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REVIEW

The Emerging Mechanisms and Therapeutic Potentials of Dendritic Cells in NSCLC

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Abstract: Non-small-cell lung cancer (NSCLC) is the predominant subtype of lung cancer. Despite the demonstrated effectiveness of established treatments such as radiotherapy, chemotherapy, and immunotherapy, the prognosis for patients with advanced NSCLC remains poor. Dendritic cells (DCs), the most potent antigen-presenting cells (APCs), play a crucial role in the tumor microenvironment (TME) of NSCLC. This review explores the classification and biological functions of DCs, highlighting the specific molecular pathways and external factors that influence their maturation and function in NSCLC, which is novel in this review. Moreover, we discuss the potential therapeutic applications of DCs in the management of NSCLC, presenting novel possibilities for future treatments.

Keywords: non-small-cell lung cancer, dendritic cells, maturation, treatment

Introduction

Lung cancer remains one of the most prevalent malignancies globally, accounting for the highest mortality rate among all cancer types. NSCLC, the most common subtype, is associated with a poor prognosis, exhibiting a 5-year survival rate of only 23%.[1] For patients diagnosed at an early stage, therapeutic outcomes can be significantly improved through multimodal approaches, including surgery, radiotherapy and chemotherapy.[2] However, most patients are diagnosed at advanced stages, where stage III–IV NSCLC exhibits a 5-year survival rate of less than 5%.[3] Conventional therapies for advanced NSCLC are often limited by challenges such as drug resistance, disease recurrence, and toxicity to healthy tissues. Immune escape, a hallmark of cancer and a critical driver of tumorigenesis, has emerged as a primary target for tumor immunotherapy.[4] Recent studies have demonstrated the potential of immunotherapeutic strategies targeting tumor cells in the TME, including cancer vaccines and chimeric antigen receptor (CAR) T-cell therapies.[5–7] Despite encouraging therapeutic efficacy, a substantial proportion of patients eventually develop either primary or acquired resistance to current immunotherapeutic regimens, highlighting the critical need for identifying novel immunotherapeutic targets and developing rationally designed combination strategies to enhance clinical outcomes.[8]

DCs, the most potent APCs in the immune system, play a pivotal role in initiating immune responses. They activate both CD8+ T cells, known as cytotoxic T lymphocytes (CTLs), and CD4+ T cells, commonly referred to as helper T cells (Th cells), through presentation of antigens via major histocompatibility complex (MHC) class I and class II molecules.[9,10] This critical function of mature DCs (mDCs) enables them to orchestrate robust anti-tumor immunity and drive adaptive immune defenses against malignancies.[11] Recent studies have revealed that DCs may influence CTLs

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by shaping their developmental trajectories and functional states, thereby contributing to the heterogeneity and plasticity observed in CTLs.[12] Consequently, DC-based immunotherapeutic strategies have emerged as a promising therapeutic paradigm for NSCLC treatment. Nevertheless, the precise molecular mechanisms influencing DC differentiation, maturation, and immune function within the NSCLC TME remain to be fully elucidated.

This review systematically examines current understanding of DC classification and immunobiology, with particular emphasis on their therapeutic potential in NSCLC treatment. We further elucidate the multifaceted regulatory factors modulating DC maturation and function in NSCLC, encompassing signaling pathways, glycolysis, long non-coding RNAs (lncRNAs) expression, tumor-derived factors, and macrophage polarization. Furthermore, this review critically evaluates current advances in DC-based therapeutic strategies for NSCLC while identifying persistent challenges and future directions in translational research and clinical implementation.

Classification and Biological Characteristics of DCs

In 1868, the German scientist Paul Langerhans discovered a class of dendritic-like epidermal cells, which were named Langerhans cells (LCs).[13] In 1973, Canadian scientist Ralph Steinman et al found a group of dendritic-like cells containing Birbeck granules in mouse spleen cells, and Ralph Steinman named this type of cells as DCs.[14] Since then, DCs have officially become a part of immunology research. After years of research, it has been discovered that DCs can be classified based on various criteria (Table 1), but there is currently no unified classification standard.

Classification and Function of DCs Based on Origin

Conventional DCs (cDCs)--cDC1s, cDC2s

According to the different surface molecules of DCs, cDCs can be further divided into cDC1s and cDC2s. cDC1s highly expressed CD141, moderately expressed CD11c, and uniquely expressed C type lectin receptor 9A (Clec9a) and X-C Motif Chemokine Receptor 1 (XCR1).[15–17] They are mainly involved in cross-presentation of $CD8^+$ T cells and can affect the initial activation of $CD4^+$ T cells, playing a major role in antiviral and tumor immune responses.[18–20] cDC2s, also known as $CD1c^+$ DCs, characteristically expressed CD1c, CD11c and signal regulatory protein α (Sirp α), with low levels of CD14, CD123 and CD26.[21] cDC2s are involved in presenting antigens to $CD4^+$ T cells, promoting T helper 1 (Th1) and Th17 effects, and have a central impact on antibacterial, autoimmune diseases and inducing allergic reactions.[22,23]

With the widespread application of single-cell RNA sequencing (scRNAseq) technology in immune cell research, several studies have identified additional functional DC subpopulations alongside the cDC1s and cDC2s clusters. In the research conducted by Dutertre et al the $CD5^-CD163^+CD14^+$ phenotype of cDC2s population was named "DC3s".[30] However, Ginhoux et al propose defining DC3s as a subpopulation of DCs that independently expand from the cDC1s/

