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REVIEW

Cancer Focus

Leveraging cDC1 biology and function for enhanced immunotherapy

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Conventional type 1 dendritic cells (cDC1s) promote antitumor immunity through efficient cross-presentation of tumor antigens and production of key mediators. Crucially, in the tumor microenvironment, cDC1s orchestrate immune hubs and signaling axes that support T cell responses and are associated with improved patient outcomes. During tumor progression, however, cDC1 activity is increasingly constrained by immunosuppressive signals and inhibitory cellular interactions. Many immunotherapies, including immune checkpoint blockade and adoptive cell transfer, depend on functional cDC1 populations for optimal efficacy, underscoring the need to define both the mechanisms that enable cDC1-mediated immunity and those that suppress it. Emerging strategies aim to harness cDC1s by expanding their numbers, reprogramming suppressed DC states, or strengthening interactions with CD8⁺ and CD4⁺ T cells and natural killer cells. Here, we discuss the molecular pathways, cellular phenotypes, and spatial features that govern cDC1 function, highlight the prognostic and predictive value of cDC1-associated signatures, and evaluate therapeutic approaches that leverage cDC1 biology to improve cancer treatment and durability of response.

Introduction

DCs, and in particular cDC1s, though a relatively rare immune cell subset, play a central role in shaping adaptive antitumor immunity through their capacity to capture, process, and present tumor-associated antigens. cDC1s are uniquely equipped for the uptake and preservation of tumor antigens, and cross-presentation of cell-associated antigens via MHC class I. This facilitates their nonredundant role in eliciting de novo antitumor cytotoxic CD8⁺ T cell (CTL) responses, with a critical role for *Batf3*$^{-/-}$-dependent CD8α⁺ DCs for induction of CTLs and antitumor immunity first identified in 2008 (Hildner et al., 2008). The prognostic importance of BATF3/IRF8/Zbtb46 transcription factor–dependent CD103⁺ DCs, in the human TME, was first characterized in 2014 (Broz et al., 2014). The authors noted that these cells were enriched in regressing tumors and were associated with better disease outcomes. These cells are now classified as cDC1s, in line with the cDC nomenclature first proposed by Guilliams et al., (2014). Since then, higher cDC1 signatures have been shown to correlate with better disease and therapeutic outcomes among many cancer types (see Table 1), and cDC1s have been demonstrated to be required for the efficacy of various immunotherapeutic strategies (see Table 2).

Beyond their role in cross-priming, cDC1s facilitate key cellular interactions that promote antitumor immunity, for example, in orchestrating CD4⁺ T cell help, via tumor antigen presentation via MHC class I and II coupled to CD40-dependent licensing interactions (Ferris et al., 2020; Wu et al., 2022) (See Fig. 1). This dual functionality and help enhance CD8⁺ T cell expansion and effector differentiation and ultimately response to immune checkpoint blockade (ICB) approaches (Lei et al., 2023). cDC1s additionally are central in facilitating and shaping key immune axes that shape antitumor immunity, such as those involving NK cells (Barry et al., 2018; Böttcher et al., 2018), CD8⁺ T cells (Meiser et al., 2023; Piot et al., 2025; Carbone et al., 2025, *Preprint*), CD4⁺ T cells (Ferris et al., 2020; Wu et al., 2022), tumor-associated macrophages (TAMs) (Ray et al., 2025), and regulatory T cells (Tregs) (Moreno Ayala et al., 2023; You et al., 2024). Indeed, growing evidence reveals that the presence, activation state, and spatial distribution of cDC1s within tumors correlate strongly with responsiveness to immunotherapy (Carbone et al., 2025, *Preprint*; Piot et al., 2025; Gobbini et al., 2025). Insights from high-dimensional profiling approaches, including single-cell transcriptomics and spatial analyses, have illuminated the complex regulation of cDC1 localization and function within the TME, and have uncovered key pathways that govern their recruitment, maturation, and interaction with other immune populations. In this Review, we highlight recent advances in our understanding

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Table 1. **Intratumoral cDC1 signatures and disease outcomes in human cancer patients**

Cancer type	Correlation observed between the presence of cDC1 signature in TME and favorable outcome	Dataset(s) utilized	Reference(s)
Liver hepatocellular carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023) TCGA (Gu et al., 2020), own cohort (Magen et al., 2023)	Régnier et al. (2023), Gu et al. (2020), and Magen et al. (2023)
Bladder cancer	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Prostate adenocarcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Adrenocortical carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Lung squamous cell carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Lung adenocarcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023), TCGA (López et al., 2024; Böttcher et al., 2018), TCGA (Broz et al., 2014; Gu et al., 2020)	Régnier et al. (2023) López et al. (2024) Böttcher et al. (2018) and Gu et al. (2020) Broz et al. (2014)
Non–small-cell lung cancer	Positive correlation	Own cohort (Wang et al., 2024b)	Wang et al. (2024b)
Mesothelioma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Malignant pleural mesothelioma	Positive correlation	Own cohort (Espinosa-Carrasco et al., 2024)	Espinosa-Carrasco et al. (2024)
Sarcoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Skin cutaneous melanoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023), TCGA (Spranger et al., 2017; Barry et al., 2018; Böttcher et al., 2018; Lei et al., 2023; Ghislat et al., 2021; Cueto et al., 2021; Gu et al., 2020; Heras-Murillo et al., 2025; De León-Rodríguez et al., 2024), own cohort (Gobbini et al., 2025; Yang et al., 2025)	Régnier et al. (2023) Spranger et al. (2017) Barry et al. (2018) Böttcher et al. (2018) Lei et al. (2023) Sosa Cuevas et al. (2020), Ghislat et al. (2021), Cueto et al. (2021), Gu et al. (2020), Heras-Murillo et al. (2025), Gobbini et al. (2025), and Yang et al. (2025)
Uterine corpus endometrial carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Cervical	Positive correlation	TCGA (Rotman et al., 2020; Cueto et al., 2021)	Rotman et al. (2020) and Cueto et al. (2021)
Ovarian	Positive correlation	TCGA (Mastelic-Gavillet et al., 2020)	Mastelic-Gavillet et al. (2020)
Head and neck squamous cell carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023), TCGA (Böttcher et al., 2018; Broz et al., 2014; Gu et al., 2020)	Régnier et al. (2023) Böttcher et al. (2018), Broz et al. (2014), and Gu et al. (2020)
Kidney renal clear cell carcinoma	Positive correlation	TCGA and TARGET (Régnier et al., 2023), TCGA (Gu et al., 2020)	Régnier et al. (2023) and Gu et al. (2020)
Kidney renal papillary cell carcinoma	Positive correlation	TCGA (Gu et al., 2020)	Gu et al. (2020)
Wilms tumor	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)

Table 1. **Intratumoral cDC1 signatures and disease outcomes in human cancer patients (*Continued*)**

Cancer type	Correlation observed between the presence of cDC1 signature in TME and favorable outcome	Dataset(s) utilized	Reference(s)
Breast cancer	Positive correlation + negative correlation	**Positive correlation** TCGA and TARGET (Régnier et al., 2023), TCGA (Böttcher et al., 2018; Mattiuz et al., 2021; Broz et al., 2014; Wang et al., 2024c; Iwanowycz et al., 2021; Cueto et al., 2021; Heras-Murillo et al., 2025), TCGA (Hubert et al., 2020), the Molecular Taxonomy of Breast cancer International Consortium (Michea et al., 2018) **Negative correlation** TCGA (Iwanowycz et al., 2021)	Régnier et al. (2023) Böttcher et al. (2018) and Mattiuz et al. (2021) Michea et al. (2018) Broz et al. (2014) Wang et al. (2024c), Iwanowycz et al. (2021), Cueto et al. (2021), and Heras-Murillo et al. (2025)
Pancreatic ductal adenocarcinoma	Positive correlation	TCGA (Mahadevan et al., 2024), own cohort (Plesca et al., 2022)	Mahadevan et al. (2024) Plesca et al. (2022)
Neuroblastoma	Positive correlation	Own cohort (Melaiu et al., 2020)	Melaiu et al. (2020)
Pheochromocytoma and paraganglioma	Positive correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
HPV⁺ tonsillar cancer	Positive correlation	Own cohort (Jimenez et al., 2023)	Jimenez et al. (2023)
Uveal melanoma	Negative correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Cholangiocarcinoma	Negative correlation	TCGA and TARGET (Régnier et al., 2023)	Régnier et al. (2023)
Stomach adenocarcinoma	Negative correlation + positive correlation	**Negative correlation** TCGA (Han and Ju, 2024), TCGA and TARGET (Régnier et al., 2023) **Positive correlation** (Han and Ju, 2024) Tumor Immune Dysfunction and Exclusion (TIDE) database and GEO	Régnier et al. (2023) Han and Ju (2024)

The following signatures and methodologies were used: Barry et al. (2018) utilized a stimulatory DC (CD103⁺ BDCA-3⁺) signature: KIT, CCR7, BATF3, FLT3, ZBTB46, IRF8, BTLA, MYCL1.
Böttcher et al. (2018) utilized a cDC1 signature: CLEC9A, XCR1, CLNK, BATF3.
Broz et al. (2014) utilized a signature based on CD103⁺/CD103⁻ gene ratio signature.
Cueto et al. (2021) utilized a CCL5/CCR5 and FLT3L signature.
De León-Rodríguez et al. (2024) utilized a cDC1 signature: CD11c, HLADR, BDCA3.
Espinosa-Carrasco et al. (2024) utilized CD4⁺ and CD8⁺ T cell and CD11c⁺ APC triads.
Ghislat et al. (2021) demonstrated prognostic implications of NF-κB/IRF1 activation of cDC1: BATF3, CLNK, CLEC9A, XCR1, IRF1, NFKB1, IKBKB.
Gobbini et al. (2025) demonstrated colocalization of XCR1⁺ cDC1 and CD8⁺ T cells.
Gu et al. (2020) utilized a cDC1 signature: THBD, CLEC9A.
Han and Ju (2024) utilized a cDC1 signature: THBD, XCR1, CLEC9A, CADM1, BTLA, and a higher cDC1 signature associated with favorable outcome in patients with advanced disease treated with chemotherapy/ICB.
Heras-Murillo et al. (2025) utilized a cDC1 signature: CLNK, BATF3, XCR1, and CLEC9A.
Hubert et al. (2020) utilized a cDC1 signature: CLEC9A, XCR1.
Iwanowycz et al. (2021) utilized a cDC1 signature: XCR1, CLEC9A, BATF3, and reported dependence on immune contexture for cDC1 prognostic value. In lymphocyte-depleted BRCA tumors, a negative correlation for cDC1 signature levels was observed. In IFNγ dominant tumors, a positive correlation was observed.
Jimenez et al. (2023) utilized a cDC1 signature: CLEC9A, CLNK, XCR1.
Wang et al. (2024b) utilized a STING-activated cDC1 signature (XCR1⁺ STING⁺ CXCL9⁺) in neoadjuvant-treated chemotherapy and anti-PD1–treated patients.
Lei et al. (2023) utilized the presence of cDC1 helped signature: ACHE, ACTB, ACTG1, ADAM19, AL357060.1, ANKLE2, ANTXR2, ANXA6, APOBEC3G, APOL1, APOL2, APOL3, ARAP2, ARHGAP22, ARID5A, ARL8B, ARNTL2, ARRB2, ATF5, ATG3, B2M, BASP1, BAZ1A, BCL2A1, BCL2L14, BIRC3, BLVRA, BST2, BZW1, C3orf14, CALHM6, CCL19, CCL5, CCR7, CD200, CD274, CD40, CD83, CD86, CDKN1A, CELF2, CEP135, CFLAR, CLIC2, CLPTM1, CNTLN, COA1, CREG1, CTSS, CUL1, CXCL10, CXCL11, CXCL9, CYB5A, DAPP1, DEPP1, DHX58, DNAJA1, DNAJB6, DNAJC15, DST, DTX3L, DUSP1, DUSP22, DUSP4, DYNLT1, EBI3, EEF1A1, EHD1, EIF1, ENTHD1, EPSTI1, ERGIC1, ERICH1, ETV7, FAM129A, FAM177A1, FAM241A, FAM49A, FAS, FBXO6, FGD2, FLT3, FNBP1, FSCN1, G3BP2, GADD45B, GBP1, GBP2, GBP4, GBP5, GCSAM, GPR132, GRSF1, HAPLN3, HES4, HLA-A, HLA-B, HLA-C, HLA-DOB, HLA-E, HLA-F, HMSD, ICAM1, ID2, IDO1, IER3, IFI35, IFIH1, IFNGR2, IL15, IL15RA, IL18BP, IL2RA, IL32, IL4I1, IL6R, IRF1, IRF2, IRF7, IRF8, ISG20, JUNB, KDM2B, KIF2A, LACTB, LAD1, LAMP3, LAP3, LGMN, LITAF, LMNB1, LSP1, LY75, MAFF, MALAT1, MAP3K13, MARCKS, MARCKSL1, MCL1, MGLL, MIR155HG, MSRB1, MT2A, MVP, MYL6, MYO1G, N4BP2L1, NAA25, NCCRP1, NCOA7, NDE1, NECAP2, NECTIN2, NFKB1, NFKBIA, NMI, NUB1, ODF3B, OPTN, OSBPL9, PARP12, PARP14, PARP9, PCGF5, PFN1, PIAS1, PML, PNRC1, POGLUT1, POMP, PPA1, PPP1R18, PRRG4, PSD3, PSMA2, PSMB10, PSMB8, PSMB9, PSME1, PSME2, PTK2B, PTPN1, RAB10, RAB29, RAB8B, RAB9A, RALB, RARRES3, RASSF4, RCN1, RDX, RELB, RFTN1, RGS1, RHOF, RIPK2, RNF115, RNF213, RRAGC, RSU1, SAMD9L, SAMSN1, SAT1, SECTM1, SERPINB1, SERPINB6, SERPINB9, SINHCAF, SLAMF7, SLC31A2, SLCO5A1, SMCO4, SMS, SNN, SNX11, SOCS1, SOCS3, SOD2, SPPL2A, SRGN, SRI, ST3GAL5, STAT1, STAT3, STOM, SUB1, SYNGR2,

