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The Role of Dendritic Cells in Cancer and Anti-Tumor Immunity

Ariel E. Marciscano[1], **Niroshana Anandasabapathy**[2,3,*]

[1]Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, United States.

[2]Department of Dermatology; Meyer Cancer Center; Englander Institute for Precision Medicine, Weill Cornell Medical College, New York, NY, United States.

[3]Immunology and Microbial Pathogenesis Program, Weill Cornell Medical College, New York, NY, United States.

Abstract

Dendritic cells (DC) are key sentinels of the host immune response with an important role in linking innate and adaptive immunity and maintaining tolerance. There is increasing recognition that DC are critical determinants of initiating and sustaining effective T-cell-mediated anti-tumor immune responses. Recent progress in immuno-oncology has led to the evolving insight that the presence and function of DC within the tumor microenvironment (TME) may dictate efficacy of cancer immunotherapies as well as conventional cancer therapies, including immune checkpoint blockade, radiotherapy and chemotherapy. As such, improved understanding of dendritic cell immunobiology specifically focusing on their role in T-cell priming, migration into tissues and TME, and the coordinated *in vivo* responses of functionally specialized DC subsets will facilitate a better mechanistic understanding of how tumor-immune surveillance can be leveraged to improve patient outcomes and to develop novel DC-targeted therapeutic approaches.

Keywords

Dendritic Cells; antigen presentation; cross-presentation; cancer; anti-tumor immunity; immunotherapy

1.0 Introduction

Dendritic cells (DC) comprise a diverse group of functionally specialized myeloid-derived antigen presenting cells (APCs) that orchestrate antigen-specific immunity and tolerance, including immunity to cancer and self-tolerance [1]. This specialization of DC to interpret

*Corresponding Author: Niroshana Anandasabapathy, M.D., Ph.D., Department of Dermatology, 1305 York Avenue, 9th Floor, New York, NY, 10021., Telephone: 646-962-9970, Fax: 646-962-0033, nia9069@med.cornell.edu.

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and respond to environmental stimuli includes detecting pathogens and transformed cells. The ability of DC to interpret these cues and to successfully capture, process and present both self and non-self antigens for T-cell priming determines the host's ability to discriminate self from non-self. Under steady-state conditions, the ability of DC to regulate innate and adaptive immunity carries importance for maintaining tissue homeostasis [2–4]. Alternatively, in an inflammatory context, such as infection or cancer, danger signals promote DC activation and/or maturation that culminates in an antigen-specific T-cell response that is necessary for pathogen clearance and tumor rejection [5].

The success of immune checkpoint blockade (ICB) was a transformative advance immuno-oncology [6]. It validated the concept that cancer immunotherapy targeting immune checkpoints that activate or may re-invigorate neoantigen-specific T-cells clones promote robust and durable anti-tumoral immunity [7]. Despite this, only a subset of patients respond to ICB. This benefit is generally ascribed to tumors that harbor a pre-existing intratumoral T-cell infiltrate and an immunologically permissive tumor microenvironment (TME) – a so called "hot" or T-cell-inflamed TME [8]. In turn, focus has shifted towards understanding the molecular-genetic and immunologic mechanisms that define distinct cancer-immune phenotypes and regulate T-cell infiltration into the TME [9, 10].

Because DC are able to initiate *de novo* T-cell immunity and are responsible for priming of antigen-specific T-cells they have been implicated as key regulators that guide response to ICB and other cancer immunotherapies [11, 12]. This is now supported by several lines of evidence that have associated the presence of intratumoral DC or the expression of DC-specific transcriptional signatures with the T-cell inflamed phenotype and CD8 T-cell infiltration [3, 13, 14], to favorable prognosis among patients with cancer [15, 16] and to response to various cancer immunotherapies [17–19]. Along these lines, a paucity of DC in the TME or dysregulated DC function correlate with poorly immunogenic tumor types [20, 21]. Accordingly, there is growing interest to harness the DC compartment to more effectively activate and mobilize T-cells into the TME in order to enrich the number of responders to ICB, particularly among patients with poorly immunogenic and non-inflamed tumors types. Emerging data suggests that DC are more directly linked to the mechanism of action of ICB and other cancer therapies than previously suspected. These mechanisms include ligation of DC-expressed immune checkpoints and co-stimulatory molecules as well as sculpting of adaptive immunity via immunogenic cell death (ICD) and activation of innate DNA or RNA sensing pathways [22–26]. This area of investigation has also led to novel insights regarding immunological barriers that limit DC abundance or subvert DC function that must be overcome to optimize DC-targeted strategies [27].

Here, we summarize an evolving understanding of DC biology as it shapes the behavior of DC in tumors. This includes discussion of mechanisms by which DC promote anti-tumor immunity, DC ontogeny and how DC subset diversity yields important functional implications. We also consider how the TME can disrupt these efforts as a form of immune evasion. We discuss how current cancer therapeutics influence DC function. Finally, we speculate on opportunities to exploit unique and potent characteristics of DC to improve cancer outcomes.

2.0 The diverse landscape and functions of Dendritic Cells

Since the discovery and initial characterization of DC by Steinman and Cohn in 1973 [28–31], there have been ongoing efforts to clarify the developmental origins and characterize unique functional aspects of DC subsets. Advances in available technologies, including the advent of single-cell RNA sequencing (scRNA-seq) and mass cytometry (i.e. CyTOF), facilitated a high-resolution view of DC ontogeny and the transcriptional programs that regulate DC development and differentiation [32–36]. How DC reconcile subset-specific developmental programing with the ability to differentiate in response to instructive environmental cues in a context-dependent or tissue-specific manner remains unresolved [37, 38]. However, this suggests a highly versatile and adaptable model where DC subtypes exists across a range of functional states. Dynamic changes in the local milieu may ultimately shape how diverse subsets of DC balance host immunity and tolerance [39, 40]. In the setting of tumor immune surveillance, DC continually sample antigen within the TME and sense danger signals via pattern recognition receptors (PRRs) that recognize damage associated molecular patterns (DAMPs) originating from malignant cells and/or pro-inflammatory cytokines [41]. These signals license DC to initiate tolerogenic or immunogenic actions in a coordinated and often subset-specific fashion [42]. In immune-edited tumors, malignant cells can evade host immune recognition through subversion of DC sensing and activation, dysfunctional antigen processing and presentation that ultimately lead to defects in T-cell priming or inappropriate induction of tolerance [43–45]. In addition to loss of tumor immunogenicity during immune escape, malignant progression of advanced tumors is also characterized by infiltration of DC that are overtly immunosuppressive and directly abrogate T-cell immunity [45].

2.1 Anti-tumor immune functions of Dendritic Cells

The cancer immunity cycle provides an important conceptual framework to understand how DC drive anti-tumor immunity that, when successful, leads to T-cell-mediated eradication of malignant cells [46]. Dendritic cells transport antigens to the tumor-associated draining lymph node (tdLN) and prime helper and cytotoxic effector T-cell populations as well as long-lived memory cells. Indeed, the quality of this initial priming event may often be overlooked but is likely critical to govern long-lived protective immunity in cancer as occurs in anti-viral memory responses [47]. To mount an effective anti-tumor response, DC are responsible for coordinated actions involving: (1) antigen capture and processing, (2) licensing and activation in response to sensing and integration of environmental cues, (3) maturation and migration to the tdLN, (4) antigen-presentation and priming of naïve T-cells, (5) recruitment of T-cells into the TME via DC-derived chemotactic gradients, and (6) *in situ* interaction with effector T-cells and local cytokine production in the TME [44].

Understanding DC function as it relates to their local site-specific development, orchestrated migration upon antigen capture, spatio-temporal relationships, and tissue or organ-specific compartmentalization provides a roadmap to understand the critical role that DCs play in initiating and sustaining anti-tumor immunity. In parallel, it is important to consider the functional specialization of DC subsets and how this division of labor is often partitioned in a subset-specific manner. Briefly, DC subsets are often classified by developmental origin

as conventional DC [including type 1 conventional DC (cDC1) and type 2 conventional DC (cDC2)], monocyte-derived DC (MoDC), plasmacytoid DC (pDC) as well as the emerging appreciation of a population, termed DC3. To this end, several scRNA-seq datasets of human tumor-infiltrating DC across a spectrum of tumor types as well as a recent in-depth meta-analysis by Gerhard et al. have demonstrated conservation of five distinct DC states across tumor types [48–53]. These five states include cDC1, cDC2, cDC2/MoDC, pDC and DC3 and represent the nomenclature that will be adopted henceforth. DC may also be defined by their tissue-specific compartmentalization as migratory DC (migDC) that possess capacity for trafficking between peripheral tissues and draining lymph nodes, and exist in a state of semi-maturation when leaving the tissues (in the absence of pathogens or other inflammatory stimuli). These are distinct from resident DC (resDC) that reside in peripheral lymphoid organs, such as the spleen and draining lymph nodes and seed from blood-based progenitors. While these classifications provide a useful operational framework to discuss DC subsets, they fail to address the immense complexity and functional overlap among DC subsets – particularly with respect to local environment conditioning cues and maturation status. Future efforts are needed to reconcile and harmonize our understanding of DC heterogeneity by both site and ontogeny, and the functional consequences of this heterogeneity [54]. For the purposes of the review, we first discuss DC function as it pertains to cancer and anti-tumor immunity which is followed by an in-depth discussion of DC subsets in section 3.0.

2.2 Dendritic Cell recruitment and activation within the tumor microenvironment

Within the TME, the localization and accumulation of DC is dependent on local production of growth factors and chemokines that promote DC recruitment, differentiation and/or expansion [55, 56]. Innate lymphoid cells and specifically natural killer (NK) cells are the predominant source of intratumoral FMS-like tyrosine kinase-3 ligand (FLT3-L) that instruct differentiation of conventional DC precursors and expansion of tumor-infiltrating cDC1 [18, 56]. NK cell production of XCL1 and CCL5, DC chemo-attractants, facilitate recruitment cDC1 into the TME [16]. Notably, XCL1 is the ligand for XCR1, a chemokine receptor that is exclusive to cDC1 – this suggests that intratumoral NK-DC crosstalk may bias towards cDC1 accumulation for tumor-immune surveillance [57, 58]. Tumor-derived CCL4, in contrast to NK cell-derived CCL5 (both CCR5 ligands), has also been associated with recruitment of cDC1 into the TME [59]. The presence of NK cells within the TME positively correlates with accumulation of cDC1 and responsiveness to anti-PD-1 ICB among patients with melanoma [18]. Innate immune sensing and consequent PRR pathway activation converge on tumor-intrinsic as well as DC autocrine production of IFN-I programs. IFN-I attracts and activates DC, providing necessary licensing stimuli for maturation and antigen presentation that ultimately link innate and adaptive immunity [60–62]. Of relevance to cancer therapy, DAMPs generated in response to ICD of dead or dying tumor cells also provide important licensing signals and maturation cues for DC in the TME. Further, the recent discovery of a diverse landscape of intratumoral microbiota poses additional questions regarding the potential contribution of microbe-derived pathogen-associated molecular patterns (PAMPs) as additional mediators of anti-tumor immunity via DC activation [63, 64].

