Immunotherapy: A new target for cancer cure (Review)

FUQIAN ZHAO[1*], DAOFU SHEN[1*], MINGQUAN SHANG[1], HAO YU[1], XIAOXUE ZUO[1], LIXIN CHEN[2], ZHIJIN HUANG[3], LIANXING LI[4] and LEI WANG[1,5]

[1]Medical Laboratory Center, Chifeng Municipal Hospital/Chifeng Clinical College, Inner Mongolia Medical University; [2]Medical Laboratory Center, Songshan Hospital, Chifeng 024000; [3]Medical Laboratory Center, Ningcheng County Central Hospital, Ningcheng 0242004; [4]Department of Teaching and Research, Chifeng Municipal Hospital/Chifeng Clinical College, Inner Mongolia Medical University; [5]Chifeng Municipal Key Laboratory of Nerve Injury and Functional Repair, Inner Mongolia Medical University, Chifeng 024000, P.R. China

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Abstract. Cancer is the leading cause of death globally and there is a worldwide cancer epidemic. Immunotherapy has emerged as a promising anticancer therapy. In particular, oncolytic viruses destroy cancer cells without destroying normal tissue via viral self-replication and anti-tumor immune responses, showing potential for cancer therapy. The present review discusses the role of the immune system in the treatment of tumor. The strategies for treating tumors are briefly introduced from aspects of active immunization and passive immunotherapy and the dendritic cell vaccines and oncolytic viruses are highlighted, as well as use of blood group A antigen in the treatment of solid tumors.

Correspondence to: Dr Lei Wang, Medical Laboratory Center, Chifeng Municipal Hospital/Chifeng Clinical College, Inner Mongolia Medical University, 1 Zhaowuda Road, Chifeng 024000, P.R. China
E-mail: lncyly@126.com

Dr Lianxing Li, Department of Teaching and Research, Chifeng Municipal Hospital/Chifeng Clinical College, Inner Mongolia Medical University, 1 Zhaowuda Road, Chifeng 024000, P.R. China
E-mail: 547635179@qq.com

*Contributed equally

Abbreviations: cDC, conventional dendritic cell; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; FDA, Food and Drug Administration; NK, natural killer; HSV, herpes simplex virus; PD-1, programmed death receptor 1; CAR, chimeric antigen receptor; TCR, T cell receptor; APC, antigen-presenting cell; TME, tumor microenvironment; mAb, monoclonal antibody; GM-CSF, granulocyte macrophage colony-stimulating factor

Key words: immunotherapy, tumor, oncolytic virotherapy, A blood group antigen

Contents

1. Introduction

Cancer is the main cause of death in the world and there is even a view that the world is experiencing a cancer epidemic (1). In 2018, China had 4.3 million new cancer cases and 2.9 million cancer deaths (2). The huge economic burden puts notable pressure on the medical system and patient wellbeing. Surgical treatment is considered to be the most effective way to treat tumors; after the advent of chemotherapy in 1940 and targeted therapy in the late 1990s, immunotherapy is the third important era of cancer treatment (3). In the past few decades, anti-cancer immunotherapy has transformed from an emerging tumor treatment theory to a well-known alternative tumor therapy. Anti-cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and anti-programmed death receptor 1 (PD)-1/PD-ligand (L) 1, as immunotherapy, for the treatment of melanoma, colorectal cancer and breast cancer plays an important role (4-6).

Immunotherapy refers to the method of artificially enhancing or inhibiting the immune function of the body to cure diseases. Tumor immunotherapy is based on the immune surveillance theory proposed by Frank Macfarlane Burnet and Lewis Thomas (7). The theory of immune surveillance posits that the system can play a surveillance role to identify and eliminate foreign components or mutant cells that express new antigens to maintain the stability of the host environment. When the immune function is low and cannot effectively eliminate foreign or mutated cells, tumors may occur (8). Dunn *et al* (9) put forward the theory of immune editing, which further improved the framework of tumor immunity. The immunoediting theory posits that the development of tumors

needs to go through three stages: Immune clearance, balance and escape (10). Tumor cells that can escape the immune system may survive natural selection. If tumors are regarded as immunogens, decades of research have not found valuable tumor antigen-regulated immune escape theory, and a large number of experiments have proved that tumor stem cells with reduced expression of tumor antigens further prove that the search for tumor-specific antigens or wrong research direction (11,12). Hypoxia at the tumor site may cause attenuation of tumor immunogens (13). It can hypothesized that the immune system recognizes and destroys tumor cells expressing strong immunogenicity, while tumor cells with weak (or no) immunogenicity selectively survive and eventually form tumors. Immunotherapy may become the most advantageous tool to overcome this (14). The relationship between the immune system and tumors is complicated. In 1891, American doctor William Coley discovered that postoperative infection of *Streptococcus pyogenes* in patients with sarcoma could cause tumor regression. This discovery provided a new idea for cancer immunotherapy (15). With the emergence of new technologies such as humanized antibodies, virus packaging and gene high-throughput sequencing, tumor therapy has achieved rapid development. This review summarizes strategies for immunotherapy to treat cancer (16,17).

2. Association between the immune system and tumor

The immune system consists of immune organs (bone marrow, thymus, spleen, lymph nodes, tonsils, small intestinal Peyer's lymph nodes, appendix, thymus, etc.), immune cells (lymphocytes, mononuclear phagocytes, neutrophils, basophils, eosinophils, etc.) Granulocytes, mast cells, platelets, etc.), and immune molecules (complement, immunoglobulin, interferon, interleukin, tumor necrosis factor and other cytokines, etc.) (18). The immune system recognizes and eliminates antigenic foreign bodies, coordinating with other systems of the body, and maintaining the stability of the host environment and physiological balance (19). Immune organs are be divided into central (bone marrow and thymus) and peripheral immune organs (spleen, lymph nodes and tonsils); immune cells occur, differentiate and mature in central organs and B lymphocytes colonize and proliferate in peripheral organs, where the immune response primarily occurs (20,21). Immune cells comprise innate (dendritic (D) and natural killer (NK) cells and macrophages) and adaptive immune cells (T and B cells) (22). Immune molecules comprise membrane-type (such as T and B cell receptor (CR), adhesion and major histocompatibility complex (MHC) molecules and cytokine receptors) and secreted molecules (such as immunoglobulin, complement and cytokines) (23,24). The most important function of the innate immune system is to respond quickly to infection or inflammation and to recruit innate immune cells or activate complement via cytokines secreted by the injured site (such as ILs and chemokines) (25). Both B and T cells originate from a common lymphoid progenitor cell (B cells mature in the bone marrow and T cells mature in the thymus) and mediate humoral and cellular immunity, respectively (26). B cells participate in production of antibodies, and T cells participate in proliferation of B cells, directly attack pathogens and regulate immune responses (27). Adaptive immunity is associated with immune memory and long-term effects of the immune system and serves a key role in fighting tumors (28).

