Deciphering myeloid (progenitor) cell function and communication in (tumor) tissues

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Chapter

4

Immune checkpoints targeting dendritic cells for antibody-based modulation in cancer

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Abstract

Dendritic cells (DC) are professional antigen-presenting cells which link innate to adaptive immunity. DC play a central role in regulating antitumor T-cell responses in both tumor-draining lymph nodes (TDLN) and the tumor microenvironment (TME). They modulate effector T-cell responses via immune checkpoint proteins (ICPs) that can be either stimulatory or inhibitory. Functions of DC are often impaired by the suppressive TME leading to tumor immune escape. Therefore, better understanding of the mechanisms of action of ICPs expressed by (tumor-infiltrating) DC will lead to potential new treatment strategies. Genetic manipulation and high-dimensional analyses have provided insight in the interactions between DC and T-cells in TDLN and the TME upon ICP targeting. In this review, we discuss (tumor-infiltrating) DC lineage cells and tumor tissue specific "mature" DC states and their gene signatures in relation to anti-tumor immunity. We also review a number of ICPs expressed by DC regarding their functions in phagocytosis, DC activation, or inhibition and outline position in, or promise for clinical trials in cancer immunotherapy. Collectively, we highlight the critical role of DC and their exact status in the TME for the induction and propagation of T-cell immunity to cancer.

1. Introduction

The discovery of dendritic cells (DC) is a key breakthrough in the field of immunology (Steinman & Cohn, 1973). DC play an important role in the induction of protective adaptive immunity, including the antitumor T-cell response. Immature DC and DC progenitors can be recruited into the TME, where progenitors can differentiate into DC (Diao et al., 2010; Salmon et al., 2016), and depending on the molecular signals they receive, DC can be successfully or inefficiently activated. Migratory DC of the classical DC (cDC) type have the unique ability to transport tumor-associated antigens (TAAs) from the tumor microenvironment (TME) to the tumor-draining lymph nodes (TDLN) where they can initiate tumor-specific T-cell responses (Broz et al., 2014; Roberts et al., 2016). Primed T-cells then enter the TME to directly kill tumor cells or to modulate the state of resident immune cells, which may eventually lead to tumor control (D. S. Chen & Mellman, 2013). Type 1 cDC (cDC1) can be licensed by $CD4^+$ T-cells to mature, optimizing antigen presentation, costimulatory and other function that foster clonal expansion, effector- and memory differentiation of T-cells in both TDLN and TME (Borst et al., 2018; Ferris et al., 2020; Lei et al., 2023). A recent study supports the importance of the interaction between tumor-infiltrating DC and $CD4^+$ T-cells via MHC-II-restricted antigen presentation in preventing tumor-reactive $CD8^+$ T-cell dysfunction (Kilian et al., 2023). DC provide co-stimulatory signals in the TME that are crucial for further effector differentiation of $TCF1^+$ stem-like $CD8^+$ T-cell primed in TDLN (Prokhnevska et al., 2023). DC not only help maintain a $TCF1^+$ stem-like $CD8^+$ T-cell reservoir in TDLN (Schenkel et al., 2021) but also shape T-cell heterogeneity (Burger et al., 2021) in specific niches in the TME, such as specific DC-rich niches (Duraiswamy et al., 2021; Jansen et al., 2019), tertiary lymphoid structures (TLS) (Meylan et al., 2022) or "stem-immunity hubs" (J. H. Chen et al., 2023). Patients with progressive cancer lack these "immune niches" (Jansen et al., 2019) (non-inflamed tumors), suggesting that these "immune" niches in the TME (inflamed tumors) are one of the key determinants of cancer immune control.

While being pivotal for the induction of antitumor immunity, DC also have an essential function in the maintenance of immune tolerance (Steinman, 2012). This task is accomplished through multiple immune checks and balances (Pardoll, 2012), which include stimulatory immune checkpoint proteins (ICPs) that promote protective immunity and inhibitory ICPs that prevent immunopathology and autoimmunity (Webster, 2014). ICPs regulate diverse immune functions in a context-dependent manner.

In the TME, tumor cells via various factors and signal pathways exert suppressive properties which contribute to the abnormal regulation of DC. The key features of the negative regulation on DC functions (Wculek et al., 2020) by tumors include inhibiting DC differentiation/recruitment/maturation, interfering with TAA cross-presentation, modifying DC metabolism and compromising DC viability. DC can be polarized into immunosuppressive/tolerogenic states, that are incapable of migrating to the TDLN and have no ability to (cross) present TAAs, resulting in tumor growth and disease progression because of insufficient DC-mediated antitumor immunity. T-cell based tumor immunity is compromised when cDC are absent in the TME and/or cDC are not able to migrate to the TDLN (Broz et al., 2014; Roberts et al., 2016; Spranger et al., 2017). Thus, better understanding of ICP functions on DC is crucial for strategies to reinvigorate impaired DC functions in cancer patients, which will potentially lead to conversion of the TME from a non-inflamed to an inflamed state.

Using blocking antibodies against inhibitory ICPs, an approach called immune checkpoint blockade (ICB), is a key strategy in immune-oncology research and some approaches have successfully been translated to the clinic (Gaikwad et al., 2022). However, the response rate for ICB and agonists of stimulatory ICPs is still unsatisfactory (Mayes et al., 2018; Ribas & Wolchok, 2018). Until now, efforts have been made mainly on targeting T-cells, which are critical for successful immunotherapies (Pardoll, 2012; Wei et al., 2018). Innate ICP biology is a relatively new area of research and increasing evidence indicates that therapeutic intervention of ICPs on DC contributes to the efficacy of checkpoint therapies (Mayoux et al., 2020; Sharpe & Pauken, 2018). In this review, we discuss DC functions in tumor immunology and elaborate therapeutic potential of DC-intrinsic ICP currently under investigation for in the cancer context.

2. DC ontogeny and functions

2.1 Ontogeny and lineage relationship of DC subsets

DC development occurs in the bone marrow from self-renewing/multipotent hematopoietic stem cells (HSC) via more dedicated granulocyte/monocyte/macrophage progenitors (GMP), also defined as granulocyte/monocyte/osteoclast/DC progenitors (GMODP) (Xiao et al., 2015), and then common DC progenitors (CDP) (Álvarez-Errico et al., 2015; Ginhoux & Jung, 2014; K. Liu et al., 2009). A recent study demonstrates two distinct pathways of DC development that are dependent on IRF8 expression levels. $CD123^{+}IRF8^{high}$ progenitors give rise to plasmacytoid (p)DC, cDC1 and cDC2A subtype,