2.3 Coordination of antigen capture, trafficking and presentation by Dendritic Cells

The efficiency of antigen capture and mode of antigen processing/presentation modulates the quality and type of T-cell response [65]. cDC1 are recognized for superior processing of exogenous and dead-cell associated antigens for cross-priming of $CD8^+$ T-cells to facilitate immunogenic tumor rejection [56, 66, 67]. cDC1 cross-presentation is WDFY4-dependent, whereas other groups also have suggested an indispensable role for SEC22B [68–71]. While MoDC also cross-present antigen, a divergent crosspresentation program is employed underscoring the notion that subset diversity has functional outcomes [72]. DC can also be classified by anatomic location/compartmentalization as lymphoid-resident or tissue-migratory. In the TME, tissue-migratory DC sample and process tumor-derived antigens. If proper licensing cues are present, an activated DC undergoes complete maturation and traffics MHC-loaded antigen to the tdLN. Maturation is a multi-faceted process whereby DC modify their morphology and cell surface marker expression to enhance antigen presentation and co-stimulatory interactions with T-cells in the tdLN. Mechanistically, migratory DC upregulate CCR7 upon maturation and are recruited to T-cell rich zones within the tdLN via a CCL21 chemokine gradient secreted by the lymphatic endothelium [73–75]. Roberts et al. utilized intravital imaging of various DC populations including resident $CD8\alpha^+$ cDC1 (resDC1), resident $CD11b^+$ cDC2 (resDC2), migratory $CD11b^+$ cDC2 (migDC2) and migratory $CD103^+$ cDC1 (migDC1) to further dissect mechanisms of antigen trafficking from the TME to the tdLN. These investigators concluded that the $CD103^+$ migDC1 population in mice and BDCA-3+ migDC1 population in humans are the dominant subset responsible for CCR7-dependent trafficking of tumor antigens for cross-priming of tdLN-resident naïve $CD8^+$ T-cells [76]. Supporting the clinical relevance of their findings, intratumoral *CCR7* expression in human melanoma specimens correlated with robust T-cell infiltration and patients with $CCR7^{hi}$ tumors had superior survival relative to $CCR7^{lo}$ counterparts. Interestingly, while migDC1 were the primary source of intratumoral antigen capture and trafficking for cross-presentation, there was evidence of antigen transfer to other resDC within the tdLN [76]. These findings echo earlier data demonstrating that the success of autologous tumor-loaded DC-based vaccines is dependent on the transfer of antigen to other endogenous antigen-presenting cells rather than direct CD8+ T-cell priming [77]. This was further explored by Ruhland and colleagues to clarify mechanisms of T-cell priming in the tdLN demonstrating that compartmentalization of DC subsets has functional consequences for effector T-cell responses. The authors elegantly demonstrated that both migDC1 and migDC2 are able to transfer tumor antigen-laden vesicles to resident DC subsets via synaptic contact within the tdLN [78]. Priming of $CD4^+$ T-cells was restricted to migDC2; however, $CD8^+$ T-cells were also able to be primed by migDC2 and resDC1 (in addition to direct crosspresentation by migDC1), suggesting tiers of redundancy. *In vitro*, OT-1 $CD8^+$ T-cells primed by resDC1, as compared with migDC1, exhibit a short-lived effector phenotype (elevated KLRG1/CD127 ratio) rather than skewing towards the migDC1-associated memory phenotype. These OT-1 T-cells primed by resDC1 also exhibit downregulated IFN-I/II and PRR signaling gene expression programs alluding to a potentially tolerogenic effect of antigen presentation by resDC1. Taken together, these finding suggest that highly complex and coordinated process of antigen trafficking and presentation where maturation and migration as well as DC-subset specificity and compartmentalization sculpt T-cell immunity [77].

2.4 Crosstalk of T-cells and Dendritic Cells in the tumor microenvironment

In addition to antigen-presentation, co-stimulation and priming of *de novo* antigen-specific T-cells in the tdLN, DC also interact directly with T-cells within the TME to promote anti-tumoral immunity. The production of T-cell homing CXCR3-ligand chemokines (CXCL9/CXCL10) by tumor-infiltrating $CD103^+$ DC have been shown to be important for recruitment of effector T-cells into the TME in certain models and tumor types [79, 80]. Abrogation of this DC-generated chemotactic gradient and/or CXCR3-signaling axis compromises the efficacy of ICB and adoptive cellular therapy [17, 81]. Importantly, intratumoral $CD103^+$ cDC1 are able to re-stimulate previously activated antigen-specific $CD8^+$ T-cells. Thus DC play an important role in initiating *de novo* T-cell immunity but also in sustaining an intratumoral adaptive immune responses by local *re-priming* of effector T-cells [15, 82]. These investigators propose that re-priming is facilitated by the superior cross-presenting capacity of cDC1 directly to T-cells within the TME. These findings also suggest CXCR3 ligand activity extends beyond T-cell recruitment or chemotaxis and may regulate spatiotemporal organization and distribution of immune subsets thereby facilitating co-localization and immune cell crosstalk within the TME. There is increasing evidence that the anatomical distribution and organization of T-cells within distinct niches within lymph nodes are coordinated by non-redundant CXCR3 ligands which influence both DC-T-cell co-localization and T-cell fate decisions, including priming of stem-like memory versus effector phenotypes [47, 83]. Whether the CXCR3 axis governs similar crosstalk in TME remains an open question and the importance of organization and co-localization of DC and T-cells within the TME is an area of investigation receiving increasing attention. Garris et al. provided additional insight into the dynamic intratumoral interplay that occurs between DC and T-cells finding that positive feedback loop exists that involves IL-12 secretion by cDC1 via non-canonical NFκB-dependent mechanism in response to IFN-γ secreted by activated $CD8^+$ T-cells [84]. This T-cell/DC cytokine positive feedback loop provides licensing cues for DC activation and also, in part, uncovers an underappreciated component of the mechanism of action of anti-PD-1 ICB which stimulates IFN-γ production from T-cells [73, 84]. Whether this crosstalk and IFN-γ-mediated DC licensing step represents a component a *de novo* immune response where an antigen-loaded DC matures and traffics towards the tdLN to prime naïve T-cells or represent a local re-stimulation event that expands T-cells within the TME remains the be further elucidated. It is plausible that both coordinated actions occur during the evolution of an anti-tumoral immune response [15, 82, 84]. Recently, an intratumoral niche of $TCF1^+$ stem-cell-like T-cells was identified in human kidney tumors that gives rise to terminally differentiated T-cells [85]. Interestingly, these stem-like T-cells reside within $CD11c^+MHC\text{-}II^+$ DC-dense nests – while these nests are quite sparse relative to the entire tumor volume the absence of this APC niche confers defective T-cell responses and inferior progression-free survival. Additional functional characterization and profiling of the DC within these intratumoral APC-rich niches is warranted, particularly with respect to cross-priming and re-stimulation. Nevertheless, these finds support a vital role for intratumoral DC crosstalk with T-cells that supports and promotes anti-tumor immunity.

3.0 Evolving understanding of Dendritic Cell heterogeneity - developmental hierarchy and functional diversity

DC comprise a relatively infrequent immune population that represent only a small fraction of the cells of hematopoietic origin. The mouse and human developmental ontogeny of DC has recently been comprehensively reviewed and knowledge in this arena continues to rapidly evolve [34, 38]. Lineage tracing studies in mice confirm that DC arise from multipotent bone marrow progenitors, termed common myeloid progenitors (CMP), with a notable exception that certain pDC may be derived from lymphoid origins [34]. Briefly, high IRF8 expression instructs CMP differentiation into the common DC precursor (CDP) population that eventually gives rise to conventional DC and pDC. The zinc finger and BTB domain-containing transcription factor, ZBTB46, is selectively expressed by conventional DC (both type 1 and type 2) and can be used to distinguish conventional DC from pDC and other DC or macrophage populations [86, 87]. Alternatively, MoDC, originate from a non-CDP precursor, known as common monocyte precursor (cMoP) that ultimately differentiates into MoDC, macrophages or Langerhans cells. As mentioned, recent studies have reported that IFNα-producing pDC can arise from a common lymphoid progenitor population that diverges from conventional DC before CMP differentiation while earlier work suggests that pre-pDC may arise from both lymphoid and myeloid precursors and share features with both lineages [88]. In addition to lineage-specific transcription factors, DC growth factors and local cytokine milieu carry DC-subset specific functional implications for DC development and differentiation. FLT3-L provides homeostatic developmental signals within the bone marrow, and is instructed by TLR cues and also instructs DC expansion as DC migrate from blood into peripheral tissues and secondary lymphoid organs [2, 89, 90]. As such, FLT3-L can both tonically and acutely govern the relative size of the DC compartment. Additional growth factors and cytokines, such as granulocyte monocyte colony-stimulating factor (GM-CSF) and type I interferons (IFN) also regulate DC differentiation and/or function providing activation and licensing cues in an inflammatory context, including cancer [61, 91–93].

Conventional DC can be further subdivided into two major subsets – cDC1 and cDC2 [55]. Recent data highlight substantial heterogeneity within cDC2 [94]. Some studies have further distinguished cDC2 as two transcriptionally and phenotypically distinct cDC2 populations including the anti-inflammatory cDC2A subset defined by T-bet expression and the pro-inflammatory cDC2B population defined by RORγt expression [33]. Similarly, human scRNA-seq analysis by Villani et al. had previously reported the existence of two cDC2 subpopulations, termed DC2 and DC3, with the cDC2B subset overlapping with markers of both DC2 and DC3 clusters [35]. Furthermore, emerging data have assigned the DC3 population, originally described as a cDC2 subpopulation by Villani et al., as a separate DC lineage with distinct ontogeny from cDC1, cDC2 and monocyte-derived counterparts with origins independent of CDP or cMoP precursors [14, 95]. Substantial phenotypic overlap between cDC2 and MoDC (as well as DC3) under inflammatory conditions make it challenging to define these subsets independent of environmental context [96, 97]. An alternative view is that DC functional specialization is determined more so by environmental cues than developmental fate specification. This is supported by the convergence of a transcriptional program among '*activated*' $CCR7^{+}$ DC that exhibit a

gene signature associated with maturation and migration shared across DC subsets *in vivo* which appears to be particularly relevant within the TME [3, 38, 76]. Ultimately, a conceptual shift from more rigid hierarchical models to an understanding of DC phenotype, transcriptional regulation, and function as plastic process influenced by tissue-specificity, local cues determining maturation and licensing, and the presence or quality of danger signals could help resolve these findings.

3.0.1. Type 1 conventional Dendritic Cells (cDC1)

In the context of anti-tumor immunity, cDC1 are perhaps the most extensively studied subset with an established role in promoting tumor rejection given their specialization in recognition of dead and dying cells, cross-presentation and ability to drive $CD8^+$ T-cell responses [66, 67, 98]. cDC1 are generally defined by dependence on key transcription factors IRF8, BATF3 and ID2 as well as selective expression of C-type lectin receptor, CLEC9A (also known as DNGR-1) and chemokine receptor, XCR1 [57, 58, 99]. BDCA-3 (CD141) in humans is an additional marker that selectively identifies the cDC1 subset [67]. Additionally, expression of CD8α and CD103 (integrin αE) can help distinguish lymphoid-tissue resident cDC1 (resDC1) and tissue-migratory cDC1 (migDC1) in mice, respectively.

