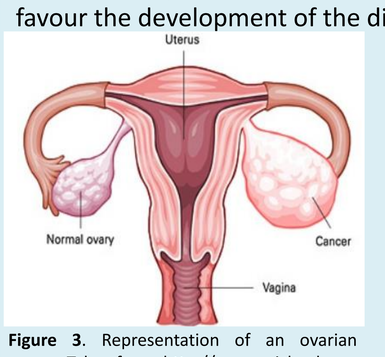

Figure 3. Representation of an ovarian cancer. Taken from: http://www.michaelwos-nick.com/new-promise-detecting-ovarian-cancers-earlier/

On the contrary, giving birth, taking oral anti-conceptives or having tubal ligation prevent the apparition of this cancer.

Genetic factors

10% of the ovarian cancers are hereditary: Association with tumour suppressors that act as Knudson model

P53 PTEN ATM

The most important genes are BRCA1 and BRCA2, both of them codifies proteins that repair double strand breaks (DBSs)

- **BRCA1**: Associated with a probability of 39% of causing ovarian cancer.
- **BRCA2:** Associated with a probability of 11-17% of causing ovarian cancer

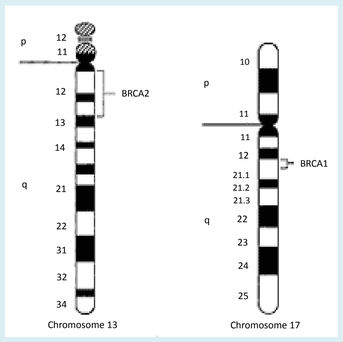

Figure 4. Chromosomic localization. Modified from: Bolton KL, Chenevix- Trench G, Goh C, et al. (2012)

Hormonal regulation

Different studies suggest that oestrogens and other hormones, as progesterone or androgens, could be involved in the regulation of hTERT transcription

- **Oestrogens:** Studies in vitro have shown that an increment of oestrogen expression in tumour cells increases hTERT transcription. Specifically oestrogens directly interact with the hTERT promoter because it has an imperfect oestrogen element response (ERE), it only has one nucleotide of difference with the consensus sequence of oestrogen receptor (ER):

GGTCAGGCTGATC / GGTCAN3TGACC

ERE Sequence ER Sequence

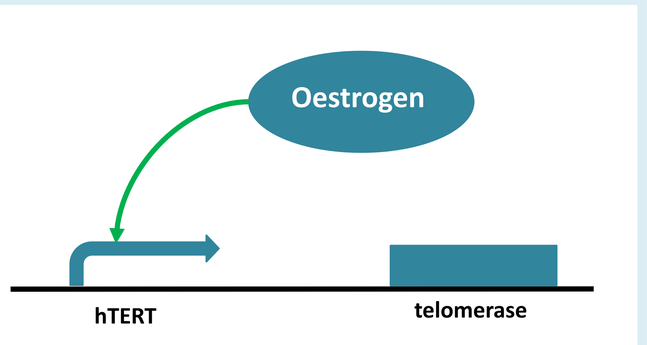

Figure 9. Effects of oestrogen in hTERT promoter.

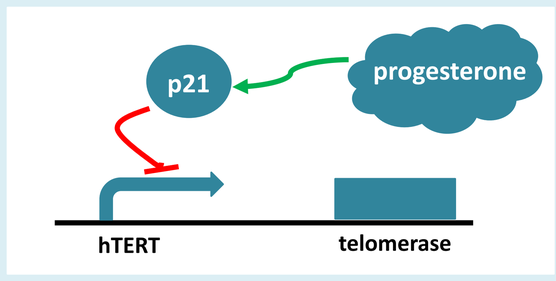

Figure 10. Effects of progesterone in hTERT

- **Progesterone:** It has an antagonistic effect to oestrogens. It inhibits the expression of hTERT because the hormone upregulates p21, a kinase that inhibits the hTERT transcription. This way progesterone indirectly regulates hTERT expression because other studies have demonstrated that does not exist any imperfect progesterone element response (PRE) in hTERT promoter

Telomeric dysfunction

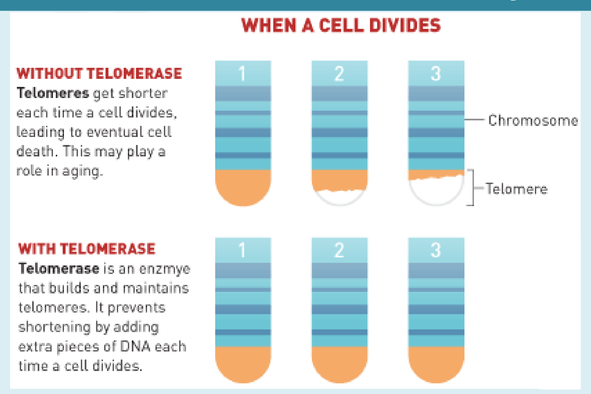

Figure 5. Graphic of telomeres and telomerase. Modified from: http://www.massgeneral.org/news/graphic_nobel.aspx

