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Tissue-specific properties of type 1 dendritic cells in lung cancer: implications for immunotherapy

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ABSTRACT

Checkpoint inhibitors have led to remarkable benefits in non-small cell lung cancer (NSCLC), yet response rates remain below expectations. High-dimensional analysis and mechanistic experiments in clinical samples and relevant NSCLC models uncovered the immune composition of lung cancer tissues, providing invaluable insights into the functional properties of tumor-infiltrating T cells and myeloid cells. Among myeloid cells, type 1 conventional dendritic cells (cDC1s) stand out for their unique ability to induce effector CD8 T cells against neoantigens and coordinate antitumoral immunity. Notably, lung resident cDC1 are particularly abundant and long-lived and express a unique tissue-specific gene program, underscoring their central role in lung immunity. Here, we discuss recent insights on the induction and regulation of antitumoral T cell responses in lung cancer, separating it from the tissue-agnostic knowledge generated from heterogeneous tumor models. We focus on the most recent studies dissecting functional states and spatial distribution of lung cDC1 across tumor stages and their impact on T cell responses to neoantigens. Finally, we highlight relevant gaps and emerging strategies to harness lung cDC1 immunostimulatory potential.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, with an estimated 1.8 million deaths annually (WHO).[1] Lung cancer can be divided into small cell lung cancer (SCLC, around 15% of diagnosed cases) and the more prevalent form of non-small cell lung cancer (NSCLC, 85% of lung cancer cases).[2] Conventional therapies, including surgery, chemotherapy and radiation, have been the mainstay of NSCLC treatment.[3] The past decade has seen a revolutionary shift with the introduction of immune checkpoint inhibitors (ICB), antibodies that target inhibitory receptors expressed on exhausted T cells to reinvigorate their activity. Currently, six ICBs are approved for NSCLC. These include molecules targeting CTLA-4 (ipilimumab), PD-L1 (atezolizumab, durvalumab), and PD-1 (nivolumab, pembrolizumab, cemiplimab). The fraction of patients with NSCLC experiencing clinical benefits from ICBs reaches up to 30% in selected groups with high PD-L1 expression, and it is further enhanced when combined with chemotherapy.[4 5] The molecular determinants of response to ICB and the mechanisms of primary and acquired resistance remain ill-defined. Emerging data suggest that tumor heterogeneity and an immune suppressive microenvironment may curb the action of ICB (extensively covered in previous works[6–8]). In this scenario, disentangling the complexity of infiltrating myeloid cells and their impact on anticancer responses is essential to complement or substitute current therapeutic approaches. In this respect, type 1 conventional dendritic cells (cDC1) hold a central position by instructing multiple steps along the life cycle of anticancer T cells. Experimental studies across diverse tumor settings demonstrated the role of cDC1 in shaping the antitumoral T cell repertoire, and clinical datasets support a positive correlation between cDC1-specific gene signatures and better prognosis/response to therapy.[9–15] However, there is still a major gap in understanding tissue-specific properties in diverse tumor types. Furthermore, we still know little about cDC1 at early stages of tissue transformation. Studies based on genetic models of experimental NSCLC have provided formal evidence that lung tissues imprint a specific dysfunctional program in CD8 T cells and shape the reprogramming of myeloid cells.[16–19] The transcriptional profiles and spatial distribution of lung tissue cDC1 are also emerging, supporting a central role of the subset in orchestrating anticancer T cell responses locally.[13 20 21] Notably, findings in mouse models of NSCLC recapitulate quite faithfully the profiles of cDC1 in human cancer tissues, validating preclinical testing.[20 22] Strategies to empower cDC1 immunostimulatory potential are beginning to show promising results in lung cancer models and clinical trials.[23–26] Here, we will

discuss key general concepts and focus specifically on cDC1 in lung cancer, in humans and relevant experimental models.