The tumor antigen-specific T cells produced by adaptive immunity are considered to be the key factor in killing tumors (29). This process is inseparable from the innate immune response and includes the following steps: Phagocytes engulf and digest tumor cells to produce tumor antigens; antigen-presenting cell (APC) cross-presentation of tumor antigens to T cells; initiation and activation of initial T cells; transport and infiltration of activated T cells into the tumor microenvironment (TME) and activated CTL-mediated malignant cell death. The generation of tumor antigen-specific T cells reflects the coordination between the innate and the adaptive immune system (30-33). This dynamic interaction is guided by the phenotype and function of innate immune cells to influence tumor antigen-specific T cells, resulting in different biological states (tolerance or responsiveness) (34). As the APC in TME, DCs initiate cancer immunity by cross-presenting tumor-associated antigens to naive T cells (35). Although antigen-loaded DCs are potent stimulators of T cell activation, DCs activate antigen-specific CTL expansion through the CD40/CD40L pathway (36). CD40 is a member of the tumor necrosis factor (TNF) receptor superfamily that is expressed in large quantities on the DC membrane. After recognizing its homologous antigen, $CD4^+$ T helper (Th) cells can express CD40L and then combine with the complementary CD40. After activation, the expression of MHC II, CD80and CD86 on the surface of DCs is increased, which supports T cell activation (37). Conventional DCs (cDCs) in mice are divided into two lineages with different functions: $CD103^+$ cDC1 lineage is responsible for the initiation of $CD8^+$ CTL and $CD11b^+$ cDC2 lineage is associated with priming $CD4^+$ Th cells (38,39). In a melanoma mouse model, $CD103^+$ cDC1s promote T cell recruitment to the TME by releasing the chemokine CXCL9/10 (40). Similar to DCs, macrophages are key innate immune cells that promote or hinder the activation of effector T cells (41). This is because their functional characteristics are affected by signals from the surrounding microenvironment and the cell phenotype has strong plasticity. IFN-γ and toll-like receptor agonists induce differentiation into M1 phenotypes related to anti-tumor activity; IL-4 and IL-13 induce differentiation into M2, which is associated with tumor-promoting activity (42,43). M1 macrophages are mainly involved in the immune response against foreign pathogens and M2 macrophages help wound healing and secrete anti-inflammatory cytokines (44). In tumorigenesis and metastasis, M1 macrophages serve an adaptive immune surveillance function, while M2 macrophages inhibit the anti-tumor immune function of T cells (45). M1-like macrophages in TME phagocytose tumor cells and present tumor antigens to initiate the anti-tumor activity of $CD8^+$ T cells (46). Macrophages residing in tissues other than tumors can also transfer phagocytosed tumor antigens to DCs to trigger an adaptive immune response by inducing CTL cross-reactions (47). Macrophages are commonly used by tumors to suppress adaptive immune responses. M2 macrophages inhibit T cell activation by secreting IL-10 to destroy the TCR (48). In addition, tumor-infiltrating macrophages express a variety of immune checkpoint proteins (such as PDL1) that bind to T cell inhibitory signal receptors to inhibit cell function (49). $CD169^+$

