

Modulation of the immune response by heterogeneous monocytes and dendritic cells in lung cancer

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Abstract

Different subpopulations of monocytes and dendritic cells (DCs) may have a key impact on the modulation of the immune response in malignancy. In this review, we summarize the monocyte and DCs heterogeneity and their function in the context of modulating the immune response in cancer. Subgroups of monocytes may play opposing roles in cancer, depending on the tumour growth and progression as well as the type of cancer. Monocytes can have pro-tumour and anti-tumour functions and can also differentiate into monocyte-derived DCs (moDCs). MoDCs have a similar antigen presentation ability as classical DCs, including cross-priming, a process by which DCs activate CD8 T-cells by cross-presenting exogenous antigens. DCs play a critical role in generating anti-tumour CD8 T-cell immunity. DCs have plastic characteristics and show distinct phenotypes depending on their mature state and depending on the influence of the tumour microenvironment. MoDCs and other DC subsets have been attracting increased interest owing to their possible beneficial effects in cancer immunotherapy. This review also highlights key strategies deploying specific DC subpopulations in combination with other therapies to enhance the anti-tumour response and summarizes the latest ongoing and completed clinical trials using DCs in lung cancer.

Key Words: Lung cancer; Dendritic cell; Monocyte; Tumour microenvironment; Cancer immunotherapy; Dendritic-cell vaccination

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Core Tip: Monocytes and dendritic cells (DCs) as heterogeneous subpopulations may play a key role in the modulation of the immune response in malignant tumours. Monocytes may have a pro- and anti-tumour function and may differentiate into monocyte-derived DC. DCs have the properties of antigen presenting cells. These cells show a different phenotype depending on their maturity and on the influence of the tumour microenvironment. The DCs are of growing interest for their possible beneficial effects in lung cancer immunotherapy. This review highlights specific DC subpopulations in the anti-tumour response and summarizes the latest ongoing DC clinical trials in lung cancer.

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INTRODUCTION

Lung cancer is responsible for approximately 1.8 million deaths annually worldwide and is now one of the most common cancers and the leading cause of cancer mortality [1,2]. The prognosis for lung cancer remains poor despite advances in treatment strategies including immunotherapy with immune check inhibitors (ICIs)[3,4]. Further investigation of tumour immunology and the different cells subpopulations influencing the anti-tumour immune response could enable the development of novel immunomodulatory strategies such as targeted monoclonal antibodies against specific cell receptors.

The results of research on lung cancer show that cells of the same type can have both pro-cancer and anti-cancer properties. Tumour heterogeneity drives a diverse and plastic spectrum of various subpopulations of non-cancer cells. In this review, we focus on assessing different subpopulations of monocytes and dendritic cells (DCs) that may have a key impact on the modulation of immune response in lung cancer.

The role of macrophages, mainly of tumour associated macrophages (TAM) is well recognized. However, the place of monocytes in the anticancer immune response is not fully understood. We previously presented the results of investigation of macrophages in the direct lung cancer milieu[5] and preliminary studies on monocytes maturation in lung cancer[6]. Monocytes have both pro-inflammatory and anti-inflammatory properties. A phenotype of monocytes can be divided into classical (pro-inflammatory) and non-classical (anti-inflammatory). Both monocyte subpopulations have been detected among the peripheral blood (PB) mononuclear cells and may differentiate into macrophages. Studies demonstrate that monocytes are capable of both inhibition and stimulation of tumour growth[7]. Previous research on monocytes shows that their function in different cancer microenvironments may vary[8,9].

DCs form another heterogeneous population with the most efficient function of antigen presenting cells (APCs)[10]. They take up antigens and pathogens, generate major histocompatibility complex (MHC) peptide complexes, migrate from antigen acquisition sites to secondary lymphoid organs and finally interact with T lymphocytes. DCs infiltrate a tumour, next they process it and then they present tumour-derived antigens to naïve T-cells. DCs play a critical role in priming anti-tumour T-cell immunity and thereby represent a possible therapeutic target for cancer immunotherapy[11].

Moreover, various cell types and factors within the tumour microenvironment (TME) can act on monocytes and DCs, control their differentiation, and affect their biology, function and longevity. The local TME can also influence the activation and the direction of maturation of monocytes and DCs. Specific local microenvironmental factors may influence the formation of monocytes and DCs with tolerogenic or immunosuppressive activity and conversely, specific subpopulations of these cells can stimulate and inhibit the anti-tumour response.

In this review, we summarize the ongoing investigations on monocyte and DCs heterogeneity and function in the context of modulation of the immune response in lung cancer and highlight key strategies using specific monocyte subpopulations and

DCs to improve cancer therapies.

We discuss the heterogeneity of monocytes, their relationship with DCs and the potential of monocyte-derived DCs (moDCs) in the design of vaccines against lung cancer.