TISSUE-RESIDENT LUNG DENDRITIC CELLS (DCS)

The lung is continuously exposed to various external substances and insults, including pathogens and allergens. Therefore, the organ has evolved highly specialized immune circuits to balance homeostasis with defense from threats that may impair gas exchange. Monocytes, macrophages and DCs create a dense network of cells under the lung's epithelial barrier and serve as sentinels to protect lung homeostasis. As other reviews have covered lung monocytes and macrophages,[27 28] in this section, we will revise key knowledge about cDCs in lung tissues, at steady state or in contexts other than cancer. Similarly to other peripheral tissues, the normal lung contains two broad subsets of cDCs: cDC1 and cDC2.[29] Lung cDC1s were initially described in mouse lung tissues as cells expressing CD103, localized primarily in the lung parenchyma and around vessels.[30–32] Later studies demonstrated that peripheral tissue cDC1s express XCR1 and originate from pre-DC precursors under the control of FMS-like tyrosine kinase 3 ligand (Flt3L) and depend on the transcription factors Batf3, the inhibitor of DNA protein 2 (Id2) and IFN regulatory protein 8 (IRF8).[33–35] Functionally, cDC1 excel in cross-presentation, the capacity to capture and process cell-associated antigens for presentation to CD8 T cells.[36 37] Specific studies to address the role of lung resident cDC1 confirmed their superior ability to engulf apoptotic and virally infected cells and to induce cytotoxic T cells and T cell memory by cross-presentation.[38–41] cDC2 are more complex and heterogeneous, express high levels of CD11b and depend on IRF4 for their development. Within the broad cDC2 lineage, the exact subset composition, developmental trajectories and functions are still under examination.[42 43] However, consistent evidence suggests a preferential involvement of cDC2 in T helper cell activation.[43 44] In the specific case of lung tissues, cDC2 were shown to promote the differentiation of CD4 T cells into Th2 or Th17, depending on the context, in asthma and allergy.[45 46] More recent data highlight a subpopulation of hyperactivated lung cDC2 that arise during inflammation and acquire properties of cDC1 and macrophages.[47] During respiratory viral infections, chemokines recruit pre-DCs that expand the cDC compartment in situ for amplification of antiviral T cell responses, underscoring the ability of the compartment to adapt to the organ requirements.[48] Consistently, the lungs of SARS-CoV-2 infected patients show an increase in the abundance of inflammatory cDCs.[49] Initial efforts to define the human counterpart of murine conventional DCs were based on blood circulating cells and lymph nodes, anticipating a high degree of developmental and functional conservation across species. Hence, a homogeneous population of cells expressing CD141, XCR1, Clec9a, high levels of TLR3 and genes related to cross-presentation was identified as the human counterpart of mouse cDC1.[50 51] In keeping with the analogies, cells expressing BDCA1 and CD1c, SIRPα and IRF-4 are the human counterpart of murine cDC2 and are functionally poised to induce CD4 T cell proliferation and Th17 activation.[52] High-resolution analysis revealed further distinction within cDC2, with the identification of a rare subset of cells expressing CD1c and CD14 and a monocyte-like signature.[53 54] This subset, named DC3, represents a novel lineage that expands in inflammation and has a specific developmental pathway, distinct from cDC1, cDC2 and monocytes.[55–57] More recently, fate-mapping in mouse models established that DC3 develop from Ly6C monocyte progenitors.[58] As discussed in the next section, profiling of lung cancer tissues from patients with cancer and experimental models uncovered further complexity and plasticity in the cDC compartment.