SYNPO2, TAGLN2, TAP1, TAP2, TAPBP, TBC1D4, TBCB, THEMIS2, TMSB10, TNFAIP2, TNFAIP3, TNIP1, TNIP2, TRADD, TRAF1, TRAFD1, TRIP10, TSPAN13, TSPAN15, TSPAN33, TUBA1C, TUBB, TUBB2A, TUBB4B, TVP23A, TXN, TYMP, U62317.2, UBB, UBD, UBE2E2, UBE2F, UBE2L6, VAC14, VAMP5, VOPP1, WARS, YBX3, ZFAS1, ZFP36L1, ZNFX1.
López et al. (2024) utilized a cDC1 signature: BATF3, IRF8, THBD, CLEC9A, XCR1.
Magen et al. (2023) utilized PD-1$^+$ CD8$^+$ T cells, CXCL13$^+$ Th cells, and mregDC (DC-LAMP$^+$) triads.
Mahadevan et al. (2024) utilized BATF3, XCR1, CLEC9A, CADM1.
Mastelic-Gavillet et al. (2020) utilized a CLEC9A signature.
Mattiuz et al. (2021) used a cDC1 signature: CLEC9A, CLNK, XCR1.
Melaiu et al. (2020) utilized a THBD signature.
Michea et al. (2018) utilized a cDC1-enriched signature.
Plesca et al. (2022) utilized CLEC9A staining and IHC techniques.
Régnier et al. (2023) utilized a cDC1 signature: CD38, ST7, RUFY3, PARP3, LIMA1, ASNS, AP3M2, PAFAH1B3, CPNE3, TMEM14A, LGMN, CCNB1IP1, CST3, NME4, NCALD, CPVL, IFT20, CCND1, CCDC86, HPS5, PPM1H, SNX3, EEF1B2, CD207, OSBPL9, HSDL2, ECHDC2, PDCD2L, APOL3, CYP2E1, IDO1, PPT1, PTPRE, TCEAL4, GYPC, TPMT, RAB30, NAAA, SLC46A3, OCIAD2, PPM1J, KIT, TSPAN33, CSRP1, ACP6, AIM2, DNASE1L3, TLR3, VCP, GPT2, SPINT2, SERPINF2, TAP1, PTK2, XCR1, NET1, TLR10, UCP2, BASP1, ZNF366, THBD, DCTPP1, SLC9A9, CADM1, TACSTD2, BTLA, KATNA1, PLCD1, FNBP1, IDO2, ENPP1, DPP4, CLEC9A, UVRAG, TOX, TAP2, HMGN1, GOLGA8B, NME1, HLA-DOB.
Rotman et al. (2020) utilized cDC1 score: BATF3, XCR1, CLEC9A, CLNK.
Sosa Cuevas et al. (2020) utilized a cDC1 signature in peripheral circulation for Lin$^-$ HLADR$^+$ CD11c$^+$ BDCA1$^+$ assessed via flow cytometry.
Spranger et al. (2017) utilized BATF3, IRF8, THBD, CLEC9A, and XCR1.
Wang et al. (2024c) utilized a high MHC signature (HLA-A, HLA-B, HLA-C, HLA-DMA, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, and HLA-E) coupled to XCR1.
Yang et al. (2025) utilized a mregDC signature in metastatic melanoma patients treated with ICB.
TCGA, The Cancer Genome Atlas; TARGET, Therapeutically Applicable Research to Generate Effective Treatments.

of cDC1 biology and function, with particular emphasis on how these cells initiate and sustain productive T cell responses against cancer. We discuss how cDC1s shape key immune axes in antitumor immunity and the mechanisms limiting their activity, and contribute to the efficacy of existing immunotherapies. We additionally highlight emerging next-generation therapeutic strategies, reflecting a shift from broad DC targeting toward (1) selective expansion/mobilization of cDC1, (2) *in situ* vaccination (ISV) approaches that activate intratumoral cDC networks and synergize with checkpoint blockade, and (3) precision delivery platforms (e.g., XCR1/CLEC9A-targeted vaccines, bispecifics, and engineered lipid nanoparticles [LNPs]) designed to codeliver antigen and innate activation while minimizing systemic toxicity.

cDC1 classification—human and mouse

cDCs consist of two major subsets, cDC1 and cDC2, with distinct phenotype and specialized functions. While most of the knowledge on cDC biology has been obtained from murine models, it is essential to explore the parallels and differences between human and murine DC subsets, particularly in the context of tumor immunology and translational therapeutic insights.

Murine cDC1s are classified as T, B, NK, monocyte and macrophage lineage marker negative, CD11c$^+$, and MHC class II$^+$ cells that are: (1) negative for cDC2 marker expression (i.e., SIRPα, CD4), pDC marker expression (B220, Siglec-H), and moDC/macrophage marker expression (Ly6G/C, CD64, F4/80, CD88); and (2) positive for characteristic cDC1 marker expression including XCR1, Clec9a, CADM1, CD103 (migratory cDC1s), and CD8α (lymphoid tissue) (Durai and Murphy, 2016; Balan et al., 2019). Human cDC1s are classified as T, B, NK, monocyte and macrophage lineage marker negative, CD11c$^+$, and HLA-DR$^+$ DCs that are: (1) negative for cDC2 marker expression (i.e., SIRPα, CD11b), pDC marker expression (CD123, CD45RA, BDCA2), and moDC/macrophage marker expression (CD88, CD14, CD16); and (2) positive for characteristic cDC1 marker expression including XCR1, Clec9a, and CADM1 (Collin and Bigley, 2018; Balan et al., 2019). Pattern-recognition receptor (PRR) expression in cDC1 is more selective than in other DC subsets. Notably, both mouse and human cDC1 are relatively enriched for TLR3 expression (Lauterbach et al., 2010; Jongbloed et al., 2010), providing mechanistic rationale for the extensive preclinical and clinical use of TLR3 agonists to promote cDC1 activation (see Harnessing recent advances...). Broader profiling of PRR expression across DC subsets has been reviewed elsewhere (Collin and Bigley, 2018; Balan et al., 2019).

Mice lacking the *Batf3* (Hildner et al., 2008) and *Irf8* (Schiavoni et al., 2002) transcriptional factors exhibit ablated cDC1 frequency, highlighting their significance in cDC1 lineage determination. IRF8 has emerged as the master regulator of cDC1 development, with its role recently eloquently reviewed elsewhere (Murphy and Murphy, 2026).

cDC1s as mediators of tumor immunity and disease outcomes in cancer

While intratumoral DC composition can vary across cancer subtypes and patients, there are DC states and signatures conserved between a wide range of solid human tumors (Gerhard et al., 2021; Heras-Murillo et al., 2024). Deciphering these signatures and how they change throughout disease progression is crucial to rationally design therapeutic interventions. The key role cDC1s play in initiating and supporting antitumor immunity is evidenced by the array of cancers whereby cDC1 intratumoral presence correlates with improved disease outcomes (Table 1). While the infiltration of bona fide cDC1s holds prognostic value, it is imperative to decipher the phenotypic state and resulting antitumor functionality of infiltrating cDC1s. The "mature DC enriched in immunoregulatory molecules" (mregDC) phenotypic state constitute one such important phenotype and can be derived from cDC1 or cDC2 populations, upon acquisition of tumor antigen and signaling via AXL (Maier et al., 2020).

Table 2. **Key preclinical studies demonstrating dependence on cDC1 for successful immunotherapy**

Immunotherapy approach	Genetic model utilized	Tumor model utilized	Key findings	Reference
ICB				
αCXCR4 + αPD-1 IgG combination	*Batf3*$^{-/-}$ C57BL/6J	Orthotopic (HCA-1) and autochthonous HCC models	cDC1 prevalence and proximity to CD8^{+} T cells increased following combination therapy. Combination therapy effectiveness was compromised in KO mice	Morita et al. (2025)
αPD-L1 IgG	Chimeric mice: BM from CD11c-DTR-eGFP mice mixed with WT or *Batf3*$^{-/-}$ mice	B16-SIY and MC8-SIY SC models	Presence of cDC1s in the TME expressing the costimulatory molecule 4-1BBL required for optimal response to anti-PD-1 blockade	Ziblat et al. (2024)
αPD-1 + α4-1BB IgG combination	C57BL/6 XCR1^{DTRVenus} B6.129S(C)-Batf3$^{tm1Kmm/J}$	MC38 SC model	cDC1 depletion impaired therapeutic efficacy associated with reduced intratumoral T cell infiltration	Teijeira et al. (2022)
αPD-1 + αCTLA4 IgG alone and in combination	C57BL/6 *Xcr1*^{DTRVenus}	E0771 SC model	cDC1 depletion impaired therapeutic efficacy	Teijeira et al. (2022)
αCTLA4 IgG	*Batf3*$^{-/-}$ C57BL/6 *Xcr1*^{DTRVenus}	Orthotopic MOSC1 tongue tumor model	αCTLA4-targeted therapy resulted in increase of cDC1s in tdLN. Therapeutic response was diminished in *Batf3*$^{-/-}$ mice Early depletion of cDC1s relative to treatment impairs response, while later depletion had less impairment on therapeutic efficacy	Saddawi-Konefka et al. (2022)
αPD-1 IgG + CCL7 combination	N/A	Autochthonous *Kras*$^{LSL-G12D/+Tp53fl/fl}$ (KP) and the *Kras*$^{LSL-G12D}$/+*Lkb1*$^{fl/fl}$ (KL) NSCLC mouse models	Combined treatment prolonged survival of mice compared with untreated and PD-1 treatment alone. Therapeutic efficacy was associated with increased infiltration of cDC1s and CD8^{+} T cells	Zhang et al. (2020)
αPD-L1 IgG	CD11c-Cre; Pdl1$^{\wedge fl/f}$ and *Batf3*$^{-/-}$ C57BL/6J	MC38 and EG.7 SC models	PD-L1 expression on DCs essential for response to αPD-L1–targeted therapy. Efficacy of αPD-L1–targeted therapy was diminished in *Batf3*$^{-/-}$mice. cDC1s upregulate PD-L1 upon antigen uptake driven by IFNγ signaling	Peng et al. (2020)
-	*Clec9a*-Cre *Cd274*$^{fl/fl}$ C57BL/6N mice (not cDC1 specific—all mature DCs)	PD-L1–deficient and PD-L1–sufficient MC38, and HEPA1-6.X1.1 SC models	Deletion of PD-L1 expression on DCs, and not macrophages, leads to restriction of tumor growth and enhanced antitumor T cell responses. DCs identified as key mediators of PD-1:PD-L1 axis	Oh et al. (2020)
αPD-1 + α4-1BB IgG	*Batf3*$^{-/-}$ BALB/C	Orthotopic 4T1.2 mammary carcinoma model	Adjuvant or neoadjuvant immunotherapy efficacy was diminished in *Batf3*$^{-/-}$ mice associated with reduced CD8^{+} T cell priming	Liu et al. (2019)
αPD-1 IgG	*Zbtb46*-Dtr chimera models	MC38 SC model	Efficacy of αPD-1–targeted therapy was impaired when DCs were depleted or when IL-12 was neutralized. Authors demonstrate a role for IL-12^{+} cDC1s for optimal therapeutic response	Garris et al. (2018)

Table 2. **Key preclinical studies demonstrating dependence on cDC1 for successful immunotherapy (*Continued*)**

