DC-T cell axis is an effective target for treating non-small cell lung cancer

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Abstract

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Abstract: The DC-T cell axis is a bridge connecting innate immunity and adaptive immunity. The initial immune response against tumors is mainly induced by mature antigen-presenting dendritic cells (DC). Enhancing the crosstalk between DC and T cells could improve the immune response to non-small cell lung cancer. This article reviews the interaction between DC-T cells in the treatment of non-small cell lung cancer and how this interaction impacts the treatment outcome.

Keywords: non-small cell lung cancer; dendritic cells; T cells; Artificial DC; Chimeric Antigen Receptor T-Cell Immunotherapy.

Preface:

Lung cancer is a common cause of cancer-related death worldwide[1-4], and the incidence and mortality rate of lung cancer are projected to rise in the next few decades. Therefore, lung cancer remains a public health concern [5]. Histopathologically, lung cancer is broadly classified into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The NSCLC accounts for about 85% of lung cancer cases, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the main histological subtypes. NSCLC is the most common histologic type, with a 5-year overall survival rate (OS) of approximately 15%[6-8]. Therefore, it is particularly important to identify more critical factors influencing efficacy of NSCLC treatment.

Recently, immunotherapy based on immune checkpoint inhibitors (ICIs) alone or in combination with chemotherapy has greatly improved cancer treatment outcomes. However, only a few patients (15%) respond to ICIs, which has generated considerable urgency in identifying immune factors affecting its efficacy [9-11].

Recent advances in understanding tumor immunity have led to the rapid development of cell-based immunotherapy strategies targeting antigen-presenting cells (APC), T cells, and tumor cells. Among them, the DC-T cell axis has been the focus of recent aims for developing anticancer therapies. DC can mediate the initiation of adaptive immune responses of T cells and directly kill tumor cells[12-13]. The DC-T cell axis is a bridge connecting innate immunity and adaptive immunity, playing a pivotal role in the development of specific immunity. Therefore, focusing on the DC-T cell axis provides a comprehensive understanding of the interaction of DC and T cell in the treatment of NSCLC. Additionally, the work explores new therapeutic opportunities to overcome the immune tolerance of NSCLC and improve the prognosis of NSCLC patients.

1. Crosstalk between DC and T cells

1.1 T cells are the key to the occurrence and development of tumor immune response

T cells derived from lymphoid stem cells in bone marrow and undergo differentiation and maturation in the thymus, and then distributed to immune organs and tissues throughout the body through lymphatic and blood circulation. T cells mediate cellular immunity and coordinate the whole immune response [14-15]. $CD4^+$ or $CD8^+$ T cells are the two most important types of T cells [16-17] studied in the development of adaptive immunity. The most important feature of adaptive immunity is characterized by specificity via stimulation of specific antigens from tumor or pathogens. The $CD4^+$naive T cells ($CD4^+$ Tn) can develop and differentiate into $CD4^+$ T cells under stimulation by antigens presented by DCs. Of them, Th1, Th2, Th17, and regulatory T cells (Treg) have been extensively studied [18-20]. Th1 mainly secretes IL-2, IL-12, IFN- γ, and TNF- α, promoting the proliferation of Th1, and plays critical roles in the cellular immunity. Furthermore, these cytokines inhibit the proliferation of Th2[21-22]. IFN- γ activates and enhances the phagocytotic property of macrophages and promotes the production of IgG[23-24]. IL-2, IFN- γ and IL-12 can enhance the killing ability of NK cells [25]. IL-2 and IFN- γ synergistically stimulate the proliferation and differentiation of cytotoxic T cells (CTL). On the other hand, TNF directly induces apoptosis of target cells and also promotes inflammatory response[26-27]. Th2 mainly secretes IL-4, IL-5, IL-6, IL-10, and IL-13, which promotes the proliferation of Th2 cells and participates in the activation of B cells. In addition, these cytokines induce humoral immunity and inhibit the proliferation of Th1[28-30]. Th17 induces innate immunity and inflammation by secretion of IL-17 (IL-17A to IL-17F), IL-21, IL-22, IL-26, TNF-α, and

