Personalized cell-mediated immunotherapy and vaccination: combating detrimental uprisings of malignancies

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Summary
A large number of researchers worldwide have conducted various investigations to advance the cell-based immunotherapies and to examine their clinical benefits as an ultimate prevention and/or treatment modalities against life-threatening malignancies. This dominion needs integration of science and technology to change the face of treatment of diseases towards much more personalized medicines. It is now plausible to reprogram the human cells for the prevention and treatment of diseases through various mechanisms such as modulation of immune system, nonetheless we should understand the complexity of biological functions of the cells in a holistic way to be able to manipulate the central dogma of the life to prevent any inadvertent mistake. We should, if not must, comprehend the interrelations of the cellular components (e.g., transport machineries) in the developmental processes of diseases. Still, we do not have a complete image of life, perhaps as expressive barcodes, and many pieces are missing. While completing this puzzle to picture the whole image and examine new treatment modalities, we should take extra caution upon unknown/little-known biological phenomena because trifling modulation/alteration in the complex systems of the life may result in tremendous impacts. In short, it seems we need to consider malignancies as complex systems and treat them in a holistic manner by targeting its hallmarks. Taken all, the immune system reinforcement would be one of the main foundations in combating detrimental malignancy uprising.

Immunization of cancer
After successful accomplishment of a number of studies as “proof-of-concept” upon the cell-based vaccinations, the first “proof-of-technology” and more realistically “proof-of-marketing” was emerged as sipuleucel-T (also known as APC8015/Provenge™) by Dendreon Corp. (Seattle, WA, USA). Sipuleucel-T was approved by the United State Food and Drug Administration (FDA) in 2010 for the treatment of prostate cancer, which showed evidence of efficacy in lessening mortality risk among men with metastatic castration-resistant prostate cancer (MCRPC). As the first FDA approved autologous active cellular immunotherapy modality, Sipuleucel-T opened a new horizon for the cancer therapy and raised great hopes for the development of futuristic personalized immunotherapies and vaccines. For the proof-of-technology, Kantoff et al carried out a double-blind multicenter phase III trial, in which randomly assigned 512 patients were administered either sipuleucel-T (341 patients) or placebo (171 patients) intravenously every...
As the first personalized medicine, sipuleucel-T has successfully been used for the treatment of asymptomatic/minimally symptomatic metastatic hormone-refractory prostate cancer (HRPC). Fig. 1 schematically epitomizes the cell-based immunotherapy process using sipuleucel-T modality.

As shown in Fig. 1, the administration of sipuleucel-T needs three key steps of (a) isolation of the patient’s antigen-presenting cells (APCs) such as dendritic cells (DCs) using a leukapheresis system, (b) incubation of the isolated cells with the fusion protein PA2024, which consists of the antigen prostatic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM–CSF) as immune responses enhancer (panel A), to reprogram the patient’s APCs to present the required antigens, and (c) infusion of the activated blood product.

It should be noted that during invasion and metastasis in the most, if not all, of malignancies, traveling single cancer cells escape the “anoikis” phenomenon that is the main mechanism of death program for the homeless single cells unanchored the extracellular matrix. In 2004, Douma et al showed that the functional expression of TrkB protein favors cancer cells to run away the anoikis, in which the brain-derived neurotrophic factor (BDNF) stimulated TrkB protein can in turn activate the AKT/PKB proteins whose functions result in survival and proliferation of separated traveling cancer cells. Since then, several studies revealed that cancer cells recruit various bioelements to escape the anoikis. Taken all, some pivotal questions still remain unanswered, for example we must know how can really homeless single cancerous cells survive the anoikis and immunosurveillance? And, how effective would be the applied vaccination/immunotherapy against malignancies if some cancerous cells alter its characteristics to evade the immune system functions? We believe that the transitional alteration of differentiated cancer cells to the undedicated cancer stem cells, which can act as progenitor for the second colonization and relapse, is possible mechanism for the survival of single cancer cell invaders even though the detailed mechanism(s) by which invading tumor cells survive the anoikis process are yet to be fully understood.

In the case of cancer immunotherapy, two key strategies have currently been utilized for the tumor targeting, including (a) the antibody-directed targeting of toxic agents or cytolytic activity and (b) intensification of cellular immune responses against malignant cells. However, these approaches have resulted in limited successes, largely because of (a) the inadequate penetration and dissemination of antibodies (Abs) or Ab-conjugates in the tumor microenvironment (TME) as well as cancer cells
and (b) the trivial activation of tumor-specific cytotoxic lymphocytes. In fact, in the solid tumors, the TME forms a permissive milieu with unique characteristics, including (a) altered energetic pathways; for example glucose is hugely metabolized via glycolysis in favor of fueling of the lenient milieu of TME and remodeling of the extracellular matrix (ECM), (b) acidified extracellular fluid within the TME to reprogram the ECM and stromal cells in favor of the further invasion and metastasis, (c) transformed metabolism profile for some important biomolecules; for example, L-tryptophan is metabolized to produce kynurenine to favor the cancer cells to escape the anticancer immunosurveillance function of immune system and immunotherapies, (d) reprogrammed stromal cells, (e) altered tumor interstitial fluid with high oncotic pressure, and (f) changed pattern of drug penetration into the core of solid tumor, in which passive diffusion no longer is the key player, and convection and migration phenomena of molecules/macromolecules impact dissemination of endogenous/exogenous compounds/particulates within TME.

