

Dendritic cells instruct T cell anti-tumor immunity and immunotherapy response

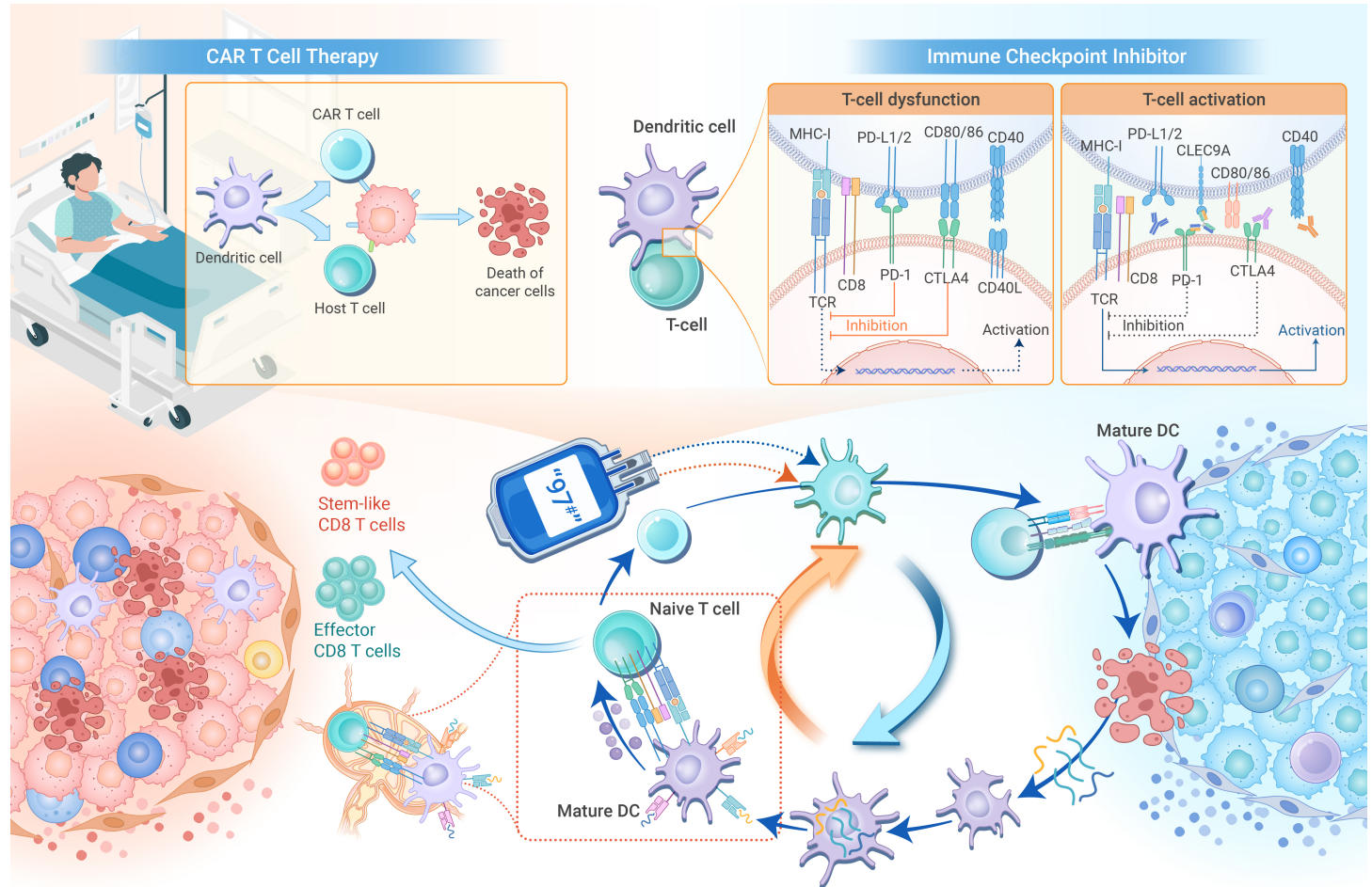
Zhen Xiao,^{1,2,6} Jiajia Wang,^{1,2,6} Jingxing Yang,^{1,2,6} Feng Guo,^{3,*} Liyuan Zhang,^{4,5,*} and Lianjun Zhang^{1,2,*}

*Correspondence: zlj@ism.cams.cn (L.Z.); guofeng27@gmail.com (F.G.); zhangliyuan@suda.edu.cn (L.Z.)

Received: December 25, 2024; Accepted: April 23, 2025; Published Online: April 24, 2025; <https://doi.org/10.59717/j.xinn-med.2025.100128>

© 2025 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- T cell-based immunotherapeutic approaches are critically dependent on the cross-presenting dendritic cells.
- DC-mediated antigen cross-presentation and DC maturation are pivotal for initiating effective T cell responses.
- DC-T cell crosstalk is impaired in the context of cancer and can even be hijacked to facilitate tumor progression.
- DC-based immunotherapeutic strategies hold great potential to improve the efficacy of cancer immunotherapy.

Dendritic cells instruct T cell anti-tumor immunity and immunotherapy response

Zhen Xiao,^{1,2,6} Jiajia Wang,^{1,2,6} Jingxing Yang,^{1,2,6} Feng Guo,^{3,*} Liyuan Zhang,^{4,5,*} and Lianjun Zhang^{1,2,*}

¹National Key Laboratory of Immunity and Inflammation, Suzhou Institute of Systems Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Suzhou 215123, China

²Key Laboratory of Synthetic Biology Regulatory Element, Institute of Systems Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Suzhou 215123, China

³Department of Oncology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou 215001, China

⁴Center for Cancer Diagnosis and Treatment, The Second Affiliated Hospital of Soochow University, Suzhou 215004, China

⁵Department of Radiotherapy & Oncology, The Second Affiliated Hospital of Soochow University, Suzhou 215004, China

⁶These authors contributed equally

*Correspondence: zlj@ism.cams.cn (L.Z.); guofeng27@gmail.com (F.G.); zhangliyuan@suda.edu.cn (L.Z.)

Received: December 25, 2024; Accepted: April 23, 2025; Published Online: April 24, 2025; <https://doi.org/10.59717/j.xinn-med.2025.100128>

© 2025 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Xiao Z., Wang J., Yang J., et al. (2025). Dendritic cells instruct T cell anti-tumor immunity and immunotherapy response. *The Innovation Medicine* 3:100128.

Dendritic cells (DCs) are a heterogeneous population of antigen-presenting cells (APCs). They play pivotal roles in orchestrating innate and adaptive immune responses, particularly in cancer. In tumor-draining lymph nodes (tdLNs), *de novo* priming occurs, where DCs present antigens to naive T cells, activating them and initiating their clonal expansion. In the tumor microenvironment (TME), intratumoral DCs provide survival or co-stimulatory signals to shape T cell differentiation. However, the scarcity and dysfunctional states of DCs can greatly limit anti-tumor responses, and DCs can even be hijacked by tumor-related factors to promote tumor progression. Therefore, comprehensively understanding the anti- or pro-tumor activities of DCs is crucial. In this review, we discuss the ontogeny of DC lineages and the emerging complexity of intratumoral DCs states. Importantly, we emphasize the significant roles of DCs in priming and sustaining productive T cell anti-tumor immunity. In light of these findings, we also explore promising approaches for targeting DCs to boost anti-tumor immunity and overcome resistance to cancer immunotherapies. We propose that insights into the rational design of DC-based immunotherapeutic strategies against cancer hold immense, underexploited potential.

INTRODUCTION

The incomplete elimination of cancer cells by the immune system results in the persistence of "immune-edited" tumors. This leads to the failure of immune surveillance and unchecked cancer development.^{1–3} Cytotoxic CD8⁺ T (CTL) cells play a pivotal role in eliminating cancer cells through a highly specific, antigen-dependent manner, making them a focus of cancer therapy development.⁴ Currently, strategies aimed at activating CD8⁺ T cells or enhancing their anti-tumor activity form the foundation of most existing immunotherapeutic strategies. These include immune checkpoint inhibitors (ICIs), adoptive cell transfer therapy (ACT), and cancer vaccines. However, generating an effective CD8⁺ T cell response is a complex process involving multiple immune system components.⁵ Also, the efficacy of immunotherapies is greatly limited by insufficient infiltration or dysfunction of tumor-infiltrating CD8⁺ T cells.⁶ Therefore, understanding of factors that govern the quality and quantity of intratumoral CD8⁺ T cells is crucial for the designing more effective therapies.

The cancer-immunity cycle provides a useful framework for understanding anti-tumor immunity. Each step in the cycle can act as a rate-limiting factor for generating an optimal immune response, and a successful anti-tumor immune response has the potential to amplify itself throughout the cycle.⁷ Dendritic cells (DCs) constitute indispensable components of the cancer-immunity cycle by initiating and regulating the adaptive immune response.⁷ Specifically, DCs encounter and process tumor antigens, subsequently presenting processed antigen peptides to naive T cells. In the tumor-draining lymph nodes (tdLNs), DCs prime naive T cells and trigger their clonal expansion and effector differentiation. Activated T cells exit the tdLNs and enter the blood circulation, and are then recruited into the tumor via chemokine gradients produced by tumor-resident DCs or other antigen-

presenting cells (APCs). Tumor-resident DCs can also further support the effector functions of T cells by providing essential co-stimulatory signals and cytokines.

Increasing evidence has demonstrated a strong correlation between T cell inflammatory characteristics and DC gene signatures in tumors.^{8–12} T cell responses do not occur in isolation but are directly regulated by DCs.¹³ The interaction between T cells and DCs is essential for effective tumor control,⁷ and this concept is increasingly recognized. While DCs do not exhibit direct anti-tumor activity, they play an important role in orchestrating effective T cell-mediated immune responses at multiple levels.¹⁴ However, the efficacy of these responses is often compromised by the scarcity or dysfunctionality of DCs, which is largely due to tumor-associated factors.^{7,14} Therefore, a more in-depth understanding of the precise activities and functional states of DCs in the cancer-immunity cycle is essential for enhancing the efficacy of immunotherapies.

Herein, we discuss recent advancements in our understanding of DC biology under homeostatic conditions and within the tumor microenvironment (TME), with a particular emphasis on insights gained through single-cell multi-omics. We also examine the mechanisms underlying antigen cross-presentation and the intricate functional crosstalk between DCs, T cells, and B cells. Furthermore, we delve into how the TME-associated factors disrupt DC function to facilitate tumor immune evasion. By highlighting recent progress in cancer immunology related to DCs, we emphasize how insights into DC biology can be harnessed to reprogram tumor immunotherapy. This addresses the critical challenge that only a small fraction of patients currently responds to therapy. Finally, we present promising DC-based immunotherapeutic approaches designed to elicit robust and durable anti-tumor immunity.

DIVERSITY OF DC IN CANCER

DC ontogeny, subsets, and function

Ontogenic and transcriptomic studies have identified distinct DC subsets that are conserved between mice and humans, and across tissues and cancer types.¹⁵ DC lineages classified on the basis of developmental, phenotypic, and functional criteria have also been identified in both mice and humans (Figure 1). DCs are broadly classified into conventional dendritic cells (cDCs), plasmacytoid dendritic cells (pDCs), and monocyte-derived dendritic cells (Mo-DCs). In both mice and humans, cDCs are divided into two distinct subsets, cDC1 and cDC2.¹⁶ Despite being derived from common DC precursors (CDP),¹⁷ cDC1 and cDC2 are highly distinct in terms of developmental and phenotypic aspects.

cDC1 is considered a transcriptionally homogeneous and clearly defined subset. It is characterized by CD8α⁺ or XCR1⁺ in mice and CD141⁺ in humans.^{16,18} Emerging evidence has shown that BATF3 and IRF8 are key transcription factors (TFs) involved in the development of the cDC1 lineage.^{19–22} Additionally, recent studies have defined the roles of DC-SCRIPT and TRIM33 in determining DC commitment and function.^{23–26} In contrast, there is significant heterogeneity within the cDC2 population, as revealed by single-cell RNA sequencing (scRNA-seq) and lineage tracing.^{27–35} For

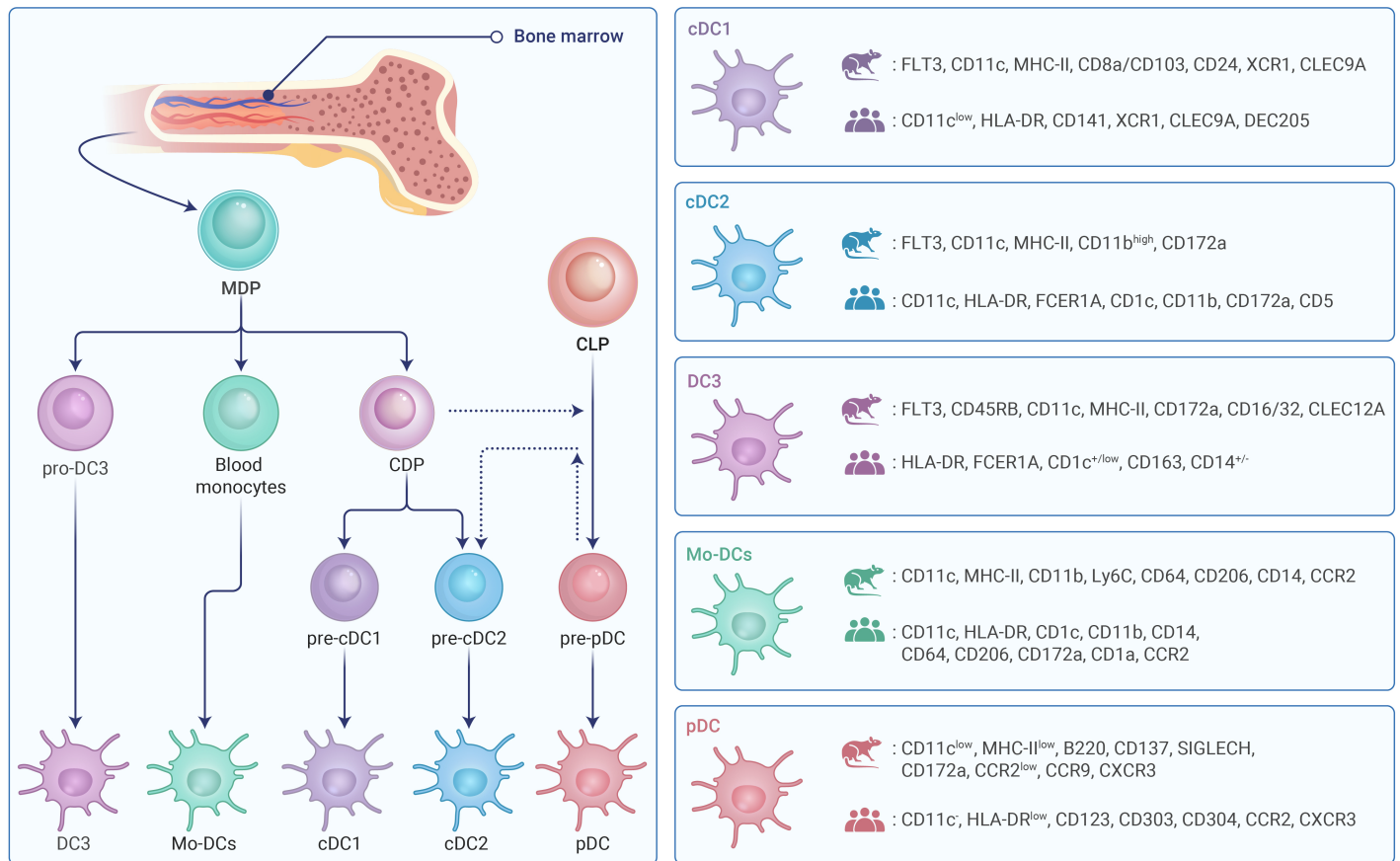


Figure 1. Dendritic cell (DCs) lineage and molecular markers In the bone marrow of mouse and humans, monocyte-dendritic cell progenitors (MDP) differentiate into pro-DC3, blood monocytes, and common DC progenitors (CDP). Pro-DC3 eventually mature to become type3 DCs (DC3), while blood monocytes differentiate into monocyte-derived DCs (Mo-DCs). CDPs give rise to type1 and type2 conventional dendritic cells (cDC1 and cDC2). Plasmacytoid dendritic cells (pDCs) develop from the common lymphoid progenitor (CLP) or from CDP, and in mice, pre-pDC can differentiate into ESAM⁺ cDC2 cells. The right panel lists specific molecular markers associated with various DC subtypes in both humans and mice.

instance, cDC2s can be further classified into T-bet⁺ cDC2A and T-bet⁻ cDC2B.³⁵ Recent studies have distinguished nonconventional type 3 dendritic cells (DC3) from cDC2 in phenotype and ontogeny (Figure 1).^{27,29–31,36} pDCs are identified by the expression of CD123 and CD303 in humans, or by CD11c and B220 in mice (Figure 1). Interestingly, a population known as transitional dendritic cells (tDCs) has been identified in both mice and humans. These cells are positioned along the phenotypic continuum between pDCs and cDC2.^{33,37} Mo-DCs primarily differentiate from infiltrating monocytes under inflammatory conditions rather than bona fide cDCs (Figure 1). Moreover, they do not express the cDCs marker ZBTB46.³⁸

cDCs are central to the cancer-immunity cycle and play crucial roles in initiating and regulating adaptive immune response. High expression of cDC1-associated gene characteristic in tumors is typically correlated with increased infiltration of T cells and improved response to ICIs.^{8,9,39–41} cDC1-deficient mouse models have also underscored the critical necessity of cDC1 in anti-tumor immunity.^{42–45} The expression of cDC2-defined genes has also been associated with improved prognosis of breast cancer, head and neck squamous cell carcinoma, and melanoma.^{46–49} For example, intratumoral CD5⁺ cDC2 related to improved overall survival in some cancer types.⁴⁶ Yet, cDC2-associated genes predict poor prognosis in non-small cell lung cancer (NSCLC).⁴⁹

pDCs represent an important source of type I interferons (IFN-I) and also play a role in anti-tumor immunity by modulating the activity of natural killer (NK) cells and T cells within the TME. For instance, *in vitro*-activated pDCs can effectively recruit and activate tumor-specific T cells in melanoma patients.^{50,51} However, pDCs have also been reported to be associated with poor prognosis, depending on cancer type.⁴⁹ Additionally, Mo-DCs are generally believed to have inferior immunostimulatory capacity compared to cDCs

but can induce T cell response in certain settings.⁵² Indeed, Mo-DCs acquire and present peptide-MHC-I (pMHC-I) complexes from tumor cells through "cross-dressing" to T cells, mediating effective T cell stimulation.⁵³ Clinical studies have identified CD14⁺CD16⁺HLA-DR^{hi} monocytes as a potent predictive biomarker for ICIs response.⁵⁴

Functional states of intratumoral DCs revealed by scRNA-seq

The unbiased characterization of single-cell transcriptomes has revealed the heterogeneity of intratumoral DCs lies not only in their ontogeny but also in their functional states.^{15,55} For example, a distinct population of stimulatory MHC-II^{high}CCR7^{neg} cDC1 has been identified, which can produce CXCL9, fostering a cDC1-TCF1⁺CD8⁺ T cell (Tpex) niche.⁵⁶ Similarly, interferon-stimulated gene (ISG) cDC2s have been observed in regressing fibrosarcoma models in mice and various human cancers.^{55,57} Moreover, a cluster of intratumoral DCs are also characterized by the expression of immunoregulatory genes (*Cd274*, *Pdcd1lg2*, and *Cd200*) and immunostimulatory genes (*Cd40*, *Car7*, *Cd86*, and *Il12b*) (Figure 2).⁵⁸ However, there is currently no consensus on the nomenclature for these DC subsets, with terms such as mregDC (mature DCs enriched in immunoregulatory molecules),⁵⁸ DC3,³⁴ CCR7⁺ DC,⁵⁹ or LAMP3⁺ DC are used.⁶⁰ A growing body of research indicates that these DCs represent a heterogeneous population with distinct functional states,^{34,55,61–63} and CITE-sequencing analyses also have revealed that CCR7⁺ DCs express surface markers of cDC1 and cDC2, suggesting a potential dual origin of these cells.^{58,64}