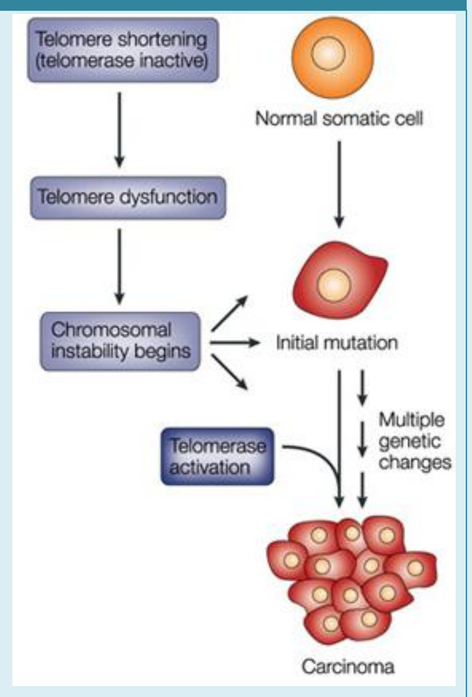

Figure 6. Consequences of telomere shortening. Taken from: Feldser, D. et al. (2003)

Studying ovarian cancer is difficult because normally when it is detected it has already formed metastasis, so there are not many papers of early stages. However, some studies stablish the importance of telomeres and telomerase in ovarian cancer:

- **Counter, C.M. et al (1994):** Studies in cells from metastatic ovarian carcinomas. → Extremely short telomeres were maintained in tumour cells and only telomerase was active in malignant cells, while normal ones did not present this expression.

Hormonal therapy

Hormonal therapies consist in using hormones or drugs that block some hormones to heal or treat some types of cancer. In ovarian cancer there are three, but no one of them are really effective, so they are not normally used.

1. **LHRH antagonists**: Remove the oestrogen production in the ovary.
2. **Tamoxifen:** It is very used in mammalian cancer, it acts like an anti-oestrogen.
3. **Aromatase inhibitors:** Blocks the aromatase enzyme, which can transform diverse hormones into oestrogen.

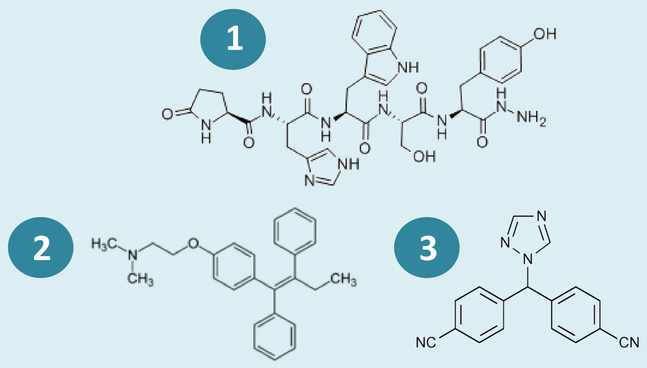

Figure 11. Structure of a LHRH antagonist (1), tamoxifen (2), and an aramotase inhibidor (3)

Conclusions

It can be concluded that both telomeres and telomerasa have key roles in the development and the progress in ovarian cancer. In the early stages of the disease it can be supposed that the telomeric dysfunction is fundamental for the formation of tumour cells. Moreover, it can be proved that an activation of telomerase is needed for the maintenance of telomeres that have been shortened as a consequence of multiple divisions.

In addition, it has been proved that both, oestrogens and BRCA1 gene, two factors associated with this cancer, are important regulators of telomerase and telomeres, either directly or indirectly. The deregulation of oestrogens levels that occurs in ovarian cancer and mutations in BRCA1 that are associated with the disease propitiate the activation of telomerase conducing to immortalization of tumour cells.

The use of techniques that analyse the telomerase activity and the state of telomeres in women with genetic predisposition for ovarian cancer could help to improve her diagnostic and even implant a screening in menopausal women. Finally, further studies in hormonal regulation could help to improve the therapies and with everything together decrease the mortality of ovarian cancer.

Figure. 12 Ovarian cancer ribbon. Taken from: http://www.ovariancancer.org

References

1. Permuth-Wey, J. and Sellers, T. A. (2009) Epidemiology of Ovarian Cancer. *Methods Mol Biol.; 472:413-37*
2. Rosen, M. E. (2013) BRCA1 in the DNA damage response and at telomeres. Frontiers in Genetics; 4, 85
3. Mungenast, F. and Thalhammer T. (2014) Estrogen biosynthesis and action in ovarian cancer. *Frontiers in Endocrinology; 5, 192*
4. Bayne, S. and Jun-Ping, L. (2005) Hormones and growth factors regulate telomerase activity in ageing and cancer. *Molecular and Cellular Endocrinology; 240 11–22*
5. Jun-Ping, L. and He, L. (2010) Telomerase in the ovary. *Society for Reproduction and Fertility*
6. Xifeng Wu et al. (2003) Telomere Dysfunction: A Potential Cancer Predisposition Factor. *Journal of the National Cancer Institute; 95,16*
7. Brown S. B. and Hankinson S. E (2014) Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. *Steroids*
8. Counter, C.M et al. (1994) Telomerase activity in human ovarian carcinoma. *Proc. Natl. Acad. Sci.*
9. Feldser, D. et al. (2003) Telomere dysfunction and the initiation of genome instability. *Nature Reviews Cancer* 3, 623-627
10. Bolton KL, Chenevix- Trench G, Goh C, et al. (2012) "Association between BRCA1 and BRCA2 mutations and survival in women with invasive endothelial ovarian cancer". *JAMA*. 307(4):382-389.