In the TME, exogenous tumor-derived antigens and other cellular debris released from necrotic and apoptotic tumors are engulfed and cross-presented by cDC1 on major histocompatibility complex class I (MHC-I) to prime naïve tumor-specific $CD8^+$ T-cells [11]. Interestingly, exposure of F-actin filaments, a hallmark of necrotic cells, is the natural ligand for cDC1-restricted CLEC9A and ligation initiates a signaling cascade that mediates cross-presentation – this represents a potential mechanistic link between sensing of DAMPs and initiation of *de novo* $CD8^+$ T-cell immunity [100]. cDC1 also express a wide array of PRRs, including selective expression of TLR3 – a double-stranded RNA (dsRNA) sensor and the therapeutic target of dsRNA analogue, poly(I:C). More recently, WDF4Y has been shown to be indispensable for crosspresentation of cell-associated antigens in cDC1 [69]. BATF3-deficient mice exhibit defects in cDC1 development and maturation leading to the inability to reject immunogenic tumors and mount anti-viral responses [101]. $Batf3^{-/-}$ mice and other cDC1 depletion models have highlighted additional anti-tumor properties of cDC1 including production of IL-12, secretion of type I and type III IFN, and maintenance of IRF8 expression. Tumors have also been found to disrupt IRF8-dependent development of cDC1 resulting in a systemic paucity of cDC1 and its precursors that impairs cancer immunosurveillance [102]. Further, regulation of a set of BATF3-dependent genes in cDC1 also appears to promote tumor rejection independent of cross-presentation and overexpression of IRF8 is able to compensate for BATF3-deficiency and restores cDC1-mediated tumor rejection [103]. Of note, BATF3 expression, among other transcription factors, are not exclusive to the cDC1 subset with an emerging role in T-cell development including tissue-resident memory $CD8^+$ T-cells (TRM) and memory formation [104, 105].

3.0.2. Type 2 conventional Dendritic Cells (cDC2)

cDC2 orchestrate host barrier protection as well as immunity to extracellular pathogens and/or allergens largely by promoting $CD4^+$ helper T-cell responses through presentation of soluble antigens via MHC class II (MHC-II) [44]. This contrasts cDC1 function, which

regulates host defense to viruses and other intracellular pathogens and promotes $CD8^+$ T-cell-mediated anti-tumor immunity. The cDC2 subset is defined by high IRF4 expression and is dependent on additional transcription factors RELB, ZEB2, KLF4 and NOTCH2 [106]. Certain transcription factor expression patterns may bias towards TH2 versus TH17 responses [65, 106, 107]. Further, an AP1-IRF Composite Elements (AICE)-dependent gene program that is responsive to high IRF8 (and IRF4) expression levels yields a cDC1-specific transcriptional signature that is distinct from its cDC2 counterparts [108]. The heterogeneity and context-dependence of cDC2 pose a challenge for defining a uniform panel of cell surface markers – however, in humans, BDCA-1 (CD1c) can be used to identify cDC2 in conjunction with SIRPα (CD172a) and CLEC10A (also known as CD301b or MGL) [109]. cDC2 also express other prototypical markers including CD11b, CD11c, CD5 (in humans) and MHC-II but are not exclusive to this subset and can share overlap with cDC1s and monocytes.

In cancer, the role of cDC2 is less well defined, in part, resulting from the heterogeneity and functional diversity of this subset that may have differential effects on anti-tumoral immunity [65]. Further, the subset-specific functions ascribed to cDC1 and cDC2 in mice are less clearly defined in humans. It has been shown the tumor-infiltrating migratory cDC2 can drive potent $CD4^+$ T-cell responses, where cDC2 capture antigen and migrate to the tdLN where they can either transfer antigen to resident DC populations or directly prime naïve $CD4^+$ T-cells [78, 110]. Binnewies et al. eloquently demonstrated that BDCA-1^+ cDC2 and regulatory T-cell (Treg) immune contexture is predictive of $CD4^+$ T-cell infiltration of the TME [110]. A higher cDC2:Treg ratio was associated with robust $CD4^+$ T-cell tumor infiltration whereas a paucity of cDC2 or abundance of Tregs correlated with less $CD4^+$ infiltration. These findings suggest that Tregs restrain cDC2 licensing ultimately leading to a defect in $CD4^+$ T-cell priming. These investigators extended their observations by demonstrating that Treg depletion restored cDC2 priming in murine models. Further, in a cohort of patients with head & neck cancer that responded to PD-1 blockade, those patients with high relative cDC2 abundance and $CD4^+$ T-cell accumulation were a distinct subset of responders from those with cDC1-dominant responses. High CD207 on tumor-infiltrating myeloid cells, a putative cDC2 marker, has also been associated with improved survival in patients with non-small cell lung cancer [48]. Recently, it was reported that cDC1 is required for early priming of $CD4^+$ T-cells (in addition to $CD8^+$ T-cells) to drive anti-tumor immunity which has challenged conventional dogma [111]. Future efforts will focus on the interplay between cDC1 and cDC2 subsets and how this relationship regulates $CD4^+$ T-cell tumor infiltration and treatment response.

3.0.3. Plasmacytoid Dendritic Cells (pDC)

pDC are functionally specialized for anti-viral responses and are an important source of IFN-I (and IFN-III) upon viral infection. pDC are considered to have a similar role in potentiating anti-tumoral immune responses via IFN-I production, however, pDC may also drive tolerance and immune suppression in the context of malignancy. While pDC are able to cross-present antigen to prime CD8+ T-cells, they exhibit inferior cross-presenting capacity relative to their conventional DC counterparts [66, 112–114]. Despite limited antigen presentation, pDC secretion of IFN-I (predominantly IFNα) is critical to support

cDC1 maturation with additional roles in local stimulation of local $CD8^+$ cytotoxic T-cell and NK cell effector functions [115–117]. Notably, using deep scRNA-seq, Villani et al. described a novel $AXL^+Siglec6^+$ DC (termed DC5 or AS) population that shares many expression and phenotypic features previously assigned to classically defined pDC (as well as conventional DC) [35, 38]. However, relative to classical pDC, $AXL^+Siglec6^+$ DC were efficient at antigen-presentation with consequent T-cell activation and exhibited low IFN-I secretion in response to TLR9 stimulation. $AXL^+Siglec6^+$ DC also preferentially express KLF12 [118]. These functional differences from classical pDC led the investigators to define this population as distinct from both conventional DC and pDC.

The transcription factor TCF4 is critical for pDC development with additional transcription factors including IRF8 expression and RUNX1 guiding pDC differentiation. Notably, there appears to be reciprocal repression of TCF4 by cDC1 precursors that allow divergence of cDC1 and pDC lineages from a shared CDP origin [34]. BDCA-2 (also known as CLEC4C or CD303) is a commonly used marker for identification of pDC in humans with additional markers including CD123 (IL-3 receptor α-chain) and CD304 (BDCA-4 or neuropilin-1). B220 and Siglec-H may help identify pDC in mice [119]. Expression of TLR7 and TLR9 in the endosomal compartment of pDC recognize single-stranded RNA (ssRNA) and unmethylated CpG-DNA, respectively. This pattern of PRR distribution underlies key function of pDC in host defense again viral infection and tumors whereby presence of these nucleic acid species trigger cyclic GMP-AMP synthase / stimulator of interferon genes (cGAS/STING) signaling to drive a robust IFN-I response and IFN-stimulated gene (ISG) programs [120]. Indeed, imiquimod, a TLR7/TLR8 ligand, and CpG oligonucleotides, a TLR9 agonist, highlight pDC as a key therapeutic target to drive adaptive immunity, promote tumor rejection and reverse tolerance [121]. Alternatively, pDC have been shown to be tolerogenic and their dysregulation in the TME can promote tumor progression. pDC hypofunction has been observed across a spectrum of cancer subtypes – manifesting as a muted response to TLR7 or TLR9 activation and/or poor induction of IFN-I responses. Tolerogenic pDC actions have been attributed to TME-derived immunosuppressive molecules including IL-10 and TGF-β as well as expansion of Tregs [122–127]. In contrast to conventional DC, pDC, particularly in a tolerogenic context, have been correlated with adverse prognosis among patients with advanced cancer [128, 129].

3.0.4. Monocyte-derived Dendritic Cells (MoDC)

MoDC are a highly context-dependent DC subset that differentiate in response to inflammatory stimuli and are recruited to sites of inflammation, including the TME, via the CCR2-CCL2 chemokine signaling axis [130]. MoDC are heterogeneous and share substantial overlap with certain cDC2 subsets and monocytes, which is reflected in the diverse range of immune actions initiated by MoDC. Several scRNA-seq datasets have been unable to de-convolute certain cDC2 subsets from MoDC, therefore defining a cDC2/MoDC state that represents a spectrum of differentiation between MoDC and cDC2 with variation in function and phenotypic expression markers along this continuum. This is further supported by additional CyTOF and/or scRNA-seq-based studies noting substantial heterogeneity across DC subsets leading to discordance in classifying DC3 as a distinct population or a subset of conventional DC or as a MoDC [97]. There is additional

controversy regarding the use of CD14 expression as a monocyte-lineage marker, which potentially conflates classification of a distinct DC3 population with MoDC; with CD88 expression demonstrating utility as a marker of monocyte-lineage [14, 35, 94, 96].

Nevertheless, a population of inflammation-associated DC (termed MoDC in this review) that respond to inflammatory stimuli and are derived from monocyte precursors does exist. However, the relationship to and overlap with other DC subsets, particularly cDC2 and DC3 remains to be fully elucidated [38]. Inflammatory MoDC can skew CD4+ T-cell response towards TH1, TH2 or TH17 phenotypes and a tolerogenic milieu can drive differentiation of monocytes towards a regulatory MoDC phenotype [131, 132]. MoDC also cross-present captured cell-associated antigens to prime CD8+ T-cell responses [72]. Despite shared ability to cross-prime $CD8^+$ T-cells, Briseño and colleagues reported that a distinct transcriptional program governs this function in MoDC as compared with conventional DC. These authors conclude that GM-CSF-derived MoDC are IRF4-dependent and require IL-4, but not BATF3, to acquire cross-presenting function. However, a CyTOF-based analysis revealed that *ex vivo* MoDC generated from monocytes when cultured in the presence of GM-CSF and IL-4 were not found to be representative of any human DC subset identified in blood, lymphoid tissues or skin [94].

3.0.5. Tumor-infiltrating DC3

Recently, a tumor-infiltrating DC3 population has been consistently identified in a number of studies across multiple cancer types, suggesting an important role for DC3 in the context of cancer [48–52, 133]. The DC3 subset has been described to share overlapping phenotypic features with conventional DC, including both cDC1 and cDC2, yet harbor a distinct transcriptional profile [53, 133]. Indeed, a DC3 program is signified by the co-existence maturation/activation markers and an immunoregulatory profile that includes markers of DC migration (CCR7, FSCN1), DC maturation (LAMP3, CD80, CD83, CD40) as well as immune-regulation (PD-L1/PD-L2, IDO1, CD200) [49, 51, 52], molecules previously associated to a semi-maturation/migration program arising in DC in peripheral tissues [3, 134, 135]. Given the recent introduction of this DC3 population, largely aided by in depth single-cell profiling, it is plausible that other groups have previously described a DC3-like population using different nomenclature and phenotypic markers or have attributed functional properties of DC3 to other DC subsets or by cell state. Indeed, Gerhard et al. recently highlighted the transcriptional similarities among the CCR7+ LAMP3+ DC [22, 51, 133], mature DC enriched in immunoregulatory molecules (mregDC) [49], as well as datasets describing tumor-infiltrating ‘activated’ or ‘mature’ conventional DC [22, 48], suggesting that these clusters likely represent the same tumor-infiltrating DC3 state [53]. Further, a pan-cancer analysis by Cheng et al. confirmed that the LAMP3+ DC closely resembles mregDC and their developmental trajectory can be tracked back to either cDC1 and cDC2 – although, most of the tumor-infiltrating DC3 population appears to be cDC1-derived [133]. An alternative view is that DC3 simply represent a continuum of conventional DC undergoing maturation that capture antigen and acquire migratory capacity, as denoted by high CCR7 expression, suggesting that DC converge upon a unified activation/maturation program determined by the local TME or tissue microenvironment that supersedes developmental origin [37, 48]. While the aforementioned studies suggest

that conventional DC likely differentiate into activated DC3 in the inflammatory context of peripheral tissues and tumors, other groups have suggested the existence of a corresponding blood-based DC3 progenitor [14, 95]. This suggests a model where DC3 may represent an independent DC lineage arising from an IRF8^{lo} non-CDP granulocyte-monocyte-DC precursor exhibiting early developmental divergence from cDC1, cDC2 and pDC in the bone marrow – however, this population may more closely resemble inflammatory MoDC/cDC2 [14, 95]. Further confounding a precise classification of DC – DC, monocytes and macrophages entering and migrating from tissues share site-specific programs that can supersede their ontogeny [3, 134, 135]. These controversies highlight a critical need to develop uniform and consistent nomenclature and definitions in order to contextualize the evolving understanding of the DC3 state.