Table 1 Classification and Functional Roles of DCs

Name	Surface Markers	Function	References
cDC1s	$CD141^{high}$, CD11c, Clec9a, XCR1	Involved in cross-presentation of $CD8^+$ T cells, affect the initial activation of $CD4^+$T cells, antiviral and participate in the tumor immune response	[15–20]
cDC2s	CD1c, CD11c, Sirpα, $CD14^{low}$, $CD123^{low}$, $CD26^{low}$	Involved in presenting antigens to $CD4^+$ T cells, promote Th1 and Th17 effects, antibacterial, involved in autoimmune diseases, induced allergic reactions	[21–23]
pDCs	CD123, CD45RA	Produces type I interferon and participates in antiviral immunity	[21,24]
LC	CD207	Present antigen to T cells and induce humoral immunity	[25,26]
MoDCs	CD1c, CD1a, CD1b, CD206, CD14, CD11b	Involved in local inflammatory response	[27,28]
imDCs	FcR, human mannose receptor/ mouse DEC-205 molecules	Uptake of antigen	[29]
mDCs	MHC I/ II^{high}, CD80, CD86, CD40, CD54, CD1a, CD11c, CD83, FcR^{low}	Present the processed antigen to naive T cells, and elicite antigen-specific T lymphocyte responses.	[29]

cDC2s lineage under inflammatory conditions.[31] Research has reported that DC3s have the ability to activate tissue-homing T cells, and exhibit a superior Th17 polarizing capability.[32]

Plasmacytoid DCs (pDCs)

pDCs were different from cDCs in that they did not express the myeloid antigens CD11c, CD33, CD11b, and CD13. However, they retained the surface markers CD123 and CD45RA of the granulocyte-macrophage DC progenitor (GMDP). They primarily respond to viral stimulation and carry out their functions by producing type I interferon.[21,24]

LCs and Monocyte-Derived DCs (MoDCs)

LCs represent a distinct subset within the DC population, uniquely located in the epidermis. They are capable of presenting antigens to T cells and inducing humoral immunity.[25,26] Research has shown that under inflammatory conditions, monocytes in the bone marrow or blood can differentiate into DCs, termed MoDCs. Although these cells exhibit limited migration capacity, they are highly active in secreting inflammatory factors and playing a crucial role in amplifying the local inflammatory response.[27,28]

Biological Characteristics of DCs at Different Differentiation Stages

DCs can be classified into four distinct stages based on their level of differentiation and maturation: precursor DCs (pre-DCs), immature DCs (imDCs), migrating DCs, and mDCs (Figure 1). Initially, bone marrow hematopoietic stem cells differentiate into pre-DCs under the influence of FMS-like tyrosine kinase 3 ligand (FLT3L).[33] These pre-DCs migrate through the bloodstream and colonize both lymphoid and non-lymphoid organs. During this process, pre-DCs differentiate into imDCs in response to tissue-specific signals, such as Notch2.[34]

Under normal conditions, the majority of DCs in the body exist in the imDC state. These imDCs express various surface receptors, such as Fc receptor (FcR), mannose receptor, or DEC-205, allowing them to efficiently take up antigens through pinocytosis and phagocytosis.[35] As a result, imDCs are highly capable of antigen uptake but are less

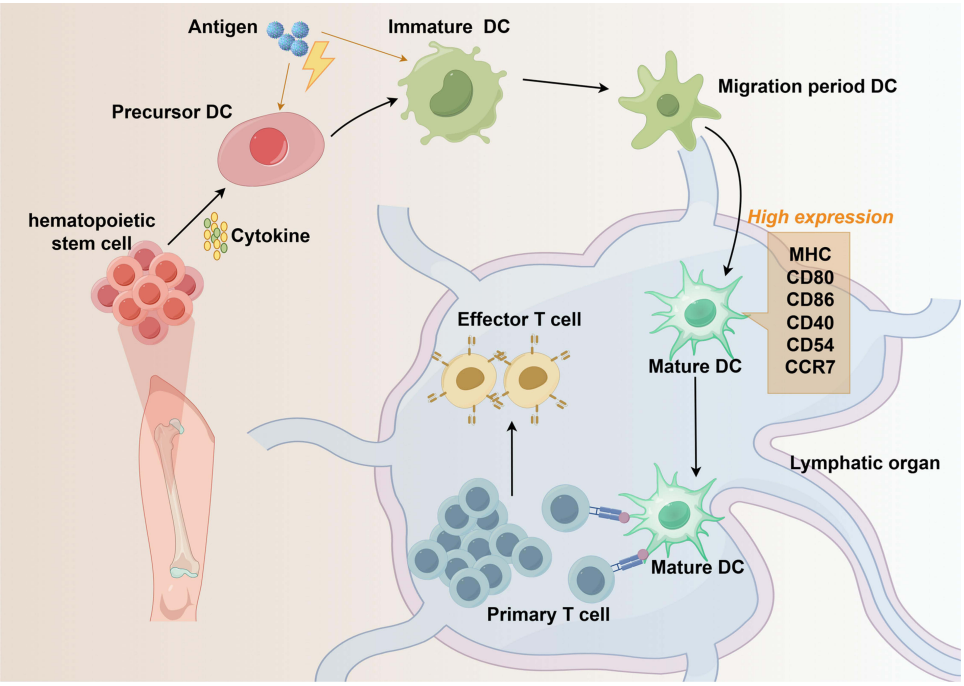

Figure 1 The whole process of differentiation, maturation and function of DCs. Hematopoietic stem cells in bone marrow undergo differentiation into pre-DCs under the influence of cytokines. Subsequently, pre-DCs further transform into imDCs upon stimulation by cytokines and antigens. imDCs possess a high capacity for antigen uptake and migrate through the blood and lymph circulation. During the migration process, the surface molecules and cell morphology of imDCs changed and gradually transformed into mDCs. mDCs highly expressed MHC, CD80, CD86, CD40, CD54 and CCR7. In secondary lymphoid organs, mDCs present MHC class II-peptide complexes to naive T cells, prompting their differentiation into effector T cells.

