Clinical Cancer Research

Vaccination for Pancreatic Ductal Adenocarcinoma: A Hard Nut to Crack

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No immunotherapy strategy is yet offering consistent results against pancreatic ductal adenocarcinoma. A randomized clinical trial testing repeated immunization with a *Listeria monocytogenes*–based vaccine encoding for mesothelin in combination with a GM-CSF–transfected allogeneic pancreatic cell vaccine reports no survival benefit for the vaccinated patients.

See related article by Le et al., p. 5493

In this issue of *Clinical Cancer Research*, Le and colleagues (1) show the results from a randomized phase IIb clinical trial recruiting patients with metastatic pancreatic ductal adenocarcinoma (PDAC) in three arms. Vaccination live-attenuated *Listeria monocytogenes*–expressing mesothelin (CRS-207) was used, alone or in combination with granulocyte–macrophage colony-stimulating factor–secreting allogeneic pancreatic tumor cells (GVAX) + pretreatment cyclophosphamide. The third arm was physician choice of single-agent chemotherapy. The rationale for this randomized trial came from a previous phase II published in 2015 in *Journal of Clinical Oncology* by Le and colleagues, in which patients were treated with CRS-207 in combination with cyclophosphamide/GVAX, that showed an overall survival of 9.7 months for those patients who received at least three doses of the vaccines as well as evidence for immunogenicity of the vaccines. In spite of well conducted trials, no clinical benefit was observed, which may underscore immunotherapy against PDAC, and especially vaccination, in the clinical arena.

Bailey and colleagues (2) classified PDAC in four subtypes based on RNA-seq: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine. Squamous subtype shares gene profile features with other squamous cancer type and express an inflammatory pattern, as the immunogenic one. Among all PDAC subtypes, these authors established 10 gene programs (GP) more frequently found in PDAC. Each gene program predominantly arises in one or two PDAC subtypes. GP6, 7, and 8 were enriched with genes associated with immune cell signature (B cell, CD4, CD8, antigen presentation, and Toll-like receptor gene expression profile) and are related to the immunogenic subtype. PDAC is classified as a type 2 tumor based on the basis of low mutational tumor burden (MTB) and low expression levels of inflammatory gene signatures as published by O'Donnell and colleagues (3). PDAC could also be aligned with immune-ignored or immune-excluded tumors. The question is whether any particular subtype of pancreatic cancer is more susceptible to immunotherapy.

The history of therapeutic vaccination against cancer is a string of excellent results in mouse models and discouraging failures in the clinic (4). More recently, the use of vaccines in melanoma, prostate cancer, and cervical cancer has showed promising results. Subsets of this type of tumor histologies are characterized by relatively high immune infiltration and either comparative high or low MTB or expression of foreign viral oncogenes.

Cancer vaccination faces two key points: choosing the best antigen and promote a good inflammatory adjuvant response. Regarding the best antigen, it is perceived that neoantigens derived from nonsynonymous mutations abundantly expressed on malignant cells are the best option perhaps because they are expected to behave as foreign antigens toward which no or low level immune tolerance occurs. Identifying and formulating tumor-exclusive patient-tailored neoantigens for vaccination is a daunting task only recently tested in small series of patients with melanoma and glioblastoma. In principle an alternative would be to use autologous tumor cells or tumor cell–derived material as the source of neoantigens. The use of allogenic pancreatic cancer cell or mesothelin might be laden with suboptimal immunization performance. Perhaps neoantigen-based pancreatic cancer vaccination holds hope but its efficacy remains to be seen.

Employing optimal vaccine adjuvants and vehicles is also of utmost importance and the best approaches are still matter of debate and investigation. Some vaccines combine various approaches as it is the case with Le and colleagues. Autologous dendritic cells, viral vectors, liposomal microspheres, and immunogenic RNA of DNA with self-adjuvanticity are commonly used. Gene-modified bacterial strains are used as adjuvant based on its ability to induce powerful immune stimulation, such as that observed with the intracellular pathogen *Listeria monocytogenes*. Moreover, priming and boosting with sequential vaccination strategies to improve immune responses has been tested, this is the strategy used by Le and colleagues in their clinical trial with the use of CRS-207 and GVAX.