other cytokines. Moreover, Th17 induces the occurrence and development of immunepathological damage, especially autoimmune diseases [31-33]. Treg cells exert the immunosuppression by inhibiting the activation and proliferation of $CD4^+$ and $CD8^+$ T cells and function of DC[34], negatively regulating the immune response. The act is performed mainly in two ways: Inhibiting the ability of the APC to activate the T cells mainly through the molecules CTLA-4, LAG-3 on the surface of Treg to interact with the CD80, CD86, and MHC on the DC surface, respectively; Suppressing effector T cells by secreting TGF-β、IL-10 and IL-35[34]. Generally,cytokines secreted by $CD4^+$ T cells regulate the function of immune cells,monitor the development, differentiation, and function of other immune cells such as $CD8^+$ T cells, B cells, NK cells, DC. Therefore, $CD4^+$ T cells play a key and central role in the immune system. Naïve $CD8^+$ T cells ($CD8^+$ Tn) can develop and differentiate into $CD8^+$ T cells upon stimulation by antigens presented by DC. Consequently, $CD8^+$ T cells can differentiate into CTL that kill pathogen-infected cells and tumor cells through cytolytic molecules, such as perforin and granzyme, and are essential for a cell-mediated antitumor immune response[35-37]. Alternatively, CTLs induce tumor cell apoptosis by promoting the binding of FasL to Fas on the surface of tumor cells [38-39] (Fig. 1).

1.2 DC is the initial factor inducing adaptive tumor immunity

DCs were first reported in skin by Langerhans in 1868. Steinman and Cohn later described DC in peripheral lymphoid organs in 1973. DCs form an essential link between innate immunity and adaptive immunity. More importantly, DCs induce the occurrence of adaptive immunity[40].

DC represents a complex heterogeneous population of antigen-presenting cell with significant phenotypic heterogeneity and functional plasticity. DCs can be divided into two main subpopulations: conventional DC (cDC) and plasmacytoid DC (pDC). DCs are derived from bone marrow and migrate through blood circulation to lymphoid tissues such as lymph nodes and spleen and non-lymphoid tissues such as skin, lung, and intestine [41]. cDCs are further subdivided into type 1 cDC and type 2 cDC [42-43]. cDC1 can cross-present antigens and trigger an antitumor immune response and, thus, often referred to as cross-presenting DCs. cDC1 presents tumor antigen to $CD8^+$ Tn cells via the MHCI, activating the initial immune response [44-45]. After activating $CD8^+$ Tn, $CD8^+$ Tn gradually develop and differentiate into immune memory cells, such as Tscm, Tcm, Tem, and Tte, inducing the occurrence of recall response by re-stimulation of past antigen encounters. The quick responses to the secondary stimulation of antigen form a large number of specific immune cells in a short time and effectively kill tumor cells[46-47]. It is worth noting that among several antigen-presenting cells, only DC can stimulate the initial immune response and induce Tn to produce an immune response targeting "new" antigens. It is speculated that the damage of DC is closely related to refractory tumors. cDC1 plays a key role in lung immunity[48]. On the other hand, cDC2 is a major DC subpopulation in different human tissues and organs. Besides, cDC2 presents tumor antigens to $CD4^+$ Tn cells via the MHCII and activates the initial immune response of $CD4^+$ Tn. Like $CD8^+$ Tn, after activation, $CD4^+$Tn also gradually develop and differentiate into immune memory cells such as Tscm, Tcm, Tem, and Tte, forming a memory immune response to coordinate the immune response and homeostasis[49]. In addition, pDC are key players in antiviral immunity. The pDCs can produce high levels of type I interferon (IFN), promoting innate and adaptive immunity[50] (Figure 1). The IFN is considered the key natural immune defense of the body against pathogen infection. Furthermore, IFN inhibits the proliferation of tumor cells and regulates immunity [51-52].