whereas $CD33^{+}IRF8^{low}$ progenitors give rise to cDC2B subtype and monocytes (Cytlak et al. 2021) (Fig. 1A). DC are classified into distinct subsets based on their ontogeny and phenotype with a certain level of tissue imprinting (Segura, 2022; Villar & Segura, 2020). In human peripheral blood and lymphoid tissues, there are four main DC subsets: pDC, cDC1, cDC2, and monocyte-derived (mo)DC. The homeostatic development of pDC, cDC1 and cDC2 lineages is controlled by distinct transcriptional factor (TF) networks (Anderson et al., 2021; Murphy et al., 2016; Segura, 2022). The key TFs that drive the development of pDC, cDC1 and cDC2 lineages are, respectively, *ZEB2*, *BATF3*, and *IRF4* (Anderson et al., 2021; Collin & Bigley, 2018) (Fig. 1A). These DC lineages are distinct from moDC, that are generated under inflammatory conditions (Dutertre et al., 2019; Merad et al., 2013; Villani et al., 2017). The four main DC lineages are also discerned by their key surface markers in combination with a common MHC-II expression. pDC express CD123, CD303, and CD304, while not expressing CD11c. cDC1 express CD141, XCR1, CLEC9A and a low level of CD11c. cDC2 express CD1c, SIRP-α and CD11c. moDC express CD14, CD206 and CD1c (Durand & Segura, 2015). Recent studies have revealed remarkable homogeneity of cDC1 as a subset present in all healthy and diseased tissues analyzed, whereas pDC and cDC2 populations are found to be heterogeneous (Cytlak et al., 2020; Segura, 2022; Villani et al., 2017). scRNAseq has demonstrated an overlap in the signatures of cDC2 and cDC1 that indicates a common function in T-cell activation (Zilionis et al., 2019). Some studies (See et al., 2017; Segura, 2022; Villar & Segura, 2020) suggest a DC progenitor or a "transitional" population between pDC and cDC2. This $AXL^{+}SIGLEC6^{+}$ DC type was first identified by Villani *et al*. as pre-cDC, which shared properties with pDC. Later, $CD163^{-}$ cDC2 derived from $AXL^{+}SIGLEC6^{+}$ pre-DC (Villani et al., 2017) were ontogenically distinguished from $SIRP\alpha^{+}CD163^{+}$ cDC2 that are different from but closely related to monocytes (Cytlak et al., 2020). pDC, cDC1 and $CD163^{-}$ cDC2 develop from $IRF8^{hi}$ DC progenitors, while $SIRP\alpha^{+}CD163^{+}$ cDC2 and monocytes develop from $IRF8^{low}$ progenitors. As the name suggests, moDC are derived from monocytes by definition. Mouse studies have shown that moDC are dependent on *IRF4, BLIMP1* and *AHR* (Goudot et al., 2017). Although gene signatures of *in vitro* generated moDC largely overlap with direct *ex vivo* isolated moDC, the moDC developmental pathway has not been defined in human (Balan et al., 2014;Goudot et al., 2017) (Fig. 1A).

2.2 Functions of DC

DC are the "sentinels" of the immune system (Reis e Sousa, 2006). They are specialized in sensing and phagocytosing microbes, infected- and dead or damaged cells, or fragments thereof. The pattern recognition receptors (PRR) that acts as sensors localize to the cell-surface, endosomes or cytoplasm, recognizing pathogen- or danger-associated molecular patterns (PAMP/DAMP), including DNA and RNA. DC regulate adaptive immune cell responses via ICPs and soluble mediators. The key function of DC is the regulation of antigen specific T-cell responses. DC can present exogenous antigens from dying or infected cells via MHC-I to $CD8^+$ T-cells in a process termed cross-presentation, and via MHC-II to $CD4^+$ T-cells. T-cell activation starts from the T-cell receptor (TCR)-mediated recognition of peptide/MHC complex. Apart from triggering TCR, DC can also express co-stimulatory ICPs, including CD80, CD86, CD70, 4-1BBL, OX40L and ICOSL to regulate T-cell activation, proliferation and differentiation (D. S. Chen & Mellman, 2013). At the same time, DC can also express co-inhibitory ICPs such as PD-L1 and PD-L2 (Sharpe & Pauken, 2018) to control the T-cell response and to balance between tolerance and immunity (Fig. 1B).

Depending on the status of T-cells, some ICPs on DC may have opposing functions. One important example is the CD80/CD86-CD28/CTLA4 axis. CD80/CD86 are costimulatory by binding to their receptor CD28 that is expressed on both naïve and activated T-cells. This interaction supports TCR-induced T-cell activation and division by transcriptional (Butte et al., 2012), epigenetic (DuPage et al., 2015) and metabolic changes, as well as cytoskeletal remodeling (Tan et al., 2014) (Fig. 1C). Of note, CD86 is reported to be the dominant ligand to CD28 co-stimulation for peripheral $CD4^+$ regulatory T-cells (Treg) proliferation and maintenance of a regulatory phenotype (Halliday et al., 2020). In contrast, CTLA4 that is constitutively expressed on Treg and transiently on activated conventional T cells, can attenuate T-cell responses. CTLA4 has a higher affinity for CD80 and CD86 than CD28 (Collins et al., 2002; Engelhardt et al., 2006; Halliday et al., 2020) and can reduce their surface expression via trans-endocytosis (Qureshi et al., 2011), which inhibits CD28 costimulation and thereby T-cell activation. CTLA4 can also enhance the expression of immunosuppressive IDO (Munn et al., 2004) and inhibit autophagy (Alissafi et al., 2017) in DC (Fig. 1D left). Furthermore, recent studies show in cis interaction between CD80 and PD-L1 (Chaudhri et al., 2018; Zhao et al., 2019) that form a costimulatory heterodimer that only binds to CD28 but not PD-1 and cannot be downregulated by CTLA4. Heterodimerization between CD80 and PD-L1

on the DC will also limit PD-L1/PD-1 interaction between DC and T-cells. Conversely, CD80 trans-endocytosis may increase the quantity of free PD-L1 on DC to augment T-cell inhibition via PD-L1/PD-1 axis (Tekguc et al., 2021) (Fig. 1D, right). Overall, CD80/CD86 serve as a switch between T-cell tolerance and immunity.

Each DC subset has its unique properties. The pDC is a major source of type I interferon (IFN-I) especially upon viral infection and reportedly can induce Treg responses via high expression of ICOS-ligand (T. Ito et al., 2007) or IDO (W. Chen et al., 2008). The T-cell priming capacity previously attributed to classically defined pDC is likely due to the contamination of $AXL^{+}SIGLEC6^{+}$ pre-DC that cannot make IFN-I but do make IL-12p70 (Villani et al., 2017). The cDC1 is the rarest of all DC subsets, constituting less than 0.05% of total blood cells (Lei et al., 2023). In the first scRNAseq study of human $HLA\text{-}DR^{+}CD14^{-}$ DC from blood performed in 2017 by Villani et al., cDC1 are confirmed to be a separate subset with cross-priming ability. Among the four human DC subsets, the cDC1 was found to preferentially relay $CD4^{+}$ T-cell help to $CD8^{+}$ T cells. In this process, cDC1 acquire a gene expression/protein signature highlighting pathways involved in antigen (cross)presentation and costimulatory molecule-, cytokine- and chemokine production (Lei et al., 2023). The cDC1 boosted by $CD4^{+}$ T-cell help is superior in cross-presenting cell-associated TAAs and induction of potent anti-tumor CTL responses (Ferris et al., 2020; Lei et al., 2023). The absence of IFN-I in the TME or the inability of cDC1 to sense IFN-I are sufficient to impair antitumor $CD8^{+}$ T-cell responses (Diamond et al., 2011; Fuertes et al., 2011). The cDC2 can induce polarization of naïve $CD4^{+}$ T-cells into T helper (Th)1, Th2 or Th17 cells upon exposure to extracellular pathogens (Durand et al., 2019; Merad et al., 2013). cDC2 may play a role in certain immunopathologies (Goudot et al., 2017), because $CD163^{-}$ cDC2 or $CD163^{+}$ cDC2 are found abundant in inflamed tissues and in the blood of patients with chronic diseases. In addition, both cDC1 and cDC2 are subdivided into migratory and lymph-node resident subsets. The resident cDC can receive antigen from migratory cDC (Ruhland et al., 2020). Finally, moDC have been used in most anti-cancer DC vaccine trials because large-scale *in vitro* moDC generation is an easy approach. However, the clinical outcome of moDC vaccines is not satisfactory due to their suboptimal intrinsic capacity to induce T-cell responses (Collin & Bigley, 2018; Osugi et al., 2002), which partially can be explained by their inability to relay $CD4^{+}$ T-cell help (Lei et al., 2023). Whether cDC outperform *in vitro* generated moDC in DC-based vaccination therapy remains to be investigated in patients.