PDAC is known to create an immunosuppressive microenvironment that would difficult success even if the vaccines are actually immunogenic and elicit measurable immune responses to relevant tumor antigens. In PDAC, vaccination strategies

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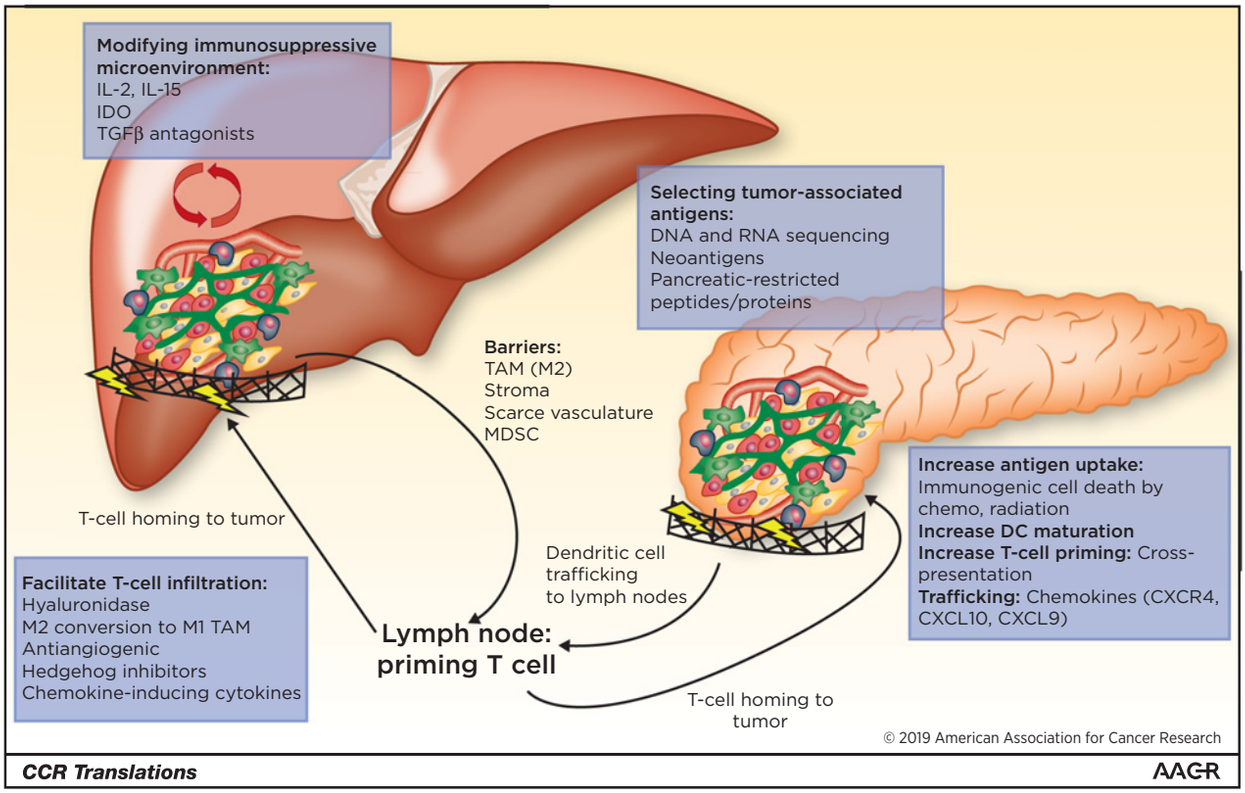

Figure 1.

