CANCER VACCINES: STATE OF THE ART

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Objectives

1. Listing the types of antigens used in cancer vaccines, detailing their main characteristics.
2. Listing the most relevant vaccine vectors, distinguishing their strengths, weaknesses, and applications.
3. Commenting on the available data on cancer vaccine efficacy.

Methodology

To achieve the objectives, a bibliographic research has been conducted, focusing on research papers and reviews on the topic. The selection criteria were as follows: published less than 10 years ago, preferably less than 5 years ago, and obtained only from reliable databases (such as PubMed or the NML catalog). Relevant clinical trials, selected under the same criteria, have also been included.

Introduction

The **immunoediting hypothesis** describes the dynamics between immune system and cancer cells. Because of the immune system's pressure, cancer cells evolve to evade detection, which causes the **immune system's efficacy loss** [3].

This loss of function results from **immunosuppressive mechanisms** set by the cancer cells, like the alteration of local immune cell subpopulation or overproduction of molecular immune checkpoints, amongst others [3, 4].

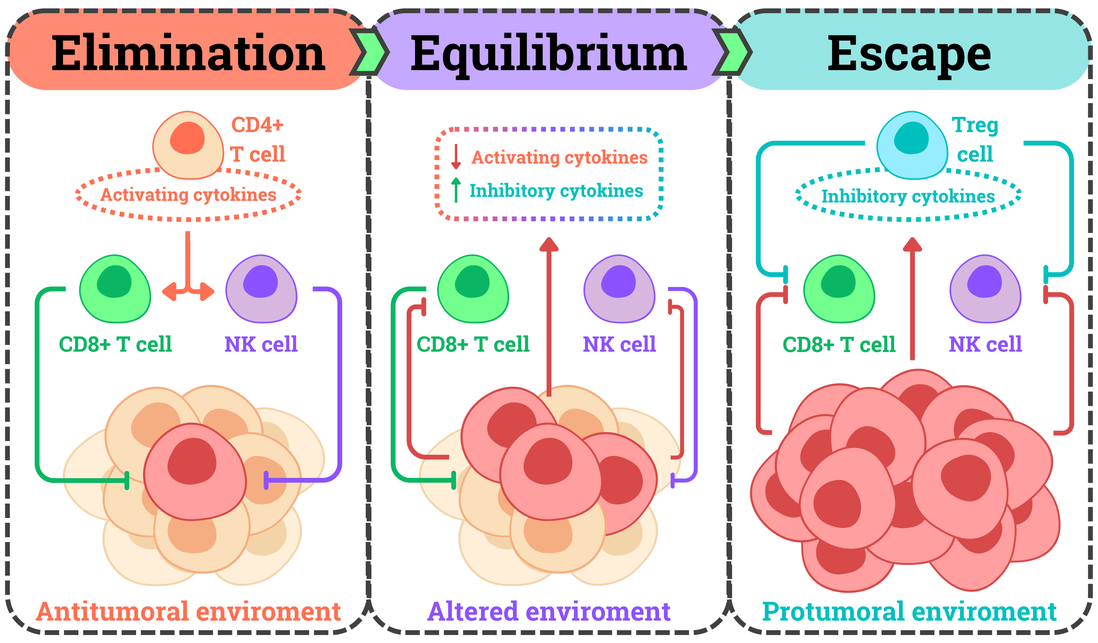


Figure 1: Immunoediting phases.

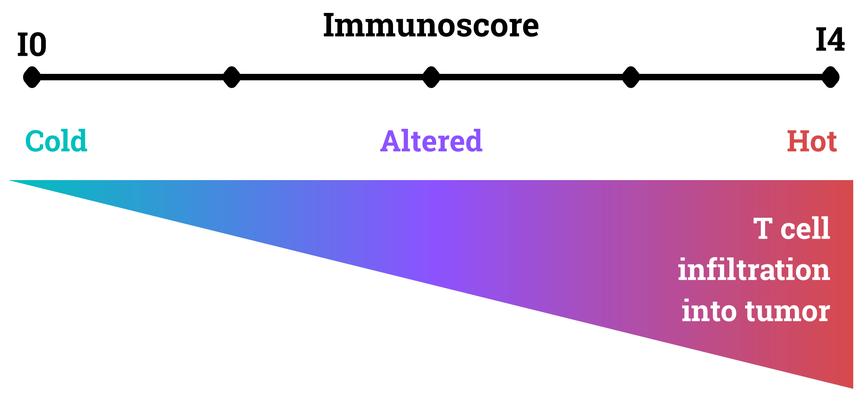
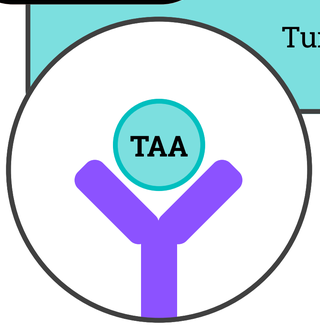