Immunotherapy approach	Genetic model utilized	Tumor model utilized	Key findings	Reference
αPD-L1 IgG	*Batf3*$^{-/-}$ C57BL/6J	B16 SC models	Efficacy of αPD-L1–targeted therapy was diminished in *Batf3*$^{-/-}$mice. CD103^{+} DCs were required to induce treatment-induced antitumor immunity. Therapeutic synergy was observed between systemic FLT3L, αPD-L1 IgG, and intratumoral poly I:C treatment	Salmon et al. (2016)
αPD-1 + α4-1BB IgG alone and in combination α4-1BB IgG + IL-12 αPD-1 or α4-1BB IgG in combination with FLT3L and poly-ICLC	*Batf3*$^{-/-}$ C57BL/6J	MC38, MC38-OVA, and B16-OVA SC models	Efficacy of each immunotherapeutic approach trialed was diminished in *Batf3*$^{-/-}$ mice associated with the absence of CD8^{+} T cell priming	Sánchez-Paulete et al. (2016)
Costimulatory agonist therapy				
Systemic α4-1BB IgG in combination with intratumoral HMGN1 (TLR4 agonist) and 3M-052 (TLR7/8 agonist) ISV	*Batf3*$^{-/-}$ C57BL/6J	MC38 SC models	Combination therapy efficacy was diminished in *Batf3*$^{-/-}$ mice associated with lower secretion of IFNγ by T cells in treated mice	Wang et al. (2025)
αCD40 IgG + systemic recombinant FLT3L protein	C57BL/6 *Xcr1*^{DTRVenus}	Orthotopic KP2 OVA–expressing models	Intratumoral expansion of total CD8^{+} T cells, IFNγ^{+} CD8^{+} T cells, and therapeutic benefit following treatment was diminished in the absence of cDC1s. Additionally, cDC1 numbers in TME following treatment may be sustained via IFNγ signaling	Hogg et al. (2025)
αCD40 IgG + systemic recombinant FLT3L protein	*Batf3*$^{-/-}$ C57BL/6J	WT- and *Mlh1*-deficient KP NSCLC SC models	Therapeutic strategy to boost DC prevalence and activation via FLT3L and αCD40 IgG delivery exhibits diminished efficacy in cDC1-deficient mice, associated with diminished CD8^{+} T cell infiltration into tumor	López et al. (2024)
Bispecific antibodies targeting CD40 and DC/cDC1 cell surface markers	*Batf3*$^{-/-}$ C57BL/6J *Xcr1-iDTR*	MC38 SC, B16-OVA SC, and MCA-205 SC models	cDC1s are responsible for therapeutic efficacy of therapy but are not implicated in toxicity αCD40-targeted treatment does not induce tumor-specific CD8^{+} T cells, or therapeutic efficacy in *Batf3*$^{-/-}$ mice	Salomon et al. (2022)
N/A	*Xcr1*$^{Cre/+}$ *Cd40*$^{fl/fl}$ (cDC1-specific CD40 deletion)	1956-mOVA fibrosarcoma SC model	Loss of CD40 signaling in cDC1 diminishes (1) endogenous antitumor CD8^{+} T cell responses due to lack of cDC1 licensing, (2) early CD4^{+} T cell activation	Ferris et al. (2020)
αCD40 IgG + αPD-1/CTLA4 IgG	B6.129S(C)-*Batf3*^{tm1Kmm}/J	PDA SC model	Therapeutic efficacy was ablated in *Batf3*$^{-/-}$ mice	Morrison et al. (2020)
αCD40 IgG + gemcitabine/Nab-paclitaxel chemotherapy	*Batf3*$^{-/-}$ C57BL/6J	PDA SC model	Therapeutic efficacy was diminished in *Batf3*$^{-/-}$ mice	Byrne and Vonderheide (2016)
Oncolytic virus therapy				
Oral reovirus therapy	B6.129S(C)-*Batf3*^{tm1Kmm}/J	CT26 SC models	Demonstrates the efficacy of oral delivery of oncolytic virus for, with effects dependent on cDC1s, type I IFN signaling and CD8^{+} T cells. Oral delivery was not therapeutically effective in cDC1-deficient mice	Lee et al. (2024b)

Table 2. **Key preclinical studies demonstrating dependence on cDC1 for successful immunotherapy (*Continued*)**

Immunotherapy approach	Genetic model utilized	Tumor model utilized	Key findings	Reference
Intratumoral recombinant FLT3L and oncolytic NDV delivery	*Batf3*$^{-/-}$ BALB/C	A20 SC models	Therapeutic synergy observed between intratumoral recombinant FLT3L delivery and intratumoral NDV delivery. Synergistic effects absent in cDC1-deficient mice Lack of therapeutic efficacy in cDC1-deficient mice associated with lack of induction of tumor-specific T cells	Svensson-Arvelund et al. (2022)
Intratumoral delivery of heat-inactivated or live oncolytic vaccinia virus engineered to express GM-CSF	*Batf3*$^{-/-}$ C57BL/6J	B16 ID models	cDC1s required for antitumor effects of both live and inactivated oncolytic virus delivery	Wang et al. (2021)
Intratumoral delivery of inactivated modified vaccine virus Ankara	*Batf3*$^{-/-}$ C57BL/6J	B16 ID models	Therapeutic efficacy was dependent on cDC1s and additionally STING signaling in host. cDC1s required for induction of tumor-specific CD8^{+} T cell responses following therapy	Dai et al. (2017)
ACT				
ACT cells expressing XCL1, FLT3L, or combination of both (ACT-FX)	*Batf3*$^{-/-}$ *C57BL/6N*	B16-OVA and MC-38 OVA SC models	cDC1s required for efficacy of WT ACT or XCL1-expressing ACT. Additionally, ACT-FX were most effective at controlling tumor growth associated with enhanced DC:T cell interactions in the TME	Xiao et al. (2025)
ACT of OT-I cells	XCR1-DTR-Venus C57BL/6J	B16-OVA and MC-38 SC models	cDC1 depletion impaired the efficacy of ACT utilizing OT-I cells associated with decreased intratumoral infiltration, decreased stemness, and increased expression of exhaustion markers	Teijeira et al. (2022)
ACT of TYRP1-targeted CAR-T cells alone or in therapeutic combination with STING agonism	*Batf3*$^{-/-}$	B16 SC models	cDC1 depletion impaired the efficacy of CAR-T therapy ± STING agonism associated with a loss of epitope spreading and associated expansion of tumor-directed endogenous CD8^{+} T cell responses	Conde et al. (2021)
ACT of CAR-T cells expressing FLT3L in combination with poly I:C treatment	N/A	E0771-OVA-*Her2* & MC38-*Her2* SC models	CAR-T cells engineered to express FLT3L, given alongside poly I:C and α4-1BB IgG, promoted more effective tumor control, associated with expansion of cDC1, cDC2 populations in the TME and induction of epitope spreading in treated mice	Lai et al. (2020)
ACT of CD40L-overexpressing CAR-T cells	*Batf3*$^{-/-}$ BALB/C	Systemic A20 lymphoma model	Therapeutic efficacy diminished in *Batf3*$^{-/-}$ mice. Differentiation and expansion of cDC1s in the TME noted in response to ACT	Kuhn et al. (2020)
ACT of Pmel-1 CD8^{+} T cells alone and in combination with hgp100 peptide vaccination	*Batf3*$^{-/-}$ C57BL/6J	B16 SC model	Expansion of transferred cells was absent in *Batf3*$^{-/-}$ mice. Utilizing bone chimera models, authors confirm role for CD40 and CD70 signaling in host BATF3-reliant cells for ACT expansion and efficacy	Oba et al. (2020)
ACT of CD8^{+} T cells isolated from matched 2C donor mice and subsequently activated *ex vivo*	CD11c-DTR/*Batf3*$^{-/-}$	Autochthonous BP, BP-SIY, BPC-SIY melanoma models	CD103^{+} BATF3-dependent cells in the TME produce CXCL9/10 that promote intratumoral infiltration of transferred cells	Spranger et al. (2017)

Table 2. **Key preclinical studies demonstrating dependence on cDC1 for successful immunotherapy (*Continued*)**

Immunotherapy approach	Genetic model utilized	Tumor model utilized	Key findings	Reference
ACT of OT-I cells	XCR1-DTR:*Ccr7*$^{-/-}$ mixed BM chimeras	B78ChOVA SC model	CCR7-dependent migration of CD103$^+$ DCs is required in the dLN to effectively prime previously transferred antitumor T cells	Roberts et al. (2016)
ACT of OT-I cells	FTY720-treated zDC-DTR mice	EG7.1 SC model	CD103$^+$ DCs in tumor are required for antitumor effect of ACT	Broz et al. (2014)
cDC1-based vaccination				
Intratumoral vaccination with peptide-loaded/activated CD34$^+$ HSC-derived human cDC1s in combination with systemic anti–PD-1 IgG	N/A	SC humanized A375 melanoma model	Establishes the therapeutic feasibility and efficacy of a scalable, serum-free platform for generation of bona fide cDC1 from CD34$^+$ progenitors. Intratumoral delivery of activated, antigen-loaded cDC1s combined with anti-PD-1 treatment reduced tumor growth in a humanized melanoma model	Balan et al. (2025)
Vaccination with splenic cDC1 or cDC2 loaded with tumor cell lysate via UV-irradiated tumor cells and stimulated with CpG *ex vivo*	N/A	SC B16-OVA and MC38	cDC1 vaccination more effective than cDC2 based in delaying tumor growth/prolonging survival and induction of Th1 and CD8$^+$ T cell effector and memory responses	Heras-Murillo et al. (2025)
Intratumoral cDC1 vaccination in combination with αPD-1 IgG. XCR1$^+$ cDC1s isolated from the spleen of mice harboring B16-FLT3L tumors were utilized. cDC1s were treated with poly I:C and tumor antigen peptides prior to delivery	N/A	Orthotopic MOC1esc1 (HNSCC model)	Intratumoral cDC1 vaccination restored αPD-1 responsiveness associated with expansion of tumor antigen–specific response and intratumoral infiltration	Saito et al. (2024)
Antigen agonistic approach involving intratumoral vaccination with cDC1, cDC2, or GM-CSF/IL-4–cultured DCs	N/A	1956 mOVA SC model	cDC1-based vaccination outperformed cDC2 or GM-CSF/IL-4 DCs in terms of tumor control and induction of tumor-specific CD8$^+$ T cell responses. Vaccination was only effective via intratumoral and not intravenous route. cDC1-based vaccination was not reliant on the presence of host cDC1s	Ferris et al. (2022)
Intratumoral delivery of autologous CD141$^+$ combined with αPD-1 IgG in humanized mouse model	N/A	Humanized mouse model—LM-MEL28 human melanoma cell line	Vaccination of humanized mouse autologous CD141$^+$ DCs (previously activated with poly I:C) synergizes with αPD-1 therapy	Lee et al. (2021)
Vaccination with *in vitro* generated, tumor antigen–loaded, and poly I:C-activated CD103$^+$ DCs alone and in combination with αPD-1 or αCTLA4 IgG	N/A	B16 and K7M3 (osteosarcoma) SC and metastatic models	CD103$^+$ DC-based vaccination outperformed moDC-based vaccination in delaying tumor growth and inducing tumor-specific T cell responses. CD103$^+$ cDC1 vaccination exhibited therapeutic synergy with ICB approaches	Zhou et al. (2020)
Vaccination with splenic cDC1 loaded with tumor cell lysate via UV-irradiated tumor cells and stimulated with poly I:C *ex vivo*	N/A	B16, B16-OVA, and MC38 SC models	First study to demonstrate the efficacy of cDC1-based cancer vaccination. Vaccination with dead tumor cell–loaded cDC1s promoted therapeutic efficacy alone and synergized with PD-1–directed ICB	Wculek et al. (2019)

Table 2. **Key preclinical studies demonstrating dependence on cDC1 for successful immunotherapy (*Continued*)**

Immunotherapy approach	Genetic model utilized	Tumor model utilized	Key findings	Reference
Vaccination with DCs isolated from LLC-OVA tumors: cDC2 (MHC class II$^+$ CD11c$^+$ CD64$^-$ CD24$^-$ CD11b$^+$ Ly6C^{lo}), cDC1 (MHC class II$^+$, CD11c$^+$ CD64$^-$ CD24$^+$ CD11b^{lo})	N/A	B16-OVA, LLC-OVA SC models	cDC1-based vaccination promoted strong induction of antitumor cytotoxic CD8$^+$ T cells cDC1-based vaccination outperformed cDC2-based approaches in the B16-OVA tumor model cDC2-based vaccination outperformed cDC1-based approaches in the LLC-OVA tumor model, with authors hypothesizing role of MDSCs and TAMs in TME mediating lack of cDC1 efficacy	Laoui et al. (2016)

ACT, adoptive cell therapy; TME, tumor microenvironment; NSCLC, non–small-cell lung cancer; BM, bone marrow; SC, subcutaneous; PDA, pancreatic ductal adenocarcinoma; NDV, Newcastle disease virus.