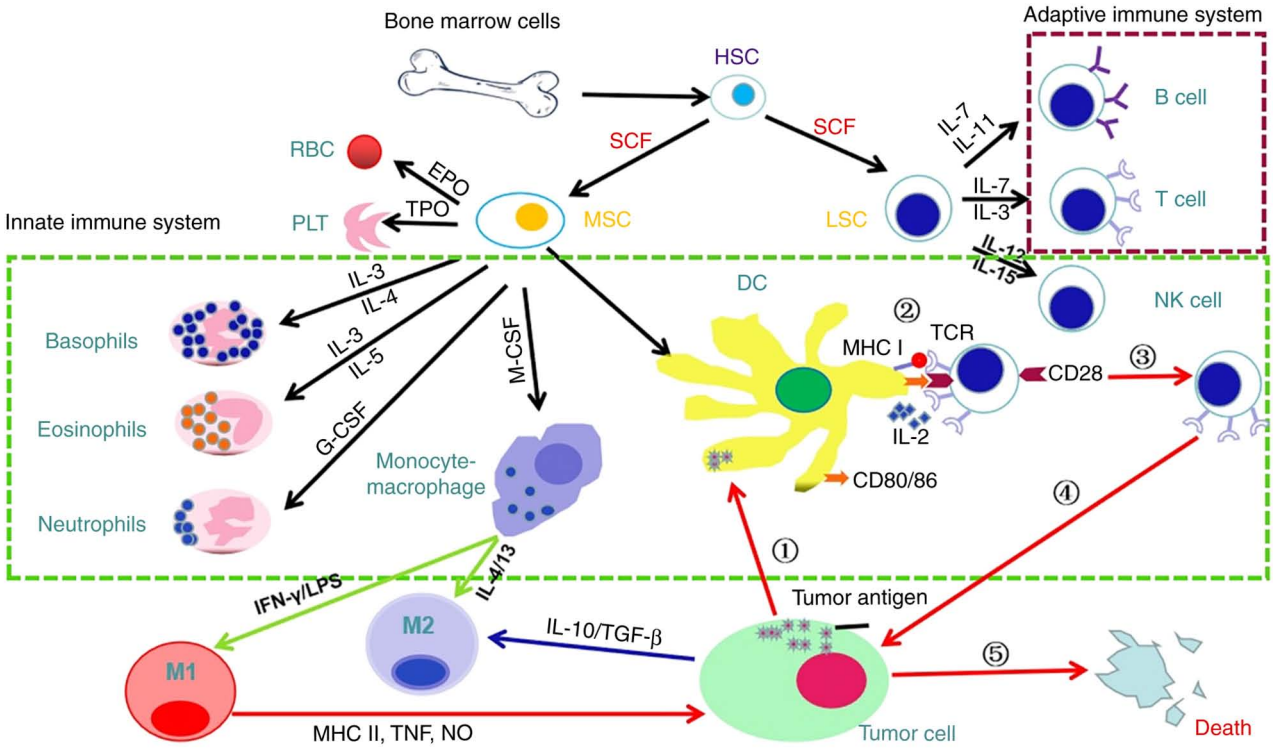

Figure 1. Origin of immune cells and the mechanism of antitumor action. HSCs originate from bone marrow and differentiate into MSCs and LSCs under the action of SCF. MSCs differentiate into other myeloid-derived immune cells under the action of cytokines and constitute the innate immune system. SCF differentiates into adaptive immune cells composed of B and T lymphocytes and NK cells evolve into innate immune cells. The monocyte-macrophage system differentiates into two cell types, M1 and M2, which serve as tumor suppressors and tumor promoters, respectively. DCs can process neoantigens derived from host tumor cells. Neoantigens are processed and presented to TCRs via peptide-MHC complexes and toll-like or other receptors. Co-stimulation upregulates the expression of molecules such as CD80 or CD86 on the cell surface. Cytokines (such as IL-2) are released by DCs and T cells, further shaping antigen-induced T cell formation. Antigen-specific T cells recognize and attack tumor cells, which are killed. HSC, hematopoietic stem cell; MSC,mesenchymal stem cell; LSC, lymphoid stem cells; SCF, stem cell factor; NK, natural killer; DC, dendritic cell; MHC, major histocompatibility complex; EPO, erythropoietin; RBC, red blood cell; TPO, thrombopoietin; PLT, platelet; G-CSF,granulocyte colony factor; M-CSF, macrophage colony stimulating factor; LPS, lipopolysaccharide; TCR, T cell receptor.

macrophages capture tumor antigens to prevent them inducing an immune response (Fig. 1).

3. Passive immunotherapy

Anti-cancer immunotherapy is classified as passive or active according to the ability to activate the host immune system against malignant cells. Tumor-targeted monoclonal antibodies and adoptively transferred T cells are considered passive forms of immunotherapy because exhibit inherent anti-tumor activity (50). Anti-cancer vaccines and immune checkpoint inhibitors that only exert anti-cancer effects when the host immune system is involved are classic examples of active immunotherapy (51).

Immunoglobulins, also called antibodies, are the first molecules involved in specific immune responses (52). Antibodies with unique specificities that recognize different target molecules have been used to attack tumor cells that express certain antigens (53). There are five mechanisms for tumor-targeting antibodies to produce anti-tumor effects. Therapeutic antibodies, such as epidermal growth factor receptor (EGFR)-specific monoclonal antibody cetuximab for the treatment of head and neck and colorectal cancer, inhibit the signaling pathways required for tumor cell survival or progression. Therapeutic antibodies, such as tigatuzumab, a monoclonal antibody specific to TNF receptor superfamily member 10B, activate potentially lethal receptors expressed on the surface of tumor cells. Immunoconjugates (tumor antigen-specific antibodies conjugated to toxins or radionuclides), such as gemtuzumab and ozogamicin (an anti-tumor cell membrane-expressed CD33 calicheamicin conjugate approved for use in patients with acute myeloid leukemia), directly kill tumor cells. Simple antibodies directed against tumor-specific or -associated antigens (such as rituximab, which is currently approved for the treatment of chronic lymphocytic leukemia and non-Hodgkin's lymphoma) work by activating antibody-dependent cell-mediated cytotoxicity and cellular phagocytosis and complement-dependent cytotoxicity. Bispecific T cell conjugates are composed of two monoclonal antibodies from different monoclonal antibodies (54-59). An artificially modified antibody, the chimeric protein of its variable region, one targets tumor cells, and the other specifically targets T cell surface antigens, shortening the distance between T cells and tumor cells in space, allowing T cells to directly Kill tumor cells. For example, blinatumomab, a therapeutic antibody that targets the CD19 molecule on tumor cells and the CD3 molecule on T cells, is used in the treatment of Philadelphia chromosome-negative precursor B cell acute lymphoblastic leukemia (60). Approved antibodies targeting tumor cells (such as Catumaxoma) and other antibody drugs