The combined expression of immunostimulatory and immunoregulatory molecules endows these DCs with dual functionality, a feature has become the focus of recent research.⁶⁵ Immunohistochemical analyses of human tumors have shown that CCR7⁺ DCs are often closely associated with PD-

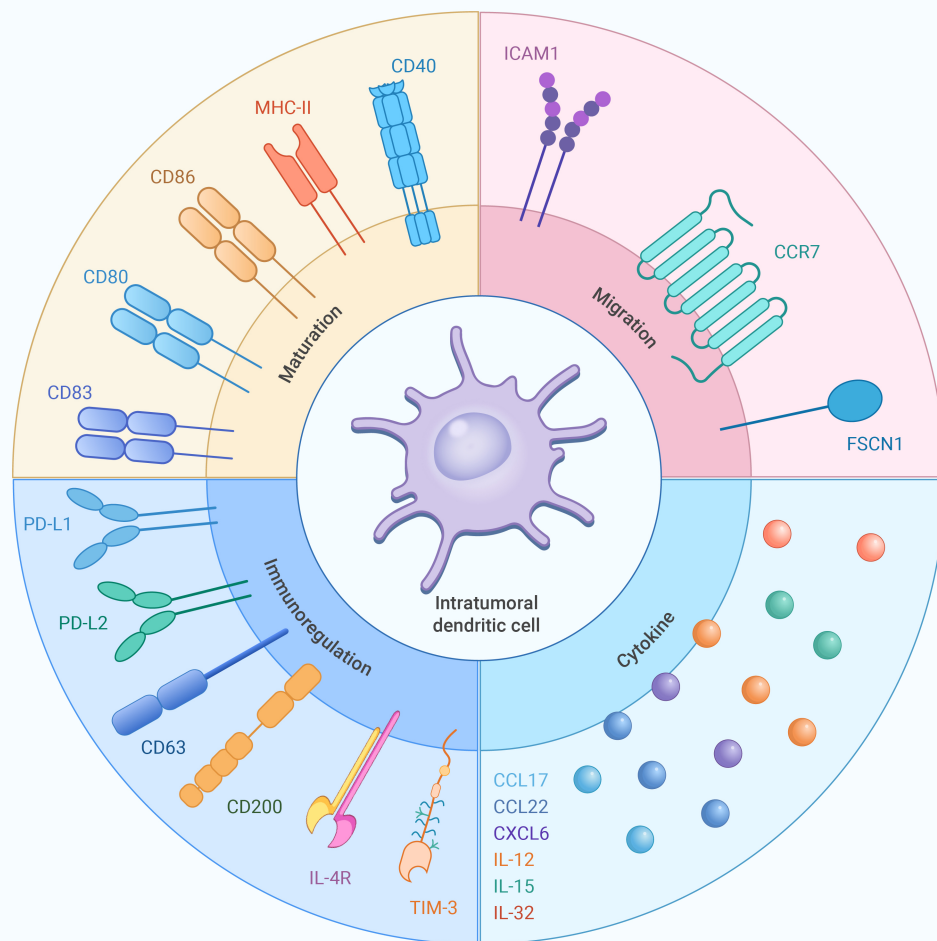


Figure 2. Intratumoral DCs characteristics Intratumoral DCs are present in a variety of tumor types and are considered to exert immunostimulating or immunosuppressive functions. They have remarkable characteristics in terms of their maturation status, migratory ability, cytokine secretion, and immunomodulatory ability. Top left: intratumoral DCs express a variety of co-stimulatory molecules, such as CD80, CD86, CD83, MHC-II, and CD40, that promote maturation of interacting immune cells, especially naive T cells; top right: high CCR7 expression facilitates DCs migration from the tumor site to the lymph nodes; bottom right: DCs recruit and regulate various immune cells to reshape the TME by secreting a variety of cytokines, such as CCL17, CCL19, CXCL6, IL-12, IL-15, and IL-32; bottom left: such as PD-L1, PD-L2, TIM-3, CD63, CD200, and IL-4R.

tionally separated.

ANTIGEN PROCESSING AND PRESENTATION BY DC

CD8⁺ T cells serve as primary effector cells involve in fighting against infection and tumors, with DC-mediated presentation of exogenous antigens is cornerstones of initiating T cell response.^{74,75} DCs capture and process antigens through various mechanisms to produce pMHC complexes and subsequently present them to T cell.⁷⁶⁻⁷⁸ This process is highly specific and determines the antigen specificity of the ensuing T cell response.^{79,80} Notably, DC-mediated cross-priming is a primary mechanism for activating anti-tumor or anti-viral CD8⁺ T cells.⁸¹ However, the mechanisms by which DCs present exogenous antigens to T cell through

cross-presentation or cross-dressing remain incompletely understood.^{76,77}

Cross-presentation

The antigen processing and presentation pathways are highly complex and involve multiple steps.⁸² Two main pathways of cross-presentation in DCs have been proposed: the vacuolar pathway and the cytosolic pathway.^{74,76} In the vacuolar pathway, exogenous antigens are processed within endosomal compartments into peptides, which are subsequently loaded onto MHC-I.⁸³ In contrast, the cytosolic pathway involves antigen translocation from endosome to the cytosol, where proteasomal degradation generates antigenic peptides.⁸⁴ These peptides are then transported into the endoplasmic reticulum (ER) via transporters associated with antigen processing (TAP) and loaded onto MHC-I (P2C pathway) or transferred back to vesicular compartments (P2C2P pathway).^{82,85} In case of TAP dysfunction, DCs employ a non-canonical cross-presentation pathway that is mediated by ER-SNARE Sec22b-dependent vesicular traffic of MHC-I from the ER-Golgi intermediate compartment (ERGIC).^{78,86}

Evidence from *LMP7*^{-/-} mice, which lack a key proteasomal subunit, suggests that the cytosolic (proteasome-dependent) pathway is predominantly utilized.^{74,84} This pathway relies on the "leakiness" of endocytic compartments due to phagosome rupture in DCs.⁷⁶ However, the precise mechanism by which antigens escape into the cytosol remains unclear. Some studies suggest that the endoplasmic reticulum-associated degradation (ERAD) complex may contribute to this process.^{76,77} For example, Sec61/Sec22b have been described to be involved in antigen translocation across the membrane into the cytosol.⁸⁷⁻⁸⁹ An alternative hypothesis suggests that lipid peroxidation of endosomal membranes facilitates antigen escape into the cytosol. This is triggered by reactive oxygen species (ROS) generated by the NADPH oxidase NOX2.⁹⁰ In detail, when the DC endocytic receptor DNGR-1 (also called CLEC9A) binds to its ligand F-actin on necrotic cells, it activates the key adaptor SYK and increases recruitment of NOX2 to

1⁺CD8⁺ T cells and ICIs efficacy.^{49,55,60,63} NSCLC and liver cancer data also suggest that CCR7⁺ DCs closely interact with CD4⁺PD-1⁺CXCL13⁺ T-helper tumor cell subsets, which are crucial for anti-tumor efficacy of ICIs.^{54,66} Furthermore, CCR7⁺ DCs produce CXCL16 to recruit CXCR6⁺CD8⁺ T cells and support the proliferation and survival of T cells through *trans*-presented IL-15.⁵⁹ A distinct subset termed LAMP3⁺ DCs are frequently observed in tertiary lymphoid structures (TLS), particularly in NSCLC patients.⁶⁷ Pan-cancer analyses have revealed that LAMP3⁺ DCs express higher levels of CCL19 compared to other DC subsets,¹⁵ a molecule critical for T cell homing and TLS formation. Giving that the presence of TLS is associated with favorable responses to ICIs, the initiation of adaptive immune responses by LAMP3⁺ DCs in TLS may serve as a key mechanism of anti-tumor immunity.⁶⁷ Furthermore, the expression of immunoregulatory factors, such as IDO1 and IL411,^{58,68} by CCR7⁺ DCs increases generation of regulatory T cell (Treg) cells. These DCs appear to lack immunogenicity due to reduced expression of IL-12 and upregulated expression of PD-L1,⁴⁹ this is partially due to enhanced IL-4 and AXL signaling.^{58,68} Hypoxic conditions further strengthen the inhibitory function of these cells.⁶⁹ Additionally, intratumoral DCs highly express CCL17/22, potentially promoting the recruitment of CCR4⁺ Tregs to the TME and limiting the initiation of immune responses.⁷⁰⁻⁷²

Overall, increasing evidence indicates that concurrent expression of immunostimulatory and immunoregulatory molecules results in highly variable functional states of intratumoral DCs. These functional differences are highly context-dependent.⁴⁹ Such evidence emphasizes the complexity of DCs in shaping anti-tumor immunity. Future research should focus on fully characterizing these functionally heterogeneous intratumoral DCs and conducting in-depth functional analyses to explore relevant therapeutic strategies. A promising direction is to identify novel markers specific to mregDC, an example of which is the recent discovery of CD63.⁷³ Currently, it remains unclear whether the immunostimulatory and immunoregulatory modules that are often co-upregulated during DC maturation can be func-

the phagosome.⁹⁰ This leads to sustained ROS production, which induces lumen alkalization, lipid oxidation, and membrane disruption of the phagosome,⁹¹ facilitating the translocation of antigens to the cytosol. Recent reports have identified some components involved in disruption of the phagosome membrane, including VAMP8,⁹¹ ZEB1,⁹² and members of the Ras superfamily of small GTPases, such as Rac2 and Rab27a.^{93–95} However, the function of DNNG-1 in anti-tumor immunity remains ambiguous. While DNNG-1 contributes to the cross-presentation of antigens derived from dead cells, it appears to be dispensable for the cross-presentation of soluble antigens and bacterial antigens. Additionally, DNNG-1 deficiency does not produce significant defects in the control of immunogenic tumors.^{21,44,57,96–97} Paradoxically, DNNG-1 appears to restrict anti-tumor immunity by suppressing the expression of CCL5.⁹⁸ These findings suggest the existence of DNNG-1-independent cross-presentation mechanisms. Indeed, two pore-forming proteins, perforin-2 and apolipoprotein APOL7C, were recently identified as key effectors of endosomal antigen escape in cDC1.^{99,100} But further research is needed to clarify their roles in antigen cross-presentation and T cell cross-priming.

Specialized vesicular transport mechanisms, potentially regulated by Sec22b and RAB43,^{85,88,101} are also thought to mediate antigen translocation in the cytosolic pathway. Functional CRISPR screen identified the BEACH domain-containing protein WDFY4 as a key factor for cross-presentation, potentially due to its role in vesicular transport.⁹⁶ However, the precise mechanisms by which WDFY4 influences cross-presentation remain unclear. Additionally, other molecules involved in cross-presentation, such as the m6A reader protein YTHDF1 and palmitoyl-protein thioesterase 1, have been proposed to regulate peptide degradation, either directly or indirectly.^{102–104} Additionally, the antigen cross-presentation pathways also involve other critical yet understudied steps, such as antigen ubiquitination and proteolytic processing. Systematic CRISPR screening may facilitate the identification of key ubiquitin ligases that regulate antigen cross-presentation.

Cross-dressing

In addition to cross-presentation, cross-dressing is an emerging antigen presentation pathway that increasingly attracts attention in tumor immunology. In this process, DCs acquire pre-formed functional pMHC complexes from neighboring cells without processing the antigen themselves.^{105,106} pMHC-I complexes can be transferred through diverse mechanisms,¹⁰⁷ including trogocytosis,¹⁰⁸ extracellular vesicles (EVs),¹⁰⁷ or membrane nanotubes that allow to protein traffic.¹⁰⁹ Cross-dressing can also occur between two DCs. For example, migratory DCs carry tumor antigen-laden vesicles to tDLNs and form tight synaptic contacts with resident DCs, facilitating antigen transfer.¹¹⁰ Arisa et al. also demonstrated that DCs can swiftly acquire MHC-I-containing membrane fragments from dead cells through phosphatidylserine recognition.¹¹¹ Moreover, recent studies in mouse tumor models have revealed that, in the absence of cross-presentation, both cDC1 and cDC2 are capable of obtaining tumor-derived pMHC-I complexes via cross-dressing.^{57,112} Interestingly, a study using *Wdfy4*^{-/-} mice discovered that the contribution of cDC1 cross-presentation to CD8⁺ T cell activation is marginal.¹¹² This suggests that cross-dressing plays an important role in T cell activation in certain context. Furthermore, another study revealed that ISG⁺ cDC2 cells in tumor-bearing mice can load tumor-derived pMHC-I complexes by cross-dressing, thereby inducing a robust anti-tumor CD8⁺ T cell response in the absence of cDC1.⁵⁷ The ISG⁺ cDC2 gene signature is also present in human tumors and could potentially be harnessed through strategies such as IFN-I administration or vaccination.⁵⁷

While it is evident that cross-dressing is a prevalent antigen spread mechanism that is significant for driving anti-tumor immunity, our understanding of when, why, and how it occurs is far from complete. Based on existing evidence,¹⁰⁶ the advantage of cross-dressing appears to lie in its ability to enable DCs to initiate CD8⁺ T cell responses against tumor antigens that are processed and presented by tumor cells only and not by DCs. Our current knowledge of how cross-dressing and cross-presentation differently impact CD8⁺ T cell function is also limited. *In vivo* studies demonstrated that optimal priming of CD8⁺ T cells requires both cross-presentation and cross-dressing.¹¹³ Indeed, owing to their inherent differences and complementary nature, the co-existence of these two antigen presentation pathways may

increase the likelihood of effectively activating the adaptive immune response.

However, tumors have evolved various mechanisms to inhibit the antigen presentation of DCs. For instance, tumor cells can secrete gelsolin (sGSN), which inhibits DNNG-1 binding with F-actin.¹¹⁴ Moreover, CBL E3 ligases can be recruited to the DNNG-1 receptor complex to mediate the ubiquitination of SYK, terminating DNNG-1 signaling.¹¹⁵ Intratumoral DC-intrinsic XBP1-driven oxidative lipid accumulation has also been linked to defects in antigen cross-presentation.¹¹⁶ Additionally, activation of the ER stress sensor IRE1 α curbs DC cross-presentation through regulated IRE1 α -dependent decay (RIDD) of MHC-I.¹¹⁷ Collectively, these findings underscore the complexity of antigen presentation in intratumoral DCs.

DC MATURATION

The diverse functions of DCs are acquired through a complex, multi-stage process known as maturation. Single-cell multi-omics analysis of DC maturation has revealed that it is not a uniform activation process, but rather a heterogeneous differentiation program with varied outcomes,⁶² including stimulatory DCs, hyperactive DCs, and tolerogenic DCs.⁶⁵ Therefore, it is crucial to understand the molecular programs of DC maturation, and how tumors hijack this process to suppress the immunogenic functions of DCs. This will aid in the development and improvement of DC-targeted therapies and synergistic T-cell-based immunotherapeutic strategies.

Immunogenic maturation

In order to effectively activate T cells, DCs must undergo immunogenic maturation. During this process, DCs undergo phenotypic and functional changes, providing the necessary co-stimulatory signals such as CD80, CD86, and CD40, as well as cytokines such as IL-12 and IFN-I. These allow them to effectively prime T cells.^{5,62}

The immunogenic maturation process of DCs is induced by the activation of pattern recognition receptors (PRRs) (Table 1), which are triggered by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs).¹¹⁸ In the TME, the immunogenic maturation of DCs can be induced by tumor-derived DNA and microbes. These activate the cGAS-STING signaling pathway and induce secretion of IFN-I and the chemokines CXCL9/10.^{119,120} Toll-like receptors (TLRs) constitute another well-known class of PRRs that trigger DC maturation.¹²¹ Numerous findings have shown a significant correlation between TLR activation and the induction of DC maturation.^{52,122,123} However, the mechanisms of TLR-induced DC maturation differ depending on the specific TLR receptor. For instance, TLR4-TRIF-induced DC maturation is independent of IRF3 and IFN-I, whereas TLR3-mediated DC maturation relies entirely on IFN-I feedback.¹²⁴ Notably, TLR3 agonists specifically induce cDC1 maturation, promoting the production of type III interferons (IFN- λ) and enhancing anti-tumor immune response.⁴⁷ Although PRRs are potent in activating anti-tumor immunity, not all PRRs are beneficial. For instance, the mitochondrial antiviral signaling protein (MAVS) has been shown to inhibit a noncanonical NF- κ B (ncNF- κ B) signaling pathway in DCs, thereby suppressing their immunogenicity within tumors.¹²⁵ Additionally, chronic TLR and STING signaling can lead to intratumoral DC dysfunction.^{126,127}

In addition to engagement of PRRs by PAMPs or DAMPs, soluble factors and other signaling pathway have been implicated in modulating DC maturation. Two relevant transcriptional programs are characteristic of mature DCs, represented by ISG⁺ DC and mregDC, are enriched in IFN-I/II-induced and NF- κ B-induced signaling pathway, respectively.^{57,127} Since the 1990s, IFN-I have been recognized as critical regulators of DC maturation and function.¹²⁸ Both intrinsic and extrinsic IFN-I signaling in DCs enhance the expression of co-stimulatory molecules and the chemokine receptor CCR7.^{129–132} The activation of DCs represents a fundamental mechanism underlying the concept of immunogenic cell death (ICD). In ICD, tumor-derived danger signals trigger endogenous or exogenous IFN-I signaling in DCs.¹³³ For example, IFN-I signaling maintains a basal state of DC maturation, enabling them to respond to additional maturation signals from PAMPs or CD40 stimulation.¹³⁴ Additionally, although both IFN-I and IFN- γ signaling promote DC maturation, IFN- γ plays a unique and non-redundant role in DC maturation and anti-tumor immunity. Particularly, IFN- γ signaling can orchestrate DC maturation by

Table 1. Agents inducing immunogenic functions of DCs.