HETEROGENEITY OF MONOCYTES

Monocytes are mononuclear immune cells that circulate in PB and direct to tissues at a steady state and at an increased rate during inflammation. Apart from their key role in supporting tissue homeostasis and promoting the immune response to pathogens monocytes take part as regulators of cancer development and progression[12]. As a heterogeneous population, monocytes play opposing roles in inhibiting and stimulating tumour growth and metastases. Monocytes are also precursors of TAM and DCs which are involved in shaping the TME[13]. Monocyte subpopulations perform functions that are involved in both pro- and anti-tumour immunity, including promoting angiogenesis, tumour mediators secretion, phagocytosis, remodelling of the extracellular matrix, influencing lymphocytes, and differentiating into TAM and DCs [14]. Human monocytes express the MHC-II receptor Human Leukocyte Antigen-DR isotype (HLA-DR), integrin α M (CD11b) and CD86. Recent studies demonstrate that monocytes can be divided into three subsets based on the specific surface markers[15, 16]. They develop from the lineage-associated bone marrow (BM) precursor, a common monocyte progenitor (cMoP)[17]. cMoPs are monocyte progenitors that express stem cell marker CD117, C-type lectin CLEC12A, CD64 and CD135, a cytokine receptor and an early hematopoietic marker. cMoP may differentiate into classical monocytes and then convert to non-classical monocytes in the blood, with intermediate monocytes at a transition state[18,19].

These cells perform specific functions: Classical (approximately 85%), intermediate (approximately 5%) and non-classical (approximately 10% of the monocyte population), which are characterized by the degree of CD14 and the expression of CD16[20,21]. There are three types of monocytes in PB: Classical monocytes with high the expression of CD14 cell surface receptor and no CD16 expression (CD14⁺⁺ CD16⁻), non-classical monocytes with the low/negative level of CD14 expression and the co-expression of CD16 receptor (CD14⁻ CD16⁺⁺) and intermediate monocytes with the expression of CD14 and the expression of CD16 (CD14⁺ CD16⁺)[22,23]. The majority of non-classical monocytes appears to be derived from classical monocytes. However, the current studies show that there may be a limited progenitor lineage capable of differentiating into non-classical monocytes without classical monocyte origin[19,24, 25]. After differentiation, classical monocytes exit the BM using C-C chemokine receptor type 2 (CCR2) and next migrate into tissues and lymph nodes by I-selectin (CD62L)[26,27]. Monocyte maturation and a scheme of monocyte subpopulations are presented in **Figure 1**. Classical monocytes and nonclassical monocytes have a different half-life in the circulation: For classical monocytes it is less than 1 d and for nonclassical monocytes it is 7 d[28]. The mechanisms involved in the recruitment of tissue-specific monocytes remain unclear, possibly they depend on the environmental and tissue availability during both homeostasis and inflammation. However, it is known that classical monocytes are more quickly targeted at the site of inflammation and are able to attract other immune cells by secreting cytokines[26,29]. Non-classical monocytes remain in a state of homeostasis mainly in the vascular system and are likely to be able to exit vessels at a slower rate than classical monocytes during inflammation. They are likely to shift into alternative TAMs and exhibit anti-inflammatory properties[28,30].

Different subgroups of monocytes may play various roles in cancer, depending on the tumour growth and progression, differences in the type of cancer, and depending on the influence of TME[14]. Both classical and non-classical monocytes can have pro-tumour and anti-tumour functions. The protumoural phenotype properties consist of: Differentiation into pro-tumoural TAMs, metastatic cell seeding, the suppression of T-cell function, the recruitment of T regulatory cells (Tregs), the promotion of angiogenesis and contribution to extracellular matrix remodelling (ECM)[31,32]. Classical monocytes exit the vasculature to the primary tumour sites using CC-chemokine ligand 2 (CCL2). They produce carcinogenic mediators and are reprogrammed in the TME to limit their cytotoxicity[32]. Then, they differentiate into TAMs or moDCs in the tumour. TAMs are involved in promoting immunosuppression by inhibiting the activity of CD8 T-cells and in stimulating the formation of Tregs[33]. Moreover, they participate in remodelling of ECM and promote angiogenesis[34].

