What Would Happen If We Attack Telomerase To Cure Cancer?

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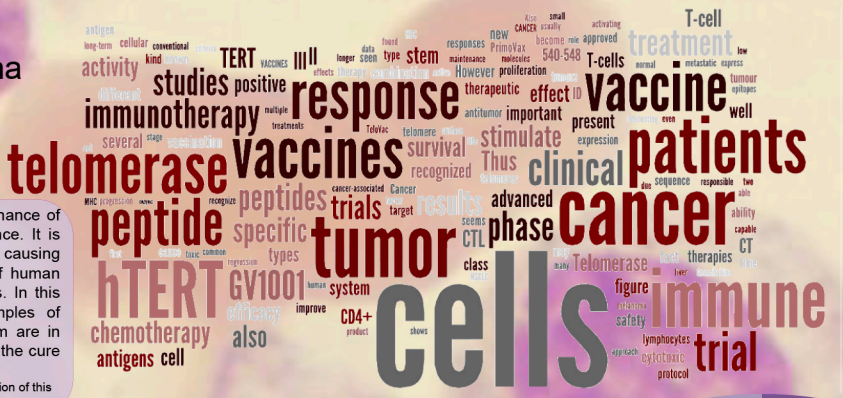
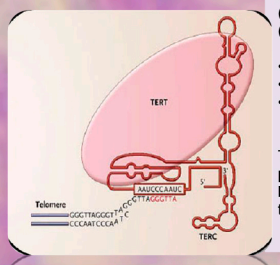


Telomerase is a ribonucleoprotein polymerase responsible for the maintenance of telomere length by adding new copies of the repeated telomere sequence. It is normally repressed in somatic cells but it could be abnormally reactivated causing cell immortality and oncogenesis. It is expressed in the vast majority of human cancers, a feature that makes it an attractive target for cancer therapies. In this review we explore this therapeutic alternative showing several examples of **telomerase peptide vaccines** as cancer immunotherapy. Some of them are in advanced clinical stage and show promising results and progress towards the cure of cancer without many adverse effects.

This work of literature review based on the search and selection of information, aims the description of this therapeutic strategy.

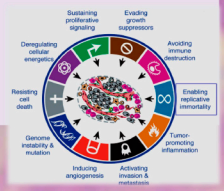


Telomerase

Formed by hTERT (Telomerase Reverse Transcriptase) and TERC (Telomerase RNA Component), template for the synthesis of telomeres (cellular clocks). It plays an important role in

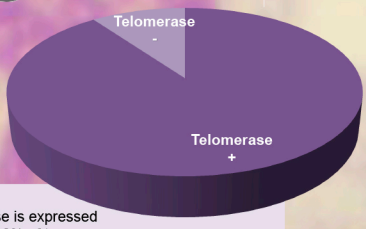
- Telomeres become very shorter → cell can not replicate → senescence.
- Some cells ignore arrest of cell division signals → cellular crisis and die.
- Small proportion of cells reactivate telomerase → unlimited proliferation →immortalized and tumor cells.

This activation occurs in a very small proportion of cells in the tumor mass, but it is essential for malignant transformation and tumor progression[1].



Senescence

Cell Immortalization
Oncogenesis

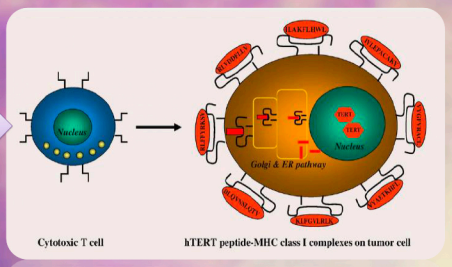


Telomerase is expressed in about 90% of tumors:
→ Ideal target of antineoplastic treatment.
→ Therapy would be non-toxic to normal cells.

The hTERT processing in proteasomes results some peptides which have been found to act as antigenic epitopes. These peptides are presented on tumor cells surface as antigens by the major histocompatibility complex (MHC) class I and II pathway.

hTERT derived-peptides act as tumor-associated antigens. They stimulate B lymphocytes and cytotoxic T lymphocytes (CTL) to recognize and kill telomerase-expressing cells ergo, the immune destruction of tumor cells[2].

Telomerase shows a prototype of universal tumor antigen ⇒ **Immunotherapy based on telomerase-derived peptides injected by vaccines could be a good approach to fight cancer.**



TELOMERASE PEPTIDE VACCINES

Examples

- GV1001
- Universal Cancer Peptides (UCP)
- hTERT 540-548 peptide

hTERT: 540-548 peptide

- ❑ First hTERT peptide identified as epitope, which binds MHC class I.
- ❑ Recent studies: CTL response was only detected when the exogenous added peptide was present but not when tumours express endogenous telomerase → cleavage in proteasome but not presentation on the tumor cells surfaces.

COULD THESE VACCINES CURE CANCER?

Advanced → hepatocellular carcinoma

- A phase II open label trial (ID: NCT00444782)
- Preferably patients ineligible for sorafenib.
- With low dose of cyclophosphamide to decrease the inhibitory effect of regulatory T-cells over the specific CTLs.

Only tumor stabilization in a few cases. ✗

Inoperable → Non-Small Cell Lung Cancer

- **GemVax** (ID: NCT01579188)
- Phase III clinical trial
- Patients with few treatment options and short life expectancy.

Encouraging for this deadly tumor. √

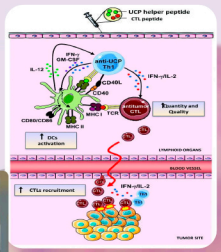
Advanced → un-resectable pancreatic cancer

- **PrimoVax**: phase III trial (ID:NCT00358566):
- GV1001-gemcitabine vs alone gemcitabine.
- Preliminary data: no survival benefit → stop trial.
- **Telovac**: phase III trial (ID: NCT00425360):
- Similar comparison.

TeloVac: Good immune response. √

UCP

- ❑ Induce high activity CD4+ T cells → cytokines and tumor necrosis factor production → interleukin production by dendritic cells[4].
- ❑ Increase tumor-reactive CD4+ T helper 1 cells activity.
- ❑ UCPs addition to other cancer vaccines or chemotherapy (CT) increase specific CTL responses → tumor regression and survival.



GV1001

- ❑ Promiscuous peptide vaccine consisting of 16 amino acids.
- ❑ It stimulates CTLs and long-term T-cell memory.
- ❑ Also used with CT and to GM-CSF (granulocyte/macrophage colony-stimulating factor) to enhance its effectiveness.
- ❑ **In an advanced stage of clinical development.**

SUCCESS OR FAILURE?

- ➢ **Mixed results**: no toxic effects and ability to improve patients' survival. But not clinical effects were found in some trials. Important → better immune response monitoring strategies and a good selection of hTERT-derived peptide (different immunogenic effect).
- ➢ **Chemo-immunotherapy**: the immune response may have an enhancer effect on pro-apoptotic therapies but, *what is the best way to combine them?*
- ➢ **Vaccination effects in stem cells:** telomerase activity would be much higher in malignant cells → immune system could discern both cells and cause tumor cells death firstly (ideally without harming normal cells[3]).

CONCLUSION

- ▪ Telomerase peptide vaccines seem to be capable to stimulate the immune system against tumor cells, getting tumor regression without toxicity.
- ▪ These studies are very useful to find more effective and less toxic antitumor drugs than conventional therapies, which cause high morbidity and mortality, and involve huge health expenditure. They are a step forward in targeted therapy. **New strategies as immunotherapy targeting telomerase, could become the future cancer cure.**

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4. Dosset et al. *Clin Cancer Res* 2012; 18: 6284-6295.
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