Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2024**; 29(8): 293
https://doi.org/10.31083/j.fbl2908293

Review

Effector Functions of Dendritic Cells in Cancer: Role of Cytotoxicity and Growth Inhibition

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Academic Editor: Amancio Carnero Moya
Submitted: 2 April 2024 Revised: 25 May 2024 Accepted: 31 May 2024 Published: 20 August 2024

Abstract

The tumor microenvironment plays a critical role in modulating immune responses associated with tumorigenesis, tumor progression, and metastasis. Dendritic cells (DC) play a key role in preventing and progression of metastatic neoplasia by driving and restoring dysfunctional immune systems and obliterating immunosuppression, thus obstructing tumor evasion. In this review, we will discuss the functions of tumor-infiltrating DC in anti-tumor resistance, prevention of tumor recurrence, and immunosuppression. We will also describe DC metabolism, differentiation, and plasticity, which are essential for its function. Cancers like Lymphomas may be able to corrupt immune surveillance by reducing natural killer cell numbers. Thus, interactions between lymphoma and DC with reference to cytotoxicity may be an important event, likely to be mediated via activation with interferon-γ (IFN-γ) and Toll like receptors (TLR) ligands. Mechanisms of DC-mediated cytotoxicity and the role of apoptosis and death receptors, including the role played by nitric oxide, etc., are of immense significance. We will also look into the molecular mechanisms in the tumor microenvironment, reduced drug sensitivity, and tumor relapse, as well as methods for combating drug resistance and focusing on immunosuppressive tumor networks. We will address how DC mediated cytotoxicity in combination with drugs affects tumor growth and expansion in relation to checkpoint inhibitors and regulatory T cells. Innovative approaches for therapeutic modulation of this immunosuppressive adoptive DC immunotherapy will be highlighted, which is necessary for future personalized therapeutic applications.

Keywords: cancer; dendritic cells; cytotoxicity; effector functions; immunosuppression; metastasis; anti-cancer drugs; combination therapy; tumor microenvironment; cross-priming; regulatory T cells

1. Introduction

Dendritic cells (DC) represent a diverse group of lymphocytes considered specialized antigen-presenting cells (APC) having critical roles in innate immunity and initiation and regulation of adaptive immune responses [1,2]. Modulating DC functions is one of the sought-after strategies to improve cancer immunotherapy. DC is considered as professional APC and consists of a variety of cell subsets, which are either residents in organs or migrating among the non-lymphoid and lymphoid organs. Subsets of DCs differ in morphology, ontogeny, surface phenotype, functions, and key transcription factors, which are important for their functions. In a steady state condition, DCs process and present antigens on class I and II major histocompatibility complexes (MHC). DC comprises three major subsets, which include plasmacytoid (pDC), type-1, and type-2 conventional DC (cDC1 and cDC2), respectively [3]. Other DC subtypes are inflammatory monocyte-derived DCs (MODCs) and Langerhans cells (LCs). DC is also present in the vicinity of tumors, where they are exposed to tumor-associated antigens (TAAs) and then migrate to draining lymph nodes in order to present these antigens to lymphocytes (CD8$^+$ or CD4$^+$ T cells) [4–6]. Cross-presentation of antigens by cDC1s contributes to the priming of tumor-associated antigens (TAA) specific cytotoxic T cells [7]. cDC1 also supports T helper 1 (Th1) cell polarization from naive CD4$^+$ T cells [8,9]. cDC2 comprises a heterogeneous population and preferentially prime naïve CD4$^+$ T cells for Th2 or Th17 polarization [10–12]. Little is known about the role of the cDC2 subset in tumor immunity. DC efficiently cross-presents TAA in order to prime tumor antigen-responsive CD8$^+$ T cells for controlling tumor growth [13–16], and thus, it makes DC-based vaccines a significant therapeutic strategy to potentiate effector and memory anti-tumor CD8$^+$ T cell responses for cancer immunotherapy [4,17–19]. Despite being a rare population, several studies have documented the heterogeneous nature of DCs with functional flexibility [2].

Among the professional APCs, DCs have potential in terms of migration and priming of T cells compared with monocytes/macrophages and B lymphocytes. DC regularly surveys peripheral tissues for antigens, which are captured and processed, followed by migration to lymphoid organs and deliver the antigens to T lymphocytes [20–22]. The existence of danger signals from pathogens, etc., induces maturation of the DCs, which leads to the T cell activation and polarization. Immature DCs, unlike their mature counterparts, induce tolerance [23]. Semi-mature DCs stimulated by cytokine interleukin-10 (IL-10) or transforming growth factor-beta (TGF-β) or activated by apoptotic cells also show tolerogenic potential. Thus, the quality and extent of immune responses (IR) depends on the maturation states of DC. Extracellular antigens (e.g., TAA) following internalization by APC are degraded in the endo/lysosome compartment and presented to $CD4^+$ T cells through the MHC-II molecule. Cytosolic antigens (viral infection) are processed through the MHC-I molecule presentation pathway. DC subsets also cross-present extracellular antigens through the MHC-I molecule in order to induce $CD8^+$ T cell responses. This property is significant in tumor immunity because it could induce efficient anti-tumor $CD8^+$ T cell responses via cross-presentation. Therefore, DCs act as a balance between immunity and tolerance and engineered T-cell mediated tumoricidal response.

Multiple strategies have been explored by targeting DC functions in cancer immunotherapies. There are approximately four approaches, which include protein and nucleic acid-based vaccines; endogenous DCs targeting antigens; tumor antigens loaded and matured *ex vivo* generated DCs; and reprogrammed endogenous DC using biomaterial-based platforms for *in situ* recruitment to tumor [24,25]. Clinical trials performed with DC-based anti-cancer vaccines commonly depend on the use of *ex vivo* generated and differentiated DCs from leukapheresis enriched from $CD14^+$ monocytes following culture in granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4 [26]. Although promising with good safety and ingenuity, the therapeutic efficacy of cell therapy is only limited to less than 20% of the patients [26,27]. The occurrence of immune suppression imposes an increasing burden of tumor antigens plus regulatory factors in mid to late-stage cancer, which may limit the efficacy of monocyte-derived DC [28,29]. The underperformance of monocyte-derived DC involves a lack of migration from the injection site to the lymph nodes and an inability to induce strong tumor-specific cytotoxic T lymphocyte (CTL) responses [30–34]. The effector functions of DC include direct cytotoxicity against the tumor cells, which influence immunity and tolerance in neoplastic conditions. In this review, we will describe how different DC subsets induce and influence tumoricidal activity, including cytotoxicity and growth inhibition, and discuss their implications for established cancer treatments (chemotherapy) and novel immunotherapeutic strategies.

2. Origin and Development of DC

Origin and differentiation of DCs from blood or splenic monocytes and macrophages constituted the major focal areas of studying DC biology. Monocytes are reported to differentiate *in vitro* into DCs upon stimulation with GM-CSF, tumor necrosis factor-α (TNF-α), and IL-4 [35]. DCs can also be derived from non-lymphoid and lymphoid tissues. Monocytes are identified as precursor sources of peripheral non-lymphoid organ DCs and migratory DCs during inflammation, termed monocyte-derived DC (MODC) [3,36–38] besides the occurrence of DC-restricted progenitor, the common-DC progenitor (CDP) [39]. Multipotent progenitors (MMPs) or multi-lymphoid progenitors (MLPs) are defined as $Lin^-CD34^+CD38^-$ present in bone marrow and umbilical cord blood. In the fetal liver, there is a ratio of $CD34^+CD38^-$ stem cells and $CD34^+CD38^+$ progenitors having abundant oligo potential activity [40] (Fig. 1). Both cDCs and pDCs are derived from bone marrow's common myeloid progenitors (CMPs) and differentiated from the multipotent hematopoietic stem cells (HSC) via differentiation steps termed "hematopoiesis". Development and maturation of DC depend on purine rich box 1 (PU.1), a family member of the erythroblast transformation specific (ETS) transcription factor (TF), which also has a critically important role in the development of macrophages, neutrophils, and co-stimulatory molecules like CD80 and CD86, and fms-like tyrosine kinase 3 (Flt3) [41–43]. The transcription factor ReIB, a member of the Nuclear factor kappa B (NF-kB) family, induces the monocyte precursor intermediates and promotes the differentiation of some DC subsets [44]. cDCs precursors differentiate to form DC-mediated by key transcription factors, like BATF3 (Basic Leucine Zipper ATF-Like Transcription Factor 3), IRF8, ID2 (Inhibitor of DNA binding 2), ZFBTB46 (Zinc Finger and BTB Domain Containing 46) [24–27], the growth factors Fms-like tyrosine kinase 3 ligand (FLT3L) and GM-CSF [45–48]. Notch and PU.1 are also important for the differentiation and maturation of DC. PU.1 is responsible for the induction of the Flt3 receptor [49,50] and in the discrimination of the cDC1 differentiation pathway [50] (Fig. 1).

3. DC Subtypes and Their Functions in Mouse and Human

Exposure to antigen matures DCs and upregulates the expression of MHC and co-stimulatory molecules (CD80/86), cytokines, and chemokines receptors, including CCR7 [51]. Mature DCs migrate to regional lymphoid tissues via CCR7 and activate naïve T lymphocytes and enable them to differentiate into effector T cells, including T helper (Th) 1 cells, Th2 cells, Th17 cells, T follicular helper (TFH) cells, regulatory T (Treg) cells, and $CD8^+$ CTLs, resulting in T-cell responses [51,52]. Experimental evidence has revealed that DCs are heterogeneous, and there are different DC subsets that are specialized in priming different types of effector T lymphocytes and skew effector response accordingly [53]. Four major subsets of DC are recognized, namely, conventional DCs (cDCs), plasmacytoid DCs (pDCs), monocyte-derived DCs (MODCs), and Langerhans cells (LCs). cDCs are further subdivided into cDC1s and cDC2s. Analogous subsets have been identified in humans and mice [4,53,54]. The phenotypic and functional characteristics of these DC subsets are summarized in Table 1 (Ref. [55–57]).