Functionally, DC3 harness the capacity to prime naive T-cells and may have a specific role in TRM programing [14, 35]. Activated DC3 are able to upregulate CCR7 expression upon TLR stimulation (TLR3, TLR4 and TLR7/8) and secrete IL-12 and other T-cell-homing chemokines including CXCL9 and CXCL10 [14]. In contrast to cDC2, DC3 induce CD103 expression on CD8$^+$ and CD4$^+$ T-cells, potentially via a TGF-β regulated program [14, 49, 110]. Intriguingly, examination of primary tumors from patients with luminal breast cancer reveal an association between abundance of DC3 and CD8$^+$CD103$^+$ T-cells alluding to a potentially critical role in TRM formation. Alternatively, Zhang et al. identified an intratumoral LAMP3$^+$ DC population in hepatocellular carcinoma with an activated yet immune-regulatory phenotype that traffics from the TME to hepatic lymph nodes [51]. A LAMP3$^+$ population has also been identified in breast and lung tumors whereas both conventional DC (both cDC1 and cDC2) upregulate LAMP3 expression upon polyI:C or IFN-γ stimulation suggesting that a DC3 state represents a convergence of DC activation where inflammatory cues supersede ontogeny [48, 51, 133, 136]. Interestingly, a LAMP3$^+$ DC3 gene signature strongly correlated with Treg and exhausted T-cell phenotype and PD-L1-expressing LAMP3$^+$ DC3 co-localize with T-cells in tumors and was further substantiated in a subsequent pan-cancer analysis [51, 133]. As mentioned, these findings are concordant with the mregDC population described by Maier et al. where an immune-regulatory program in tumor-infiltrating DC is characterized by co-expression of maturation markers and PD-L1/PD-L2 – a potential mechanism of immune evasion co-opted by the TME to dampen anti-tumor immunity [3, 49]. While the *in vivo* effects including migratory function and cross-priming capacity of DC3 need to be further elucidated in relevant models, the available data that DC3 can license CD8$^+$ T-cells and correlate with CD103$^+$ TRM tumor infiltration suggests a role in driving anti-tumor immunity. However, DC3 also appear to employ immune-regulatory modules that counterbalance T-cell-mediated immunity that may be particularly relevant to T-cell dysfunction in the TME[3].

4.0 Role of Dendritic Cells in cancer therapy

DC are also increasingly recognized as key mediators of therapeutic response to immunotherapy as well as conventional cancer treatments including radiotherapy and chemotherapy. Certain cancer therapies promote *immunogenic cell death* – a process by which dying cells stimulate innate immunity through exposure of immunogenic antigens (antigenicity). ICD may also produce danger signals (adjuvanticity), including DAMPs

and cytokines that recruit and/or license DC [137]. Additionally, endogenous nucleic acid species released into the cytosolic or extracellular compartment as a result of DNA damage from cytotoxic therapies can function as DAMPs that trigger PRR activation leading to a robust IFN-I production similar to the host anti-viral response [25, 62, 93, 138–140]. Spatiotemporal coordination of DC antigen capture and licensing cues is important for effective DC maturation, underscoring ICD as a critical process that bridges innate and adaptive immunity. Alternatively, some immunotherapies directly target the DC compartment by providing adjuvants to stimulate innate sensing and PRR activation (i.e. TLR agonists) or growth factors (i.e. FLT3-L, GM-CSF) that promote expansion or differentiation. Further, the traditional understanding of the mechanism of action of several T-cell-based immunotherapies, including as ICB and cytokines, is being reexamined as DC have come to the forefront – this highlights the inextricable link between DC and T-cells in the TME and tdLN. While cancer vaccines are beyond the scope of this review, DC-based vaccine platforms and the majority of vaccination strategies are built on the foundational principle of providing sufficient antigen(s) and adjuvant(s) to DC to generate adaptive immunity and protective memory.

4.1 Immunogenic Chemotherapy

While immunosuppressive effects of chemotherapy are well established, in the proper context, cytotoxic therapy also promotes immunogenicity [141, 142]. Mechanistic studies of ICD in immunogenic chemotherapy, particularly anthracyclines and certain platinum-based regimens, have defined key molecular events that initiate DC-based immune responses. The translocation of intracellular calreticulin to the tumor cell surface (ecto-calreticulin) on a dying tumor cell promotes $CD11c^+$ DC phagocytosis [142]. The release of high mobility group box protein (HMGB1) from cancer cells undergoing ICD ligate TLR4 on DC to promote maturation and cross-presentation [141]. Similarly, extracellular secretion of ATP during ICD functions as a potent chemoattractant for DC that binds P2XR7, a purinergic receptor on DC, triggering NLRP3 inflammasome activation and pro-inflammatory cytokine secretion [143–145]. However, additional work suggests that P2X7R-dependent STING activation occurs primarily in macrophages and other monocytic populations rather than DC [146]. Dying tumor cells establish chemotactic gradients that recruit DC (generally CCR2-dependent MoDC) into the TME and promotes their differentiation [130, 147]. Formyl peptide receptor 1 (FPR1) expression on DC appears to be necessary for chemotherapy-induced antitumoral immunity, as FPR1 (on DC) interacts with dying tumor cells via Annexin A1 (ANXA1 on tumor cells) leading to subsequent DC maturation and T-cell priming [148, 149]. This relationship parallels recognition of F-actin on necrotic cells by CLEC9A-expressing DC [100]. Notably, administration of polyI:C, a synthetic TLR3 ligand, is able to circumvent FPR1 deficiency and restore responsiveness to anthracycline-based chemotherapy [149]. Tumor-derived production of IFN-I also recruits and activates DC to potentiate responses to immunogenic chemotherapy [150]. Collectively, chemotherapy-induced ICD fosters immunity through the generation of various dangers signals and DAMPs that result in a diverse range of effects on the DC compartment including DC recruitment, DC interaction with dying tumors cells and DC activation/maturation [137].

4.2 Radiotherapy

Radiotherapy exerts therapeutic effect via DNA damage, however, it is increasingly recognized that the nucleic acid species generated from radiation-induced DNA damage are also inflammatory and potentially immunogenic. Radiotherapy enhances antigenicity via tumor cell death-associated antigen release, radiation-induced exposure of immunogenic neoantigens and upregulation of MHC-I [151–153]. In addition, radiotherapy exhibits characteristic hallmarks of ICD – including calreticulin surface translocation, ATP secretion into the extracellular space and passive release of HMGB1 [154].

Mechanistically, radiotherapy employs a form of viral mimicry through generation of endogenous nucleic acid species that activate innate immune sensing pathways akin to viral RNA and DNA detection by host PRRs [25]. To this point, radiation-induced micronuclei resulting from double-stranded DNA (dsDNA) breaks are able to activate the cytosolic DNA-sensing cGAS/STING axis [138]. Additional PRRs have been implicated in radiation-induced innate sensing including the RIG-I axis, where expression of LGP2 in DC (an RNA-sensing RIG-I-like receptor) is essential for radiation-driven anti-tumor immunity and promotes cross-priming of T-cells [155–157]. Ultimately, cytosolic accumulation of nucleic acids from both nuclear and mitochondrial sources leads to robust IFN-I production and activation of ISG programs that recruit and license DC in the TME [158–161]. BATF3-dependent cDC1 are critical to radiation-mediated immunogenicity and are responsible for engulfment of tumor-associated antigen, migration to the tdLN and cross-priming of naïve antigen-specific T-cells in the tdLN [160, 162–164]. Moreover, cDC1 govern the responsiveness of tumors to radiotherapy [165]. Blair et al. observed that failure of intratumoral cDC1 maturation defines poorly radio-immunogenic tumors suggesting that radiotherapy provides an insufficient source of endogenous adjuvant in this setting and that administration of exogenous adjuvants might help overcome this defect [165]. In parallel, radiotherapy also initiates immune-regulatory and/or homeostatic actions that dampen DC function within the TME. For example, higher fractional doses of radiation have been associated with dose-dependent TREX1 induction in preclinical models [158]. TREX1 is a DNA exonuclease that attenuates cytosolic accumulation of radiation-induced dsDNA thereby reducing cGAS/STING signaling and IFN-I production. STING activation also appears to promote radioresistance through CCR2-dependent recruitment of immunosuppressive myeloid-derived suppressor cells [166]. Similarly, radiation-induced activation of non-canonical NFκB signaling in DCs negatively regulates IFN-I production and counteracts canonical NFκB-mediated anti-tumor immunity [167]. Further, cytosolic RNA sensor LGP2 has opposing functions in tumor cells and DC – suppressing IFN-I activity in tumor cells while promoting radiation-mediated cross-priming by DC [155]. Taken together, radiotherapy drives anti-tumoral immunity through DC-mediated innate sensing and cross-priming but can simultaneously exert tolerogenic effects that counteract DC function.

4.3 Immunotherapy

Although disruption of the PD-1/PD-L1 axis with ICB has been the most successful cancer immunotherapy to date, it is now evident that a T-cell-centric view of this mechanism of action is incomplete. Initial dogma presupposed that the effects of PD-1/PD-L1 blockade

predominated in the TME during the effector phase of the anti-tumor immune response where dysfunctional intratumoral T-cells become reinvigorated when the immune-inhibitory interaction between exhausted PD-1^+ T-cells and PD-$L1^+$ tumor cells is disrupted. However, PD-L1 expression on host immune cells appears to be indispensable for the efficacy of PD-L1 ICB [168, 169]. While various myeloid populations within the TME express PD-L1, recent mechanistic studies have provided convincing evidence that PD-L1 on conventional DC is a direct target of ICB and a determinant of ICB response [19, 23, 24]. Mayoux et al. demonstrated that the *cis* interaction of PD-L1 and CD80 (B7.1) on DC prevents co-stimulatory signaling (signal 2) between DC and T-cells. Disruption of CD80 sequestration with PD-L1 blockade allows CD80 to interact (in trans) with CD28 for T-cell priming [19]. Oh et al. extended these findings using a mouse model with DC-specific genetic deletion of PD-L1 [24]. These investigators demonstrate that both the *cis* interaction of CD80:PD-L1 on DC and the *trans* interaction of PD-1:PD-L1 between T-cell and DC are necessary for optimal anti-tumoral T-cell responses and that both interactions are targets of PD-1 axis blockade. While the aforementioned studies focused primarily on PD-$L1^+$ tumor-infiltrating DC, Dammeijer et al. selectively targeted anti-PD-L1 antibodies to the tdLN (excluding the TME) and demonstrated that dual-positive migratory cDC2 ($CD80^+$PD-$L1^+$ mDC2) are likely key targets of nodal-directed ICB and can potentiate anti-tumor immunity [170]. Interestingly, mDC2 expressed significantly more PD-L1 than cDC1 counterparts express and were found to co-localize with $CD8^+$ T-cells. As the current understanding of ICB is actively revised, additional mechanisms by which DC are central to therapeutic efficacy are emerging. DC were recently implicated as an indirect target of IL-2 cytokine therapy – a classically T-cell-directed immunotherapy. Cytokine therapy with IL-2 has largely been shown to mediate immune effects via T-cell expansion and activation. Conventional DC lack functional IL-2 receptors, but proliferate and differentiate in response to IL-2 as a consequence of several DC growth factors (FLT3-L, CSF2 and TNF) that are produced by IL-2-stimulated lymphoid cells, including innate lymphoid cells. IL-2 treatment was also found to augment DC antigen capture and processing [171]. Successful adoptive T-cell therapy also depends on the presence of intratumoral cDC1, to provide T-cell homing chemokines and aid the local expansion of adoptively transferred T-cells by CD40 and CD70-dependent mechanisms [17, 172].