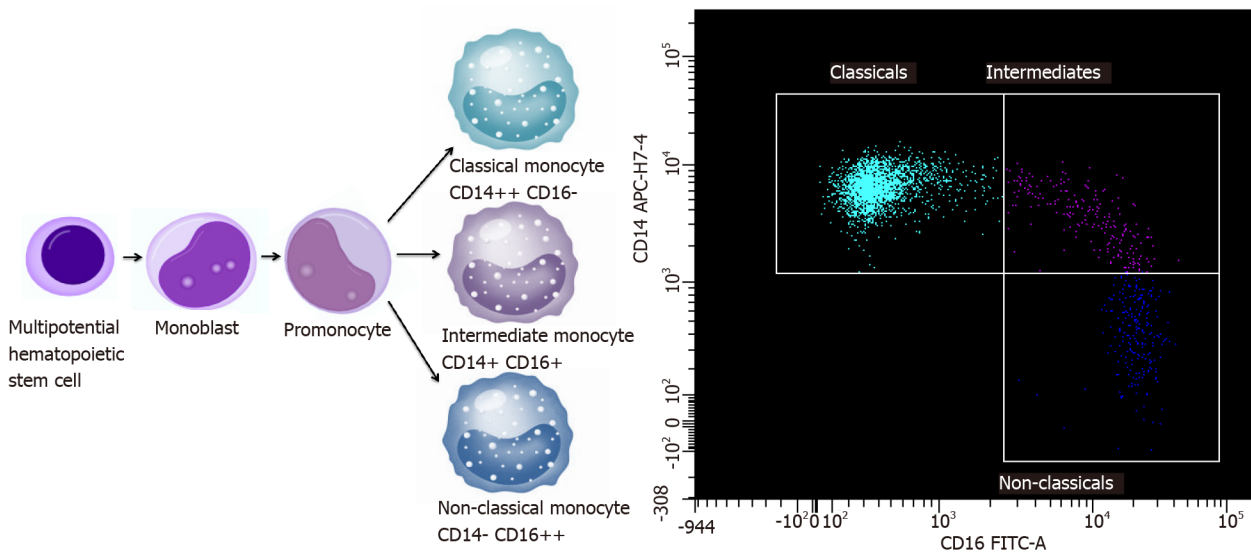


Figure 1 Monocyte maturation and subpopulations scheme. An example of identification of these cells by flow cytometry.

They have a similar protumoural effect at the metastatic sites and are capable of promoting the spread of metastases. The number of protumoural signals at the tumour site and metastatic sites leads to the predominance of the anti-tumour response from the host's immune system. On the other hand, monocytes have a number of antitumoural functions such as: Antigen presentation, tumour cytotoxicity, the recruitment of natural killer cells, the inhibition of Tregs, the prevention of metastasis[35].

Long-lived non-classical monocytes are well adapted to the removal of cancer cells and debris. Non-classical monocytes migrate towards the sites of cancer spread where they engulf tumour material and produce cytokines that regulate the anti-tumour immunity[36,37]. This population of monocytes could control metastatic process[37]. The third population is a subset of intermediate monocytes, the function of which is under investigation. However, it is known that the relationship between non-classical and intermediate subsets is close[38,39]. The exact maturation and functional relationship between the individual blood monocyte subpopulations and their tissue distribution profiles have yet to be discovered[40,41]. The results of current research confirm that each subpopulation may play a different role depending on the homeostatic and pathological conditions[16]. Infections, inflammation as well as malignant disease can lead to sudden monopoiesis and the formation of a new subset of monocytes with altered functions[35,42].

Monocytes can differentiate into moDCs. MoDCs have a similar antigen presenting ability as classical DCs, including cross-presentation. Blood monocytes can be a reservoir of DC in response to inflammation[43].

HETEROGENEITY OF DCs

Understanding DCs heterogeneity and their role in modulating the immune response in cancer is critical to the better recognition of cancer's ability to bypass the immune system and, consequently, to the ultimate design of novel therapies aiming at boosting anti-cancer immunity.

The studies conducted in order to gain understanding of the biology of DCs have resulted in the identification of a large number of their populations. The main criterion of division is the origin, which distinguishes DCs on plasmacytoid origin cells (pDCs): CD123+ CD11c- and myeloid origin cells: CD123+ CD11c+, also called conventional (cDCs)[44,45]. Identification of antigens called blood DC antigens: BDCA-2, BDCA-3 and BDCA-4 and BDCA-1 (CD1c) allowed further discrimination of human blood DCs into two major subsets: cDC1 and cDC2: cDC1 expresses CD1c, while cDC2 (cCD141+) is characterized by the expression of BDCA-3 (CD141) and Clec9A. BDCA-2 (CD303) and BDCA-4 (CD304), together with CD123, characterize pDC. Additionally, cDCs can be divided into resident and migrating cells[46,47]. DCs derive from the CD34+ hematopoietic stem cell that produces BM myeloid precursors (MPs) and lymphoid precursors (LPs). MPs develop into monocytes, macrophages, and DC precursor

(MDP) from which they differentiate to monocytes and DC precursors (CDP). CDP are precursors of both cDCs and pDCs[48]. Also, cDCs can differentiate directly from monocytes under the influence of various cytokines[49]. Maturation and DC subpopulations scheme is presented in [Figure 2](#).

PDCs

PDCs usually complete their differentiation in BM during the development process and as completely differentiated cells circulate into PB. They are mainly located in the vicinity of the endothelium from where they can easily circulate to the lymph nodes to reside in the T-cell zone[50]. They express the CD123 antigen and the low levels of major MHC-II, the wide range of costimulatory molecules without the expression of CD11c. Additionally, the presence of pattern recognition receptors such as Toll-like receptors (TLRs) allows them to recognize pathogen-associated molecular patterns (PAMP) derived from various microbes and secrete a large amount of type I interferon (INF), tumor necrosis factor (TNF)- α and interleukin (IL)-6[45,51]. What is more, TLR-mediated pDC activation promotes efficient antigen presentation and stimulation of T lymphocytes to the immunological response, but in a less effective manner compared to cDCs[51-53]. Nevertheless, pDCs have also been shown to stimulate Tregs for the production of IL-10, suggesting that this subgroup may also play an immunosuppressive role[54].

CDCs

On the contrary, cDC precursors emerge from the BM transiently transported through the blood and accumulate as cDC pool in tissues[55]. CDCs, also defined as myeloid DCs, expressing CD11c, refer to all DC subsets other than pDC[56]. cCD1c and cCD141 cells belong to the migrating subset of DCs, while epidermal Langerhans cells and interstitial cells are residual cDCs.