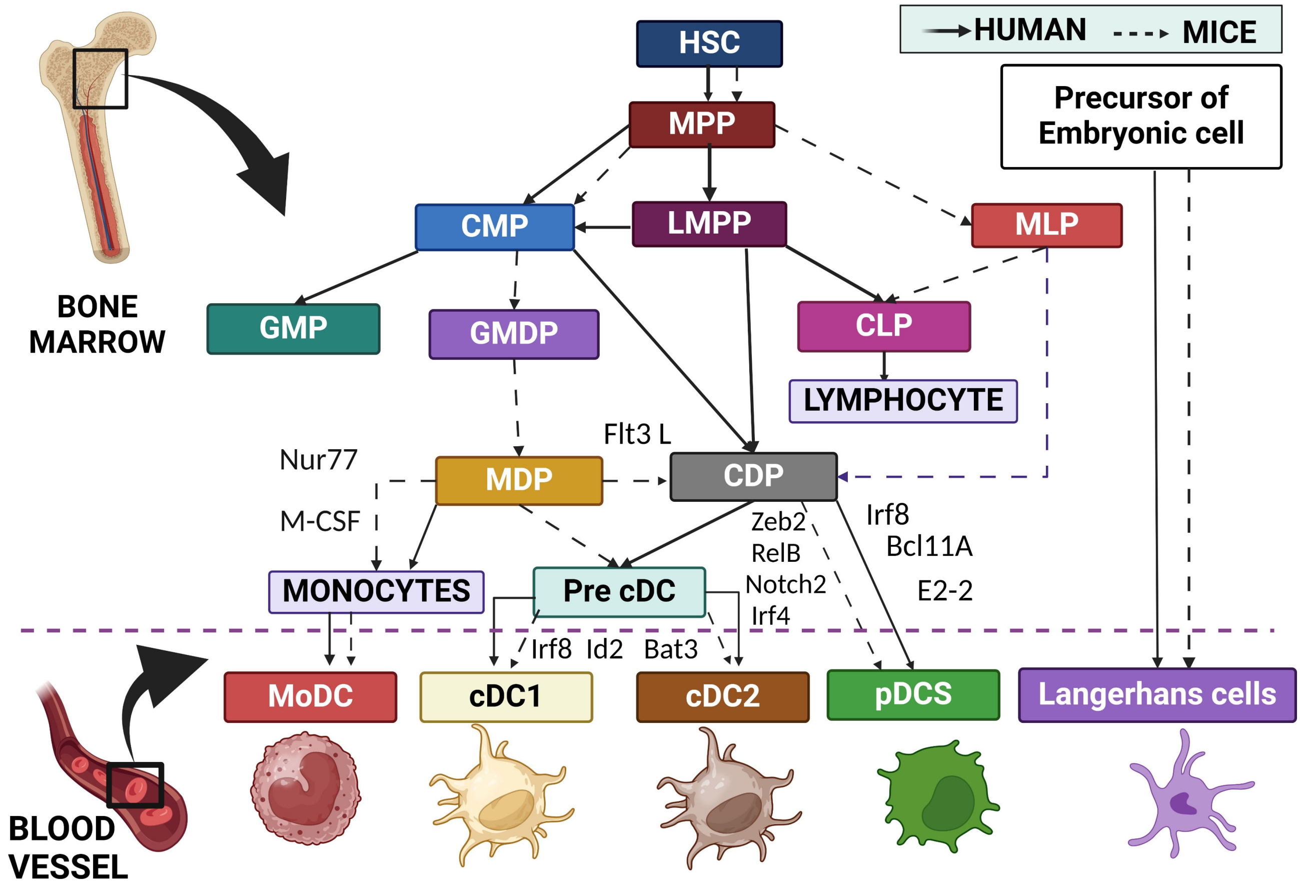

Fig. 1. Origin and development of DC subtypes in mice and humans as indicated with acronyms depicted. DC, Dendritic cells; HSC, Hematopoietic stem cell; MPP, Multipotent progenitor; CMP, Common myeloid progenitor; LMPP, Lympho-myeloid primed progenitor; MLP, Multipotent lymphoid progenitor; GMP, Granulocyte and monocyte progenitor; GMDP, Granulocyte, monocyte DC Progenitor; CLP, Common lymphoid progenitor; MDP, Macrophage and DC progenitor; CDP, Common or conventional DC progenitor; Pre-cDC, pre-Conventional DC; Nurr77, Nuclear receptor NR4A1; M-CSF, Macrophage colony-stimulating factor; Irf8, Interferon regulatory factor 8; Id2, Inhibitor of DNA Binding 2; Zeb2, Zinc finger E-box-binding homeobox 2; Irf4, Interferon regulatory factor 4; Notch 2, Neurogenic locus notch homolog protein 2; Bcl11A, Transcription factor B-cell lymphoma/leukemia 11A. Created with BioRender.com.

3.1 cDC1

Both cDC1s and cDC2s are formed from the common DC precursors; however, they possess different functions. cDC1s play an important role in antigen-specific immune responses against intracellular pathogens and induce CD8$^+$ T cell responses via MHC class I [4,53,54,58]. Batf3 deficiency in mice causes the elimination of CD103$^+$ cDC1s in the intestine, lung, mesenteric lymph nodes, skin, and skin-draining lymph nodes and thus reduces CD8$^+$ CTL responses [59,60]. cDC1s are responsible for the cross-presentation of extracellular antigens to CD8$^+$ T lymphocytes besides other DC subsets [61–63]. CD8α^+ DCs in tissues and dermal CD103$^+$ DCs in murine lymph nodes also perform cross-presentation of extracellular antigens [64,65]. CD141/blood dendritic cell antigen-3 (BDCA-3)$^+$ DCs in humans are considered functional homologs of murine CD8α^+ DCs [66]. cDC1 human and mouse DC express dendritic and epithelial cell-205 (DEC-205), C-type lectin domain family 9 member A (CLEC9A), and XC chemokine receptor 1 (XCR1) [58,64,67–69]. The activation of toll receptor 3 (TLR3) in cDC1 produces IL-12, which induces the generation of type-II interferon (IFN-) [70] and is responsible for CD8$^+$ CTL responses. cDC1s also present exogenous antigens to activate CD4$^+$ T cells and thus provide CD4 help to boost CD8-mediated immune responses against tumors [71]. Besides that, cDC1s secrete IL-12 for activation of CD4$^+$ T cells and natural killer (NK) cells and thus contribute to anti-tumor immunity [72,73] (Fig. 2).

3.2 cDC2

cDC2s sdubset are more abundant in blood and lymphoid tissue and are heterogeneous in their phenotype and functions. Murine cDC2s express high CD11 band signal regulatory protein alpha SIRPα (CD172α), although these markers are not as specific as Clec9A and XCR1 cDC1s

Table 1. Surface markers and distinct functions of DC subtypes with specialized functions.

Dendritic Cell Subsets	Conventional type 1 dendritic cells (cDC1)	cDC2	Plasmacytoid Dendritic Cells (pDC)	Monocyte derived dendritic cells (MoDC)	Langerhans Cells (LC)	References
Surface marker for Mice	CD11c CD205 CD207 (Langerin) CD24 CD8α (Spleen/LN) CD103 (Tissue) Clec9A MHCII TLR3/TLR8 XCR1	CD11c MHCII CD172α (SIR Pα) CD11b TLR1/TLR6 CD301b (Tissue)	B220 PDCA1 Siglec-H Ly6C TLR7/TLR9 CCR9 CD317 Bst2 MHCII CD11clow	FcγRI CD14 FcεRI CD11b CD172 (SIRPα) CD206 CD88 MerTK Ly6C CD64 CD11c MHCII CD209 CCR2	CD11c NHCII CD207 CD326 CD11b CX3CR1	[55–57]
Surface Marker for Human	CD141 (BDCA3)	CD11c	CD123	CD11c	CD11c low	[55–57]
	CD11c	human leukocyte antigen DR (HLA-DR)	CD303 (BDCA2)	HLA-DR	HLA-DR	
	HLA-DR	CD172α	CD304 (BDCA4)	CD1c	CD207	
	XCR1 Clec9A	CD1c(BDCA1) CD11b SIRPα CD301a IRF4	HLA-DR B220 Bst2 CXCR3	CD14 CD206 CD11b CD64 CD209 CCR2 FcγRI CD14 FcεRI CD1a/CD1c CD172α (SIR Pα)	CD326 CD11b CD172α CX3CR1 CD1a CD1c	
Significant Characteristics	IL 12 initiation, The cytotoxic responses, and Cross-presentation	T helper 1 (Th1), Th2 and Th17 reactions. Assists CD4 anti-tumor immunity. Enhanced chemotaxis towards CCL21. Initiate IL10+, IL22+, IL4+ T cell polarization. Enhanced MHC-II expression	IFN- Interferon secretion. Antiviral immunity. Direct apoptosis of tumor cells	Functions of regulation in a stable state. Modulate the immune system against certain experimental tumor model	Sustain skin homeostasis via mediating tolerance. Cancer vaccinations. Elicit anti-tumor immunity	[55–57]

FcγRI, Fc gamma receptor I; PDCA1, plasmacytoid dendritic cells Antigen 1; NHCII, N-Heterocyclic carbene II; CCR9, C-C motif chemokine receptor 9; CX3CR1, chemokine (C-X3-C motif) receptor 1; MHCII, Major Histocompatibility Complex class II; MerTK, MER proto-oncogene, tyrosine kinase; TLR3/ TLR8, Toll like receptor 3/ Toll like receptor 8; XCR1, chemokine (C motif) receptor 1; BDCA3, Blood Dendritic Cell Antigen 3; HLA-DR, Human Leukocyte Antigen – DR isotype; CXCR3, Chemokine Receptor CXCR3.

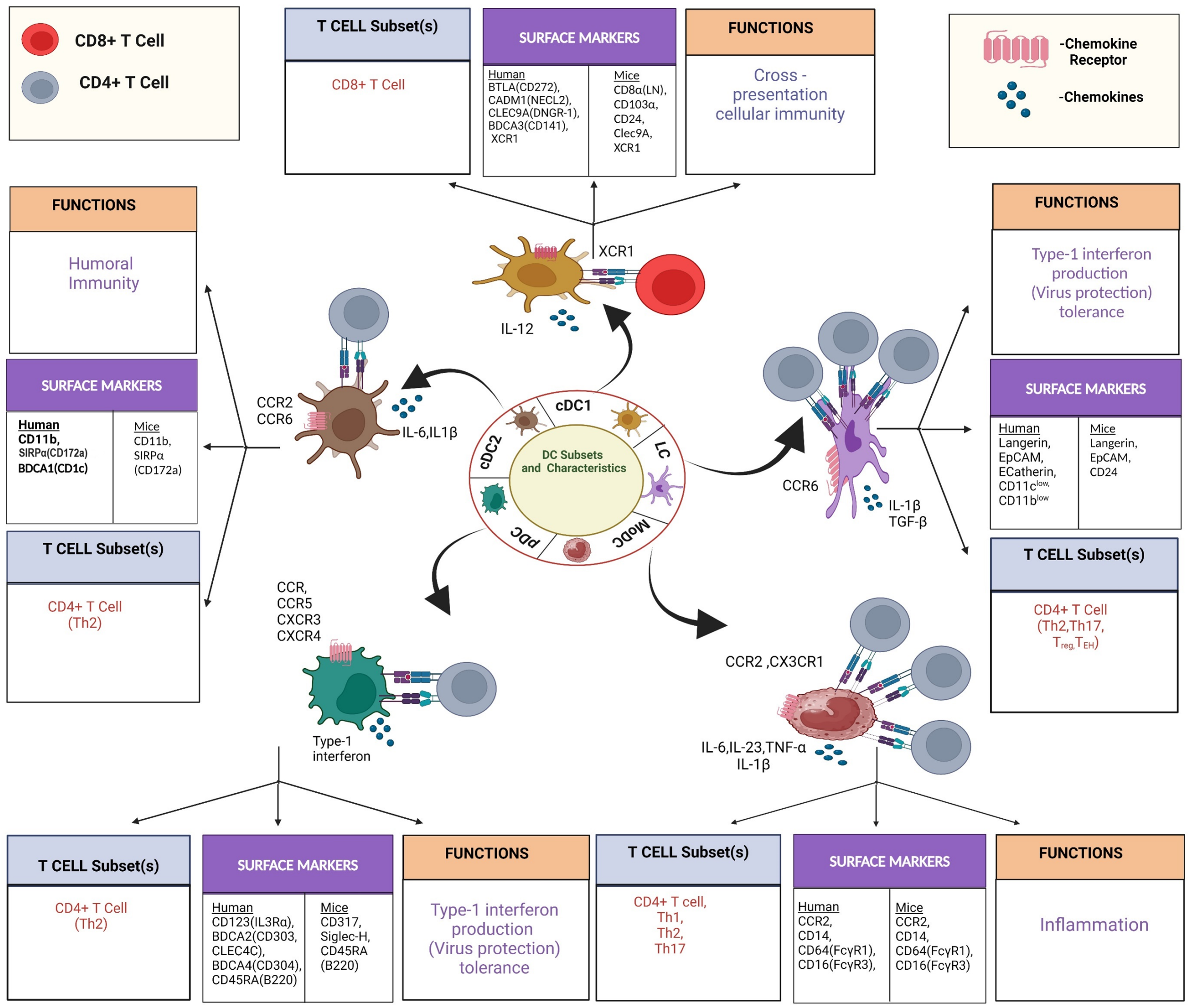

Fig. 2. DC subtypes with cellular interaction involving DC and other immune cells with cytokine and chemokine involvement in DC functions. Participation of major T cell subsets and the functions plus expression of surface markers of individual DC subtypes is presented. IL, cytokine interleukin; CCR, Chemokine Receptor; TGF, transforming growth factor-beta; Th 1, T helper 1; BTLA, B and T cell lymphocyte attenuator; CADM, Cell Adhesion Molecule; NECL, Nectin like protein; SIRPα, signal regulatory protein alpha; BDCA, Blood Dendritic Cell Antigen; TNF, tumor necrosis factor; Th2, T helper 2; CLEC, C-type lectin; EpCAM, epithelial cell adhesion molecule; ECatherin, epithelial cadherin. Created with BioRender.com.