Compounds	Characteristics	Effect on DCs and immune consequences	Clinical trials
GM-CSF	Cytokine essential for cDC development	DCs homeostasis, development, migration and activation	NCT04106180
FLT3L	Cytokine essential for DC and NK cell development	Promotes cDC1 and cDC2 mobilization/expansion, enhances tumor immunity	NCT01811992
TLR2/TLR4 agonists	Synthetic or microbial-derived PRR ligands	Mainly activates human cDC2, promotes cytokine secretion, CD8 ⁺ T cell induction, and immune response	NCT02615574
TLR3 agonists	Synthetic PRR ligands, mainly poly(I:C) derivatives	Activates cDC1, induces Th1 immunity, NK cell activation, and CD8 ⁺ T cell response	NCT03403634
TLR5 agonists	TLR5 ligand recognizes bacterial flagellin	Activates DCs, promotes antigen presentation and pro-inflammatory cytokine secretion	NCT01289210
TLR7/TLR8 agonists	Various ligands targeting PRRs, mainly imidazoquinolines	Activates pDCs and cDCs, induces cytokine production, Th1 immunity, CD8 ⁺ T cell activation, and anti-tumor responses	NCT02826434
TLR9 agonists	Synthetic PRR ligands, unmethylated CpG oligonucleotides	Activates pDCs and cDCs, induces Th1 immunity and CD8 ⁺ T cell response	NCT02254772
STING agonists	Activators of the STING pathway, crucial for detecting intracellular DNA	Induces type I interferons, activates DCs, and enhances tumor immunity	NCT05916274
IFN-I	Includes IFN- α and IFN- β , crucial for antiviral and antitumor immunity	Enhances DC antigen presentation, activates NK cells and T cells, suppresses tumor growth	NCT02615574
CD40 agonists	Target CD40, a costimulatory molecule on antigen-presenting cells	Enhances DC maturation, antigen presentation, and T cell activation for tumor immunity	NCT04059588 NCT04547777
TIM-3 antibody	Block TIM-3, an immune checkpoint receptor on T cells and DCs	Prevents DC dysfunction, restores T cell responses, and enhances antitumor immunity	NCT06608940
Hyperactivators	Hyperactive DCs by 1-palmitoyl-2-glutaryl phosphatidylcholine (PGPC) with LPS	Enhance DC function, T cell activation, and inflammatory cytokine production	Pre-clinical mice model

inducing the expression of CXCL9/10, which recruit CXCR3⁺ CTLs and facilitate DC-T cell interactions.¹⁰ Moreover, IFN- γ signaling establishes a feedforward loop of IL-12-IFN- γ as part of the DC-T cell crosstalk.¹¹ This mechanism has been highlighted in multiple preclinical tumor models as a crucial determinant of effective anti-tumor immunity. Despite the well-documented role of interferons in promoting DC maturation, clinical outcomes of interferon therapies in cancer treatment have yielded mixed results, particularly in solid tumors.¹²⁷ Emerging technologies offer potential strategies for precisely delivering interferons and thereby maximize their anti-tumor potential.

The canonical NF- κ B (cNF- κ B) and ncNF- κ B signaling pathways also play pivotal roles in DC maturation and function. Intratumoral DC maturation and priming of CD8⁺ T cells by cDC1 are orchestrated by a cNF- κ B-dependent program mediated through the activation of interferon regulatory factor 1 (IRF1).¹³⁵ Specific deletion of *Ikbkb* in DCs impairs their maturation, decreases CD8⁺ T cell infiltration, and consequently promotes tumor growth.¹³⁵ Although the cNF- κ B and ncNF- κ B pathways share interconnected signaling nodes, they have distinct functions. Loss-of-function mutations in NF- κ B-inducing kinase (NIK) reveal that ncNF- κ B exhibits unique immunological and inflammatory functions.¹³⁶ Current research on the role of ncNF- κ B in DC maturation primarily focuses on CD40 signals, which induce ncNF- κ B signaling activation. This upregulates the expression of maturation and co-stimulatory molecules while promoting IL-12 secretion.¹³⁷ CD40 deficiency in cDC1 leads to impaired cDC1 survival and maturation.¹³⁸ Furthermore, loss of CD40 signaling disrupts mitochondrial function in DCs, suggesting that metabolic reprogramming mediated by ncNF- κ B activation plays a role in DC maturation.¹³⁹ Intriguingly, during radiotherapy, components of ncNF- κ B (p52/RelB) are recruited to the *Irfn* promoter, which suppresses the production of IFN-I in DCs and anti-tumor efficacy.¹⁴⁰

Of note, recent studies have identified a new mode of DC maturation that produces “hyperactive” DCs.^{141,142} Typically, inflammasome activation in DCs triggers the release of large amounts of active IL-1 β , which is often accompanied by pyroptosis.¹⁴¹ However, combination of LPS and oxidized phospholipids oxPAPC or PGPC has been shown to initiate a unique transcriptional program in DCs (Table 1), pushing them into a hyperactive state. In this state,

IL-1 β is released in a caspase-11-dependent manner without pyroptosis.¹⁴¹ Importantly, mouse models have revealed that excessive activation of DCs uniquely induces durable CTL-mediated anti-tumor immunity, particularly in tumor models resistant to PD-1 inhibition. Interestingly, hyperactive DCs elicit Th1-skewed CD4⁺ T cell response in an NLRP3 inflammasome-dependent manner, which can correct age-related anti-tumor immune deficiencies.¹⁴³ These findings suggest that the mechanism of DC hyperactivation deserves in-depth investigation to uncover its therapeutic potential. Currently, questions remain on how the combination of LPS and PGPC promote DC entry into the hyperactivated state. It is also unclear whether there are other DC agonist combinations that could more effectively induce DC hyperactivation.

Tolerogenic maturation

Tolerogenic DCs were once thought to be immature or semi-mature. However, emerging evidence suggests that they undergo a full maturation program and express inhibitory molecules such as PD-L1 and PD-L2,¹⁴⁴ which stands in contrast to the quiescent state of immature DCs. Recent studies have intriguingly shown that the transcriptional program of IFN-I-induced ISG⁺ DCs is highly enriched in early mature cDC1, but it is downregulated in a later mature cDC1 subset that harbors the mregDC transcriptional program.^{127,145} These findings imply that tolerogenic DCs reflect a remodeling of the maturation process, rather than a completely new maturation program.

Intratumoral DC maturation is shaped by factors within the TME, where tumor- or stroma-derived soluble mediators induce tolerogenic DC formation.¹⁴⁶ For instance, IL-10, IL-27, transforming growth factor-beta (TGF- β), aryl hydrocarbon receptor (AhR) ligands, vitamin D, and rapamycin have all been shown to induce tolerogenic DCs under tumor conditions.^{144,146–148} In addition, the role of metabolic shifts in DC maturation has garnered significant attention. Various metabolic conditions within the TME can disrupt normal metabolic homeostasis and maturation state in intratumoral DCs,^{149,150} including hypoxia, ER stress, lactate accumulation, nutrient deprivation, ROS accumulation, and dysregulated amino acid and adenosine metabolism. One example is that tumor-derived liver X receptor (LXR) ligands weakens CCR7 expression on DCs, which is essential for the migration of

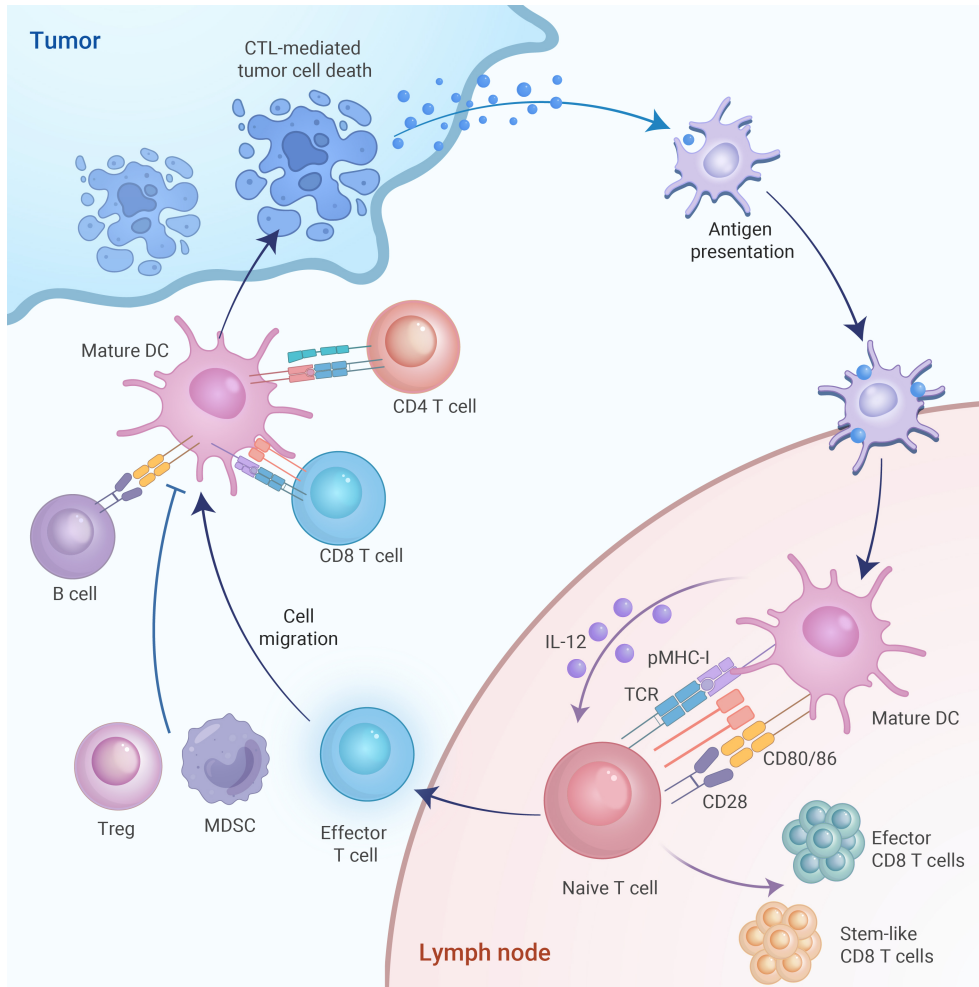


Figure 3. DC prime T cell activation in the tdLN and TME In the tumor microenvironment (TME), DCs play a crucial role in orchestrating the immune response. Mature DCs capture tumor antigens and migrate to the tumor-draining lymph nodes (tdLNs), where they present captured antigens to naive T cells, initiating the immune response. This interaction results in the activation of naive T cells, which differentiate into effector and memory CD8⁺ T cells. Effector T cells migrate to the tumor site, where cytotoxic T lymphocytes (CTLs) exert their cytotoxic effects by inducing death of tumor cells. In the TME, regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs) modulate CTL activity, and efficient antigen presentation by mature DCs sustains CTL activation.

that DCs not only mediate T cell priming but also affect their local immune landscape (Figure 3).¹⁵⁶ This depends on the physical proximity of DC-derived signals.

Interactions between DCs and CD8⁺ T cells

T cell responses are orchestrated within distinct microanatomical environments in lymph nodes (LNs) and the TME, where the interaction between DCs and CD8⁺ T cells significantly impact the activation and differentiation of T cells. For example, effector and stem-like CD8⁺ T cells are generated within LNs and are associated with spatially distinct DC subsets.¹⁵⁷ Specifically, effector-like T cells are generated at the periphery of LNs in a CXCR3-dependent manner and are associated with CXCL10-expressing cDC2.¹⁵⁸ In contrast, stem-like T cells co-localize with CXCL9-expressing cDC1 in the paracortex of LNs in a CCR7-dependent manner.¹⁵⁸ The spatial organization

intratumoral DCs to tdLNs,^{61,151} and induces a tolerogenic maturation program by promoting cholesterol efflux.¹⁴⁵ The tyrosine kinase receptor AXL has been identified as a key regulator of cholesterol metabolism, promoting tolerogenic DC maturation by inhibiting the biosynthesis and transport of cholesterol.⁶⁸ Additionally, phagocytic receptors that recognize “eat-me” signals facilitate dead cell engulfment under certain conditions, which is considered an “immunologically silent” process.¹²⁷ Phosphatidylserine recognition receptors, such as MERTK and AXL, contribute to immune suppression by blocking NF- κ B signaling or inducing SOCS1 and SOCS3 expression.¹²⁷ Furthermore, TIM-3 on DCs can drive tolerogenic programming by inhibiting the cGAS-STING pathway and inflammasome activation.^{152–154} Blocking phosphatidylserine recognition or inhibitory phagocytic receptors has been shown to enhance the immunogenic maturation of DCs and tumor control.^{68,152–154} Moreover, it is noteworthy that many of the mechanisms that inhibit or enhance the maturation and function of DCs are associated with the presence and composition of the gut microbiota, a field of active ongoing research.

Overall, tumor cells and the TME can directly or indirectly regulate DC maturation, reshaping the immune landscape of the tumor. Understanding these different DC maturation states will help develop better immunotherapeutic strategies to optimize anti-tumor immune responses.

DC-T/B-CELL INTERACTIONS SHAPE THE ANTI-TUMOR IMMUNE RESPONSE

The unique spatial localization and interactions of immune cells within tumors, are critical determinants of the efficacy of immunotherapy in solid tumors, and are more important than just their quantity, an example is the formation of immunological triads and TLS.^{67,155} DCs produce chemokines to attract T cells and profoundly influence the fate decisions of infiltrating CD8⁺ and CD4⁺ T cells. The latest two-step activation model of T cells suggests

of DCs and CD8⁺ T cells significantly shapes T cell fate through DC-derived signals. Inflammation-induced DC repositioning within the LNs or selective disruption of DC-derived chemokine signaling can directly affect the phenotype of activated CD8⁺ T cells.^{158,159}

DCs in the TME also influence the spatial organization and effectiveness of CD8⁺ T cell responses. Intratumoral DCs produce the chemokine CXCL9/10 to attract CD8⁺ T cells to the tumor site, resulting in colocalization of intratumoral cDC1 and CD8⁺ T cells.^{9,10,56} This could be why CD8⁺ T cells exposed to cDC1-derived IL-12 generate a stronger anti-tumor response.¹⁶⁰ The function of cDC1 can be therapeutically enhanced through TIM-3 and PD-L1 blockade, which has been shown to increase CXCL9 expression in cDC1 and enhance cDC1-CD8⁺ T crosstalk.^{152–154,161} DCs can provide critical survival signals to co-localized CD8⁺ T cells within the perivascular niche of the tumor stroma. For instance, CXCL16⁺ DCs *trans*-present IL-15 to CXCR6⁺ CTLs,⁵⁹ promoting the local expansion of T cells in the TME. Additionally, DCs provide auxiliary signals from T helper (Th) cells to CD8⁺ T cells through the CD70-CD27 axis.¹⁶² Chimeric switch receptors designed to exploit this axis significantly improved the efficacy and persistence of CAR T cells.¹⁶³

Tpex cells are crucial for maintaining anti-tumor immunity, especially during ICIs therapy.¹⁶⁴ They give rise to more differentiated effector cells that effectively control tumor progression. Studies have demonstrated spatial correlations between the Tpex and MHC-II⁺ APCs,¹⁶⁵ and tumor-associated macrophages (TAM) have been shown to drive T cells terminal exhaustion.¹⁶⁶ These findings imply that DCs may provide critical support the maintenance of the Tpex population. Recent studies support the concept that cDC1s maintain the Tpex population in an MHC-I-dependent manner, preventing activation-driven T cell exhaustion in a chronic LCMV infection model.¹⁶⁷ Furthermore, increasing the number and activity of cDC1 enhances the pool of TCF1⁺CD8⁺ T cells in tdLNs.¹⁶⁸ However, key questions remain regarding the origin of TCF1⁺CD8⁺ T cells within tumors and the specific mechanisms by

which cDC1 sustain Tpex formation. Latest evidence suggests that Tpex formation in tdLNs and their persistence within tumors depend on the proximal location of DCs and optimal TCR signals.¹⁶⁹ Other studies have shown that the CXCL9-producing cDC1 co-localize with TCF1⁺CD8⁺ T cells in LNs and tumors.^{56,158} However, it was also shown that deletion of CXCL9 did not alter CD8⁺ T cell differentiation.¹⁵⁸ Our unpublished findings indicate that Tpex cells highly express XCL1, and overexpression of XCL1 in T cells preserves TCF1 expression within the TME. Nevertheless, it remains unclear whether XCL1 expression by Tpex cells is a prerequisite for forming memory-like populations or a result of their differentiation. Future studies using the strategies of XCL1-specific deletion could provide valuable insights into how cDC1s facilitate the formation of Tpex subset. Additionally, although studies indicate that DC-T cell interactions are essential for the maintenance of Tpex cells, the specific signals provided by DCs (such as TCR signaling, cytokines, co-stimulatory or co-inhibitory signals, and metabolites) remain largely unknown. A comprehensive understanding of how these signals sustain Tpex and how they can be modulated to enhance Tpex persistence will offer new perspectives in rationally designing therapies to optimize anti-tumor immunity of CD8⁺ T cells.

Interactions between DCs and CD4⁺ T cells

CD4⁺ T cells enhance the maturation and function of DCs through CD40, endowing DCs with anti-tumor activity.^{21,164} Reciprocally, it was recently shown that CD40 signaling to cDC1 is also crucial for CD4⁺ T cell priming and anti-tumor activity.¹³⁸ Moreover, CD4⁺ T cells themselves produce inflammatory cytokines that stimulate the immunogenic maturation of DCs. For example, type 1 T helper (Th1) cells secrete IFN- γ and IFN- γ , which enhance the antigen cross-presentation ability of DCs.^{132,170} Type 2 T helper (Th2) cells produce IL-4 and IL-5, which can affect the migration and function of DCs.¹⁷¹

DC-CD4⁺ T cell interactions also have spatial coordination with other immune cells, particularly CD8⁺ T cells.¹⁷² During the effector phase, CD4⁺ T cells interact with CD8⁺ T cells on the surface of the same DC forming a three-cell cluster that licenses CD8⁺ T cell anti-tumor cytotoxicity. Owing to the complexity of the interaction, it is challenging to study this configuration directly *in vivo*. The technique "Labeling Immune Partnerships by Sorting Intercellular Contacts" (LIPSTIC) provides a valuable means to analyze the mechanisms of dynamic cell-cell interactions directly.¹⁷³ This method was used to show that there are two distinct modes of interaction between DCs and CD4⁺ T cells during T cell priming, offering important insights into the intricacies of immune cell interactions. Additionally, it was observed that, while interacting with CD4⁺ T cells in both tdLNs and the TME, DCs adopt a hyperactivated phenotype, characterized by the production of IL-27, and DCs exhibit a similar transcriptional profile while interacting with CD4⁺ T cells.¹⁷⁴ Latest evidence indicates that DC-derived IL-27 also supports tumor control by CD8⁺ T cells.¹⁷⁵

Additionally, the interaction between DCs and Tregs has also been widely discussed.¹⁸ On one hand, DCs induce Treg development through various molecules, including retinoic acid (RA), IDO, IL-10, and TGF- β .¹⁸ In the TME, DCs typically upregulate inhibitory molecules to enhance Treg differentiation and accumulation via chemokines such as CCL17/22.^{71,72} Specifically, mregDC maintain Treg activation via the CCL17/22-CCR4 axis, forming a Treg-mregDC-lymphatic niche that restricts mregDCs migration and T cell responses.⁷⁰ On the other hand, Treg actively remodel the characteristics of tumor-infiltrating DCs, particularly by inhibiting their maturation and antigen-presenting capabilities.⁵² While cDC1-derived CXCL9/10 are crucial for recruiting tumor-infiltrating T cells, recent studies have shown that Treg co-localize with DCs in tumors via the CXCR3-CXCL9/10 axis, inhibiting DC function.¹⁷⁶ Interaction between Tregs and DCs also plays a non-redundant role. For instance, CTLA-4 on Tregs reduces the expression of stimulatory molecules on DCs, weakening DC-CD8⁺ T cell crosstalk.¹⁷⁷ Additionally, lung tdLNs specifically enrich IFN- γ -induced inhibitory Th1-like effector Treg, driving cDC1 inhibition through MHC-II dependent DC-CD4⁺ T contact.¹⁷⁸ Similarly, HDVax-induced type 1 regulatory T (Tr1) cells selectively kill cDC1, leading to a reduction in the number of cDC1 within the tumor.¹⁷⁹

Increasing evidence highlights the crucial role of DC-T cell interactions in tumor control and successful immunotherapy.^{56,172,180} However, it should be noted that DC-T cell interactions also promote the proliferation and function

of Tregs, favoring tumor progression. Deconstructing the different modes of DC-T cell interactions will be a key focus in future efforts to develop interventions that enhance beneficial interactions in anti-tumor immunity while blocking unwanted ones.

DC-B Cell Interactions in Tertiary Lymphoid Structures

TLS are lymphoid-like formations that emerge in non-lymphoid tissues under chronic inflammation conditions, such as cancers, chronic infections, and autoimmune diseases. B cells are critical components of TLS,^{57,181} and play a pivotal role by acting as substitutes for lymphoid tissue inducer (LTi) cells and secreting the lymphotoxins α 1 β 2 (LT α 1 β 2) or LIGHT (TNFSF14). These signals activate lymphoid tissue organizer (LT α) cells expressing lymphotoxin- β receptor (LT β R),¹⁸² facilitating TLS formation.