As evidence accumulates that DC govern therapeutic efficacy of several cancer treatments, there is growing interest in directly targeting DC to improve outcomes [173]. Treatment strategies that promote abundance, intratumoral localization and/or function of DC are under investigation and have been comprehensively reviewed [44]. Providing DC mitogens and -poietins such as FLT3-L and GM-CSF have the potential to expand, differentiate and mobilize DC for recruitment into the TME, but require further parsing of their individual and collective impact [174]. Alternatively, stimulation of innate sensing and PRR pathways using TLR agonists represents a promising strategy to promote DC activation and maturation whereas agonist antibodies directed at CD40 may function to boost DC-mediated T-cell priming [175–177]. Ultimately, different DC-targeted approaches may be required to overcome tolerance and tumor-specific immune evasion mechanisms and targeting of specific DC subsets may help fine-tune this approach. It will also be necessary to pursue combination strategies focusing on multiple facets of the cancer immunity cycle

to fully harness the potential of DC for cancer therapy [46]. Along these lines, combining DC-targeted immunotherapy with conventional cancer therapy promises to augment the immunogenicity of these regimens [178].

5.0 Immunological barriers that limit Dendritic Cell-mediated anti-tumor immunity

Several tumor-intrinsic mechanisms within the TME limit DC function and hamper tumor-immune surveillance [98]. The absence or exclusion of DC from the TME is a major barrier to generation of *de novo* adaptive immunity as well as *in situ* re-priming of T-cell responses [15]. A constellation of immuno-genetic and metabolic factors regulates DC recruitment into tumors and a paucity of DC is often the result of a failure to generate an effective chemotactic gradient within the TME [20]. Furthermore, tumor-infiltrating DC are subject to a hostile milieu where various immunosuppressive factors promote tolerance and DC dysfunction [21]. The now established concept that the T-cell inflamed TME is a direct consequence of effective recruitment and activation of DC is an important advance for immuno-oncology [10]. As such, an improved understanding of non-T-cell inflamed tumors will facilitate development of novel therapies to address the immune-desert and immune-excluded phenotypes – subtypes with traditionally poor response to ICB and other T-cell-based approaches [9].

The concept that oncogenic signaling axes restrict DC access to the TME is emerging and now supported by several lines of evidence [179]. Spranger et al. reported that tumor-intrinsic WNT/β-catenin signaling is associated with T-cell exclusion in both preclinical models and human melanomas [59]. β-catenin-driven tumors were characterized by poor $CD103^+$ DC infiltration of the TME. These investigators attributed these findings to attenuation of CCL4 secretion by tumor cells that disrupted CCL4-dependent chemo-attraction of BATF3 DC into the TME. Similarly, in a preclinical model of hepatocellular carcinoma, β-catenin-signaling was linked to immune evasion and impaired cDC1 recruitment that was attributed to the absence of a tumor-derived CCL5 (rather than CCL4) chemokine gradient in β-catenin-driven tumors [180]. Several additional molecular-genetic pathways have been associated with the immune-excluded phenotype, including PTEN loss, with some models suggesting that pharmacologic inhibition of genetic signaling pathways can promote immune infiltration and restore responsiveness to immunomodulating therapies [10, 181]. Beyond aberrant WNT/β-catenin, additional examination of how other oncogenic signaling pathways specifically alter DC immunobiology is needed. Intriguingly, the STK11/LKB1 axis appears to play a pivotal role in the regulating DC induction of tolerance and Treg homeostasis whereby LKB1-deficient DC have been shown to promote expansion of Tregs and immune-regulatory programs via IL-6 dependent mechanisms [182, 183]. STAT3-mediated oncogenic signaling also suppresses DC differentiation and maturation through production of immune-suppressive soluble factors including IL-10 as well as tolerogenic interactions with immune-regulatory subsets including TGF-β-dependent induction of Tregs and induction of indoleamine 2,3-dioxygenase (IDO) expression [184]. Of note, DC also express a variety of immune-inhibitory checkpoints that may function as viable targets to boost anti-tumor immunity [24]. To this point, TIM-3-expressing $CD103^+$ tumor-infiltrating

cDC1 were found to be a primary target of therapeutic antibody blockade and indispensable for treatment efficacy. TIM-3 blockade on intratumoral cDC1 increased CXCR3-ligand expression thereby enhancing recruitment of $CD8^+$ effector T-cells into the TME [22].

Other DC-intrinsic signaling pathways function to balance tolerance and immune-surveillance, which can become dysregulated in the tumor microenvironment as a form of immune evasion. Nirschl et al. identified a broadly conserved IFN-γ-dependent module that functions to preserve tissue homeostasis during steady state that is co-opted in the TME to promote tolerance [3]. Suppresor-of-cytokine-2 (SOCS2) expression in tumor-infiltrating DC was identified as a critical IFN-γ-induced negative regulator of anti-tumor immunity resulting in decreased T-cell priming *in vivo*. Supporting the critical homeostatic role of IFN-γ, loss of SOCS1 (another family member) amplified IFN-γ signaling in $CD11c^+$ DC which favored innate immune signaling pathways but drove a defect in adaptive CD8+ T-cell priming in a *Listeria monocytogenes* vaccine model [185]. As discussed, counter-regulatory measures exist between canonical and non-canonical NFκB signaling where the non-canonical pathway in DC may oppose downstream consequences of cGAS/STING activation and abrogate IFN-I production [167]. Cubillos-Ruiz and colleagues reported that the TME induces an endoplasmic reticulum (ER) stress response in tumor-infiltrating DC that disrupts homeostasis through constitutive activation of the IRE1/XBP1 axis [186]. This ER stress response results in abnormal lipid metabolism and accumulation of lipid peroxidation byproducts within DCs that has immunological consequences. XBP1 activation confers reduced T-cell priming capacity and promotes tumor progression whereas DC-specific genetic ablation of XBP1 was able to restore anti-tumor immunity. Collectively, these findings suggest that disruption of homeostatic programs in DC that are subverted within the TME may be a promising strategy to promote immune-mediated tumor rejection.

Immunometabolism is also an important regulator of DC function within the TME. Zelenay et al. reported that a pro-tumorigenic inflammation program mediated by COX-2 expression contributes immune evasion. These investigators demonstrated in a murine $Braf^{V600E}$ melanoma model that COX-2-dependent production of prostaglandin E2 (PGE2) in the TME restricts tumor-infiltration of $CD103^+$ cDC1 [187]. Further work by this group clarified that NK cell production of the cDC1 chemoattractants, CCL5 and XCL1, is restrained by PGE2 production in a COX-dependent manner, which established a complex interaction between NK cells, cDC1 and tumor cells that limits DC-mediated anti-tumor immunity [16, 187]. While most efforts have focused on conventional DC subsets, the tumor-infiltrating inflammatory MoDC subset may suppress T-cell immunity. Compared with conventional DC counterparts, MoDC were found to be highly efficient at antigen capture but were non-migratory to the tdLN [65]. Further, MoDC were potent inhibitors of antigen-specific T-cell proliferation *in vitro* and exhibited an elevated IL-10:IL-12 ratio consistent with an immune-suppressive profile – this suppressive effect was attributed to high production of nitric oxide within the TME. Further, lactic acidosis has been shown to reduce both the frequency and function (IFNα production) of pDC in patients with metastatic melanoma [188].

6.0 Conclusions

The functional specialization of DC underlie their critically important role in governing the balance between self-tolerance and anti-tumor immunity. In the TME, the ability of DC to sense and interpret danger signals, environmental stimuli, licensing cues as well as capacity for antigen trafficking and presentation are the foundational steps necessary to generate *de novo* antigen-specific T-cell immunity. Improved understanding of the functional impact of DC subset diversity and how DC are differentially conditioned by licensing cues, environmental context and anatomic compartmentalization will be important to develop improved precision immunotherapy platforms. Further, decoding immune crosstalk and cooperative interactions between DC and various components of the TME and tdLN, including T-cells, innate lymphoid cells and stroma will be an important future direction to harness the full potential of DC-based therapy. The rapidly expanding clinical use of immunotherapy provides urgency to dissect mechanisms of therapeutic response and resistance to understand how DC immunobiology can be leveraged to improve response rates and treatment outcomes for patients with cancer.

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References

1. Steinman RM, Decisions about dendritic cells: past, present, and future. Annu Rev Immunol, 2012. 30: p. 1–22. [PubMed: 22136168]
2. Anandasabapathy N, et al. , Classical Flt3L-dependent dendritic cells control immunity to protein vaccine. J Exp Med, 2014. 211(9): p. 1875–91. [PubMed: 25135299]
3. Nirschl CJ, et al. , IFNγ-Dependent Tissue-Immune Homeostasis Is Co-opted in the Tumor Microenvironment. Cell, 2017. 170(1): p. 127–141.e15. [PubMed: 28666115]
4. Baratin M, et al. , Homeostatic NF-κB Signaling in Steady-State Migratory Dendritic Cells Regulates Immune Homeostasis and Tolerance. Immunity, 2015. 42(4): p. 627–39. [PubMed: 25862089]
5. Matzinger P, Tolerance, danger, and the extended family. Annu Rev Immunol, 1994. 12: p. 991–1045. [PubMed: 8011301]
6. Galluzzi L, et al. , The hallmarks of successful anticancer immunotherapy. Sci Transl Med, 2018. 10(459).
7. McGranahan N, et al. , Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science, 2016. 351(6280): p. 1463–9. [PubMed: 26940869]
8. Gajewski TF, et al. , Cancer Immunotherapy Targets Based on Understanding the T Cell-Inflamed Versus Non-T Cell-Inflamed Tumor Microenvironment. Adv Exp Med Biol, 2017. 1036: p. 19–31. [PubMed: 29275462]
9. Chen DS and Mellman I, Elements of cancer immunity and the cancer-immune set point. Nature, 2017. 541(7637): p. 321–330. [PubMed: 28102259]
10. Garris CS and Luke JJ, Dendritic Cells, the T-cell-inflamed Tumor Microenvironment, and Immunotherapy Treatment Response. Clin Cancer Res, 2020. 26(15): p. 3901–3907. [PubMed: 32332013]
11. Albert ML, Sauter B, and Bhardwaj N, Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature, 1998. 392(6671): p. 86–9. [PubMed: 9510252]