CD1c DC subpopulation is the main population of cDCs detected in blood and tissues and lymphatic organs. CD1c cells are identified by major markers CD1c, CD11c, MHC-II (HLA-DR), CD141 and also express other antigens as: CD13, CD33, CD172 and CD45RO. However, they can show a slightly different phenotype, which depends on the place they occur. CD1c+ DCs present in the skin have additional CD1a expression, whereas those present in the gut express CD103[53]. DCs heterogeneity results not only from phenotypic differences but also from the maturity stage. Immature DCs (iDC) are usually found in peripheral tissue, then migrating to the lymph nodes carrying their own antigens, maintaining immune tolerance on their own tissues. They are characterized by increased endocytosis, a decreased expression of MHC and costimulatory molecules and a low ability to produce cytokines[57]. After the antigen is absorbed, the cells begin to mature and change phenotypically and functionally. A peptide complex is formed and an MHC molecule is transported to the cell surface[58]. Maturing DCs migrate to the lymph nodes, increase the expression of MHC-peptide complex, up-regulate the costimulatory molecules and the production of cytokines essential for the T lymphocyte response[55,59]. DCs are considered to be the most important APC, activating T-cells and inducing an immune response. Many factors such as an inflammatory process, an immune response in TME, tissue damage or viruses may promote DCs maturation[60,61].

Many studies show a positive correlation of the number of DCs in the tumour area with a significant extension of patients' survival[62,63]. DCs are able to recognize cancer cells and present neoplastic antigens to effector T lymphocytes. This process depends on the state of maturity and the number of DCs and a local immune status [64].

In fact, amount of data confirm that the accumulation of DCs in the tumour area is influenced by the TME, which modulates their maturation and activation. DCs undergo incomplete differentiation and the number of mature cells decreases with the growth of immature cells[65]. Tumour cells secrete suppressor factors such as transforming growth factor β (TGF- β), IL-10 that reduce the expression of cancer antigens and costimulatory molecules on DCs and that convert them into regulatory DCs (DCreg). DCregs occur among the main cells of the immune system responsible for inhibiting of the immune response, which is conducive to the further development and tumour growth[66,67]. DCs in TME can show an increased expression of programmed death ligand (PD-L1), which interacts with PD-1 molecules on the lymphocytes T surface, inducing their apoptosis, causing the immune response to be muted. DCregs also begin to secrete IL-10, thereby stimulating the proliferation of Tregs and their own polarity to DCregs[68]. Therefore, it seems important to investigate the ways to direct DCs for activating the immune system and inducing an anti-tumour response in an attempt to reverse their suppressive effects. It was