During TLS formation, CXCL13⁺ follicular dendritic cells (FDC) guide the distribution of CXCR5⁺ B cells, establishing B cell-rich regions with a reticular structure. FDC produce cytokines such as B cell activating factor (BAFF), APRIL, and IL-6, which support B cell survival, proliferation, and differentiation into plasma cells.¹⁸² Additionally, B cell signaling through CXCR5 induces the expression of LT α 1 β 2. This initiates a positive feedback loop that sustains lymphoid chemokine production and preserves the lymphoid niche. The FDC-B cell interaction within TLS is akin to their interaction in the germinal center of secondary lymphoid organs. Recent studies also highlight the critical role of mature DCs, particularly cDC1, in TLS formation and function.¹⁸³ Spatial transcriptomics analyses by Mattiuz et al. revealed molecular signatures significantly enriched in TLS, including those of mature DCs (CCR7, FSCN1), cDC1 (XCR1), T follicular helper cells (TFH), memory B cells (CD19, BANK1), and germinal center B cells (LMO2, MEF2B, RGS13).¹⁸³ Proximity analysis revealed that mature DCs are closely located (within 30 μ m radius) to naive B cells, T cells, and germinal center B cells. Notably, cDC1 depletion significantly reduced TLS formation and the presence of germinal center B cells. Altogether, this underscores the importance of DC-B cell interactions in TLS maintenance and function. These findings have profound implications for cancer immunotherapy. However, the precise spatial organization and molecular mechanisms governing DC-B cell interactions in TLS remain unclear. Further investigations are required to elucidate how these interactions shape T-cell mediated immune responses and impact therapeutic outcomes.

DCs ARE CRITICAL FOR THE CLINICAL EFFICACY OF CANCER THERAPY

Current cancer therapy, including chemotherapy, radiotherapy, and small molecule inhibitors, may require or even rely on the activation of DCs to induce T cell responses.¹³³

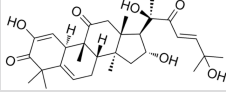
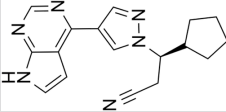
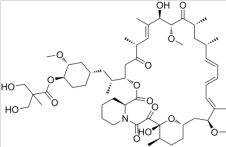
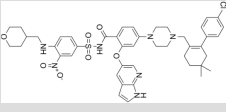
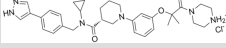
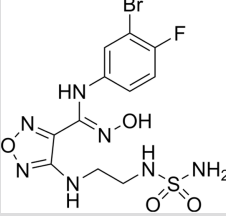
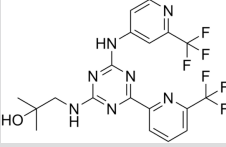
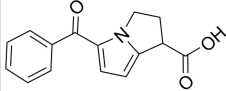
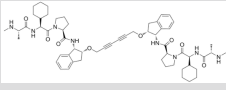
Radiotherapy and DCs

Radiotherapy induces the release of DNA from tumor cells, which activates cGAS-STING sensor and promotes IFN- γ production, thereby enhancing anti-tumor immunity.^{184,185} Evidence has shown that this process involves cDC1-mediated CD8⁺ T cell activation via the cGAS-STING pathway.¹⁸⁴ Additionally, the ZBP1-RIPK3-MLKL necroptotic cascade in tumor cells can activate the cGAS-STING pathway, inducing DC activation.¹⁸⁶ However, radiotherapy can also suppress anti-tumor immunity. For example, high doses of non-fractionated radiotherapy can induce the expression of DNase TREX1, which degrades cytosolic DNA.^{187,188} A recent report noted that radiation can upregulate YTHDF1 expression in DCs through STING-IFN signaling, inhibiting their antigen presentation capacity.¹⁸⁹ Additionally, non-canonical NF- κ B signaling dampens radiation-induced anti-tumor immunity by inhibiting IFN- γ producing.¹⁴⁰ These evidence highlights the dual influence of radiotherapy on DC function.

Small-molecule inhibitors and DCs

Small molecule inhibitors target key oncogenic signals in tumor cells can restore DC function (Table 2), examples include STAT3 and mTOR, which can impair DC differentiation and survival.¹⁴ STAT3 inhibitors can reverse abnormal DC function in the TME.¹⁹⁰ Activation of WNT- β -catenin signaling induces immunosuppression through mTOR-IL-10 dependent pathways in DCs. Consistently, the mTOR inhibitor temsirolimus enhances the efficacy of DC vaccines.¹⁹¹ Interestingly, genome-wide CRISPR screens revealed BCL2 as an

Table 2. Small-molecule inhibitor in cancer therapy.

Inhibitor	Product	Chemical structure	Effect on DCs	Cancer-treatment approved examples
STAT3 inhibitors	JSI-124		DC activation, prevention of DC survival	Mice tumor model
	Ruxolitinib		Reprogramed immunostimulatory state of DC	Myelofibrosis, NCT03681561
mTOR inhibitor	Temsirolimus		Enhanced the activity of DC vaccines	kidney cancer
BCL2 inhibitor	Venetoclax		DC immunogenic maturation	Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or acute myeloid leukemia (AML)
BCL9 inhibitor	ZW4864		DC activation, enhanced antigen presentation of DC	Mice tumor model
IDO inhibitor	Epacadostat		Prevention of IDO-mediated tryptophan depletion, tolerogenic functions of DC	NCT03516708 (Phase II) NCT02752074 (phase III)
IDH inhibitor	Enasidenib		DC activation via IFN-1 pathway	NCT03343197, IDH-mutated acute myeloid leukemia (AML)
Cox inhibitor	ketorolac		Prevention of PGE2 prodction, preserved the proliferation and functionality of DC	Nonsteroidal anti-inflammatory drug (NSAID) used to treat pain
IAP Antagonist	AZD5582		non-canonical NF-kB pathway activation, DC maturation	Mice tumor model

endogenous inhibitor of DC function.¹⁹² When combined with ICIs, the BCL2 inhibitor venetoclax enhances DC-dependent tumor regression. This is potentially due to increased mitochondrial DNA release and enhanced DC immunogenic maturation.

Immune checkpoint therapy and DCs

The therapeutic efficacy of ICIs is shaped not only by their direct effects on T cells but also by their direct or indirect modulation of DC-mediated anti-tumor activities. Preclinical data indicate that ICIs primarily exert their effects through DCs, particularly cDC1s, to prime and maintain T cell response.¹⁹³ Tumor-bearing mice lacking CD11c⁺ cells or cDC1 exhibit significant resistance to ICIs.⁴⁹ A key example of this paradigm is that the anti-tumor efficacy of anti-PD-1/PD-L1 therapy is largely dependent on DC-T cell crosstalk.^{11,161,194–196} Anti-PD-1 treatment activates CD8⁺ T cell immune responses mediated by IFN- γ -IL-12 loop in DC-T cell interaction. Additionally, anti-PD-1 treatment also increases the intratumoral abundance of cDC1, which enhances both the frequency and duration of DC-T cell interactions by modulating the CXCR3-CXCL9 axis.^{10,11,42} In preclinical melanoma models, anti-PD-1 also increase the number of CD11c⁺CD5⁺ cDCs, thereby driving the activation of CD5^{high} CD4⁺ and CD8⁺ T cells in tDLNs and the TME.⁴⁶

Growing evidence highlights the pivotal role of DCs in the therapeutic effi-

cacy of anti-PD-L1 therapy.^{197–199} Although macrophages are the primary source of PD-L1 in the TME, studies have shown that selective deletion of PD-L1 in DCs leads to effective tumor control.¹⁶¹ Furthermore, PD-L1-deficient tumors remain responsive to anti-PD-L1 therapy.¹⁶¹ These findings suggests that PD-L1 expression on DCs is essential for the success of PD-L1 blockade. Interestingly, while PD-L1 expression on DCs is necessary for an effective response to PD-L1 blockade, it also paradoxically enhances DC-mediated anti-tumor immunity by protecting DCs from T cell-mediated cytotoxicity.^{200,201} Additionally, PD-L1 interacts *in cis* with CD80 on cDCs,^{202,203} forming CD80-PD-L1 heterodimers that block the inhibitory *trans*-interaction between PD-L1 and PD-1, as well as that between CD80 and CTLA4.²⁰⁴ At the same time, it preserves the activating *trans* CD80-CD28 interaction between DCs and T cells. Despite the seemingly opposing effects of *cis*- and *trans*-CD80-PD-L1 interactions on anti-tumor immunity, disrupting PD-L1/CD80 interactions *in vivo* has been shown to enhance immune responses.²⁰⁵ Based on these findings, bispecific antibodies (bsAb) targeting CD3/PD-L1 and CLEC9A/PD-1 have shown potent anti-tumor effects through the activation of DC.^{194,206} Additionally, bi-specific CD40 agonists have been demonstrated the ability to reverse the immunosuppressive TME in a DC-dependent manner.²⁰⁷

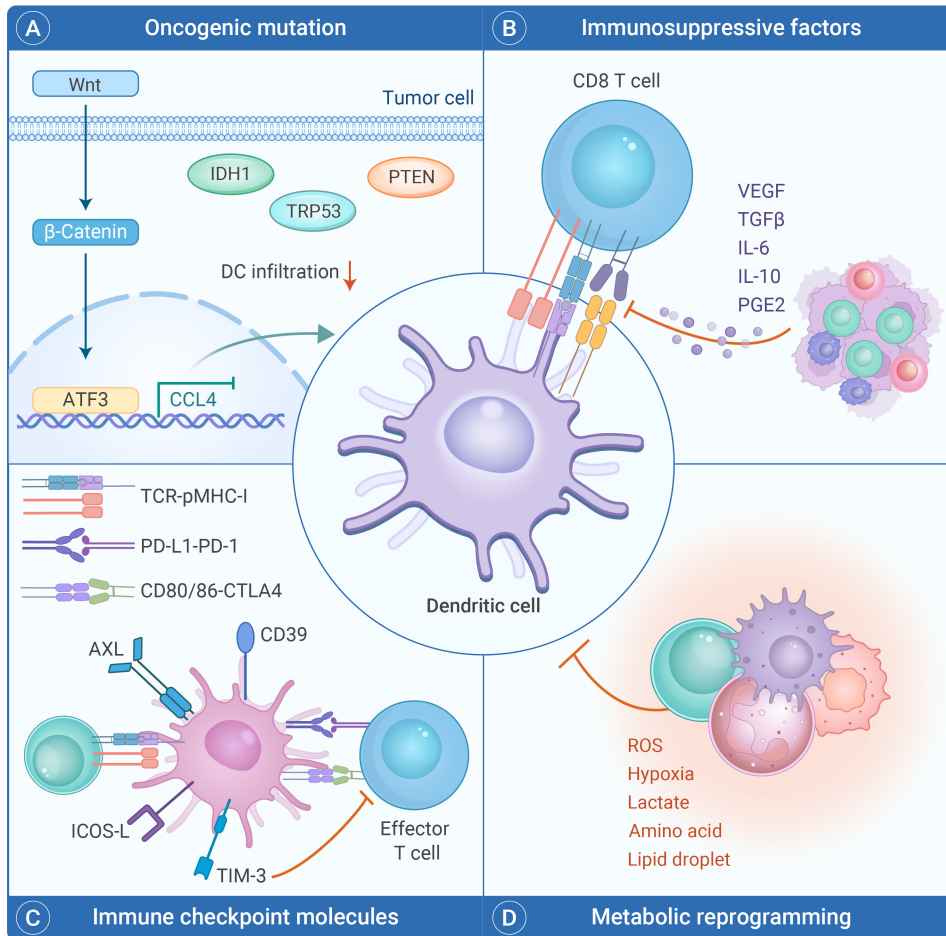


Figure 4. DCs are functionally impaired in the TME Various tumor-intrinsic and extrinsic mechanisms impair DC function in the TME and result in immune suppression or immune evasion. (A) Oncogenic mutation: activation of the Wnt/ β -catenin signaling pathway reduces CCL4 secretion from tumor cells, which leads to reduced DC infiltration and immune escape. *TRP53*, *IDH1*, *PTEN* mutation. (B) Immunosuppressive factors: immunosuppressive factors are present in the TME, including VEGF, TGF β , IL-6, IL-10, and PGE2, which inhibit CD8⁺ T-cell activity, leading to immune escape and tumor progression. (C) Immune checkpoint molecules: DCs express a variety of immune checkpoint molecules, such as PD-L1, CTLA-4, TIM-3, ICOS-L, AXL, and CD39, which inhibits effector T cell function, leading to suppression of their anti-tumor activity. (D) Metabolic reprogramming: microenvironmental factors, including but not limited to the presence of reactive oxygen species (ROS) and hypoxia, impairs DC function through metabolic reprogramming in the TME. VEGF, Vascular Endothelial Growth Factor; TGF β , Transforming Growth Factor-beta; IL, Interleukin; PGE2, Prostaglandin E2; ROS, Reactive Oxygen Species; PD-L1, Programmed Death-Ligand 1; CTLA-4, Cytotoxic T-Lymphocyte-Associated Protein 4; TIM-3, T-cell Immunoglobulin and Mucin-domain containing-3; ICOS-L, Inducible T-cell Costimulatory Ligand; ATF3, Activating Transcription Factor 3; CCL4, C-C Motif Chemokine Ligand 4.

Immune cell therapy and DCs

Innovative cell therapies are also being explored to harness DCs for tumor control. DC-based CAR-T and TCR-T cell therapies represent cutting-edge strategies to boost the immune response. ACT therapy has shown limited efficacy in melanoma patients with low cDC1 infiltration.⁹ CAR-T cells armed with chemokines (CCL19) or cytokines (Flt3L) can enhance the infiltration of cDC1 into tumor,²⁰⁸⁻²¹⁰ which in turn boosts endogenous polyclonal T cell responses. Additionally, T cells armed with CCR4 or CD40L show increased capacity to interact with DCs.^{211,212} LN-targeted vaccines can enhance CAR-T and host DC crosstalk and generate potent antigen spreading.^{213,214} Similarly, DC vaccines armed with CXCL9/10 and CCL21 promote the infiltration and activation of T cells in a lung cancer model.²¹⁵⁻²¹⁷

Impaired DC function in the TME

The duration and magnitude of immune response are tightly regulated by the balance between pro- and anti-tumor immune factors. Immunosuppressive factors in the TME impair DC functionality, thereby limiting the effectiveness of anti-tumor immune response and favoring immune evasion.^{218,219} Given the pivotal role of DCs in tumor immunology and immunotherapy, understanding the mechanisms by which DCs are impaired in TME is paramount (Figure 4).

Oncogenic mutation

Exclusion of DCs from tumors is emerging as a critical mechanism of cancer immune evasion. Tumor-intrinsic β -catenin signaling reduces the expression of CCL4, leading to decreased cDC1 infiltration and increased tumor growth (Figure 4).⁸ Other gene mutations associated with immune-cold TME may also interfere with DC function. Examples include *TRP53* loss, *PTEN* deficiency, isocitrate dehydrogenase 1 (*IDH1*) mutation (mIDH1), and abnormal epigenetic modifications. The loss of *TRP53* leads to a decreased expression of CCL4/5 by tumor cells, which inhibits the tumoral recruitment of DCs.²²⁰ *PTEN*-deficient melanomas are associated with poor T cell infiltra-

tion and immune response.²²¹ Importantly, *PTEN*-deficient tumors present decreased CXCL10 and increased VEGF expression, indicating a DC-suppressive environment. Treatment with PI3K inhibitors or reactivation of *PTEN* by an mRNA vaccine has been shown to enhance the response to ICIs,^{222,223} but *PTEN* can inhibit Flt3L signaling in DC development.²²⁴ Finally, compared with IDH

Tumor-derived suppressive factors

In addition to genetic alterations, suppressive factors released by the TME also directly inhibit DC differentiation and maturation, examples include IL-6,²²⁶ IL-10,²²⁷ IL-4,⁵⁸ VEGF,¹⁴ granulocyte colony-stimulating factor (G-CSF),²²⁸ PGE2,²²⁹ TGF- β ,²³⁰ and lactate acid (Figure 4).²¹⁸ IL-6 and IL-10 released from myeloid-derived suppressor cells (MDSCs), in particular, can synergistically activate the STAT3 signaling pathway.^{231,232} This has long been associated with DC dysfunction in the TME. Previous studies have shown that IL-21 induces cDC apoptosis through STAT3 and BIM, and this effect is inhibited by GM-CSF-induced STAT5.²³³ IL-6 may have multiple DC-inhibitory effects, including its ability to induce C/EBP β in CDPs, which activates ZEB2 and prevents cDC1 development.²²⁶ IL-10 plays a dual role in regulating immune responses. It induces the transformation of tolerogenic DCs by reducing the expression of co-stimulatory factors.²²⁷ Conversely, other findings suggest that IL-10 can enhance anti-tumor immunity by preventing CD8⁺ T cell apoptosis through interactions with IL-10R on DCs.²³⁴ Tumor can also interfere with DC function remotely through the secretion of G-CSF, which inhibits the expression of IRF8.²³⁵ Similarly, tumor-driven PGE2 can reduce IRF8 expression through the EP2/EP4-PKA axis or counteract the NK cell-mediated production of Flt3L.^{229,236} TGF- β may impact the activity of cDCs by inducing the expression of other immunosuppressive molecules.¹⁴⁶ Recent data indicate that TGF- β induces hyperglycosylation and subsequent pSAP secretion,²³⁰ leading to lysosomal sphingolipid depletion and impaired antigen presentation. Additionally, tumor-derived chemokines facilitate Tregs recruitment via CCL20/28, while CXCL5 released by Tregs attracts CXCR2⁺

MDSCs. In turn, these MDSCs further increase Treg accumulation by releasing CCL2/17, ultimately suppressing DC function through direct and indirect mechanisms.⁸¹ Finally, high levels of lactate in the TME can inhibit IL-12 production and antigen presentation by DCs via GPR81 signaling,^{237,238} and drive the transformation of cDCs into mregDCs through the activation of SREBP2.⁷³

DC-intrinsic immunosuppressive factors

The activity of cDC1 in tumors may also be further restricted by immunosuppressive molecules that they express (Figure 4), such as PD-L1, TIM-3, and CD39.^{52,239} cDC1 expresses high levels of the receptor PD-L1 and TIM-3, which inhibits DC functions.^{152–154} High CD39 expression on DCs in metastatic tDLNs show spatial proximity with Tpx cells.²⁴⁰ CD39 inhibitors enhance anti-tumor efficacy in a cDC1-dependent manner.²⁴¹ Intratumoral DCs can also regulate T cell function by altering the availability of metabolic substrates. L-tryptophan, essential for T cell responses, is depleted when converted to L-kynurenine under the action of IDO1 or IL4I1.^{149,242} Elevated IDO1/IL4I1 expression in intratumoral DCs inhibits the proliferation and function of CD8⁺ T cells and NK cells. It also promotes Treg differentiation, thus suppressing the immune response.^{149,242}

Overall, factors that disrupt the recruitment, differentiation, and maturation of DCs may allow tumor immune evasion. Interventions targeting these microenvironmental abnormalities hold promise for reprogramming anti-tumor immunity.

DC-BASED THERAPEUTIC APPROACHES IN CANCER IMMUNOTHERAPY

Given the central role of DCs in orchestrating anti-tumor immunity, much attention should be paid to designing the next-generation of DC-based therapeutics that aim to enhance DC abundance and functionality in both tDLNs and tumors in order to better elicit strong and durable T cell immune responses (Figure 5).