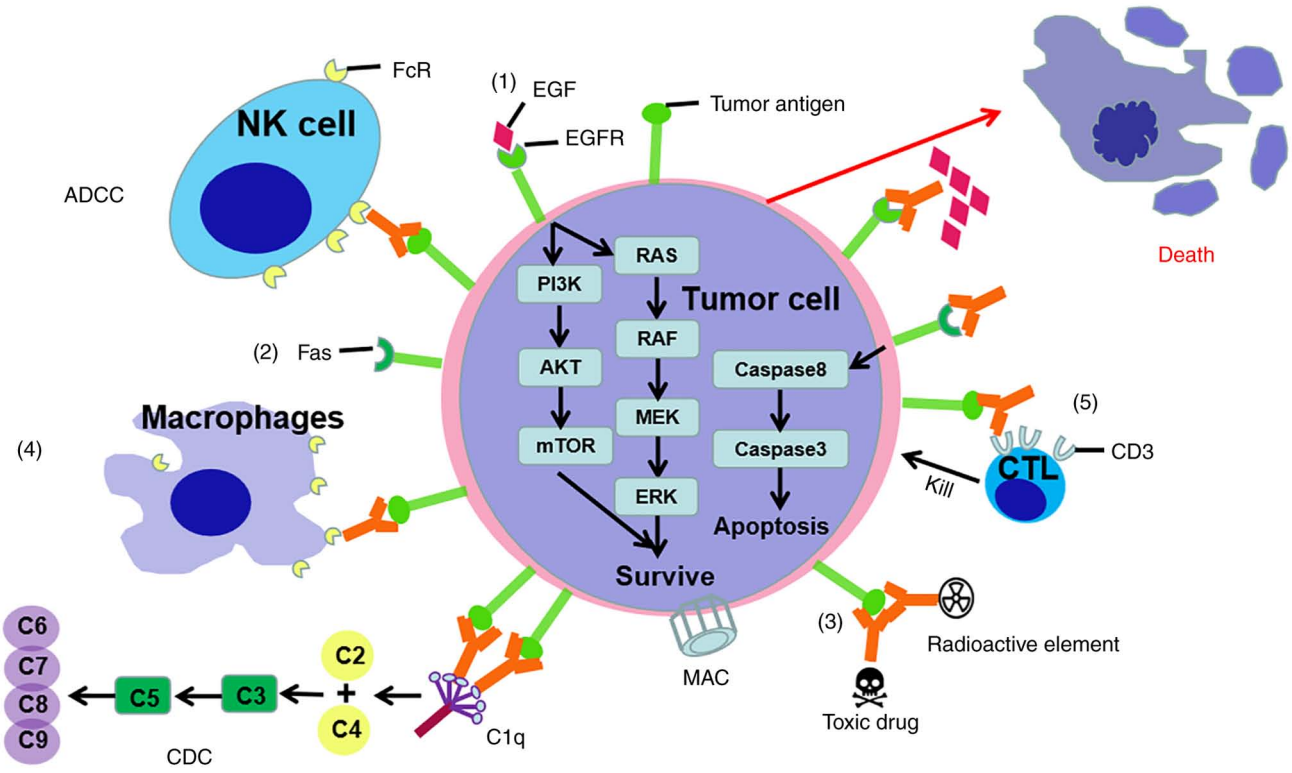

Figure 2. Role of antibodies in tumor treatment. Therapeutic antibodies inhibit signaling pathways required for tumor cell survival or progression, such as EGFR. Therapeutic antibodies activate Fas, a potentially lethal receptor expressed on the surface of tumor cells. Toxin- or radionuclide-conjugated tumor antigen-specific antibodies directly kill tumor cells by activating ADCC, antibody-dependent cellular phagocytosis and CDC. Bispecific T cell conjugates are chimeric proteins composed of two different variable regions of the same antibody, one targeting tumor cells and the other specifically targeting T cell surface antigens, shortening the distance between T cells and tumor cells. Spatial distance allows T cells to directly kill tumor cells. EGFR, epidermal growth factor receptor; NK, natural killer; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; MAC, membrane attack complex; CTL, cytotoxic T lymphocyte.

(such as Veltuzumab) under development belong to the IgG class. IgA molecules are also used as anticancer agents. For example, the anti-EGFR IgA2 containing the variable region of cetuximab significantly decreases the number of metastases in a melanoma cell lung metastasis model of transgenic mice expressing human EGFR (61). This effect of IgA2 lasts a week longer than the corresponding IgG cetuximab (62,63). IgE is another antibody class being explored as a potential cancer treatment (64). The research on the function of using IgE-mediated immune response against tumor cells in the context of cancer belongs to the rapidly developing allergoncology field (Fig. 2) (65).

Cell therapy refers to the transfer of autologous or allogeneic cell material into the body for medical purposes (66). Adoptive cell transfer is a cell-based anti-cancer immunotherapy. The usual practice is to use immune enhancers to activate blood circulation or tumor-infiltrating lymphocytes to achieve the purpose of fighting tumors (67). Other anti-cancer immunotherapies involve live cell transfusion, such as hematopoietic stem cell transplantation, to rebuild a healthy, allogeneic immune system; adoptive cell transfer is the infusion therapy of immune cells with potential antitumor immune activity (68). Interventions based on DCs are different from the aforementioned cell therapies. Infused DCs do not have anti-cancer activity but can be used as anti-cancer vaccines to trigger tumor-targeted immune responses (69). The cellular immune response against tumors primarily depends on T cells. A large number of antigens have been identified in tumors that are recognized by T cells, suggesting the potential role of T lymphocytes in anti-tumor immune responses (70). In certain patients with melanoma or pancreatic cancer, Epstein-bar virus-associated malignancy and murine tumor models, functional CTL have been shown to fight tumor cells that express tumor antigens (71,72). The permanent establishment of memory immune T cells serves a key role in preventing tumor recurrence (73). However, due to the poor immunogenicity of most tumors, it is difficult to cultivate a lymphocyte population with sufficient affinity for TCRs, and it is difficult to introduce engineered surface receptors with enhanced affinity for a tumor-specific antigen (74). Chimeric antigen receptors (CARs) consist of antibody-derived antigen recognition domains that are connected to the internal T cell signaling domain and recognize antigen targets through a mechanism different from that of classical TCR (75). Unlike traditional TCRs that recognize intracellular peptide antigens presented by MHC molecules, CARs directly recognize antigens expressed on the surface of tumor cells so are not limited by the patient HLA subtype, and can recognize a variety of antigen structures, including proteins, carbohydrates and glycolipids (60). Gene therapy viral vectors can transfect genes encoding CAR constructs into T cells to express high-affinity extracellular antigen-recognition moieties and membrane proteins derived from monoclonal antibody single-chain variable fragment-binding TCR signaling domains (76). The

internal domain of CAR is originally derived from the CD3ζ chain of traditional TCR, and after technical development, it can include one or more costimulatory domains (most commonly CD28 and 41BB) to enhance the persistence and cytotoxicity of CAR-expressing cells (77).

4. Active immunotherapy

DC cells were first discovered in 1868 by Langerhans in the skin (78). In 1973, Ralph Steinman discovered similar cells in the spleen of mice and proposed dendrites and their functions (79). In March 2007, after Steinman was diagnosed with advanced pancreatic cancer, he used his own developed DC cells for treatment, extending his life expectancy from a few months to 4.5 years (80). American Food and Drug Administration (FDA)-approved Sipuleucel-T is a vaccine against advanced castration-resistant prostate cancer and the first therapeutic DC vaccine against cancer. DCs are the key cells that initiate and respond to pathogens to activate naive T cells (81). DC cells also serve a key role in maintaining immune tolerance. DCs are derived from B cells, macrophages, Langerhans cells and inflammatory/monocytes Together with DCs, B cells and macrophages, are considered to be antigen-presenting cells (82). Pattern-recognition receptor (PRR) ligand expressed on DCs can lead to activation and can induce simultaneous antigen uptake and processing to produce peptide antigen, together with MHC molecules, pMHC complexes are formed (83). In secondary lymphoid organs, DCs present pMHC complexes to naive T cells, presents pMHC to TCRs by activating or inhibiting membrane receptors. Subsequently, soluble cytokines are expressed and secreted by DCs as signaling molecules (84). Although they are ubiquitous in most tissue, the absolute number of DCs is very low. For example, mature DCs only account for ~1% of the total peripheral blood mononuclear cells (85). With the improvement of DC *in vitro* derivation, a variety of precursor cells can be used to prepare DCs, such as non-proliferative $CD14^+$ monocytes from peripheral blood and proliferative $CD34^+$ precursor cells from bone marrow and blood in the umbilical cord (86). In addition, by direct transdifferentiation or indirect dedifferentiation and differentiation, myeloid and lymphoid DCs can differentiate to DCs (87).

There are several forms of DC-based immunotherapies, most of which involve isolation of circulating monocytes from patients or donors and their expansion and differentiation *in vitro* to promote the maturation of DCs by cytokines (such as TNF-α, IL-1β) (78). Immature DCs have an immunosuppressive function rather than an immune enhancing function, and the use of macrophage colony-stimulating factor to stimulate immature DCs to differentiate into mature DCs plays an important role in their anti-tumor function (88).

For tumor cells with low expression of MHC I, their tumor antigen presentation ability is weakened and it is difficult to activate T cells to kill tumor cells (89). To better present tumor antigens to T cells, DC vaccines introduce tumor-associated antigens (including proteins, peptides or tumor lysate) from patients into DCs. The pMHC is expressed on the cell surface to initiate an immune response. The preparation methods of DC vaccines include directly sensitizing DCs with tumor antigens and cell lysates to produce activity; viral vectors encoding tumor associated antigen (TAA) gene to infect DCs to express the corresponding antigens and Tumor antigen mRNA is electroporated or chemically transfected into DC cells or fused with DC cells using a fusion agent with tumor cells expressing tumor antigens (Fig. 3) (90,91).