2.3 Tumor-infiltrating DC classification and signatures

2.3.1 Tumor-infiltrating DC lineages

DC are the key immune component in the TME that kick starts the cancer immunity cycle (D. S. Chen & Mellman, 2013). The abundance of DC in the TME is critical for the therapeutic responses to ICB (Salmon et al., 2016; Spranger et al., 2017). Thus, understanding the biology of tumor-infiltrating DC in-depth is important for developing rational, DC-targeted immunotherapies. The advances in single-cell technologies allow researchers to determine fundamental properties of DC across different tumor types in great detail and in an unbiased manner (Cheng et al., 2021; Gerhard et al., 2021; Luca et al., 2021). Tumor-infiltrating pDC, cDC1 and cDC2 have their counterparts in peripheral blood (Del Prete et al., 2023; Gerhard et al., 2021; Villani et al., 2017) (Fig. 2A). Although the TME studied are heterogeneous, the transcriptional profiles of tumor-infiltrating DC show conservation across multiple tumor types (Cheng et al., 2021; Gerhard et al., 2021; Kvedaraite & Ginhoux, 2022). The cDC compose 15-20% of tumor-infiltrating myeloid population whereas the frequency of pDC in the TME is low and not consistent across different tumor types (Cheng et al., 2021) (Fig. 2B).

pDC are generally considered to be tolerogenic in the TME, due to their impaired IFN-I production capability and their role in $ICOS^+$ Treg expansion (Faget et al., 2013; Sisirak et al., 2012). cDC1 are critical for orchestrating antitumor responses due to their ability to cross present tumor-cell associated antigens, interact with multiple immune cells such as $CD4^+$ T-cells, $CD8^+$ T-cells (Spranger et al., 2017) and NK cells (Böttcher et al., 2018) both in the TDLN and the TME. cDC2 are an important source of costimulatory molecules in the TME for further effector differentiation of stem-like T-cells (semi) primed in TDLN (Prokhnevska et al., 2023). The role of cDC2 in cancer immunology is less established than that of cDC1, probably due to their high degree of heterogeneity (Fig. 2B) and likely depends on the local environment (Cheng et al., 2021).

2.3.2 LAMP3+DC/mregDC reflect a (tumor) tissue-specific "mature" cDC state

Since 2019, multiple transcriptome-based immune-cell profiling studies of the TME have revealed a tumor tissue-specific "mature" DC state. This state was originally identified by Zhang *et al.* (Q. Zhang et al., 2019) in hepatocellular carcinoma as "$LAMP3^+$ DC", and next by Maier *et al.* (Maier et al., 2020) in non-small cell lung cancer as mature regulatory DC (mregDC) and by Gerhard *et al.* (Gerhard et al., 2021) in lung, breast,

liver, colorectal and ovarian cancer as "tumor-infiltrating DC3". The "mature" DC state is present exclusively in tumor tissues without a similar counterpart in the blood (Gerhard et al., 2021), and most studies on immune cell communication in the TME currently use the term "mregDC" to refer to it (J. H. Chen et al., 2023; Cohen et al., 2022; Magen et al., 2022). Recently, Cheng *et al*. (Cheng et al., 2021) have further confirmed the conservation of this LAMP3^{+}DC/mregDC population across 15 human cancer types. Both tumor-infiltrating cDC1 and cDC2 have been shown to acquire a common "mature" gene expression program to become LAMP3^{+}DC/mregDC characterized by expression of immune stimulatory- (e.g., *CD40, CD86* and *CD83*), immune regulatory-, (e.g., *CD274* and *CD200*), migratory- (e.g., *CCR7*) and antigen processing- (e.g., *B2M* and *LAMP3*) genes (Cheng et al., 2021; Maier et al., 2020). We (Lei et al., 2023) recently found that "helped" cDC1 licensed by CD4^{+} T-cells overlap in their gene expression signature with DC_S3 state (Luca et al., 2021) identified in the TME of many human cancer types that are CD4^{+} and CD8^{+} T-cell infiltrated and show overall good survival and response to PD-1-targeting immunotherapy. Notably, "helped" cDC1 and DC_S3 contain the common signature of LAMP3^{+}DC/mregDC (Fig. 2C). Tumor tissue-specific "mature" DC are enriched within "immune" niches (Dieu-Nosjean et al., 2014; Goc et al., 2014; J. H. Chen et al., 2023) and associated with improved prognosis (J. H. Chen et al., 2023; Luca et al., 2021; Lei et al., 2023; Truxova et al., 2018; J. H. Chen et al., 2023), suggesting that they favor T-cell responsiveness.

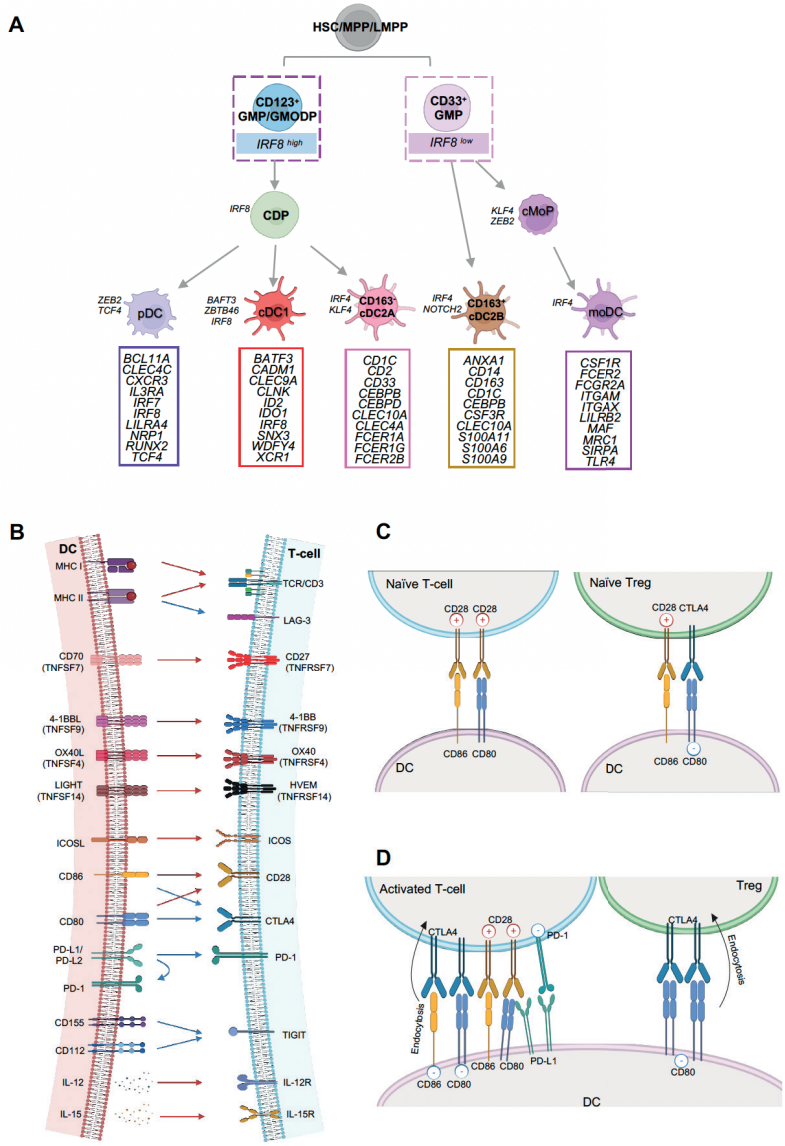

Fig. 1. Ontogeny and function of DC subsets. (**A**) Illustration depicting ontogeny and key transcription factors of pDC, cDC1, CD163^{-} cDC2A, CD163^{+} cDC2B and moDC. (**B**) Illustration depicting T-cell activation signals. Signal 1 (peptide/MHC complex), signal 2 (costimulation) and signal 3 (cytokines) are provided by DC for proper T-cell activation. At the same time, DC also provide co-inhibitory signals to control the T-cell response. Red arrows indicate T-cell activation, blue arrows indicate T-cell inhibition. (**C**) Illustration depicting CD80/CD86-CD28/CTLA4 interactions on naïve T-cells and naïve Treg cells. (**D**) Illustration depicting CD80/CD86-CD28/CTLA4 interactions on activated T-cells. HSC, hematopoietic stem cell; MPP, multipotent progenitor; LMPP, lymphoid-primed MPP cell; GMP, granulocyte/monocyte/macrophage progenitor; GMODP, granulocyte/monocyte/osteoclast/DC progenitor; CDP, common DC progenitor; cMoP, common monocyte precursor; moDC, monocyte-derived DC; Treg, regulatory T-cell.

