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COMMENTARY

The revival of cancer vaccines — The eminent need to activate humoral immunity

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ABSTRACT

In light of the increasing number of approved monoclonal antibodies for the treatment of cancer, it seems peculiar that the development of antibody inducing vaccines gets so little attention. In our view there is a tremendous opportunity in the development of cancer vaccines inducing humoral immune responses, involving a couple of major advantages. Firstly, the effectivity of a polyclonal antibody response is expected to exceed the one of monoclonal antibodies. This is supported by preclinical data that show pronounced anti-tumor responses and early clinical trials in which benefit is observed in patients with advanced cancer. Secondly, vaccination strategies are expected to reduce hospital visits, resulting in enhanced quality of life. And last but not least, vaccination strategies are extremely cost effective, alleviating the socioeconomic problems of prohibitively high drug costs. To reach further clinical success, efforts should focus on target identification, optimization of vaccination strategies and adjuvant development.

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Introduction

Over the past decades there has been a focus on cancer immunotherapy. A specific issue in this field is the development of cancer vaccines. Most efforts in this regard have been focused on vaccine strategies that induce anti-tumor immune responses of cytotoxic T lymphocytes (CTLs). Different strategies are used to direct the CTLs toward the tumor. These include DNA vaccines, checkpoint inhibitors, adoptive T cell transfer and chimeric antigen receptor (CAR) T cells.[1-3] Anti-tumor activity of these treatments is limited by tumor immune evasion. A part of the immune system that is often neglected in cancer treatment is the humoral immunity. This part of immunity is based on activation of B lymphocytes and induction of a polyclonal antibody response against the tumor, thereby leading to eradication of the tumor by antibody- and complement dependent cytotoxicity. A humoral anti-tumor response can be achieved by use of conjugate vaccines or modified tumor antigens. In a conjugate vaccine the to be targeted self-antigen (tumor antigen) is fused (conjugated) to a foreign antigen, *e.g.* a bacterial protein. By this means the immune system can be triggered to produce antibodies against the tumor antigen and mount an anti-tumor response.[4,5] When modified tumor antigens are used, the immune system can recognize the modification and produce antibodies that cross react with the endogenous antigen. An example of this strategy is the VEGF mimic vaccine used by Wentink *et al.*[6]

Target identification and specificity

In order to avoid auto-immunity the vaccine target selection is of major importance. The antigen should either be a tumor-neoantigen, an antigen that is generated by the tumor upon mutation, a specific molecule that is selectively expressed by the tumor cells, or the antigen should be a marker that is selective for a stromal component of the tumor, e.g., the tumor vasculature. Several of such antigens have been identified, such as the cancer testis-antigens, which are antigens only expressed in the testis and in cancer cells.[7] Our laboratory has performed a screen in which the gene expression profile of tumor endothelial cells was compared to endothelial cells of the normal healthy vasculature. This study revealed several genes that are specifically expressed by tumor endothelial cells.[8,9] Furthermore, suitable targets for inducing humoral anti-tumor responses include antigens that are specifically employed during embryonal development, such as the extra-domains A and B of oncofetal fibronectin and, for example, the C domain of the extracellular matrix molecule tenascin-C, since these were found to be reused by endothelial cells under angiogenic conditions. [10-12]

Potent adjuvants for use in humans

To induce an effective humoral immune response in cancer patients toward self-antigens, it is of crucial importance to exclusively break the immune tolerance to these antigens. To achieve this it is key to select an efficient immune adjuvant. Different adjuvants for use in cancer vaccines against self-antigens are currently under investigation, a topic elegantly reviewed in Temizoz *et al.* Modern adjuvants for use in humans can be liposomes or emulsions, immunostimulants comprising of e.g., cytokines or toll-like receptor (TLR) ligands, polysaccharides or a combination thereof.[13]

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The success of humoral immune responses

Preclinical and clinical studies support the potential of vaccines inducing humoral immunity for the treatment of cancer. Gavilondo *et al.* have developed a vaccine in which the self-antigen VEGF is fused to the first 47 amino acids of the *N. meningitides* protein P64K and combined with the adjuvant VSSP (very small proteoliposomes). The vaccine named CIGB-247 showed efficient anti-tumor efficacy and anti-metastatic capacity in mice, rats, rabbits en monkeys.[14-17] In patients with advanced solid tumors a clinical benefit was observed with this vaccine in 12 out of 30 vaccinated patients.[18] A heptavalent vaccine, in which seven different tumor surface antigens were conjugated to keyhole limpet hemocyanin (KLH), induced antibody responses in patients with ovarian, fallopian tube or peritoneal cancer. The adjuvant used in this vaccine was the saponin-based QS-21, a purified fraction derived from the bark of Chilean tree *Quillaja saponaria* (QS).[19] Okaji *et al.* achieved antibody responses in 8 out of 9 patients with recurrent malignant brain tumors (n = 6) or metastatic colorectal cancer (n = 3) after vaccination with non-adjuvanted glutaraldehyde-fixed human umbilical vein endothelial cells (HUVEC).[20] Three out of 6 patients with malignant brain tumors had a partial or complete response with this vaccine, which lasted for at least 9 months after the first immunization. A study by Ehlken *et al.* found the induction of strong patient-specific humoral immune responses against several different tumor-associated antigens in patients vaccinated with cytokine gene-modified autologous melanoma tumor cells.[21] Our laboratory showed promising anti-VEGF antibody responses in mice and cynomolgus monkeys with a peptide vaccine directed against the bevacizumab binding site of VEGF.[6] The vaccine adjuvanted with the raffinose fatty acid sulfate ester (RFASE) adjuvant, a TLR4 agonist, is currently under investigation in a phase I clinical trial (NCT02237638). A phase I clinical trial (NCT01003808) in advanced/metastatic esophageal cancer patients with a vaccine consisting of cholesteryl pullulan (CHP) nanoparticles, containing the cancer-testis antigen NY-ESO-1, showed induction of anti-tumor antibody responses and a correlation of vaccine dose with patient survival.[22] Potent anti-tumor antibody responses were also achieved in mice vaccinated against the extra domain A (EDA) or extra domain B (EDB) of fibronectin.[4,23] In these studies the squalene-based adjuvant Montanide ISA 720 combined with a CpG oligonucleotide (a TLR9 agonist) was used as adjuvant.[24,25]

Conclusions and future directions

In our opinion vaccination approaches should thus focus on evoking a humoral immune response against the tumor. The fact that many efficient drugs approved for treatment of cancer are monoclonal antibodies, supports this view. It is an attractive approach to exploit the body's own defense system to produce antibodies against cancer antigens. This would provide us with enormous treatment options in which either combination therapy can be given in form of multi-target vaccines or vaccination is combined with conventional therapy.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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