Crucially, this phenotypic state has been characterized in a range of human tumors, highlighting a conserved DC activation status across cancers. Importantly, mregDCs should not be interpreted as a functionally uniform or intrinsically suppressive cDC subset, as they represent a maturation-associated, context-dependent activation state characterized by the concurrent expression of classical maturation markers alongside regulatory or inhibitory molecules. We believe that their sometimes-

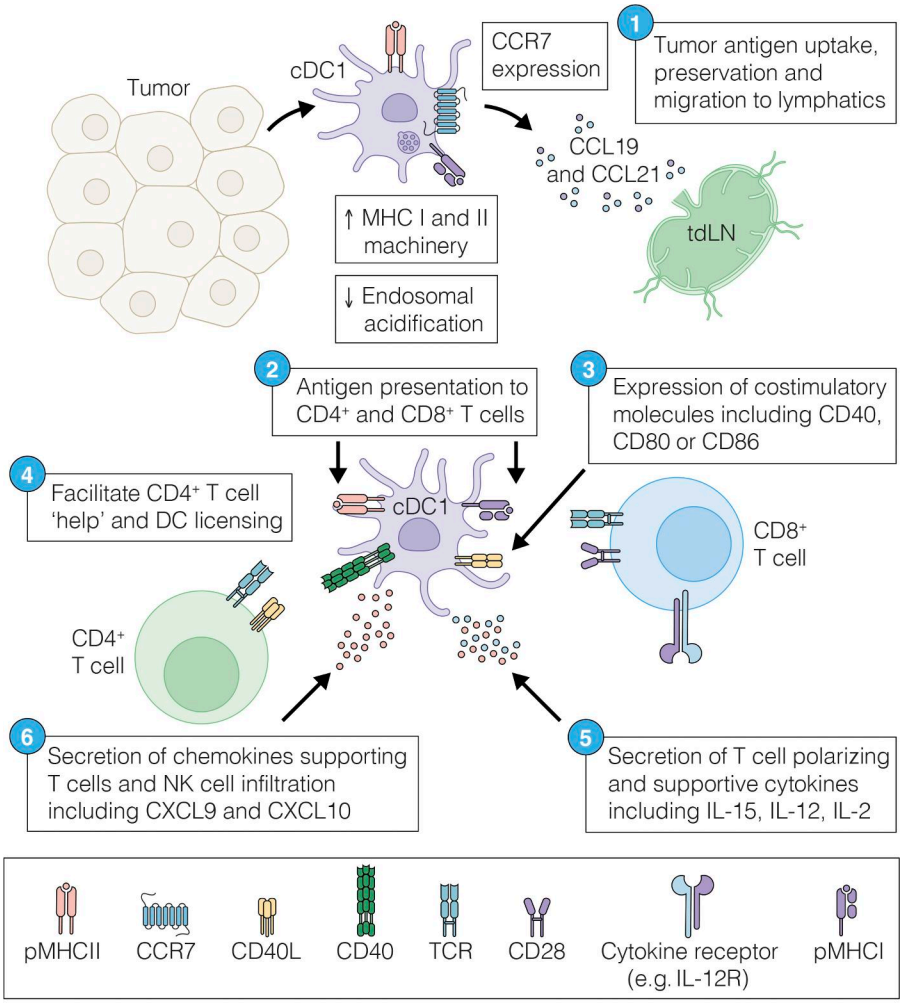

Figure 1. **Antitumorigenic functions of cDC1s—cDC1s are functionally adapted to take up and structurally preserve tumor-associated antigens.** Upon uptake of antigen, cDC1s upregulate CCR7, which alongside a CCL19 and CCL21 gradient mediates migration to the draining lymphatics. cDC1s can effectively present tumor-associated antigens via MHC class I and II molecules to CD8$^+$ and CD4$^+$ T cells, respectively. Elevated expression of costimulatory molecules, e.g., CD40, and the facilitation of CD4$^+$ T cell–mediated help ensure effective priming of cytotoxic CD8$^+$ T cell responses. Additionally, cDC1s are important sources of chemokines that promote CD8$^+$ T cell and NK cell recruitment to the tumor including CXCL9/10 and cytokines that support CD8$^+$ T cell and NK function including IL-15 and IL-12.

paradoxical contribution to antitumor immunity is likely dependent on tumor type, tumor immune contexture, spatial localization, and therapeutic intervention. This phenotype has been associated with both productive cDC-T cell interactions and immunosuppressive niches that favor Treg engagement and impaired antigen trafficking. The phenotype, pro- and antitumor roles, prognostic value, and phenotypic characterization of mregDCs have been previously reviewed in Li et al. (2023). The antitumor functionality of cDC1s will be discussed below and is illustrated above (Fig. 1). The importance of cDC1s in antitumor functionality is additionally demonstrated by the reliance of immunotherapeutic approaches on cDC1 presence in the TME and associated draining lymphatics, detailed in Table 2 and Fig. 3.

Tumor antigen uptake, preservation, and trafficking to draining lymphatics

While sentinel tissue–resident DCs play an important role in early disease, nonresident cDC1s are additionally recruited initially via chemokine production (e.g., CCL4) from the TME (Spranger et al., 2015). Additionally, early responding NK cells are a key source of FLT3L, CCL5, and XCL1 in the TME, which play a key role in mobilizing and recruiting cDC1s (Barry et al., 2018; Böttcher et al., 2018), and the presence of NK cells directly correlates with cDC1 prevalence in human melanoma and HNSCC (Barry et al., 2018). IL-2/15-mediated activation of NK cells has been recently implicated in promoting optimal FLT3L production (Avanessian et al., 2026). $CD8^+$ T cells in the TME constitute another important source of XCL1, with $CD8^+$ progenitor exhausted exhibiting elevated XCL1 expression compared with exhausted counterparts (Xiao et al., 2025). Additionally, this $XCL1^+$ $CD8^+$ T cell signature was shown to correlate better with ICB outcomes in patients.

cDC1s are proficient in the uptake of tumor antigens in the TME and subsequent trafficking to the tumor-draining lymph nodes (tdLNs) (Salmon et al., 2016; Roberts et al., 2016). This proficiency in tumor antigen capture is in part due to the expression of specialized receptors such as CLEC9A, which mediates the recognition of dead cell material (via exposed F-actin) and promotes antigen routing toward cross-presentation pathways (Zhang et al., 2012; Canton et al., 2021). cDC1s can acquire tumor material through mechanisms shared with other DC subsets, including uptake of soluble or vesicular cargo (e.g., macropinocytosis and extracellular vesicle [EV] uptake). Indeed, vesicular-mediated transfer between migratory cDCs and lymph node (LN)–resident cDC1s has been documented (Ruhland et al., 2020). Additionally in the TME, it has been shown that cDC1s can acquire cancer cell–derived pMHC class I via "cross-dressing" and can subsequently mount antitumor $CD8^+$ T cell responses (MacNabb et al., 2022). Proficient uptake of tumor antigens and pMHCs is coupled to the preservation of captured antigen integrity via lower endosomal acidification (Savina et al., 2009). Notably, regulated control of lysosomal proteolysis and antigen persistence is a core DC adaptation that was defined in seminal work on MHC class II–restricted antigen processing and presentation (Trombetta et al., 2003; Delamarre et al., 2005). In parallel, CLEC9A/DNGR-1 signaling further supports preservation of dead cell–derived antigenic material by directing cargo into cross-presentation–permissive pathways and promoting phagosomal remodeling/rupture (Zelenay et al., 2012; Canton et al., 2021; Weimershaus et al., 2012).

Upon acquisition of antigen, DCs upregulate CCR7 to facilitate LN migration (via CCL19 and CCL21 chemokine gradients). Intracellular cGMP pools in migratory DCs have recently been shown to mediate draining LN (dLN) trafficking via promoting myosin II–mediated interstitial motility, and reduced cGMP synthesis in tumor-infiltrating DCs has been identified as a mechanism limiting tdLN trafficking, particularly in later stage tumors (Tang et al., 2025). Interestingly, sildenafil, a PDE5 inhibitor, has been shown to restore DC LN trafficking via preservation of intracellular cGMP pools (Tang et al., 2025). The importance of $CD103^+$ DC-mediated uptake and trafficking of tumor antigens to the tdLNs was first shown to be critical for the response to ICB in preclinical tumor models in 2016 (Salmon et al., 2016) with roles for $IL\text{-}12^+$ DC-mediated T cell crosstalk in the TME subsequently identified (Garris et al., 2018) (see Table 2 and Fig. 3). Utilizing an orthotopic lung adenocarcinoma model, the presence of functional cDC1s in the tdLN has been shown to be crucial for the maintenance of stem-like $CD8^+$ T cell populations (Schenkel et al., 2021), and crucially, this migratory population decreases as disease progresses, indicating a breakdown of tumor–tdLN migratory cycle. However, a recent preprint (Mattiuz et al., 2024, *Preprint*) demonstrated that the importance of tumor–tdLN cDC1 migration may change throughout tumor development. While cDC1 tumor–tdLN trafficking is demonstrated to be crucial for tertiary lymphoid structure (TLS) generation in early tumor development, the authors highlight the importance of tumor-intrinsic interactions later in tumor growth. These later interactions, necessary for TLS maintenance, rely on the recruitment of mature cDC1s directly to the CCR7 ligand–expressing stromal hubs, where interactions with $CD4^+$ and $CD8^+$ T cells are facilitated. Crucially, this negates the necessity for T cell recruitment from associated lymphatics. These insights into TLS generation and maintenance are crucial as the presence of TLS hubs has been shown to possess beneficial prognostic implications for cancer patients.

This migratory process is additionally guided by central and cell-intrinsic circadian rhythms. Circadian studies conducted in mice, under a standard 12-h on/off light cycle, utilize zeitgeber time (ZT), whereby ZT0 indicates the time when lights are switched on and ZT12 indicates the time when the lights are switched off. Translation of these findings to humans relies on considering the nocturnal behavior of mice versus the diurnal behavior of humans, i.e., a finding at ZT12 in mice when they are most active would translate to morning in humans when we are most active. Intriguingly, endothelial cell–intrinsic circadian rhythms dictate the oscillations of immune cell infiltration in the tumor via fluctuating expression of ICAM-1, with different T cell signatures in the TME observed depending on the time of day, with potential functional implications for the time of administration of CAR-T and ICB therapies (Wang et al., 2024a). Rhythmic trafficking of DCs to the tdLNs has also been observed alongside circadian regulation of CD80 expression, as BMAL1 (a key transcription factor in the regulation of circadian rhythm)

binds upstream of CD80 promoter region (Wang et al., 2023). These authors observed smaller tumors when engraftment was done between ZT9 and ZT13 compared with late night ZT21. This correlated with more cDC1 and cDC2 populations observed in the dLNs of ZT9-challenged mice compared with those challenged at ZT21, when measured 24 h after tumor inoculation. Crucially, an increased population of cross-presenting CD103$^+$ DCs was observed, while no impact of time of day was noted on cell-intrinsic antigen processing was observed, highlighting cell migration and costimulatory molecule expression as key mediators of these effects. *Clec9a-^{cre}:Bmal^{flox}* mice were used to confirm the dependence on BMAL1 expression in DCs for these time-of-day effects on antitumor immunity; additional work in more cDC1-specific genetic models, e.g., *Xcr1^{cre}* (Mattiuz et al., 2018), will be needed to isolate the exact contribution of cDC1s. On the other hand, Cervantes-Silva et al. (2022) showed that cells taken from mice at different times displayed altered antigen processing *ex vivo*, with two times higher levels of cDC1-mediated antigen processing noted at ZT19 compared with ZT7. The authors hypothesize that this is due to changes in mitochondrial morphology, impacting Ca^{2+}-dependent metabolic events and subsequent antigen processing. All-in-all these findings provide insights into the contribution of circadian rhythm to cDC1 and overall cDC function. It remains to be fully determined the impact of time-of-day administration on immunotherapy efficacy in patients, and the subsequent contribution of cDC1s to observed effects. In parallel, a key area to address will be how central and cell-intrinsic circadian rhythms are altered as disease progresses. There is evidence that defects in the circadian rhythm can promote tumorigenesis in mouse models (Zeng et al., 2024) and cDC1s are likely contributors to this owing to their nonredundant role in antitumor immunity and the impact of circadian clock on their antitumor function.

Tumor antigen presentation and induction of CD4$^+$ and CD8$^+$ antitumor T cell responses

Alongside tumor–tdLN trafficking capabilities, cDC1s are functionally adept at the cross-presentation of tumor cell–associated antigens via MHC class I molecules, crucial for the induction of antitumor CD8$^+$ T cell responses. WDFY4 has emerged as an essential protein for the cross-presentation of tumor- and virus-derived antigens, and recent work suggests that in cDC1s, this WDFY4-dependent pathway can proceed through a vacuolar route involving post-Golgi/endosomal compartments and recycled MHC class I, rather than exclusively via the canonical ER–TAP pathway (Theisen et al., 2018; Postoak et al., 2025). In addition, a recent study demonstrated that upon tumor antigen uptake by cDC1s, MS4A7, a membrane-associated protein implicated in signaling, localizes to antigen-processing vesicles and is required for efficient cross-priming and antitumor immunity without altering antigen uptake itself, further supporting the concept that cDC1 superiority reflects specialized handling and presentation of captured cargo rather than antigen acquisition alone (Xie et al., 2025).