1.3 DC interacts with T cells at the immune synapse

The activation of T cells by DC is mainly through the interaction between DC and T cells, and the formation of immune synapses is the most important feature of this process. The immune synapse is a special structure formed at the cell-cell contact interface when APC and T cells interact [53-54]. In this process, DC provides three key signals.

The initial signal is generated when T cells recognize homologous peptide antigens presented on MHC I or MHC II on the surface of DC through their T cell receptor (TCR)[55-58]. MHC I molecules bind to $CD8^+$ Tn cells, and MHC II molecules bind to $CD4^+$ Tn cells to present specific antigens to the Tn [59].

MHC, antigen and TCR interaction triggers the activation of T cells, initiating downstream signasl via the immune receptor tyrosine-based activation motif (ITAM)[60]. Subsequently, in addition to the MHC-antigen-TCR complex, a second costimulatory signal is required to initiate and maintain T cell activation and proliferation. The second signal can be divided into costimulatory molecules and co inhibitory molecules according to different effects[61-62]. The key costimulatory molecules involved in T cell activation include CD28 (binding to CD80/86 on DC), ICOS (binding to icosl on DC), OX40 (binding to OX40L on DC), and CD40L (binding to CD40 on DC), all the key signaling molecules are responsible for T cell activation, differentiation, and survival. The costimulatory signals cooperate with MHC-antigen -TCR complexes to enhance T cell activation. For instance, the costimulatory molecule CD28 is an important signaling molecule that determines the quality and quantity of T cell immune response[63-64]. In addition, after CD28 activation, PI3K/Akt and other signals are induced to promote the proliferation and development of Tn. Consequently, Tn-Tscm-Tcm-Tem-Tte forms the initial immune response and memory immune response, enabling the body to respond to both the "old" antigens generated by tumor recurrence and the "new" antigens generated by tumor variation[65-66]. After CD28 activating, followed by activating PI3K/Akt [67], NF-κB[68] and other signaling pathway,Tn and Tm then complete their development, differentiation, and proliferation, forming effector T cells to kill tumors and other pathogens. Contrarily,T lymphocyte-associated protein 4 (CTLA-4) competes with CD28 for binding to CD80/86 on DC while PD-1 binds to programmed cell death ligand 1 (PD-L1) on the surface of DC, inhibiting the activation signals[69-70]. Positive and negative costimulatory molecules interact to effectively start, moderately effect, and timely terminate the immune response[71]. The third signal in the form of cytokines secreted by DC is triggered once T cells receive MHC antigen TCR complex signals and sufficient costimulation[72-73]. Combined with T cells, DC can secrete plenty of IL-12 and IL-18. In addition, DCs are dominant partners of T cells and necessary for activating the proliferation of T cells, inducing CTL production, dominating priming of Th1 type immune response, and facilitating tumor clearance [74-76].

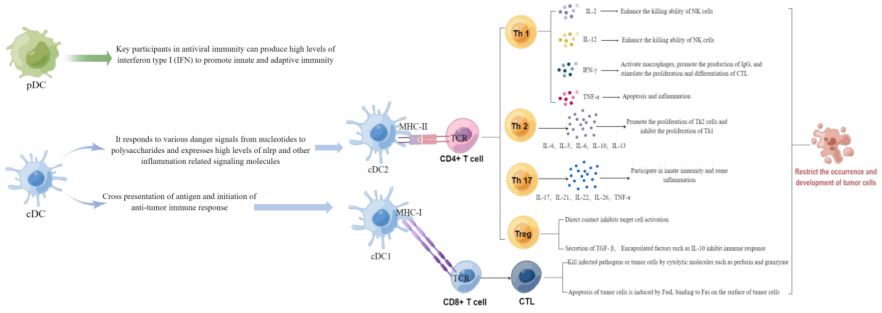

Fig 1: The schema chart of a complex interaction between DC, T cells, and tumor cells