Figure 2: Immunoscore scale.

The baseline antitumor response of a patient depends on the **tumor-immune microenvironment (TIME)**, which can be classified under the **immunoscore metric** as a hot, altered or cold tumor [3].

The goal of cancer vaccines is to **tackle the immunosuppressive mechanisms** set by the tumor cells and **enhance the immune system's antitumor response** [2].

Antigens



Tumor-associated antigens
Tumor components not exclusive to cancer cells

Simple to detect and characterize
Cheap, simple to up-scale
Common across cancer patients
"Off-the-shelf" medicine
Must **break off central tolerance**
Notable risk of **autoimmunity**

Tumor-specific antigens
Tumor components exclusive to cancer cells

Complex to detect
Long and costly production
Almost **patient exclusive**
Personalized medicine
Not affected by central tolerance
Very **low risk** of **autoimmunity**

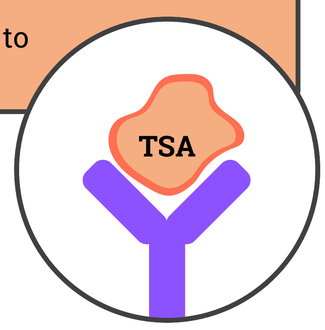


Figure 3: Comparison of TAA and TSA's characteristics. Based on [3, 4, 5, 6].

Vectors

Peptide vaccines

Simple and cheap to produce
High safety

Dependent on **adjuvants**
Short half-lives

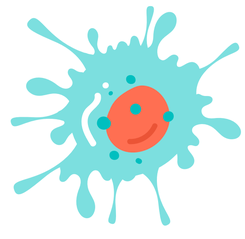
Compared to typical short peptides, synthetic long peptides (SLPs) offer great advantages: **multiple epitopes** in a sequence (with both **class I and class II MHC epitopes**), **MHC-haplotype-independent** efficacy and selective APC uptake [2, 4, 6].

Nucleic acid vaccines

Facilitated **multi-epitope vaccination**
Well tolerated across **repeated dosage**

Dependent on **delivery systems**
Poor stability in systemic circulation

RNA is generally more advantageous due to **DNA's genome integration risks** and because RNA vaccines only needs to cross the cytoplasmic membrane of the cells to become effective. However, **RNA's side effects are less understood** [2, 4, 5].



Cell vaccines

High safety and **effectiveness** (even in **late stage cancer** patients)

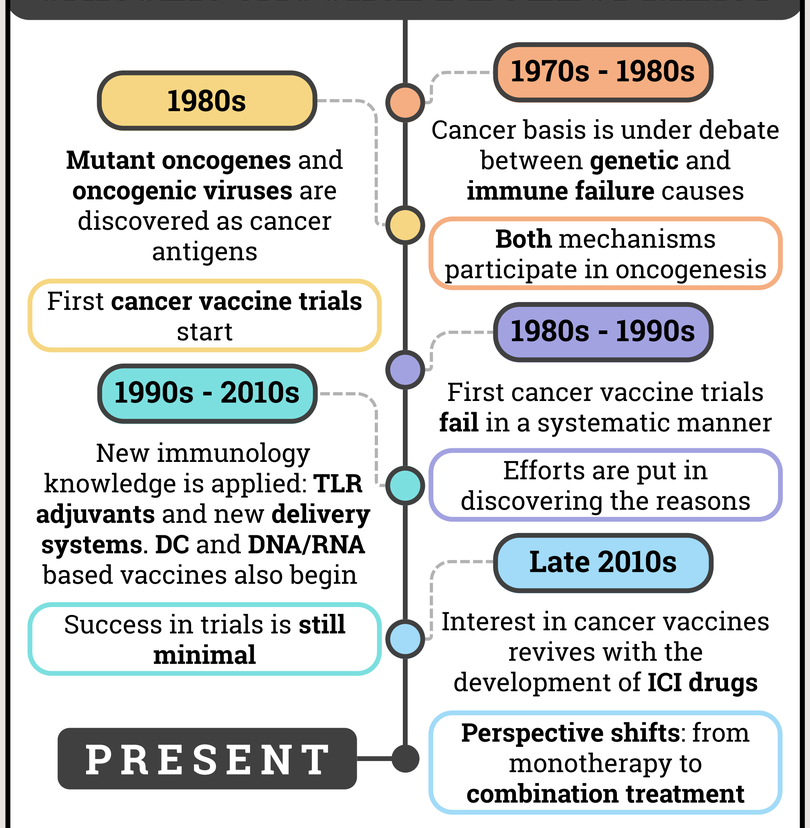
High complexity of production
High production **costs**