Sensitization of DCs with tumor antigens and cell lysates is the most common method for preparing DC vaccines (92). Immature DCs phagocytose tumor antigens and differentiate into mature DCs *in vitro*. These cells carrying antigenic information are returned to the body to activate the anti-tumor immune response (93). After DCs carrying antigens, such as carcinoembryonic antigen and melanoma antigen-A1, are returned to patients with lung cancer, the body can produce specific T lymphocytes (94). However, tumor-associated antigens are not unique to tumor cells and it is difficult to induce a specific immune response against tumor cells. Therefore, sequencing and mass spectrometry have been used to analyze and identify neoantigens on the surface of tumor cells (95). Excised tumor tissue is lysed by ultrasonic disruption, subjected to repeated freezing and thawing and used as an active ingredient to prepare DCs that induce anti-tumor responses (96). DCVax®-L is a personalized DC vaccine sensitized by lysate of malignant glioblastoma developed by Northwest Biotherapeutics in the United Kingdom that infects DCs with viral vectors to insert the gene encoding TAA into a lentivirus, recombinant poxvirus or adenovirus vector (97). After the virus infects DCs, it expresses TAA and maturation is induced. The low efficiency of virus infecting DC means the development of DC vaccines has been limited (98). Tumor cells and DCs are fused under the action of fusion agents, and the fused cells not only have the function of DCs, but also express tumor antigens on the cells.

DC vaccines are highly immunogenic and highly specific. Electrical, viral and chemical fusion are commonly used methods for preparing DC vaccines. Due to the instability of electric fusion, this technology is no longer used (99). Viruses commonly used to induce animal cell fusion include Sendai, Newcastle disease and herpes virus (100,101). Inactivated Sendai virus is used to induce cell fusion; the fusion rate is high and it is suitable for various types of animal cell. Because Sendai virus is unstable, the preparation process it is cumbersome and may affect the normal function after entering the cell (102). Polyethylene glycol has good water solubility and adhesion, and is a commonly used chemical reagent for the fusion of cells. In DC immunotherapy, the immunosuppressive nature of the tumor microenvironment inhibits the antigen presentation ability of DC cells (103), the limited ability of DC cells to target tumors cannot specifically recognize tumor antigens, and the specific T cells produced by DCs after presenting antigens Cells have low affinity for tumor cells (35,93,104). Due to the multiple roles of DCs in the immune response, DC vaccines are still a promising treatment.

Cytokines are key biomolecules that communicate with each other and exert biological functions in immune cells (105). As a family of proteins, they regulate almost all biological functions of cells via autocrine, paracrine or endocrine effects. Based on the powerful immunomodulatory ability, the immunotherapy of cancer with cytokines has been tried (106,107). The therapeutic effect of IFN is considered important in cancer immunoediting and has been studied in many clinical trials (108,109). Type I IFN

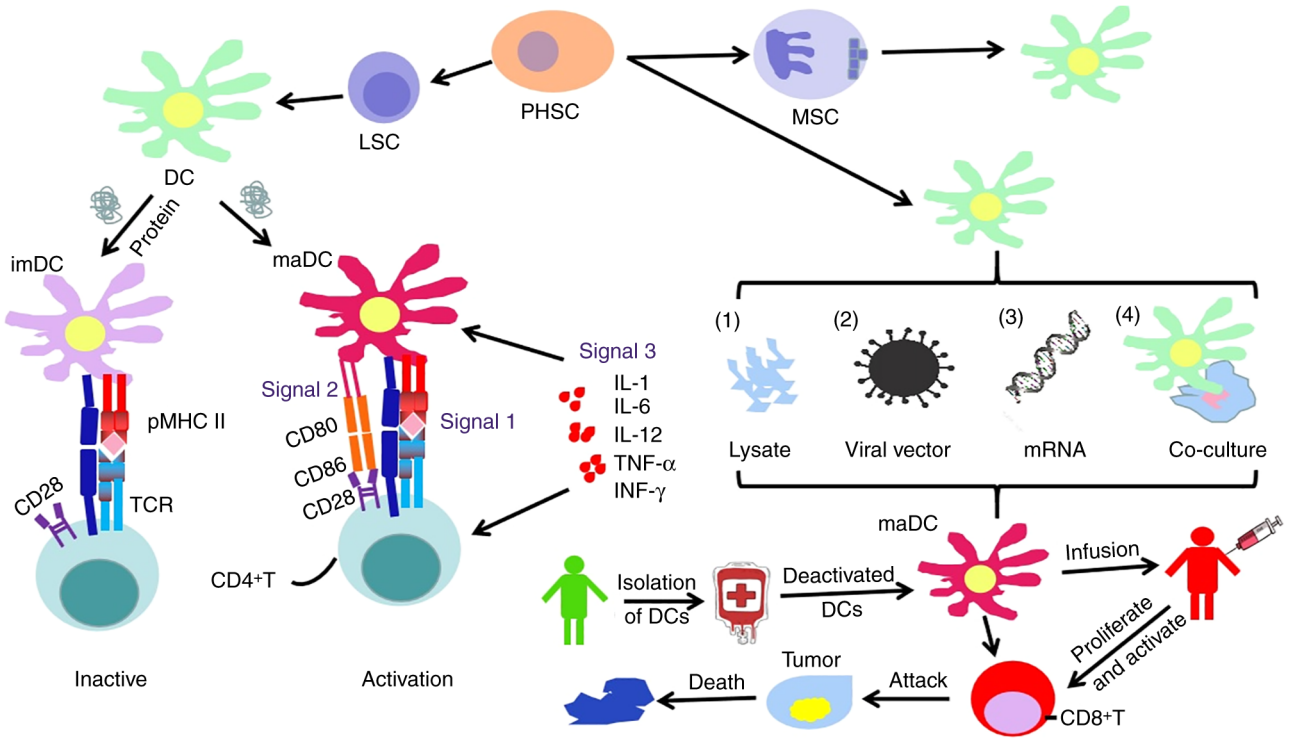

Figure 3. Basic principle and treatment using DC vaccine. DCs are derived from cells via direct differentiation of HSCs or differentiation of MSCs and LSCs. Usually, after phagocytizing antigen, DC cells become mature and directly transmit antigen signals to CD4+ T cells via signals 1 and 2 generated by molecules on the cell surface and receive signal 3. DC vaccines are prepared to treat tumors. Common operation methods include directly sensitizing DCs with tumor antigens and cell lysate; infecting DCs with viral vectors encoding the TAA gene to express corresponding antigens; mRNA expression of tumor antigens after DC infection with corresponding antigens and fusion of tumor cells and DCs. Currently commonly used DCs are derived from peripheral blood circulation. After *in vitro* intervention, DC cells are reinfused to activate T cells *in vivo* to treat tumors. DC, dendritic cell; HSC, hematopoietic stem cell; MSC, mesenchymal stem cell; LSC, lymphoid stem cells; TAA, tumor-associated antigen; PHSC, pluripotent hematopoietic stem cells; im, immature; ma, mature; pMHC, peptide-MH complex; TCR, T cell receptor.