Note: DC promotes immunity by presenting antigens to T cells and providing immunomodulatory signals through cell-cell contact and cytokines. DC can recognize, ingest and process tumor antigens. After processing and presentation, antigens are presented to $CD4^+$ T cells or $CD8^+$ T cells via MHC class I or class II molecules on the surface of DC, initiating T cell activation. Mature DC highly expresses costimulatory molecules such as CD80, CD86, and CD40, providing a second signal for the full activation of T cells. DCs secrete several cytokines, including IL-2/IL-12/IFN-γ, which further induce the proliferation and differentiation of activated T cells to complete the initiation of the immune response. Unlike activating memory T cells, the activation of naive T cells is more dependent on the presence of DC stimulation signals. Therefore, DC is the most potent mature APC, unique in its ability to prime naive T cells.

2. Function of DC and T cells in NSCLC

2.1T cells affect prognosis and efficacy of immunotherapy in NSCLC patients

The number of circulating lymphocytes, including the proportion of and the absolute number of lymphocytes, is an important indicator of the efficacy of the body's immune function and the degree of stress[77]. Interaction

and influence each other exist between the various cells in the immune system,the appropriate ratio for immune cells in the body is an important guarantee for their function. Peterson et al explored the prognostic relevance of Treg cells in 64 patients with stage INSCLC and found that a higher proportion of Treg cells in the tumor significantly increased the risk of recurrence. Immunohistochemistry has detected Treg cells in 51% of NSCLC patients. Therefore, Treg cells can be identified as an important risk factor for postoperative recurrence of NSCLC [78]. In addition, Liu et al reported that a high $Foxp3^+$Treg/$CD8^+$ T cell ratio predicted poor response to platinum-based chemotherapy in advanced NSCLC. Given this apparent functional relevance of Treg cells in NSCLC, targeting Treg cells might be an interesting approach for immunotherapy of lung cancer[79].

Clinically, the absolute number of lymphocytes is much more important than the proportion. Tumors can significantly inhibit the proliferation of bone marrow cells during the developmental period, significantly decreasing the absolute number of various immune cells, including lymphocytes [80-81]. At the same time, one of the main consequences of chemotherapy and radiotherapy is damaging the bone marrow[82]. As a result, it decreases the absolute number of lymphocytes that is closely related to the prognosis and efficacy of immunotherapy[83-84]. Numerous studies have shown that low lymphocyte absolute count (ALC) is an independent negative prognostic factor for advanced malignant tumors[85]. Oh et al found that the baseline absolute lymphocyte count level is an independent prognostic factor of rectal adenocarcinoma patients receiving preoperative radiotherapy and chemotherapy in different treatment periods and follow-up periods. In one study, the absolute lymphocyte count decreased after preoperative radiotherapy and chemotherapy, reaching the lowest level at 1 month but gradually increased after the end of radiotherapy and chemotherapy[86]. Furthermore, Xia Ying et al. found that the absolute numbers but not the relative numbers of lymphocyte subsets $CD3^+$, $CD4^+$, $CD8^+$, B, and NK cells were significantly damaged in NSCLC patients,and were closely related to the disease progression and progression-free survival period. And they were served as biomarkers for disease prognosis and efficacy. The work indicated that only paying attention to the proportion of lymphocyte subsets in clinic is easy to lead to clinical misjudgment [87].