Cell-based vaccines allow **antigen presentation in tandem**, and, in comparison, **do not require extensive antigen identification**. Dendritic cell (DC) vaccines are prominent but stem cell and tumor cell lysate vaccines have also been proposed [2, 4, 6].

Figure 4: Comparison between vaccine vectors.

Efficacy data

Figure 5: Cancer vaccine development timeline. Based on [3, 7].



Peptide vaccines haven't had success in the past, but **SLPs** and other innovations could be key to change that [4]. **RNA vaccines** are the **main vector of TSA** vaccines, and have proven to deliver robust responses [5]. **DC vaccines** have proven to be really effective and safe [6], while other kinds of cell-based vaccines haven't been as successful [2, 4].

There is currently a growing interest in **combining cancer vaccines with other treatments**, mainly with **ICI compounds**, which has shown greater potential than single agent treatments [5].

Conclusions

- Cancer vaccines can target **tumor-associated antigens**, which are easy to produce but carry more autoimmunity risks, or **tumor-specific antigens**, which are much more effective but very costly.
- The most relevant cancer vaccine vectors are **SLPs**, **mRNA** and **dendritic cells**. These are among the most effective and safest options, but their high cost limits their applicability.
- The **paradigm shift** from using cancer vaccines as a monotherapy to a **combination treatment** agent holds the greatest potential of all recent innovations.
- **Further research is required** across all areas of the field, specially regarding the combination of cancer vaccines with other cancer treatment agents.

References

[1] Gubin, M. M., & Vesely, M. D. (2022). Cancer immunoediting in the era of immuno-oncology. Clinical Cancer Research, 28(18), 3917–3928. https://doi.org/10.1158/1078-0432.ccr-21-1804 **[2]** Sheikhlary, S., Lopez, D. H., Moghimi, S., & Sun, B. (2024). Recent findings on Therapeutic Cancer Vaccines: An updated review. Biomolecules, 14(4), 503. https://doi.org/10.3390/biom14040503 **[3]** Galon, J., & Bruni, D. (2019). Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nature Reviews Drug Discovery, 18(3), 197–218. https://doi.org/10.1038/s41573-018-0007-y **[4]** Hollingsworth, R. E., & Jansen, K. (2019). Turning the corner on therapeutic cancer vaccines. Npj Vaccines, 4(1). https://doi.org/10.1038/s41541-019-0103-y **[5]** Li, X., You, J., Hong, L., Liu, W., Guo, P., & Hao, X. (2023). Neoantigen Cancer Vaccines: A new star on the Horizon. Cancer Biology & Medicine, 1–38. https://doi.org/10.20892/j.issn.2095-3941.2023.0395 **[6]** Melief, C. J. M., van Hall, T., Arens, R., Ossendorp, F., & van der Burg, S. H. (2015). Therapeutic cancer vaccines. Journal of Clinical Investigation, 125(9), 3401–3412. https://doi.org/10.1172/jci80009 **[7]** Finn, O. J. (2017). The dawn of vaccines for cancer prevention. Nature Reviews Immunology, 18(3), 183–194. https://doi.org/10.1038/nri.2017.140