More than 60% of the tumor infiltrating LAMP3^{+}DC/mregDC are cDC1-derived, even though cDC2 greatly outnumber cDC1 in the TME (Cheng et al., 2021). cDC1- and cDC2-derived LAMP3^{+}DC/mregDC still maintain their specific transcriptomic properties (Fig. 2C), thus suggesting the requirement of different external signals, and different functions for tumor-infiltrating cDC1- and cDC2 upon the acquisition of the "mature regulatory" gene program (Cheng et al., 2021). For instance, cDC1 but not cDC2 acquire an activation/maturation signature after encountering activated CD4^{+} T-cells (Lei et al., 2023) in "immune niches" (J. H. Chen et al., 2023) within the TME, which is associated with antitumor immunity. cDC1-derived LAMP3^{+} DC also have higher expression of BTLA (Cheng et al., 2021) which could potentially induce Treg differentiation and result in immune tolerance (Jones et al., 2016; Simon & Bromberg, 2016). In the (treatment naïve) TME of responders to ICB, "stem-immunity hubs" have been identified that - in contrast to TLS - lack B-cells, where cDC1-derived LAMP3^{+}CCL19^{+}IL12B^{+} mregDC are most frequently adjacent to conventional CD4^{+} T-cells and Treg cells (J. H. Chen et al., 2023). In addition, the CXCL9^{+}CD163^{-} cDC2 subset is the dominant one out of six cDC2 subsets found in the TME that can differentiate into LAMP3^{+} DC. CXCL9^{+}CD163^{-} cDC2 have no counterpart in peripheral blood (Cheng et al., 2021), indicating their "imprinting" by the TME. cDC2-derived LAMP3^{+} DC downregulate CXCL9 and upregulate IDO1 upregulation upon acquiring the "maturation" program (Cheng et al., 2021), indicating an immunosuppressive function. Taken together, these findings indicate that both cDC1 and cDC2 can acquire tumor tissue-specific "mature" states that within the TME orchestrate adaptive immunity.

3. Candidate targets and currently targeted ICPs expressed by DC

As mentioned above, knowledge of tumor infiltrating DC biology helps us to find novel ICP targets for reinvigorating DC functions. DC can regulate immune responses via phagocytosis, antigen presentation, co-stimulation/inhibition, and cytokine and chemokine secretion. Therefore, harnessing ICPs which are involved in innate immune sensing, detection and clearance of cancer cells, activation and recruitment of T-cells is one of the promising areas in immune-oncology research. In this section, we first provide an overview of ICPs that directly act on DC to augment or inhibit their functions (**Fig. 3A**). Next, we discuss the mechanisms of action of several selected ICPs according to their functional categories: targets of phagocytosis (SIRPα and Siglec10), targets of immune activation (CD40 and IFN-I

receptor), and targets of immune inhibition (T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), triggering receptor expressed on myeloid cells 2 (TREM2), V-domain Ig-containing suppressor of T cell activation (VISTA) and CD155) (**Fig. 3B**). We also summarize the completed clinical trials targeting abovementioned ICPs (**Table 1**).

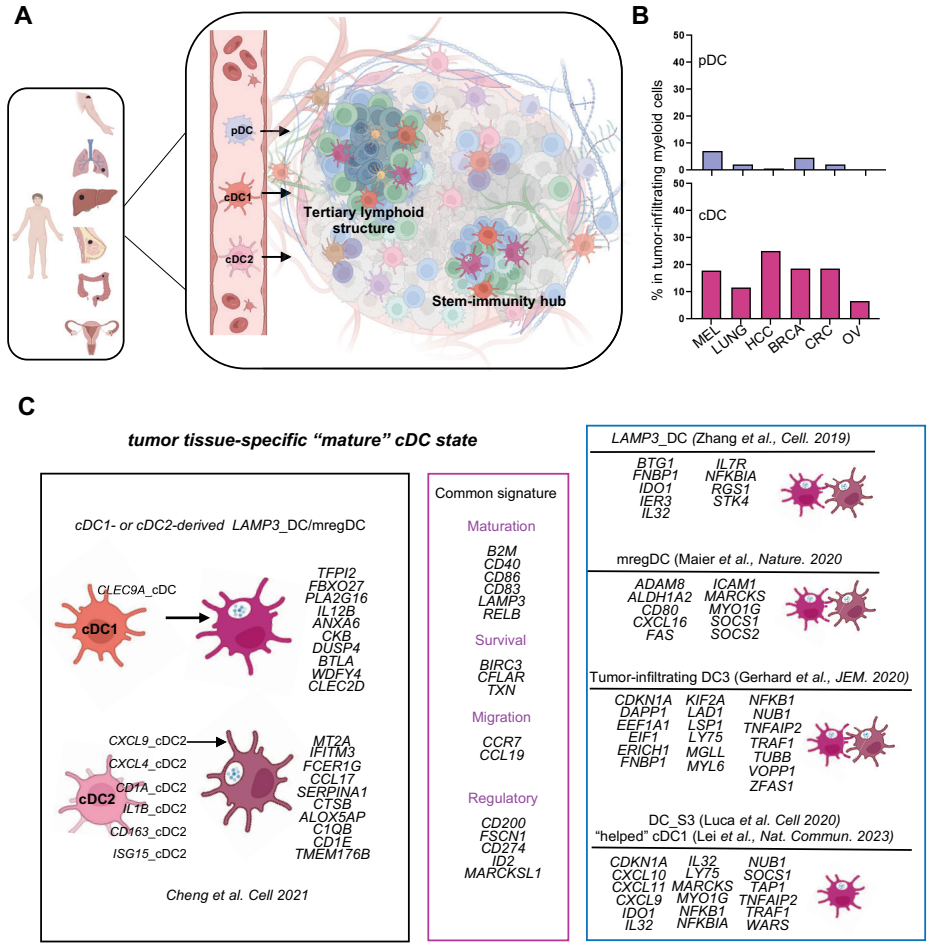

Fig. 2. Tumor-infiltrating DC classification and signatures. (**A**) Illustration depicting pDC and cDC migration from peripheral blood to tumor tissue and cDC presence in multi-cellular communities such as TLS and stem immunity hubs (left). (**B**) Frequencies of pDC and cDC tumor-infiltrating myeloid population (adapted from Cheng et al. 2021) (right). (**C**) Multiple studies have identified the tumor tissue-specific "mature" DC state albeit with different names. cDC1- and cDC2-derived "mature" DC maintain their specific transcriptomic properties (black box). Tumor tissue-specific "mature" DC identified by different studies share a common signature (purple box), but also display their unique properties (blue box). pDC, plasmacytoid dendritic cells; cDC, classical dendritic cells.