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effective at antigen presentation due to their low expression of MHC class II and chemokines. Consequently, imDCs have limited capacity to activate naive T cells.[29]

When imDCs encounter pathogens, they rapidly mature in response to the activation of pathogen recognition receptors (PRRs). During this maturation process, imDCs migrate to secondary lymphoid tissues, where they further differentiate into mDCs. This transition is crucial as it enhances the ability of DCs to present antigens and effectively stimulate naive T cells, initiating a robust immune response.[36]

mDCs are characterized by their irregular shape and numerous surface protrusions, which enable them to play a pivotal role in immune surveillance within secondary lymphoid organs.[37] mDCs exhibit high expression of MHC class I and II molecules, costimulatory molecules such as CD80 and CD86, adhesion molecules like CD40 and CD54, and chemokine receptors such as CCR7, as well as integrins. Key markers of human mDCs include CD1a, CD11c, and CD83.[29] However, mDCs have a diminished capacity for antigen uptake and processing due to the absence of FcR and pathogen receptors. Despite this, mDCs excel at presenting processed antigens to naive T cells via antigen peptide-MHC class II complexes, thereby triggering antigen-specific T cell responses. In addition to their T cell activation function, mDCs can also promote tolerance in certain contexts.[38] However, the induction of immune tolerance is primarily mediated by imDCs, as they are better equipped to suppress T cell activation during antigen presentation.[39]

Important Roles of DCs in Immunotherapy of NSCLC

Presently, advancements in NSCLC immunotherapy have been notable; however, challenges such as inter-individual variability in treatment efficacy and the occurrence of adverse reactions post-treatment suggest that the execution of tumor immunotherapy may be more intricate than initially perceived.[40] Several studies have shown that the TME consists of tumor cells, immune cells, tumor-associated fibroblasts, signaling molecules, and extracellular matrix, all of which critically impact immunotherapy efficacy. Among these, the immune microenvironment, defined by immune cells infiltration, plays a particularly pivotal role.[41]

DCs are recognized as the preeminent APCs in the organism, possessing the exclusive capability to prime the initial T cells. Serving as the instigators of the immune response, DCs hold a pivotal position in orchestrating T cell-mediated anti-tumor immunity. Some studies suggest that increased expression of tumor-infiltrating cDC2s is associated with improved survival in NSCLC patients, potentially due to the presence of regulatory T cells (Tregs) that suppress the differentiation of $CD4^+$ T cells into pro-inflammatory, anti-tumor effector cells.[42,43] Additionally, it was discovered that tumor-infiltrating DC3s can achieve anti-tumor immunity through the molecular action of interferon-γ (IFN-γ) and IL-12, and activate tumor-specific $CD4^+$ T cells response. Relevant studies indicate that increased DC3s expression in tumors is associated with improved survival of NSCLC patients.[42,44]

Upon maturation in response to tumor-related stimuli, DCs will upregulate cell surface expression of MHC class II, CD40, CD80, CD83, and other co-stimulatory molecules. Furthermore, they will release the cytokine IL-12 and induce activation of CTLs, leading to inhibition of tumor growth in vivo.[45,46] However, various immunosuppressive factors present in the TME have the potential to hinder the functionality of DCs through the inhibition of their maturation and antigen presentation processes. This disruption can lead to compromised proliferation and activation of T cells. Lu et al discovered that NSCLC cells impede anti-tumor immunity in vivo by reducing the expression of mature co-stimulatory molecules (CD80 and CD86) and pro-inflammatory cytokines (IL-12 and IL-23) on the surface of DCs.[47] Therefore, the differentiation and maturation of DCs play a crucial role in the immune response within the TME and the improvement of NSCLC immunotherapy.

Factors Affecting DC Maturation and Function in NSCLC

Activation of Nuclear Factor kappaB (NF-κB), Signal Transducer and Activator of Transcription 3 (STAT3) and Mitogen-Activated Protein Kinase (MAPK) Signaling Pathways in DCs

Studies have shown that the NF-κB, STAT3, and MAPK signaling pathways play a crucial role in regulating the maturation and function of DCs in NSCLC (Figure 2A). NF-κB consists of transcription factors such as p65, p50/