T cells can also effectively reduce NSCLC by increasing their activity. IFN- γ promotes the activity of T cells by inducing the presentation of antigen-presenting cells (APCs) and upregulating the expression of MHC I / peptide complex on APCs to reactivate and induce the proliferation of antigen-specific $CD8^+$ T cells. The activated tumor antigen-specific $CD8^+$ T cells can recognize and secrete cytotoxic molecules to kill tumor cells[88]. Wu et al showed that Fuzheng anticancer formula effectively enhances the secretion of IFN- γ by $CD8^+$ T cells, which is critical in clearing tumor cells[89] . CTLA-4 and PD-L/PD-lL are the most studied checkpoint pathways, and they inhibit T cell activity in different ways[90-91] . CTLA-4 regulates T cell proliferation early in immune response[92] , whereas PD-1 suppresses T cells later in immune response[93] . The immune checkpoint inhibitors including ipilimumab and tremelimumab (CTLA-4 monoclonal antibody), nivolumab and pembrolizumab (PD-1 monoclonal antibody), atezolizumab and durvalumab (PD-L1 monoclonal antibody) have opened a new era in the treatment of advanced NSCLC. Nivolumab and pembrolizumab have been approved by FDA and EMA for the second-line treatment of NSCLC[94-95] .

2.2 DC plays an important role in NSCLC

As a professional antigen-presenting cell, DC plays a vital role in NSCL prognosis[96]. The proportion of DCs positively correlates with the progression-free survival of NSCLC. The expression of certain genes, such as TOP2A and TLR3, is related to DC infiltration in NSCLC. Based on the recent findings related to gene expression characteristics and DC infiltration in NSCLC patients, effective strategies for patients with refractory cancer can be designed[97]. The plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDC) are the main DCs in NSCLC[98]. Zahran et al demonstrated the possible impact of pDC and mDC on the treatment outcome of NSCLC. Zahran et al reported that higher levels of pDCs in the peripheral blood of NSCLC patients were related to a good NSCLC prognosis, lower tumor stage and longer mean overall survival time (OS). However, mDCs are the opposite[99-100]. Bianchi et al. reported that the overall survival positively correlated with the proportion of TLR3-CD1-3^+ dendritic cells and the corresponding activation

of $CD8^+$T cells [101]. The maturation rate of DC is significantly lower in healthy individuals than in NSCLC patients. The main manifestations of poor tumor prognosis are as follows: lack of functional DCs in the lung tumor lesions; recruitment of pDC to the surrounding lung tumor tissues; Lung tumor-induced regulatory DC; underexpression of DC effector molecules in the lung tumors; secretion of immunosuppressive molecules by infiltrating DCs in the Lung cancer tissue [102].

3. Development trend of clinical immunotherapy based on DC and T cells

Currently, immune checkpoint inhibitors have been widely used in clinical cancer treatments and are an important treatment for advanced NSCLC. CAR-T has emerged as a genuine modality for treating blood tumors. However, their low efficacy in treating solid tumors limits their application. Although it has been reported, it is still in the exploratory stage [103-104]. In combination with the clinical application of immunotherapy and advances made in understanding immune cells, especially DC, the trend of next-generation immunotherapy is moving towards developing artificial DC and CAR-T that can be used to treat solid tumors. Both can override the limitation of low immunity in tumor patients.

3.1 Engineered DC is the latest treatment strategy for NSCLC

Artificial APCs (aAPCs), which can be readily prepared from "off-the-shelf" components, are promising alternatives to custom-made autologous APCs that can effectively stimulate antigen-specific T cells in vitro [105-106]. Several aAPCs for in vitro activation and expansion of antigen-specific T cells have been successfully developed [107]. For example, cell-based aAPCs have been studied in several different cell lines, including fly black stomach cells [108], NIH3T3 mouse fibroblasts [109], and K562 human erythroid leukemia cells [110]. These cells were generated using retroviral or lentiviral transduction to introduce molecules that provide TCR, costimulatory, and adhesion molecules necessary for synaptic formation. Given that these cells can be stored for a long time, they can be easily obtained from source companies and distributors[111]. Although cellular aAPCs can induce a high expansion rate of $CD8^+$ T cells, their performance of specific control on the expression level of T cell activation signals is limited. In addition, non-tumor antigens and other stimulatory or inhibitory molecules may be present in cellular aAPCs.