Additionally, cDC1s contribute to MHC class II–restricted antigen presentation and CD4$^+$ T cell activation and have been demonstrated to facilitate triad interactions with CD8$^+$ and CD4$^+$ T cells via presentation of cognate tumor antigen on MHC class I and MHC class II molecules. These interactions facilitate cDC1 "licensing" by CD4$^+$ T cells via CD40 (Ferris et al., 2020) and type I IFN (Lei et al., 2024) signaling, which supports induction of optimal antitumor T cell responses (Fig. 1). The cDC1 cross-priming and licensing effect have been recently reviewed (Luri-Rey et al., 2025). The presence of cDC1 and CD8$^+$ T cell clusters has been shown to positively correlate with response to ICB in melanoma patients (Gobbini et al., 2025), and likewise, the presence of a cDC1 "helped" signature is associated with better outcome in melanoma patients (Lei et al., 2023). Additionally, cDC1 vaccination was recently shown to protect mice from experimental tumor relapse in both neoadjuvant and adjuvant settings, while promoting antitumor CD8$^+$ and CD4$^+$ T cell responses in preclinical models (Heras-Murillo et al., 2025). Notably, this included induction of CD4$^+$ tissue–resident memory (Trm)–like cells, and the presence of these cell types in human cancers was shown to correlate with cDC1 abundance and improved outcomes in BRCA and SKCM patients (Heras-Murillo et al., 2025).

Immunogenic cDC maturation, and resulting upregulation of costimulatory, chemotactic, and cytokine signaling machinery are key for cDC1 antitumor functionality. The mechanisms underlying and dictating "homeostatic" versus "immunogenic" maturation have been eloquently reviewed for DCs (Moon et al., 2025) and specifically for cDC1s (Akyol and Dalod, 2025).

Key cell–cell interactions and hubs in the TME

In addition to the immune triads mentioned above, cDC1s are key orchestrators of immune cell networks/interactions and hubs in the TME, which play a crucial role in shaping antitumor immunity and provide prognostic value. NK cells, CD8$^+$ T cells, and cDC1s comprise one such network, with early NK cell–mediated production of CCL5, XCL1, and FLT3L promoting cDC1 intratumoral homing and accumulation (Barry et al., 2018; Böttcher et al., 2018), which in turn facilitates induction of antitumor CD8$^+$ T cell responses, which additionally are important sources of cDC1 chemokines such as XCL1. Interestingly, CD206$^+$ CXCL9$^+$ TAMs were recently demonstrated to play a crucial role in establishing the cDC1:NK:CD8$^+$ axis, via promoting CD8$^+$ T cell recruitment (Fig. 2). This macrophage signature correlated with improved outcome in grouped CRC, HNSC, kidney, gynecological, and lung cancer patients (Ray et al., 2025). Additionally, the crosstalk between cDC1s and Tregs appears to be instrumental in the prognostic implications of these signatures. Régnier et al. (2023) demonstrated the importance of cDC:Treg:Teff:NK interactions in the tumor for therapeutic outcomes, with high expression of FLT3L and low presence of Tregs, an ideal therapeutic scenario, providing rationale for Treg depletion approaches.

mregDCs have been implicated in mediating key cell–cell interactions in the TME, and have been linked with more favorable ICB outcomes in patients (Yang et al., 2025; Magen et al., 2023). Here, we use "mregDC" to denote a lineage-convergent mature activation state (LAMP3$^+$ and CCR7-enriched) that can arise from either cDC1 or cDC2, rather than a distinct DC lineage; in contrast, "CCR7$^+$ DCs" refer more broadly to CCR7-expressing

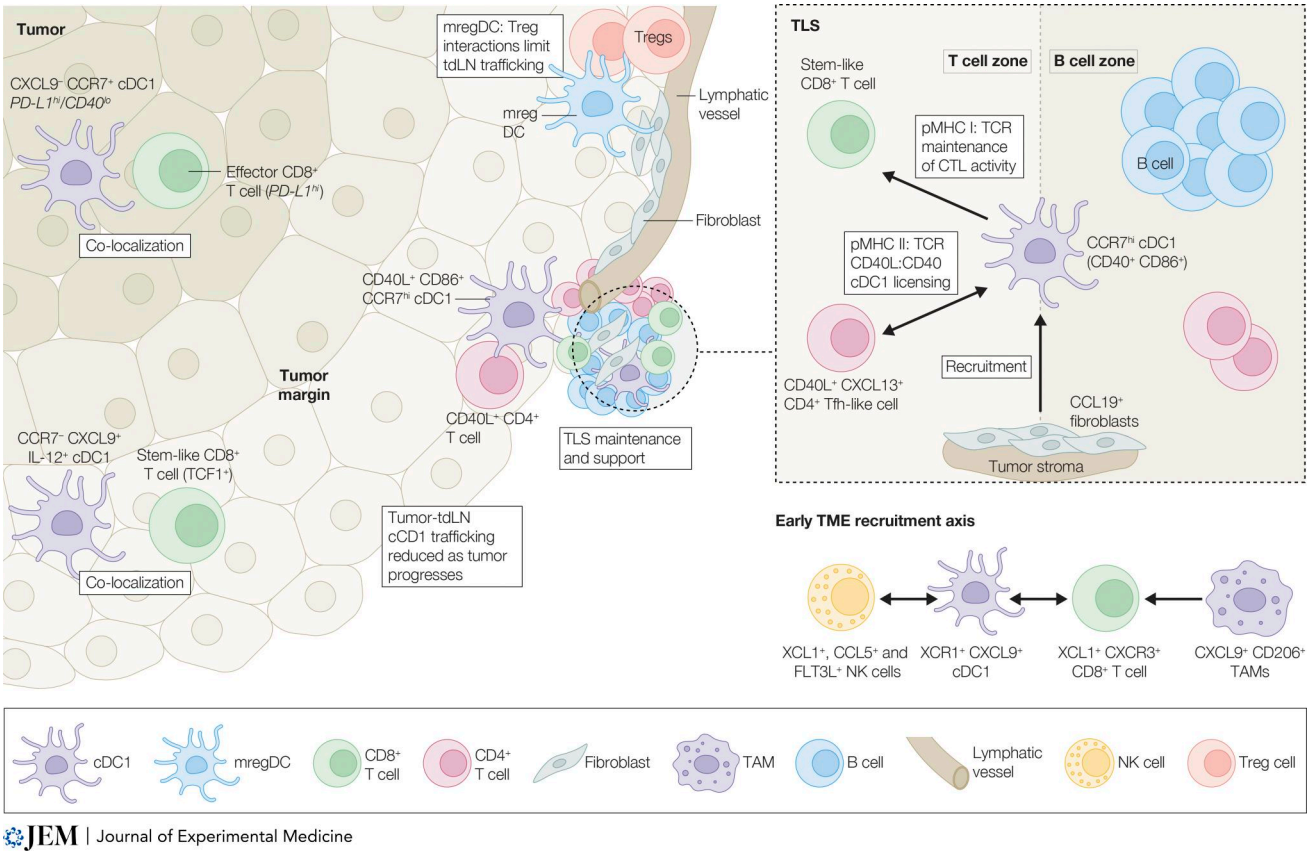

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Figure 2. **Spatiotemporally organized cDC1-centered immune networks and hubs in the TME.** Schematic summarizing key cellular circuits and spatial niches in which cDC1s coordinate antitumor immunity. In the tumor core, a tumor-retained CCR7⁺ DC state (derived from cDC1/cDC2) with reduced costimulatory capacity (PD-L1^{hi}/CD40^{lo}) colocalizes with PD-1^{hi} effector CD8⁺ T cells. At the tumor margin, CCR7⁻ CXCL9⁺ cDC1s colocalize with stem-like TCF1⁺ CD8⁺ T cells (Piot et al., 2025). CCR7^{hi}, CD40⁺CD86⁺ cDC1s accumulate within stromal immune hubs and contribute to TLS maintenance/support, including through CD40-dependent interactions with CD40L⁺ CXCL13⁺ Tfh-like CD4⁺ T cells and ongoing antigen presentation to CD8⁺ T cells. In parallel, mregDC–Treg interactions in lymphatic-associated regions can limit antigen trafficking to tdLNs and restrain adaptive priming (You et al., 2024). An "early TME recruitment axis" is depicted in which NK cell–derived chemokines (e.g., XCL1/CCL5 and FLT3L) promote intratumoral cDC1 accumulation, while CXCL9⁺ CD206⁺ macrophages support CXCR3-dependent recruitment of CD8⁺ T cells, facilitating the establishment of this cDC1-NK-CD8 circuit. Arrows indicate proposed directions of interaction; "colocalization" denotes spatial association. TME, tumor microenvironment.

migratory/tumor-retained DCs irrespective of the transcriptional program. In tumor settings, these designations likely overlap, and some studies may be capturing the same or closely related activated DC state under different nomenclatures. Mechanistically, PD-1 engagement recruits SHP2 and preferentially drives dephosphorylation of CD28 (Hui et al., 2017), underpinning the reliance on intact CD28:B7 costimulation (Kamphorst et al., 2017) and, consequently, close APC–T cell interactions for effective anti-PD-1/PD-L1 ICB therapy. For instance, Magen et al. characterized the prognostic value of cellular triads between PD-1⁺ CD8⁺ T cells, CXCL13⁺ Th cells, and mregDCs. The presence of these triads was associated with better outcome following ICB in HCC patients receiving anti-PD-1 (Magen et al., 2023). The authors hypothesize that triad formation facilitates costimulatory interactions between the mregDC and CD8⁺ T cell, via CD28 interactions, and support of T cell function via mregDC-mediated IL-15 production. It is important to note that in human studies, these immune triads are primarily an associative spatial correlate of response rather than direct evidence of causality. However, murine studies provide the closest experimental support for functional relevance of such aggregates. Espinosa-Carrasco et al. (2024) showed that CD4⁺ and CD8⁺ T cells must co-engage the same DC/APC in intratumoral triads to license CD8⁺ T cell cytotoxicity, and that disrupting triad formation results in tumor progression despite comparable numbers of tumor-reactive T cells. In parallel, authors demonstrated that CD4⁺, CD8⁺ T cells, and CD11c⁺ triads in pleural mesothelioma patient samples were associated with pathologic responses to ICB.

Beyond simple cell–cell interactions, cDC1s organize and are regulated within spatially defined immune hubs in the TME, where their positioning, maturation state, and cellular partners critically determine whether antitumor immunity is amplified or restrained. Notably, because mregDC programs are frequently CCR7-enriched, tumor-retained CCR7⁺ DC niches may encompass mregDC-like cells depending on context, although CCR7 expression alone does not necessarily imply the full mregDC transcriptional state. Lee et al. (2024a) recently identified a population of tumor-retained CCR7⁺ DCs, derived from both cDC1 and cDC2s, that display an altered phenotype

compared with their tdLN-migrated counterparts. These DCs colocalize with CD8⁺ T cells and downregulate the expression of costimulatory molecules (e.g., CD40), alongside migratory and antigen presentation machinery while upregulating co-inhibitory molecule expression (e.g., PD-L1). This phenotype and CD8⁺ T cell interaction were additionally conserved in human tumors. Crucially, upon ICB treatment these DCs become functionally reinvigorated and upregulate costimulatory molecules including OX40L and CD70. In the same vein, a recent preprint demonstrated that later in tumor development, mature CCR7⁺ cDC1s accumulate in intratumoral hubs that are required for the maintenance and generation of beneficial TLS in the tumor via CD8⁺/CD4⁺ T cell and CD40 interactions, signifying a shift in reliance from tdLN–tumor cDC1 migration for TLS generation and support (Mattiuz et al., 2024, *Preprint*). MHC class II^{hi} CCR7⁻ cDC1s have previously also been implicated in the generation of cDC1:CD8⁺ immune clusters in stromal regions of the tumor, with clusters possessing prognostic value in patients (Meiser et al., 2023). In line with these data, a recent preprint recently demonstrated the importance of intratumoral cDC1:CD8⁺ T cell coinfiltration and clustering for successful tumor rejection utilizing an innovative high-throughput skin-tumor array model, allowing the profiling of the TME of many microtumors in the same mouse (Carbone et al., 2025, *Preprint*). cDC1 state is likely instructive for these spatiotemporal effects and functions, as Piot et al. (2025) recently demonstrated that CXCL9⁺ CCR7⁻ (IL-12b⁺ cDC1 in mice) cDC1s were mainly observed at the tumor margins, colocalizing with stem-like CD8⁺ T cells, while CXCL9⁻ CCR7⁺ cDC1s were predominantly found in the tumor core colocalizing with cytotoxic effector CD8⁺ T cells. In line with these data, fibroblasts in the perivascular regions of tumors have been shown to secrete CCL19, promoting sequestering of CCR7⁺ DCs and resulting in immune hub generation (Zitti et al., 2025).