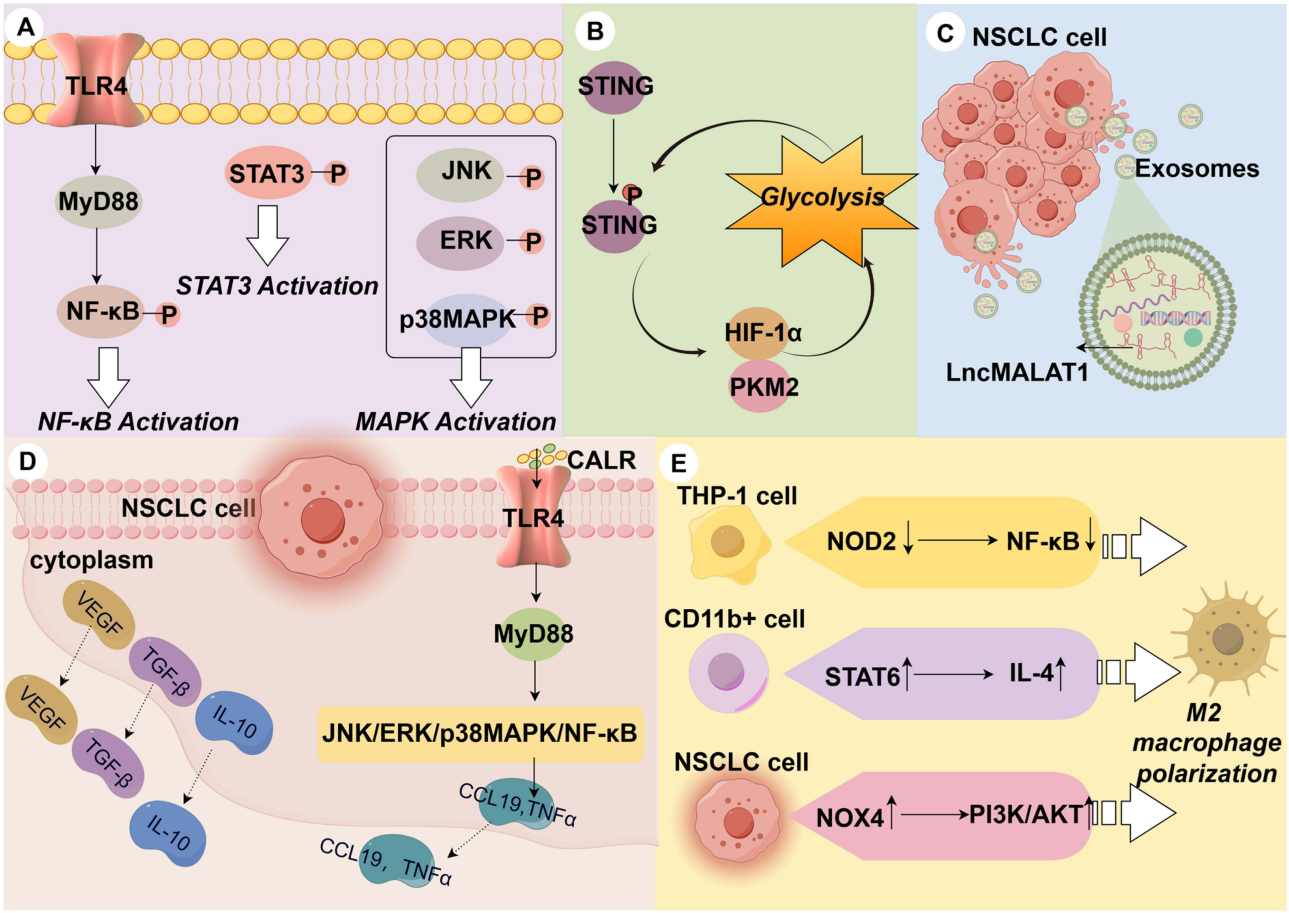

Figure 2 Factors affecting DC maturation and function in NSCLC. (**A**) The activation of NF-κB, STAT3 and MAPK pathways promotes the maturation of DCs. NF-κB signaling pathway can be activated by the elevation of TLR4, MyD88, and NF-κB levels. SHP-1 binds to STAT3 can mediate its dephosphorylation. MAPK signaling pathway can be activated through the phosphorylation of JNK, ERK, and p38 MAPK. (**B**) Glycolysis promotes STING signal-dependent tumor-infiltrating DC activity in NSCLC, which accelerates PKM2 and HIF-1α-mediated glycolysis and establishes a positive feedback loop. (**C**) LncMALAT1 can be transferred to DCs via exosomes released by NSCLC tumor cells. Elevated expression of LncMALAT1 has been shown to inhibit the maturation phenotype and function of DCs in NSCLC. (**D**) The release of tumor-derived factors such as VEGF, TGF-β, and IL-10 inhibits DC maturation, while the release of CCL19 and TNF-α promotes DC migration and maturation. (**E**) Several pathways can regulate M2 macrophage polarization. In THP-1 cells, reduced NOD2 expression and inhibited NF-κB pathway promote M2 macrophages polarization. In CD11b$^+$ cells, high STAT6 expression promotes IL-4 secretion, leading to M2 polarization. In NSCLC cells, abundant NOX4 expression activates the PI3K/AKT signaling pathway, causing M2 polarization.

p105 (NF-κB1), and p52/p100 (NF-κB2), while the STAT family encompasses STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. The MAPK family includes c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinases (ERK), and p38 MAPK. Dysregulation of these pathways has been linked to the progression of various diseases, including chronic inflammatory disorders and tumors.[48]

Rui Li et al established an in vitro model to study the effects of NSCLC patient serum on DCs. Transcriptomic analysis revealed that the expression of key functional genes in the DCs induced by cancer serum was affected compared to control cells, including chemokines, cytokines, MHC Class II molecules, and co-stimulatory molecules.[49] Further analysis showed that both NF-κB and STAT3 signaling pathways were inhibited by the cancer serum, suggesting that this inhibition could contribute to DC dysfunction in NSCLC.[49] Additionally, the study revealed that SHP-1, a protein-tyrosine phosphatase, regulates the STAT3 signaling pathway by binding to and dephosphorylating STAT3.[50] Western blotting results showed an increase in SHP-1 expression during DC differentiation in the TME, accompanied by a decrease in STAT3 phosphorylation. These findings suggest that SHP-1 may play a role in inhibiting STAT3 signaling and contributing to DC dysfunction in NSCLC.[49]

Huang et al found that ginsenoside Rg1 treatment of human peripheral blood mononuclear cell (PBMC)-derived imDCs increased the secretion of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-8, and IL-6, promoting DC

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activation.[51] Wu et al suggested that Rg1 may activate DCs through the NF-κB signaling pathway, although the exact molecular mechanism requires further investigation.[52] Liu et al treated myeloid-derived DCs in Lewis lung cancer (LLC) mice with cryptotanshinone (CT) and found that CT induced DC maturation via a myeloid differentiation factor 88 (MyD88)-dependent mechanism, characterized by downregulation of the NF-κB inhibitor α (I-κBα) and upregulation of phosphorylated JNK and p38 MAPK.[53] In a Lewis NSCLC mouse model, Zhao et al observed that Yangyinwenyang (YYWY), a traditional Chinese medicine, could enhance toll-like receptor 4 (TLR4), MyD88, and NF-κB levels, leading to the activation of the TLR4-MyD88-NF-κB pathway. YYWY also activated the MAPK pathway through phosphorylation of JNK, ERK, and p38 MAPK.[54] This led to increased numbers of mDCs and enhanced secretion of pro-inflammatory cytokines such as IFN-γ, IL-1β, TNF-α, IL-2, and IL-12.[54,55] These findings highlight the intricate interconnection between NF-κB and MAPK signaling pathways in the immune regulation of DCs.