Schematic view of antigen processing, immune infiltration barriers, and possible approaches to improve vaccine therapy in PDAC. PDAC (red cells as tumor cells) TME is characterized by abundant stroma (green lines) with fibroblast (yellow cells), poor vasculature (red "tubes"), and immunosuppressive cells (green cells as M2 macrophages, blue cells as MDSC), all of them build a barrier to immune infiltration. Antigen uptake by dendritic cells (DC; not shown) after cell death and trafficking to lymph nodes are the first steps. T cells are primed by DCs, and then travel to TME, where they find a barrier to enter access TME. Text box summarizes the ideas to improve vaccination in PDAC. Abbreviations: PDAC, pancreatic ductal adenocarcinoma; MDSC, myeloid derived suppressor cells; TME, tumor microenvironment; TAM, tumor associated macrophages; DC, dendritic cells.

should pursue pathways that increase immune infiltration and endogenous antigen presentation to T cells. These mechanisms that offer room for improvement are summarized in Fig. 1. However, the panorama is dire because many vaccines have been employed in PDAC with poor clinical results: different tumor-associated antigens and vehicles and combination with chemo/radiotherapy in concurrent or sequential schedule.

Several steps in immunization could be optimized at least from a theoretical point of view (Fig. 1): the first one is an adequate innate system activation allowing dendritic cells antigen uptake and maturation inside the tumor microenvironment (TME). The second step is priming T cells in the lymph nodes. The third one is T-cell trafficking and penetration into TME to mediate tumor-specific antigen recognition and tumor cell killing. These steps are known to require Th1 cytokines and chemokines to guide T-cell homing. PDAC that are included in the subtypes GP6, 7, and 8 (2) may benefit the most from these therapies, because TME in these cases has all the necessary elements to respond in place (high expression of antigen processing and presentation genes, and also genes related to adjuvancity to immune system such as Toll-like receptor pathways) thus the use of molecular subtypes of PDAC for patient selection maybe key for future studies or to try to understand which patients benefited the most from the ongoing or already published trials in PDAC using vaccines.

It must be taken into account that immune cells infiltrating PDAC TME usually exhibit an immunosuppressive functional profile: tumor-associated macrophages (TAM) M2, myeloid-derived suppressor cells (MDSC), and regulatory T cells. Immunotherapy strategies fighting these immunosuppressive conditions might synergize in combination with vaccines to modify the TME. Le and colleagues (1) use a combination with cyclophosphamide pretreatment with the aim of reducing MDSC and regulatory T cells but the effects of this strategy are probably suboptimal. Combination with other agents that could reverse immunosuppression (inhibitors of IDO, STAT-3, and TGF-β), enhance immune activation (IL2, GM-CSF, IL12, IL15, IL17, and IL21), or facilitate T-cell infiltration (antiangiogenic agents, hyaluronidase, hedgehog inhibitors, or CXCR4 axis inhibition) might improve results (Fig. 1). Perhaps, vaccination-based therapies could be merged with the mentioned strategies but improving antigen selection by using personalized vaccines encompassing neoantigens.

We do not know whether concurrent or sequential treatment using vaccines and chemotherapy/radiotherapy would have a better effect. Conceivably, inducing some immunogenic cell

death with chemo/radiotherapy, as well as myelotoxicity may prepare TME for a better immune infiltration as mechanistically dissected by Melief and colleagues (5). Investigating and understanding how the different chemotherapy drugs routinely used against PDAC (gemcitabine, fluoropyrimidines, irinotecan, nab-paclitaxel, or oxaliplatin) may affect immune responses or induce favorable TME changes is probably a route forward in the quest for efficacy.

Sadly, tough lessons are to be learnt from negative clinical results coming from well-designed and conducted trials in spite of testing best state-of-the-art clinically feasible immunogens. Reporting negative clinical trial results is of utmost importance to guide subsequent efforts. Progress in immunotherapy of PDAC promises to be extremely difficult. (i) Neoantigens, (ii) biomarker-based selection of amenable patients to draw benefit, (iii) combination of truly synergistic strategies, and (iv) adjuvant/neoadjuvant treatment of early stages of the disease to avoid relapse are all to be considered. However, the field of immunotherapy for advanced PDAC desperately needs a breakthrough.

Disclosure of Potential Conflicts of Interest

I. Melero reports receiving commercial research grants from Alligator, Roche, and Bristol-Myers Squibb, speakers bureau honoraria from MSD, and is a consultant/advisory board member for Bristol-Myers Squibb, Roche, AstraZeneca, Numab, Pieris, Genmab, Catalym, Boehringer Ingleheim, F-Star, and MSD. No potential conflicts of interest were disclosed by the other authors.

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