3.1 Targets of phagocytosis

3.1.1 SIRPα

SIRPα is one of the SIRP family proteins (Barclay & van den Berg, 2014), and a member of the immunoglobulin superfamily. It is expressed on many myeloid cell types, such as monocytes and cDC2 (Collin & Bigley, 2018; Merad et al., 2013). SIRPα interacts with CD47, which is broadly expressed across different cell types in the body (Reinhold et al., 1995), and highly expressed by cancer cells. SIRPα engagement results in the recruitment and activation of the SH2-domain-containing protein tyrosine phosphatases SHP-1 and SHP-2 in myeloid cells, resulting in the inhibition of phagocytosis, thus provide a 'don't eat me' signal (Barclay & van den Berg, 2014; Feng et al., 2019). The SIRPα- CD47 axis can be exploited by tumor cells to avoid their clearance by phagocytic cells (Feng et al., 2019), and thus serves as a targetable myeloid ICP in cancer immunotherapy. Macrophages (MΦ) (Bian et al., 2021; Lin et al., 2017; Tseng et al., 2013) are considered the main target of blocking SIRPα-CD47 interaction, but preclinical studies suggest that DC are the predominant drivers for T-cell cross-priming following this blockade (Hsieh et al., 2022; X. Liu et al., 2015). Tumor-infiltrating DC have increased SIRPα expression in HCC patients and silencing of DC-expressed SIRPα led to enhanced DC survival and TAA cross-presentation, cytokine and co-stimulatory molecule expression, thereby facilitating the cross-priming of $CD8^+$ T-cells (Hsieh et al., 2022; X. Liu et al., 2015). Furthermore, inhibition of SIRPα signaling in DC enhanced sensing of phagocytosed tumor mitochondrial DNA, which triggered a cGAS-STING-mediated IFN-I response (Hsieh et al., 2022; X. Liu et al., 2015). Importantly, blocking the SIRPα-CD47 interaction could reshape the TME into a proinflammatory tumoricidal niche and induced T-cell memory against an implanted tumor (de Silva et al., 2020; Hsieh et al., 2022). Other data indicate that blocking SIRPα-CD47 interaction alone has a minor impact on phagocytosis of tumor cells and therapeutic efficacy against solid tumors (Weiskopf et al., 2013). This might be due to lack of endogenous phagocytosis-activating signals on tumor cells (Logtenberg et al., 2020). In line with these observations, treatment with a high affinity SIRPα monoclonal antibodies (mAb) has little effect on breast cancer growth, whereas the combination with trastuzumab (anti-HER2 receptor mAb) results in a major tumor reduction *in vivo*, likely due to phagocytosis-promoting Fc receptor signaling (Weiskopf et al., 2013). Currently, there are multiple phase I/II clinical trials targeting SIRPα using bispecific antibodies (i.e., NCT04406623) or single specificity mAb in combination with other cancer treatments (i.e., NCT03783403) for both hematologic and solid tumors.

3.1.2 Siglec10

Siglec10 is one of the Siglec family proteins, and a member of the immunoglobulin superfamily. Siglec10 in human is broadly expressed on T-cells, B-cells, DC and MΦ (Yin & Gao, 2020). Siglec10 can bind to both CD52 (M. Clark & Cooke, 2013) and CD24 (Crocker et al., 2007). The binding of Siglec10 to CD24 triggers an inhibitory signaling cascade, which inhibits DAMP/PAMP-mediated inflammation, the cytoskeletal rearrangements required for cellular engulfment (Abram & Lowell, 2017; Crocker et al., 2007) and intracellular signal transduction in which cytokines, extracellular matrix, and cell adhesion molecules are involved (Crocker et al., 2007; Yin & Gao, 2020). Siglec-G, the homologue of Siglec10 in mice, can recruit the phosphatase SHP-1, which dephosphorylates the NADPH oxidase component $p47^{phox}$ and inhibits the activation of NOX2 on phagosomes (Ding et al., 2016). The ligation of Siglec-G leads to diminished formation and increased degradation of peptide/MHC-I complex via hydrolysis of exogenous antigens and phagosomal acidification. Thus, Siglec10 signaling is a potent antiphagocytic "don't eat me" signal. In addition, Siglec10-CD24 can interact with high mobility group protein B1 (HMGB1), which forms trimolecular complex on DC. This interaction negatively regulates HMGB1 activity and selectively inhibits NF-κB activation, leading to decreased production of IL-6 and TNFα (G.-Y. Chen et al., 2009). Siglec-G can also inhibit innate immune responses by promoting c-Cbl-mediated ubiquitination and degradation of RIG-I in DC (W. Chen et al., 2013). Many tumors overexpress CD24 (Barkal et al., 2019; Panagiotou et al., 2022), thus tumor cells can exploit the Siglec10-CD24 interaction to modulate mononuclear phagocyte functions, contributing an immunosuppressive TME. Preclinical studies have demonstrated that genetic ablation of Siglec10, and blockade of the Siglec10-CD24 interaction robustly augment the phagocytosis of CD24-expressing tumors (Barkal et al., 2019), increase antigen-presentation by DC and anti-tumor CTL responses(Ding et al., 2016) *in vivo*, leading to an increase in survival time. More importantly, there is a cooperative therapeutic effect when using combinatorial blockade of CD24 and CD47 (Barkal et al., 2019). However, in contrast to the SIRPα-CD47 axis, clinical trials (i.e., NCT04060407; NCT04552704) are targeting Siglec10-CD24 axis to harness its role in tissue homeostasis, aiming for a novel treatment of immune related adverse events caused by other ICB treatment.

3.2 Targets of immune activation

3.2.1 CD40

CD40 belongs to tumor necrosis factor receptor (TNFR) superfamily. It is constitutively expressed on antigen presenting cells (APC) such as DC, monocytes, MΦ and B-cells (E. A. Clark, 2014; Elgueta et al., 2009), as well as non-immune cells such as platelets, endothelial cells (Henn et al., 2001; Yellin et al., 1995), and certain tumor cells (Vonderheide & Glennie, 2013). CD40 interacts with CD40 ligand (L), which is transiently expressed by conventional- but not regulatory T-cells upon their TCR-mediated activation $CD4^+$ T-cells (Bullock, 2022). CD40-CD40L interaction is a key regulator of DC maturation and function, and cDC1 licensing by $CD4^+$ T-cells operates at least in part via CD40 signaling into cDC1 (Borst et al., 2018; Ferris et al., 2020). The recruitment of TNFR-associated factor (TRAF) proteins after CD40 ligation initiates signaling via the NF-kB, p38/MAPK and JNK (Jun Kinase) pathways (Pullen et al., 1999). In APC, this induces expression of molecules involved in antigen presentation such as MHC molecules, costimulatory molecules such as CD80, CD86, CD70, 4-1BBL and OX40L (Vonderheide & Glennie, 2013), and cytokines such as IL-12 (Schulz et al., 2000). CD40 signaling is also critical for sustaining DC survival via upregulation of Bcl-xL (Miga et al., 2001; Wu et al., 2022), which is a key anti-apoptotic molecule (Boise et al., 1993). All these effects are important for Th1 differentiation, $CD8^+$ T-cell and NK-cell effector function (Borst et al., 2018) and cDC1-mediated tumor rejection (Ferris et al., 2020). Notably, some *in vivo* studies suggest that next to CD40 signaling, additional signals are required to optimize DC for induction of T-cell responses (Krug et al., 2001; Schulz et al., 2000), and that CD40 on cDC1 is not required for initial antigen presentation but enhances expansion of tumor antigen-specific $CD8^+$ T-cells (Ferris et al., 2020). Overall, CD40 as a crucial signal for T-cell immunity is an attractive target for cancer immunotherapy. Currently, there are multiple phase I/II clinical trials (i.e., NCT04491084, NCT02482168, NCT04491084) using CD40 agonistic mAb as monotherapy or in combination with other cancer treatments targeting both hematological and solid cancers.