Regulating Glycolysis in DCs

Recent studies have showed that TLR stimulation can trigger the transformation of DC metabolism, which is characterized by the up-regulation of aerobic glycolysis. Blocking this process of glycolysis will damage the maturation of DCs.[56–59] Studies on DCs have reported that DCs mainly rely on oxidative phosphorylation (OXPHOS) and fatty acid oxidation as energy sources when they are not activated or tolerated. However, immunogenic DCs or activated DCs mainly rely on glycolysis.[60,61]

Guan et al observed that in NSCLC, enhanced glycolysis can promote a significant increase in the proportion of $CD11b^{-}CD11c^{+}$ mDCs, which may be related to inhibition of adenosine A2B receptor (A2BR) signaling.[62] And Hu et al noted that glycolysis can promote the activity of stimulator of interferon genes (STING) signal-dependent tumor-infiltrating DCs in the tissue samples of NSCLC patients, and this process will also accelerate pyruvate kinase M2 (PKM2) and hypoxia-inducing factor-1α (HIF-1α) mediated glycolysis and establish a positive feedback loop, thus promoting anti-tumor immunity (Figure 2B).[63]

In conclusion, glycolysis appears to play a significant role in the development and maturation of DCs in NSCLC. However, the precise mechanisms by which the glycolytic pathway influences DC maturation in NSCLC require further investigation.

Secreted lncMALAT1 by Exosomes in NSCLC TME

Increasing evidence indicates that the activity of DCs within tumor tissues is influenced by both tumor cells and the surrounding TME. Exosomes, small vesicles measuring 30–150 nm in diameter, play a crucial role in mediating communication between tumor cells and DCs in the TME.[64] These exosomes can be released by various cell types, fuse with the target cell membrane, and deliver their contents to the cytoplasm of the target cell, thereby facilitating intercellular communication.[65] New evidence suggests that exosomes in the TME may be involved in promoting tumorigenesis by regulating tumor angiogenesis, tumor immunity, and tumor metastasis.[66] In recent years, a large number of studies have confirmed that regulating tumor-derived exosomes can effectively reduce tumor-derived exosome-mediated immune dysfunction in the TME.[64] For instance, Exosomes secreted by squamous cancer cells have the ability to stimulate DC maturation, thereby enhancing anti-tumor immunity.[67]

LncRNA, characterized by its length exceeding 200 nucleotides and its inability to encode proteins, plays a significant role within exosomes, facilitating their transfer to DCs via exosomes released by tumor cells to carry out vital biological functions.[68] Studies have shown that lncRNAs participate in a variety of biological processes by regulating gene expression.[69] lncRNA expression imbalance in tumors is associated with tumor prognosis.[70,71] Wang et al reported the first lncRNA carried by exosomes from lung cancer in 2016, and verified the new mechanism by which exosomes from lung cancer cells regulate mesenchymal stem cells in the TME through lncRNA delivery.[72]

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA originally identified in NSCLC. The overexpression of lncMALAT1 was closely associated with patient survival.[73] As studies on lncMALAT1 continue to grow, a significant number of research findings have shown that lncMALAT1 can also alter its expression in various types of tumors, making it a potential tool for tumor diagnosis and prognosis.[74] Our previous studies have also shown that lncMALAT1 can participate in the regulation of immune cells in the immune microenvironment of lung cancer, and

thus affect the proportion of $CD4^+/CD8^+$ T cells in lung cancer patients. The expression level of lncMALAT1 in NSCLC and its secreted exosomes have a central impact on the occurrence and development of NSCLC (Figure 2C).[75,76] Additionally, Liu et al confirmed that lncMALAT1 expression was abnormally increased in exosomes secreted by lung cancer cells. High expression of lncMALAT1 carried by exosomes could inhibit the phenotypic maturation and function of DCs. Conversely, DCs with low lncMALAT1 knockdown could significantly inhibit tumor growth in mouse models of lung cancer.[4]

Tumor-Derived Factors in NSCLC

Several studies have indicated that tumor-derived factors in NSCLC play a significant role in regulating the maturation of DCs (Figure 2D). Vascular endothelial growth factor (VEGF), the first tumor-derived factor reported to affect the maturation of DCs, is produced by nearly all tumor cells.[77,78] Fan et al discovered that VEGF can inhibit the differentiation of hematopoietic progenitor cells (HPCs) into functional DCs by blocking NF-κB activation.[78,79] Transforming growth factor-β (TGF-β), secreted by lung cancer cells, prevents DC differentiation into regulatory DCs (DCregs) within the TME, as demonstrated by Liu et al.[80] Additionally, IL-10 released by lung cancer cells has been shown to impair DC maturation and reduce their ability to stimulate T cells, further contributing to immune evasion.[81,82]

Furthermore, chemokines originating from tumors have the ability to selectively affect DCs by modulating their migration patterns and maturation processes. Studies have showed that after anthracyclines treatment of NSCLC tumor cells, calreticulin (CALR) on the cell membrane interacts with its own receptor TLR4 to activate the CALR-TLR4-MyD88 signaling pathway, phosphorylating NF-κB, JNK, ERK, p38 MAPK and other signaling pathways.[83,84] Subsequently secreted C-C motif chemokine ligand 19 (CCL19) and TNF-α promote the migration and maturation of imDCs, ultimately inhibiting NSCLC progression.[84] In mouse lung cancer models, S. Hillinger et al identified CCL19 as a potential immune stimulator that significantly increases DCs in the lung.[85] In addition, TNF-α exhibits strong inflammatory and tumor-promoting properties and can influence tumor progression through complex signal transduction phenomena, including NF-κB, MAPK, AKT, etc.[86] A study revealed that $CD34^+/CD86^+$ cells, common precursors for macrophages and DCs, differentiate into macrophages when cultured with granulocyte-macrophage colony-stimulating factor (GM-CSF). In contrast, the addition of TNF-α alongside GM-CSF drives their differentiation into $CD1a^+/CD83^+$ DCs, underscoring the essential role of TNF-α in DC differentiation and maturation.[87] Furthermore, Jankowska et al also confirmed in NSCLC that TNF-α plays a key role in DC maturation.[88]