DC SUBSETS IN LUNG CANCER TISSUES

NSCLC comprises two major histologic subtypes: lung adenocarcinoma (LUAD, 70% of cases) and lung squamous carcinoma (LUSC, 20% of cases).[59] Neutrophils and T cells have shown distinct compositions in the two subtypes.[60 61] However, unique and subtype-specific features have not yet emerged for cDCs. Therefore, we present data on NSCLC, without distinguishing between LUAD and LUSC. Earlier studies based on immunohistochemistry and flow cytometry provided initial evidence that lung cancer tissues harbor rare cDC subsets with analogies to circulating DCs in the blood.[27 62] Subsequent high-dimensional analysis combining mass cytometry by time-of-flight with single-cell transcriptomics and multiplex tissue imaging captured DCs in tumor tissues, adjacent healthy tissues and blood. Two conventional DC clusters, the first marked by CD207, Clec9A, and Xcr1 and the second expressing CD1c, CX3CR1 and IRF4, were identified and aligned to cDC1 and cDC2, respectively.[22] Shortly after, an scRNA analysis focusing at a higher resolution on infiltrating myeloid cells confirmed the presence of a well-defined cluster of $Xcr1^+$, $Clec9a^+$, $Tbhd^+$ cells carrying genes related to cross-presentation and corresponding to cDC1. A second subset with a prevalent expression of Cd1a, Cd1c, Cd1e, Cd207, Fcer1a and genes governing interaction with CD4 T cells was identified as cDC2. Moreover, the analysis revealed a subset of mature activated DCs, lacking cDC1 and cDC2 lineage-defining genes.[63] A further scRNAseq analysis of NSCLC biopsies confirmed the presence of a similar cluster showing concomitant expression of immunoregulatory (Cd274, Pdcd1lg2 and Cd200) and maturation genes (Cd40, Ccr7 and Il12b), which represent a cellular state to which cDC1 and cDC2 converge.[20] These cells are found in diverse cancer tissues and have been variably named migratory DCs (migDCs), $LAMP3^+$ DCs or "mature DCs enriched in immunoregulatory molecules" mRegDCs.[20 64] In addition, the DC3 subset is well represented in NSCLC, more abundantly than migDC, and it has been associated

with an immune suppressive phenotype.[65 66] The gene signatures derived from high-dimensional single-cell technologies have been applied to large RNA seq datasets to infer correlation with patient outcomes. As a result, classical cDC1 signatures have been invariably associated with better patient outcomes across cancers, including NSCLC.[11–15] Moreover, CCR7^{+}LAMP3^{+} cDCs expressing features of mRegDCs correlate with better responses to immunotherapy in lung cancer.[21] The function of cDC2, classically associated with CD4 T cell activation, is less defined and controversial in tumors because of the complexity and heterogeneity of the subset and the difficulties in targeting it in mouse models. cDC2s are shown to support antitumoral responses when relieved from suppression by regulatory T cells in melanoma models[67] and to acquire an inflammatory phenotype capable of acquiring MHC-I peptide complexes by cross-dressing.[68] While several studies have associated cDC2 with a positive prognosis across human cancers, the prognostic value in lung cancer remains controversial.[69]

EXPERIMENTAL MODELS OF NSCLC

Mouse models of lung cancer have been instrumental in investigating the principles of antitumoral immunity and the opposing mechanism that counteracts protective responses. Lewis lung carcinoma cells (LLCs) have long been used for preclinical studies in syngeneic mice, providing earlier breakthroughs in cancer biology and therapy and the first analysis of cDCs in lung tumor tisues.[70 71] As a drawback, LLC is a fast-growing metastatic model carrying a hypermutated phenotype accumulated during long-term laboratory passages, precluding the analysis of early oncogenic events and their interplay with immune cells. The introduction of genetic models of NSCLC based on Cre-inducible Kras activating mutation and p53 loss of function (KP) in early 2000 represented a paradigm shift in lung cancer research. These models, which faithfully recapitulate the histopathologic features and spatiotemporal dynamics of human tumors and mimic immune remodeling in the native tumor environment, have become a reference for exploring tumorigenesis and the interplay with the immune microenvironment.[72]