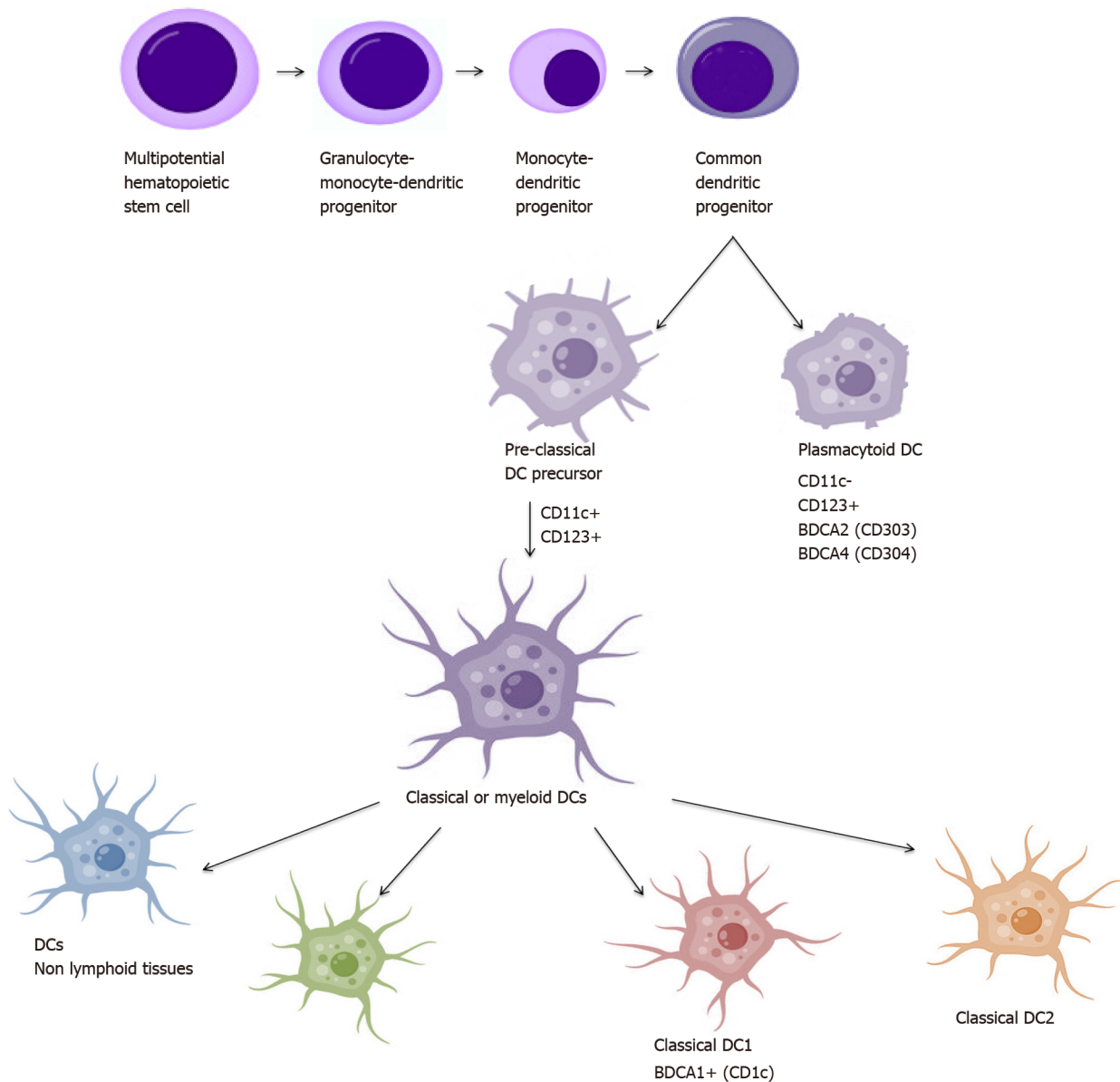


Figure 2 Dendritic cell maturation and subpopulations scheme. DCs: Dendritic cells.

supported by our studies on the identification of DCs in the aspirates from lymph nodes in lung cancer patients. We found an elevated proportion of DCs in metastatic lymph nodes with a high expression of check- point molecules and the phenotype of DCregs.

To sum up, the aforementioned findings confirm the significant participation of DCs in TME. Considering the high heterogeneity of DCs and their plasticity in anti-tumour activity, it seems reasonable to look for a specific subpopulation of these cells.

GENERATION OF moDCs AND APPLICATION IN IMMUNOTHERAPY

Due to the extensive subject matter, we find it valuable to focus on the moDCs population in this review and to discuss DC subpopulation's role in cancer therapy and a possible therapeutic value associated with these populations in lung cancer.

MoDCs arise from monocytes recruited into tissues and become the most abundant DC population during inflammation[69]. *In vivo*, the maturation of DCs into moDCs is induced by pathogens, tissue damage and cancer antigens. *In vitro* human moDCs arise from CD14+ monocytes cultured in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4. This process is triggered *in vitro* by incubation with pathogen recognition receptor agonists or a pro-inflammatory

cytokines cocktail such as: TNF- α , IL-1 β , IL-6, IFN- α and prostaglandin E2 (PGE2) or medium conditioned with monocytes with TNF- α and PGE2[70-72]. TLRs or electro- poration with coding proteins have recently been used to induce moDCs maturation [73-75].

Human moDCs always express: HLA-DR, CD11c and frequently express CD16, CD14 due to their monocytic origin upon differentiation[76,77]. Maturation scheme of moDCs is presented in Figure 3.

As an APCs, DCs are crucial in the innate and adaptive response of the immune system and play a crucial role in inducing anti-tumour immunity[78]. Mature DCs present exogenous antigens to naive CD4+ T-cells by MHC-II and endogenous peptides to CD8+ T-cells by MHC-I. What is more, they have the ability to cross-present exogenous MHC-I antigens to CD8+ T-cells, which induces a cytotoxic T-cell response against neoplastic cells[79,80]. MoDC cross-presentation plays a key role in the rapid activation of CD8+ memory T-cells residing in the tissues after infection. This process has been found to be active in immunostimulatory anticancer therapies or chemotherapy[81-84].

In order to stimulate T lymphocytes in lymphoid tissues, it requires three signals between DCs and T lymphocytes. Firstly, the antigen is presented by the MHC peptide complex, secondly stimulation by costimulatory molecules from DC to the T-cell occurs. The third one is the secretion of immunostimulating cytokines in the microenvironment[85-87].

Ex vivo produced moDCs are commonly used in clinical trials. Mature antigen loaded moDCs can be easily obtained from PB derived CD14+ monocytes or a hematopoietic stem and progenitor cell CD34+ by treatment with GM-CSF and IL-4 [88,89]. Multiple clinical trials have demonstrated the safety and immunogenicity of moDC vaccines. However, clinical responses have been largely disappointing. Admittedly, studies show that *ex vivo* produced moDCs were able to cross-prime T-cells and produce anti-cancer cytokines such as IL-12[90-92]. MoDCs seemed to be a promising population in anti-cancer therapy. Although, in clinical practice, only in a few groups of treated patients an active anti-cancer response was achieved. This may be due to functional cell deficiencies in conventional vaccines-such as insufficient antigen presentation, impaired migration, and impaired cytokine release, which is insufficient for gaining a strong immunosuppressive TME[88,93,94]. Some studies show that *ex vivo* stimulation of DCs precursors leads to the production of moDCs that are transcriptionally and phenotypically different from their naturally occurring (primary) cells[92,95]. *Ex vivo* derived moDCs have a reduced ability to stimulate T-cells compared to natural moDCs isolated from PB and may have a limited ability to migrate to lymph nodes, contributing to reduced vaccine efficacy[56,96-98]. All the aforementioned findings explain the lack of efficacy vaccine in lung cancer.

APPLICATION DCs IN COMBINATION WITH OTHER THERAPIES

Although, moDCs can be produced in large quantities with minimal side effects from therapy, their effectiveness remains limited in cancer therapy[99,100].

