Editorial

Mutation burden: a limiting factor for personal cancer vaccines?

Jia Li, Feng Wang-Johanning, Gary Johanning

Biosciences Division, SRI International, 333 Ravenswood Ave, Menlo Park, CA 94025, USA

Correspondence to: Jia Li. Biosciences Division, SRI International, 333 Ravenswood Ave, Menlo Park, CA 94025, USA. Email: jia.li@sri.com.

Provenance: This is a Guest Editorial commissioned by Section Editor Ziwei Li (Department of Surgery, the 1st Hospital Affiliated to Kunming Medical School, Kunming, China).

Comment on: Ott PA, Hu Z, Keskin DB, *et al.* An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017;547:217-21.

Received: 14 April 2018; Accepted: 02 May 2018; Published: 29 June 2018.

doi: 10.21037/amj.2018.06.04

View this article at: http://dx.doi.org/10.21037/amj.2018.06.04

Cancer vaccines are not a new therapy; they have been tried on patients as early as 1890. Since diseases have increasingly been cured or controlled with the benefit of vaccines, tumor vaccines have also drawn much attention and become one of the promising therapies to cure cancer. A great number of studies of cancer vaccines have been carried out, but only vaccines against viruses whose infection could cause cancer, such as HBV and HPV, have been proved effective and used by large population groups. Vaccines targeting tumor antigens cannot achieve the effect expected, mostly because of two major obstacles. One is the lack of an appropriate cancer antigen. The optimal antigen for a tumor vaccine should be expressed only on tumor cells but not normal cells, and should be consistently expressed by all of the tumor cells. Most importantly, it should be immunogenic (1). However, tumor cells usually are heterogeneous as a result of mutations, which makes the relevant tumor antigen difficult to identify. The majority of traditional cancer vaccine studies are based on tumor associated antigens (TAA), but elevated immunogenicity of TAAs is difficult to achieve because tolerance for the antigen has already developed in the body. The other obstacle is the immunosuppressive tumor microenvironment, which makes the immune response less robust than that observed for other disease caused by foreign antigens. Therefore, immune cells have submaximal function in tumor tissues after vaccine stimulation.

With the noteworthy progress that has been achieved using next generation sequencing, whole genome information from individual patients becomes feasible and low-cost, and multiple new technologies have been developed to manipulate the tumor microenvironment. This has enabled tumor vaccine approaches based on neoantigens to become remarkably effect. In two papers published in Nature [Ott *et al.* (2) and Sahin *et al.* (3)], the groups used similar methods to sequence the whole genome exon of melanoma patients, and identified neoantigen candidates after RNA-seq confirmation and HLA-binding prediction. The neoantigens were then used as tumor vaccines to treat melanoma with or without other therapies (2,3). The Ott group synthesized long peptide for use in six patients with high mutation rates. Two patients in stage IVM1b achieved complete radiographic response when the peptide vaccines were combined with anti-PD-L1 treatment. The Sahin group used RNA mutanome vaccines, with a result that most patients had tumors controlled except for one patient with a B2M-deficient mutation. Both of the groups stimulated autologous T cells with the neoantigens *in vitro* to characterize the vaccine effect, and reported that the neoantigen vaccine can achieve a robust immune response.

Compared to TAA, neoantigens are from mutated tumor cells, so they are not expressed by normal cells. Moreover, only mutations with high affinity to HLA are selected as neoantigen. Thus, neoantigens have more advantages with respect to specificity and immunogenicity than TAA. Personally, designed vaccines based on the mutations in each individual patient further promotes the idea of precision medicine, which would lead to the development of medicines according to the patient's personal genome mutation information. In addition to synthetic long peptide and RNA vaccines, other types of neoantigen vaccine have been tested. In 2015, Carreno *et al.* developed a personalized vaccine based on dendritic cells (DCs) (4). They produced the neoantigen peptide

candidate after sequencing the patient's DNA, and the DC vaccine treatment was evaluated and shown to enhance neoantigen-specific immune response. Currently, the two papers that address personal neoantigens advance the DC story by providing a good indication that the neoantigen itself can achieve the expected vaccine results and control the tumor in patients.