The cell-free aAPCs have been developed to better define the transmission of different signals and avoid the use of allogeneic cells[112]. Compared to cellular aAPCs, acellular aAPCs allow for more stringent control over the signals delivered and are attractive tools because of their relatively easy preparation through micro latex, polyethylene glycol, magnetic beads, and lipid-based vesicles [113]. In general, the aAPCs approach has focussed on the induction of $CD8^+$ CTLs through MHC I stimulation because these cells are capable of antigen-specific tumor cell lysis [114-115]. Other immune cells, such as $CD4^+$ T helper cells, mediate anticancer immune responses by activating CTLs. Artificial APCs comprising various sizes, shapes, surface ligand distribution, and ligand mobility have been developed, and these properties affect the level of T cell activation. Various cell-free aAPCs structures reflect different attempts to simulate different aspects of natural DC [112].

It has been shown that DCs usually exhibit poor maturity in the tumor microenvironment and are less effective in presenting tumor antigens[116]. Therefore, targeting delivery of antigens and adjuvants to cells in vivo is an important method for developing DC vaccines. Sun et al developed intelligent artificial DC cells (iDCs) comprising nanoparticles loaded with a photothermal agent (IR-797) and coated with mature DC cell membranes. The DC cell membrane on the surface of iDCs preserves the ability to present antigens and prime T cells. The iDCs injected into mice enter lymph nodes and stimulate T cell activation and proliferation. Cancer-specific T cells are activated in a TCR-dependent manner and kill tumor cells upon TCR binding of antigens presented via MHCs. Alternately, activated T cells secrete cytokines (TNF- α),reducing the expression of heat shock proteins (HSPs) in tumor cells, thus, enhancing the sensitivity of tumor cells to heat stress. Subsequently, mild photothermal treatment can kill the remaining tumor cells (42-45°C). At the same time, low temperature photoheat can also induce the death of immunogenic cells, thereby activating the body's own DC cells and restarting the tumor immune cycle. As a new precise antitumor nanosystem, iDCs combine the advantages of DC cell immunotherapy and photothermal therapy. Consequently, iDCs effectively

enhance the antitumor immune response of the body, improve the efficacy of tumor treatment, and provide a new strategy for immunosensitized low-temperature photothermal therapy[117]. Concurrently, Suarez et al developed an Artificial Immune Modulation nanoparticle (AIM-np) technology, a customizable "off-the-shelf" technology that can be used for synthesizing APCs to guide antigen-specific natural $CD8^+$ T cells. AIM-np provides a controlled method for antigen presentation and T cell costimulation by directly binding to antigen-specific T cells. This method uses proprietary nanoparticles combined with a proprietary manufacturing process to enrich and expand antigen-specific $CD8^+$ T-cell products with consistent purity, identity, and composition required for effective and durable anti-tumor response. AIM-np consists of superparamagnetic iron oxide nanoparticles as the main structure, which is decorated with two humanized signal proteins. HLA-A2-IgG4 hinge dimer molecules are conjugated with core nanoparticles to deliver signal 1 (antigen presentation). In addition, together with humanized anti-CD28 antibodies, the conjugated HLA-A2-IgG4 hinge dimer molecules deliver signal 2 (costimulation). Subsequently, AIM-np acts as a synthetic APC, directly engaging target T cells through naturally occurring signaling mechanisms. Signal 1 is transmitted by a peptide-loaded HLA class I dimerization fusion protein that presents antigenic peptides to cognate T cell receptors. On the other hand, signal 2 is delivered by monoclonal antibodies against CD28 receptors, which deliver costimulatory signals, also known as "danger signals", to induce antigen-specific T cell activation and proliferation [118].