3.2.2 IFN-I receptor (IFNAR1/2)

The IFN-α/β receptor (IFNAR) is composed of IFNAR1 and IFNAR2 subunits that are ubiquitously expressed, albeit at highly variable levels (Weerd & Nguyen, 2012). The IFN-I signal is transmitted via ternary complexes, composed of IFNAR1 homodimers or IFNAR1–IFNAR2 heterodimers and one IFN-I ligand (Ali et al., 2019), and subsequent

activation of JAK-STAT signaling pathways (Weerd & Nguyen, 2012). Mouse studies have shown that innate immune cells are critical IFN-I targets during development of protective antitumor responses (Borden, 2019; Diamond et al., 2011). In particular, IFN-I acts on DC especially cDC1 to enhance their ability to migrate from peripheral tissue to LN via increased CCR7 expression (Borden, 2019), and to activate $CD8^+$ T-cells through upregulating costimulatory molecules such as CD80, CD86 (Diamond et al., 2011), chemokines and cytokines such as CXCL9/10 and IL-15 (Borden, 2019; Groom & Luster, 2011; Mattei et al., 2001), and molecules involved in antigen retention (Lorenzi et al., 2011) and cross-presentation such as MHC-I, β2m and TAP1/2 (Diamond et al., 2011; Heise et al., 2016). The critical role of IFN-I signaling in DC-mediated antitumor immunity is further demonstrated by Salmon *et al*. (Salmon et al., 2016) where they showed that IFN-I signaling was required for the therapeutic immunity induced by FLT3 ligand combining with additional poly I:C (TLR3 ligand) adjuvant. Currently, there are multiple strategies used in clinical trials to target the IFN-I pathway such as STING-dependent adjuvant (i.e., NCT04144140, NCT05321940), TLR3-dependent adjuvant (i.e., NCT02834052, NCT01976585) and IFN-I (i.e., NCT02615574, NCT02479230). The outcome of IFN-I signaling depends on many factors such as local environment and duration (Zitvogel et al., 2015). Therefore, results from clinical trials can provide critical information regarding which cancer types can regress and which cell types are important when promoting the IFN-I response in the human TME.

3.3 Targets of immune inhibition

3.3.1 TIM-3

TIM-3 is a member of TIM immunoregulatory proteins family and was first identified as a surface molecule expressed on IFNγ–producing T-cells. Now it has been detected on many other types of blood cells, including monocytes, MΦ (Y. Zhang et al., 2011), DC (especially cDC1) (Carenza et al., 2019) and NK-cells (Ndhlovu et al., 2012). Four ligands of TIM-3 have been identified so far, which are Galectin-9 (Zhu et al., 2005), phosphatidyl serine (Cao et al., 2007), HMGB1 (Chiba et al., 2012; Tang & Lotze, 2012) and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) (Huang et al., 2015). TIM-3 is involved in the phagocytosis and clearance of apoptotic material by DC (Carenza et al., 2019; de Mingo Pulido et al., 2018), inhibition of DC activation via dampening JAK or NF-kB signaling (Chiba et al., 2012; de Mingo Pulido et al., 2018, 2021)**,** and the expansion of myeloid-derived suppressor cells (Dardalhon et al., 2010). Originally, TIM-3 has been

investigated as an inhibitory ICP on T-cells in the cancer research field. However, a recent study has shown intriguing results in which conditional deletion of TIM-3 in both $CD4^+$ and $CD8^+$ T-cells only lead to a modest reduction in tumor burden (Dixon et al., 2021). Therefore, the effect of blocking TIM-3 on other cell compartments such as DC are increasingly being investigated. $CD11c^+$ DC especially $CD103^+LAMP3^+$ cDC1 were proven crucial in the therapeutic effect of TIM-3 blockade (Chiba et al., 2012; de Mingo Pulido et al., 2018, 2021). Blocking TIM-3 does not increase the expression of activation/maturation markers nor the expression of IL-12 in $CD103^+LAMP3^+$ cDC1, but enhances the expression of chemokines CXCL9/10, thereby promoting T-cell infiltration of tumors in a CXCR3-dependent manner (de Mingo Pulido et al., 2018). Further work from the same group has demonstrated that TIM-3 suppresses HMGB1-dependent endocytosis of extracellular DNA and the subsequent activation of the cGAS-STING pathway. Thus, blocking TIM-3 can improve the IFN-I response and chemokine CXCL9/10 expression by tumor-infiltrating $CD103^+LAMP3^+$ DC (de Mingo Pulido et al., 2021). Furthermore, conditional TIM-3 deletion is shown to prevent $CD11c^+$ DC from expressing a regulatory program, to increase the accumulation of reactive oxygen species and inflammasome activation, thereby facilitating the maintenance of effector- and stem-like $CD8^+$ T-cells (Dixon et al., 2021). Conditional TIM-3 deletion in monocyte/MΦ using $Lysm^{cre}$ or $Cx3cr1^{cre}$ mice showed minimal effect on tumor growth, confirming the unique role of DC in TIM-3 blockade as cancer treatments (Dixon et al., 2021). There are many ongoing phase I/II clinical trials using TIM-3 blocking mAb as monotherapy (i.e., NCT03489343, NCT03099109) or in combination with other cancer treatments (i.e., NCT03680508, NCT04370704), or using bispecific antibodies (i.e., NCT03708328) targeting mainly solid cancers.

3.3.2 TREM2

TREM2 is a transmembrane receptor of the immunoglobulin superfamily. TREM2 is expressed mainly on myeloid cells including monocytes and MΦ, osteoclasts and DC (Bouchon et al., 2001; Cella et al., 2003; Gonçalves et al., 2013). TREM2 expression can be induced by M-CSF, GM-CSF, IL-4, and IL-13 (Cella et al., 2003). In addition, TREM2 can be cleaved by disintegrin and metalloproteases 10 (ADAM10) and ADAM17, and then released in a soluble isoform (Wunderlich et al., 2013). TREM2 can bind to a variety of ligands such as bacteria, DNA, lipoproteins and phospholipids (Kober & Brett, 2017), and then a signal is transmitted through its association with the adapter proteins DAP12 and DAP10 (Peng et al., 2010). Although the role of TREM2 as an inhibitory ICP on tumor-infiltrating MΦ has been extensively studied (Bugler-Lamb

& Guilliams, 2020; Molgora et al., 2020; Park et al., 2023), how TREM2 regulates DC function is not yet clear. Studies have indicated an inhibitory role of TREM2 in DC upon TLR stimulation. TREM2-deficiency was shown to result in increased IFN-I responses, inflammatory cytokine secretion (i.e. IL-6 and TNF) and antigen-specific T-cell priming (H. Ito & Hamerman, 2012; Nakao et al., 2019). In addition, tumor-infiltrating $TREM2^{+}$ DC were shown to manifest a tolerogenic phenotype with reduced endocytic capability, lower expression of MHC-II, CD80 and CD86, impaired IL-12 secretion and increased IL-10 production (Yao et al., 2016). However, some studies have indicated a stimulatory role of TREM2 on DC. TREM2 signaling is reported to elicit a rapid rise of intracellular calcium concentration in DC, which in turn promotes DC activation and survival through PTK/ERK-dependent pathways (Bouchon et al., 2001; Hall & Agrawal, 2017). Notably, when comparing to CD40L or TLR stimulation, TREM2 does not induce upregulation of adhesion molecules (i.e., ICAM1) or cytokines (i.e., IL-12, IL-15) in DC, indicating a partial maturation status. The controversial results could be due to the heterogeneity of the bulk DC population studied. Thus, it is of interest to dissect different DC subsets to investigate the role of TREM2 in DC functions. Currently, there is one clinical trial investigating the effect of TREM2 blocking mAb in treatment of solid tumors (NCT04691375). Although the main target population is tumor-associated MΦ, this trial may also provide valuable information on how TREM2 regulates the transcriptome of different DC types in the TDLN and the TME.