and IL-2 have been approved by the US FDA for the treatment of certain types of malignancy, such as Melanoma, metastatic renal cell carcinoma (110,111). Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been approved for adjuvant therapy of malignant tumors due to its ability to stimulate proliferation and differentiation of immune cells (112). In addition, GM-CSF promotes antigen presentation by DCs, making it widely used in tumor vaccines (113,114). Although the antitumor activity of cytokines has been observed in many studies (115-117), few cytokines induce complete tumor regression. To the best of our knowledge, the mechanism of action of immune-stimulating cytokines has not been fully explored and some tumor treatment modalities in the clinic may promote cytokine cascades with unexplained potentially lethal effects (118). Radiotherapy and chemotherapy trigger a cytokine storm in the tumor stroma, including release of the pro-tumor cytokines IL-6 and TNFα. Apoptotic tumor cells activate macrophages to produce pro-inflammatory mediators and cellular debris can also stimulate anti-tumor immunity; therefore, dead and dying tumor cells contribute to a TME that may promote tumor progression (119,120). The anti-tumor function of cytokines is complex, and studies have shown that their anti-tumor activity depends on the host immune system (121-123). Cytokines are functionally divided into pro- and anti-inflammatory. Pro-inflammatory cytokines (such as IL-1α/β, TNF-α/β, IL-6, IL-11, IL-18 and IFN-γ) upregulate inflammatory responses and enhance recruitment, infiltration and resistance of immune cells to tumor site (124-126). Anti-inflammatory cytokines (such as IL-10, IL-6, TGF-β, IL-27 and IL-35) downregulate inflammatory responses and promote tissue healing and tumor growth (127,128). Cytokine-induced inflammatory responses are context-dependent; the same cytokines induce pro-inflammatory or anti-inflammatory responses depending on factors such as target cells, dose, and presence of other cytokines (129). Cytokine classification in tumor therapy stems from the association between cytokines and T cell responses. T cells differentiate into cell populations with different functions, characterized by production of certain cytokine groups. Th1 cells produce type 1 cytokines such as IL-2, IL-12 and IFN-γ; Th2 cells produce type 2 cytokines, such as IL-4, IL-5, IL-6, IL-10 and IL-13; regulatory T cells produce IL-10 and TGF-β (130). In general, type 1 cytokines mediate the development of strong cellular immune responses, while type 2 cytokines facilitate strong humoral immune responses (131). Tumors are often associated with a tolerant and immunosuppressive microenvironment. Cytokine-mediated therapy uses type 1 cytokines to stimulate anticancer immune responses (132). Vaccine-based therapies use type 2 cytokines as adjuvants based on their role in B cell maturation, while autoimmune diseases may benefit from regulatory cytokines (133). In many cases, these distinctions are not sufficient to classify cytokines because their effects on the immune system are complex. For example, IL-18 can promote Th2-biased cytokine production by T cells but in the presence of IL-15 or IL-12, IL-18, leads to potent Th1-biased cytokine

production (134). Furthermore, type 1 cytokines are not limited to cellular immune responses, as they contribute to the development of certain antibody classes and functional differentiation of B cells (135).

Cytokine storm involves a variety of cytokines such as TNF-α, IL-1, IL-6, IL-12, IFN-α, IFN-β, IFN-γ, monocyte chemotactic protein 1 and IL-2 (136). The phenomenon of rapid and massive production of IL-8 is an important cause of acute respiratory distress syndrome and multiple organ failure (137). Injected CAR T cells to treat $CD19^+$ lymphoma induce a cytokine storm, with levels of IFN-γ and IL-6 exceeding physiological levels, due to high levels of activated CAR T cells (138). The cytokines that mediate the cytokine storm are achieved not by CAR T cells but by macrophages, and their damage to the body can be mitigated by the use of IL-6 and IL-1 drugs (139). Glucocorticoids and IL-6 inhibitors are also effective in treating this type of cytokine storm (140). To the best of our knowledge, no cases of cytokine storm or elevated IL-6 levels have been reported in NK cell CAR therapy.

In conclusion, cytokines are potent but complex immune mediators. Developing cytokine drugs is a challenge that requires a deep understanding of cytokine biology and contemporary biotechnology to exploit their antitumor activity, while minimizing toxicity. In future, how to confine the action of cytokines to the desired site to avoid systemic pro-inflammatory effects and how to incorporate these treatments into combination immunotherapy strategies should be investigated.

5. Future immunotherapy

Oncolytic viruses refer to non-pathogenic viruses that specifically infect tumor cells and cause their death. Oncolytic viruses are an emerging class of antitumor immunotherapy (141). The effectiveness of oncolytic viruses depends on sufficient numbers of oncolytic virus to infect tumor cells. Because oncolytic viruses have intrinsic anticancer activity, they are considered passive immunotherapy (142). Although not fully understood, it is hypothesized that oncolytic viruses mediate anti-tumor activity through two distinct mechanisms of action: Selectively replicating within tumor cells, resulting in direct lytic effects or inducing systemic antitumor immune response (143). Specifically, oncolytic virus therapy relies on tumor cell-specific changes associated with tumor characteristics, including increased receptor expression, impaired antiviral response and alterations in cellular metabolism; it is hypothesized that oncolytic virus replication is limited to the tumor site and healthy tissue is not harmed (144). In addition to directly lysing tumors, oncolytic viruses induce extracellular matrix remodeling, thus exerting anti-angiogenic effects (145). In the anti-tumor immune response, tumor cells release cytoplasmic components such as intracellular tumor-associated antigens, damage and pathogen-associated molecules after death to stimulate the body's innate immunity, and a large number of cytokines and chemokines are produced to promote subsequent specific immunity of the tumor. Mediate the maturation of APC and enhance its antigen presentation ability, promote the initiation, activation, proliferation, transport, memory formation, cytokine release and cytotoxic activity of polyclonal T cells, and generate systemic anti-tumor immune response (146). Various oncolytic viruses have been used to treat different forms of cancer, including adenoviruses, poxviruses, rhabdoviruses, herpes viruses, paramyxovirus (PV) and reoviruses. Due to the difference in innate immune response to virus, anti-tumor mechanisms differ. Herpes viruses are DNA viruses capable of establishing lytic and latent infection in the host; the utility of herpes simplex virus 1 (HSV-1) as an oncolytic agent has been the most widely explored. Using gene editing method to make HSV-1 express GM-CSF can promote the recruitment of T cells to the tumor site and enhance the anti-tumor effect (147). PVs are members of the Paramyxoviridae family of disease-causing viruses in humans and animals. PV is a strong inducer of IFN and other immunostimulatory cytokines that activate various immune factors to mount excellent antitumor innate and adaptive immune responses (148). Mumps virus, which has been proven to have cytopathic effects, causes infected cells to secrete various cytokines and IFN pathway-associated genes or receptors to achieve anti-tumor effects (149).