These studies highlight a dynamic shift in cDC1 function throughout tumor progression tied to their spatiotemporally governed cellular colocalizations. Early in antitumor responses, cDC1s enriched within the tumor–stroma interface preferentially engage stem-like TCF1⁺ CD8⁺ T cells. As tumors evolve, cDC1s are mobilized into the tumor parenchyma where they colocalize with more differentiated, effector CD8⁺ T cells. At later stages, mature cDC1 populations accumulate in stromal immune hubs within the TME, where they help sustain and shape developing TLS via CD40 and CD4⁺/CD8⁺ T cell–dependent cues (Fig. 2). Overall, these studies suggest a dynamic and context-dependent shift from reliance on LN migration–driven cDC1 priming to a more self-sustaining intratumoral circuit.

On the other hand, mregDCs can impair antitumor immunity, and deciphering how to counteract these effects is crucial to glean therapeutic targets. For instance, a recent study identified mregDCs as key promoters of Treg accumulation around lymphatic vessels in the TME, creating a niche that limits antigen trafficking to dLNs (You et al., 2024). This interaction between Tregs and mregDCs can impede the initiation of antitumor adaptive immune responses, thereby contributing to tumor progression (You et al., 2024). CCL22 has been identified as a key mediator in facilitating the interaction between CCR7⁺ DCs and Tregs in perivascular immune hubs in the TME, which ultimately leads to impairment of antitumor functionality via CD40 downregulation and subsequent impairment of ICB-induced antitumor immunity (Zitti et al., 2025). It remains to be determined whether the cDC1 versus cDC2 origin of mregDCs impacts their prognostic implications.

Mapping these spatiotemporally governed interactions, summarized in Fig. 2, i.e., cDC1:NK:CD8⁺ T cell circuits, TLS-associated CCR7⁺ DC niches, CD4⁺ T cell/CD8⁺ T cell/DC triads, and suppressive mregDC:Treg aggregates, provides a framework for therapeutic strategies aiming to amplify beneficial networks while disrupting those that constrain immunity and which will be discussed in Harnessing recent advances… These insights are crucial for the further optimization of immunotherapeutic approaches owing to the instrumental role played by cDC1s in their efficacy (see Table 2 and Fig. 3). The tumor-derived factors and mechanisms that modulate cDC1 antitumor functionality will be discussed below.

Mechanisms limiting cDC1 antitumor functionality

Physical exclusion

Tumor stroma remodeling by tumors and CAFs can create a physical barrier to immune cell recruitment and impair the functionality of immune cells including DCs (Mao et al., 2021). The tumor and associated stromal tissue can produce an array of mediators to mediate remodeling of the tumor and surrounding tissue including VEGF, FGF, TGF-β, matrix metalloproteinases, collagen, and fibronectins, which can culminate in the exclusion of immune cells including cDC1s. However, as detailed above cDC1s can be retained at the peritumoral stromal regions and can mediate induction of antitumor T cell responses. Papadas et al. (2022) illustrated the importance of stromal composition and dynamics in the activity of cDC1s. The authors demonstrate that proteolysis of a matrix proteoglycan versican, leading to the production of versikine, in this region leads to "stromally licensed" cDC1s with enhanced sensitivity to DNA triggers and T cell priming capabilities. This versikine-mediated direct cDC1 activation was TLR2-independent and is associated with enhanced cDC1:NK cell crosstalk. Our group previously demonstrated that MMP-2, which is frequently upregulated in tumors, can condition DCs to skew CD4 T cell priming toward Th2 phenotypes through inhibition of DC-mediated IL-12 production via cleavage of the IFNAR1 receptor, alongside induction of OX40L expression (Godefroy et al., 2011). Additionally, we have demonstrated that MMP-2 promotes tumor growth in B16 melanoma models, driving pro-tumorigenic immune programs in the TME via TLR2/4 signaling. Notably, this effect was lost in *Batf3*$^{-/-}$ mice, indicating that cDC1s are essential mediators of MMP-2–induced immune dysfunction (Muniz-Bongers et al., 2021). Altogether, these studies suggest that the regulation of proteolytic activity and associated by-products in the stromal regions may have a key role in shaping cDC1 functionality in the region.

Inhibitory cell–cell interactions

For a comprehensive recent review of the modulation of cDC1 antitumoral activity by tumor-derived soluble mediators, please see Luri-Rey et al. (2025). In addition to soluble mediators, direct

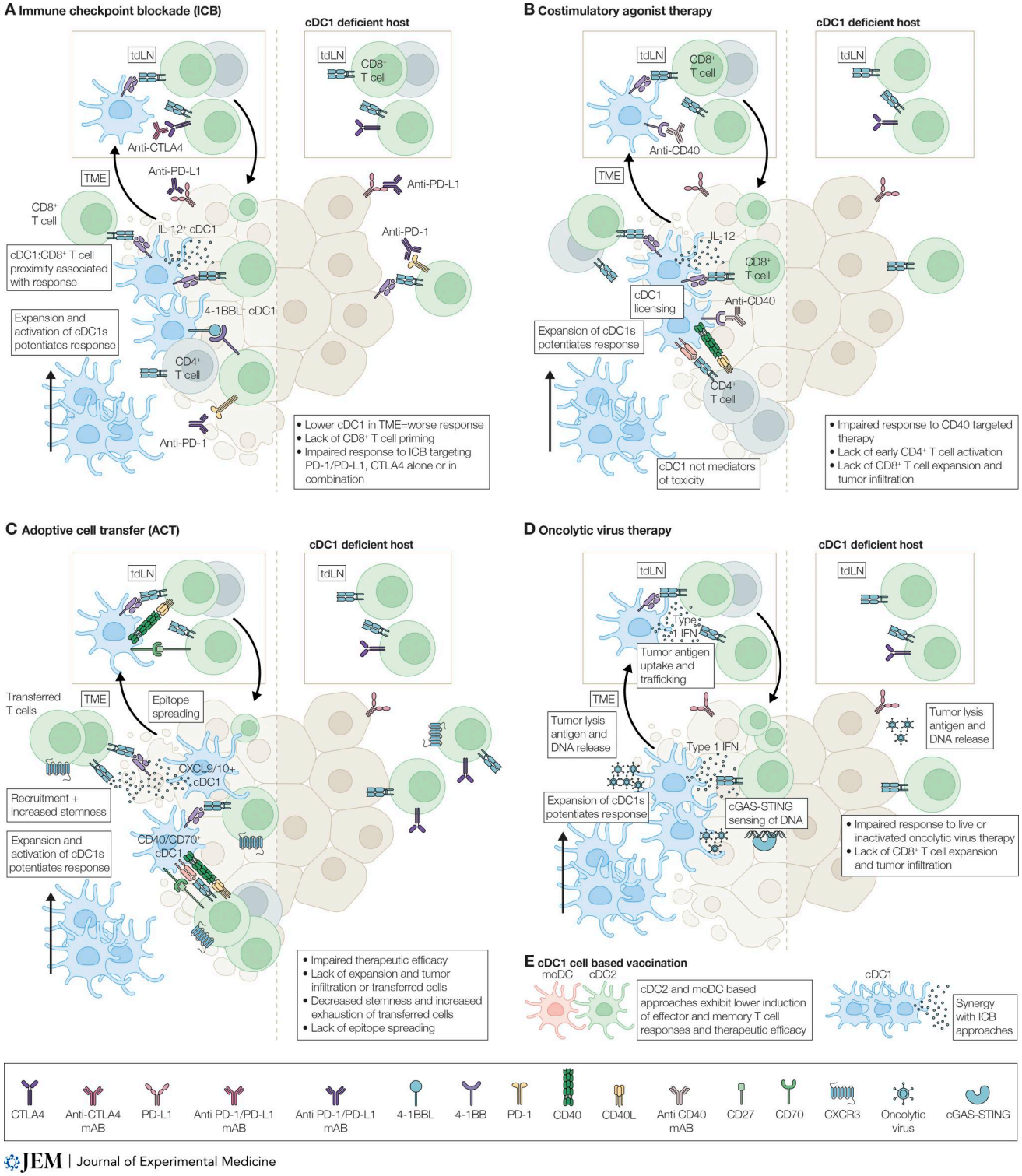

Figure 3. **cDC1-dependent mechanisms that support efficacy across major immunotherapy classes.** For each therapy class, the left side shows an immunocompetent setting with functional cDC1, and the right side shows a cDC1-deficient host summarizing common phenotypes when cDC1s are absent. **(A)** ICB. Anti-PD-1/anti-PD-L1 and anti-CTLA-4 responses rely on cDC1-mediated cross-presentation and continued restimulation of tumor-reactive CD8⁺ T cells. cDC1-derived mediators including IL-12 and cDC1-CD8⁺ T cell proximity associate with response, and increasing cDC1 abundance/activation can potentiate benefit. cDC1 deficiency reduces CD8⁺ T cell priming and weakens responses to ICB. **(B)** Costimulatory agonist therapy. CD40 agonism activates and licenses cDC1 to drive CD8⁺ T cell expansion and tumor infiltration. Antitumor activity is cDC1-dependent, while toxicities reported for CD40 agonists are not. **(C)** ACT. ACT (including CAR-T and other transferred T cell therapeutics) benefits from cDC1-mediated chemokine support (e.g., CXCL9/10) that enhances recruitment of transferred cells to the TME, and for the induction of epitope spreading. In cDC1-deficient settings, transferred cells show reduced expansion/infiltration, increased exhaustion, and diminished epitope spreading. **(D)** Oncolytic virus therapy. Oncolytic viruses induce tumor lysis with release of antigen and immunostimulatory nucleic acids that promote type I IFN release and activation of cDC1, enabling cross-priming in tdLN and subsequent CD8⁺ T cell expansion

and accumulation in tumors. cDC1 deficiency compromises responses to live or inactivated viruses and limits intratumoral CD8⁺ T cell expansion/infiltration. **(E)** cDC1-based vaccination. *Ex vivo*–generated/activated cDC1 vaccines (delivered intratumorally) promote antitumor effector and memory T cell responses and synergize with ICB. cDC2- or moDC-based approaches induce weaker T cell responses and reduced therapeutic efficacy.

cell-to-cell interactions play a central role in impairing cDC1 activity in the TME. As mentioned previously, Tregs have been shown to interact with mregDCs, impairing tdLN trafficking (You et al., 2024). Moreno Ayala et al. (2023) recently demonstrated high expression of CXCR3 on Tregs facilitates homing to CXCL9⁺ cDC1s in the tumor and dLN, and accordingly, Treg-restricted deletion of CXCR3 favored induction of CD8⁺ T cell responses in the TME and impaired tumor growth. Similarly using murine lung tumor modes, Zagorulya et al. (2023) demonstrated that IFNγ in the tdLN polarized Tregs toward a "Th1-like" phenotype, which favored their association with cDC1s. These Tregs suppressed the activation of cDC1s and subsequent induction of CD8⁺ T cell responses, reliant on direct MHC class II interactions with cDC1s. This IFNγ-induced Treg signature was subsequently shown to negatively correlate with response to ICB in melanoma patients. Similarly in the context of vaccination, inclusion of high doses of class II neoepitopes delivered as peptides promoted induction of FOXP3⁻ GRZMB⁺ LILRB4⁺ CD4⁺ type I regulatory cells, which exerted cytotoxic effects on cDC1 populations leading to reduced intratumoral frequencies (Sultan et al., 2024). Induction of these cell types following vaccination was primarily mediated by cDC2 and monocyte populations. Overall, it is imperative to decipher these tumor-induced alterations in cDC1 phenotypes and composition, which infer therapeutic avenues and provide insights into potential resistance mechanisms to immunotherapies.

Harnessing recent advances in cDC1 biology for improved immunotherapy

cDC1 mobilization and activation strategies

Expanding the repertoire and tumor availability of functional cDC1 populations is an attractive strategy to improve disease outcomes and response to other immunotherapies. To this effect, recombinant FLT3L delivery to mice has shown therapeutic benefit when combined with other therapeutic strategies including tumor antigen–encoding mRNAs, the TLR3 agonist poly-ICLC, chemotherapies including BRAF inhibition and cisplatin, radiotherapy, ICB, and ACT (Kreiter et al., 2011; Salmon et al., 2016; Lam et al., 2024; Hammerich et al., 2019; Tu et al., 2024) (Fig. 3). *In situ* delivery of FLT3L drives expansion of effector-like CD8⁺ T cells in a cDC1–derived IL-12–dependent manner, with enhanced clonal diversity additionally observed (Chun et al., 2024). Clinically, *in situ* delivery of FLT3L, poly I:C, and localized radiotherapy induced tumor regression in B cell lymphoma patients, associated with an increase in systemic activated cDC1 and pDCs and infiltration of migratory CD141⁺ cDC1s into the tumor site (Hammerich et al., 2019). These important results have led to a subsequent trial incorporating pembrolizumab and evaluation in additional tumor types (NCT03789097) (see Table 3). Systemic delivery strategies may offer a pragmatic path to clinical translation. In a phase II randomized study in resected/high-risk melanoma, systemic FLT3L (CDX-301) expanded circulating DC subsets (including cDC1) and was incorporated with poly-ICLC and a DC-targeting vaccine, supporting feasibility of systemic DC mobilization/priming regimens (Bhardwaj et al., 2020). However, systemic administration, particularly of potent innate agonists such as poly-ICLC, can be limited by off-target inflammation and dose-limiting systemic toxicities, motivating approaches that localize or target adjuvant activity. Consistent with the concept that systemic innate stimulation may enhance checkpoint blockade efficacy, Grippin et al. (2025) reported that SARS-CoV-2 mRNA vaccination can sensitize tumors to ICB, supported by mechanistic preclinical data and by an association between vaccination within 100 days of ICB initiation and improved overall survival in retrospective NSCLC and melanoma cohorts.