Effect of Macrophage Polarization on DCs

Macrophages can polarize into distinct phenotypes, primarily M1 and M2, depending on signals from the TME.[89] Several pathways can regulate this polarization. For instance, in lung cancer, the expression of nucleotide-binding and oligomerization domain-containing protein 2 (NOD2) decreases in human myeloid leukaemia mononuclear cells (THP-1) when co-cultured with tumor cells. This reduction leads to diminished phosphorylation of I-κBα, thereby inhibiting the NF-κB pathway and promoting the transition from M1 to M2 polarization in tumor-associated macrophages (TAMs).[90] Additionally, STAT6 activation, highly expressed in $CD11b^+$ cells of lung cancer, induces the secretion of IL-4, which further drives M2 polarization through a positive feedback loop that supports tumor growth.[91] Moreover, nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4) in NSCLC cells generates reactive oxygen species (ROS), activating the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathway and promoting the secretion of cytokines like CCL7 and IL-8, which also contribute to M2 polarization (Figure 2E).[92]

M1 macrophages are primarily induced by Th1 cytokines, lipopolysaccharide (LPS), and TLR agonists, leading to the production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-23, and TNF-α.[93,94] In contrast, M2 macrophages are polarized by Th2 cytokines like IL-4 and IL-13, producing anti-inflammatory cytokines like IL-10 and TGF-β.[93,94] The inflammatory microenvironment in tumors, including lung cancer, plays a critical role in macrophage polarization, which in turn influences tumor progression.[95] Recent studies suggest a link between macrophage polarization and DC maturation. For instance, Kudling et al found in an immunocompetent NSCLC model that combining adenovirus and anti-programmed cell death protein 1 (anti-PD-1) with TNF-α and IL-2 promoted M1 macrophage polarization and enhanced DC maturation and migration.[96] Similarly, Astragalus polysaccharide (PG2), combined

with macrophage colony-stimulating factor (M-CSF) and IL-4, increased the ratio of $CD80^+$ M1/$CD206^+$ M2 macrophages and enhanced the number of functional $CD80^+CD103^+CD86^+$ mDCs in NSCLC patients.[97] Additionally, in an LLC mouse model, endostatin reduced M2 macrophages and immunosuppressive factors like IL-10 and TGF-β, while increasing M1 macrophages and enhancing the infiltration of mDCs and $CD8^+$ T cells into the TME.[98]

Cytokines like TNF-α are known to promote DC maturation, whereas IL-10 and TGF-β exert inhibitory effects on DCs in NSCLC patients.[80,82,87,88] Therefore, by increasing the polarization of M1 macrophages and decreasing M2 polarization, the secretion of these cytokines can be modulated. This regulation of the immune-inflammatory state indirectly enhances DC function and maturation, which could ultimately inhibit the progression of NSCLC.

The Application of DCs in the Treatment of NSCLC

The utilization of DCs in the management of NSCLC encompasses the use of DC vaccines, DC-cytokine-induced killer cells (CIK) therapy, and the modulation of DCs to enhance the anti-tumor immune response (Table 2). These strategies have exhibited encouraging outcomes in clinical investigations and have displayed potential therapeutic advantages.

DC Vaccines

Due to the strong antigen-presenting ability of DCs and its ability to promote the differentiation and maturation of T cells, DC vaccines have been used more and more frequently in the research and treatment of NSCLC.[108] DC vaccines are designed to stimulate specific effector T cells by injecting mDCs loaded with tumor antigens. This process enables the effector T cells to recognize and eliminate cancer cells, while also generating immune memory to control tumor growth.[109] As technology advances, the design of DC vaccines has become more diverse to enhance the immune response. The design can be tailored to the patient's specific TME phenotype by adjusting several factors, including the method of DC generation, the route of injection, genetic engineering techniques, combination therapies, and the approach to antigen pulsing.[108,110,111]

Several studies have suggested that the effectiveness of DC vaccines in treating NSCLC may be limited, potentially due to immune suppression within the TME.[112,113] In the TME of NSCLC, T cell infiltration is typically limited, and their anti-tumor function is further suppressed by immune checkpoint molecules expressed on tumor cells.[113,114] Recent advances in immunotherapy have established immune checkpoint inhibitors (ICIs) as a mainstream treatment. ICIs block key checkpoint proteins, including cytotoxic T lymphocyte antigen (CTLA)-4, PD-1, and programmed death ligand 1 (PD-L1), to relieve T cell suppression and boost the immune system's anti-tumor response.[9] However, a major hurdle in advancing ICIs-based therapies is the risk of inflammatory toxicity.[99,115] In a retrospective analysis by Wang et al, the

Table 2 Application of DCs in NSCLC

Application	Mechanism of Action/Effect	References
DC vaccines combined with ICIs	ICIs can alleviate the suppressive state of T cells in TME by inhibiting CTLA-4, PD-1, or PD-L1, thereby promoting the therapeutic efficacy of DC vaccines.	[99,100]
DC-CIK	Activate the killing sensitivity of CIK, promote the proliferation and maturation of CIK, increase the secretion of IL-12 by DCs, promote the proliferation of antigen-specific T cells, enhance the activity of killer cells, and improve the effect of tumor cure or control when combined with traditional radiotherapy and chemotherapy.	[101–103]
Laricitrin	Reduce the expression of IL-10 in DCs under lung cancer conditions by inhibiting the phosphorylation of STAT3, promote the differentiation and maturation of DCs, and enhance anti-tumor immunity.	[104]
Low-dose doxorubicin	Promote the maturation and antigen presentation ability of DCs, produce more IL-12 and IFN-γ, thereby enhancing the function of Th1 cells.	[105]
PG2	Promote the activation of DCs by increasing the expression of immune-related factors such as MHC-II, CD80, and CD86 on the surface of DCs, promote the functional maturation of DCs, and enhance T cell-mediated anti-tumor immune response.	[97,106]
SAL	Activate ERK signaling pathway to promote the secretion of IL-12p70 by DCs and enhance the cytotoxicity of CTLs.	[107]

mortality rate due to immune-related adverse reactions was 0.6% among 3545 patients treated with ICIs.[116] On the other hand, a clinical study by Ding et al found that all treatment-related adverse events in 12 subjects were grade 1–2, with no delays in administration due to toxic effects when DC vaccines were combined with immune ICIs.[100] This suggests that the adverse effects of combining DC vaccines with ICIs are relatively mild. As such, this combination therapy shows promise as a feasible treatment option.[117] Nonetheless, further research and clinical trials are needed to establish its safety and efficacy in treating NSCLC.