The first FDA- and European Medicines Agency-approved oncolytic virus, talimogene laherparepvec (T-VEC), is a modified HSV virus for the treatment of malignant melanoma that encodes GM-CSF to enhance antitumor immune responses (150). A recombinant adenovirus (Oncorine®) was approved by Chinese regulators as early as November 2005 for the treatment of HNC (in combination with chemotherapy) and a number of oncolytic viruses are in clinical development (151,152). The multifunctional properties of oncolytic viruses in tumor therapy make them highly synergistic when used in combination with other drugs (153). Currently, a large body of evidence suggests that oncolytic virus therapy induces tumor cell death by enhancing the antigenicity of tumor cells or their susceptibility to immune cells when used in combination with radiotherapy, chemotherapy and other immunotherapies (154,155). Many naturally occurring viruses, such as parvovirus, measles virus, reovirus and Newcastle disease virus, exhibit a natural preference for cancer cells (156). However, other viruses such as adenovirus, vesicular stomatitis and vaccinia virus and HSV need to be engineered to be cancer specific (Table I). Four approaches are commonly used to design oncolytic viruses to selectively target tumor cells. The first is use of virus-specific receptor-mediated cellular targeting, such as EGFR and HER-2 (157). The second approach exploits the rapidly dividing nature of tumor cells to increase the efficiency of viral replication compared with normal cells. For example, mutations in tumor drivers or other enzymes such as protein kinase R increase viral replication in tumor cells (158). Numerous types of tumor cell exhibit a lack of normal antiviral IFN or TNF responses that promote selective viral replication (159). The fourth is that normal cells respond to viral infection by inducing apoptosis or inhibiting translation, transcription and/or transduction targeting to prevent cell lysis, which may limit viral spread (160).

The immune response to oncolytic viruses is an important part of the antitumor effect, but it can be a double-edged sword. On the one hand, viruses promote immune responses against tumor cells by increasing tumor antigen presentation via viral infection. On the other hand, neutralizing antiviral responses may prevent viral replication and persistent infection of tumor cells (161). Therapeutic outcomes depend on the complex interplay between these opposing forces, and local injection of the tumor can be used to observe the therapeutic

Table I. Drugs used in oncolytic virus anti-tumor clinical trials.

Virus type	Product	Method of administration	Cancer type	Approved
Adenovirus	Onyx-015	Intratumoral	Head and neck, pancreatic, ovarian, colorectal, glioma, lung and liver metastasis	Yes
	H101	Intratumoral	Squamous cell carcinoma, head and neck cancer	Yes
	DNX-2401	Intratumoral	Glioblastoma, ovarian	No
	VCN-01	Intratumoral	Pancreatic	No
	Colo-Ad1	Intratumoral	Colon, non-small cell lung, renal, bladder, ovarian	No
	ProstAtak	Intratumoral	Pancreatic, lung, breast, mesothelioma, prostate	No
	Oncos-102	Intratumoral	Solid tumor	No
	CG0070	Intratumoral	Bladder	No
	ICOVIR5	Intravenous	Melanoma, solid tumor	Yes
	Ad5-yCD/ mutTKSR39-rephIL12	Intratumoral	Prostate, pancreatic	No
	Ads/HSV-tk	Intratumoral	Triple-negative breast, non-small cell lung	No
	LOAd703	Intratumoral	Malignant melanoma	No
	Tasadenoturev	Intratumoral	Recurrent glioma	No
Vaccinia	Pexa-vac (JX-594)	Intratumoral, intravenous	Melanoma, liver, colorectal, breast, hepatocellular carcinoma	No
	GL-ONC1	Intraperitoneal, intratumoral, intravenous	Lung, head and neck, mesothelioma	No
Herpes	T-VEC	Intratumoral	Melanoma, head and neck, pancreatic	Yes
	G207	Intratumoral	Glioblastoma	Yes
	HF10	Intratumoral	Breast, melanoma, pancreatic	Yes
	HSV1716	Intratumoral	Hepatocellular carcinoma, glioblastoma, mesothelioma, neuroblastoma	Yes
	OrienX010	Intravenous	Glioblastoma	Yes
Reovirus	Reolysin	Intravenous, intratumoral	Glioma, sarcoma, colorectal, non-small cell lung, ovarian, melanoma, pancreatic, multiple myeloma, head and neck	Yes
Seneca Valley	SVV-001	Intratumoral	Neuroendocrine-featured tumor, neuroblastoma, lung	Yes
Coxsackievirus	Cavatak (CVA21)	Intratumoral	Melanoma, breast, prostate	Yes
Newcastle disease	PV701	Intravenous	Squamous cell carcinoma of the larynx, salivary gland	No
	NDV-HUJ	Intravenous	Glioblastoma, sarcoma, neuroblastoma	No
Vesicular stomatitis	VSV-hIFNβ	Intratumoral	Head and neck squamous cell carcinoma, non-small cell lung, hepatocellular carcinoma	No
Measles	MV-NIS	Intraperitoneal, intratumoral	Myeloma, ovarian, mesothelioma, non-small cell lung	No
	MV-CEA	Intraperitoneal, Intratumoral	Glioblastoma, ovarian, fallopian tube endometrioid adenocarcinoma	No

response. To balance this response of the immune system, methods to optimize current oncolytic viruses or develop novel viruses to enhance the stimulation of the host immune response to tumor cells without triggering rapid clearance of oncolytic viruses (for example, deletion of Herpes simplex virus protein ICP34.5 and ICP47 in T-VEC) have been investigated (162). In addition, genes for cytokines or chemokines can be integrated into the genome to enhance the therapeutic effect of oncolytic viruses. GM-CSF, an immune-associated cytokine, can increase APC activation and trigger systemic antitumor immune responses, which increases oncolytic virus efficacy (163). TAAs, immune-associated ligands, or bispecific T-cell engager antibodies can also be used to modify oncolytic viruses (164).