CD40 has additionally been targeted to improve antitumor functionality, owing to its functional importance discussed above in cDC1s as mediators of tumor immunity and disease outcomes in cancer. In preclinical studies, it has been demonstrated that administration of recombinant FLT3L and anti-CD40 agonistic antibodies can rejuvenate and activate cDC1 populations in the tdLN (Schenkel et al., 2021) and that *in situ* mobilization and activation of tumor-resident cDC1s with intratumoral delivery of recombinant FLT3L, anti-CD40, and a TLR3 agonist alongside localized radiotherapy (Oba et al., 2020) can restore antitumor immunity and response to ICB. The synergistic effects between FLT3L treatment and CD40 agonism are particularly important in tumors exhibiting low cDC1 infiltration basally as recently demonstrated in a murine PDAC model (Hogg et al., 2025). A recent study demonstrated the efficacy of intratumoral delivery of FLT3L and CD40L encoding mRNAs encapsulated in a immunogenic cell death-inducing LNP formulation, achieved through incorporation of a chemotherapeutic-derived ionizable lipid (Hou et al., 2025). Similar approaches to CD40 targeting are currently being clinically investigated in a broad range of tumors outlined in phase I/II trialing (see Table 3). The elicitation of a helped cDC1 phenotype and generation of TLS likely contribute to the efficacy of these approaches clinically. CD40 agonistic therapies have been hampered by dose-limiting toxicities associated with cytokine release syndrome. However, localized delivery or direct targeting of antibodies to cDC1s are attractive strategies to circumvent such issues. In a recent preclinical study, bispecific antibodies simultaneously targeting CD40 and DC surface markers, such as CD11c, DEC-205, or CLEC9A, were designed to directly target DCs, enhancing the safety profile while promoting antitumor immunity (Salomon et al., 2022). The same research group also recently demonstrated the efficacy of a CLEC9A, and PD-1–targeted bispecific engager (BiCE), which successfully promoted cDC1:CD8⁺ T cell interactions in the TME and tdLN, resulting in robust antitumor CD8⁺ T cell responses after i.p. delivery in preclinical models (Shapir Itai et al., 2024). BiCE administration outperformed PD-1 mAb delivery in terms of

Table 3. **Representative ongoing clinical trials investigating strategies for (1) cDC1 mobilization and activation and (2) cDC1-based vaccination**

Trial phase and number	Tumor type	Approach	Rationale—preclinical/clinical	Refs
1. cDC1 mobilization and activation strategies				
Phase I/II—Recruiting (NCT03789097)	HNSCC, MBC, indolent NHL	*In situ* delivery of CDX-301 (FLT3L), poly-ICLC, localized low-dose radiotherapy, and systemic delivery of pembrolizumab	Therapeutic strategy was well tolerated and showed early signs of efficacy in NHL and MBC patients, including instance of regression of large metastatic tumor in patient (Marron et al., 2022)	Hammerich et al. (2019) and Marron et al. (2022)
Phase I—recruiting (NCT05029999)	Metastatic or unresectable stage III/IV HER2 negative breast cancer (TNBC or HR(+))	Intravenous PEGylated liposomal doxorubicin (PLD) and CDX-1140 (agonistic anti-CD40 mAb), subcutaneous CDX-301	Combination of PLD, CD40 agonist mAb, and FLT3L promoted tumor control in the TNBC 4T1 mouse model (Ramani et al., 2022)	Ramani et al. (2022) and Reddy et al. (2023)
Phase I—active (NCT04616248)	Range of solid tumors—unresectable melanoma, squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, bone or soft tissue sarcoma, HER(-) breast cancer	(A) *In situ* delivery of CDX-1140, CDX-301, poly-ICLC, and localized radiotherapy (B) *In situ* delivery of CDX-1140, CDX-301, poly-ICLC, and localized radiotherapy. IV delivery of pembrolizumab and SC tocilizumab (anti-IL-6)	Combinations of intratumoral FLT3L, peritumoral poly-ICLC, and agonistic CD40 mAb, and localized radiotherapy led to clearance of non–T cell–inflamed murine tumor models (AT-3, B16, and 4T1)	Ito et al. (2024)
2. cDC1-based cellular vaccine approaches				
Phase I/II—recruiting (NCT05773859)	Epithelial ovarian cancer	Autologous tumor lysate–loaded cDC1s. cDC1s isolated from peripheral circulation of patients. cDC1 vaccination will be given in combination with standard-of-care carboplatin/paclitaxel and cytoreductive therapy	Advances in cell sorting technologies allowing purification of cDC1s in sufficient quantity from peripheral blood. Enhanced cDC1 functionality compared with alternative DC vaccination platforms (see Table 2)	Koeneman et al. (2025)

HNSCC, head and neck squamous cell carcinoma; MBC, metastatic breast cancer; NHL, non-Hodgkin's lymphoma.

therapeutic efficacy and in reprogramming of TILs toward more favorable antitumor phenotypes.

Bispecific antibodies targeting CLEC9A and PD-L1 have also recently been utilized to deliver a modified type I IFN cargo, in efforts to reduce systemic toxicities, promoting robust antitumor immunity with increased intratumoral and tdLN accumulation of cDC1 and induction of CTL responses in preclinical models (Van Lint et al., 2023). Another innovative approach to reduce systemic toxicities involves the generation of CD45-targeted cytokines termed "immunocytokines," achieved via fusion of anti-CD45–targeted IgG heavy chains to cytokine cargo (Santollani et al., 2024). A therapeutic strategy involving sequential localized delivery of CD45-targeted IL-12 and IL-15 led to induction of systemic antitumor immunity, which was compromised in BATF3 KO or $CD8^+$ T cell–depleted mice.

In addition to ICB, cDC1 expansion and activation have also been utilized to improve responses to ACT approaches. Lai et al. generated a FLT3L-expressing CAR-T and co-administered poly I:C and an anti-41-BB antibody, with mice displaying expanded breadth of antitumor T cell responses due to induction of epitope spreading. These observations were associated with expansion and activation of DCs (Lai et al., 2020). Similarly, CAR-T cells expressing FLT3L and IL-7 have shown efficacy in a murine GBM model, similarly associated with an expansion of migratory cDC1 populations and support of intratumoral CAR-T populations (Swan et al., 2023). Tu et al. (2024) demonstrated that FLT3L treatment conditioned DCs to induce $CD8^+$ T cells with superior activation and memory profiles, dependent on pDC-mediated type I IFN production and IFNAR signaling in $CD8^+$ T cells.

XCL1 constitutes an attractive chemokine for use in such *in situ* approaches to promote cDC1 intratumoral infiltration. Better understanding of the interactions between XCL1 and XCR1 has enabled the development of a more potent XCL1 candidate (XCL1-V21C/A59C) (Matsuo et al., 2018). The same research group recently demonstrated that intratumoral delivery of XCL1-V21C/A59C, utilizing a hydrophilic gel patch, promoted recruitment of $CXCL9^+$ cDC1s and subsequent CTL responses into the tumor associated with impaired tumor growth in preclinical models (Kamei et al., 2024). In the same vein, engineering of CAR-T cells to express XCL1 is a promising strategy to co-opt endogenous cDC1s to strengthen T cell response and resulting antitumor immunity (Li et al., 2025). Xiao et al. (2025) recently demonstrated the efficacy of CAR-T cells engineered to express both FLT3L and XCL1, exerting tumor control in murine and humanized tumor models, associated with TME remodeling and expansion of the breadth of antitumor T cell responses. Strategies utilizing XCL1 as part of *in situ* treatment have yet to be clinically evaluated.

PRR agonists have been trialed in ISV approaches with varying clinical efficacy. These strategies rely on immunologically heating up tumors to induce antitumor immune responses.

As mentioned above, TLR3 agonists, including poly I:C–based agents, have been utilized extensively in preclinical and clinical studies. The therapeutic efficacy associated with *in situ* delivery of BO-112, a viral mimetic composed of polyethyleneimine-complexed poly I:C, has been shown to preclinically rely on cDC1s for efficacy (Rodriguez-Ruiz et al., 2023). Clinically, BO-112 has shown promising early activity in combination with systemic pembrolizumab in anti-PD1–resistant melanoma (Márquez-Rodas et al., 2025) with further clinical evaluation ongoing. Activation of intrinsic STING signaling in cDC1s has been shown to mediate therapeutic effects following delivery of a STING-activating nanoparticles into MC38 tumors (Wang et al., 2024b), and additionally, cDC1s and DC-intrinsic STING signaling were required for therapeutic effects following delivery of the STING agonist cGAMP via virus-like particles (VLPs) into B16-OVA tumors (Jneid et al., 2023). Additionally, the cGAMP-VLPs were shown to potently activate cDC1 and cDC2 populations in the TME. This VLP incorporation of cGAMP is an example of targeting STING agonists to DC populations. Another interesting approach is the development of polySTING, which incorporates diABZI, a small molecule STING agonist, linked to a DC targeting mannose moiety via a cleavable linker. PolySTING induced activation of cDC1s and CD8⁺ T cell responses in the TME and antitumor efficacy in B16F10 tumors following systemic delivery (Nguyen et al., 2024). There are multiple ongoing clinical trials investigating STING agonists in ISV approaches.

Oxidized phospholipids have been preclinically shown to induce a "hyperactive" phenotype in cDC1s via activation of caspase 11 and subsequent inflammasome assembly, associated with increased migration and capacity to promote CD8 T cell responses with applications for *in situ* or *ex vivo* DC vaccination approaches (Zhivaki et al., 2020). Additionally, induction of DC hyperactivation was shown to correct age-associated defects in antitumor immunity, promoting induction of cytotoxic Th1 cells (Zhivaki et al., 2024).

Recent advances in delivery platforms, such as novel insights into the development and optimization of LNPs, can facilitate enhanced cell targeting approaches, which may enhance the cDC1-specific delivery of PRR agonists for ISV approaches. In addition to the examples highlighted above, recent advances in biomaterials research have opened exciting avenues for the use of innovative biomaterial-based approaches to enhance cDC1 antitumor activity. These include the controlled delivery and release of antigens or key mediators directly to the TME or DCs themselves, reviewed elsewhere (Dong et al., 2023).

Immunosuppressive TME remodeling

As detailed above, there is strong rationale for the depletion of Tregs to support cDC1-mediated induction of antitumor immunity (Régnier et al., 2023; You et al., 2024; Zagorulya et al., 2023; Moreno Ayala et al., 2023; Zitti et al., 2025). To avoid systemic side effects associated with depletion of Tregs, efforts are being made to develop therapeutic strategies, which selectively deplete Tregs in the TME as recently reviewed in Tay et al. (2023) and Yang and Bae (2023), with mAbs targeting CCR8 (enriched in tumor-associated Tregs), one such strategy (Roider et al., 2024; Kidani et al., 2022) now advanced to clinical trials. In preclinical models, therapeutic effects were dependent on CD8⁺ T cell induction and were associated with an increase in the expression levels of maturation markers in tumor-infiltrating DCs (Kidani et al., 2022). Similarly, inhibition of CD39 has been shown to mediate antitumoral effects in preclinical bladder cancer models, with reinvigoration of the cDC1:NK cell:CD8⁺ T cell axis, and a decrease in Treg abundance underlying therapeutic efficacy (Liu et al., 2022). Alongside Tregs, as discussed there is strong rationale for the depletion of MDSCs, which produce many of the soluble immunosuppressive mediators (e.g., TGF-β, IL-10, oxidized lipids) in the TME that limit DC function. Therapeutic targeting of MDSCs through depletion strategies or through induction of differentiation, including into a "DC-like" phenotype, has recently been reviewed (Lu et al., 2024; Kurt et al., 2023). While depletion of immunosuppressive TAMs has been investigated as an approach to remodel the immunosuppressive TME, recent data showing the contribution of CD206⁺ TAMs to antitumor immunity via stimulating the cDC1:NK:CD8⁺ T cell axis (Ray et al., 2025) alongside previous demonstration of their antitumor capabilities (Modak et al., 2022) caution the broad depletion of TAM subsets, particularly those that have been classified using outdated nomenclature such as "M1" and "M2". This may be one reason broad TAM depletion (e.g., CSF1R blockade) has not consistently translated into strong clinical benefit in solid tumors (Gomez-Roca et al., 2019).

