# hTERT off: A switch from MYC to MAD

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## TELOMERES AND TELOMERASE

**Telomeres** are repetitive sequences of nucleotides at the ends of each chromosome in order to prevent them from degradation during replication.

**Telomerase** is a an enzyme that maintains and extends telomeres. It is active in germ line cells and becomes deactivated during differentiation. Nevertheless, its function is kept in high proliferative cells.

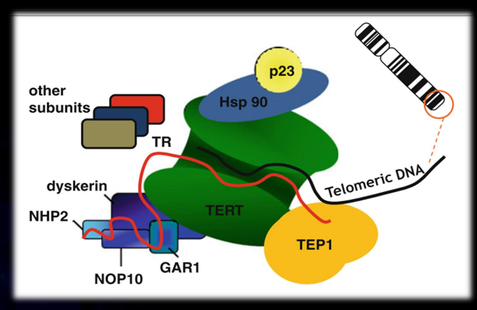
### What happens in cancer?

85% of cancer cells dispose of telomerase while 15% activate an alternative lengthening of telomeres (ALT) system or do not maintain their telomeric length.

## TELOMERASE STRUCTURE

**Figure 1 (right).** Telomerase is fundamentally composed by hTERT (*human TElomerase Reverse Transcriptase*) and hTR (*human Telomerase RNA*).

**hTERT is the rate-limiting step for the complex formation.**




Liu, J. P. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **13**, 2091–104 (1999).

## hTERT AND ITS PROMOTER

Its promoter becomes activated during immortalization. This suggests a telomerase regulation mainly at transcriptional level

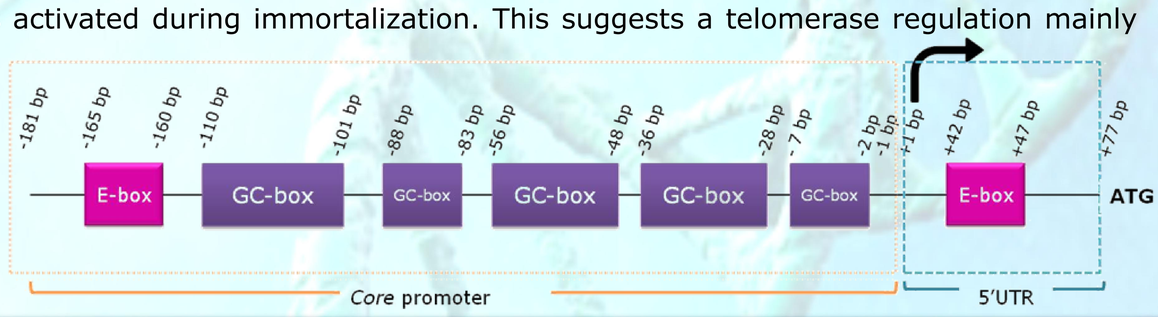



**Figure 2**. Structure of *hTERT* promoter

## MYC/MAX/MAD NETWORK

MYC, MAX and MAD are transcription factors that can bind to the promoter E-boxes. While MYC and MAD have a short half-life, MAX remains constant.

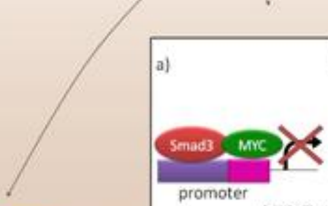
**hTERT repression**

### In normal conditions:

✓ High levels of MAD

✓Possible recruitment of histones deacetylases


**Figure 3 (right).** MAD/MAX dimerization leads to*hTERT* repression




### In cancer:

✓ High levels of MYC

✓Possible recruitment of histones acetyltransferases

**hTERT expression**

**Figure 4 (left).** MYC/MAX dimerization leads to *hTERT* expression

## REGULATION




**Figure 5 (left)**

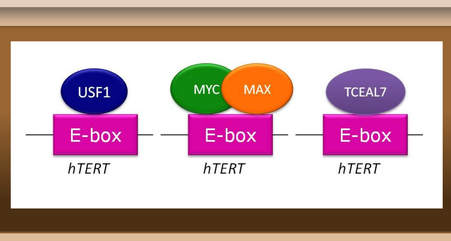
There are several pathways involved in this network.

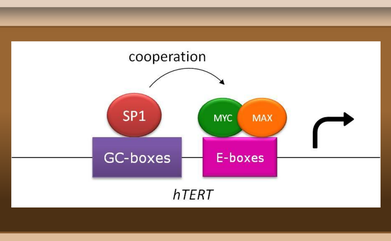
Concerning **MYC**, its **transcription** can be favoured by **leptin**, **MMP-9** or by activation of **NFκB.** It can also be stabilized or degraded at a **posttranscriptional level** depending on the **phosphorylations** it has. On the other hand, its levels can be diminished by **TCEAL7**.

At the level of **MAD**, its **transcription** can be increased by **G-CSF** or **IKKα-Smad3** dimer. At a **posttranscriptional level,** MAD can be degraded by **PI3K/AKT** and **MAPK/ERK** signalling pathways.

***hTERT*** can also be regulated directly. For instance, **leptin** can directly stimulate the *hTERT* promoter, too. On the other hand, **TGF-β**, **AP-1** (activated by PI3K/AKT pathway) and **TCEAL7** can inhibit *hTERT* expression.

Other factors can bind to the E-boxes interfering in MYC/MAX function.




Cooperation with factors from other boxes also leads to a better *hTERT* expression.

## WHAT ABOUT ITS APPLICATION?

### Concerning *hTERT* expression

- Antisense technologies

### Concerning *hTERT* promoter

- Introduction of suicide genes and/or genes that enhance an immune response driven by *hTERT* promoter into cancer cells.
- **Drawback**: Not useful in ALT systems

### Concerning factors that regulate *hTERT* promoter (e.g. MYC)

- Target *MYC* expression through siRNA
- Target MYC interactions and preventing it from binding the E-boxes
- Suppress signalling pathways which end in *MYC* expression

## BIBLIOGRAPHY

Horikawa, I. *et al. Molecular Biology of the Cell* **13**, 2585–2597 (2002).

Wojtyla, A., Gladych, M. & Rubis, B. *Molecular biology reports* **38**, 3339–49 (2011).

Liu, J. P. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **13**, 2091–104 (1999).

Lamy, E., *et al. Mutation research* 1–10 (2012).doi:10.1016/j.mrrev.2012.12.005