[3]. CD301b, also known as macrophage galactose-type C-type lectin 2 (MGL2), is expressed by mouse cDC2. Human cDC2s are CD1c (BDCA1), CD115 (M-CSF), and CD172α (SIRPα) positive with a relatively nonuniform expression of CD11b [74]. cDC2 development requires TF, including the interplay of interferon regulatory factor 4 (IRF4), zinc finger E-box-binding homeobox 2 (ZEB2), Krüppel-like factor 4 (KLF4), reticuloendotheliosis viral oncogene homolog B (RelB), and neurogenic locus notch homolog protein 2 (Notch2) [75]. cDC2 also expresses several toll-like receptor (TLR) family members, including TLR2, TLR4, TLR5, TLR6, TLR8, and TLR9 [76]. cDC2s present exogenous antigens onto class II MHC molecules for priming CD4$^+$ T cells, and induce differentiation of either Th2- or Th17-based on Transcription factor (TF) [18,54]. cDC2s in tumors induce potent antigen-specific CD4$^+$ T cell responses upon its migration to tumor-draining LN [77,78]. Depletion of regulatory T cells (Tregs) restored cDC2-driven anti-tumor CD4$^+$ T cell functions [77]. In head and neck cancer patients, the abundance of cDC2s also correlates with anti-PD-1 immunotherapy, indicating its role in anti-tumor immunity [77]. Depending upon the expression of T-bet and RORt, cDC2s are further classified into two subsets with distinct metabolic

and immunoregulatory properties [79]. In mice, Brown *et al.* [79] identified two subsets of cDC2 in the spleen: the anti-inflammatory cDC2A, which expresses *T*-bet, and the pro-inflammatory cDC2B with signature expression of RORγt markers. Transcriptomic analysis of scRNA-seq data indicates two new subtypes termed DC2 and DC3 in human CD1c$^+$ cDC2 subset: DC2 subset of cDC2 expresses CD1c$^+$CD5$^+$CD14$^-$CD163$^-$ and the DC3 subset expresses CD14 and exhibits inflammatory and monocyte like gene signature [76]. By analyzing high-dimensional single-cell protein and RNA expression data, Dutertre *et al.* [80] demonstrated distinct phenotypic and functional subsets of human cDC2s depending on CD5, CD163, and CD14 and identified a distinct subset of circulating inflammatory CD5$^-$CD163$^+$CD14$^+$ cells termed as DC3 (Fig. 2).

3.3 pDC

Plasmacytoid DC (pDC) is derived from common DC precursors and also from common lymphoid progenitors [81]. pDCs express lymphocyte marker B220, but not the myeloid markers CD11b and CD33 [23]. PDCs rapidly induce antiviral immune response and produce significant amounts of type I and III IFNs via TLR-mediated activation in viral infection. They are also poor in antigen-presenting capacity to I T lymphocytes [82]. pDCs in mice can be identified as CD11c intermediate, Ly6C$^+$, B220$^+$, Bst2 (PDCA1, CD317)$^+$, and Siglec H$^+$ cells, and the human counterpart express human leukocyte antigen DR (HLA-DR), B220, CD303 (BDCA2), CD304 (BDCA4), CD123 (IL-3R) without CD11c [82–84]. pDCs also develop from common lymphoid progenitors (CLP) and are differentiated from IL-7R$^+$ lymphoid progenitors, which also differentiate into B cells [85,86]. IL-7R$^+$ lymphoid progenitors constitute the majority of murine mature BM and splenic pDCs [86] (Fig. 2).

pDCs cooperate with cDCs to induce optimal cross-priming and CD8$^+$ T CD8 T cell immunity under different settings [87,88], indicating that pDCs transfer antigens to cDCs and provide an explanation for the observed synergy [89]. pDCs are found to be tolerogenic and perform suppressive functions as they accumulate in multiple types of cancers like head and neck, ovarian, breast, and melanoma with poor prognosis [82,90–92]. pDCs induced the expansion of T regulatory cells (Tregs) through inducible T cell co-stimulatory ligands (ICOSL) [93]. Human and murine pDCs kill cancer cells directly through tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and/or granzyme B-dependent mechanisms [94,95]. pDCs may also induce anti-tumor immunity against human colon cancer [96]; activation of pDCs by TLR ligands induces anti-tumor immunity in multiple clinical trials, indicating the role of pDCs for cancer immunotherapy [97–100]. OX40+ pDC induces potent anti-tumor CD8$^+$ T cell function in synergy with cDC1s subset [101]. pDCs are also reported to be associated with poor prognosis in breast and ovarian cancer by promoting expansion and activation of Treg cells via ICOSL expression [102,103]. pDCs activated by TLR7 ligands in mouse models of breast cancer exhibit anti-tumor properties and suppress tumor growth and proliferation *in vivo* [104]. TLR7 ligand-activated CD8α^+ pDCs demonstrated direct tumor cell killing mediated by granzyme B.

3.4 Monocyte-Derived DC (MODC)

Circulating blood monocytes under the inflammatory settings differentiated into inflammatory DC populations and are designated as monocyte-derived DC (MODCs) [105]. MODCs are a highly heterogeneous group of cells and share markers with monocytes, macrophages, and cDC2s. Unlike pDC and cDC, MODCs differentiated from Ly6C^{hi} monocytes in inflammatory sites through the CCR2/CCL2 axis, independent of Flt3L [18, 106]. Human MODCs express CD1c$^+$CD11c$^+$HLA-DR$^+$CD14^{int}CD206$^+$ while murine MODCs hasCD11b, CD11c, MHCII, CCR2, and CD209 with an intermediate level of Ly6C and CD64. For *in vivo* development, MODCs need macrophage colony-stimulating factor (M-CSF) but not FLT3L or GM-CSF and are dependent on IRF4 for differentiation [107]. MODCs are also generated *ex vivo* from human and mouse blood or bone marrow monocytes in the presence of GM-CSF and/or IL-4 for use in pre-clinical and clinical studies. MODCs play critical roles in anti-tumor immunity [108]. MODCs are inflammatory DC differentiated from monocytes during inflammation and infection, which are recruited in the inflamed zones for the removal of inflammation and then differentiated into macrophages [109]. A subtype of MODCs also includes TNF/iNOS-producing DCs (Tip-DCs) [110]. MODCs share functional similarities with both cDC1s and cDC2s, which include the expression of co-stimulatory molecules and cytokines. Like cDC1 and cDC2, MODC has the ability to present antigens to CD4$^+$ and CD8$^+$ T cells. MODCs promote the differentiation of CD4$^+$ T cells into Th1, Th2, and Th17 cells, as well as their potential to differentiate CD8$^+$ T cells into CTLs [111–114]. MODC-based DC vaccines have been developed against various cancers, including clinical trials with mixed results [115] (Fig. 2).

3.5 Langerhans Cells (LC)

LCs are DC subsets present in the skin that have the efficient migratory potential to drain lymph nodes. They share a common ontogeny with macrophages but function as DC. Developmentally, the origin of LC is traced to embryonic macrophage lineage precursors and not to common DC precursors [116]. LCs can also be formed under inflammatory conditions from circulating monocytes [117]. LCs share similarities in phenotype and function with cDCs as well as with tissue macrophages. Like tissue macrophages, LC undergoes self-renewal in the skin [118,119]. LCs express langerin/CD207, a C-type lectin that forms the Birbeck granules, and epithelial cell adhesion molecule (EpCAM) [120,121] serves as the first line of immunological defense [122]. LCs present antigens to both CD4$^+$ and CD8$^+$ T lymphocytes and are dispensable for cross-presentation for induction of CD8$^+$ CTL responses [65]. LCs also efficiently induce Th2, Th17, and T follicular helper (TFH) responses [123–125]. In LC-deficient mice, there are impaired Th2 responses and antibody production, while TH1 responses remain unaltered [126]. LCs also induce the differentiation of Treg cells [127]. LCs require transforming growth factor-β (TGF-β) but are not dependent on Flt3L for their development and maintenance. Transcription factors like Id2, PU.1, and Runx3 are implicated in the development of LC [128]. LCs, upon infection, maintain homeostasis, mediate immune tolerance in a steady state, and induce adaptive immune responses. LCs also reduce basal cell carcinoma and squamous cell carcinomas (SCCs) [129]. Clinical trials with LC loaded with mRNA-encoded tumor antigens have shown anti-myeloma immunity following autotransplantation [130,131] (Fig. 2).