Additionally, the latest research of Chen et al highlights the rapid advancements of artificial intelligence and big data analytics in the pharmaceutical field, which provide new opportunities to enhance the efficiency of drug development.[118] For example, Han et al used T cell receptor (TCR) sequencing to analyze peripheral blood $PD^{-}1^{+}CD8^{+}$ T cells from NSCLC patients treated with immune checkpoint inhibitors, demonstrating a strong correlation between TCR diversity and treatment response. Patients with higher TCR diversity generally exhibit better clinical outcomes.[119] These emerging technologies may provide valuable support for further exploring strategies to improve clinical responses when combining DC immunotherapy with immune checkpoint inhibitors.

DC-CIK Therapy

Studies have demonstrated that co-culturing DCs and CIKs generates a stronger anti-tumor effect compared to culturing each cell type individually. This interaction enhances IL-12 secretion by DCs and boosts the cytolytic activity of CIKs. The DC-CIK co-culture system is highly efficient, MHC-independent, and non-specific, offering a promising approach for immune-based cancer therapy.[101,120–122]

A study involving 60 patients with advanced-stage NSCLC was conducted, in which patients were randomly assigned to two groups using a double-blind method. The control group (n = 30) received standard chemotherapy: squamous cell carcinoma patients were treated with gemcitabine + cisplatin, while adenocarcinoma patients were treated with pemetrexed + cisplatin. The experimental group (n = 30) received the same chemotherapy regimen as the control group, in addition to DC-CIK adoptive immunotherapy.[102] The results showed that the overall cancer control rate in the experimental group (70.00%) was slightly higher than that in the control group (56.67%), though the difference was not statistically significant ($P > 0.05$). Furthermore, the experimental group had higher levels of $CD4^{+}$ T cells and natural killer cells in peripheral blood compared to the control group. Another study involving 63 patients with stage IIIB NSCLC was conducted, with patients assigned to two groups. The study group (n = 30) received DC-CIK plus docetaxel + cisplatin chemotherapy with concurrent conformal radiotherapy, whereas the control group (n = 33) received chemotherapy and radiotherapy alone.[103] The results revealed an effective response rate of 83.3% (25/30) in the study group, which was significantly higher than the 54.5% (18/33) in the control group. Additionally, the study group showed significantly better Karnofsky performance status (KPS) and 12-month survival rates compared to the control group. Their findings provide a new strategy for DC-CIK optimization research. In a preclinical study by Zhou et al, DC-CIK were co-cultured with human lung adenocarcinoma A549 cells after blocking the T-cell immunoglobulin and mucin domain-containing protein 3 (Tim-3) and PD-1 signaling pathways in T cells within the DC-CIK cultures. The results showed that blocking the Tim-3 and PD-1 pathways increased the cytotoxic activity of DC-CIK against A549 cells and significantly suppressed their invasion and migration.[123] These findings offer a new strategy for optimizing DC-CIK therapy.

These studies suggest that combining DC-CIK immunotherapy with chemotherapy and radiotherapy enhances NSCLC treatment outcomes, while targeting Tim-3 and PD-1 pathways could optimize DC-CIK efficacy.

Modification and Modulation of DCs

The main function of DCs in vivo is to process antigens and present them to T cells, thereby inducing specific CTLs to exert anti-tumor immune effects. In order to activate T cells, one of the commonly used strategies is to modify DCs to enhance their antigen presentation ability, so as to enhance the stability of DC-T cell interaction.[124] Some studies have shown that glycopolymer-modified DCs exhibit enhanced ability to activate T cells and improve their antigen-specific recognition.[125] Chang et al found that Laricitrin reduces IL-10 expression in DCs under lung cancer conditions by suppressing STAT3 phosphorylation. This process promotes DC differentiation and maturation, ultimately enhancing anti-tumor immunity.[104] Another study pointed out that low-dose chemotherapy drug doxorubicin can promote the

maturation and antigen presentation ability of DCs, produce more IL-12 and IFN-γ, thereby enhancing the function of Th1 cells, and achieving an anti-tumor effect.[105]

In recent years, research on the effects of traditional Chinese medicine preparations on DCs has significantly increased. For instance, one study revealed that PG2 enhances DC activation by upregulating the expression of immune-related factors, including MHC-II, CD80 and CD86 on the surface of DCs. This promotes the functional maturation of DCs and strengthens T cell-mediated anti-tumor immune response.[97,106] Another study showed that salidroside (SAL) could activate the ERK signaling pathway, thereby promoting DCs to secrete IL-12p70 and enhancing the cytotoxicity of CTLs in order to inhibit tumor proliferation.[107]

The various methods of DC modification and modulation mentioned above are mostly still in the preclinical trial stage. Although these methods have shown promising therapeutic potential in animal models, further clinical trials are necessary to validate their safety and efficacy in humans. Before widespread clinical application, it is crucial to assess the long-term side effects, immune tolerance, and the impact of individual patient differences on treatment outcomes.

Discussion and Conclusion

DCs are recognized for their significant role in the immunotherapy of NSCLC. Research has extensively studied various aspects of DCs, including: classifications and biological characteristics, factors affecting the maturation and function of DCs, and the application of DCs for NSCLC treatment. Through an examination of DC classification and biological features, it has been established that mDCs possess the capability to present antigens to naive T cells, thereby eliciting CTLs response and bolstering anti-tumor immune responses. The precise mechanisms governing the differentiation and maturation of DCs in NSCLC remain incompletely elucidated. However, current research has identified multiple factors affecting mDCs in NSCLC, including: NF-κB, STAT3 and MAPK signaling pathways, glycolysis metabolism, lncMALAT1 contained within exosomes released by NSCLC cells, tumor-derived factors in NSCLC and macrophage polarization.