Induction of primary KP tumors in the lung relies on viral delivery of Cre, impacting the microenvironment of nascent cancer lesions, which imposes the use of appropriate controls when assessing immune changes.[73] Alongside the elegant possibility of inducing tumors in situ, KP-derived cell lines and 3D organoids can be implanted orthotopically to avoid viral-mediated infection. This approach enables convenient genetic manipulation of cancer cells while preserving the histopathologic features of primary tumors and can be tuned to control the speed of tumor progression.[13 20 74 75] Experimental NSCLC using KP provided important insights into the mechanism underlying T cell immunity to lung cancer. As illustrated in figure 1a, diverse approaches have been used to introduce model antigens, as the intrinsic immunogenicity of the model is very low (figure 1a). By engineering a lentiviral cassette that encodes Cre and two model antigens (SIY, a synthetic antigen and SIIN, a class-I peptide derived from ovalbumin), it was first demonstrated that antitumoral CD8 T cells transiently control tumor growth before undergoing suppression by regulatory T cells.[76 77] Later analysis using the same two antigens demonstrated that responses to a dominant antigen (SIIN in this case) outcompete responses to subdominant antigens (SIY), limiting the amplitude of the antitumoral response. Interestingly, vaccination can revert the subdominant phenotype to engage simultaneous T cell responses against multiple antigens, improving tumor control.[78] By tracking tumor-specific CD8 T cells against the model antigen ovalbumin, a later study identified the transcriptional profiles of exhausted cells in the lung and the presence of a reservoir of TCF-1^{+}Slamf6^{+} CD8 T cells in lymph nodes.[23 79] Delving into the roots of suboptimal CD8 T cell activation in transplantable KP-OVA tumors, the Spranger group demonstrated a tissue-specific dysfunctional program which depends on suboptimal priming in the mediastinal lymph node.[16 17] Elegant refinements of the tools to express model antigens in KP include a lung epithelial cell-specific promoter (Spc) and a system to control the kinetics of neoantigen expression, improving the translational potential of the KP model.[73 80] Moreover, the KP model has been engineered to mimic the neoantigen load of human tumors, as thoroughly discussed in the next sections[24 81 82] (figure 1a).

Interestingly, KP models also recapitulate the composition and features of macrophages and neutrophils, the most prominent immune infiltrates in NSCLC[83 84] (figure 1b). Thus, transcriptional states, mechanism of recruitment and properties of tumor-infiltrating neutrophils are consistent across humans and mice, establishing a precious resource for target discovery and validating the preclinical value of the KP model.[19 63 85] Moreover, a seminal study in KP established a detrimental interaction of the commensal lung microbiome with infiltrating immune cells.[86] High-dimensional deconvolution of tissue-resident macrophages uncovered the transcriptional profiles and developmental trajectories of protumorigenic resident macrophages, conserved across humans and mice, providing novel axes for potential manipulation in human cancers.[18] More recently, the impact of aging of the myeloid compartment on tumor progression was demonstrated using KP lung tumors and validation in human cancers[87] (figure 1b).

CDC1S AND THE CONTROL OF ANTITUMORAL IMMUNITY

The mechanisms governing cDC1 functions in tumors have been quite extensively investigated, as the subset is homogeneous and transcriptionally stable, and experimental models to delete it in vivo have been available for several years (extensively covered in several excellent reviews).[69 88–91] Briefly, multiple cellular specializations underline the antitumoral properties of cDC1. First,