In addition, it is difficult for some viruses to obtain extremely high titer products required for clinical doses, which limits large-scale production of oncolytic viruses due to the high cost of current technologies (165). The host immune barrier and antiviral response can inhibit viral replication and lead to resistance to oncolytic viruses, such as macrophages, which directly capture viruses in organs such as the liver, thereby decreasing viral titers in the body and affecting oncolysis (166). The most common adverse reactions to oncolytic viruses are fever and local injection site reactions but can also include chills, nausea and vomiting, flu-like symptoms, fatigue and pain (167).

In conclusion, although oncolytic viruses have potential, there are some obstacles to their production and application. Current molecular biotechnology strategies enhance the targeting and killing effects of oncolytic viruses, but further research is needed to develop tumor treatments with higher efficacy and lower adverse reaction rates. The production technology of oncolytic virus is imperfect, and there is no uniform standard for industrial production quality and inspection, which is an obstacle to its application.

A recent strategy is to make tumors express ABO blood group antigens and using a mechanism similar to that caused by blood group incompatibility to activate the immune system to kill tumor cells (168). This differs from passive immunotherapy as it does not activate the immune response systemically; it also removes the need to identify tumor-associated antigens as it does not require the body to produce specific anti-tumor CTL cells. Different from the mechanism of oncolytic viruses, the virus does not directly lyse cells but serves as a carrier to express blood group antigens on the tumor cell membrane and is recognized and activated by naturally occurring blood group antibodies. The complement response produces cytolysis, which demonstrates the key anti-tumor role of the innate immune system (169). Although studies have detected loss of blood group antigen expression in primary breast tumors and their metastases, loss of blood group antigen expression may be considered a marker of invasion and half of proximal colon tumors show loss of antigen expression (170-172). However, this does not simply activate the immune system by allowing the tumor to express blood group antigens. If a tumor expresses an antigen, there will be an antibody that can bind to it naturally in the body, and it will react with the antigen and antibody, and then activate the immune system to produce cell lysis. There are similar antigens that can treat tumors, such as the Rhesus blood group antigen. Expressing the corresponding antigens on tumor cells of patients with autoimmune diseases is also a strategy for treating tumors (173). The advantages of adopting such a strategy to treat tumors include lack of tumor resistance to treatment; the lentiviral vector itself has little immunogenicity and is not easily cleared by the body. Theoretically, as long as the tumor tissue expresses an antigen that can be recognized by the body's immune system, tumor cells can be directly recognized by the immune system and produce a lytic reaction. With the development of molecular biology, vector viruses can be used to make tumor cells express any protein. Therefore, this treatment method can solve the problem of tumor drug resistance. Intratumoral drug injection therapy is safer than systemic medication and can avoid the failure of body organs caused by the storm of inflammatory factors caused by systemic medication. Simple intratumoral injections decrease the risk and pain associated with surgery and chemotherapy; the procedure is simple and can be performed by doctors in the primary hospital. Although the local administration method is safer compared with systemic administration, the optimal injection dose still needs to be determined to ensure adequate dispersion of drug in the tumor tissue and minimize the leakage from the tumor tissue. As a novel tumor treatment strategy, further research is required to develop use of naturally occurring antigen-antibody immune response to treat tumors.

6. Conclusion

In the past decades, anti-cancer immunotherapy has changed from a promising treatment method to a reality of clinical treatment. Many immunotherapy programs that can be used for patients with cancer have now been approved by the US FDA and European Medicines Agency and many other treatment programs are being studied as independent therapeutic interventions or in combination with clinical routine treatment (174,175). Treatment strategies are no longer based solely on interfering with metabolism of tumor cells or whether it is a purely clonal proliferative disease. A number of studies has shown that the survival of tumor cells depends to a large extent on the surrounding environment, which contains abundant and heterogeneous untransformed components, including stroma and endothelial and immune cells (176-178).

Immunotherapy has become a clinical reality, and an increasing number of patients with cancer will receive immunotherapy at some stage. The treatment of tumors by interfering with immune checkpoints has become an important and effective form of immunotherapy. Drugs targeting CTLA-4, PD-1 and PD-L1 are the most widely studied (179). Numerous studies have also shown that what was previously classified as passive immunotherapy, including several tumor-targeting monoclonal antibodies, adoptive T cell transfer, and oncolytic viruses, may constitute a potent active form of immunotherapy (115,180,181). Drugs such as immunosuppressive metabolic inhibitors and PRR agonists have attracted interest not only as adjuvants to conventional vaccines, but also as therapeutic measures that may mediate the antitumor effect or enhance the therapeutic effects of other anticancer drugs (182).

In 2013, the clinical success of immunotherapy was named 'Breakthrough of the Year' by *Science* (183). Clinical research is also focused on whether immunotherapy can be used as a stand-alone treatment or in combination with other antitumor drugs to improve the efficacy and safety in patients with cancer.

One of the key challenges in developing cancer vaccines is to identify specific tumor antigens for use as immunotherapeutic targets. Good target antigens should exhibit high antigenicity and homologous expression in tumor tissue to overcome problems caused by tumor heterogeneity. Tumor cells can undergo antigen modulation, which means that the immune system attacks tumor cells, resulting in reduction or loss of tumor antigen epitopes on the surface, thereby escaping recognition and killing by the immune system (32,184). Studies have also confirmed that tumor cells exhibit characteristics of stem cells and may actively decrease expression of antigens (185-187). The development of therapeutic oncolytic viruses is faced with challenges regarding how to formulate a reasonable clinical trial design, dosing regimen, pharmacodynamic analysis and

biosafety issues (188). Immunocompromised patients may not be candidates for oncolytic virus therapy because oncolytic virus-mediated antitumor immunity may be compromised in these patients (189). The treatment of tumors with blood group antigens is different from that of oncolytic viruses; it actively allows tumors to express naturally occurring antigens in the body to activate the natural immune response and treat tumors (190). Further studies are required to determine clinical feasibility.

In summary, tumor immunotherapy may enhance the direct killing effect of CTLs on tumors and weaken the immunosuppressive TME.

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Authors' contributions

FZ, DS and LW performed the literature review and wrote the manuscript. MS, HY, XZ, LC and ZH wrote the manuscript. LL and LW conceived, reviewed and revised the article. All authors revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

LW is the corresponding author of ABO blood group antigen therapy: A potential new strategy against solid tumors. The other authors declare that they have no competing interests.

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