4. Dendritic Cells and Tumor Microenvironment

DCs in the Tumor Microenvironment (TME) interact with other immune and stromal cells and lymphoid organs, resulting in induction or inhibition of DC functions and antitumor immunity based on the type of cells encountered. Damage-associated molecular patterns (DAMPs), predominantly intracellular proteins released from apoptotic dying cells, induce the generation of cytokines and activation of T lymphocytes [132]. Tumor cells evade IR by following strategies like preventing the infiltration of cDC1 cells in the TME and thus increasing its chance to survive [72]. In patients with ovarian and breast cancer, pDC function becomes aberrant with poor production of type I interferon accompanied by Treg differentiation [133,134]. Augmentation in infiltration, expansion, and activation of cDC1 control the tumors and response to immunotherapies via stimulation with NK cells or intratumoral delivery of XCL1 and sFlt3L, encoded in recombinant Semliki forest virus-derived vectors [72,135]. In a recent clinical study, PDL-1 expression was found to be significantly augmented in DCs located in TME and also in circulation. PD-L1 blocking relieved B7.1 receptors, which allow it to interact with CD28 and enhance the priming of T lymphocytes [136]. Anti-PD-1 immunotherapy depends on DC-derived IL-12 in association with IFN-secreting T cells [137]. DCs are also essential for the reactivation of circulating T memory lymphocytes [138]. Wingless-related integration site (WNT)/β-catenin pathway activation in tumors partly blocks the infiltration of cDCs and T lymphocytes by impeding the expression of CCL4, resulting in reduced CXCL10, limiting the CD8$^+$ T cells, leading to nonfunctional cross-priming episodes [139]. Necrotic tumor-derived prostaglandin E2 (PGE2) prevents immunostimulatory properties of DCs [140]. In hypoxic TME, overexpression of cyclooxygenase (COX) 1 and 2 (COX1 and 2) and PGE2 production prevents the accumulation and activation of cDC and thus increases the chance of immune evasion [141,142]. A conserved dendritic-cell regulatory program with immunoregulatory genes like *CD274*, *CD200*, and *Pdcd1lg2* was found to be deficient in blocking inflammation in spite of antigen uptake without stimulation of T cell activation [143]. Oxidized lipids in DC adversely affect the cross-presentation, likely due to the elevated expression of scavenging receptor MSR1 [144,145]. Chaperone HSP70 prevents the MHC-peptide complex from reaching the cell surface [145]. Poly I: C (TLR3, MDA5, and RIG-I. agonist) treatment causes elevated IFNα/β-related transcriptomic profile and increased infiltration of DC and T lymphocytes in mouse models of melanoma [146]. STING activation by agonists in the TME leads to potent and systemic regression of the tumor, leading to the maturation of DC via cytokines and chemokines [147]. Immunotherapy with checkpoint inhibitor (CPI) and administration of tumor-stroma-directed CCL4 recruit CD103$^+$ DCs and CD8$^+$ T lymphocytes in cancers that poorly respond to CPI-based immunotherapy [148]. cDC1 presence has also been associated with immunotherapy with checkpoint blockade, indicating that the composition of TME and infiltrating DC is critically important for the efficacy of checkpoint inhibitors [149,150]. Tumor-derived IL-6 and PGE2 convert cDC2 to suppressive CD14$^+$ DCs [151].

Prolong physical interactions of Tregs with DCs, an engagement which is significantly intense compared with DC-CD8$^+$ T cell association in the TME, results in upregulation of the immunosuppressive Indoleamine 2,3 dioxygenase (IDO) and reduces the co-stimulatory molecules on DC [152]. DCs also interact with NK cells, resulting in the generation of cytokines and chemokines, including XCL1, which allow the recruitment of cDC1 to the TME [72]. DC-derived cytokines like IL-12, IL-15/IL-15Rα complex, etc., stimulate NK cells and augment their function for the elimination of neoplastic cells [153]. The Cancer Genome Atlas (TCGA) analysis suggests that NK cell/XCL1/cDC1 gene signature is directly associated with better prognosis and survival in several types of cancer [72]. In breast cancer, tumor-associated macrophage (TAM)-derived immunosuppressive IL-10 contributes to the suppression of Tumor micro environment (TME) and simultaneous reduction of IL-12 secretion by DCs, resulting in dampened tumor-specific CD8$^+$ T cell activation [153]. Within the TME, activated CD8$^+$ T lymphocytes in the tumor help to form tertiary lymphoid structures (TLS), which recruit antigen-responsive T cells and facilitate DC-mediated activation, and are associated with better prognosis in many human cancers [154,155]. The TLS atmosphere incorporates multiple cell types, which include T and B cells and DC-Lamp$^+$ (CD208) mature DC subsets (including cDCs and pDCs). Infiltration of effector and memory CD8$^+$ T lymphocytes plus Th1 cells within the tumor suggests the importance of crosstalk between DCs and other cells for trafficking of CTL [156]. B cells in Tertiary lymphoid structures (TLS) of lung cancers showed DC-mediated promotion of antibody response against many TAAs and thus provide anti-tumor immunity [157]. DCs also communicate with stromal cells, including cancer-associated fibroblasts (CAFs), via WNT signaling [158,159]. β-catenin tumor cells cause suppression of CCL4 (CCR5 ligand) mediated by ATF3, resulting in defective cDC1 recruitment in the TME, and thus adversely affecting CD8$^+$ T cell priming against TAAs [160].

4.1 Tumor-Infiltrating DC Subsets (TIDCs)

Transcriptomic analysis demonstrated high frequencies of different DC subtypes in the TME compared to non-neoplastic tissue [161,162]. Several factors are responsible for determining the variability of DC phenotype and its function, which include tumor immunophenotype (hot versus cold), TME characterization, tumor stage, age, gender, histology, treatment history, and schedule. Qualitative and quantitative features specific to each DC subtype have been observed in breast cancer subtypes ("cold" versus "hot" tumors) [149]. The TME harbors ontogenically distinct DC populations with resistant effects on tumor malignancies [163]. Tumor-infiltrating DC states are conserved across solid human cancers as studied by meta-analysis of eight currently available scRNA-seq datasets revealing five different DCs regardless of tissue origin, genetic signatures of cancer cells, or composition of the TME [164]. Transcriptomic analysis in colorectal, lung, ovary, and breast cancers has shown infiltration of alternative cDC2 subtype with a Langerhans-like phenotype (CD1C, CD1A, and CD207), indicating a pan-cancer blueprint of heterogeneous TME [162]. Here, we document the recent status of each subset in relation to cancer.

4.1.1 Tumor Infiltrating cDC1

cDC1 (CD45$^+$CD141$^+$CD8α^+XCR1$^+$CLEC9A$^+$BATF3$^+$) is a rare population, representing <0.2% of infiltrating DC in human cancer [7,149,161]. Single-cell analysis suggests that cDC1 transcriptomic signature is present in lung adenocarcinoma, melanoma, and breast cancer [7,149,161,165,166]. A positive correlation exists between elevated expression of cDC1 transcript cell signatures and better prognosis of tumors [167,168]. cDC1 presence in TME also correlates with augmented levels of NK cell infiltration, which is responsible for increased survival and favorable clinical outcomes following anti-PD1 therapy in patients with melanoma [72]. cDC1 number and activity are impaired in ovarian and prostate cancer patients [169]. Systemic suppression of hematopoiesis or reduced production of FLT3 and G-CSF in some types of cancer leads to low infiltration of cDC1s [163,170,171]. Also, pancreatic cancer patients have defects in pre-DCs and cDCs in bone marrow and high levels of G-CSF in tumors [171]. Tumor intrinsic Wnt-β catenin signaling and Corelease by PGE2 the drive exclusion of cDC1 from the tumor [72,172]. Chemokine also modulates cDC1 recruitment intratumorally, leading to low frequency and directly modulating CXCR3+ effector T cell infiltration [59]. cDC1 expression of XCR1, CXCL9, and IL-12 are critical for breast tumor rejection [173]. NK cells also draw cDC1 in the tumor lesion aided by CCL5 and XCL1 and promote differentiation [72,166]. Additionally, cDC1s in TME express elevated CCR7 expression, predicting T cell migration and thus improving the outcome in patients with melanoma [6].

Enhanced IFN-α/β signaling in cDC1s is critical for cross-presentation and immunosurveillance in cancer [173]. cDC1s modulates tumoricidal response through the production of IFN-λ [174]. A high percentage of activated IFN λ+ cDC1s in breast carcinoma and melanoma correlates with better clinical outcomes and enhances the targetability *in vivo* [174]. Higher expression of PD-L1, T cell immunoglobulin, and mucin domain-containing protein 3 (TIM-3), and cytotoxic T lymphocyte antigen 4 (CTLA-4) on cDC1 was observed in human breast carcinomas [175,176]. Anti-Tim3 antagonistic antibodies improve chemotherapy by upregulating CXCR3 and its ligand CXCL9 expression in cDC1 in triple-negative breast cancer [176].

4.1.2 Tumor Infiltrating cDC2

CD1c$^+$CD14$^-$cDC2s infiltrate tumors and trigger CD4$^+$ T cell responses at draining lymph nodes [77,163]. Together with pDC, cDC2 constitutes 35% of cellular constituents in melanoma. In the TME, cDC2s show higher expression of CD1A, CD1B, CD1E, CD207, a"d FC"R1A and IRF8 [163,177,178]. cDC2 is associated with a positive prognosis and infiltrates abundantly in head and neck and non-small cell lung cancer (NSCLC) cancer patients with better clinical outcomes [77,177]. Treg depletion positively correlates with enhanced cDC2 percentage, aids in the induction of CD4$^+$ T cell responses, and protects against tumors [77]. cDC2 also induces CTL responses, indicating their potential in DC-based vaccination besides their role in Th17 activation and secretion of inflammatory cytokines, including IL-1β, IL-6, and IL-23 [163,179]. cDC2s have higher potential compared with cDC1 vaccination, which is more enriched with Myloid derived supressor cells (MDSCs) and tumor-associated macrophages (TAMs) and less dependent on CTL [163]. Patients with melanoma have dysfunctional cDC2s with high CD80 expression and production of IL-12p40/p70 at basal conditions, besides impairment in the generation of TNF-α upon TLR stimulation [180]. Higher frequency of CD14$^+$cDC2 was also reported in metastatic leukemia, melanoma, and carcinoma of the lung, colorectal, and breast [163,178,181]. In luminal breast cancer, tumor inflammatory population of DC has been identified as $CD11c^+CD14^+FCeRI^+CD5^+CD1c^+$ and are phenotypically related to DC3, and their presence is associated with the recruitment of $CD8^+CD103^+CD69^+$ memory resident T cells in the tissue [182].

4.1.3 Tumor Infiltrating pDCs

In TME, a cell population has been identified with high expression of *TLR9*, *IL3RA*, *CLEC4A*, *GZMB*, *LILRA4*, *IRF7*, and *TCF4* genes [177,178]. Following activation with TLR7/9, pDCs participate in IR via antigen presentation; however, it is weaker than the cDC subsets [183]. pDCs derived from IFN-α/β block tumor cell proliferation, the occurrence of angiogenesis and metastasis, and modulate the functions of other cells, including cDCs, T, and NK cells [184]. Intratumoral infiltration of pDC is responsible for the survival of colorectal and triple-negative breast cancer patients [178,185–187]. Tumor-associated peptide-loaded autologous pDC in melanoma patients induce specific $CD4^+$ and $CD8^+$ T lymphocyte function [188]. In humans, tumoral infiltration of pDCs is associated with the aggressiveness of tumor growth and failure of the immune system in neoplasias like oral and ovarian cancer [189,190]. pDC in TME contributes to lymph node metastasis in breast cancer via the CXCR4/SDF-1 axis [191]. In head and neck squamous cell carcinoma (HNSCC) patients, pDCs are readily recruited in the TME, and their high number is responsible for poor prognosis and shows reduced production of IFN-α generation upon stimulation with CpG-oligonucleotide [192,193]. This favors the expansion of Treg cells and abates tumor progression [134]. High expression of LAG3 in a pDC population has been documented in tumor-affected lymph nodes and in skin metastasis with reduced secretion of IFN-α and higher production of IL-6 [194]. pDC supports the progression of melanoma by promoting Th2 response and immune regulatory molecules like OX40L and ICOSL [93]. $ICOSL^+$ pDC infiltration in breast and ovarian carcinoma is associated with poor prognosis, leading to catastrophic progression of the disease [102,103]. OX40L co-stimulation in pDCs also exacerbates melanoma progression by polarizing the Th2 response besides promoting regulatory immunity [93]. A pDC subset having $OX40^{hi}ICOSL^{lo}$/null expression is also documented in HSCC, which enhances the priming of antigen-specific CDCs for $CD8^+$ T cell stimulation [104].