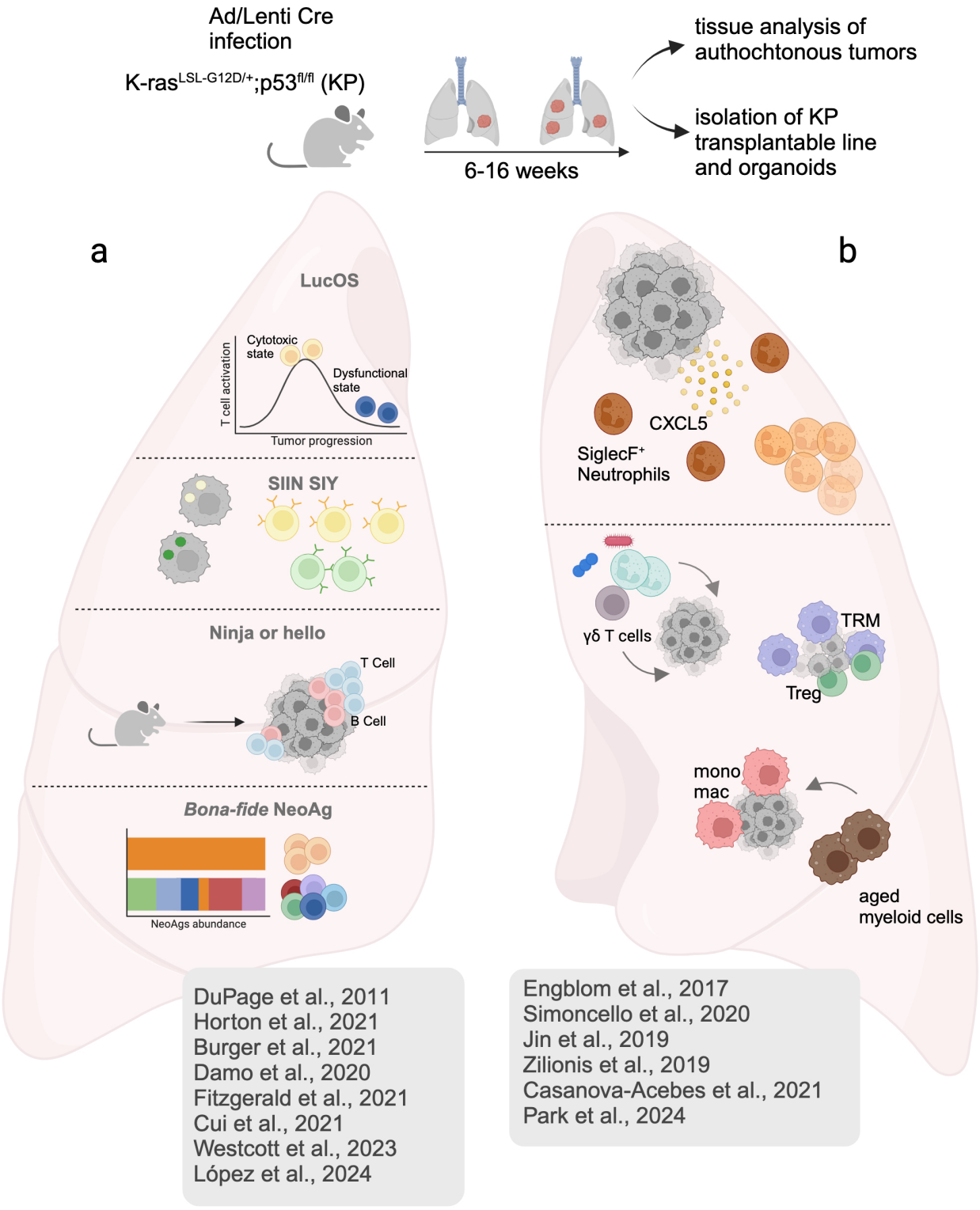

Figure 1 Experimental models to study the immune microenvironment of non-small cell lung cancer (NSCLC). Genetically engineered mouse models of NSCLC are driven by a Cre-inducible Kras activating mutations combined with p53 loss of function (KP), providing a robust system to control tumor initiation in situ. (a) The left panel shows a summary of the strategies used to investigate antitumoral CD8 responses by introducing exogenous antigens or increasing the tumor mutational burden. The main conceptual findings on the persistence/functional states/dominance/clonality and spatial organization of CD8 responses are depicted in the scheme. (b) The right panel depicts the composition and impact of myeloid cells in KP lung tumors. Diverse neutrophil states accumulate during progression, with divergent impacts on tumor progression. Commensal bacteria can activate myeloid subsets, contributing to tumor growth and immune modulation. Tissue-resident macrophages (TRMs) promote epithelial-mesenchymal transition and Treg-mediated immune evasion, while mono/derived macrophages drive the progression of established tumors. During aging, altered hematopoiesis supply the lung with suppressive myeloid cells.