3.3.3 AXL

AXL is one member of the Tyro3, Axl and MerTK (TAM) receptor tyrosine kinases (RTK). It is expressed in cells of the nervous, reproductive, vascular and immune systems (Lemke & Rothlin, 2008; Rothlin et al., 2015), and can be activated by the binding to vitamin K-dependent ligands—Gas6 and Protein S (PROS1) (Lemke & Rothlin, 2008; Rothlin et al., 2015). AXL is involved in inhibiting innate immune responses and has been associated with therapy resistance and poor clinical prognosis in cancer. It broadly inhibits both TLR signaling events such as NF-kB and MAPK pathways, and the feed-forward amplification of cytokine production. Correspondingly, AXL-deficient DC express elevated levels of MHC-I/II and CD86 and show hyperresponsiveness to TLR activation (Lemke & Lu, 2003; Lu & Lemke, 2001; Rothlin et al., 2007). AXL also inhibits inflammation by hijacking the IFNAR–STAT1 complex. AXL expression is increased upon IFN-I stimulation, while in turn AXL is crucial for the induction of SOCS1 and SOCS3 upon IFNAR activation, thereby

forming a negative feedback loop (Rothlin et al., 2007). In addition, PROS1 expressed by activated T-cells can bind to and activate AXL on DC, restraining DC activation and cytokine production (Carrera Silva et al., 2013). AXL on DC is also involved in phagocytic removal of apoptotic cells and debris in adult organs (Seitz et al., 2007; Subramanian et al., 2014), which is important for maintaining homeostasis. Notably, TAM signaling in DC can be paracrine and/or autocrine, in which AXL^+ cells also express the ligands, forming a feed-forward loop. In cancer, TAM signaling in tumor-infiltrating myeloid cells is shown to decrease antigen presentation and proinflammatory cytokine expression, leading to a suppressive myeloid microenvironment and inhibition of antitumor $CD8^+$ T-cell responses in mouse tumors refractory to combinatorial irradiation and immunotherapy (Aguilera et al., 2016). Correspondingly, AXL inhibition suppressed tumor growth by remodeling the TME toward stimulatory antitumor immune response via activation of tumor-infiltrating $CD103^+$ DC (Guo et al., 2017). In addition, combining AXL inhibition with PD-1 blockade had a synergistic antitumor efficacy (Guo et al., 2017), which is supported by a multi-omic study from metastatic melanoma patients showing that AXL modulates innate immune cells to dampen the immune response upon anti-PD-1 treatment (Hugo et al., 2016). Apart from targeting immune cells, TAM signaling can also favor tumor growth by promoting cancer cell proliferation (Linger et al., 2008), invasion (Y.-X. Zhang et al., 2008), stemness (M. Ott et al., 2012) and epithelial-mesenchymal transition (Goyette et al., 2018). However, there appears to be a paradox regarding the outcome of inhibiting AXL in cancer, as an anti-tumorigenic role of TAM signaling is observed in AXL-deficient mice where inflammation-induced colon cancer models have been used (Bosurgi et al., 2013). Thus, although targeting TAM signaling may be promising for cancer treatment, understanding the different functional effects of TAM signaling during immune cell–cancer cell interaction will be important for the design of future therapeutic targeting strategies. Currently, there are multiple phase I/II clinical trials (i.e., NCT03965494, NCT02729298) ongoing where AXL inhibitors are used for treating advanced solid tumors.

3.3.4 VISTA

VISTA bears features of both the B7 and CD28 families of immunoregulatory molecules (El Tanbouly et al., 2020). VISTA is constitutively expressed on both myeloid and lymphoid compartments (Xu et al., 2018), and its expression on myeloid cells is upregulated upon activation by TLR and cytokine stimulation (Bharaj et al., 2014) and under hypoxic conditions (Deng et al., 2019). Human VISTA has three identified binding partners, P-selectin glycoprotein ligand 1 (PSGL1), V-set and Ig domain-containing 3 (VSIG3) and

Galectin-9 (Im et al., 2022; Yuan et al., 2021). In addition, VISTA can act as its own ligand (El Tanbouly et al., 2020). Previous studies have shown that VSIG3 is the immunologically active partner for VISTA at neutral pH as opposed to PSGL1 at acidic pH (Johnston et al., 2019; Xie et al., 2021). Emerging data have indicated a central role of VISTA in controlling innate inflammation. VISTA may function to maintain quiescence in DC by regulating MHC-II expression (Lena Dübbel, 2020), cytokine and chemokine production (Broughton et al., 2019) at steady state. In addition, VISTA can regulate TLR-mediated proinflammatory signaling in DC. VISTA negatively controls TLR-mediated activation of MAPK/AP-1 and NF-kB signaling cascades in DC by regulating the polyubiquitination and protein expression of TRAF6 as well as phosphorylation/activation of extracellular signal-regulated kinases (Erk1/2) and c-Jun N-terminal kinase (Jnk1/2) (Li et al., 2017; Xu et al., 2019). The critical role of VISTA in regulating anti-tumor immunity has been demonstrated by genetic deletion of the VISTA gene or treatment with a VISTA-blocking mAb (Le Mercier et al., 2014; J. Liu et al., 2015; Xu et al., 2018). Preclinical studies have indicated that absence of VISTA alters the suppressive features of the TME by decreasing the presence of myeloid-derived suppressor cells and enhancing the activation state of DC with higher expression of MHC-II, CD80 and proinflammatory cytokines such as IL-12, IL-6 and TNFα. These effects collectively lead to a T-cell permissive TME that facilitates tumor rejection (Le Mercier et al., 2014; Xu et al., 2019). In addition, both preclinical (Le Mercier et al., 2014; J. Liu et al., 2015) and clinical (Calvo et al., 2018; Ott et al., 2017) (i.e., NCT01288911, NCT02812875) data indicate that combined VISTA blockade and other immunotherapy such as PD-L1 blockade show good safety tolerance and enhanced antitumor activity compared to monotherapy for treating solid tumors. Apart from using antibody-based blockade, increasing the pH or oxygen level in the TME might represent another strategy to reduce the immunoinhibitory activity of VISTA, given the fact that the TME is often hypoxic and acidic, which induces VISTA expression and binding to PSGL1 (Johnston et al., 2019; Xie et al., 2021).

3.3.5 CD155

CD155 is a glycoprotein of the immunoglobulin superfamily, and it is the only known molecule that poliovirus uses to enter cells (Koike et al., 1990). CD155 is constitutively expressed at low levels on DC, T-cells and non-immune cell types such as tumor cells (Dougall et al., 2017). CD155 expression on DC is upregulated upon TLR activation, which depends on MyD88, TRIF, NF-kB and IRF3 (Kamran et al., 2013; Pende et al., 2006). CD155 is the ligand for both the costimulatory receptor CD226 and the

coinhibitory receptors TIGIT and CD96. Multiple models have been proposed for how CD155-TIGIT interaction exerts immune inhibition, and most mechanisms involve DC-T-cell communication. For instance, CD155-TIGIT interaction competes with CD226 co-stimulation (Yu et al., 2009), interferes with homodimerization of CD226 (Johnston et al., 2014), and promotes Treg function (Joller et al., 2014). Notably, CD155 interaction with TIGIT is also reported to inhibit Erk activation in DC, which results in a shift in cytokine production from immune-activating IL-12 to immune-suppressive IL-10 thus making DC more tolerogenic (Yu et al., 2009). As CD155 interaction with its receptors is dynamic and the integration of costimulatory and coinhibitory signals from CD155 modifies T-cell and NK-cell functions in a context-dependent manner, CD155 is potentially an attractive target for immune-oncology. Both tumor-infiltrating myeloid cells and cancer cells have high expression of CD155, and blocking CD155 has been shown to increase effector function of $CD8^+$ T-cells and NK cells and reduce tumor metastatic burden (O'Donnell et al., 2020). Currently, there are several clinical studies (NCT05378425, NCT04965493) using monoclonal antibodies targeting CD155 as monotherapy and combinational therapy as cancer treatment. Notably, apart from using mAb, oncolytic poliovirus targeting CD155 expressed on both tumor-infiltrating DC and cancer cells (Brown et al., 2017) has also been used in clinical trials (i.e., NCT03712358, NCT01491893) as monotherapy or in combination with other cancer treatments, which showed promising antitumor activities (Beasley et al., 2021; Desjardins et al., 2018).

4. Concluding remarks

An important function of DC is to provide T-cell costimulatory and coinhibitory signals that act as ICP. Studies using mAbs and genetic manipulation have revealed that ICP expressed on DC can be targeted to facilitate antitumor immune response. In this review, we elaborate the ontogeny, lineage relationships and functions of DC and highlight the complexity of tumor-infiltrating DC and the importance of DC-rich niches in the TME in the clinical outcome of cancer patients. We also summarize the biological functions of different kinds of ICP that directly act on DC and have potential as targets in cancer immunotherapies. Improved knowledge of ICP function on DC will in our opinion be critical to understand how to promote tumor immunogenicity and to overcome tumor-associated immune suppression. Insight into the communication between specific DC types and T-cells in the TME, the molecular mechanisms involved and their relation to clinical outcome in patient studies will be very valuable in gaining the required mechanistic insights.

