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 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 these 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.

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

Senescence

Telomerase

- Formed by hTERT (Telomerase Reverse Transcriptase) and TERC (Telomerase RNA Component), template for the synthesis of telomeres (cancerous replicating)

- 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.

The hTERT processing in proteasomes results some peptides which have been found to act as antigenic epitopes. These peptides are present 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 T lymphocytes and cytotoxic T lymphocytes (CTL) to recognize and kill telomerase-expressing cells, the immune destruction of tumor cells

- 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.

COULD THESE VACCINES CURE CANCER?

- A phase II open label trial (ID: NCT0044782)
  - Preferably patients ineligibile for sorafenib
  - With low dose of cytosine phosphoribosyltransferase to decrease the inhibitory effect of regulatory T-cells over the specific CTLs

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

- PrimoVax: phase III trial (ID: NCT00358566)
  - Preliminary data: no survival benefit → stop trial
  - Telovo: phase III trial (ID: NCT00425380)
  - Similar comparison

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 immunoresponse 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 (idealy without harming normal cells).

REFERENCES

CONCLUSION

- Telomerase peptide vaccines seem to be capable of stimulating 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.