specific phagocytic receptors enable cDC1 to acquire cancer-cell-associated antigens in tumor tissues. These include DNGR-1/Clec9, the AXL/LRP-1/RANBP9 complex, TIM3 and TIM4, depending on the tissue.[69] Second, a complex antigen processing machinery routes engulfed antigens for presentation to both CD8 and CD4 T cells, providing a critical platform to support the CD4-CD8 cross-talk and launching of efficient antitumoral immunity.[36 92–94] Importantly, CD4 licensing of cDC1 for optimal CD8 T cell priming has been confirmed in humans.[95] The unique ability to cross-present antigens derived from apoptotic or necrotic cells depends on the slow acidification of the endocytic pathway to preserve epitopes and the regulated leakage of phagosomal content into the cytosol to enter the MHC class-I presentation pathway.[96] In addition, sensing of danger factors by cDC1 in the tumor microenvironment induces the expression of chemokine receptors like CCR7 to migrate to tumor-draining lymph nodes and Cxcl9 and Cxcl10 to attract T cells in the tumor bed. Costimulatory molecules and T cell instructing cytokines, notably interleukin-12 (IL-12), secreted by activated cDC1 complete the toolbox to program T cell responses (extensively reviewed in previous works[97 98]). However, the tumor microenvironment counteracts the immunostimulatory potential of cDC1 at multiple levels, impairing their differentiation and survival, blunting phagocytosis, antigen presentation and cytokine production and inducing cell-intrinsic metabolic stress.[97] Alongside the loss of immunostimulatory properties, cDC1 in cancer tissue acquire active mechanisms of immune suppression. Of note, PD-L1 expression by cDC1 engages PD-1 on T cells, restricting T cell activation during cross-presentation and impeding antitumoral immunity.[99 100] Several other inhibitory receptors are induced on cDCs in tumors, and diverse soluble mediators of suppression have been identified across diverse tumor settings (nicely reviewed in the literature[89]). However, given the heterogeneity of the experimental models, it is not yet possible to conclude whether these mechanisms are universal or vary depending on the environment of specific tumor tissues.

cDC1 and the control of antitumoral immunity: focus on lung cancer.

As just mentioned, we still lack an appreciation of how cDC1 activities may be modulated differently, depending on the tumor's tissue of origin. Aligning to the emerging idea that the anatomical site profoundly shapes anticancer immune responses,[101–104] we will focus the next section on the existing data about cDC1 in lung orthotopic experimental models, selecting the reports based on robust identification of bona fide cDC1.

Of note, cDC1 are significantly more abundant and long-lived in the lung than in the liver or the spleen[33 105 106] and further adapt their numbers in response to tissue perturbation.[48] Indeed, the transcriptional profile of lung cDC1 diverges substantially from the core program shared across tissues (figure 2, from the Immunological Genome Consortium[107]). The genes showing selectively