Therefore, other ways of using personalized vaccines with DCs are also being considered. Recent studies show their use in combination with other therapies.

Emerging data suggests that combining DCs vaccination with other cancer treatments could fully unlock the potential of DCs cancer vaccines and improve patient survival. With the advent of combination immunotherapy, personalized DCs vaccination could integrate the current standard of care in the treatment of a wide variety of cancers, among them in lung cancer[88].

The first method is to combine vaccination with chemotherapy to obtain a synergistic effect. In addition to immunosuppressive activity, chemotherapy also strengthens immunity by depleting myeloid derived suppressor cells (MDSCs), Tregs and increases the permeability of cancer cells to cytolytic factors derived from CD8+ T lymphocytes[101,102]. Chemotherapy creates a specific cytokine environment by depleting immune cells, and its combination with DC vaccination and adoptive T-cell transfer has been tested in many trials[103-105]. So far, numerous studies are ongoing in which combination chemotherapy and other methods with DCs vaccines are tested. Chemotherapy with DCs vaccination has been tested with the addition of a Cytochrome c oxidase subunit II inhibitor in patients with melanoma in a phase III trial showing encouraging data. Such a therapy with the addition of autologous T-cells showed longer overall survival compared to chemotherapy alone in two randomized trials in lung cancer[106-108].

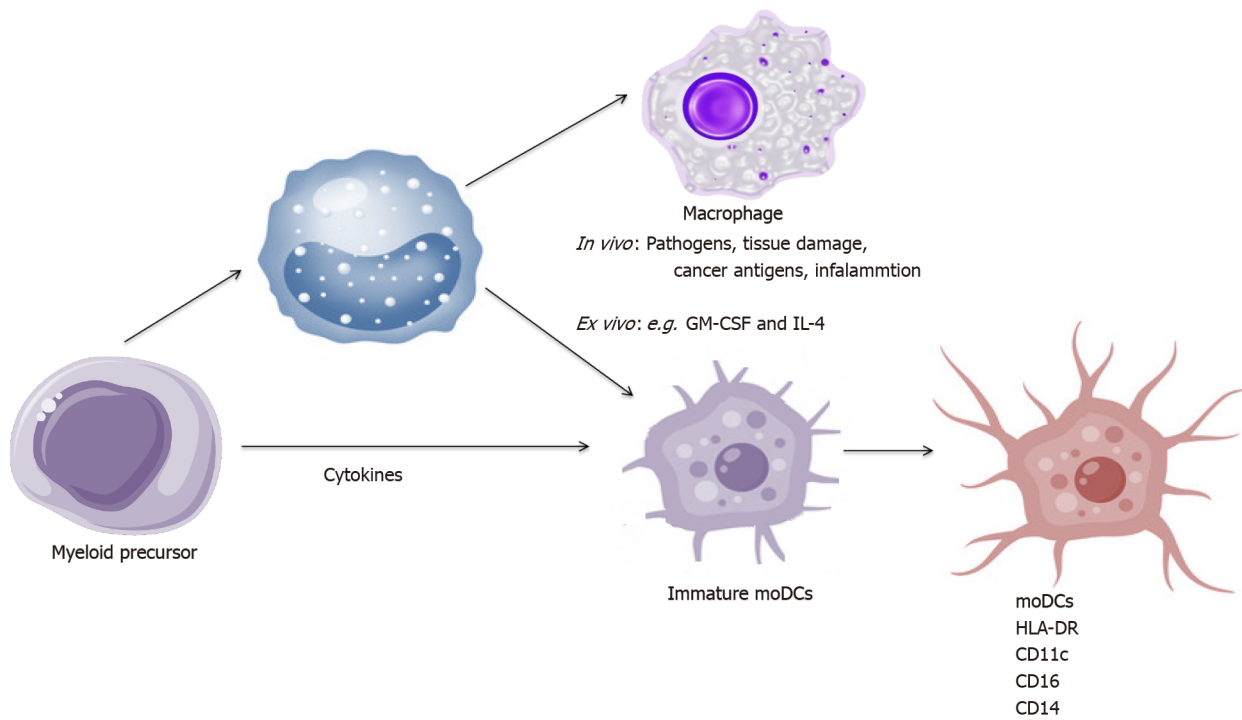


Figure 3 Maturation scheme of monocyte-derived dendritic cells. IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; DCs: Dendritic cells.

Other treatment method is the combination with immunotherapy. For example, preclinical studies showed that this combination decreased MDSCs in the TME, downregulated the PD-1 expression on DCs, and decreased the secretion of immunosuppressive cytokines[109,110]. One clinical trial in advanced renal cell carcinoma patients showed the expansion of CD8+ T-cells and promising survival data [111].

