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Precision medicine meets cancer vaccines

Promising results from recent trials of personalized vaccines against cancer highlight the potential and challenges of precision vaccines.

Vaccines for treating cancer have been in development for decades, but their clinical efficacy has been elusive. Thus far, only one therapeutic vaccine against cancer — sipuleucel-T — has been approved by the US Food and Drug Administration for the treatment of prostate cancer, extending patient survival by only 4 months. Now, two independent efforts using mRNA vaccines tailor-made to target each patient's tumor have reported initial success in melanoma and pancreatic cancer and are energizing the field of anti-cancer vaccines.

In February 2023, the US Food and Drug Administration awarded breakthrough designation to the combination of a personalized mRNA vaccine (mRNA-4157/V940) and a monoclonal antibody to the immunoinhibitory receptor PD-1 (pembrolizumab) for the treatment of patients with resected stage III/IV melanoma at high risk of recurrence, on the basis of the unpublished (at the time of this writing) results of the randomized phase 2b KEYNOTE-942 trial. Patients treated with the combination of pembrolizumab and an individualized mRNA vaccine encoding up to 34 tumor-specific, mutant antigens (neoantigens) had a 44% higher rate of recurrence-free survival than that of patients treated with pembrolizumab alone, a first for an mRNA vaccine against melanoma. Initiation of a larger phase 3 trial in patients with melanoma is now anticipated.

In May, Rojas et al. reported results from a phase 1 trial in which patients with resected pancreatic cancer received chemotherapy, a monoclonal antibody to the PD-1 ligand PD-L1 (atezolizumab) and a personalized mRNA vaccine[1]. After a median of 18 months of follow-up, half of the vaccine recipients, all of whom had expanded neoantigen-specific T cells after vaccination, remained cancer free. For a cancer with some of the highest post-resection recurrence and mortality rates and an immunosuppressive tumor microenvironment that has frustrated immune-targeted interventions, these findings offer exciting hope of an attainable clinical advance.

In both trials, neoantigens were predicted from sequenced tumor tissue, and a customized vaccine was delivered to each patient after surgical removal of the tumor. Whether more-profound clinical responses might be achieved if vaccines were administered prior to surgery when tumor burden is high, as has been seen for the treatment of advanced melanoma with pembrolizumab in the neoadjuvant setting[2], or whether a neoadjuvant vaccine regimen coupled with immune checkpoint blockade might induce excessive toxicity, remains to be determined. An ongoing trial of mRNA vaccines in patients with incurable cancers may shed some light on these issues.

Although these results build on previous clinical studies of neoantigen-based vaccines[3], the mechanisms that directly account for the encouraging results of these mRNA vaccine trials still need to be delineated. Eliciting vaccine responses to tumors is challenging because the immune system deletes self-reactive immune cells to prevent toxic, autoreactive responses. This requires that tumor-associated antigens (such as neoantigens) be found that are largely absent from normal cells, and which the immune system might identify as foreign in order to elicit a tumor-focused response. Predicting which neoantigens will bind and be presented by major histocompatibility complex molecules on tumor cells for potential recognition by immune cells is a further computational hurdle.

However, identifying the factors that promote or mitigate vaccine-mediated T cell expansion could enable further tailoring of these approaches to broaden their therapeutic impact. If these initial results are replicated and prove durable in diverse populations, they will lend support to efforts to create scalable, off-the-shelf components of mRNA vaccines that target tumor antigens common among cancers with similar genetic alterations. Decreasing the cost and manufacturing time of personalized vaccines will ensure timely and equitable access.

However, before patient-tailored mRNA vaccines become a mainstay of cancer therapy, the long-term safety of targeting self antigens must be assessed. Thus far, each recipient of a personalized mRNA vaccine has been essentially an n-of-1 trial, each with their own potential risk of self-reactive toxicity. Follow-up has been relatively short, and few patients have been treated thus far. Longitudinal analysis of larger numbers of recipients of personalized vaccines will be needed to capture signals of toxicity that are not initially apparent in the patients with late-stage cancer who are currently eligible to receive these therapies.

Should the combination of rationally designed mRNA vaccines and immunotherapy succeed in reproducibly eliciting immune responses that safely and effectively keep cancers in check, it offers potential for broad application. Therapeutically, these vaccines could be used against cancers with the lowest survival rates, such as glioblastoma and mesothelioma, or as metastasis-suppressing adjunct therapies. They also have enormous potential as preventive vaccines, such as for people at elevated risk of cancer due to genetics or environmental exposure. Beyond cancer, chronic infections caused by viruses — such as HIV, HBV or herpes viruses — that have successfully evaded eradication by the immune system may also be amenable to this combination of immune checkpoint blockade and personalized, epitope-specific mRNA vaccines.

Short of gene editing, vaccines are unique in inducing a lasting reconfiguration of the immune system capable of preventing and treating disease. Precision vaccines may be the next advance to transform the health landscape.

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References

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