TUMOUR VACCINATION

Devil in the details of adjuvant choice

“ IFA turns the vaccination site into a persistent source of T cell priming as well as a target tissue in a positive feedback loop, where it outcompetes tumour sites

Teaching the immune system to destroy cancer and prevent its re-emergence through vaccination strategies has long been pursued as an attractive therapeutic concept, but the success of such approaches lags far behind their promise. Now, reporting in *Nature Medicine*, Overwijk and colleagues show that the widespread use of incomplete Freud's adjuvant (IFA) in vaccination protocols might be to blame.

IFA is a mineral-oil-based adjuvant that has been used in almost 100 completed clinical cancer vaccine trials so far, and is thought to boost and maintain antitumour responses by creating persistent inflammatory vaccine depots that slowly release antigen. However, the nature of the

IFA-induced CD8⁺ T cell responses, which are crucial for cancer eradication, is poorly understood.

To investigate whether IFA-based cancer vaccines might have inherent properties that limit their clinical efficacy, the authors injected mice with the melanoma-specific gp100 peptide in IFA, followed by luciferase-transduced Pmel-1 effector CD8⁺ T cells, which are specific for gp100. They showed that these cells undergo initial expansion but then drop to near-undetectable levels after 3 weeks and do not rebound after re-vaccination.

In mice bearing gp100-expressing melanoma cells (B16), Pmel-1 T cells were shown to preferentially accumulate at the vaccination site, where they largely became hyporesponsive and underwent apoptosis. This was found to be due to the presence of interferon- γ at the vaccination site, which upregulated the apoptosis-inducing FAS ligand (FASL) and the immunosuppressive programmed cell death ligand 1 (PD1L) on myeloid cells, and FAS on Pmel-1 T cells.

As it was also found that persistent interaction of T cells with antigen at the vaccination sites induces T cell apoptosis, the authors tested vaccination protocols in which the persistence of vaccine depots was more limited. By replacing the poorly biodegradable IFA with saline, peptide presentation at the vaccination site and the vaccine-draining lymph nodes (VdLNs) was abolished within 7 days. Furthermore, to boost T cell priming, a cocktail of immunostimulatory molecules, referred to

as covax (a monoclonal antibody against CD40, the Toll-like receptor 7 agonist imiquimod and interleukin-2) was added.

This protocol induced strong Pmel-1 T cell expansion, but not hyporesponsiveness, and led to Pmel-1 T cell accumulation at the tumour site rather than the vaccination site. Importantly, it was shown that gp100–saline–covax vaccination induced a stronger suppression of melanoma growth than gp100–IFA–covax. Chemokine analysis of the vaccination site, and gene expression analysis of Pmel-1 T cells after vaccination with IFA–covax or saline–covax, provided further clues to the molecular basis of IFA vaccination-mediated T cell recruitment and induction of apoptosis and exhaustion in T cells.

The authors point out that sequestration and deletion of primed T cells at the vaccination site has also been observed in patients treated with IFA-based tumour vaccination protocols. They hypothesize that IFA turns the vaccination site into a persistent source of T cell priming as well as a target tissue in a positive feedback loop, where it outcompetes tumour sites. This suggests that a new class of vaccines, based on nonpersistent rapidly biodegradable vaccine adjuvants, might hold promise for future anticancer vaccination approaches.

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