Within the TME, even the transportation of the macromolecular nanosystems (NSs) through different paths (e.g., diffusion, migration and/or convection) would entirely differ from that of the normal tissues/cells. The tumor interstitial fluid pressure (IFP) is markedly high and hence the penetration of macromolecular anticancer agents into the deep core of solid tumor, where encompasses the cancer stem cells, appears to be intriguingly low in solid tumors. Further, the high microvascular density in the primary tumor is often associated with increased incidence of lymph node metastases as well as poor clinical outcome, and tumors with high IFP were reported to be dense in microvasculature in the periphery but possess large hypoxic fractions centrally. Hence, all these issues can limit the anticancer activity of immune system and immunotherapies. Up until now, a large number of clinical trials have been conducted for the cell-mediated vaccination of solid tumors, most of which were based on the use of tumor cells vaccines, modified lymphocytes and reprogrammed APCs such as DCs to stimulate the immune responses through both CD4+ T helper cells and CD8+ cytotoxic T-lymphocytes (CTLs). Of these studies, implementation of fused DCs and tumor cells hybrids (the so-called dentritoma) seems to be a promising strategy even though some important inadequacies may limit its clinical usefulness as reported for DCs-based vaccination in the late stage melanoma. Combined immunotherapy and antivascular therapy has been proposed as an effective therapeutic modality in mouse model bearing B16-F10 melanoma tumors to polarize the TME using a tumor cell-based vaccine (CAMEL peptide as a B16-F10 cell death-inducing agent). The combined therapy was found to induce profound inhibitory impacts as compared to monotherapies, resulting in lessened angiogenesis and increased tumor-infiltrating CD4+, CD8+ and NK cells with lowered suppressor T-lymphocytes (Tregs).

Table 1 represents some selected clinical trials on the cell-based vaccination of cancer.

Table 1. Selected clinical trials for the cell-based vaccination of solid tumors

| Vaccination modality                                      | Trial description                                                                 | Cancer                  | Phase, status            | Clinical trial identifier |
|----------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------|--------------------------|--------------------------|
| Autologous Ad HER2 dendritic cell vaccine                 | Ad/HER2/Neu dendritic cell cancer vaccine testing                                | Breast                  | I, recruiting            | NCT01730118              |
| Aldesleukin, Iflgastim, anti-p53                          | Gene-modified lymphocytes, high-dose aldesleukin, and vaccine therapy in treating patients with progressive or recurrent metastatic cancer | Various solid tumors    | II, terminated with results | NCT00704938              |
| T-cell receptor-transduced peripheral blood lymphocytes, autologous dendritic cell-adenovirus p53 vaccine | Vaccine therapy with or without sirolimus in treating patients with NY-ESO-1 expressing solid tumors | Various solid tumors    | I, active, not recruiting | NCT01522820              |
| DEC-205/NY-ESO-1 fusion protein CDX-1401                  | Vaccine therapy in treating patients with NY-ESO-1 expressing solid tumors        | Various solid tumors    | I, completed             | NCT00057915              |
| CAP 1-6D and CMVpp65 peptide-pulsed, autologous dendritic cells | Vaccine therapy in treating patients with refractory stage IV cancer | Unspecified adult solid tumors | I, completed             | NCT01132014              |
| Dendritic cell vaccine loaded with autologous tumor       | Autologous OC-DC vaccine in ovarian cancer                                        | Ovarian cancer          | 0, recruiting            | NCT02224599              |
| Tumor Associated Peptide Antigens (TAPAz)-pulsed DC vaccine | Treatment of patients with progressive and/or refractory solid malignancies     | Various solid tumors    | I/I, just initiated      | NCT00019890              |
| Dendritic cell-gp100-MART-1 antigen vaccine               | Vaccine therapy in treating patients with high-risk stage III or completely resected metastatic melanoma | Stage III/IV melanoma   | II, completed            | NCT00019890              |

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strategy against solid tumors. We believe that the status of TME in different solid tumors and penetration of macromolecules and immune system cells into such microenvironments must be fully understood. Further, we must address some pivotal issues to make sure upon the clinical benefits of the cell-based vaccination strategy. We need to answer some key questions. How effective would be the cell-based vaccination strategy if the core of solid tumors hosts some undedicated cancer stem cells (CSCs)? If such assumption is true, then what would be the best strategy for targeting CSCs? What would be the behavior of immune system components within TME with acidified tumor interstitial fluid and high oncotic pressure? Ideally, the use of panel of cancer molecular markers (CMMs) involved in TME can be beneficial for the development of the cell-based immunotherapies and vaccination which will literally benefit both the antibody-directed and cell-mediated immunotherapy, and hence improve the survival rate. Thus, key CMMs of TME should be recognized. To this end, we need to comprehend the whole panel of molecular event in the TME as complex systems and design the cell-based immunization/vaccination in a holistic manner for each cancer patient exclusively.

Acknowledgments
Authors are very grateful to Tabriz University of Medical Sciences for hosting the “Publish Free” and “Access Free” journal “BioImpacts”, which is an international platform for publication of the bench-to-beside translational researches in the field of pharmaceutical and biomedical sciences.

Ethical issues
There is none to be declared.

Competing interests
There is none to be disclosed.

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