4.1.4 Tumor Infiltrating mregDCs

A unique DC type, characterized by the expression of maturation markers (MHC-II, IL-12, CD40, CD86, PD-L1 and 2) and immunoregulatory markers like CD200, CD274, and PD-L1 has been documented in human and murine non-small lung cancers [143]. This DC has been named DC3 [164], $LAMP3^+$ DC [195], $CCR7^+$ DC [162], or $BATF3^+$ DC [167]. High mregDCs are observed inside the tumor lesions and are positively associated with improved survival in patients with NSCLC and colorectal cancer [80,167]. mregDCs in tumors stimulate anti-tumor $CD8^+$CTLs or NK cells by IL-12, produced upon sensing IFN-γ derived from T or NK cells [73,137,143]. mregDCs in TME were upregulated PD-L1 expression, induced by Axl (the phagocytic receptor) and signalized by IL-4 secretion, suppressing IL-12 production in resistant tumors.

4.1.5 Tumor Infiltrating MODCs

MODCs represent $HLA\text{-}DR^+CD11c^+CD14^+$ in the TME derived from differentiation from the monocytes [196]. CCL2 neutralization or inhibition of colony-stimulating factor-1 receptor (CSF-1R) downscale monocyte infiltration in the lymph node or tumor lesions, reducing the recruitment of tumor-responsive T lymphocytes and downregulates anti-tumor immune responses [196]. APCs, like monocytes, are important for the PD1 blockade and act as a therapeutic target for binary or combination therapy [197]. MODCs in the TME are associated with the production of IL-15, which promotes Th1 responses [198]. MODC exerts tumoricidal effect via iNO production, serves as APC, and performs effector functions via the production of TNF-α and IL-12 (Th1 signature cytokines) [163,197]. Transcriptomic analysis revealed MODC accumulation in breast, lung, and colorectal cancers and correlated with the activation of $CD8^+$ T cells and positive response to treatment [177,178,196]. In colorectal cancer patients, MODC generation from monocytes is impaired, leading to defective immune response [199]. In the murine model of sarcoma, retinoic acid in TME polarized intratumoral differentiation of monocytes toward tumor-associated macrophages (TAMs) by downregulating the expression of IRF4 [200]. Lysosomes secreted in melanoma induce apoptosis in MODC and downscale the success of immunotherapy [201]. MODCs in patients with multiple myeloma are defective with respect to migration and the ability for autocrine secretion [202].

5. Effector Functions of DC: Cytotoxicity and Tumor Growth Inhibition

DCs are regarded as the sentinels and messengers of the immune system and are universally considered professional APCs, playing a fundamental role in anti-tumor immunity. DCs have the unique ability to acquire, process, and present tumor-derived antigens to T cells, as well as the potential to drive the differentiation of naïve T cells into activated tumor-specific effector cells. DC also engages in crosstalk in NK-T cells, anti-tumoral immunity, and B cell functions. In addition to innate and adaptive immune functions, DCs also functioned as direct cytotoxic effectors, including growth inhibition against various types of tumors. This DC function is less conventional and may be controversial since it goes against the documented origin and functions of DC in addition to induction, regulation, and mechanisms of tumoricidal functions. In recent times, these un-

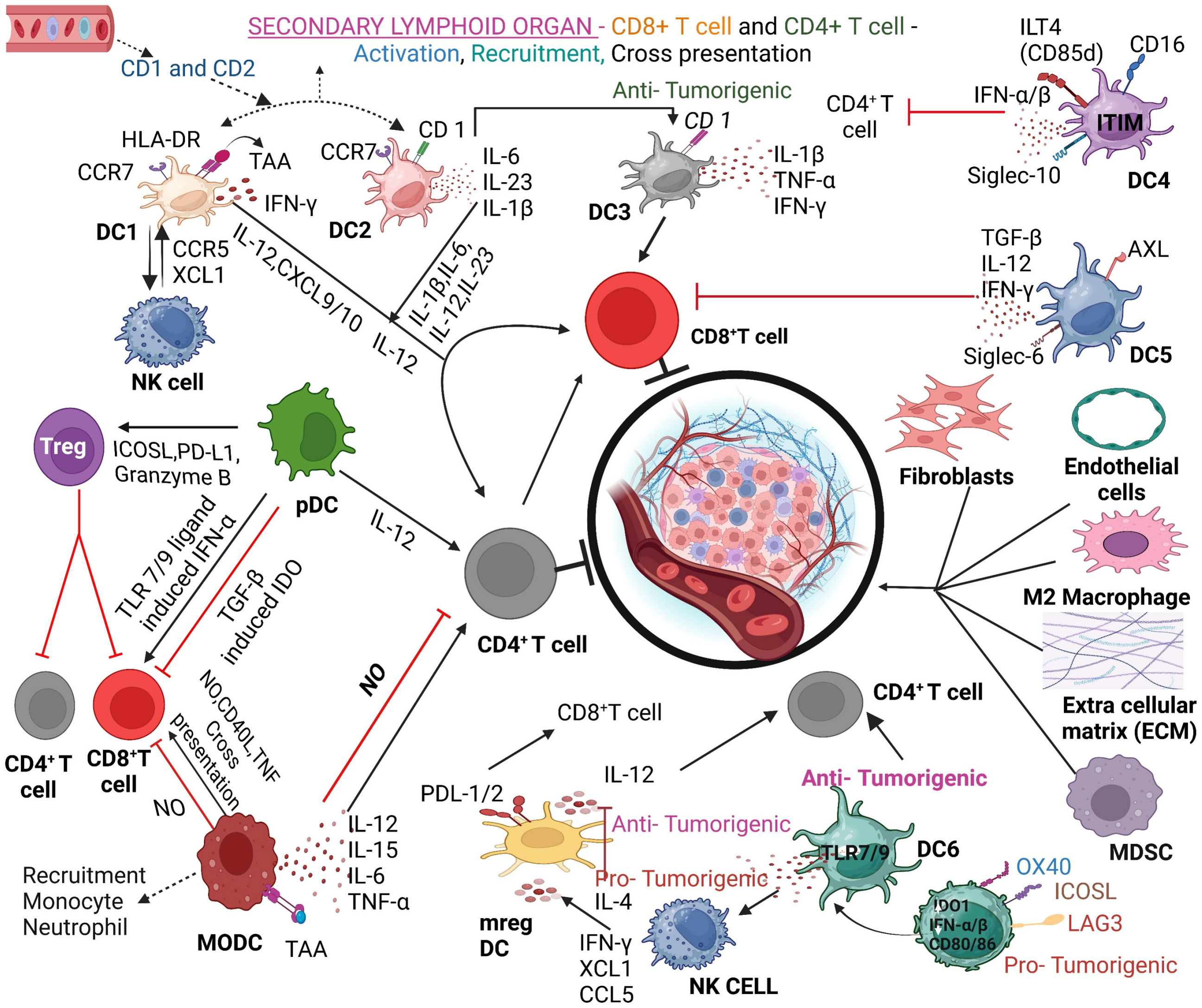

Fig. 3. DC and tumor microenvironment involving participation of DC subtypes and cellular interactions. DC subtypes and their crosstalk with cells in the tumor microenvironment (TME) are presented in the context of cytokine and chemokine-induced intervention of various functions presented. TAA, tumor-associated antigen; NK, natural killer; MDSC, myeloid-derived suppressor cell; ITIM, immunoreceptor tyrosine-based inhibition motif; AXL, a receptor tyrosine kinase; ICOSL, Inducible T Cell Costimulator Ligand; PD-L1, programmed death-Ligand 1; TAA, tryptophan aminotransferase; ICOSL, Inducible T Cell Costimulator Ligand; LAG3, Lymphocyte activation gene 3 protein. OX40 is a type of tumor necrosis factor (TNF) receptor, also called CD134. Created with BioRender.com.

conventional functions and another face of DC, in addition to their capability of antigen presentation, have become the subject of intensive research [203] (Fig. 3).

5.1 Killer Dendritic Cells

5.1.1 Killer MODC

MODCs are the widely studied cell type for demonstrating the functions of human DCs *ex vivo* (Table 1). Several differentiating and maturating agents, like pattern recognition receptors (PRR), can recognize and occupy antigens in order to trigger cytotoxic effector functions of human MODC. Cytolytic potential in these monocytic precursor cells has been reported (Table 1). CD14^{+} and CD16^{+} human monocytes stimulated with type I or II IFN, a ligand for TLR4 (LPS), TLR7, and TLR8 (R848), exert anti-tumor activity against a panel of tumor cell lines [204–206] (Table 1). TRAIL was implicated in the direct tumoricidal activity by human monocytes [204,207,208]. IFN-α skews monocytes into CD56^{+} expressing DC with potent functional anti-tumor activities *in vitro* and *in vivo* [209]. Anguille *et al*. [210] showed that IL-15-induced CD56^{+} myeloid DC possesses the potent capacity for antigen presentation and direct tumoricidal potential. CD40 ligation blocks TRAIL expression in MODCs; however, the cytotoxic potential of these DCs remains unaltered, suggesting the existence of a TRAIL-independent mechanism for cell death [211]. The possible mechanism of MODC-mediated tumor cell killing is related to the expression of DR1 and DR2, the TRAIL decoy receptors, and activation of anti-apoptotic mechanisms, including upregulation of FADD-like IL-1β converting enzyme protease inhibitory protein (c-FLIP) [208]. These findings indicate that human monocytes and MODCs, following appropriate stimulation, can function as cytotoxic effectors against tumor cells and, in chronic infection, act as immunoregulatory cells with T-cell killing potential. Monocyte-derived DC may also activate cytokine-induced killer (CIK) cells, including cytotoxic activity against various types of tumor cells *in vitro* and in animal models of cancer [212] (Fig. 3).