DC vaccines

The application of DC vaccines in cancer treatment has been widely studied, but their success rates are varied. While DC vaccines have shown consistent clinical safety, their objective response rates remain low. Only one DC vaccine (Provenge, Sip-T) have been approved by the FDA.⁵² Given the significant potential of DCs to induce anti-tumor immunity, there is an urgent need to rationally design DC vaccines.²⁴³ Existing data suggest that Mo-DCs may have impaired function and require antigen transfer to host DCs for effective function.^{45,244} As a result, *bona fide* DC subsets with more specialized functions have been proposed as the foundation for next-generation vaccines (Figure 5).⁵² However, results from a recent phase III clinical trial (NCT02993315) in melanoma patients showed no improvement in recurrence-free survival (RFS). Although patients vaccinated with autologous DCs exhibited specific immune responses and good tolerance, no clinical benefit was observed.²⁴⁵ This may be due to the dysfunctional state of autologous DCs in cancer patients.²⁴⁶ Thus, strategies to optimize the activity of patient-derived DCs *ex vivo* or to use iPS-derived DCs as vaccine carriers may hold promise. Inducing cDC1-like subsets from CD14⁺ monocytes or CD34⁺ progenitors through small molecules or genetic manipulation is also worth exploration.

Despite current limitations of Mo-DCs as the mainstay of DC vaccines, new approaches, such as the use of cytokine combinations (IL-15) or mRNA/LNP technology (encoding CD40/CD40L),^{247–249} are being developed to enhance vaccine efficacy. For example, in a phase III clinical trial (NCT00045968) in glioblastoma patients, DCVAX-L,²⁵⁰ an autologous tumor lysate-loaded DC vaccine, significantly improved overall survival (OS). Similarly, the MesoPher vaccine induced reactive T cell responses against autologous tumors in a phase I clinical trial in PDAC patients.²⁵¹ The route of administration also influences the efficacy of DC vaccines. While Sip-T can be safely administered via intravenous injection, the optimal method of DC delivery remains under debate. Additionally, understanding the role of circadian rhythms in DC function and vaccination responses could lead to more effective timing of vaccine administration.^{252,253}

Adjuvants and cytokines

Cytokines that mobilize DCs and immunostimulatory adjuvants have been explored as strategies to enhance DC activity.²⁵⁴ Examples include TLR/cGAS agonists and the cytokines Flt3L and GM-CSF (Figure 5). The low abundance of cDC1 within tumors may result from decreased cDC1 development. Flt3L administration has been shown to expand cDC1 populations and improve anti-tumor response in both mouse models and clinical trials in non-Hodgkin's lymphoma patients.^{255–258} However, systemic administration of Flt3L produces significant toxicity. This highlights the need for exploring more feasible and effective delivery methods, such as mRNA delivery, synNotch technology. A recent report proposed a cell therapy platform based on mouse or human DC progenitors (DCPs). This platform produces cytokine (IL-12/Flt3L)-armed DCP vaccines and has demonstrated the ability to eradicate intracranial glioma in mice.²⁵⁹ Of particular interest is XCL1, which specifically attracts XCR1⁺ cDC1. It appears to be a highly promising target, both in the context of antigen-XCL1 fusion strategies and in combination with cellular immunotherapies (Figure 5).

Adjuvants that drive the immunogenic activation of DCs are also under active investigation. These particularly include derivatives of ligands for TLRs expressed on DCs. *In vitro* and preclinical studies have shown that the synthetic TLR3 agonist poly (I:C) effectively activates DCs, making it a promising candidate for cancer immunotherapy.⁵² Recent findings have revealed that TLR4 ligands, combined with oxidized phospholipids (PGPC or oxPAPC), can drive DCs into a hyperactive state and potent tumor rejection (Figure 5).^{141–143} Given the increasing recognition of IFN-I as a crucial aspect of protective intratumoral immunity, the cGAS-STING signaling pathway has gained significant attention. Several novel STING agonists have been developed, such as LND-CDNs and PolySTING,^{260,261} which significantly enhances anti-tumor immunity. Additionally, the use of metal ions as activators of signal transduction has garnered increasing attention. Mn²⁺ acts as an activator of cGAS, thereby enhancing the production of IFN-I and promoting the maturation of DCs and macrophages. In phase I clinical trials, the combination of Mn²⁺ and anti-PD-1 has shown promising efficacy.²⁶²

CD40 agonists and DC-T cell engagers (BiCE)

CD40 is upregulated on mature DCs, agonistic antibodies targeting CD40 stimulates DCs to produce pro-inflammatory signals. The degree of CD40 stimulation depends on Fc-FcR interactions.²⁶³ Second-generation Fc-engineered variants are now undergoing clinical trials for solid tumors (NCT04059588, NCT04547777, NCT05126472).¹⁴ While CD40 agonists exhibit cDC1-dependent anti-tumor activity,²⁰⁷ they have shown modest single-agent activity in clinical trials. Engineered bsAbs that specifically target CD40 signaling in DCs (CD40×CD11c, and CD40×Clec9A bsAbs) more significantly enhanced anti-tumor efficacy, with reduced toxicity (Figure 5).²⁰⁷

Importantly, improving DC-T cell interactions is a promising strategy to enhance anti-tumor immunity.^{10,152} Compared with mono-specific anti-PD-L1, PD-L1 blockade combined with T cell recruitment to DCs, such as CD3×PD-L1 or LAG3×PD-L1, results in superior anti-tumor activity.^{194,264} A novel PD-1×CLEC9A bsAb (BiCE) designed to enhance interactions between T cells and cDC1s has been shown to bolster anti-tumor responses (Figure 5).²⁰⁶ Despite these encouraging findings, precisely targeting functionally relevant DC subsets *in vivo* remains highly challenging, especially given that scRNA-seq has revealed the diversity and heterogeneity of intratumoral DC functional states. In order to design innovative BiCE and next-generation CD40 agonists, further research is required to understand the specific roles of different DC subsets.

Genetic and epigenetic modifications

Advances in knowledge of genetic and epigenetic modifications offer new avenues to enhance DC function. For instance, genetic engineering techniques, such as CRISPR/Cas9, can be used to modify DCs, which can enhance their immunogenic function or resistance to tumor-induced suppression (Figure 5).^{265,266} For instance, genetic deletion of histone deacetylase 1 (HDAC1) in DCs can induce immunological switching and increase cDC1 maturation and IL-12 production.²⁶⁷ Additionally, targeting YTHDF1 in DCs can restore their antigen-presenting function.¹⁰⁴ These findings suggest that manipulation of epigenetic factors has the potential to transform into novel DC-targeted anti-tumor therapies. Moreover, lipid nanoparticle-mRNA

responses,^{229,275,276} and using COX inhibitors in combination with DC-targeted therapies holds the potential to generate strong immunotherapeutic effects (Table 2).

CONCLUSION AND PERSPECTIVES

DCs play a central role in orchestrating anti-tumor immunity, by acting as the bridge between innate and adaptive immune responses. Over the past decade, advances in single-cell technology and functional genomics have significantly expanded our understanding of DC subsets and their diverse roles within the TME. These insights have revealed the complexity of DC biology in cancer. They also have demonstrated how distinct DC subsets, functional states, and interactions with other immune cells impact the effectiveness of immunotherapies.

Looking ahead, several challenges remain. For instance, DCs are often subject to tumor-mediated suppression, thereby diminishing their abundance and functionality, which impedes the generation of robust anti-tumor immune responses. DCs within tumors also show high heterogeneity, both in their ontogeny and functional states. Additionally, how interactions between DCs and other immune cells, especially T cells, are spatially regulated remains an open question. More efforts are needed to: 1. Uncover the mechanisms and local factors that suppress DCs within the TME and tDLNs; 2. Devise strategies that more effectively enhance the abundance and function of DCs in tumors; 3. Identify and modulate specific DC subsets and/or their activation states in order to induce optimal CD4⁺ and CD8⁺ T cell response required for tumor control. In other respects, identification of predictive biomarkers, optimization of combination therapies, and exploration of DC's potential to generate protective immune memory are important. These combined with standardized methodologies for studying DCs in tumors, will be instrumental in unlocking the full potential of DCs in tumor immunotherapy.

Another significant drawback in current DC research efforts is the development of preclinical animal models. Most humanized mouse models are costly to construct and maintain and often lack DC subsets, which results in limited utility for evaluating the efficacy of antibody drugs, DC vaccines, cellular immunotherapy, or other DC-based therapies. Therefore, the establishment of fast and stable and cost-effective humanized mouse models that include DCs would be of great benefit and contribution.

REFERENCES

- Schreiber R. D., Old L. J. and Smyth M. J. (2011). Cancer Immunoediting: Integrating immunity's roles in cancer suppression and promotion. *Science* **331**:1565–70. DOI:10.1126/science.1203486
- Lu X., Cheng L., Yang C., et al. (2024). Crosstalk between bladder cancer and the tumor microenvironment: Molecular mechanisms and targeted therapy. *Innov. Med.* **2**:100094. DOI:10.59717/j.xinn-med.2024.100094
- Zhou X., Zhang B., Hu J., et al. (2024). Igniting cold tumors of intrahepatic cholangiocarcinoma: An insight into immune evasion and tumor immune microenvironment. *Innov. Med.* **2**:100052. DOI:10.59717/j.xinn-med.2024.100052
- Zagorulya M. and Spranger S. (2022). Once upon a prime: DCs shape cancer immunity. *Trends Cancer* **9**:172–184. DOI:10.1016/j.trecan.2022.10.006
- Chen L. and Flies D. B. (2013). Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat. Rev. Immunol.* **13**:227–42. DOI:10.1038/nri3405
- Binnewies M., Roberts E. W., Kersten K., et al. (2018). Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat. Med.* **24**:541–50. DOI:10.1038/s41591-018-0014-x
- Mellman I., Chen D. S., Powles T., et al. (2023). The cancer-immunity cycle: Indication, genotype, and immunotype. *Immunity* **56**:2188–205. DOI:10.1016/j.immuni.2023.09.011
- Spranger S., Bao R. and Gajewski T. F. (2015). Melanoma-intrinsic β -catenin signalling prevents anti-tumour immunity. *Nature* **523**:231–5. DOI:10.1038/nature14404
- Spranger S., Dai D., Horton B., et al. (2017). Tumor-residing Batf3 dendritic cells are required for effector T cell trafficking and adoptive T cell therapy. *Cancer Cell* **31**:711–723.e4. DOI:10.1016/j.ccell.2017.04.003
- Chow M. T., Ozga A. J., Servis R. L., et al. (2019). Intratumoral activity of the CXCR3 chemokine system is required for the efficacy of anti-PD-1 therapy. *Immunity* **50**:1498–1512.e5. DOI:10.1016/j.immuni.2019.04.010
- Garris C. S., Arlauckas S. P., Kohler R. H., et al. (2018). Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving the cytokines IFN- γ and IL-12. *Immunity* **49**:1148–1161.e7. DOI:10.1016/j.immuni.2018.09.024
- Pfirschke C., Siwicki M., Liao H. W., et al. (2017). Tumor microenvironment: No

- effector T cells without dendritic cells. *Cancer Cell* **31**:614–5. DOI:10.1016/j.ccell.2017.04.007
- Eisenbarth S. C. (2019). Dendritic cell subsets in T cell programming: Location dictates function. *Nat. Rev. Immunol.* **19**:89–103. DOI:10.1038/s41577-018-0088-1
- Pittet M. J., Di Pilato M., Garris C., et al. (2023). Dendritic cells as shepherds of T cell immunity in cancer. *Immunity* **56**:2218–2230. DOI:10.1016/j.immuni.2023.08.014
- Gerhard G. M., Bill R., Messemaker M., et al. (2021). Tumor-infiltrating dendritic cell states are conserved across solid human cancers. *J. Exp. Med.* **218**:e20200264. DOI:10.1084/jem.20200264
- Cabeza-Cabrero M., Cardoso A., Minutti C. M., et al. (2021). Dendritic Cells Revisited. *Annu. Rev. Immunol.* **39**:131–66. DOI:10.1146/annurev-immunol-061020-053707
- Murphy T. L. and Murphy K. M. (2022). Dendritic cells in cancer immunology. *Cell Mol. Immunol.* **19**:3–13. DOI:10.1038/s41423-021-00741-5
- Yin X., Chen S. and Eisenbarth S. C. (2021). Dendritic Cell Regulation of T Helper Cells. *Annu. Rev. Immunol.* **39**:759–90. DOI:10.1146/annurev-immunol-101819-025146
- Grajales-Reyes G. E., Iwata A., Albring J., et al. (2015). Batf3 maintains autoactivation of Irf8 for commitment of a CD8 α conventional DC clonogenic progenitor. *Nat. Immunol.* **16**:708–17. DOI:10.1038/ni.3197
- Durai V., Bagadia P., Granja J. M., et al. (2019). Cryptic activation of an Irf8 enhancer governs cDC1 fate specification. *Nat. Immunol.* **20**:1161–73. DOI:10.1038/s41590-019-0450-x
- Theisen D. J., Ferris S. T., Briseño C. G., et al. (2019). Batf3-dependent genes control tumor rejection induced by dendritic cells independently of cross-presentation. *Cancer Immunol. Res.* **7**:29–39. DOI:10.1158/2326-6066.CIR-18-0138
- Ou F., Liu T. T., Desai P., et al. (2024). Optimization of the Irf8 +32-kb enhancer disrupts dendritic cell lineage segregation. *Nat. Immunol.* **25**:2043–2056. DOI:10.1038/s41590-024-01976-w
- Chopin M., Lun A. T., Zhan Y., et al. (2019). Transcription factor PU.1 promotes conventional dendritic cell identity and function via induction of transcriptional regulator DC-SCRIPT. *Immunity* **50**:77–90.e5. DOI:10.1016/j.immuni.2018.11.010
- Zhang S., Coughlan H. D., Ashayeripani M., et al. (2021). Type 1 conventional dendritic cell fate and function are controlled by DC-SCRIPT. *Sci. Immunol.* **6**:eabf4432. DOI:10.1126/sciimmunol.abf4432
- Tiniakou I., Hsu P. F., Lopez-Zepeda L. S., et al. (2024). Genome-wide screening identifies Trim33 as an essential regulator of dendritic cell differentiation. *Sci. Immunol.* **9**:ead11023. DOI:10.1126/sciimmunol.ad11023
- Shen X., Li X., Wu T., et al. (2024). TRIM33 plays a critical role in regulating dendritic cell differentiation and homeostasis by modulating Irf8 and Bcl2l1 transcription. *Cell Mol. Immunol.* **21**:752–769. DOI:10.1038/s41423-024-01179-1
- Brown C. C., Gudjonson H., Pritykin Y., et al. (2019). Transcriptional basis of mouse and human dendritic cell heterogeneity. *Cell* **179**:846–863.e24. DOI:10.1016/j.ccell.2019.09.035
- Dutertre C. A., Becht E., Irac S. E., et al. (2019). Single - cell analysis of human mononuclear phagocytes reveals subset - defining markers and identifies circulating inflammatory dendritic cells. *Immunity* **51**:573–589.e8. DOI:10.1016/j.immuni.2019.08.008
- Bourdely P., Anselmi G., Vaivode K., et al. (2020). Transcriptional and functional analysis of CD1c+ human dendritic cells identifies a CD163+ subset priming CD8+CD103+ T cells. *Immunity* **53**:335–352.e8. DOI:10.1016/j.immuni.2020.06.002
- Nakamizo S., Dutertre C. A., Khalilnezhad A., et al. (2021). Single-cell analysis of human skin identifies CD14+ type 3 dendritic cells co-producing IL1B and IL23A in psoriasis. *J. Exp. Med.* **218**:e20202345. DOI:10.1084/jem.20202345
- Liu Z., Wang H., Li Z., et al. (2023). Dendritic cell type 3 arises from Ly6C+ monocyte-dendritic cell progenitors. *Immunity* **56**:1761–1777. DOI:10.1016/j.immuni.2023.07.001
- Rodrigues P. F., Trsan T., Cvijetic G., et al. (2024). Progenitors of distinct lineages shape the diversity of mature type 2 conventional dendritic cells. *Immunity* **57**:1567–1585.e5. DOI:10.1016/j.immuni.2024.05.007
- Villani A. C., Satija R., Reynolds G., et al. (2017). Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. *Science* **356**:eaah4573. DOI:10.1126/science.aah4573https://science.sciencemag.org/content/356/6335/eaah4573
- Zilionis R., Engblom C., Pfirschke C., et al. (2019). Single-cell transcriptomics of human and mouse lung cancers reveals conserved myeloid populations across individuals and species. *Immunity* **50**:1317–1334.e10. DOI:10.1016/j.immuni.2019.03.009
- Minutti C. M., Piot C., Pereira da Costa M., et al. (2024). Distinct ontogenetic lineages dictate cDC2 heterogeneity. *Nat. Immunol.* **25**:448–461. DOI:10.1038/s41590-024-01745-9
- Girard M., Law J. C., Edilova M. I., et al. (2020). Type I interferons drive the maturation of human DC3s with a distinct costimulatory profile characterized by high GITRL. *Sci. Immunol.* **5**:eabe0347. DOI:10.1126/sciimmunol.abe0347
- Sulczewski F. B., Maqueda-Alfaro R. A., Alcántara-Hernández M., et al. (2023). Transitional dendritic cells are distinct from conventional DC2 precursors and mediate proinflammatory antiviral responses. *Nat. Immunol.* **24**:1265–1280. DOI:10.1038/s41590-023-01545-7