12. Nouri-Shirazi M, et al. , Dendritic cells capture killed tumor cells and present their antigens to elicit tumor-specific immune responses. J Immunol, 2000. 165(7): p. 3797–803. [PubMed: 11034385]
13. Spranger S, et al. , Density of immunogenic antigens does not explain the presence or absence of the T-cell-inflamed tumor microenvironment in melanoma. Proc Natl Acad Sci U S A, 2016. 113(48): p. E7759–e7768. [PubMed: 27837020]
14. Bourdely P, et al. , Transcriptional and Functional Analysis of CD1c(+) Human Dendritic Cells Identifies a CD163(+) Subset Priming CD8(+)CD103(+) T Cells. Immunity, 2020. 53(2): p. 335–352.e8. [PubMed: 32610077]
15. Broz ML, et al. , Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. Cancer Cell, 2014. 26(5): p. 638–52. [PubMed: 25446897]
16. Böttcher JP, et al. , NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell, 2018. 172(5): p. 1022–1037.e14. [PubMed: 29429633]
17. Spranger S, et al. , Tumor-Residing Batf3 Dendritic Cells Are Required for Effector T Cell Trafficking and Adoptive T Cell Therapy. Cancer Cell, 2017. 31(5): p. 711–723.e4. [PubMed: 28486109]
18. Barry KC, et al. , A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments. Nat Med, 2018. 24(8): p. 1178–1191. [PubMed: 29942093]
19. Mayoux M, et al. , Dendritic cells dictate responses to PD-L1 blockade cancer immunotherapy. Sci Transl Med, 2020. 12(534).
20. Hegde S, et al. , Dendritic Cell Paucity Leads to Dysfunctional Immune Surveillance in Pancreatic Cancer. Cancer Cell, 2020. 37(3): p. 289–307.e9. [PubMed: 32183949]
21. Lin JH, et al. , Type 1 conventional dendritic cells are systemically dysregulated early in pancreatic carcinogenesis. J Exp Med, 2020. 217(8).
22. de Mingo Pulido Á, et al. , TIM-3 Regulates CD103(+) Dendritic Cell Function and Response to Chemotherapy in Breast Cancer. Cancer Cell, 2018. 33(1): p. 60–74.e6. [PubMed: 29316433]
23. Peng Q, et al. , PD-L1 on dendritic cells attenuates T cell activation and regulates response to immune checkpoint blockade. Nat Commun, 2020. 11(1): p. 4835. [PubMed: 32973173]
24. Oh SA, et al. , PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer. Nature Cancer, 2020. 1(7): p. 681–691.
25. Woo SR, et al. , STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity, 2014. 41(5): p. 830–42. [PubMed: 25517615]
26. Carenza C, et al. , Costimulatory Molecules and Immune Checkpoints Are Differentially Expressed on Different Subsets of Dendritic Cells. Front Immunol, 2019. 10: p. 1325. [PubMed: 31244860]
27. Gallois A and Bhardwaj N, Dendritic cell-targeted approaches to modulate immune dysfunction in the tumor microenvironment. Front Immunol, 2013. 4: p. 436. [PubMed: 24339825]
28. Steinman RM, Adams JC, and Cohn ZA, Identification of a novel cell type in peripheral lymphoid organs of mice. IV. Identification and distribution in mouse spleen. J Exp Med, 1975. 141(4): p. 804–20. [PubMed: 1127378]
29. Steinman RM and Cohn ZA, Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med, 1973. 137(5): p. 1142–62. [PubMed: 4573839]
30. Steinman RM and Cohn ZA, Identification of a novel cell type in peripheral lymphoid organs of mice. II. Functional properties in vitro. J Exp Med, 1974. 139(2): p. 380–97. [PubMed: 4589990]
31. Steinman RM, Lustig DS, and Cohn ZA, Identification of a novel cell type in peripheral lymphoid organs of mice. 3. Functional properties in vivo. J Exp Med, 1974. 139(6): p. 1431–45. [PubMed: 4598015]
32. Merad M, et al. , The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. Annu Rev Immunol, 2013. 31: p. 563–604. [PubMed: 23516985]
33. Brown CC, et al. , Transcriptional Basis of Mouse and Human Dendritic Cell Heterogeneity. Cell, 2019. 179(4): p. 846–863.e24. [PubMed: 31668803]

34. Anderson DA 3rd, et al. , Genetic models of human and mouse dendritic cell development and function. Nat Rev Immunol, 2020.
35. Villani AC, et al. , Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science, 2017. 356(6335).
36. See P, et al. , Mapping the human DC lineage through the integration of high-dimensional techniques. Science, 2017. 356(6342).
37. Villar J and Segura E, The More, the Merrier: DC3s Join the Human Dendritic Cell Family. Immunity, 2020. 53(2): p. 233–235. [PubMed: 32814019]
38. Villar J and Segura E, Decoding the Heterogeneity of Human Dendritic Cell Subsets. Trends in Immunology, 2020.
39. Laurenti E and Göttgens B, From haematopoietic stem cells to complex differentiation landscapes. Nature, 2018. 553(7689): p. 418–426. [PubMed: 29364285]
40. Heidkamp GF, et al. , Human lymphoid organ dendritic cell identity is predominantly dictated by ontogeny, not tissue microenvironment. Sci Immunol, 2016. 1(6).
41. Joffre O, et al. , Inflammatory signals in dendritic cell activation and the induction of adaptive immunity. Immunol Rev, 2009. 227(1): p. 234–47. [PubMed: 19120488]
42. Manicassamy S and Pulendran B, Dendritic cell control of tolerogenic responses. Immunol Rev, 2011. 241(1): p. 206–27. [PubMed: 21488899]
43. Dunn GP, et al. , Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol, 2002. 3(11): p. 991–8. [PubMed: 12407406]
44. Wculek SK, et al. , Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol, 2020. 20(1): p. 7–24. [PubMed: 31467405]
45. Scarlett UK, et al. , Ovarian cancer progression is controlled by phenotypic changes in dendritic cells. J Exp Med, 2012. 209(3): p. 495–506. [PubMed: 22351930]
46. Chen DS and Mellman I, Oncology meets immunology: the cancer-immunity cycle. Immunity, 2013. 39(1): p. 1–10. [PubMed: 23890059]
47. Leal JM, et al. , Innate cell microenvironments in lymph nodes shape the generation of T cell responses during type I inflammation. Sci Immunol, 2021. 6(56).
48. Zilionis R, et al. , Single-Cell Transcriptomics of Human and Mouse Lung Cancers Reveals Conserved Myeloid Populations across Individuals and Species. Immunity, 2019. 50(5): p. 1317–1334.e10. [PubMed: 30979687]
49. Maier B, et al. , A conserved dendritic-cell regulatory program limits antitumour immunity. Nature, 2020. 580(7802): p. 257–262. [PubMed: 32269339]
50. Qian J, et al. , A pan-cancer blueprint of the heterogeneous tumor microenvironment revealed by single-cell profiling. Cell Res, 2020. 30(9): p. 745–762. [PubMed: 32561858]
51. Zhang Q, et al. , Landscape and Dynamics of Single Immune Cells in Hepatocellular Carcinoma. Cell, 2019. 179(4): p. 829–845.e20. [PubMed: 31675496]
52. Zhang L, et al. , Single-Cell Analyses Inform Mechanisms of Myeloid-Targeted Therapies in Colon Cancer. Cell, 2020. 181(2): p. 442–459.e29. [PubMed: 32302573]
53. Gerhard GM, et al. , Tumor-infiltrating dendritic cell states are conserved across solid human cancers. J Exp Med, 2021. 218(1).
54. Guilliams M, et al. , Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol, 2014. 14(8): p. 571–8. [PubMed: 25033907]
55. Cabeza-Cabrerizo M, et al. , Tissue clonality of dendritic cell subsets and emergency DCpoiesis revealed by multicolor fate mapping of DC progenitors. Sci Immunol, 2019. 4(33).
56. Salmon H, et al. , Expansion and Activation of CD103(+) Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition. Immunity, 2016. 44(4): p. 924–38. [PubMed: 27096321]
57. Crozat K, et al. , The XC chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse CD8alpha+ dendritic cells. J Exp Med, 2010. 207(6): p. 1283–92. [PubMed: 20479118]

58. Crozat K, et al. , Cutting edge: expression of XCR1 defines mouse lymphoid-tissue resident and migratory dendritic cells of the CD8α+ type. J Immunol, 2011. 187(9): p. 4411–5. [PubMed: 21948982]
59. Spranger S, Bao R, and Gajewski TF, Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. Nature, 2015. 523(7559): p. 231–5. [PubMed: 25970248]
60. Montoya M, et al. , Type I interferons produced by dendritic cells promote their phenotypic and functional activation. Blood, 2002. 99(9): p. 3263–71. [PubMed: 11964292]
61. Diamond MS, et al. , Type I interferon is selectively required by dendritic cells for immune rejection of tumors. J Exp Med, 2011. 208(10): p. 1989–2003. [PubMed: 21930769]
62. Fuertes MB, et al. , Type I interferon response and innate immune sensing of cancer. Trends Immunol, 2013. 34(2): p. 67–73. [PubMed: 23122052]
63. Nejman D, et al. , The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science, 2020. 368(6494): p. 973–980. [PubMed: 32467386]
64. Shi Y, et al. , Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy via STING signaling. J Exp Med, 2020. 217(5).
65. Laoui D, et al. , The tumour microenvironment harbours ontogenically distinct dendritic cell populations with opposing effects on tumour immunity. Nat Commun, 2016. 7: p. 13720. [PubMed: 28008905]
66. Bachem A, et al. , Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. J Exp Med, 2010. 207(6): p. 1273–81. [PubMed: 20479115]
67. Jongbloed SL, et al. , Human CD141+ (BDCA-3)+ dendritic cells (DCs) represent a unique myeloid DC subset that cross-presents necrotic cell antigens. J Exp Med, 2010. 207(6): p. 1247–60. [PubMed: 20479116]
68. Wu SJ, et al. , A Critical Analysis of the Role of SNARE Protein SEC22B in Antigen Cross-Presentation. Cell Rep, 2017. 19(13): p. 2645–2656. [PubMed: 28658614]
69. Theisen DJ, et al. , WDFY4 is required for cross-presentation in response to viral and tumor antigens. Science, 2018. 362(6415): p. 694–699. [PubMed: 30409884]
70. Alloatti A, et al. , Critical role for Sec22b-dependent antigen cross-presentation in antitumor immunity. J Exp Med, 2017. 214(8): p. 2231–2241. [PubMed: 28663435]
71. Cebrian I, et al. , Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. Cell, 2011. 147(6): p. 1355–68. [PubMed: 22153078]
72. Briseño CG, et al. , Distinct Transcriptional Programs Control Cross-Priming in Classical and Monocyte-Derived Dendritic Cells. Cell Rep, 2016. 15(11): p. 2462–74. [PubMed: 27264183]
73. Moussion C and Mellman I, The Dendritic Cell Strikes Back. Immunity, 2018. 49(6): p. 997–999. [PubMed: 30566889]
74. Johnson LA and Jackson DG, Inflammation-induced secretion of CCL21 in lymphatic endothelium is a key regulator of integrin-mediated dendritic cell transmigration. Int Immunol, 2010. 22(10): p. 839–49. [PubMed: 20739459]
75. Ohl L, et al. , CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. Immunity, 2004. 21(2): p. 279–88. [PubMed: 15308107]
76. Roberts EW, et al. , Critical Role for CD103(+)/CD141(+) Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma. Cancer Cell, 2016. 30(2): p. 324–336. [PubMed: 27424807]
77. Yewdall AW, et al. , CD8+ T cell priming by dendritic cell vaccines requires antigen transfer to endogenous antigen presenting cells. PLoS One, 2010. 5(6): p. e11144. [PubMed: 20585396]
78. Ruhland MK, et al. , Visualizing Synaptic Transfer of Tumor Antigens among Dendritic Cells. Cancer Cell, 2020. 37(6): p. 786–799.e5. [PubMed: 32516589]
79. Mikucki ME, et al. , Non-redundant requirement for CXCR3 signalling during tumoricidal T-cell trafficking across tumour vascular checkpoints. Nat Commun, 2015. 6: p. 7458. [PubMed: 26109379]
80. Thompson ED, et al. , Tumor masses support naive T cell infiltration, activation, and differentiation into effectors. J Exp Med, 2010. 207(8): p. 1791–804. [PubMed: 20660615]