5.1.2 Killer Peripheral Blood-Derived DC

Killer blood DC has two main subsets, mDCs, and pDCs, which can be cytotoxic. In humans, the blood mDC subset is characterized as HLADR$^+$CD11c$^+$CD123 (IL-3Rα) dim cells. Also, blood mDCs may present as nonoverlapping subsets depending on the expression of blood dendritic cell antigen (BDCA)-1 (CD1c) and BDCA-3 (CD141) [213]. CD11c$^+$ blood DCs, stimulated with IFN-α or IFN-γ, lysed various tumor cell lines in a TRAIL-dependent fashion [214]. TRAIL is also implicated in blood DC-mediated cytotoxicity against cancer cells [215]. Tumor-infiltrating CD11c$^+$ blood DC synthesizes and expresses perforin and granzyme B, but not TRAIL, following TLR7 and TLR8 stimulation [187]. Granzyme B has also been implicated in IL-15-activated blood DC-mediated apoptosis [185]. The direct tumoricidal activity of DC was also documented by various other groups, including us, against various tumor cells. Activated human DC is also found to suppress various types of tumor cell growth *in vitro*, suggesting a unique role of DC in anti-tumor immune responses. DCs may exhibit direct anti-tumor effector functions in broad-spectrum human cell lines [216,217]. Immature DCs were reported to kill freshly isolated tumors following stimulation with NO2 inducing apoptosis, TNF, lymphotoxin alpha and beta (LT-α/β), Fas ligand, and TRAIL [215,218,219]. DC-mediated killing of tumor cells occurs at low effector/target ratios via apoptosis, which involves DNA break, mitochondrial dysfunction, and late membrane disruption. Killing of tumor cells occur both by cell-to-cell contact as well as by soluble mediators indicating that nature of tumor target cells may determine the effector functions of the DC. Maturation of DC with LPS or IFN-γ enhances cytotoxicity against tumor cells. Vidalain *et al*. [220] demonstrated that poly(I: C) stimulation of MODC causes increased cytotoxic activity by DC-derived TRAIL aided by type I IFN. It has been reported that disrupting the balance of pro vs anti-apoptotic makes the target cells sensitized to TNF family ligand-mediated apoptosis. Besides TRAIL, immature DC kills ovarian carcinoma cells by a FAS/FASL pathway, enabling them to sensitize tumor-specific CTLs [221]. MODC exerts tumoricidal activity in Fas-associated death domain-independent (FADD) but caspase-8 dependent, mechanisms [222]. The tumoricidal activity of TLR7/8-activated inflammatory DC demonstrated tumoricidal potential in a Ca^{2+}-dependent mechanism evoking exocytosis-dependent mechanisms [187]. Immature CD4$^-$CD103$^+$ rat DC induces rapid caspase-independent apoptosis in various tumor and nontumor cells independently of granule exocytosis or apoptotic TNF family ligands [223]. In rats, NKRP2, an ortholog of mouse and human NKG2D, is expressed on DC and induces DC maturation and triggers apoptosis in cancer cells via significant release of nitric oxide (NO) [224]. We have shown that human peripheral blood DC stimulated with TNF-α, IFN-γ, or IL-15 makes DC cytotoxic against a panel of breast cancer cells, including mammaglobin-positive and negative tumor cells [225]. Recombinant IL-15 was found to be unique in making these DC potent cytotoxic cells with significant efficiency against the breast tumor cells [217]. Human killer DCs, apart from their direct cytotoxic potential, can also present antigens to T lymphocytes, suggesting a strong rationale for their use in DC-based vaccination against cancer. IL-15 or IFN-α differentiated CD56$^+$ MODCs efficiently stimulate antigen-specific T-cell responses [209,210]. Autologous tumor lysate pulsed blood DC-based therapy in mesothelioma patients induce immunological response including eliciting cytotoxicity against tumor cells [226]. CD1c$^+$ myeloid DC produces IL-12 which activate I T cells and are fully equipped to cross-prime cytotoxic T-cell responses [227] (Fig. 3).

5.1.3 Killer Murine Splenic DC

Murine splenic DCs, following stimulation with recombinant IL-15 (rIL-15), express TRAIL, which induces cytotoxicity and growth inhibition against a murine lymphoma called Dalton lymphoma (DL) [228]. DC-mediated effector functions against DL tumor cells occur downstream to STAT3 since inhibition of STAT3 by cucurbitacin I (a selective Janus kinase/STAT3 inhibitor) augments the anti-tumor effects by DC-derived TRAIL. Recombinant IL-15 priming in combination with cucurbitacin I in DL tumor-bearing mice prolonged the survival, which partly restores the TRAIL expression in DCs following its downregulation in DC of untreated animals. In the case of chronic myeloid leukemia (CML), peripheral blood DC-derived TRAIL mediates anti-tumor activity via DR5 and not by DR4 as indicated by the effect of neutralizing anti-DR5 antibody, which reduces DC-mediated cytotoxicity [228] (Fig. 4A).

Splenic DC-derived TNF-α plays a major role in cytostatic (growth inhibition) and cytotoxic to DL cells in a dose-dependent fashion. This anti-tumor efficacy of DC was further increased in the presence of rIL-15 in combination with cucurbitacin-I in a doxorubicin-resistant DL lymphoma [229]. We have found that Doxorubicin-resistant DL is susceptible to DC-derived TNF-α following stimulation with cucurbitacin-I and makes it susceptible to splenic DC-mediated growth inhibition and cytotoxicity. Doxorubicin-resistant DL-bearing mice respond to therapy with high doses of cucurbitacin-I and rIL-15. DC-derived from these mice showed cytotoxicity and growth inhibition, leading to the killing of DL tumor cells [229] (Fig. 4B).

rIL-15 activated killer DCs, cucurbitacin I plusrIL-15 prolongs survival and cures mice with highly aggressive and metastatic DL lymphomas. It rebuilds impaired DC functions and restores CD8$^+$ T-cell-mediated immune functions in vaccinated mice. It also increases TRAIL and TNF-α expression in DCs and reinstates the cytotoxic potential of impaired DC in untreated mice. This study suggests that this strategy of binary therapy against the highly metastatic DL tumor may produce desired results, indicating its broad spectrum applicability and clinical relevance in other types of cancer [230] (Fig. 4C).

5.1.4 Killer pDC

pDCs are a unique lineage of cells, and they do not express CD3, CD19, CD14, CD16, CD56, and CD11c but do express multiple signature markers. This includes blood dendritic cell antigen-2 (BDCA-2, CD303), dendritic cell antigen-4 (BDCA-4, CD304), immunoglobulin-like transcript7 (ILT7), CD123 and CD4 and are restricted to bone marrow and in peripheral blood [231]. pDCs induce indirect cytotoxicity against cancer cells via induction of apoptosis and by anti-angiogenesis via signaling through a common IFN-α receptor, thereby inhibiting tumor cell proliferation *in vitro* and *in vivo* [232]. pDC or IFN-α depletion causes loss in TRAIL-driven tumor cell killing by CD14$^+$ monocytes, thus highlighting a crucial role for pDC-derived IFN-α in anti-tumor immune response [233]. Human pDCs also present antigens and act as potent stimulators of both CD4$^+$ and CD8$^+$ T cells [34,188,234]. Although cytotoxic, the requirement of High effector: target ratios for killing potential argues in favor of DCs' role and involvement in the acquisition and presentation of antigens for immune response. Wu *et al*. [235] demonstrated that TLR7 ligand (Imiquimod) activated pDCs can kill breast cancer cells *in vitro* through Granzyme Band TRAIL. These pDCs also activate CD8$^+$ T lymphocytes and NK cells and inhibit the growth of breast cancer cells.

Recent studies on clinical trials of DC-based immunotherapy reveal many novel aspects of this therapy against cancer. In a phase I trial, in newly diagnosed and recurrent glioblastoma (GBM) with autologous DC vaccine pulsed with lysate derived from an allogeneic stem-like cell line, it was found to be safe and well tolerated. This therapy increased median progression-free survival and overall lifespan for newly diagnosed and recurrent GBM patients. Besides that, a subset of patients developed a cytotoxic T-cell response as determined by the production of IFN-γ [236]. In another study, an autologous DC-based vaccine was shown to be safe and significantly improve progression-free survival in a randomized phase II clinical trial in patients with epithelial ovarian carcinoma [237]. Superior clinical responses to DC-based therapy were observed in patients with lower-than-median tumor mutational burden and scarce CD8$^+$ T-cell infiltration. Such responses were accompanied by signs of improved effector functions and tumor-specific cytotoxicity in the peripheral blood. This paper suggests that women with "cold" epithelial ovarian carcinoma may benefit from DC-based vaccination to jumpstart clinically relevant anti-cancer immune responses.

In acute myeloid leukemia (AML), high rates of relapses can be stabilized using a combination of GM-CSF and Prostaglandin E1 (Kit-M), which converts myeloid blasts into DC of leukemic origin. Stimulation with these DC *ex vivo* activates anti-leukemic immune cells. This therapy induces leukemia-specific immunoreactive cells (e.g., non-I, effector, memory, CD3$^+\beta7^+$ T cells, NK cells), whereas leukemia-specific regulatory T cells (Treg, CD152$^+$ T cells) were significantly decreased. The cytotoxicity and fluorolysis assay indicates a significantly improved blast lysis [238]. Pepeldjiyska *et al*. [239] demonstrated that immune suppressive (leukemia-specific) regulatory T cells were significantly downregulated after Kit-M triggered mixed lymphocyte culture going along with a (reinstalled) anti-leukemic reactivity of the immune system (as demonstrated with intracellular cytokine staining assay, degranulation assay which resulted in an increased anti-leukemic Cytotoxicity. In HER-2-expressing and over-expressing metastatic breast tumors, two sequential phase I/II clinical trials demonstrated the efficacy of a multiepitope DC vaccine with cytotoxic chemotherapy and HER2-targeted therapy. The therapy protocol was safe and showed tolerability, with Ag-specific immune responses before and after therapy [240]. Xiong *et al*. [241] reported that extracellular vesicles (EVs) from *A-Pas*ch iRNA-transfected DCs produce the cell-free anti-cancer vaccine DEXA-P. Treatment of immunocompetent cancer-bearing mice with DEXA-P inhibited tumor growth and prolonged animal survival. Cancer-specific transcription-induced chimeric RNAs can be exploited to produce a cell-free cancer vaccine that induces potent CD8$^+$ T cell-mediated anti-cancer immunity. This novel approach may have better scalability and genetic modifiability as well as enhanced shelf life compared to cell-based vaccines. It could be useful for developing cancer vaccines to treat malignancies with low mutational burden or without mutation-based antigens [241].

6. DC and NK Crosstalk in TME: Relevance to Cytotoxicity against Cancer Cells

DC-NK Cross Talk is at the center stage of immunosurveillance, where DC is endowed to activate the cytotoxic potential of NK cells. Cytokines like IL-12, IL-15, IL-18, and type-I IFN are secreted by activated cDCs and pDC, which potentiate NK cell proliferation, cytotoxic

