EDITORIAL

Harnessing whole tumor cells for tumor immunotherapy

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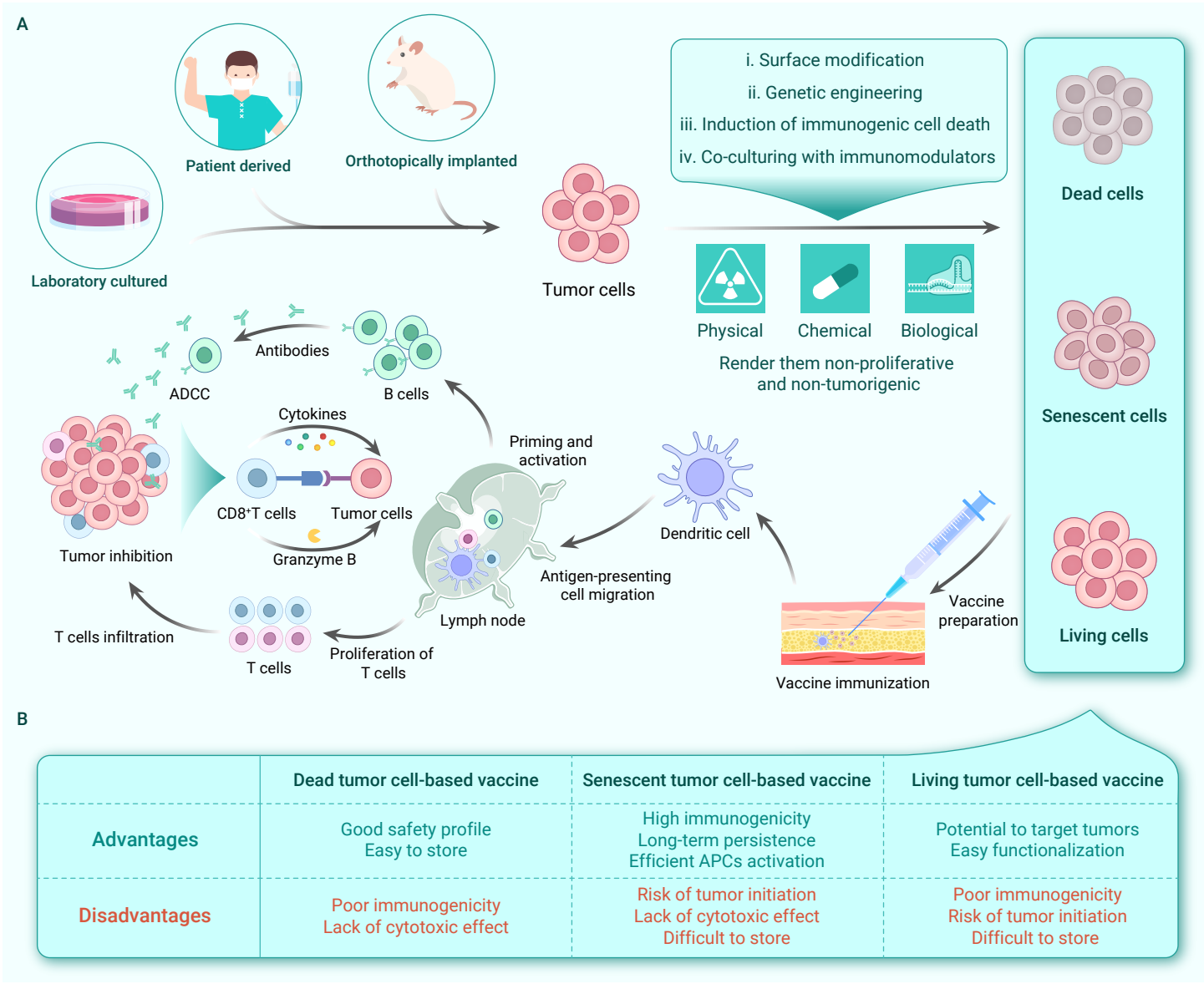
Tumor vaccines have gained recognition for their ability to deliver tumor-specific antigens to antigen-presenting cells, thereby stimulating the immune system and eliciting an effective immune response against tumors. Nonetheless, the heterogeneity, complexity, diversity, and mutagenic properties of tumor antigens significantly impede the development of universal vaccines[1]. For instance, the variability in tumor antigens among patients and cancer types poses a challenge in formulating a standardized vaccine that is effective for all patients. In contrast, whole tumor cell vaccines, which consist of a whole array of tumor antigens, have garnered significant attention as reliable and effective vaccines for both prophylactic and therapeutic applications. In



