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Editorial

Revitalizing Cancer Vaccines by Targeting Neoantigens

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ABBREVIATIONS

TMB: Tumor mutation burden; TILs: Tumor Infiltrating Lymphocytes; neoAgs: neoantigens; TAA: Tumor-associated antigen; CTLs: Cytotoxic T lymphocytes; TCR: T cell receptor

EDITORIAL

Vaccination has been one of human history's signature accomplishments [1]. Since the first vaccine – for smallpox-was demonstrated in 1796 by Edward Jenner, over a dozen of what were once our most common and deadly diseases have now practically been eradicated. Much research has attempted to develop similar vaccination approaches to prevent or treat cancers, but despite early promise in mouse models [2], such approaches have disappointed in clinical trials. A comprehensive survey describing cancer vaccine trials in 1,306 patients [3] found an objective clinical response rate of just 3.3%, which included many commonly used approaches, including peptides in adjuvant, viral vectors, transfected tumor cells, antigen-pulsed dendritic cells, and various cytokine combinations. Clearly, new strategies are needed. One such approach has been the adoptive transfer of tumor-infiltrating lymphocytes (TILs), which has shown convincing efficacy in metastatic melanoma [4,5]. While this approach is hampered by the difficulty of isolating TILs from other tumor types, we describe below a general strategy of enriching for tumor-killing TILs using neoantigens.

Cancer patients represent a unique challenge for vaccination, partly due to their low immune competence resulting from heavy disease burden and the harsh treatment they are receiving as well as the immunosuppressive microenvironment of the tumors. Most tested vaccines have been directed against the tumor-associated antigens (TAAs), while TAAs are over expressed on tumor cells, nonetheless, they are also present at low levels in healthy tissues, and hence subject to central and peripheral tolerance mechanisms. These tolerance pathways likely limit the avidity of the vaccine-induced immune responses.

To overcome tolerance, more recent attention has focused on targeting tumor-specific neoantigens (neoAgs) that are not found in healthy tissues. Some of the evidence supporting this approach has come from the stunning success of cancer immunotherapy using checkpoint inhibitors, in which signaling 'brakes 'such as PD(L)-1 and CLTA4 are released from patient immune systems to effectively fight a range of cancers [6,7]. Patients and tumor types with higher tumor mutation burden (TMB) responded better to checkpoint blockade therapies [6,7], suggesting that a vaccination approach that activates the immune system may perform better in these patients. Similarly, another study [8] revealed that patients who had responded to checkpoint blockade therapy had tumors harboring TILs (so-called 'hot' tumors), while non-responders had tumors with few TILs ('cold' tumors).

These observations lead us to the current hypothesis, specifically that tumors harboring more mutations are more likely to generate neoAgs, which would be recognized by neoAg-specific TILs. Recently, whole-exome sequencing and computational prediction algorithms were used to identify neoepitopes for vaccination of cancer patients [9]. This study observed neoAg-specific T cell responses in all three treated patients, but frustratingly no clinical improvement. This suggests that vaccination strategy requires further improvements to elicit sufficiently strong immune responses. For example, too few CTLs may be induced, the induced CTLs may be unable to infiltrate tumors, and infiltrating CTLs may not become activated after encounter with tumor antigen *in vivo*, or may be suppressed within the tumor microenvironment by the action of PD (L)-1 or CTLA4.

Combination therapy is likely to be required to overcome these challenges, and in particular an opportunity to use checkpoint inhibitors to activate neoAg-specific TILs [10], enhance co-stimulations [11], generate long-term memory T cells [12], and create an inflammatory environment at the tumor site to promote further CTL recruitment [13]. This strategy would convert 'cold' tumors lacking TILs into 'hot' tumors inside which the antitumor activity of these tumor-specific TILs could be released and even further enhanced by the checkpoint blockade therapies [10-13]. An alternative approach that should also be tested in parallel is to isolate neoAg-specific T cells from patients, expand them *in*

vitro in large numbers, and adoptively transfer back into patients to generate a sufficiently large number of properly activated T cells. Indeed, recent studies have shown that adoptive transfer of neoAg-specific TILs and CD4+ T cells can promote durable anti-tumor responses lasting for several years [14,15].

In summary, we propose that future research should use high-throughput screening of large patient cohorts, encompassing multiple tumor types, to identify and collect a library of patient-derived neoAgs. This will enable vaccination using combinations of unique and shared cancer-specific neoAgs, to be tested in conjunction with checkpoint blockade therapies. In a second step, we propose to isolate neoAg-specific CTLs from responding patients, especially the CTLs specific for the neoAgs with driver mutations, to construct a T cell receptor (TCR) library that can be used to generate cell therapies for patients where vaccination is not effective. We believe this approach is easily scalable across different tumor types, and may provide a general strategy for the eradication of multiple cancers.

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