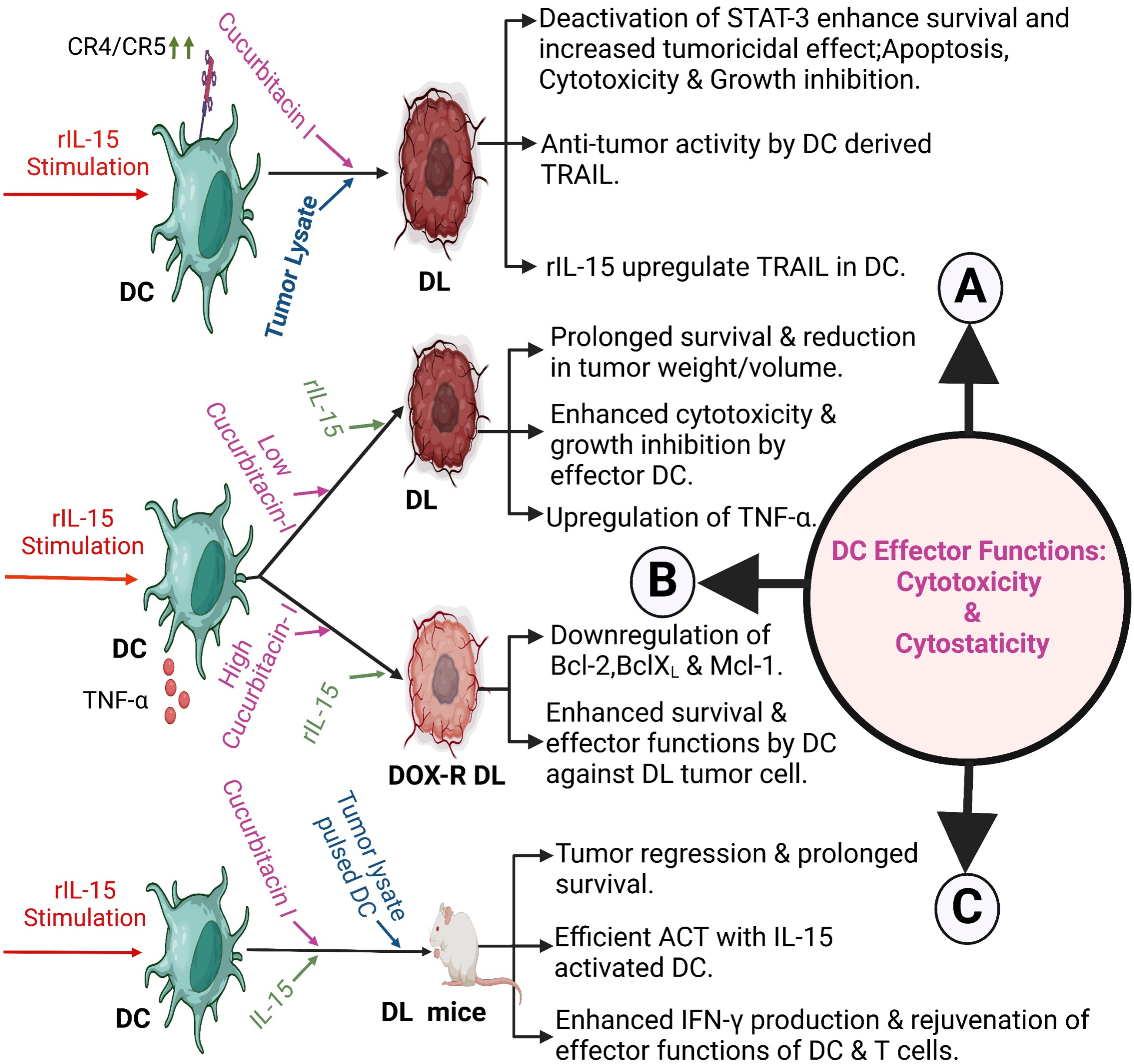

Fig. 4. Effector functions, including cytotoxicity and cytostaticity of splenic DC against experimental lymphoma. (A) IL-15 stimulation to splenic DC, in addition to cucurbitacin I treatment, enhances TRAIL-mediated tumoricidal response against DL lymphoma, inducing cytotoxicity, broad-range growth inhibition, and tumor reduction, plus increased survival [228]. (B) Assistance by high-dose cucurbitacin I and rIL-15 enhance cytotoxicity and cytostaticity in doxorubicin-resistant Dalton Lymphoma by downregulating Mcl-1 Bcl-2 and $BclX_L$ [229]. (C) Enhanced cytotoxicity and growth inhibition plus restoration of DC-mediated adaptive immunity in DL tumor-bearing mice treated with rIL-15 activated DC cucurbitacin I with additional priming with γc cytokine [230]. DOX, Doxorubicin; DL, Dalton lymphoma; STAT, Signal transducer and activator of transcription; rIL-15, recombinant IL-15; TRAIL, Tumor necrosis factor (TNF)-related apoptosis-inducing ligand; BclX, B-cell lymphoma-extra large; ACT, Adoptive cell therapies. Created with BioRender.com.

potential, and production of IFN-γ [232]. DC-NK cross talk is a two-way process where NK cells trigger and/or maturate DCs reciprocally and thereby promote a T cell-mediated anti-tumor immunity. This process is dependent on cell-to-cell contact, particularly involving NKp30 and pro-inflammatory cytokines, including TNF-α/IFN-γ [242]. NK cell-mediated 'quality inspection' of DC prime the protective CTL-mediated anti-tumor immune responses [243]. DC mediates the recruitment of NK cells in lymph nodes, which ensures early IFN-γ secretion and or induces IL-12 generation by DC, and thus promotes Th1 immune responses [244]. Cellular factors fostering DC-NK crosstalk are instrumental in the regulation of tumoricidal responses. Deficiency or silencing of Wiskott–Aldrich syndrome (WAS) protein in DC impaired DC-NK conjugate interaction, resulting in impairment in NK cell activation, growth of tumor mass, and augments metastasis of melanoma cells [245,246]. DC-derived IL-27 regulates the recruitment and activation of NK and Natural killer T cells (NKT) cells in anti-tumor immunity, supporting DC-NK crosstalk in tumoricidal function [247]. Shimizu and Fujii [248] showed that bone marrow DC (BMDC) immunization generates long-term NK cell-dependent anti-tumor immunity in an animal model of melanoma requiring endogenous DC. NK cells also contribute to DC-based immunotherapy in B16 melanoma [249]. DC editing by NK cells in the expansion of cancer-specific cytotoxic T lymphocytes (CTLs) has been reported in a mammary adenocarcinoma model in TS/A mice. In this paper, Morandi *et al*. [250] inoculated YAC-1 cells (NK sensitive) in mice, inducing NK cell activation *in vivo* and perforin-dependent elimination of total CD11c^{+} DC in the draining lymph nodes. A total reduction of CD11c^{+} DC is also accompanied by an improved capability in inducing tumor-specific CTL observed *in vitro* and *in vivo*. This study indicates that NK cells selectively destroy non-immunogenic DC in order to 'select' the immunogenic DCs for the expansion of CTLs and protect mice following the lethal challenge of cancer cells [250]. NK cells, activated by cetuximab-coated PCI-15B head and neck cancer cells, generate significantly higher production of IFN-γ, which promotes cross-presentation by DC in co-cultures [251]. Deauvieau *et al*. [252] reported that therapeutic monoclonal antibody Herceptin-coated HER2+ breast tumor cells (BT474) activate human NK cells and augment cross-presentation of tumor antigens by MODC-in an IFN-γ and TNF-dependent manner. DC expressed CD40L enhanced DC-NK interactions and maturation of DC, which increased the production of cytokines for stimulation and enhanced NK cell-mediated cytotoxicity against tumors [253]. Transduction of DC with recombinant vesicular stomatitis virus caused enhanced type I interferon (IFN-I) generation, and IL-15 aided activation of NK cells [254]. DC transduced with human adenoviral vectors induces activation of NK cells besides promoting CTL response to the melanoma antigens [255]. Tumor antigen-loaded DC and tumor cell-derived exosome induces antigen-specific CTL and NK cell plasticity, resulting in antitumor immunity *in vivo* [256]. Clinical intervention in advanced NSCLC patients by modified NK cells and DCs has shown encouraging response [257]. Tripple-negative breast cancer cells activate Cetuximab-activated NK cells on DC function, including antigen uptake and maturation, and enhance the DC-mediated cytotoxicity and IL-12 production. IL-15 stimulation increased the activation of NK cells and the maturation of DCs [258]. We also investigated the cooperative and cognitive interaction between DC and NK cells against DL lymphoma treated with a suboptimal dose of doxorubicin. Crosstalk between the DC and NK cells significantly reduced the proliferation of DL lymphoma in a dose-dependent manner. This crosstalk between DC and NK cells was regulated by rIL-15 and releases TNF-α, which is critical for the tumoricidal effects [259]. Further extension of the study on the stimulatory NK-DC axis in the TME reveals a critical role in stimulating CTL driving IR against DL lymphoma. Binary application of Adaptive cell therapy (ACT) with DC+NK cells and chemotherapy (doxorubicin) cures (95%) early-stage murine lymphoma, reinvigorates the immune system, including restoring the effector functions of DC and NK cells and restricting the regulatory T cells and reducing the expression of PD-1 positive T cells [260] (Fig. 5A,B, Ref. [259,260]).

7. Dendritic Cells and Immunogenic Cancer Cell Death

Cytotoxicity is also considered as a form of immunogenic cell death (ICD) incorporating efficient tumor antigen cross-priming. Studies have suggested that several anti-cancer agents, including chemotherapy and physical therapeutic modalities, exert immunomodulatory activities. These affect immune cells like DCs in the TME, modify the tumor cell immunogenicity via induction of immunogenic cell death (ICD), and release and expose a series of DAMPs through a well-defined spatiotemporal scheme [261]. Immune cells like DCs express pattern recognition receptors (PRRs), which recognize these DAMP sin stress, damage, or death. DCs play an essential role in the IR, triggered when malignant cells undergo ICD, suggesting functions of ICD inducers to stimulate robust T cell response aided and assisted by the occurrence of activated DC in TME [262–268]. All these indicate great potential and influence in synergy with other therapeutic approaches aiming at boosting efficient and robust anti-tumor immunity. The *ex vivo* ICD induction is a relatively recent strategy to understand the tumor immunological features providing significance of the role of TAAs, relevant molecules act as DC activating signals. ICD inducers like doxorubicin or radiotherapy can be combined with immunogenic TAAs in addition to the application of adjuvants encapsulated in nanoparticles, liposomes, or immunostimulatory complex for optimal delivery in DC vaccination [269,270]. Calreticulin (CRT), a Ca^{2+}-binding protein in the lumen of the endoplasmic reticulum (ER), acts as a strong "eat me" signal in ICD, which facilitates phagocytosis of dying cells by DCs. CRT-CD91 interaction triggers the activation pathways of NF-kB in DCs, releasing pro-inflammatory cytokines in the extracellular milieu and causing Th17 priming [271]. In non-small cell lung cancer patients, CRT expression is linked with higher infiltration of myeloid DCs (mDCs) and effector memory T-cells and correlated with favorable clinical outcomes [272]. Heat shock protein 90 (HSP90) and CD91 interaction activate DC and enhance the presentation of TAA to CTLs