The loss of cell surface functional "arms" during DC antigen presentation weakens the interaction between DCs and T cells, disrupting T cell induction [119]. Modification of DCs to enhance their antigen presentation is the most common strategy for T cell activation. "Engineering" or modifying the cell surfaces with synthetic ligands or receptors provides a novel strategy for regulating the interaction between different cell types[120-121]. Lectins are carbohydrate-binding proteins that play an important role in promoting intercellular recognition and adhesion due to their specificity and bond stability[122]. A recent study reported that mannose-modified tumor antigens greatly enhance the ability of DCs to recognize and bind antigens [123]. Therefore, researchers believe that DCs engineered with glycopolymers can specifically attach to T cells through carbohydrate lectin binding, enhancing the stability of DC-T cell binding while promoting T cell activation. Therefore, adding appropriate synthetic glycopolymers to the cell surface is a valuable and effective way to design and optimize cell vaccines [124].

3.2 Chimeric antigen receptor T cells (CAR-T) therapy is another new strategy for the treatment of NSCLC

CAR-T cells are genetically engineered T cells that express synthetic CAR vectors. On the basis of self proliferation, CAR-T cells specifically recognize and bind antigens (such as CD19) on tumor cells and specifically kill tumor cells[125-126]. Since 2017, Kymriah (CTL019) and Yescarta (KTE-C19) CAR-T therapies have successively been approved for use. Furthermore, CAR-T therapy has emerged as a novel treatment strategy with promising results against blood tumors [127].However, when the research further turned its attention to solid tumors, which account for 90% of all tumors, CAR-T therapy did not get satisfactory results. The particularity of solid tumors themselves and their microenvironment brought great challenges to CAR-T cell therapy[128].

Unlike CD19, tumor cells in solid tumors generally express multiple targets abnormally, and these abnormally expressed antigens are also expressed in normal tissues. For example, the current research targets for glioma include prostate-specific antigen (PSMA), carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2), epithelial cell adhesion molecule (EpCAM), and Mesothelin[129-130]. Cancer-associated fibroblasts (CAFs) are one of the most abundant and critical components in the tumor microenvironment [131], constituting the tumor stromal layer that releases certain inhibitory cytokines. Immunosuppressive cells such as Treg cells, bone marrow-derived suppressive cells, and M2 type macrophages secrete TGF-β, IL-10, and other cytokines to negatively regulate CAR-T cell immune response. In addition, solid tumor cells lose cytokine receptors and escape immune cell surveillance. CAR-T cells cannot effectively respond to chemotaxis secreted by tumor cells, which inhibits their homing ability. However, the high expression of immunosuppressive receptors in solid tumors inhibits the effective activation of CAR-T cells and lowers the

efficacy of CAR T-cell therapy [132-134].

As a new strategy for treating NSCLC, CAR-T therapy has made considerable breakthroughs and entered a rapid development stage[135-136]. Thus far, more CAR-T studies have focused primarily on NSCLC [137-138]. The most common target antigens of NSCLC include human epidermal growth factor receptor (EGFR), mesothelin, mucin 1 (MUC1), PD-L1[139], carcinoembryonic antigen (CEA)[140], and HER2 [141]. Studies have shown that T cells redirected to EphA2 by EphA2-specific CAR have effective antitumor activity against NSCLC in vitro and in vivo. Thus, these antigens are potentially novel targets for NSCLC treatment [142].

4. Conclusions and future prospects

Immunotherapy for NSCLC based on DC and T cells is still in the development stage, and it has been clinically proven to be effective against certain cancers. Recent studies have shown that the interaction between the DC and T cells is an emerging strategy for treating NSCLC. Determining the role of DC-T cell interaction in NSCLC not only helps to reveal the mechanism of NSCLC but also provides important clues for treating this cancer. At the same time, based on understanding the interaction between DC and T cells, engineered DC and CAR-T are of great potential for treating solid tumors.

AUTHORS' CONTRIBUTIONS

All authors contributed equally. Shuangcui Wang designed the review, prepared the figure, and wrote the manuscript. Guan Zhang and Qian Cui were involved in the conception and design of the study. Yanjie Yang and Dong Wang searched the literature.Aqing Liu and Ying Xia were involved in the conception and design of the study and revised the manuscript. Wentao Li,Jing Zhang and Yunhe Liu provided helpful comments. Jianchun Yu revised the manuscript. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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