Finally, a deeper understanding of DC states in cancer facilitates novel therapeutic approaches, with a key example being the modulation of the mregDC phenotype. IL-4 signaling was previously identified as a key driver of this phenotype with blockade of IL-4 signaling resulting in restored cDC1-mediated IL-12 production and subsequent induction of antitumor immunity in preclinical tumor models (Maier et al., 2020). While DC-intrinsic Il4ra deletion did not significantly improve tumor control in mouse models, LaMarche et al. (2024) instead implicate IL-4Rα–driven immunosuppressive myelopoiesis as a key, targetable axis limiting antitumor immunity. Translationally, in PD-1/PD-L1 blockade–progressed NSCLC patients who continued ICB therapy, the addition of dupilumab (IL-4Rα blockade; inhibiting IL-4/IL-13 signaling) was associated with immune remodeling, including reduced circulating monocytes and increased intratumoral CD8⁺ T cells. Biopsies taken pretreatment and 36 days after dupilumab showed increased LAMP3⁺ cells alongside increased CD8a⁺ cells, and CD20⁺ cells by IHC indicating expansion of activated DCs, CD8⁺ T cells, and B cells in the TME. As mentioned previously, AXL has been identified as a negative regulator of cholesterol metabolism and subsequent cDC maturation (Belabed et al., 2025). AXL had previously been clinically targeted in cancer due to its tumor cell–intrinsic pro-tumorigenic roles, including favoring tumor cell survival and epithelial–mesenchymal transition (Bhalla and Gerber, 2023). The impact of these strategies on cDC phenotypes in the TME and possible reinvigoration of functionality will yield interesting insights into clinical efficacy and provide a rationale for combination with additional immunotherapeutic strategies.

cDC1 vaccination approaches

In vivo–targeted approaches

In vivo DC vaccination strategies aim to trigger cDC1 cell activation and antigen delivery directly inside the host, which can be facilitated by (1) markers with enriched expression in cDC1s, e.g., DEC-205, and (2) markers uniquely expressed by cDC1s, e.g., XCR1, Clec9a. Direct *in vivo* targeting offers a key advantage in that any possible alterations associated with cDC1 isolation, culture, and infusion are avoided. A significant early breakthrough in this field was the development of antibodies targeting human DEC-205 fused to full-length NY-ESO1 antigens to improve vaccine targeting of APCs (Tsuji et al., 2011). Subsequently, a phase I trial demonstrated that intracutaneous administration of NY-ESO1–fused DEC-205–targeted antibody, alongside resiquimod and/or poly-ICLC, successfully induced antigen-specific T cell responses in over half of recipients (Dhodapkar et al., 2014). Our group additionally demonstrated the benefit of expanding cDC1 abundance prior to DEC-205–targeted vaccination in a phase II clinical trial, where patients who received systemic FLT3L prior to vaccination exhibited expanded magnitude and breadth of induced responses (Bhardwaj et al., 2020). Recent preclinical work has pivoted toward more cDC1-targeted approaches, for example, targeting Clec9a as reviewed elsewhere (Hussain et al., 2025; Lahoud and Radford, 2022). Emerging antibody-decorated mRNA-LNP platforms add an important new avenue for these cDC1-targeted approaches, potentially overcoming the limitations of protein–antigen conjugate production and allowing more flexibility in cargo design and customization.

Ex vivo approaches

In contrast to direct *in vivo* targeting, *ex vivo* DC vaccination involves extracting DCs from a patient or healthy donor, followed by subsequent activation and manipulation before infusion back into the recipient, usually involving PRR stimulation (e.g., poly-ICLC) and loading of tumor antigens as mRNA, DNA, or peptides, more recently focusing on patient-specific neoantigens. DC-based vaccination approaches have been extensively trialed, with significant hurdles identified including in overcoming the immunosuppressive TME and additionally in developing an optimal DC modality for use in vaccination. Traditional approaches have relied on the generation of moDC-based vaccinations, with novel approaches utilizing innovative isolation and culture protocols to generate cDC-based vaccines to enhance functionality (Table 2). Ferris et al. (2022) demonstrated the superior functionality of cDC1-based intratumoral vaccines over GM-CSF–induced moDC counterparts, with transferred cDC1s capable of sampling tumor antigens, trafficking to the tdLN, and initiating systemic antitumor immune responses in preclinical tumor models. These effects were independent of host cDC1s and crucially did not require antigen loading. Similarly, Zhou et al. (2020) demonstrated that *in vitro* generated, tumor antigen–loaded, and poly I:C–stimulated CD103$^+$ cDC1s were effective at inducing systemic antitumor immunity following antitumor immunity, displaying therapeutic synergy with ICB and outperforming moDC-based approaches. More recently, Heras-Murillo et al. (2025) demonstrated that cDC1 vaccination outperformed cDC2-based vaccination approaches, with both cell types derived from murine spleens. Antitumor immunity following cDC1 vaccination was associated with superior expansion of tumor-specific CD4$^+$ and CD8$^+$ T cells with systemic CD8$^+$ T cell and CD4$^+$ tissue Trm cells.

Even though cDC1s show great potential as cancer vaccine candidates, these observations have yet to be fully clinically translated. This is primarily due to the scarcity in circulation and the technical challenges associated with generating large quantities of functional cDC1s *ex vivo*. Crucially, large-scale generation of human cDC1, cDC2, and pDC subsets from CD34$^+$ progenitors (Balan et al., 2018; Balan et al., 2025; Liu et al., 2026, *Preprint*) can facilitate the trialing and implementation of these cDC1-based vaccination strategies. Additionally, a recent publication addresses an interesting alternative approach that circumvents the need for the prior antigen loading and differentiation utilized in DC vaccination approaches. Ghasemi et al. (2024) developed a strategy for the *ex vivo* generation of common DC progenitors (DCPs) utilizing a two-step 6- to 8-day culture protocol incorporating short-term expansion and differentiation phases, and additionally induced expression of IL-12 and FLT3L via lentiviral transduction. Infusion of these DCPs promoted IFNγ- and cDC1-dependent antitumor immune responses in multiple murine tumor models and synergized with CAR-T therapy. This group has additionally demonstrated the efficacy of IL-12$^+$ DCPs engineered to express an EV internalization receptor, to encourage internalization of EVs containing tumor antigen–MHC class I (Ghasemi et al., 2025). Additionally, authors validated the generation of human DCPs from CD34$^+$ human cord blood–derived HSPCs. These advances will pave the way for the clinical implementation of cDC1-based DC vaccination strategies, which has proved challenging. These challenges are reflected in the clinical landscape where only one study is investigating the use of patient-derived cDC1s for cancer vaccination (NCT05773859) (Koeneman et al., 2025).

DC engineering to express mediators supportive of antitumor functionality is another attractive strategy to improve efficacy. Intratumoral delivery of engineered CXCL9/10$^+$ DCs was shown to promote intratumoral and systemic T cell responses and therapeutic synergy with ICB in preclinical tumor models (Lim et al., 2024). In addition to TLR-based activation of DC vaccine prior to infusion, there have been several mediators recently identified that may prove attractive targets to enhance the activity of DCs prior to infusion. For example, Acero-Bedoya et al. (2024) recently identified PTPN22, a negative regulator of TCR signaling, as a negative regulator of DC proliferation and functionality. PTPN22 deletion in DCs enhanced proliferation in response to FLT3L, antigen processing and presentation, and enhanced spontaneous tumor control in MC38 and B16 models associated with higher prevalence of CD103$^+$ cDC1s in the tdLN. Similarly, deletion of the histone demethylase KDM6b was shown to enhance antigen presentation and interferon response genes in DCs and increase the prevalence of CD103$^+$ DCs and pDCs in

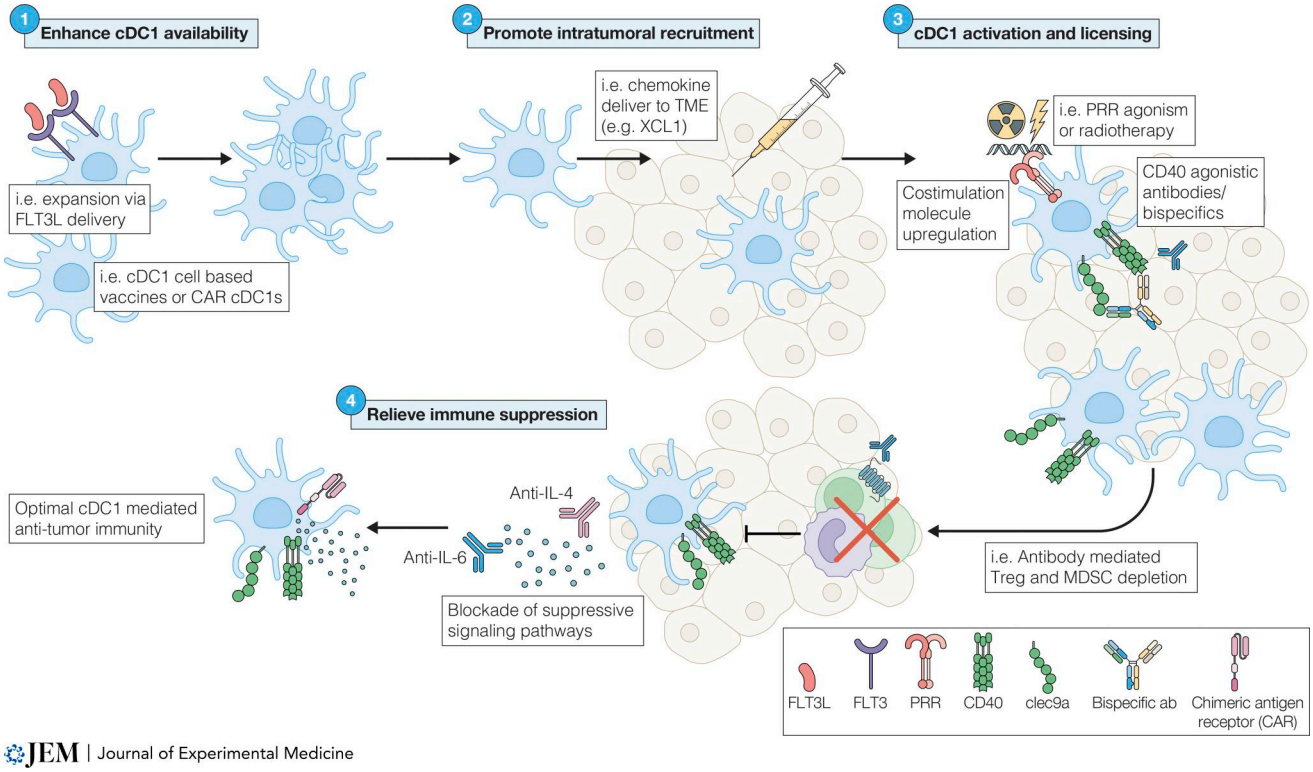

Figure 4. **Therapeutic strategies to promote cDC1 antitumor function.** Strategies aiming to harness cDC1s for antitumor functionality include (i) cDC1 expansion via the local or systemic delivery of growth/differentiation factors including FLT3L, and/or delivery of cDC1-based vaccine platforms and CAR cDC1s; (ii) cDC1 maturation via systemic targeted delivery of PRR agonists or localized radiotherapy; (iii) cDC1 activity enhancement via the agonism of cell surface molecules including CD40 and delivery of key cytokines including IL-12; (iv) cDC1 lymphatic or intratumoral homing via the delivery of key chemokines including XCL1; (v) depletion of immunosuppressive cell types that limit cDC1 functionality in the TME including Tregs and MDSCs; and (vi) the blockade of immunosuppressive pathways that limit cDC1 activity or differentiation including IL-4 and IL-6.

the spleen of tumor-bearing mice (Goswami et al., 2023). Modulation of these pathways via deletion or inhibition may enhance the functionality and fitness of DC vaccines.

Concluding remarks

cDC1s play a central role in shaping antitumor immunity, from the priming of tumor-specific T cell responses to their participation in complex cellular networks within the TME. An increasingly refined understanding of cDC1 biology, enabled by advances in *in vitro* culture systems and *in vivo* sequencing and imaging technologies, including spatially resolved approaches, has revealed critical insights into how these cells regulate antitumor immunity and influence immunotherapeutic outcomes. Importantly, the immune pathways and cellular interactions uncovered through these studies have identified actionable therapeutic targets, many of which are now being explored in preclinical and clinical settings (see Fig.4 and Table 3). Moreover, emerging evidence demonstrates that cDC1 activity contributes to the efficacy of established immunotherapies, with prognostic associations and therapy-induced alterations in cDC1 function providing a strong rationale for rational combination strategies that leverage cDC1s to enhance therapeutic responses. To most effectively harness cDC1-mediated antitumor immunity, future therapeutic strategies will likely need to move beyond simple expansion or activation and instead focus on coordinating cDC1 positioning, licensing, and durability within the suppressive TME.

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