Tumour Neoantigens: Towards Personalized Cancer Immunotherapy

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Introduction

The dual role of the immune system in cancer development and progression is now beyond doubt. It inhibits tumour cells but at the same time sculpts their immunogenicity in a Darwinian process of selection, which in turn promotes a more aggressive tumour growth. There are three phases in this so-called "immunoediting hypothesis": elimination, equivocation and death. Additionally, tumours use many strategies to evade the immune system. Thus, the antitumour T cell response is only a part of the Cancer-immune system.

Given this situation, it seems interesting to fight cancer by enhancing the patient’s immune system and tip the balance in favour of immunity as a result. In fact, the recent clinical success of several anticancer immunotherapy approaches has provided a boost to the field.

The main purpose of this project is to review the current status and future challenges of developing antigen-based personalized immunotherapy.

Tumour Neoantigens

The basis of the immune system is the recognition between self from non-self, or between "what is dangerous" from "what is not". With cancer, the fact that the targets of one’s own cells makes it difficult for the immune system to distinguish between normal and cancer cells. However, in a significant minority of patients, some autologous T cell populations are able to recognize antigens present in the malignant cells’ surface. One of these antigen types is called neoantigens and arise as a consequence of missense mutations. That is because they are tumour exclusive.

NGS and Epitope Prediction for Assessing Neoantigen T-cell Responses

Despite current limitations of epitope prediction, next-generation sequencing (NGS) has been used successfully to identify reactive neoantigen-specific T-cells in the settings of conventional cancer therapy, checkpoint blockade, vaccines and adoptive cell therapy (ACT).

Possible Clinical Applications

1. Stratifity patients for checkpoint blockade according to the number of predicted neoantigens in their tumour.
2. Determine the effective dose and duration of checkpoint blockade by monitoring neoantigen-specific T cell responses over time.
3. Design personalized neoantigen-based vaccines.
4. Generate neoantigen-specific T cells for ACT.

Unanswered Questions

- How does this approach overcome tumour heterogeneity?
- What about cancers with low mutation rates?
- Can neoantigens induce tolerance?
- Are the number of neoantigen-specific T cells sufficient to deal with tumour microenvironments?
- Is this approach too impractical for widespread use?

Future Challenges and Directions

Conclusions

The analysis of cancer genomes has revealed that tumour mutations are extremely variable among patients, even when it is the same type of cancer. There is a need for personalized cancer therapy and, in this regard, the potential of the antitumour immune response is a promising strategy.

Data supporting the critical role of neoantigens in immune control of cancer has increased in the last few years. Although it is still a young field and there is much room for improvement, what we know now for certain is:

- Neoantigens represent important targets in tumour infiltrating lymphocytes (TIL) populations in patients benefiting from adoptive cell therapy (ACT).
- Detection of neoantigens by next-generation sequencing and bioinformatics shows that processing and presentation of multiple neoantigens occurs spontaneously.
- Checkpoint blockade therapy has revealed new and amplified neoantigen-specific responses.

Methodology

Data sources have been collected from research papers and reviews, as well as other specialized literature (immunology textbooks, dissertations, expert video conferences and monographs).

Most of the information has been collected using scientific databases to identify the key concepts and the respective literature.

Selection criteria:

- Most Used Keywords: neoantigen, cancer immunotherapy, vaccine, mutanome.

Year and Journal of Publication: research has been limited mainly to the last 5 years of publication and acquired from well-indexed journals, such as Nature, Science, N Engl J Med...