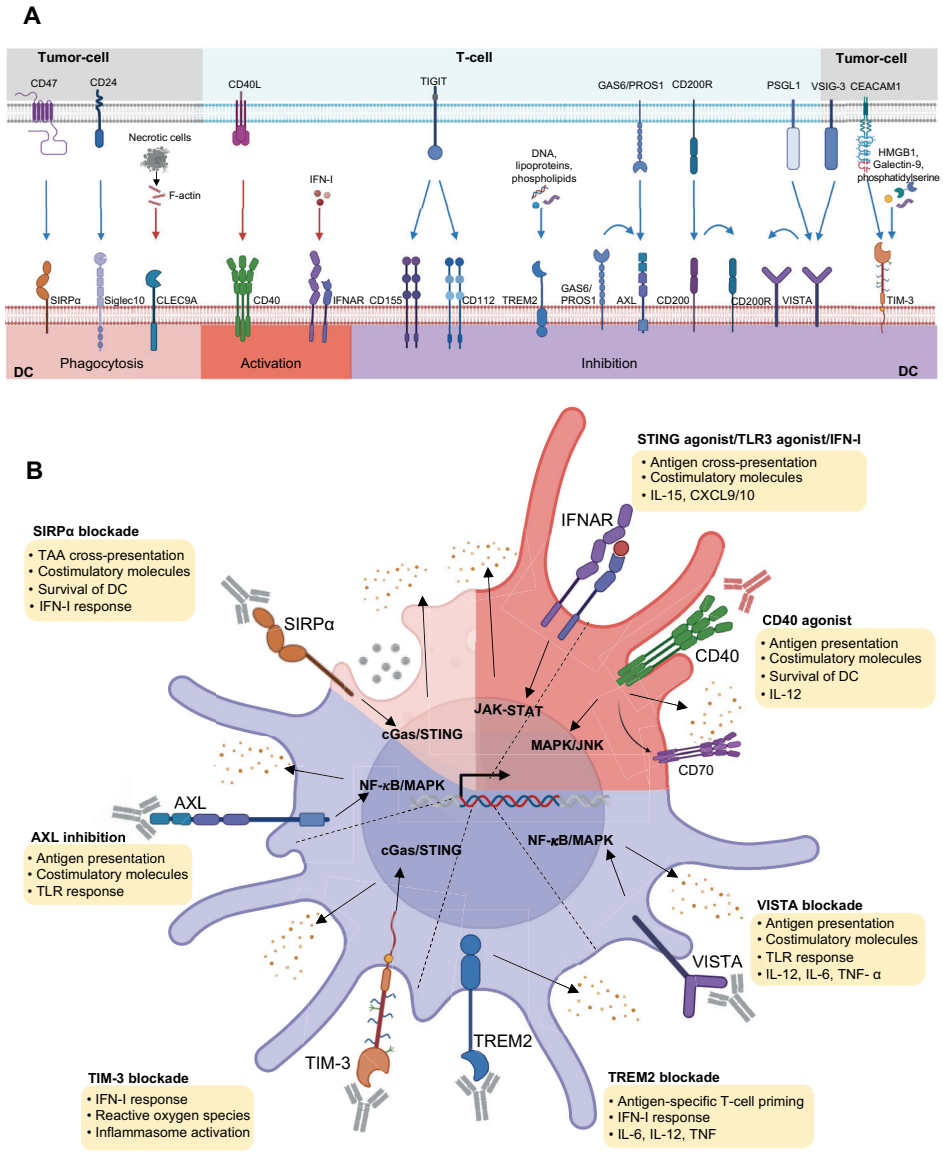

Fig. 3. Candidate targets and currently targeted ICPs expressed by DC. (**A**) Illustration depicting an overview of ICPs which directly act on DC to augment or inhibit their functions. The candidate ICPs are grouped into three categories: the target for phagocytosis (light pink), immune activation (red) and inhibition (purple). Red arrows indicate DC activation, blue arrows indicate DC inhibition. (**B**) Mechanisms in which SIRPα blockade, CD40 agonist, IFNAR stimulation, TIM-3 blockade, TREM2 blockade, AXL inhibition and VISTA blockade can promote DC function to facilitate antitumor immune response. SIRPα, signal-regulatory protein α; IFNAR, Interferon- α/β receptor; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TREM2, triggering receptor expressed on myeloid cells 2; AXL, AXL receptor tyrosine kinase; VISTA, V-domain Ig suppressor of T-cell activation.

Table 1. Completed clinical trails targeting dendritic cells

Target Molecule Drug	Effect of the drug	Indication	Phase	Status	Clinical Outcome	Reference
CD47/SIRPα						
SL-172154	Blocking the "don't eat me" signal and enhancing antigen presentation	OV, Fallopian tube cancer, Primary peritoneal carcinoma	I	Completed as bispecific therapy	The drug is well tolerated without major side affects	NCT04406623
CD40 agonists						
APX005M	Activating CD40, thereby activating the antigen-presenting cell	Solid tumor	I	Completed	Manageable safety profiles were shown alongside promising antitumor activity in untreated metastatic PDAC pts. APX005M 0.3 mg/kg was selected as the dose for a randomized Phase II study in which the primary endpoint is 1-year overall survival.	NCT02482168
APX005M	Activating CD40, thereby activating the antigen-presenting cell	NSCLC or Metastatic melanoma	I	Completed	NA	NCT03123783
GM.CD40L AND GM.CD40L.CCL21	Stimulating an anti-tumoral dendritic cell mediated immune response	Lung cancer, Adenocarcinomas	I/II	Completed in combination with tumor vaccine	GM.CD40L and CCL21 is well tolerated, but the combination did not show clear improvement over only using GM/CD40L or other treatments like chemotherapy.	NCT01433172
IFNAR/IFN-I pathway						
E7766	Sting agonist, thereby promoting the IFN-I pathway	Lymphoma, Advanced solid tumors	I	Completed	NA	NCT04144140

Target Molecule Drug	Effect of the drug	Indication	Phase	Status	Clinical Outcome	Reference
Poly-ICLC	Promote the IFN-I pathway	Solid tumor such as metastatic colon cancer	I/II	Completed as combination therapy with Pembrolizumab	Poly-ICLC is not effective in combination with Pembrolizumab for metastatic colon cancer	NCT02834052
Poly-ICLC	Promote the IFN-I pathway	Low-Grade B-cell Lymphoma	I/II	Completed as combination therapy with rhuFlt3L/CDX-301	NA	NCT01976585
Tumor blood vessel antigen peptide-pulsed alpha-type-1 polarized dendritic cell vaccine	Activate the immune system against stromal cells	(Metastatic) Breast cancer	I	Completed combined with gemcitabine hydrochloride	NA	NCT02479230
TIM-3 blockade						
Sym023	Activate multiple immune cells	Metastatic cancer, Solid tumor, Lymphoma	I	Completed	NA	NCT03489343
AXL inhibitor						
TP-0903	Activate myeloid cells, directly block tumor growth	Advanced EGFR Positive NSCLC, CRC, Recurrent OV, BRAF-Mutated melanoma	I	Completed	TP-0903 is well tolerated with a manageable safety profile.	NCT02729298
VISTA blockade						
CA-170	VISTA and PDL-1 blockade	Advanced solid tumors or Lymphomas	I	Completed	CA-170 showed a safe profile and lead to T-cell activation and an increase in circulating $CD8^+$ & $CD4^+$ T-cells	NCT02812875

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Disclosure of potential conflicts of interest

The authors declare no competing interest.

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