In general, the combination of DCs vaccines with ICIs seems to be promising. A lot of ICIs are currently being tested in clinical trials; many of them, such as: Anti-PD-L1/PD-1 and anti-cytotoxic T-cell antigen 4 (CTLA-4) blocking antibodies have been approved by the Food and Drug Administration[112]. The combination of ICIs with the DCs vaccine seems to have the potential to drive T-cell response into a more specific action[113,114]. In addition, DCs unique ability to cross-present antigens helps to elicit the immune response to more cancer antigens when used in conjunction with ICIs[115]. The anti-CTLA-4 treatment after DCs vaccination may indeed enhance DCs vaccine-induced T-cell responses and there is some evidence that anti-CTLA-4 antibodies might be more effective after DCs vaccination[116,117]. Other studies have shown that DC-based immunotherapy in combination with anti-CTLA-4 antibodies seem to be more effective than the use of these agents alone[118,119]. Anti-PD-1 antibodies are being investigated in combination with DC vaccination, which also opens new avenues of anti-tumour therapy design[120]. The aforementioned studies are conducted in various types of cancer, mainly melanoma, pancreatic cancer, prostate cancer, renal cell carcinoma, and acute myeloid leukemia. Immunotherapy with DCs appears to be capable of eliciting strong tumour-specific responses in combination with other therapies, and is workable and safe[121]. In the recent years, the use of naturally circulating DCs (nDCs) instead of cultured moDCs may have represented the next logical step in anti-cancer therapy and had an impact on long-term clinical benefits[83,122,123].

APPLICATION OF DCs IN LUNG CANCER THERAPY

Lung cancer TME is composed of a large number of phenotypically and functionally different types of cells[124]. A major hallmark of immunosuppression in the TME is the inactivation of cytotoxic CD8+ T-cells, which is achieved through diverse pathways[61,125-130]. Immature DCs produce TGF- β , which expands the population of immunosuppressive Tregs, which in turn inhibit CD8+ T-cells. DCs are recruited

Table 1 Clinical trials with dendritic cell vaccine in lung cancer patients on the basis of clinical trials registry

Status	Major trial	Condition	Study intervention	Official trial code
Recruiting	MIDRIXNEO	NSCLC	Dendritic cell immunotherapy	NCT04078269 [132]
Recruiting	MIDRIX4-LUNG	Metastatic NSCLC	Dendritic cell immunotherapy	NCT04082182 [132]
Completed	Vaccine Therapy in Treating Patients With Stage I, Stage II, or Stage III Non-small Cell Lung Cancer	Lung cancer	Autologous dendritic cell cancer vaccine	NCT00103116 [133,134]
Recruiting	Combination Immunotherapy- Ipilimumab-Nivolumab-Dendritic Cell p53 Vac-Patients With SCLC	SCLC; Lung cancer; Relapsed	Combination immunotherapy with Ipilimumab and Nivolumab plus a Dendritic Cell based p53 Vaccine	NCT03406715
Completed	Dendritic Cells in Lung Cancer	NSCLC	Allogeneic Tumour Lysate	NCT00442754
Completed	Chemotherapy Followed By Vaccine Therapy in Treating Patients With Extensive-Stage Small Cell Lung Cancer	Lung cancer	Autologous dendritic cell-adenovirus p53 vaccine combined with Carboplatin and Etoposide	NCT00049218
Completed	Vaccine Therapy in Treating Patients With Stage IIIB, Stage IV, or Recurrent NSCLC	Lung cancer	Autologous dendritic cell-adenovirus CCL21 vaccine	NCT00601094
Completed	CSET 1437	NSCLC	Dendritic cell-derived exosomes	NCT01159288
Completed	Vaccine Therapy in Treating Patients With Stage IIINSCLC	Lung cancer	Mutant p53 peptide pulsed dendritic cell vaccine combined with adjuvant therapy	NCT00019929
Completed	Vaccine Therapy in Treating Patients With NSCLC	Lung cancer	Autologous tumor cell vaccine therapeutic autologous dendritic cells combined with conventional surgery	NCT00023985
Recruiting	AST-VAC2 Vaccine in Patients With NSCLC	NSCLC in the advanced and adjuvant settings	AST-VAC2 Vaccine	NCT03371485
Recruiting	Luscid	NSCLC	Pembrolizumab with or without intratumoral avelumab/ipilimumab plus CD1c (BDCA-1)+/CD141 (BDCA-3) + myeloid dendritic cells	NCT04571632
Completed	To Immunize Patients With Extensive Stage SCLC Combined With Chemo With or Without ATRA	SCLC	Paclitaxel Ad.p53-DC vaccines. ATRA	NCT00617409
Completed	Denileukin Diftitox Followed by Vaccine Therapy in Treating Patients With Metastatic Cancer	Lung cancer; Breast cancer; Colorectal cancer; Pancreatic cancer	Denileukin diftitox recombinant fowlpox-CEA(6D)/TRICOM vaccine therapeutic autologous dendritic cells	NCT00128622
Completed	Biological Therapy in Treating Patients With Metastatic Cancer	Lung cancer; Breast cancer; Colorectal cancer; Extrahepatic Bile Duct cancer; Gallbladder cancer; Gastric cancer; Head and Neck cancer; Liver cancer; Ovarian cancer; Pancreatic cancer	CEA RNA-pulsed DC cancer vaccine	NCT00004604
Completed	Vaccine Therapy and Biological Therapy in Treating Patients With Advanced Cancer	Lung cancer; Breast cancer; Cervical cancer; Colorectal cancer; Ovarian cancer; Pancreatic cancer	Combining DCs vaccine therapy with interleukin-2	NCT00019084