However, a limitation of these studies is that both of the personalized neoantigen vaccine studies have been tried only on melanoma patients. Melanoma is one type of tumor with the highest mutation burden (5). Multiple clinical trials are urgently needed and have been started based on cancer neoantigens specific for other solid tumor types with lower mutation burdens, including triple negative breast cancer (TNBC), pancreatic cancer and ovarian cancer (1). But animal model studies for a cancer with a low mutation burden did not provide as exciting a result as for melanoma. By a similar method as used for the melanoma patients, a neoantigen peptide identified from the ID9-G7 ovarian cancer mouse model, which is the model for high grade serous carcinoma (HGSC), a low mutation rate ovarian cancer, could not control tumor growth, even though the neoantigen vaccine induced a strong immune response *in vitro* and the patient survival was correlated to tumor-infiltrating T (TIL) cells (6). Compared to the success of the neoantigen approach in melanoma, it seems likely that a high mutation rate becomes essential for impacting vaccine results. This may be the case not only for neoantigen vaccines, but also for other promising immunotherapies such as anti-PD-1 treatment, whose therapeutic efficacy is also associated with mutation burden. According to a correspondence published in *The New England Journal of Medicine*, data from an anti-PD-1/PD-L1 treatment study for 27 types of cancer revealed that the response rate to anti-PD-1/PD-L1 inhibition is highly correlated to tumor mutation burden (7). Anti-PD-1 inhibits the checkpoint molecule PD-1 on T cells to activate T cells and promote immune response. The correlation of clinical results for both neoantigen vaccine and anti-PD-1/PD-L1 to high mutation rates proves the basic concept for anti-PD-1 treatment that the tumor-specific T cells have infiltrated the tumor but they are suppressed by the tumor microenvironment to be nonfunctional, and anti-PD-L1 treatment just activates these tumor specific T cells. The mutation rate in tumor cells thus appears to be the major factor responsible for normal stimulation of antigen-specific T cells in the body. A higher mutation rate indicates more neoantigen and higher immune response for tumors, even though there is suppression in the tumor microenvironment. Therefore, with additional therapy to modify T cells or the microenvironment, these antigen-specific T cells can be stimulated and control the tumor burden.

Although neoantigen is more immunogenic compared to many tumor-associated antigens, as they do not go through central tolerance, they still undergo selection pressure since the tumor has multiple intrinsic resistance mechanisms to avoid being attacked by immune cytolytic activity (8). Therefore, it can be expected that the neoantigen vaccine would work better when combined with T cell immunotherapy in high mutation burden tumors, but there are still great opportunities to make neoantigens more effective by improving prediction, peptide delivery and adjuvants. However, for low mutation burden tumors, much more effort is still needed to develop strategies to improve immune responsiveness in the tumor microenvironment. Because most current successful immunotherapies are based on adaptive immunity, including checkpoint inhibition, chimeric antigen receptor (CAR) T cells, T cell receptor (TCR) therapy and neoantigen vaccines, there may be value in considering therapy directed toward the innate immune system, which is currently the focus of multiple preclinical and clinical trials. Targeting these cells could be the road to new combination therapies that have not previously been envisioned. With the precision medicine initiative founded in 2015, precision tumor medicine could change the view and treatment of cancer when combined with traditional therapies. And there is little doubt that neoantigen vaccines have the potential to be one of the most promising precision tumor medicine therapies for cancer patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Li L, Goedegebuure SP, Gillanders WE. Preclinical and clinical development of neoantigen vaccines. Ann Oncol 2017;28:xii11-7.
2. Ott PA, Hu Z, Keskin DB, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature

2017;547:217-21.
3. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547:222-6.
4. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 2015;348:803-8.
5. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69-74.
6. Martin SD, Brown SD, Wick DA, et al. Low Mutation Burden in Ovarian Cancer May Limit the Utility of Neoantigen-Targeted Vaccines. PLoS One 2016;11:e0155189.
7. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med 2017;377:2500-1.
8. Kumai T, Kobayashi H, Harabuchi Y, et al. Peptide vaccines in cancer-old concept revisited. Curr Opin Immunol 2017;45:1-7.

doi: 10.21037/amj.2018.06.04
Cite this article as: Li J, Wang-Johanning F, Johanning G. Mutation burden: a limiting factor for personal cancer vaccines? AME Med J 2018;3:71.