38. Satpathy A. T., Kc W., Albring J. C., et al. (2012). Zbtb46 expression distinguishes classical dendritic cells and their committed progenitors from other immune lineages. *J. Exp. Med.* **209**:1135–1152. DOI:10.1084/jem.20120030
39. Roberts E. W., Broz M. L., Binnewies M., et al. (2016). Critical role for CD103+CD141+ dendritic cells bearing CCR7 for tumor antigen trafficking and priming of T cell immunity in melanoma. *Cancer Cell* **30**:324–36. DOI:10.1016/j.ccell.2016.06.003
40. Kuhn N. F., Lopez A. V., Li X., et al. (2020). CD103+ cDC1 and endogenous CD8+ T cells are necessary for improved CD40L-overexpressing CAR T cell antitumor function. *Nat. Commun.* **11**:6171. DOI:10.1038/s41467-020-19833-3
41. Engelhardt J. J., Boldajipour B., Beemiller P., et al. (2012). Marginating dendritic cells of the tumor microenvironment cross-present tumor antigens and stably engage tumor-specific T cells. *Cancer Cell* **21**:402–417. DOI:10.1016/j.ccr.2012.01.008
42. Teixeira A., Garasa S., Luri-Rey C., et al. (2022). Depletion of conventional type-1 dendritic cells in established tumors suppresses immunotherapy efficacy. *Cancer Res.* **82**:4373–4385. DOI:10.1158/0008-5472.CAN-22-1046
43. Barboý O., Bercovich A., Li H., et al. (2024). Modeling T cell temporal response to cancer immunotherapy rationalizes development of combinatorial treatment protocols. *Nat. Cancer.* **5**:742–759. DOI:10.1038/s43018-024-00734-z
44. Hildner K., Edelson B. T., Purtha W. E., et al. (2008). *Batf3* deficiency reveals a critical role for CD8a+ dendritic cells in cytotoxic T cell immunity. *Science* **322**:1097–100. DOI:10.1126/science.1164206
45. Ferris S. T., Ohara R. A., Ou F., et al. (2022). cDC1 vaccines drive tumor rejection by direct presentation independently of host cDC1. *Cancer Immunol. Res.* **10**:920–31. DOI:10.1158/2326-6066.CIR-21-0865
46. He M., Roussak K., Ma F., et al. (2023). CD5 expression by dendritic cells directs T cell immunity and sustains immunotherapy responses. *Science* **379**:eabg2752. DOI:10.1126/science.abg2752
47. Hubert M., Gobbi E., Couillault C., et al. (2020). IFN-III is selectively produced by cDC1 and predicts good clinical outcome in breast cancer. *Sci. Immunol.* **5**:eaa3942. DOI:10.1126/sciimmunol.aav3942
48. Binnewies M., Mujal A. M., Pollack J. L., et al. (2019). Unleashing type-2 dendritic cells to drive protective antitumor CD4+ T cell immunity. *Cell* **177**:556–571.e16. DOI:10.1016/j.cell.2019.02.005
49. Heras-Murillo I., Adán-Barrientos I., Galán M., et al. (2024). Dendritic cells as orchestrators of anticancer immunity and immunotherapy. *Nat. Rev. Clin. Oncol.* **21**:257–277. DOI:10.1038/s41571-024-00859-1
50. Beek J. J. P. van, Flórez-Grau G., Gorris M. A. J., et al. (2020). Human pDCs are superior to cDC2s in attracting cytolytic lymphocytes in melanoma patients receiving DC vaccination. *Cell Rep.* **30**:1027–1038.e4. DOI:10.1016/j.celrep.2019.12.096
51. Tel J., Aarntzen E. H. J. G., Baba T., et al. (2013). Natural human plasmacytoid dendritic cells induce antigen-specific T-cell responses in melanoma patients. *Cancer Res.* **73**:1063–1075. DOI:10.1158/0008-5472.CAN-12-2583
52. Wculek S. K., Cueto F. J., Mujal A. M., et al. (2020). Dendritic cells in cancer immunology and immunotherapy. *Nat. Rev. Immunol.* **20**:7–24. DOI:10.1038/s41577-019-0210-z
53. Elewa A., Estivill G., Bayerl F., et al. (2024). Cancer cells impair monocyte-mediated T cell stimulation to evade immunity. *Nature* **637**:716–725. DOI:10.1038/s41586-024-08257-4
54. Krieg C., Nowicka M., Guglietta S., et al. (2018). High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy. *Nat. Med.* **24**:144–153. DOI:10.1038/nm.4466
55. Cheng S., Li Z., Gao R., et al. (2021). A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. *Cell* **184**:792–809.e23. DOI:10.1016/j.cell.2021.01.010
56. Meiser P., Knolle M. A., Hirschberger A., et al. (2023). A distinct stimulatory cDC1 subpopulation amplifies CD8+ T cell responses in tumors for protective anti-cancer immunity. *Cancer Cell* **41**:1498–1515.e10. DOI:10.1016/j.ccell.2023.06.008
57. Duong E., Fessenden T. B., Lutz E., et al. (2022). Type I interferon activates MHC class I-dressed CD11b+ conventional dendritic cells to promote protective anti-tumor CD8+ T cell immunity. *Immunity* **55**:308–323.e9. DOI:10.1016/j.immuni.2021.10.020
58. Maier B., Leader A. M., Chen S. T., et al. (2020). A conserved dendritic-cell regulatory program limits antitumor immunity. *Nature* **580**:257–262. DOI:10.1038/s41586-020-2134-y
59. Di Pilato M., Kfuri-Rubens R., Pruessmann J. N., et al. (2021). CXCR6 positions cytotoxic T cells to receive critical survival signals in the tumor microenvironment. *Cell* **184**:4512–4530.e22. DOI:10.1016/j.cell.2021.07.015
60. Zhang Q., He Y., Luo N., et al. (2019). Landscape and dynamics of single immune cells in hepatocellular carcinoma. *Cell* **179**:829–845.e20. DOI:10.1016/j.cell.2019.10.003
61. Lee C. Y. C., Kennedy B. C., Richoz N., et al. (2024). Tumour-retained activated CCR7+ dendritic cells are heterogeneous and regulate local anti-tumour cytolytic activity. *Nat. Commun.* **15**:682. DOI:10.1038/s41467-024-44787-1
62. Miao Y., Liu Y., Tang H., et al. (2023). Dendritic cell maturation in the tumor microenvironment. *NSO* **2**:20220053. DOI:10.1360/nso/20220053
63. Zhang L., Li Z., Skrzypczynska K. M., et al. (2020). Single-cell analyses inform mechanisms of myeloid-targeted therapies in colon cancer. *Cell* **181**:442–459.e29. DOI:10.1016/j.cell.2020.03.048
64. Cohen M., Giladi A., Barboý O., et al. (2022). The interaction of CD4+ helper T cells with dendritic cells shapes the tumor microenvironment and immune checkpoint blockade response. *Nat. Cancer* **3**:303–317. DOI:10.1038/s43018-022-00338-5
65. Li J., Zhou J., Huang H., et al. (2023). Mature dendritic cells enriched in immunoregulatory molecules (mregDCs): A novel population in the tumour microenvironment and immunotherapy target. *Clin. Transl. Med.* **13**:e1199. DOI:10.1002/ctm2.1199
66. Magen A., Hamon P., Fiaschi N., et al. (2023). Intratumoral dendritic cell-CD4+ T helper cell niches enable CD8+ T cell differentiation following PD-1 blockade in hepatocellular carcinoma. *Nat. Med.* **29**:1389–1399. DOI:10.1038/s41591-023-02345-0
67. Schumacher T. N. and Thommen D. S. (2022). Tertiary lymphoid structures in cancer. *Science* **375**:eabf9419. DOI:10.1126/science.abf9419
68. Belabed M., Park M. D., Blouin C. M., et al. (2025). Cholesterol mobilization regulates dendritic cell maturation and the immunogenic response to cancer. *Nat. Immunol.* **26**:188–199. DOI:10.1038/s41590-024-02065-8
69. Møller S. H., Wang L. and Ho P. C. (2022). Metabolic programming in dendritic cells tailors immune responses and homeostasis. *Cell Mol. Immunol.* **19**:370–383. DOI:10.1038/s41423-021-00753-1
70. You S., Li S., Zeng L., et al. (2024). Lymphatic-localized Treg-mregDC crosstalk limits antigen trafficking and restrains anti-tumor immunity. *Cancer Cell* **42**:1415–1433.e12. DOI:10.1016/j.ccell.2024.06.014
71. Chen Z., Zhou L., Liu L., et al. (2020). Single-cell RNA sequencing highlights the role of inflammatory cancer-associated fibroblasts in bladder urothelial carcinoma. *Nat. Commun.* **11**:5077. DOI:10.1038/s41467-020-18916-5
72. Rapp M., Wintergerst M. W. M., Kunz W. G., et al. (2019). CCL22 controls immunity by promoting regulatory T cell communication with dendritic cells in lymph nodes. *J. Exp. Med.* **216**:1170–1181. DOI:10.1084/jem.20170277
73. Plebanek M. P., Xue Y., Nguyen Y. V., et al. (2024). A lactate-SREBP2 signaling axis drives tolerogenic dendritic cell maturation and promotes cancer progression. *Sci. Immunol.* **9**:ead4191. DOI:10.1126/sciimmunol.adi4191
74. Joffe O. P., Segura E., Savina A., et al. (2012). Cross-presentation by dendritic cells. *Nat. Rev. Immunol.* **12**:557–569. DOI:10.1038/nri3254
75. Den Haan J. M. M., Lehar S. M. and Bevan M. J. (2000). Cd8+ but not Cd8- dendritic cells cross-prime cytotoxic T cells in vivo. *J. Exp. Med.* **192**:1685–1696. DOI:10.1084/jem.192.12.1685
76. Ohara R. A. and Murphy K. M. (2023). The evolving biology of cross-presentation. *Semin. Immunol.* **66**:101711. DOI:10.1016/j.jsmim.2023.101711
77. Moussion C. and Delamarre L. (2024). Antigen cross-presentation by dendritic cells: A critical axis in cancer immunotherapy. *Semin. Immunol.* **71**:101848. DOI:10.1016/j.jsmim.2023.101848
78. Yee Mon K. J. and Blander J. M. (2023). TAP-ing into the cross-presentation secrets of dendritic cells. *Curr. Opin. Immunol.* **83**:102327. DOI:10.1016/j.coi.2023.102327
79. Raynor J. L. and Chi H. (2024). Nutrients: Signal 4 in T cell immunity. *J. Exp. Med.* **221**:e20221839. DOI:10.1084/jem.20221839
80. Joffe O., Nolte M. A., Spörri R., et al. (2009). Inflammatory signals in dendritic cell activation and the induction of adaptive immunity. *Immunol. Rev.* **227**:234–247. DOI:10.1111/j.1600-065X.2008.00718.x
81. Luri-Rey C., Teixeira Á., Wculek S. K., et al. (2025). Cross-priming in cancer immunology and immunotherapy. *Nat. Rev. Cancer* **25**:249–273. DOI:10.1038/s41568-024-00785-5
82. Pishesha N., Harmand T. J. and Ploegh H. L. (2022). A guide to antigen processing and presentation. *Nat. Rev. Immunol.* **22**:751–764. DOI:10.1038/s41577-022-00707-2
83. Merzougui N., Kratzer R., Saveanu L., et al. (2011). A proteasome-dependent, TAP-independent pathway for cross-presentation of phagocytosed antigen. *EMBO Rep.* **12**:1257–1264. DOI:10.1038/embor.2011.203
84. Palmowski M. J., Gileadi U., Salio M., et al. (2006). Role of immunoproteasomes in cross-presentation. *J. Immunol.* **177**:983–990. DOI:10.4049/jimmunol.177.2.983
85. Alloati A., Rookhuizen D. C., Joannas L., et al. (2017). Critical role for Sec22b-dependent antigen cross-presentation in antitumor immunity. *J. Exp. Med.* **214**:2231–2241. DOI:10.1084/jem.20170229
86. Barbet G., Nair-Gupta P., Schotsaert M., et al. (2021). TAP dysfunction in dendritic cells enables noncanonical cross-presentation for T cell priming. *Nat. Immunol.* **22**:497–509. DOI:10.1038/s41590-021-00903-7
87. Grotzke J. E., Kozik P., Morel J. D., et al. (2017). Sec61 blockade by mycolactone inhibits antigen cross-presentation independently of endosome-to-cytosol export. *Proc. Natl. Acad. Sci. U. S. A.* **114**:E5910–9. DOI:10.1073/pnas.1705242114
88. Cebrian I., Visentin G., Blanchard N., et al. (2011). Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. *Cell* **147**:1355–1368. DOI:10.1016/j.cell.2011.11.021
89. Zehner M., Marschall A. L., Bos E., et al. (2015). The translocon protein Sec61 mediates antigen transport from endosomes in the cytosol for cross-presentation to CD8+ T cells. *Immunity* **42**:850–863. DOI:10.1016/j.immuni.2015.04.008
90. Canton J., Blees H., Henry C. M., et al. (2021). The receptor DNGR-1 signals for phagosomal rupture to promote cross-presentation of dead-cell-associated antigens. *Nat. Immunol.* **22**:140–153. DOI:10.1038/s41590-020-00824-x

91. Dingjan I, Paardekooper L. M., Verboogen D. R. J., et al. (2017). VAMP8-mediated NOX2 recruitment to endosomes is necessary for antigen release. *Eur. J. Cell Biol.* **96**:705–714. DOI:10.1016/j.ejcb.2017.06.007
92. Wang Y., Zhang Q., He T., et al. (2023). The transcription factor Zeb1 controls homeostasis and function of type 1 conventional dendritic cells. *Nat. Commun.* **14**:6639. DOI:10.1038/s41467-023-42428-7
93. Savina A., Peres A., Cebrian I., et al. (2009). The small GTPase Rac2 controls phagosomal alkalization and antigen crosspresentation selectively in CD8+ dendritic cells. *Immunity* **30**:544–555. DOI:10.1016/j.immuni.2009.01.013
94. Jancic C., Savina A., Wasmeier C., et al. (2007). Rab27a regulates phagosomal pH and NADPH oxidase recruitment to dendritic cell phagosomes. *Nat. Cell Biol.* **9**:367–378. DOI:10.1038/ncb1552
95. Si J., Su X., Jin Z., et al. (2025). The role of small Extracellular Vesicles (sEVs) and Rab27a in nanoparticle metastasis and tumor targeting. *Innov. Med.* **3**:100126. DOI:10.59717/j.xinn-med.2025.100126
96. Theisen D. J., Davidson J. T., Briseño C. G., et al. (2018). WDFY4 is required for cross-presentation in response to viral and tumor antigens. *Science* **362**:694–699. DOI:10.1126/science.aat5030
97. Edelson B. T., KC W., Juang R., et al. (2010). Peripheral CD103+ dendritic cells form a unified subset developmentally related to CD8α+ conventional dendritic cells. *J. Exp. Med.* **207**:823–836. DOI:10.1084/jem.20091627
98. Cueto F. J., del Fresno C., Brandi P., et al. (2021). DNGR-1 limits Flt3L-mediated antitumor immunity by restraining tumor-infiltrating type I conventional dendritic cells. *J. Immunother Cancer* **9**:e002054. DOI:10.1136/jitc-2020-002054
99. Rodríguez-Silvestre P., Laub M., Krawczyk P. A., et al. (2023). Perforin-2 is a pore-forming effector of endocytic escape in cross-presenting dendritic cells. *Science* **380**:1258–1265. DOI:10.1126/science.adg8802
100. Gonzales G. A., Huang S., Wilkinson L., et al. (2024). The pore-forming apolipoprotein APOL7C drives phagosomal rupture and antigen cross-presentation by dendritic cells. *Sci. Immunol.* **9**:eadn2168. DOI:10.1126/sciimmunol.adn2168
101. Kretzer N. M., Theisen D. J., Tussiwand R., et al. (2016). RAB43 facilitates cross-presentation of cell-associated antigens by CD8α+ dendritic cells. *J. Exp. Med.* **213**:2871–2883. DOI:10.1084/jem.20160597
102. Ou P., Wen L., Liu X., et al. (2019). Thioesterase PPT1 balances viral resistance and efficient T cell crosspriming in dendritic cells. *J. Exp. Med.* **216**:2091–2112. DOI:10.1084/jem.20190041
103. Lin W., Chen L., Zhang H., et al. (2023). Tumor-intrinsic YTHDF1 drives immune evasion and resistance to immune checkpoint inhibitors via promoting MHC-I degradation. *Nat. Commun.* **14**:265. DOI:10.1038/s41467-022-35710-7
104. Han D., Liu J., Chen C., et al. (2019). Anti-tumour immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells. *Nature* **566**:270–274. DOI:10.1038/s41586-019-0916-x
105. Wakim L. M. and Bevan M. J. (2011). Cross-dressed dendritic cells drive memory CD8+ T-cell activation after viral infection. *Nature* **471**:629–632. DOI:10.1038/nature09863
106. Schriek P. and Villadangos J. A. (2023). Trogocytosis and cross-dressing in antigen presentation. (2023). *Curr. Opin. Immunol.* **83**:102331. DOI:10.1016/j.coi.2023.102331
107. Nakayama M. (2015). Antigen presentation by MHC-dressed cells. *Front. Immunol.* **5**:672. DOI:10.3389/fimmu.2014.00672
108. Huang J. F., Yang Y., Sepulveda H., et al. (1999). TCR-mediated internalization of peptide-MHC complexes acquired by T cells. *Science* **286**:952–954. DOI:10.1126/science.286.5441.952
109. Önfelt B., Nedvetzki S., Yanagi K., et al. (2004). Cutting Edge: Membrane Nanotubes Connect Immune Cells. *J. Immunol.* **173**:1511–1513. DOI:10.4049/jimmunol.173.3.1511
110. Ruhland M. K., Roberts E. W., Cai E., et al. (2020). Visualizing synaptic transfer of tumor antigens among dendritic cells. *Cancer Cell* **37**:786–799.e5. DOI:10.1016/j.ccell.2020.05.002
111. Hori A., Toyoura S., Fujiwara M., et al. (2024). MHC class I-dressing is mediated via phosphatidylserine recognition and is enhanced by polyI:C. *iScience* **27**:109704. DOI:10.1016/j.isci.2024.109704
112. MacNabb B. W., Tumuluru S., Chen X., et al. (2022). Dendritic cells can prime anti-tumor CD8+ T cell responses through major histocompatibility complex cross-dressing. *Immunity* **55**:2206–2208. DOI:10.1016/j.immuni.2022.04.016
113. Dolan B. P., Gibbs K. D. and Ostrand-Rosenberg S. (2006). Dendritic cells cross-dressed with peptide MHC class I complexes prime CD8+ T cells. *J. Immunol.* **177**:6018–6024. DOI:10.4049/jimmunol.177.9.6018
114. Giampazolias E., Schulz O., Lim K. H. J., et al. (2021). Secreted gelsolin inhibits DNGR-1-dependent cross-presentation and cancer immunity. *Cell* **184**:4016–4031.e22. DOI:10.1016/j.cell.2021.05.021
115. Henry C. M., Castellanos C. A., Buck M. D., et al. (2023). SYK ubiquitination by CBL E3 ligases restrains cross-presentation of dead cell-associated antigens by type 1 dendritic cells. *Cell Rep.* **42**:113506. DOI:10.1016/j.celrep.2023.113506
116. Cubillos-Ruiz J. R., Silberman P. C., Rutkowski M. R., et al. (2015). ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* **161**:1527–1538. DOI:10.1016/j.cell.2015.05.025
117. Guttman O., Le Thomas A., Marsters S., et al. (2022). Antigen-derived peptides engage the ER stress sensor IRE1α to curb dendritic cell cross-presentation. *J. Cell Biol.* **221**:e202111068. DOI:10.1083/jcb.202111068
118. Pradeu T., Thomma B. P. H. J., Girardin S. E., et al. (2024). The conceptual foundations of innate immunity: Taking stock 30 years later. *Immunity* **57**:613–631. DOI:10.1016/j.immuni.2024.03.007
119. Woo S. R., Fuentes M. B., Corrales L., et al. (2014). STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. *Immunity* **41**:830–842. DOI:10.1016/j.immuni.2014.10.017
120. Shi Y., Zheng W., Yang K., et al. (2020). Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. *J. Exp. Med.* **217**:e20192282. DOI:10.1084/jem.20192282
121. Huang Y., Jiang W. and Zhou R. (2024). DAMP sensing and sterile inflammation: Intracellular, intercellular and inter-organ pathways. *Nat. Rev. Immunol.* **24**:703–719. DOI:10.1038/s41577-024-01027-3
122. Baharom F., Ramirez-Valdez R. A., Khalilnezhad A., et al. (2022). Systemic vaccination induces CD8+ T cells and remodels the tumor microenvironment. *Cell* **185**:4317–4332.e15. DOI:10.1016/j.cell.2022.10.006
123. Lynn G. M., Sedlik C., Baharom F., et al. (2020). Peptide–TLR-7/8a conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T-cell immunity to tumor antigens. *Nat. Biotechnol.* **38**:320–332. DOI:10.1038/s41587-019-0390-x
124. Hu W., Jain A., Gao Y., et al. (2015). Differential outcome of TRIF-mediated signaling in TLR4 and TLR3 induced DC maturation. *Proc. Natl. Acad. Sci. U. S. A.* **112**:13994–13999. DOI:10.1073/pnas.1510760112
125. Wu L., Hong X., Yang C., et al. (2023). Noncanonical MAVS signaling restrains dendritic cell-driven antitumor immunity by inhibiting IL-12. *Sci. Immunol.* **8**:eadf4919. DOI:10.1126/sciimmunol.adf4919
126. McGinty M. T., Putelo A. M., Kolli S. H., et al. (2025). TLR5 signaling causes dendritic-cell dysfunction and orchestrates failure of immune checkpoint therapy against ovarian cancer. *Cancer Immunol. Res.* Online ahead of print. DOI:10.1158/2326-6066.CIR-24-0513
127. Moon C. Y., Belabed M., Park M. D., et al. (2025). Dendritic cell maturation in cancer. *Nat. Rev. Cancer* **25**:225–248. DOI:10.1038/s41568-024-00787-3
128. Montoya M., Schiavoni G., Mattei F., et al. (2002). Type I interferons produced by dendritic cells promote their phenotypic and functional activation. *Blood* **99**:3263–3271. DOI:10.1182/blood.V99.9.3263
129. Diamond M. S., Kinder M., Matsushita H., et al. (2011). Type I interferon is selectively required by dendritic cells for immune rejection of tumors. *J. Exp. Med.* **208**:1989–2003. DOI:10.1084/jem.20101158
130. Fuentes M. B., Kacha A. K., Kline J., et al. (2011). Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8α+ dendritic cells. *J. Exp. Med.* **208**:2005–2016. DOI:10.1084/jem.20101159
131. Spadaro F., Lapenta C., Donati S., et al. (2012). IFN-α enhances cross-presentation in human dendritic cells by modulating antigen survival, endocytic routing, and processing. *Blood* **119**:1407–1417. DOI:10.1182/blood-2011-06-363564
132. Lei X., de Groot D. C., Welters M. J. P., et al. (2024). CD4+ T cells produce IFN-γ to license cDC1s for induction of cytotoxic T-cell activity in human tumors. *Cell Mol. Immunol.* **21**:374–392. DOI:10.1038/s41423-024-01133-1
133. Meier P., Legrand A. J., Adam D., et al. (2024). Immunogenic cell death in cancer: Targeting necroptosis to induce antitumour immunity. *Nat. Rev. Cancer* **24**:299–315. DOI:10.1038/s41568-024-00674-x
134. Schapp L., Muth S., Rogell L., et al. (2020). Microbiota-induced type I interferons instruct a poised basal state of dendritic cells. *Cell* **181**:1080–1096.e19. DOI:10.1016/j.cell.2020.04.022
135. Ghislat G., Cheema A. S., Baudoin E., et al. (2021). NF-κB-dependent IRF1 activation programs cDC1 dendritic cells to drive antitumor immunity. *Sci. Immunol.* **6**:eabg3570. DOI:10.1126/sciimmunol.abg3570
136. Shinkura R., Kitada K., Matsuda F., et al. (1999). Alymphoplasia is caused by a point mutation in the mouse gene encoding NF-κB-inducing kinase. *Nat. Genet.* **22**:74–77. DOI:10.1038/8780
137. Wu R. and Murphy K. M. (2022). DCs at the center of help: Origins and evolution of the three-cell-type hypothesis. *J. Exp. Med.* **219**:e20211519. DOI:10.1084/jem.20211519
138. Ferris S. T., Durai V., Wu R., et al. (2020). cDC1 prime and are licensed by CD4+ T cells to induce anti-tumour immunity. *Nature* **584**:624–629. DOI:10.1038/s41586-020-2611-3
139. Wu R., Ohara R. A., Jo S., et al. (2022). Mechanisms of CD40-dependent cDC1 licensing beyond costimulation. *Nat. Immunol.* **23**:1536–1550. DOI:10.1038/s41590-022-01324-w
140. Hou Y., Liang H., Rao E., et al. (2018). Non-canonical NF-κB antagonizes STING sensor-mediated DNA sensing in radiotherapy. *Immunity* **49**:490–503.e4. DOI:10.1016/j.immuni.2018.07.008
141. Zanon I., Tan Y., Di Gioia M., et al. (2016). An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells. *Science* **352**:1232–1236. DOI:10.1126/science.aaf3036
142. Zhivaki D., Borriello F., Chow O. A., et al. (2020). Inflammasomes within hyperactive murine dendritic cells stimulate long-lived T cell-mediated anti-tumor immunity. *Cell Rep.* **33**:108381. DOI:10.1016/j.celrep.2020.108381

