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Editorial

Customized immunotherapy in OSCC: Leveraging neoantigens for precision medicine

Dear Editor,

Oral squamous cell carcinoma (OSCC) presents a considerable global health burden due to its high incidence and aggressive behavior, especially in advanced cases where traditional therapies, such as surgery, chemotherapy, and radiotherapy, may offer limited efficacy and significant side effects. The rise of immunotherapy, particularly personalized approaches, has shown promise in addressing these limitations, with neoantigens—a category of tumor-specific antigens derived from cancer cell mutations—emerging as a critical component. Neoantigens, absent in normal tissues, hold potential for highly targeted therapies that enhance the immune system's recognition and attack on cancer cells (see Fig. 1).

1. Understanding neoantigens in cancer immunity

Neoantigens are distinctive peptides generated by tumor-specific mutations and are not present in normal cells. Displayed on cancer cell surfaces by major histocompatibility complex (MHC) molecules, these peptides appear foreign to the immune system, which can trigger a strong T cell-mediated immune response. In OSCC, which often displays an immunosuppressive microenvironment, neoantigen identification is essential to overcoming the tumor's immune evasion mechanisms. Since OSCC typically has a high mutational burden, a greater likelihood of neoantigen formation exists, making it a suitable candidate for neoantigen-based immunotherapies that aim to selectively target and destroy tumor cells without damaging healthy tissues [1].

2. Identifying neoantigens: Genomic and bioinformatics approaches

The process of neoantigen identification involves several steps, combining genomic sequencing with bioinformatics predictions and experimental validation. Initially, the tumor genome is sequenced, often via whole-exome sequencing (WES) or whole-genome sequencing (WGS), to identify mutations. In OSCC, these mutations frequently arise due to environmental factors like tobacco use, alcohol consumption, and HPV infections. Identifying these mutations enables personalized mapping of potential neoantigen targets for therapy.

Following sequencing, bioinformatics tools predict which mutated peptides are likely to be presented on MHC molecules, using software such as NetMHC to estimate peptide binding affinity to MHC classes I and II. Only peptides with high binding potential undergo further analysis, which includes assessing peptide stability and T cell recognition likelihood. Finally, experimental validation, often through mass spectrometry and T cell assays, confirms that these neoantigens are immunogenic, ensuring accurate selection of neoantigens for therapeutic applications [2].

3. Neoantigen-based immunotherapy approaches for OSCC

Personalized immunotherapy targeting neoantigens has shown potential in managing OSCC through strategies such as customized cancer vaccines, adoptive T cell therapy, and immune checkpoint inhibitor combinations, each aiming to enhance the immune response against tumor-specific markers [3,4].

1. Personalized Cancer Vaccines

These vaccines are designed to activate the immune system by introducing neoantigens specific to the patient's tumor. Tailored to incorporate tumor-derived peptides, these vaccines prime T cells to identify and attack cancer cells. Research indicates that neoantigen-based vaccines can effectively stimulate immune responses and reduce tumor growth. For OSCC patients with a high mutation rate, these vaccines present a targeted approach, potentially providing a robust anti-tumor response with reduced risk to normal tissues.

2. Adoptive T Cell Therapy

This therapy involves collecting the patient's T cells, expanding them outside the body, and reinfusing them to target cancer cells more effectively. Tumor-infiltrating lymphocytes (TILs), which naturally migrate to tumors, can be harvested, expanded, and reintroduced to enhance the immune response. Additionally, chimeric antigen receptor (CAR) T cells—genetically modified to target specific neoantigens—represent an emerging approach, although more studies are needed to evaluate their efficacy in solid tumors like OSCC.

3. Combination with Immune Checkpoint Inhibitors

Pairing neoantigen-based therapies with immune checkpoint inhibitors, which block suppressive pathways such as PD-1/PD-L1 and CTLA-4, can further potentiate the immune response. This approach may be particularly beneficial for OSCC patients with a high mutational

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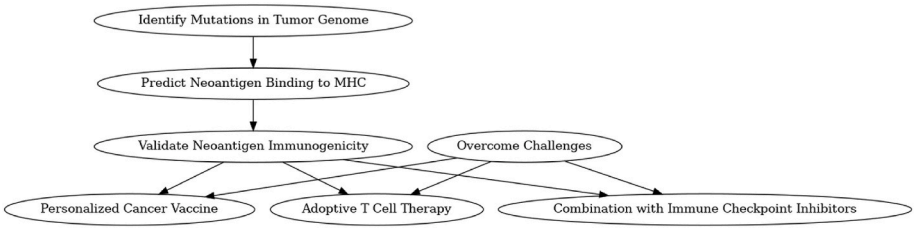

Fig. 1. Neoantigens and role in OSCC.

load, as it enhances T cell activity, potentially overcoming immune evasion and leading to better clinical outcomes [5].

4. Challenges and future directions

Although promising, neoantigen-based immunotherapy faces several challenges. Tumor heterogeneity complicates therapy as OSCC tumors vary significantly across different regions within the same tumor and between patients. This variability makes it difficult to identify universal neoantigen targets, emphasizing the need for highly individualized treatments. The immunosuppressive microenvironment of OSCC also presents a barrier; tumors may evade detection by downregulating MHC molecules or producing immunosuppressive cytokines. Overcoming these barriers may involve therapies that both target neoantigens and modify the tumor environment to support immune activation.

The cost and technical requirements of neoantigen identification also pose challenges, as sophisticated genomic and bioinformatics techniques may not be readily available in all clinical settings. Additionally, the high cost associated with personalized neoantigen therapies limits their accessibility. Research aimed at refining genomic sequencing, bioinformatics, and immunological techniques will be crucial to make these treatments more practical and affordable.

In future directions, combining neoantigen vaccines with other immunomodulatory agents, gene editing, and nanomedicine could enhance therapeutic efficacy. Advances in understanding neoantigens, their identification, and immune activation mechanisms are expected to improve the precision and impact of these therapies. This progress positions neoantigen-based treatments as potential cornerstones of personalized medicine for OSCC, offering hope for improved survival and quality of life for patients.

5. Conclusion

Neoantigens represent a transformative element in the development of personalized immunotherapy for OSCC, leveraging unique tumor mutation profiles to activate tumor-specific immune responses while minimizing harm to normal tissues. While hurdles such as tumor heterogeneity, immune evasion, and high costs remain, continued research and technological advancements are likely to make neoantigen-based therapies more feasible and effective. As the field evolves, neoantigen-targeted treatments hold promise as an innovative approach to improve patient outcomes and address the challenges of treating this difficult malignancy.

CRediT authorship contribution statement

Nitya Krishnasamy: Conceptualization, Formal analysis, Writing – original draft. **Vikram S. Amberkar:** Methodology, Resources, Writing – review & editing. **Kochli Channapa Niranjan:** Formal analysis, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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