Slowing down aging: the telomerase track?

The 2009 Nobel Prize in Medicine was awarded to American researchers Elizabeth Blackburn, Carol Greider, and Jack Szostak [1]. The three researchers were distinguished "*for solving a major biological problem*": how can **chromosomes** be **copied** completely **during cell division** and how are they **protected from degradation** over time. Nobel laureates have shown that the solution is to be found at the ends of the chromosomes: fragments of human DNA called "**telomers**" discovered by Jack Szostak [2] and in the enzyme that forms them: "**telomerase**" (discovered by Elizabeth Blackburn and Carol Greider) [3]. Elizabeth Blackburn has also shown that the length of telomeres and the activity of the telomerase enzyme are important factors in other diseases (chronic inflammatory diseases) and aging [4].

Figure 1. Elizabeth Blackburn, 2009 Nobel Prize in Medicine for her discovery of the molecular configuration of telomers. She is currently President of the Salk Institute of Scientific Research and Professor Emeritus at the University of San Francisco in California. She has been awarded the main distinctions of the medical world, including the "Albert Lasker Basic Medical Research Award". [Source : Photo © Prolineserver 2010 / Wikipedia/Wikimedia Commons]

Telomeres are **repeated DNA structures** located at the ends of chromosomes; they **protect** the ends of each chromosome **from time attacks**. As cell divisions progress, the size of telomeres decreases. Thus, cells that multiply see their telomeres crumble over generations. The **telomerase** enzyme, on the other hand, **repairs telomeres**, allowing cells to keep their chromosomes intact. In addition to the discovery of telomerase, one of the major discoveries of Professor Elizabeth Blackburn's team (Figure 1) was that stem cells had large amounts of this enzyme.

We also now know that this same **telomerase** is expressed in some **cancer cells**. It would play a role in tumour proliferation processes by contributing to the establishment of a state of "**immortality**" of certain lines of these cells that have become pathological. It would at least partly help to explain the immortality of certain malignant cell lines. This is why one of the potential applications of this fundamental knowledge, on telomeres and telomerase, concerns the fight against certain cancerous processes. **Telomerase is therefore at the borderline between aging and cancer, two major concerns of our society today.**

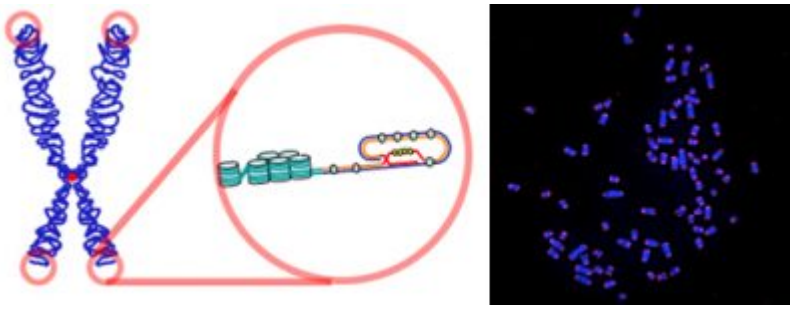

Figure 2. Telomeres and telomerase. Left: Telomerase is a "ribonucleoprotein complex" composed of a protein component and a sequence of RNA primers that protect the terminal ends of chromosomes against the action of enzymes that would otherwise degrade them. Telomers and telomerase are necessary for DNA replication. The shortening of telomeres is therefore involved in the processes of stopping the proliferation of tumor cells. We also know that telomerase is an enzyme very weakly expressed in the normal cell, just enough to maintain the size of the telomeres. Right: Metaphase dog chromosomes; telomeric DNA appears in red (at the ends). [Source: Left, Wikipedia, Creative Commons Attribution-Share Alike 3.0 Unported license; Right, Junko Maeda, Charles R. Yurkon, Hiroshi Fujisawa, Masami Kaneko, Stefan C. Genet, Erica J. Roybal, Garrett W. Rota, Ethan R. Saffer, Barbara J. Rose, William H. Hanneman, Douglas H. Thamm, Takamitsu A. Kato [CC BY 2.5], via Wikimedia Commons]

The excessive shortening of the telomers marks the entry into senescence of cells, which multiplies the risks of degenerative diseases, cancers, cardiovascular diseases etc. The biological reason is that these **senescent cells** are **dangerous** and release pro-inflammatory substances (such as **free radicals** or **cytokines** [5] released within micro-inflammatory lesions) which cause pain and chronic pathologies. Elizabeth Blackburn and Carol Greider proposed the hypothesis that two telomerase subunits (a protein and an RNA) (Figure 2) needed to coordinate to act on a single telomerase. The translation of these discoveries into biomedical applications is in its infancy. The investigations of Elizabeth Blackburn's team have had major implications for the hypothesis that **not all individuals age at the same rate because of complex interactions between their genes, as well as their emotional relationships and social environment, their lifestyle, the stresses they experience** and, in particular, the way they react. Elizabeth Blackburn, and later on other research units around the world, have demonstrated that:

(i) Under the influence of the telomerase enzyme, the telomeres could stop shortening and even lengthen;

(ii) Ageing was therefore a dynamic process that could be accelerated or slowed down or, to some extent, reversed.

With the winners of the 2009 Nobel Prize in Medicine and doctors like Dean Ornish in the USA [6], the "epigenetic revolution" - prepared by a long series of researchers, from Waddington to Hayflick - has found its decisive demonstration, even if we still have to speak of the "telomeric theory" of senescence [7].

Notes and references

[1] E Varela & MA Blasco (2010). *2009 Nobel Prize in Physiology or Medicine: telomeres and telomerase*. Oncogene 29:1561-1565.

[2] Szostak JW & Blackburn EH (1982). *Cloning yeast telomeres on linear plasmid vectors.* Cell 29: 245-255; Shampay J, Szostak JW & Blackburn EH (1984). *DNA sequences of telomeres maintained in yeast*. Nature 310:154-157.

[3] Greider CW & Blackburn EH (1989). A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. Nature 337: 331-337.

[4] Blasco MA (2005). *Telomeres and human disease: ageing, cancer and beyond.* Nat. Genet Rev. 6:611-622.

[5] Cytokines (from the Greek *cyto*, cell, and *kinos*, movement) are soluble cell signalling substances synthesized by immune system cells or by other cells or tissues. They act remotely on other cells to regulate their activity and function. They are therefore essential to the communication of our cells.

[6] Ornish D *et al* (2008). *Increased telomerase activity and comprehensive lifestyle changes: a pilot study.* Lancet Oncol. 2008

9(11):1048-57

[7] Blackburn E & Epel E. (2017). *The telomeric effect. A revolutionary approach to lengthen your life and reduce your ageing.* Guy Trédaniel editor; ISBN: 978-2-8132-1422-5