	Dead tumor cell-based vaccine	Senescent tumor cell-based vaccine	Living tumor cell-based vaccine
Advantages	Good safety profile Easy to store	High immunogenicity Long-term persistence Efficient APCs activation	Potential to target tumors Easy functionalization
Disadvantages	Poor immunogenicity Lack of cytotoxic effect	Risk of tumor initiation Lack of cytotoxic effect Difficult to store	Poor immunogenicity Risk of tumor initiation Difficult to store

Figure 1. Schematic illustration for the preparation and antitumor mechanism of whole tumor cell vaccines (A) Tumor cells used for vaccination are either sourced from the patient's tumors, orthotopically implanted tumors, or laboratory-cultured cell lines. These cells are modified to eliminate their tumorigenic properties while boosting their immunogenicity. Following vaccination, DCs play a crucial role by uptaking, processing, and presenting tumor antigens, leading to the activation of T cells, which inhibit tumor cells. Furthermore, the activated B cells contribute to tumor apoptosis through ADCC. (B) Summary of the advantages and disadvantages of the three types of tumor cell-based vaccines. DCs: dendritic cells; APCs: antigen-presenting cells; ADCC: antibody-dependent cellular cytotoxicity.

recent years, there has been substantial progress in the development of whole tumor cell vaccines, with numerous studies progressing to the clinical trials. It is estimated that more than 68 whole tumor cell vaccines are currently undergoing or have completed phase I-III clinical trials (clinicaltrials.gov).

Typically, whole tumor cells used for vaccines are derived either from the patient's tumor cells, orthotopically implanted tumors, or laboratory-cultured cell lines (Figure 1A). To ensure good biosafety, the tumor cells undergo inac-

tivation via physical (e.g., X-ray irradiation), chemical (e.g., hypochlorous acid oxidation), and biological (e.g., genetical engineering) methods to render them non-proliferative and non-tumorigenic. However, attenuated tumor cells often struggle to elicit robust immune responses due to their limited immunogenicity. As a result, current approaches commonly involve subjecting these tumor cells to surface modification, genetic engineering, immunogenic cell death induction, and co-culturing with immunomodulators (such as adjuvants, anti-programmed cell death protein 1 antibodies and cytokines). Importantly, these modifications can enhance the potential of these vaccines to synergize with other therapies, such as dendritic cell (DC) vaccines, chemotherapy, and phototherapy, to achieve optimal efficacy in both preventative and therapeutic contexts. Following vaccination, DCs play a critical role in the immune response by uptaking, processing, and presenting tumor antigens to recruit and activate immune cells. Once activated, T cells undergo proliferation and differentiation, giving rise to both memory T cells and effector T cells to suppress tumors. Additionally, follicular dendritic cells facilitate the generation of memory B cells, leading to tumor apoptosis through antibody-dependent cellular cytotoxicity (ADCC). To date, the development of whole tumor cell vaccines has progressed slowly, warranting unwavering efforts from researchers to establish highly effective and dependable whole tumor cell vaccines.

Tumor cells are commonly rendered non-viable or deactivated to minimize the risk of carcinogenicity. However, this process may lead to the potential loss of immunogenicity. Additionally, whole tumor cell vaccines face challenges in terms of long-term storage, which can hinder their further clinical application. Recently, Guo et al. devised a cellular vaccine made from cryogenically silicified tumor cells capable of decoration of pathogen-associated molecular patterns (PAMPs) to eradicate tumors and induce long-term animal survival.[2] The high adsorptive capacity of the silica surface enables tumor cells to efficiently bind various functional immunomodulators, thereby steering desired immune responses. This approach could enable long-term storage without compromising efficacy and has the potential to be adapted for inducing both preventive and therapeutic responses across various types of tumors. Nevertheless, this inactivated tumor cell approach still relies on the assistance of PAMPs to trigger robust immune responses and effective personalized immune therapy, given its intrinsic limited immunogenicity.