81. Chow MT, et al. , Intratumoral Activity of the CXCR3 Chemokine System Is Required for the Efficacy of Anti-PD-1 Therapy. Immunity, 2019. 50(6): p. 1498–1512.e5. [PubMed: 31097342]
82. Enamorado M, et al. , Enhanced anti-tumour immunity requires the interplay between resident and circulating memory CD8(+) T cells. Nat Commun, 2017. 8: p. 16073. [PubMed: 28714465]
83. Duckworth BC, et al. , Effector and stem-like memory cell fates are imprinted in distinct lymph node niches directed by CXCR3 ligands. Nat Immunol, 2021. 22(4): p. 434–448. [PubMed: 33649580]
84. Garris CS, et al. , Successful Anti-PD-1 Cancer Immunotherapy Requires T Cell-Dendritic Cell Crosstalk Involving the Cytokines IFN-γ and IL-12. Immunity, 2018. 49(6): p. 1148–1161.e7. [PubMed: 30552023]
85. Jansen CS, et al. , An intratumoral niche maintains and differentiates stem-like CD8 T cells. Nature, 2019. 576(7787): p. 465–470. [PubMed: 31827286]
86. Satpathy AT, et al. , Zbtb46 expression distinguishes classical dendritic cells and their committed progenitors from other immune lineages. J Exp Med, 2012. 209(6): p. 1135–52. [PubMed: 22615127]
87. Meredith MM, et al. , Expression of the zinc finger transcription factor zDC (Zbtb46, Btbd4) defines the classical dendritic cell lineage. J Exp Med, 2012. 209(6): p. 1153–65. [PubMed: 22615130]
88. Dress RJ, et al. , Plasmacytoid dendritic cells develop from Ly6D(+) lymphoid progenitors distinct from the myeloid lineage. Nat Immunol, 2019. 20(7): p. 852–864. [PubMed: 31213723]
89. Inaba K, et al. , Generation of large numbers of dendritic cells from mouse bone marrow cultures supplemented with granulocyte/macrophage colony-stimulating factor. J Exp Med, 1992. 176(6): p. 1693–702. [PubMed: 1460426]
90. Karsunky H, et al. , Flt3 ligand regulates dendritic cell development from Flt3+ lymphoid and myeloid-committed progenitors to Flt3+ dendritic cells in vivo. J Exp Med, 2003. 198(2): p. 305–13. [PubMed: 12874263]
91. Xu Y, et al. , Differential development of murine dendritic cells by GM-CSF versus Flt3 ligand has implications for inflammation and trafficking. J Immunol, 2007. 179(11): p. 7577–84. [PubMed: 18025203]
92. Watowich SS and Liu YJ, Mechanisms regulating dendritic cell specification and development. Immunol Rev, 2010. 238(1): p. 76–92. [PubMed: 20969586]
93. Fuertes MB, et al. , Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8{alpha}+ dendritic cells. J Exp Med, 2011. 208(10): p. 2005–16. [PubMed: 21930765]
94. Alcántara-Hernández M, et al. , High-Dimensional Phenotypic Mapping of Human Dendritic Cells Reveals Interindividual Variation and Tissue Specialization. Immunity, 2017. 47(6): p. 1037–1050.e6. [PubMed: 29221729]
95. Cytlak U, et al. , Differential IRF8 Transcription Factor Requirement Defines Two Pathways of Dendritic Cell Development in Humans. Immunity, 2020. 53(2): p. 353–370.e8. [PubMed: 32735845]
96. Dutertre CA, et al. , Single-Cell Analysis of Human Mononuclear Phagocytes Reveals Subset-Defining Markers and Identifies Circulating Inflammatory Dendritic Cells. Immunity, 2019. 51(3): p. 573–589.e8. [PubMed: 31474513]
97. Bosteels C, et al. , Inflammatory Type 2 cDCs Acquire Features of cDC1s and Macrophages to Orchestrate Immunity to Respiratory Virus Infection. Immunity, 2020. 52(6): p. 1039–1056.e9. [PubMed: 32392463]
98. Böttcher JP and Reis e Sousa C, The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer, 2018. 4(11): p. 784–792. [PubMed: 30352680]
99. Poulin LF, et al. , DNGR-1 is a specific and universal marker of mouse and human Batf3-dependent dendritic cells in lymphoid and nonlymphoid tissues. Blood, 2012. 119(25): p. 6052–62. [PubMed: 22442345]
100. Sancho D, et al. , Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. Nature, 2009. 458(7240): p. 899–903. [PubMed: 19219027]

101. Hildner K, et al. , Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity. Science, 2008. 322(5904): p. 1097–100. [PubMed: 19008445]
102. Meyer MA, et al. , Breast and pancreatic cancer interrupt IRF8-dependent dendritic cell development to overcome immune surveillance. Nat Commun, 2018. 9(1): p. 1250. [PubMed: 29593283]
103. Theisen DJ, et al. , Batf3-Dependent Genes Control Tumor Rejection Induced by Dendritic Cells Independently of Cross-Presentation. Cancer Immunol Res, 2019. 7(1): p. 29–39. [PubMed: 30482745]
104. Qiu Z, et al. , Cutting Edge: Batf3 Expression by CD8 T Cells Critically Regulates the Development of Memory Populations. J Immunol, 2020. 205(4): p. 901–906. [PubMed: 32669309]
105. Ataide MA, et al. , BATF3 programs CD8+ T cell memory. Nature Immunology, 2020. 21(11): p. 1397–1407. [PubMed: 32989328]
106. Tussiwand R, et al. , Klf4 expression in conventional dendritic cells is required for T helper 2 cell responses. Immunity, 2015. 42(5): p. 916–28. [PubMed: 25992862]
107. Schlitzer A, et al. , IRF4 transcription factor-dependent CD11b+ dendritic cells in human and mouse control mucosal IL-17 cytokine responses. Immunity, 2013. 38(5): p. 970–83. [PubMed: 23706669]
108. Kim S, et al. , High Amount of Transcription Factor IRF8 Engages AP1-IRF Composite Elements in Enhancers to Direct Type 1 Conventional Dendritic Cell Identity. Immunity, 2020.
109. Heger L, et al. , CLEC10A Is a Specific Marker for Human CD1c(+) Dendritic Cells and Enhances Their Toll-Like Receptor 7/8-Induced Cytokine Secretion. Front Immunol, 2018. 9: p. 744. [PubMed: 29755453]
110. Binnewies M, et al. , Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4(+) T Cell Immunity. Cell, 2019. 177(3): p. 556–571.e16. [PubMed: 30955881]
111. Ferris ST, et al. , cDC1 prime and are licensed by CD4(+) T cells to induce anti-tumour immunity. Nature, 2020. 584(7822): p. 624–629. [PubMed: 32788723]
112. Dudziak D, et al. , Differential antigen processing by dendritic cell subsets in vivo. Science, 2007. 315(5808): p. 107–11. [PubMed: 17204652]
113. Fu C, et al. , Plasmacytoid dendritic cells cross-prime naive CD8 T cells by transferring antigen to conventional dendritic cells through exosomes. Proc Natl Acad Sci U S A, 2020. 117(38): p. 23730–23741. [PubMed: 32879009]
114. Villadangos JA and Young L, Antigen-presentation properties of plasmacytoid dendritic cells. Immunity, 2008. 29(3): p. 352–61. [PubMed: 18799143]
115. Brewitz A, et al. , CD8(+) T Cells Orchestrate pDC-XCR1(+) Dendritic Cell Spatial and Functional Cooperativity to Optimize Priming. Immunity, 2017. 46(2): p. 205–219. [PubMed: 28190711]
116. Persson CM and Chambers BJ, Plasmacytoid dendritic cell-induced migration and activation of NK cells in vivo. Eur J Immunol, 2010. 40(8): p. 2155–64. [PubMed: 20540112]
117. Tel J, et al. , Natural human plasmacytoid dendritic cells induce antigen-specific T-cell responses in melanoma patients. Cancer Res, 2013. 73(3): p. 1063–75. [PubMed: 23345163]
118. Leylek R, et al. , Chromatin Landscape Underpinning Human Dendritic Cell Heterogeneity. Cell Rep, 2020. 32(12): p. 108180. [PubMed: 32966789]
119. Musumeci A, et al. , What Makes a pDC: Recent Advances in Understanding Plasmacytoid DC Development and Heterogeneity. Front Immunol, 2019. 10: p. 1222. [PubMed: 31191558]
120. Deb P, et al. , Triggering of the cGAS-STING Pathway in Human Plasmacytoid Dendritic Cells Inhibits TLR9-Mediated IFN Production. J Immunol, 2020. 205(1): p. 223–236. [PubMed: 32471881]
121. Nierkens S, et al. , Immune adjuvant efficacy of CpG oligonucleotide in cancer treatment is founded specifically upon TLR9 function in plasmacytoid dendritic cells. Cancer Res, 2011. 71(20): p. 6428–37. [PubMed: 21788345]
122. Terra M, et al. , Tumor-Derived TGFβ Alters the Ability of Plasmacytoid Dendritic Cells to Respond to Innate Immune Signaling. Cancer Res, 2018. 78(11): p. 3014–3026. [PubMed: 29523540]

123. Conrad C, et al. , Plasmacytoid dendritic cells promote immunosuppression in ovarian cancer via ICOS costimulation of Foxp3(+) T-regulatory cells. Cancer Res, 2012. 72(20): p. 5240–9. [PubMed: 22850422]

124. Bruchhage KL, et al. , IL-10 in the microenvironment of HNSCC inhibits the CpG ODN induced IFN-α secretion of pDCs. Oncol Lett, 2018. 15(3): p. 3985–3990. [PubMed: 29456743]

125. Sisirak V, et al. , Breast cancer-derived transforming growth factor-β and tumor necrosis factor-α compromise interferon-α production by tumor-associated plasmacytoid dendritic cells. Int J Cancer, 2013. 133(3): p. 771–8. [PubMed: 23389942]

126. Aspord C, et al. , Melanoma hijacks plasmacytoid dendritic cells to promote its own progression. Oncoimmunology, 2014. 3(1): p. e27402. [PubMed: 24701375]

127. Labidi-Galy SI, et al. , Quantitative and functional alterations of plasmacytoid dendritic cells contribute to immune tolerance in ovarian cancer. Cancer Res, 2011. 71(16): p. 5423–34. [PubMed: 21697280]