143. Zhivaki D., Kennedy S. N., Park J., et al. (2024). Correction of age-associated defects in dendritic cells enables CD4+ T cells to eradicate tumors. *Cell* **187**:3888–3903.e18. DOI:10.1016/j.cell.2024.05.026
144. Gargaro M., Scalisi G., Manni G., et al. (2022). Indoleamine 2,3-dioxygenase 1 activation in mature cDC1 promotes tolerogenic education of inflammatory cDC2 via metabolic communication. *Immunity* **55**:1032–1050.e14. DOI:10.1016/j.immuni.2022.05.013
145. Bosteels V., Maréchal S., De Nolf C., et al. (2023). LXR signaling controls homeostatic dendritic cell maturation. *Sci. Immunol.* **8**:eadd3955. DOI:10.1126/sciimmunol.add3955
146. Del Prete A., Salvi V., Soriani A., et al. (2023). Dendritic cell subsets in cancer immunity and tumor antigen sensing. *Cell Mol. Immunol.* **20**:432–447. DOI:10.1038/s41423-023-00990-6
147. Barroso A., Mahler J. V., Fonseca-Castro P. H., et al. (2021). Therapeutic induction of tolerogenic dendritic cells via aryl hydrocarbon receptor signaling. *Curr. Opin. Immunol.* **70**:33–39. DOI:10.1016/j.coi.2021.02.003
148. Mascanfroni I. D., Yeste A., Vieira S. M., et al. (2013). IL-27 acts on DCs to suppress the T cell response and autoimmunity by inducing expression of the immunoregulatory molecule CD39. *Nat. Immunol.* **14**:1054–1063. DOI:10.1038/ni.2695
149. Giovanelli P., Sandoval T. A. and Cubillos-Ruiz J. R. (2019). Dendritic cell metabolism and function in tumors. *Trends Immunol.* **40**:699–718. DOI:10.1016/j.it.2019.06.004
150. Guo C., You Z., Shi H., et al. (2023). SLC38A2 and glutamine signalling in cDC1s dictate anti-tumour immunity. *Nature* **620**:200–208. DOI:10.1038/s41586-023-06299-8
151. Villablanca E. J., Raccosta L., Zhou D., et al. (2010). Tumor-mediated liver X receptor- α activation inhibits CC chemokine receptor-7 expression on dendritic cells and dampens antitumor responses. *Nat. Med.* **16**:98–105. DOI:10.1038/nm.2074
152. de Mingo Pulido Á., Hänggi K., Celias D. P., et al. (2021). The inhibitory receptor TIM-3 limits activation of the cGAS-STING pathway in intra-tumoral dendritic cells by suppressing extracellular DNA uptake. *Immunity* **54**:1154–1167.e7. DOI:10.1016/j.immuni.2021.04.019
153. Dixon K. O., Tabaka M., Schramm M. A., et al. (2021). TIM-3 restrains anti-tumour immunity by regulating inflammasome activation. *Nature* **595**:101–106. DOI:10.1038/s41586-021-03626-9
154. de Mingo Pulido Á., Gardner A., Hiebler S., et al. (2018). TIM-3 regulates CD103+ dendritic cell function and response to chemotherapy in breast cancer. *Cancer Cell* **33**:60–74.e6. DOI:10.1016/j.ccell.2017.11.019
155. Lise V., Malenica I., Roychoudhuri R., et al. (2024). Immune cell triads reprogram exhausted CD8+ T cells for effective tumor elimination. *Cancer Cell* **42**:1152–1154. DOI:10.1016/j.ccell.2024.06.010
156. Prokhnevskaya N., Cardenas M. A., Valanparambil R. M., et al. (2022). CD8+ T cell activation in cancer comprises an initial activation phase in lymph nodes followed by effector differentiation within the tumor. *Immunity* **56**:107–124.e5. DOI:10.1016/j.immuni.2022.12.002
157. Tooley K. A., Escobar G. and Anderson A. C. (2022). Spatial determinants of CD8+ T cell differentiation in cancer. *Trends Cancer* **8**:642–654. DOI:10.1016/j.trecan.2022.04.003
158. Duckworth B. C., Lafouresse F., Wimmer V. C., et al. (2021). Effector and stem-like memory cell fates are imprinted in distinct lymph node niches directed by CXCR3 ligands. *Nat. Immunol.* **22**:434–448. DOI:10.1038/s41590-021-00878-5
159. Leal J. M., Huang J. Y., Kohli K., et al. (2021). Innate cell microenvironments in lymph nodes shape the generation of T cell responses during type I inflammation. *Sci. Immunol.* **6**:eabb9435. DOI:10.1126/sciimmunol.abb9435
160. Gardner A., de Mingo Pulido Á., Hänggi K., et al. (2022). TIM-3 blockade enhances IL-12-dependent antitumor immunity by promoting CD8⁺ T cell and XCR1⁺ dendritic cell spatial co-localization. *J. Immunother. Cancer* **10**:e003571. DOI:10.1136/jitc-2021-003571
161. Oh S. A., Wu D. C., Cheung J., et al. (2020). PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer. *Nat. Cancer* **1**:681–691. DOI:10.1038/s43018-020-0075-x
162. Feau S., Garcia Z., Arens R., et al. (2012). The CD4+ T-cell help signal is transmitted from APC to CD8+ T-cells via CD27–CD70 interactions. *Nat. Commun.* **3**:948. DOI:10.1038/ncomms1948
163. Qin L., Cui Y., Yuan T., et al. (2022). Co-expression of a PD-L1-specific chimeric switch receptor augments the efficacy and persistence of CAR T cells via the CD70-CD27 axis. *Nat. Commun.* **13**:6051. DOI:10.1038/s41467-022-33793-w
164. Sade-Feldman M., Yizhak K., Bjorgaard S. L., et al. (2018). Defining T cell states associated with response to checkpoint immunotherapy in melanoma. *Cell* **175**:998–1013.e20. DOI:10.1016/j.cell.2018.10.038
165. Jansen C. S., Prokhnevskaya N., Master V. A., et al. (2019). An intra-tumoral niche maintains and differentiates stem-like CD8 T cells. *Nature* **576**:465–470. DOI:10.1038/s41586-019-1836-5
166. Waibl Polania J., Hoyt-Miguelbrink A., Tomaszewski W. H., et al. (2024). Antigen presentation by tumor-associated macrophages drives T cells from a progenitor exhaustion state to terminal exhaustion. *Immunity* **58**:232–246.e6. DOI:10.1016/j.immuni.2024.11.026
167. Dähling S., Mansilla A. M., Knöpper K., et al. (2022). Type 1 conventional dendritic cells maintain and guide the differentiation of precursors of exhausted T cells in distinct cellular niches. *Immunity* **55**:656–670.e8. DOI:10.1016/j.immuni.2022.03.006
168. Schenkel J. M., Herbst R. H., Canner D., et al. (2021). Conventional type I dendritic cells maintain a reservoir of proliferative tumor-antigen specific TCF-1+ CD8+ T cells in tumor-draining lymph node. *Immunity* **54**:2338–2353.e6. DOI:10.1016/j.immuni.2021.08.026
169. Lan X., Mi T., Ali S., et al. (2024). Antitumor progenitor exhausted CD8+ T cells are sustained by TCR engagement. *Nat. Immunol.* **25**:1046–1058. DOI:10.1038/s41590-024-01843-8
170. Gressier E., Schulte-Schrepping J., Petrov L., et al. (2023). CD4+ T cell calibration of antigen-presenting cells optimizes antiviral CD8+ T cell immunity. *Nat. Immunol.* **24**:979–990. DOI:10.1038/s41590-023-01517-x
171. Schreiber S., Hammers C. M., Kaasch A. J., et al. (2021). Metabolic interdependency of Th2 cell-mediated Type 2 immunity and the tumor microenvironment. *Front. Immunol.* **12**:632581. DOI:10.3389/fimmu.2021.632581
172. Espinosa-Carrasco G., Chiu E., Scrivo A., et al. (2024). Intratumoral immune triads are required for immunotherapy-mediated elimination of solid tumors. *Cancer Cell* **42**:1202–1216.e8. DOI:10.1016/j.ccell.2024.05.025
173. Pasqual G., Chudnovskiy A., Tas J. M. J., et al. (2018). Monitoring T cell–dendritic cell interactions in vivo by intercellular enzymatic labelling. *Nature* **553**:496–500. DOI:10.1038/nature25442
174. Chudnovskiy A., Castro T. B. R., Nakandakari-Higa S., et al. (2024). Proximity-dependent labeling identifies dendritic cells that drive the tumor-specific CD4+ T cell response. *Sci. Immunol.* **9**:eadq8843. DOI:10.1126/sciimmunol.adq8843
175. Bréart B., Williams K., Krimm S., et al. (2025). IL-27 elicits a cytotoxic CD8+ T cell program to enforce tumour control. *Nature* **639**:746–753. DOI:10.1038/s41586-024-08510-w
176. Ayala M. A. M., Campbell T. F., Zhang C., et al. (2023). CXCR3 expression in regulatory T cells drives interactions with type I dendritic cells in tumors to restrict CD8+ T cell antitumor immunity. *Immunity* **56**:1613–1630.e5. DOI:10.1016/j.immuni.2023.06.003
177. Marangoni F., Zhakyp A., Corsini M., et al. (2021). Expansion of tumor-associated Treg cells upon disruption of a CTLA-4-dependent feedback loop. *Cell* **184**:3998–4015.e19. DOI:10.1016/j.cell.2021.05.027
178. Zagorulya M., Yim L., Morgan D. M., et al. (2023). Tissue-specific abundance of interferon-gamma drives regulatory T cells to restrain DC1-mediated priming of cytotoxic T cells against lung cancer. *Immunity* **56**:386–405.e5. DOI:10.1016/j.immuni.2023.01.010
179. Sultan H., Takeuchi Y., Ward J. P., et al. (2024). Neoantigen-specific cytotoxic Tr1 CD4 T cells suppress cancer immunotherapy. *Nature* **632**:182–191. DOI:10.1038/s41586-024-07752-y
180. Wang X. Q., Danenberg E., Huang C. S., et al. (2023). Spatial predictors of immunotherapy response in triple-negative breast cancer. *Nature* **621**:868–876. DOI:10.1038/s41586-023-06498-3
181. Helmink B. A., Reddy S. M., Gao J., et al. (2020). B cells and tertiary lymphoid structures promote immunotherapy response. *Nature* **577**:549–555. DOI:10.1038/s41586-019-1922-8
182. Teillaud J. L., Houel A., Panouillot M., et al. (2024). Tertiary lymphoid structures in anticancer immunity. *Nat. Rev. Cancer* **24**:629–646. DOI:10.1038/s41568-024-00728-0
183. Mattiuz R., Boumelha J., Hamon P., et al. (2024). Dendritic cells type 1 control the formation, maintenance, and function of tertiary lymphoid structures in cancer. (*bioRxiv*):2024.12.27.628014. DOI:10.1101/2024.12.27.628014
184. Deng L., Liang H., Xu M., et al. (2014). STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. *Immunity* **41**:843–852. DOI:10.1016/j.immuni.2014.10.019
185. Galluzzi L., Aryankalayil M. J., Coleman C. N., et al. (2023). Emerging evidence for adapting radiotherapy to immunotherapy. *Nat. Rev. Clin. Oncol.* **20**:543–557. DOI:10.1038/s41571-023-00782-x
186. Yang Y., Wu M., Cao D., et al. (2021). ZBP1-MLKL necroptotic signaling potentiates radiation-induced antitumor immunity via intratumoral STING pathway activation. *Sci. Adv.* **7**:eabf6290. DOI:10.1126/sciadv.abf6290
187. Tani T., Mathysaraja H., Campisi M., et al. (2024). TREX1 inactivation unleashes cancer cell STING-2 interferon signaling and promotes anti-tumor 3 immunity. *Cancer Discov.* **14**:752–765. DOI:10.1158/2159-8290.CD-23-0700
188. Vanpouille-Box C., Alard A., Aryankalayil M. J., et al. (2017). DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat. Commun.* **8**:15618. DOI:10.1038/ncomms15618
189. Wen C., Wang L., Piffkó A., et al. (2024). YTHDF1 loss in dendritic cells potentiates radiation-induced antitumor immunity via STING-dependent type I IFN production. *J. Clin. Invest.* **134**:e181612. DOI:10.1172/JCI181612https://www.jci.org/articles/view/181612
190. Nefedova Y., Cheng P., Gilkes D., et al. (2005). Activation of dendritic cells via inhibition of Jak2/STAT3 signaling1. *J. Immunol.* **175**:4338–4346. DOI:10.4049/jimmunol.175.7.4338
191. Fu C., Liang X., Cui W., et al. (2015). β -Catenin in dendritic cells exerts opposite functions in cross-priming and maintenance of CD8+ T cells through regulation of