Moreover, the potential utility of DC-based therapies in NSCLC treatment has been explored, encompassing strategies such as DC vaccines, DC-CIK therapy, modification and modulation of DCs. Identifying suitable candidates for DC-based therapies presents several challenges and limitations, requiring comprehensive evaluation of multiple factors: tumor type, immune status, DC functionality and quantity, TME, patient overall health, and biomarkers. For example: 1) While DC therapies are predominantly used in solid tumors such as NSCLC, melanoma, and prostate cancer, not all patients derive clinical benefit.[126–128] Tumor immune escape mechanisms, particularly TME-mediated immunosuppression, may diminish therapeutic efficacy.[112,113] 2) High levels of immunosuppressive factors such as TGF-β and IL-10, may inhibit DC function and reduce therapeutic effectiveness.[129,130] Therefore, the patient immune status needs to be thoroughly evaluated. 3) The expression levels of maturation markers such as CD80, CD86, and IL-12, can reflect DC functionality and may predict treatment outcomes.[29,36] 4) The complex and costly preparation process of DC therapy, which involves isolation of patient-derived DCs, followed by antigen loading, in vitro maturation, and reinfusion, significantly limits its application.[131,132] Through detailed screening and precise evaluation, the therapeutic efficacy of DC therapy can be improved and treatment risks reduced. In the clinical trials of DC therapy reported by Li et al and Hirschowitz et al, five patients experienced disease recurrence or progression, three of whom died.[133,134] Ethical issues must also be considered systematically, given the observed mortality and treatment failures. Patient safety continues to be the top priority, particularly in managing serious side effects like cytokine release syndrome (CRS) or autoimmune responses.[135] Given the challenges and limitations observed in these failed trials, future recommendations may include: 1) more precise patient selection criteria, particularly in areas of tumor immune escape, DC function, and immune tolerance; 2) exploring combination therapies, such as ICIs and immune modulators, to boost DC efficacy; 3) optimizing DC cultivation methods and selection criteria to enhance their functionality and immune response capabilities.

Similar to DC therapy, mRNA vaccines activate antigen-specific immune response via APCs but offer advantages such as simpler production, lower cost, and improved scalability. However, challenges remain in delivery efficiency and immune response durability.[136,137] Additionally, CAR-T cell therapy has succeeded in hematologic malignancies but struggles in solid tumors like NSCLC due to TME suppression, target antigen heterogeneity, and risks like CRS.[138–140] In contrast, DC therapies induce broader and more sustained immune responses with milder side effects.[9] Recent preclinical

studies suggest that co-culturing DC vaccines with CAR-T cells enhances the proliferation and persistence of CAR-T cells.[141] Future studies are needed to validate the efficacy and safety of this combined strategy for NSCLC treatment.

In summary, although DC-based therapies face limitations such as the patient immune heterogeneity, technical challenges in standardizing DC production, and immunosuppressive TME, they continue to demonstrate substantial clinical potential in NSCLC. Advances in combination strategies with DC-based therapies, optimization of patient selection criteria, and improvements in DC maturation and function in the future may have great potential to be transformative in the treatment of NSCLC.

Abbreviations

NSCLC, non-small-cell lung cancer; DCs, dendritic cells; APCs, antigen-presenting cells; TME, tumor microenvironment; CAR, chimeric antigen receptor; CTLs, cytotoxic T lymphocytes; Th cells, helper T cells; MHC, major histocompatibility complex; mDCs, mature DCs; lncRNA, long non-coding RNA; LC, Langerhans cell; cDCs, conventional DCs; Clec9a, C type lectin receptor 9A; XCR1, X-C Motif Chemokine Receptor 1; Sirp α, signal regulatory protein α; Th1, T helper 1; scRNAseq, single-cell RNA sequencing; pDCs, plasmacytoid DCs; GMDP, granulocyte-macrophage DC progenitor; MoDCs, monocyte-derived DCs; pre-DCs, precursor DCs; imDCs, immature DCs; FLT3L, FMS-like tyrosine kinase 3 ligand; FcR, Fc receptor; PRRs, pathogen recognition receptors; Tregs, regulatory T cells; IFN-γ, interferon-γ; NF-κB, nuclear factor kappaB; STAT3, signal transducer and activator of transcription 3; MAPK, mitogen-activated protein kinase; JNK, c-jun N-terminal kinase; ERK, extracellular signal-regulated kinases; PBMC, peripheral blood mononuclear cell; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; LLC, Lewis lung cancer; CT, cryptotanshinone; MyD88, myeloid differentiation factor 88; I-κBα, NF-κB inhibitor α; YYWY, Yangyinwenyang; TLR4, toll-like receptor 4; OXPHOS, oxidative phosphorylation; A2BR, adenosine A2B receptor; STING, stimulator of interferon genes; PKM2, pyruvate kinase M2; HIF-1α, hypoxia-inducing factor-1α; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; VEGF, vascular endothelial growth factor; HPCs, hematopoietic progenitor cells; TGF-β, transforming growth factor-β; DCregs, regulatory DCs; CALR, calreticulin; CCL19, C-C motif chemokine ligand 19; GM-CSF, granulocyte-macrophage colony-stimulating factor; NOD2, nucleotide-binding and oligomerization domain-containing protein 2; THP-1, human myeloid leukaemia mononuclear cells; TAMs, tumor-associated macrophages; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; PI3K/AKT, phosphatidylinositol-3-kinase/protein kinase B; LPS, lipopolysaccharide; anti-PD-1, anti-programmed cell death protein 1; PG2, Astragalus polysaccharide; M-CSF, macrophage colony-stimulating factor; CIK, cytokine-induced killer cells; ICIs, immune checkpoint inhibitors; CTLA, cytotoxic T lymphocyte antigen; PD-L1, programmed death ligand 1; TCR, T cell receptor; KPS, Karnofsky performance status; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3; SAL, salidroside; CRS, cytokine release syndrome.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests. Figures were created by Figdraw (www.figdraw.com).

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