128. Aspord C, et al. , Plasmacytoid dendritic cells support melanoma progression by promoting Th2 and regulatory immunity through OX40L and ICOSL. Cancer Immunol Res, 2013. 1(6): p. 402–15. [PubMed: 24778133]

129. Labidi-Galy SI, et al. , Plasmacytoid dendritic cells infiltrating ovarian cancer are associated with poor prognosis. Oncoimmunology, 2012. 1(3): p. 380–382. [PubMed: 22737622]

130. Ma Y, et al. , CCL2/CCR2-dependent recruitment of functional antigen-presenting cells into tumors upon chemotherapy. Cancer Res, 2014. 74(2): p. 436–45. [PubMed: 24302580]

131. Segura E, et al. , Human inflammatory dendritic cells induce Th17 cell differentiation. Immunity, 2013. 38(2): p. 336–48. [PubMed: 23352235]

132. Zhang X, et al. , Human Regulatory Dendritic Cells Develop From Monocytes in Response to Signals From Regulatory and Helper T Cells. Front Immunol, 2020. 11: p. 1982. [PubMed: 32973804]

133. Cheng S, et al. , A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell, 2021. 184(3): p. 792–809.e23. [PubMed: 33545035]

134. Dalod M, et al. , Dendritic cell maturation: functional specialization through signaling specificity and transcriptional programming. Embo j, 2014. 33(10): p. 1104–16. [PubMed: 24737868]

135. Miller JC, et al. , Deciphering the transcriptional network of the dendritic cell lineage. Nat Immunol, 2012. 13(9): p. 888–99. [PubMed: 22797772]

136. Michea P, et al. , Adjustment of dendritic cells to the breast-cancer microenvironment is subset specific. Nat Immunol, 2018. 19(8): p. 885–897. [PubMed: 30013147]

137. Galluzzi L, et al. , Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer, 2020. 8(1).

138. Deng L, et al. , STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity, 2014. 41(5): p. 843–52. [PubMed: 25517616]

139. Diamond JM, et al. , Exosomes Shuttle TREX1-Sensitive IFN-Stimulatory dsDNA from Irradiated Cancer Cells to DCs. Cancer Immunol Res, 2018. 6(8): p. 910–920. [PubMed: 29907693]

140. Carozza JA, et al. , Extracellular cGAMP is a cancer-cell-produced immunotransmitter involved in radiation-induced anticancer immunity. Nature Cancer, 2020. 1(2): p. 184–196. [PubMed: 33768207]

141. Apetoh L, et al. , Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med, 2007. 13(9): p. 1050–9. [PubMed: 17704786]

142. Obeid M, et al. , Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med, 2007. 13(1): p. 54–61. [PubMed: 17187072]

143. Michaud M, et al. , Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science, 2011. 334(6062): p. 1573–7. [PubMed: 22174255]

144. Aymeric L, et al. , Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity. Cancer Res, 2010. 70(3): p. 855–8. [PubMed: 20086177]

145. Ghiringhelli F, et al. , Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med, 2009. 15(10): p. 1170–8. [PubMed: 19767732]

146. Zhou Y, et al. , Blockade of the Phagocytic Receptor MerTK on Tumor-Associated Macrophages Enhances P2X7R-Dependent STING Activation by Tumor-Derived cGAMP. Immunity, 2020. 52(2): p. 357–373.e9. [PubMed: 32049051]

147. Ma Y, et al. , Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. Immunity, 2013. 38(4): p. 729–41. [PubMed: 23562161]

148. Vacchelli E, et al. , Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. Science, 2015. 350(6263): p. 972–8. [PubMed: 26516201]

149. Le Naour J, et al. , A TLR3 ligand reestablishes chemotherapeutic responses in the context of FPR1 deficiency. Cancer Discov, 2020.

150. Sistigu A, et al. , Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. Nat Med, 2014. 20(11): p. 1301–9. [PubMed: 25344738]

151. Formenti SC, et al. , Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med, 2018. 24(12): p. 1845–1851. [PubMed: 30397353]

152. Reits EA, et al. , Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med, 2006. 203(5): p. 1259–71. [PubMed: 16636135]

153. Zebertavage LK, et al. , Transcriptional Upregulation of NLRC5 by Radiation Drives STING- and Interferon-Independent MHC-I Expression on Cancer Cells and T Cell Cytotoxicity. Sci Rep, 2020. 10(1): p. 7376. [PubMed: 32355214]

154. Golden EB, et al. , Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. Oncoimmunology, 2014. 3: p. e28518. [PubMed: 25071979]

155. Widau RC, et al. , RIG-I-like receptor LGP2 protects tumor cells from ionizing radiation. Proc Natl Acad Sci U S A, 2014. 111(4): p. E484–91. [PubMed: 24434553]

156. Ranoa DR, et al. , Cancer therapies activate RIG-I-like receptor pathway through endogenous non-coding RNAs. Oncotarget, 2016. 7(18): p. 26496–515. [PubMed: 27034163]

157. Zheng W, et al. , RIG-I-like receptor LGP2 is required for tumor control by radiation therapy. Cancer Research, 2020: p. canres.2324.2020.

158. Vanpouille-Box C, et al. , DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun, 2017. 8: p. 15618. [PubMed: 28598415]

159. Vanpouille-Box C, Formenti SC, and Demaria S, Toward Precision Radiotherapy for Use with Immune Checkpoint Blockers. Clin Cancer Res, 2018. 24(2): p. 259–265. [PubMed: 28751442]

160. Burnette BC, et al. , The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity. Cancer Res, 2011. 71(7): p. 2488–96. [PubMed: 21300764]

161. Lim JY, et al. , Type I interferons induced by radiation therapy mediate recruitment and effector function of CD8(+) T cells. Cancer Immunol Immunother, 2014. 63(3): p. 259–71. [PubMed: 24357146]

162. Marciscano AE, et al. , Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy. Clin Cancer Res, 2018. 24(20): p. 5058–5071. [PubMed: 29898992]

163. Sharabi AB, et al. , Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res, 2015. 3(4): p. 345–55. [PubMed: 25527358]

164. Buchwald ZS, et al. , Tumor-draining lymph node is important for a robust abscopal effect stimulated by radiotherapy. J Immunother Cancer, 2020. 8(2).

165. Blair TC, et al. , Dendritic Cell Maturation Defines Immunological Responsiveness of Tumors to Radiation Therapy. J Immunol, 2020. 204(12): p. 3416–3424. [PubMed: 32341058]

166. Liang H, et al. , Host STING-dependent MDSC mobilization drives extrinsic radiation resistance. Nat Commun, 2017. 8(1): p. 1736. [PubMed: 29170400]

167. Hou Y, et al. , Non-canonical NF-κB Antagonizes STING Sensor-Mediated DNA Sensing in Radiotherapy. Immunity, 2018. 49(3): p. 490–503.e4. [PubMed: 30170810]
168. Lin H, et al. , Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression. J Clin Invest, 2018. 128(2): p. 805–815. [PubMed: 29337305]
169. Tang H, et al. , PD-L1 on host cells is essential for PD-L1 blockade-mediated tumor regression. J Clin Invest, 2018. 128(2): p. 580–588. [PubMed: 29337303]
170. Dammeijer F, et al. , The PD-1/PD-L1-Checkpoint Restrains T cell Immunity in Tumor-Draining Lymph Nodes. Cancer Cell, 2020.
171. Raeber ME, et al. , Interleukin-2 signals converge in a lymphoid-dendritic cell pathway that promotes anticancer immunity. Sci Transl Med, 2020. 12(561).
172. Oba T, et al. , A Critical Role of CD40 and CD70 Signaling in Conventional Type 1 Dendritic Cells in Expansion and Antitumor Efficacy of Adoptively Transferred Tumor-Specific T Cells. J Immunol, 2020. 205(7): p. 1867–1877. [PubMed: 32848036]
173. Furumoto K, et al. , Induction of potent antitumor immunity by in situ targeting of intratumoral DCs. J Clin Invest, 2004. 113(5): p. 774–83. [PubMed: 14991076]
174. Anandasabapathy N, et al. , Efficacy and safety of CDX-301, recombinant human Flt3L, at expanding dendritic cells and hematopoietic stem cells in healthy human volunteers. Bone Marrow Transplant, 2015. 50(7): p. 924–30. [PubMed: 25915810]
175. Gilfillan CB, et al. , Clec9A(+) Dendritic Cells Are Not Essential for Antitumor CD8(+) T Cell Responses Induced by Poly I:C Immunotherapy. J Immunol, 2018. 200(8): p. 2978–2986. [PubMed: 29507107]
176. Vonderheide RH, The Immune Revolution: A Case for Priming, Not Checkpoint. Cancer Cell, 2018. 33(4): p. 563–569. [PubMed: 29634944]
177. Ribas A, et al. , SD-101 in Combination with Pembrolizumab in Advanced Melanoma: Results of a Phase Ib, Multicenter Study. Cancer Discov, 2018. 8(10): p. 1250–1257. [PubMed: 30154193]
178. Walshaw RC, et al. , Toll-Like Receptor Agonists and Radiation Therapy Combinations: An Untapped Opportunity to Induce Anticancer Immunity and Improve Tumor control. Int J Radiat Oncol Biol Phys, 2020. 108(1): p. 27–37. [PubMed: 32339645]
179. Spranger S and Gajewski TF, Impact of oncogenic pathways on evasion of antitumour immune responses. Nat Rev Cancer, 2018. 18(3): p. 139–147. [PubMed: 29326431]
180. Ruiz de Galarreta M, et al. , β-Catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 Therapy in Hepatocellular Carcinoma. Cancer Discov, 2019. 9(8): p. 1124–1141. [PubMed: 31186238]
181. Peng W, et al. , Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. Cancer Discov, 2016. 6(2): p. 202–16. [PubMed: 26645196]
182. Chen S, et al. , Control of T(reg) cell homeostasis and immune equilibrium by Lkb1 in dendritic cells. Nat Commun, 2018. 9(1): p. 5298. [PubMed: 30546010]
183. Wang Y, et al. , LKB1 orchestrates dendritic cell metabolic quiescence and anti-tumor immunity. Cell Res, 2019. 29(5): p. 391–405. [PubMed: 30911060]
184. Lin A, et al. , Dendritic cells integrate signals from the tumor microenvironment to modulate immunity and tumor growth. Immunol Lett, 2010. 127(2): p. 77–84. [PubMed: 19778555]
185. Alice AF, et al. , Amplifying IFN-γ Signaling in Dendritic Cells by CD11c-Specific Loss of SOCS1 Increases Innate Immunity to Infection while Decreasing Adaptive Immunity. J Immunol, 2018. 200(1): p. 177–185. [PubMed: 29150567]
186. Cubillos-Ruiz JR, et al. , ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. Cell, 2015. 161(7): p. 1527–38. [PubMed: 26073941]
187. Zelenay S, et al. , Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity. Cell, 2015. 162(6): p. 1257–70. [PubMed: 26343581]
188. Monti M, et al. , Plasmacytoid Dendritic Cell Impairment in Metastatic Melanoma by Lactic Acidosis. Cancers (Basel), 2020. 12(8).

Highlights:

- Dendritic cells (DC) are a diverse subset of immune cells that initiate, orchestrate and regulate antitumor immune responses
- Dysregulation of DC activation, licensing and maturation dampens antigen-specific T cell immunity
- Anti-cancer treatments can directly and indirectly modulate DC function
- Therapeutic targeting of DCs may synergize with other immunotherapeutic or anti-cancer treatments to initiate *de novo* anti-tumor immunity or augment pre-existing responses.