- IL-10. *Proc. Natl. Acad. Sci. U. S. A.* **112**:2823–2828. DOI:10.1073/pnas.1414167112
192. Zhao L., Liu P., Mao M., et al. (2023). BCL2 inhibition reveals a dendritic cell-specific immune checkpoint that controls tumor immunosurveillance. *Cancer Discov.* **13**:2448–2469. DOI:10.1158/2159-8290.CD-22-1338
 193. Oliveira G. and Wu C. J. (2023). Dynamics and specificities of T cells in cancer immunotherapy. *Nat. Rev. Cancer* **23**:295–316. DOI:10.1038/s41568-023-00560-y
 194. Liu L., Chen J., Bae J., et al. (2021). Rejuvenation of tumour-specific T cells through bispecific antibodies targeting PD-L1 on dendritic cells. *Nat. Biomed. Eng.* **5**:1261–1273. DOI:10.1038/s41551-021-00800-2
 195. Mayoux M., Roller A., Pulko V., et al. (2020). Dendritic cells dictate responses to PD-L1 blockade cancer immunotherapy. *Sci. Transl. Med.* **12**:eaav7431. DOI:10.1126/scitranslmed.aav7431
 196. Dammeijer F., van Gulijk M., Mulder E. E., et al. (2020). The PD-1/PD-L1-checkpoint restrains T cell immunity in tumor-draining lymph nodes. *Cancer Cell* **38**:685–700.e8. DOI:10.1016/j.ccell.2020.09.001
 197. Sharma P., Goswami S., Raychaudhuri D., et al. (2023). Immune checkpoint therapy—current perspectives and future directions. *Cell* **186**:1652–1669. DOI:10.1016/j.cell.2023.03.006
 198. Cousin N., Cap S., Dühr M., et al. (2021). Lymphatic PD-L1 expression restricts tumor-specific CD8+ T-cell responses. *Cancer Res.* **81**:4133–4144. DOI:10.1158/0008-5472.CAN-21-0633
 199. Tang H., Liang Y., Anders R. A., et al. (2018). PD-L1 on host cells is essential for PD-L1 blockade-mediated tumor regression. *J. Clin. Invest.* **128**:580–588. DOI:10.1172/JCI96061
 200. Peng Q., Qiu X., Zhang Z., et al. (2020). PD-L1 on dendritic cells attenuates T cell activation and regulates response to immune checkpoint blockade. *Nat. Commun.* **11**:4835. DOI:10.1038/s41467-020-18570-x
 201. Chen L., Azuma T., Yu W., et al. (2018). B7-H1 maintains the polyclonal T cell response by protecting dendritic cells from cytotoxic T lymphocyte destruction. *Proc. Natl. Acad. Sci. U. S. A.* **115**:3126–3131. DOI:10.1073/pnas.1722043115
 202. Zhao Y., Lee C. K., Lin C. H., et al. (2019). PD-L1:CD80 Cis-heterodimer triggers the co-stimulatory receptor CD28 while repressing the inhibitory PD-1 and CTLA-4 pathways. *Immunity* **51**:1059–1073.e9. DOI:10.1016/j.immuni.2019.11.003
 203. Sugiura D., Maruhashi T., Okazaki I. mi, et al. (2019). Restriction of PD-1 function by cis-PD-L1/CD80 interactions is required for optimal T cell responses. *Science* **364**:558–566. DOI:10.1126/science.aav7062
 204. Xu X., Dennett P., Zhang J., et al. (2023). CTLA4 depletes T cell endogenous and trogocytosed B7 ligands via cis-endocytosis. *J. Exp. Med.* **220**:e20221391. DOI:10.1084/jem.20221391
 205. Zhang Y., Song Q., Cassidy K., et al. (2023). Blockade of trans PD-L1 interaction with CD80 augments antitumor immunity. *Proc. Natl. Acad. Sci. U. S. A.* **120**:e2205085120. DOI:10.1073/pnas.2205085120
 206. Shapir Itai Y., Barboy O., Salomon R., et al. (2024). Bispecific dendritic-T cell engager potentiates anti-tumor immunity. *Cell* **187**:375–389.e18. DOI:10.1016/j.cell.2023.12.011
 207. Salomon R., Rotem H., Katzenelenbogen Y., et al. (2022). Bispecific antibodies increase the therapeutic window of CD40 agonists through selective dendritic cell targeting. *Nat. Cancer* **3**:287–302. DOI:10.1038/s43018-022-00329-6
 208. Adachi K., Kano Y., Nagai T., et al. (2018). IL-7 and CCL19 expression in CAR-T cells improves immune cell infiltration and CAR-T cell survival in the tumor. *Nat. Biotechnol.* **36**:346–351. DOI:10.1038/nbt.4086
 209. Bhardwaj N., Friedlander P. A., Pavlick A. C., et al. (2020). Flt3 ligand augments immune responses to anti-DEC-205-NY-ESO-1 vaccine through expansion of dendritic cell subsets. *Nat. Cancer* **1**:1204–1217. DOI:10.1038/s43018-020-00143-y
 210. Lai J., Mardiana S., House I. G., et al. (2020). Adoptive cellular therapy with T cells expressing the dendritic cell growth factor Flt3L drives epitope spreading and antitumor immunity. *Nat. Immunol.* **21**:914–926. DOI:10.1038/s41590-020-0676-7
 211. Rapp M., Grassmann S., Chaloupka M., et al. (2016). C-C chemokine receptor type-4 transduction of T cells enhances interaction with dendritic cells, tumor infiltration and therapeutic efficacy of adoptive T cell transfer. *Oncol Immunology* **5**:e1105428. DOI:10.1080/2162402X.2015.1105428
 212. Kuhn N. F., Purdon T. J., van Leeuwen D. G., et al. (2019). CD40 ligand-modified chimeric antigen receptor T cells enhance antitumor function by eliciting an endogenous antitumor response. *Cancer Cell* **35**:473–488.e6. DOI:10.1016/j.ccell.2019.02.006
 213. Ma L., Dichwalkar T., Chang J. Y. H., et al. (2019). Enhanced CAR-T cell activity against solid tumors by vaccine boosting through the chimeric receptor. *Science* **365**:162–168. DOI:10.1126/science.aav8692
 214. Ma L., Hostetler A., Morgan D. M., et al. (2023). Vaccine-boosted CAR T crosstalk with host immunity to reject tumors with antigen heterogeneity. *Cell* **186**:3148–3165.e20. DOI:10.1016/j.cell.2023.06.002
 215. Salehi-Rad R., Lim R. J., Du Y., et al. (2023). CCL21-DC in situ vaccination in murine NSCLC overcomes resistance to immunotherapy and generates systemic tumor-specific immunity. *J. Immunother. Cancer* **11**:e006896. DOI:10.1136/jitc-2023-006896
 216. Lim R. J., Salehi-Rad R., Tran L. M., et al. (2024). CXCL9/10-engineered dendritic cells promote T cell activation and enhance immune checkpoint blockade for lung cancer. *Cell Rep. Med.* **5**:101479. DOI:10.1016/j.xcrm.2024.101479
 217. Lee J. M., Lee M. H., Garon E., et al. (2017). Phase I trial of intratumoral injection of CCL21 gene-modified dendritic cells in lung cancer elicits tumor-specific immune responses and CD8+ T-cell infiltration. *Clin. Cancer Res.* **23**:4556–4568. DOI:10.1158/1078-0432.CCR-16-2821
 218. Stangis M. M., Chen Z., Min J., et al. (2024). The hallmarks of precancer. *Cancer Discov.* **14**:683–689. DOI:10.1158/2159-8290.CD-23-1550
 219. Li S., Dong R., Kang Z., et al. (2023). Exosomes: Another intercellular lipometabolic communication mediators in digestive system neoplasms. *Cytokine Growth Factor Rev.* **73**:93–100. DOI:10.1016/j.cytogfr.2023.06.005
 220. Iannello A., Thompson T. W., Ardolino M., et al. (2013). p53-dependent chemokine production by senescent tumor cells supports NKG2D-dependent tumor elimination by natural killer cells. *J. Exp. Med.* **210**:2057–2069. DOI:10.1084/jem.20130783
 221. Peng W., Chen J. Q., Liu C., et al. (2016). Loss of PTEN promotes resistance to T cell-mediated immunotherapy. *Cancer Discov.* **6**:202–216. DOI:10.1158/2159-8290.CD-15-0283
 222. Bergholz J. S., Wang Q., Wang Q., et al. (2023). PI3K β controls immune evasion in PTEN-deficient breast tumours. *Nature* **617**:139–146. DOI:10.1038/s41586-023-05940-w
 223. Lin Y. X., Wang Y., Ding J., et al. (2021). Reactivation of the tumor suppressor PTEN by mRNA nanoparticles enhances antitumor immunity in preclinical models. *Sci. Transl. Med.* **13**:eaba9772. DOI:10.1126/scitranslmed.aba9772
 224. Sathaliyawala T., O’Gorman W. E., Greter M., et al. (2010). Mammalian target of rapamycin controls dendritic cell development downstream of Flt3 ligand signaling. *Immunity* **33**:597–606. DOI:10.1016/j.immuni.2010.09.012
 225. Wu M. J., Kondo H., Kammula A. V., et al. (2024). Mutant IDH1 inhibition induces dsDNA sensing to activate tumor immunity. *Science* **385**:eadl6173. DOI:10.1126/science.adl6173
 226. Kim S., Chen J., Jo S., et al. (2023). IL-6 selectively suppresses cDC1 specification via C/EBP β . *J. Exp. Med.* **220**:e20221757. DOI:10.1084/jem.20221757
 227. Ruffell B., Chang-Strachan D., Chan V., et al. (2014). Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. *Cancer Cell* **26**:623–637. DOI:10.1016/j.ccell.2014.09.006
 228. Hiam-Galvez K. J., Allen B. M. and Spitzer M. H. (2021). Systemic immunity in cancer. *Nat. Rev. Cancer* **21**:345–359. DOI:10.1038/s41568-021-00347-z
 229. Bayerl F., Meiser P., Donakonda S., et al. (2023). Tumor-derived prostaglandin E2 programs cDC1 dysfunction to impair intratumoral orchestration of anti-cancer T cell responses. *Immunity* **56**:1341–1358.e11. DOI:10.1016/j.immuni.2023.05.011
 230. Sharma P., Zhang X., Ly K., et al. (2024). Hyperglycosylation of prosaposin in tumor dendritic cells drives immune escape. *Science* **383**:190–200. DOI:10.1126/science.adg1955
 231. Park S. J., Nakagawa T., Kitamura H., et al. (2004). IL-6 regulates in vivo dendritic cell differentiation through STAT3 activation1. *J. Immunol.* **173**:3844–3854. DOI:10.4049/jimmunol.173.6.3844
 232. Nefedova Y., Huang M., Kusmartsev S., et al. (2004). Hyperactivation of STAT3 is involved in abnormal differentiation of dendritic cells in cancer. *J. Immunol.* **172**:464–474. DOI:10.4049/jimmunol.172.1.464
 233. Wan C. K., Oh J., Li P., et al. (2013). The cytokines IL-21 and GM-CSF have opposing regulatory roles in the apoptosis of conventional dendritic cells. *Immunity* **38**:514–527. DOI:10.1016/j.immuni.2013.02.011
 234. Qiao J., Liu Z., Dong C., et al. (2019). Targeting tumors with IL-10 prevents dendritic cell-mediated CD8+ T cell apoptosis. *Cancer Cell* **35**:901–915.e4. DOI:10.1016/j.ccell.2019.05.005
 235. Meyer M. A., Baer J. M., Knolhoff B. L., et al. (2018). Breast and pancreatic cancer interrupt IRF8-dependent dendritic cell development to overcome immune surveillance. *Nat. Commun.* **9**:1250. DOI:10.1038/s41467-018-03600-6
 236. Böttcher J. P., Bonavita E., Chakravarty P., et al. (2018). NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. *Cell* **172**:1022–1037.e14. DOI:10.1016/j.cell.2018.01.004
 237. Brown T. P., Bhattacharjee P., Ramachandran S., et al. (2020). The lactate receptor GPR81 promotes breast cancer growth via a paracrine mechanism involving antigen-presenting cells in the tumor microenvironment. *Oncogene* **39**:3292–3304. DOI:10.1038/s41388-020-1216-5
 238. Caronni N., Simoncello F., Stafetta F., et al. (2018). Downregulation of membrane trafficking proteins and lactate conditioning determine loss of dendritic cell function in lung cancer. *Cancer Res.* **78**:1685–1699. DOI:10.1158/0008-5472.CAN-17-1307
 239. Moesta A. K., Li X. Y. and Smyth M. J. (2020). Targeting CD39 in cancer. *Nat. Rev. Immunol.* **20**:739–755. DOI:10.1038/s41577-020-0376-4
 240. Rahim M. K., Okholm T. L. H., Jones K. B., et al. (2023). Dynamic CD8+ T cell responses to cancer immunotherapy in human regional lymph nodes are disrupted in metastatic lymph nodes. *Cell* **186**:1127–1143.e18. DOI:10.1016/j.cell.2023.02.021
 241. Liu L., Hou Y., Deng C., et al. (2022). Single cell sequencing reveals that CD39 inhibition mediates changes to the tumor microenvironment. *Nat. Commun.* **13**:6740. DOI:10.1038/s41467-022-34495-z
 242. Sadik A., Somarrivas Patterson L. F., Öztürk S., et al. (2020). IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression. *Cell* **182**:1252–1270.e34. DOI:10.1016/j.cell.2020.07.038
 243. Cao W., Xu J., Zhu F., et al. (2025). Addressing the unmet needs: Optimized vaccine design for human metapneumovirus. *Innov. Med.* **3**:100112. DOI:10.59717/j.xinn-

- med.2025.100112
244. Yewdall A. W., Drutman S. B., Jinwala F., et al. (2010). CD8+ T cell priming by dendritic cell vaccines requires antigen transfer to endogenous antigen presenting cells. *PLOS ONE* **5**:e11144. DOI:10.1371/journal.pone.0011144
 245. Bol K. F., Schreiber G., Bloemendal M., et al. (2024). Adjuvant dendritic cell therapy in stage IIIB/C melanoma: The MIND-DC randomized phase III trial. *Nat. Commun.* **15**:1632. DOI:10.1038/s41467-024-45358-0
 246. Allen B. M., Hiam K. J., Burnett C. E., et al. (2020). Systemic dysfunction and plasticity of the immune macroenvironment in cancer models. *Nat. Med.* **26**:1125–1134. DOI:10.1038/s41591-020-0892-6
 247. Zhang Y., Hou X., Du S., et al. (2023). Close the cancer–immunity cycle by integrating lipid nanoparticle–mRNA formulations and dendritic cell therapy. *Nat. Nanotechnol.* **18**:1364–1374. DOI:10.1038/s41565-023-01453-9
 248. Saeed M. A., Peng B., Kim K., et al. (2024). High-dimensional analyses reveal IL15 enhances activation of sipuleucel-T lymphocyte subsets and reverses immunoresistance. *Cancer Immunol. Res.* **12**:559–574. DOI:10.1158/2326-6066.CIR-23-0652
 249. Everson R. G., Hugo W., Sun L., et al. (2024). TLR agonists polarize interferon responses in conjunction with dendritic cell vaccination in malignant glioma: A randomized phase II Trial. *Nat. Commun.* **15**:3882. DOI:10.1038/s41467-024-48073-y
 250. Liao L. M., Ashkan K., Brem S., et al. (2022). Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: A phase 3 prospective externally controlled cohort trial. *JAMA Oncol* **9**:112–121. DOI:10.1001/jamaoncol.2022.5370
 251. Lau S. P., Klaase L., Vink M., et al. (2022). Autologous dendritic cells pulsed with allogeneic tumour cell lysate induce tumour-reactive T-cell responses in patients with pancreatic cancer: A phase I study. *Eur. J. Cancer* **169**:20–31. DOI:10.1016/j.ejca.2022.03.015
 252. Wang C., Lutes L. K., Barnoud C., et al. (2022). The circadian immune system. *Sci. Immunol.* **7**:eabm2465. DOI:10.1126/sciimmunol.abm2465
 253. Wang C., Barnoud C., Cenerenti M., et al. (2023). Dendritic cells direct circadian anti-tumour immune responses. *Nature* **614**:136–143. DOI:10.1038/s41586-022-05605-0
 254. Cao L. L. and Kagan J. C. (2023). Targeting innate immune pathways for cancer immunotherapy. *Immunity* **56**:2206–2217. DOI:10.1016/j.immuni.2023.07.018
 255. Hammerich L., Maron T. U., Upadhyay R., et al. (2019). Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. *Nat. Med.* **25**:814–824. DOI:10.1038/s41591-019-0410-x
 256. Salmon H., Idoyaga J., Rahman A., et al. (2016). Expansion and activation of CD103+ dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. *Immunity* **44**:924–938. DOI:10.1016/j.immuni.2016.03.012
 257. Sánchez-Paulete A. R., Teixeira Á., Quetglas J. I., et al. (2018). Intratumoral immunotherapy with XCL1 and sFlt3L encoded in recombinant semliki forest virus–derived vectors fosters dendritic cell–mediated T-cell cross-priming. *Cancer Res.* **78**:6643–6654. DOI:10.1158/0008-5472.CAN-18-0933
 258. Svensson-Arvelund J., Cuadrado-Castano S., Pantisulaia G., et al. (2022). Expanding cross-presenting dendritic cells enhances oncolytic virotherapy and is critical for long-term anti-tumor immunity. *Nat. Commun.* **13**:7149. DOI:10.1038/s41467-022-34791-8
 259. Ghasemi A., Martinez-Usatorre A., Li L., et al. (2023). Cytokine-armed dendritic cell progenitors for antigen-agnostic cancer immunotherapy. *Nat. Cancer* **5**:240–261. DOI:10.1038/s43018-023-00668-y
 260. Wang J., Li S., Wang M., et al. (2024). STING licensing of type I dendritic cells potentiates antitumor immunity. *Sci. Immunol.* **9**:eadj3945. DOI:10.1126/sciimmunol.adj3945
 261. Dane E. L., Belessiotis-Richards A., Backlund C., et al. (2022). STING agonist delivery by tumour-penetrating PEG-lipid nanodiscs primes robust anticancer immunity. *Nat. Mater.* **21**:710–720. DOI:10.1038/s41563-022-01251-z
 262. Lv M., Chen M., Zhang R., et al. (2020). Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy. *Cell Res.* **30**:966–979. DOI:10.1038/s41422-020-00395-4
 263. Li F. and Ravetch J. V. (2011). Inhibitory Fcγ receptor engagement drives adjuvant and anti-tumor activities of agonistic CD40 antibodies. *Science* **333**:1030–1034. DOI:10.1126/science.1206954
 264. Jiang H., Ni H., Zhang P., et al. (2021). PD-L1/LAG-3 bispecific antibody enhances tumor-specific immunity. *Oncol Immunology* **10**:1943180. DOI:10.1080/2162402X.2021.1943180
 265. Gu C., Shi X., Dai C., et al. (2020). RNA m6A modification in cancers: Molecular mechanisms and potential clinical applications. *The Innovation* **1**:100066. DOI:10.1016/j.xinn.2020.100066
 266. Zhou H., Wu M., Wu K., et al. (2025). Genetic-informed alternative RNA splicing serves an essential role in carcinogenesis and prognosis of non-small-cell lung cancer. *Innov. Med.* **3**:100111. DOI:10.59717/j.xinn-med.2025.100111
 267. De Sá Fernandes C., Novoszel P., Gastaldi T., et al. (2024). The histone deacetylase HDAC1 controls dendritic cell development and anti-tumor immunity. *Cell Rep.* **43**:114308. DOI:10.1016/j.celrep.2024.114308
 268. Zimmermannova O., Ferreira A. G., Ascić E., et al. (2023). Restoring tumor immunogenicity with dendritic cell reprogramming. *Sci. Immunol.* **8**:eadd4817. DOI:10.1126/sciimmunol.add4817
 269. Linde M. H., Fan A. C., Kohnke T., et al. (2023). Reprogramming cancer into antigen presenting cells as a novel immunotherapy. *Cancer Discov.* **13**:1164–1185. DOI:10.1158/2159-8290.CD-21-0502
 270. Ascić E., Åkerström F., Sreekumar Nair M., et al. (2024). In vivo dendritic cell reprogramming for cancer immunotherapy. *Science* **386**:eadn9083. DOI:10.1126/science.adn9083
 271. Swanton C., Bernard E., Abbosh C., et al. (2024). Embracing cancer complexity: Hallmarks of systemic disease. *Cell* **187**:1589–1616. DOI:10.1016/j.cell.2024.02.009
 272. Ma K., Wang L., Li W., et al. (2024). Turning cold into hot: Emerging strategies to fire up the tumor microenvironment. *Trends Cancer* **11**:117–134. DOI:10.1016/j.trecan.2024.11.011
 273. Duan Q., Zhang H., Zheng J., et al. (2020). Turning cold into hot: Firing up the tumor microenvironment. *Trends Cancer* **6**:605–618. DOI:10.1016/j.trecan.2020.02.022
 274. Gustafsson J., Roshanzamir F., Hagnestål A., et al. (2024). Metabolic collaboration between cells in the tumor microenvironment has a negligible effect on tumor growth. *The Innovation* **5**:100583. DOI:10.1016/j.xinn.2024.100583
 275. Thumkeo D., Punyawattananukool S., Prasongtanakij S., et al. (2022). PGE2-EP2/EP4 signaling elicits immunosuppression by driving the mregDC-Treg axis in inflammatory tumor microenvironment. *Cell Rep.* **39**:110914. DOI:10.1016/j.celrep.2022.110914
 276. Morotti M., Grimm A. J., Hope H. C., et al. (2024). PGE2 inhibits TIL expansion by disrupting IL-2 signalling and mitochondrial function. *Nature* **629**:426–434. DOI:10.1038/s41586-024-07352-w

FUNDING AND ACKNOWLEDGMENTS

We apologize to the scientists whose work was not cited because of space limitations. This study was in part supported by the National Natural Science Foundation of China (82350114, 82271775 to L.Z., 82171828 to L.-Y.Z.), the Natural Science Foundation Outstanding Youth Fund of Jiangsu Province (BK20220049 L.Z.), the CAMS Innovation Fund for Medical Sciences (2022-I2M-2-004, 2023-I2M-2-010 and 2024-I2M-TS-033 to L.Z.). We thank the Suzhou Municipal Key Laboratory (SZS2023005) and the NCTIB Fund for R&D Platform for Cell and Gene Therapy. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

L.Z. and Z.X. conceived the review and wrote the draft. J.W., J.Y., F.G. and L.Z. participated the writing and revised the manuscript. All authors critically read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.