NSCLC: Non small lung cancer; SCLC: Small cell lung cancer; CCL21: Chemokine C-C motif ligand 21; ATRA: All trans retinoic acid.

into the TME and induced to upregulate PD-1 and PD-L1 in order to directly suppress CD8⁺ T-cells. Interactions of PD-1 with PD-L1 in the TME blocks responsiveness to danger signals and prevents T-cell activation. T-cells are preferentially drawn to tumour induced DCs as they enter the TME. In addition to the lack of appropriate activating signals, T-cell response is blocked by the engagement of PD-1 by PD-L1 on the DC surface[61]. Tregs are also recruited by the tumour induced DCs to establish a tolerogenic environment[124]. TME's effect on DCs infiltrating the lung cancer tissue is presented in Figure 4. A preclinical study conducted by Lee *et al*[131]. showed that the administration of DCs transduced with the chemoattractant CCL21 led to the

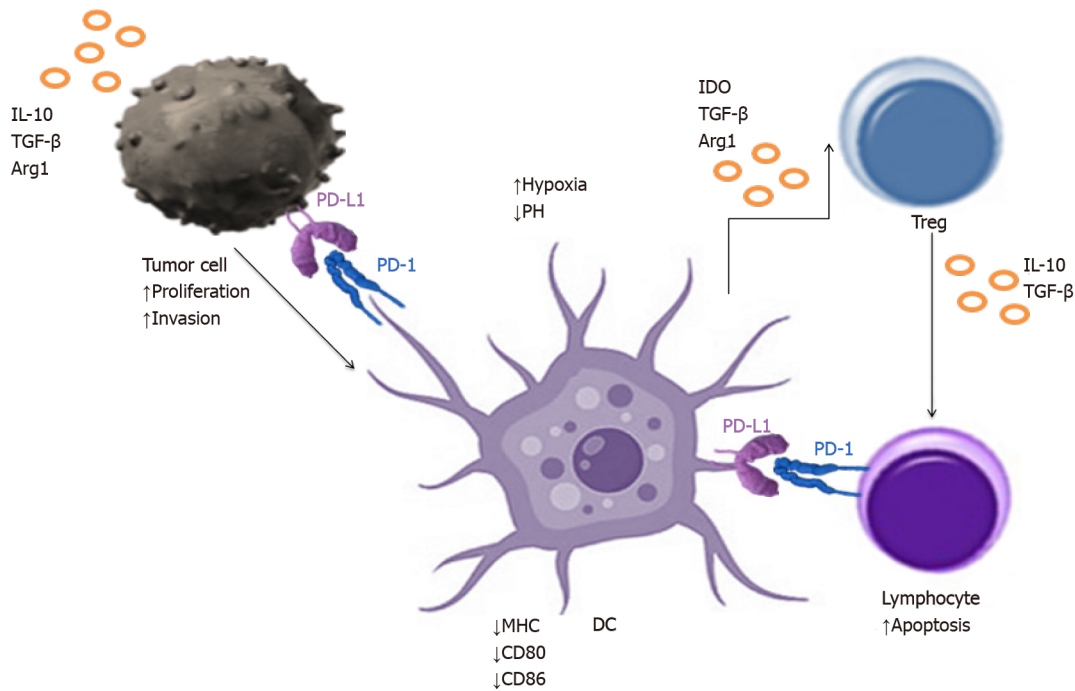


Figure 4 Tumour microenvironment effect on dendritic cells infiltrating the lung cancer tissue. IL: Interleukin; TGF- β : Transforming growth factor β ; PD-L1: Programmed death ligand; DCs: Dendritic cells.

increased infiltration of DCs, CD4⁺ and CD8⁺ T-cells in the lung TME, resulting in reduced tumour burden[131]. Given that the efficacy of DC vaccines as a monotherapy is limited by immunosuppressive mechanisms in the TME, these results provide a rationale for combining DCs vaccination with immunotherapy. Combinational approach to the lung cancer treatment in order to increase the effectiveness of DCs therapy is an attractive way to promote and stimulate the anti-cancer immunity. As the molecular basis of an effective DCs therapy inducing T-cell response are still incompletely understood, it has been difficult to identify factors associated with therapeutic success. There is also no consensus how DCs vaccination efficacy should be evaluated. However, various clinical trials have been recently conducted to evaluate the immune response and clinical efficacy of DCs in lung cancer and other tumours (Table 1). Unfortunately, it is unknown whether naturally occurring DCs outperform cultured moDCs as a source for DCs therapy in lung cancer patients, because clinical trials comparing different DCs subsets as a source for DCs therapy have not been performed.

CONCLUSION

The heterogeneity of monocytes and DCs has been extensively studied and individual subpopulations of these cells have been well described. As our understanding of monocyte and DCs heterogeneity is growing, their key role as anti-tumour response modulating cells is going to become more useful and targeting the specific subgroups to modulate or stimulate their function is going to become an attractive therapeutic approach. The role of DC in TME is of particular interest in immunological research, but our knowledge is limited, especially in lung cancer. However, the present review emphasizes the role of the DC subpopulation in cancer treatment and a possible therapeutic value associated with these populations in lung cancer. Careful definition of the different subpopulations of DCs and their role in cancer will allow for more accurate targeting of immune cells and a better understanding of their role in modulating the immune response.

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