Senescent tumor cells, characterized by low or null proliferative capacity but high immunogenicity, emerge as prime candidates for inclusion in whole tumor cell vaccines. Recently, two concurrent studies featured in *Cancer Discovery* have shed light on the role of senescence in altering the cell surface proteome to activate efficient and protective CD8-dependent antitumor immune responses.[3,4] Marin et al. provided evidence demonstrating the prolonged persistence of senescent tumor cells within the body, along with their ability to trigger the release of adjuvants, activate interferon (IFN) signaling, enhance antigen presentation, and modify the immunopeptidome.[3] These attributes render them highly immunogenic to elicit strong antitumor protection mediated by DCs and antigen-specific $CD8^+$ T cells, surpassing the established benchmark of immunogenic cell death. Meanwhile, Chen et al. established a "senescence-inducible" model by genetic modulation of endogenous p53 without affecting the host immune system.[4] These senescent tumor cells could induce the expression of senescence-associated secretory phenotype (SASP) and plasma membrane-associated proteins to boost their immunogenic potential and render them susceptible to immune surveillance *in vivo*. Collectively, the above findings open exciting avenues for utilizing senescent cancer cells as a platform for generating whole tumor cell vaccines that can effectively elicit $CD8^+$ T cell-mediated anti-tumor immune responses.

The whole tumor vaccines primarily function by stimulating the immune system to recognize and combat cancer cells without directly exerting a cytotoxic effect on the tumor cells. Interestingly, Chen et al. previously utilized CRISPR-Cas9 technology to disable the interferon-β (IFN-β)-specific receptor in living tumor cells and subsequently engineered them to secrete IFN-β, leading to direct inhibition of tumor cell growth and angiogenesis.[5] Moreover, these living tumor cells were further manipulated to coexpress granulocyte-macrophage colony-stimulating factor (GM-CSF) to facilitate the modulation of immune responses. This bifunctional tumor cell-based therapeutic strategy possesses the ability to directly induce caspase-mediated tumor cell apoptosis while concurrently activating and sustaining long-term immunity. This could allow the manipulation and modification of living tumor cells to enhance their immunogenicity and therapeutic potential, representing a groundbreaking avenue for the development of whole tumor cell vaccines. Importantly, the potential for unintended initiation of secondary tumors must be taken into account to ensure the safety of these vaccines.

Recent advancements have greatly broadened the sources of whole tumor cell vaccines, signifying a notable milestone in their development (Figure 1B). Despite these breakthroughs, the progress of whole tumor cell vaccines has encountered limited or modest clinical benefits, potentially attributed to several factors: (1) low immunogenicity of tumors and associated antigens, (2) immunosuppressive tumor microenvironment, (3) significant tumor heterogeneity, and (4) difficulties associated with developing an effective delivery system. Considering these factors, we have identified potential strategies to address the challenges in whole tumor cell vaccine development: (1) increasing immunogenicity through induction of tumor cell death in an immunogenic way (e.g., incorporation of functional materials, chemotherapeutic drugs, or photothermal/photodynamic agents into tumor cells), selecting more immunogenic subpopulations of tumor cells (e.g., senescent tumor cells), or employing genetic techniques to amplify the expression levels of immunogenic genes; (2) modulating the immunosuppressive tumor microenvironment using biomaterials (e.g., lipid-based nanoparticles, polymeric nanoparticles, inorganic nanoparticles, microspheres, or hydrogels) and nanomedicine (e.g., cytokines, costimulatory molecules, or immunomodulators) technologies to counteract immune inhibitory signals and reduce the suppressive function of immune cells; (3) addressing tumor heterogeneity by developing tumor stem cell vaccines or personalized whole cell vaccines; (4) establishing effective delivery systems by exploring novel scaffolding carriers, viral vectors, or using a cell engineering approach. Indeed, by effectively addressing these challenges, there is a strong potential to enhance the efficacy and utility of whole tumor cell vaccines, positioning them as valuable and promising additions to the array of cancer treatments accessible to patients in the foreseeable future.

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DECLARATION OF INTERESTS

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