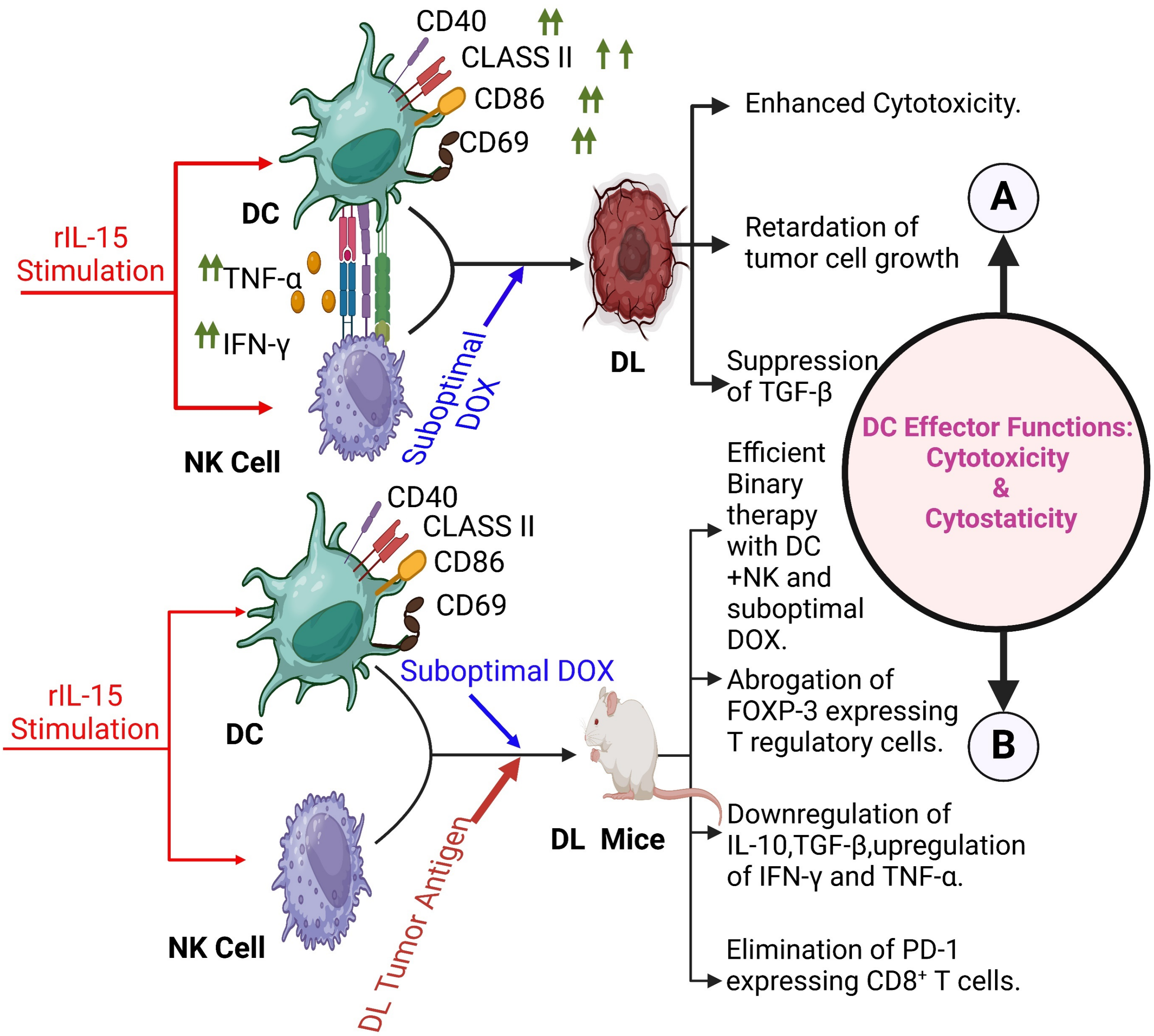

Fig. 5. DC-NK crosstalk in lymphoma. (A) Pharmacological intervention of suboptimal doxorubicin in DC-NK crosstalk mediated cytotoxicity and growth inhibition against DL tumor cells. Active participation of regulatory cytokine for the outcome of effector functions of dual cell intervention [259]. (B) Novel binary therapy with DC-NK combination, in addition to a suboptimal dose of doxorubicin, offers superior protection and cure response by enhancing effector functions of DC and NK cells and ablation of disease exacerbating T regulatory cells and PD-1 responsive $CD8^+$ T cells [260]. DOX, Doxorubicin; FOXP, Forkhead box P. Created with BioRender.com.

[273]. The binding of extracellular High mobility group box 1 (HMGB1) to TLR4 induces high-functioning cross-presentation of neoplastic antigens by DCs [274]. Dying cell-derived ATP during ICD in the extracellular milieu acts as a "find me" signal to attract DCs besides neutrophils and monocytes via the P2X7 receptor. Mice deficient in NLRP3 or P2RX7 are unable to mount organized and proactive adaptive immune responses during ICD [263]. This data indicates that immunogenic dying apoptotic cells are vital sources of both antigens and adjuvants, contributing to DC activation followed by effector T cell stimulation [275,276]. The process of cytotoxicity is a form of ICD cross-prime $CD8^+$ T cells, responsible for optimal activation of T cells and endowed with the repertoire of functional skills to recognize and eliminate neoplastic cells [277]. Thus, ICD- and DC-based immunogenic tumoricidal response is critical for translational advancement in cancer research and patient care.

8. Autophagy and Neo-Antigen Presentation by DC

Autophagy is a homeostatic and catabolic process responsible for the degradation and recycling of cellular components. Autophagy serves as cellular housekeeping and metabolic functions and constitutes a regulatory mechanism for several cellular functions. Dysregulation of autophagy is associated with tumorigenesis, tumor-stroma interactions, and resistance to cancer therapy. Autophagy affects the TME and constitutes a key factor in the function of APCs, macrophages, and T cells. Autophagy is found to be closely associated with the various functions of DCs under physiological and pathological conditions. Presentation of neo-antigens derived from tumor cells by both MHC-I and II in DCs results in functional activity of immune cells by creating T cell memory, as well as in cross-presentation of neo-antigens for MHC-I presentation and the internalization process. Autophagy plays a crucial role in immunotherapy via the presentation of neo-antigens constituting a potential target in order to strengthen or attenuate the effects of immunotherapy against different types of cancer. This is promising for long-term responses for patients who lack the ability to respond to immune checkpoint inhibitors for malignant tumors [278].

In Pancreatic ductal adenocarcinoma (PDAC) patients, the tumor cells are resistant to immune checkpoint inhibitors and have a significant reduction in MHC-I expression. Yamamoto *et al*. [279] showed that NBR1-mediated selective macroautophagy/autophagy of MHC-I represents a novel mechanism that facilitates immune evasion by PDAC cells. Autophagy or lysosome inhibition reinstates MHC-I expression, resulting in increased anti-tumor T cell response besides improvement in response to immune checkpoint inhibition in a syngeneic mouse model of transplanted tumors [279]. In addition, autophagy also influences the recruitment of APCs in TME and their maturation, leading to tumor evasion from immune surveillance via autophagy-driven activation of the STAT3 signaling pathway [280]. Autophagy also acts as a major regulator of MHC-I/II protein molecules, facilitating antigen presentation and targeting T-cell activation besides autophagy degradation of the molecules. MHC-II is degraded by membrane-associated RING-CH1 (March1) E3 ubiquitin ligase in myeloid-derived suppressor cells (MDSCs), while autophagic degradation of MHCI is induced by NBRI, resulting in tumor immune evasion. MHC-I degradation in DCs is mediated by adaptor-associated protein kinase 1 (AAK1), involving receptor-mediated endocytosis (RME), leading to impaired antigen presentation and T-cell stimulation [281,282]. In addition, opsonization in DCs autophagy induced by nanomaterials could be conducive and reasonable for a deeper understanding of the plasticity of DCs function, which may have a positive role in promoting tumor adaptive immune responses and constitute a potential strategy for novel DC vaccines [283].

9. Future Perspectives

It is essential to reduce the knowledge gap in the translational potential of DC-targeted therapies, and we need to have significant findings on the importance of the cDC1 subset for effector killer cell-mediated immunity against tumors. Major shifts should focus on the success of checkpoint inhibitor therapy to realize the binary therapy for durable, complete responses. Understanding of molecules that drive the antigen presentation and stimulation of DCs as important ‘adjuvants’ to augment the therapeutic efficiencies in poorly immunogenic tumors. Dissecting out of tumor driven immunosuppressive TME which modify the phenotype and functions of tumor associated DC (TADC) and thus prevention of dysfunctional or tolerogenic state and impaired T cell activation and priming in the TME. Understanding the roles TADC subset to enhance tumoricidal potential and sharpen the efficacy of existing immunotherapies including wide range applicability of checkpoint blockade in addition to adoptive cell therapies (ACT). Investigations are required for inadequacy in T cell priming for cold tumors (TME lacks T lymphocyte infiltration) and unresponsiveness to immune checkpoint blockade (ICB). Exploring new strategies for manipulating cDC1 aided CD8^{+} T cell cross-priming, including increase in the number of cDC1s and heightening their cross-priming capacity in tumors and tumor draining LNs in addition to efficacy of ICB and ACT. Understanding and bridging the knowledge gap in the activation signals and the immunosuppressive conditions within tumors to improve immune recognition for translational promise of DC-targeted therapies. Importance of cDC1 subset in antigen delivery to the lymph nodes for anti-tumor T-cell response needs extensive analysis. Exploration of cytokine blockers as potentially promising therapeutic agents against tumor progression irrespective of concern regarding toxicity. Up gradation in control rate of Immune checkpoint blockade (ICB) by targeting of cytokine blockers, reduction in toxicity, and optimizing their combination via application of steroid hormones. Multi center and interdisciplinary research with large samples are imperative for achieving this goal. Designing new dynamics for the clinical use of DCs in combination with neoantigen, targeting immune checkpoint inhibitors and conditioning the tumor immunosuppressive mechanisms. Rational and logical selection of adjuvants or maturating agents (e.g., TLR stimulation) for manipulation of the blood DC population may be a key approach for enhancing mechanisms. Establishment of biomaterial-based scaffolds for *in situ* recruitment and accentuation of functions of tissue-resident cDC1 subsets appears to be novel strategies with true potential for clinical translation. Exploration of immune suppression associated with TME appears to be relevant for success in therapy. Combination/binary application of DC vaccination plus appropriate anti-cancer treatments may modulate the TME for pro-inflammatory/stimulatory status for improving efficacy. Integration of ICD-based cancer treatment with *in situ* DC-vaccination or *in vivo* DC targeting needs further investigation. Inoculation of *ex vivo* generated autologous MODCs may resurge the prospect of ICD inducers and improve tumor antigen presentation to abnegate immune suppression in favor of immune stimulation. Standardization of DC-based vaccines for inducing a durable response and enhancing long-term survival. Optimization of next-generation DC-based vaccines for use in individual patients selectively based on their disease state. This includes harvesting enough tumor material; DC precursors; and sound understanding of highly heterogeneous tumors with TAAs and tumor-specific antigens (TSAs). High-throughput sequencing and bioinformatics analysis of big data for identification of novel and immunogenic tumor antigenic determinants, such as neoantigens. This includes TSAs specifically expressed in tumor for targeting by DCs *in vivo* of TSA derived peptide. Designing of flexible platforms for the targeting vector with self-adjuvant properties to enable realization of personalized vaccines. Development of new adjuvants or stimulants like TLR ligands for selective stimulation of $CD8^{+}$ CTL responses is critical for cancer immunotherapy in future despite the possibility of various adverse effects including fever, tissue damage and inflammation at the injection site etc.

10. Concluding Remarks

Despite significant advancement and breakthrough, the overall interpretation on DC-mediated cytotoxicity and cross-priming needs more study to decipher and link the precise molecular mechanisms governing ICD with particular relevance to T-and NK-cell cytotoxicity. As a professional APC, DCs are viewed as sentinels of the immune system which collect and phagocytose apoptotic cells resulting in elimination of tumor cells by cytotoxic effectors or spontaneous death. Tumors on the other hand opt for unsettling of the mechanisms of immunogenic cytotoxicity and cross-priming, responsible for destabilization and termination of malignancies. DCs are proficient in processing TAAs and are superiorly adept for cross-presenting them to CTLs. In addition, a growing and significant body of literature reports the direct tumoricidal activity of DCs, indicating that DC subsets are capable of detecting signs of cellular stress via expression of NKG2D and TRAIL. Beside identification of these specialized DC subsets for recognition and killing of the therapeutically targeted tumor cells, deciphering counteracting immunosuppressive mechanisms that may downregulate the efficiency of cDC1 cross-priming in tumor tissue may attribute for the development of precise biomarkers for immunotherapies. By mimicking or enforcing cytotoxicity in part of the tumor lesions, endogenous vaccines can be designed against complicated malignancies. Identification of strong and durable cDC1 maturation stimuli, including TLR agonist or co-stimulatory CD40 assault, could render super-effective results. With all the things considered, the interplay of cytotoxic lymphocytes and cDC1 mediated antigen cross-priming will be a fertile field of research to harvest novel biomarkers and immunotherapy in addition to available options. Cytotoxicity by DC is a form of ICD having significant implications for organ-specific neoplasias besides other dysfunctions like autoimmunity and viral infections.

Author Contributions

PPM, PC and PS contributed in conceptualization, and writing the review. PC and PS written the preliminary draft and contributed for analysis and making the figures. PPM contributed to overall supervision including editing of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by IOE grant No. R/Dev/D/IOE/ Incentive/2021–22/32275 to Partha Pratim Manna by Banaras Hindu University (BHU).

Conflict of Interest

The authors declare no conflict of interest.

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