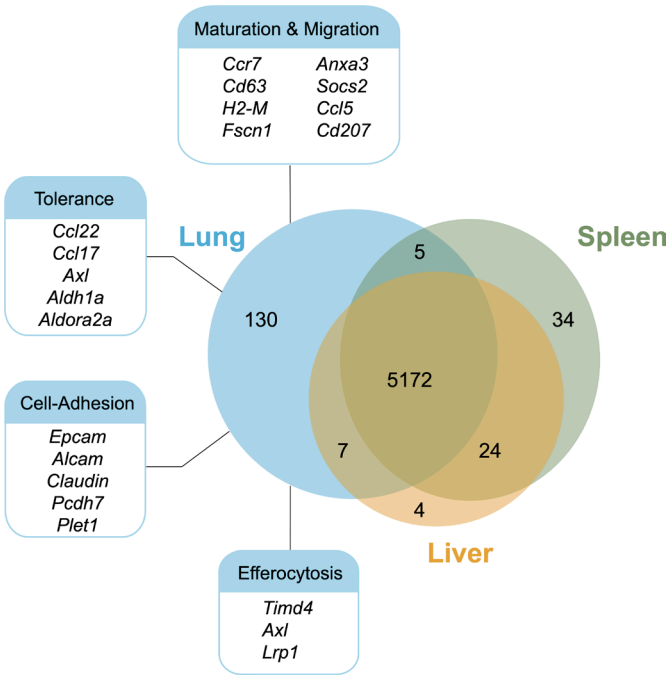

Figure 2 Transcriptional identity of lung cDC1. Venn diagram showing the core genes shared between cDC1 isolated from lungs, spleen and liver and those selectively expressed in each of the indicated tissues. Transcriptomics data for cDC1 sorted from lung, liver and spleen were retrieved from the Immunological Genome Project website (https://www.immgen.org/) and analyzed in R (V.4.3.1). Normalized reads from each tissue were used to calculate the ratio between gene expression across tissues (lung vs spleen, lung vs liver and liver vs spleen). Genes with a ratio >5 in both comparisons were identified as tissue-exclusive. Shared genes have a ratio <2, between the two tissues but >5 with the third tissue. Only genes with more than 100 normalized reads were included in the analysis.

high expression in lung cDC1 include adhesion molecules controlling the interaction with the extracellular matrix and cell-cell contact, receptors for clearance of apoptotic cells (efferocytosis), genes controlling migration and genes controlling maturation and expression of costimulatory molecules[20 47] (figure 2). Concomitantly, lung cDC1s highly express gene modules governing tolerogenic function, like Treg attracting chemokines (Ccl17 and Ccl22) and enzymes controlling immune suppression (Adora 2a, Aldh1a2), reflecting a tissue-specific program poised to maintain lung homeostasis.

In the tumor setting, earlier analyses of lung cDCs in an orthotopic Lewis lung carcinoma model first established the role of cDC1 in inducing cytotoxic CD8 T cells and cDC2 in inducing Th17 cells.[70] Later, a milestone report identified a further population of cDCs in lungs carrying KP tumors, marked by concomitant expression of maturation and regulatory markers (named mRegDCs).[20] This same study investigated the mechanism triggering the mature/tolerogenic state, showing that it is a transcriptional program arising in cDC1 and cDC2 on engulfment of apoptotic cells. Remarkably, the checkpoints

PD-L1 and PD-L2 are highly induced on DCs, in both transplantable and autochthonous KP tumors.[99 108] The other negative regulators in the mRegDCs program (Axl, Ccl19, Ccl22, Aldh1) largely overlap with those defining lung cDC1, indicating that cancer cell uptake amplifies tolerogenic axes already prominent in lung tissue cDC1 (figure 2). Hence, although broad modules within the mRegDCs program are similar to those encoded by mature/migratory DCs and are shared across cancers,[109] tissue-specific properties likely imprint differences in submodules, according to the tissue. Blockade experiments and genetic deletion further demonstrated that IL4r and AXL induced in cancer cell-containing cDCs are directly implicated in blunting CD8 T cell activation and that AXL directly counteracts the productive assembly of costimulatory molecules on the surface of mature DCs, diminishing their immunostimulatory potential.[20 109 110]

Steady-state cDC1 in the murine lung tissues expresses uniquely high levels of the receptor Tim4, which is implicated in the capture and processing of cancer cell debris for tumor antigen presentation.[13 111] However, Tim4 is downregulated in advanced tumors, suggesting that cells entering the regulatory program also cease antigen sampling. In parallel, lung tumors are known to induce a peculiar tissue-specific dysfunctional program in antitumoral CD8 T cells.[16] This mechanism depends, at least partially, on Treg-mediated suppression of cDC1 in lymph nodes.[16 17] Collectively, these findings from experimental models suggest a lung tissue-specific behavior of cDC1, whose molecular determinants remain to be fully elucidated. In addition, the timeline of cDC1 functional adaptation to lung cancer progression is poorly explored. Early KP lesions are enriched in functional cDC1 that efficiently capture and cross-present tumor antigens to CD8 T cells. Conversely, lung cDC1s are depleted and dysfunctional in established lung tumors[13 22] (figure 3). Deactivation encompasses the downregulation of receptors to acquire cancer cell fragments, diminished cross-presentation and decreased expression of adhesion molecules to interact with CD8 T cells.[13 101 108] Further insights into the state and activity of cDC1 in early tumor lesions will be critical to understand the mechanisms underlying the transition from immunostimulatory to immune-suppressive cDC1. In this respect, tumors slowly developing in situ will help

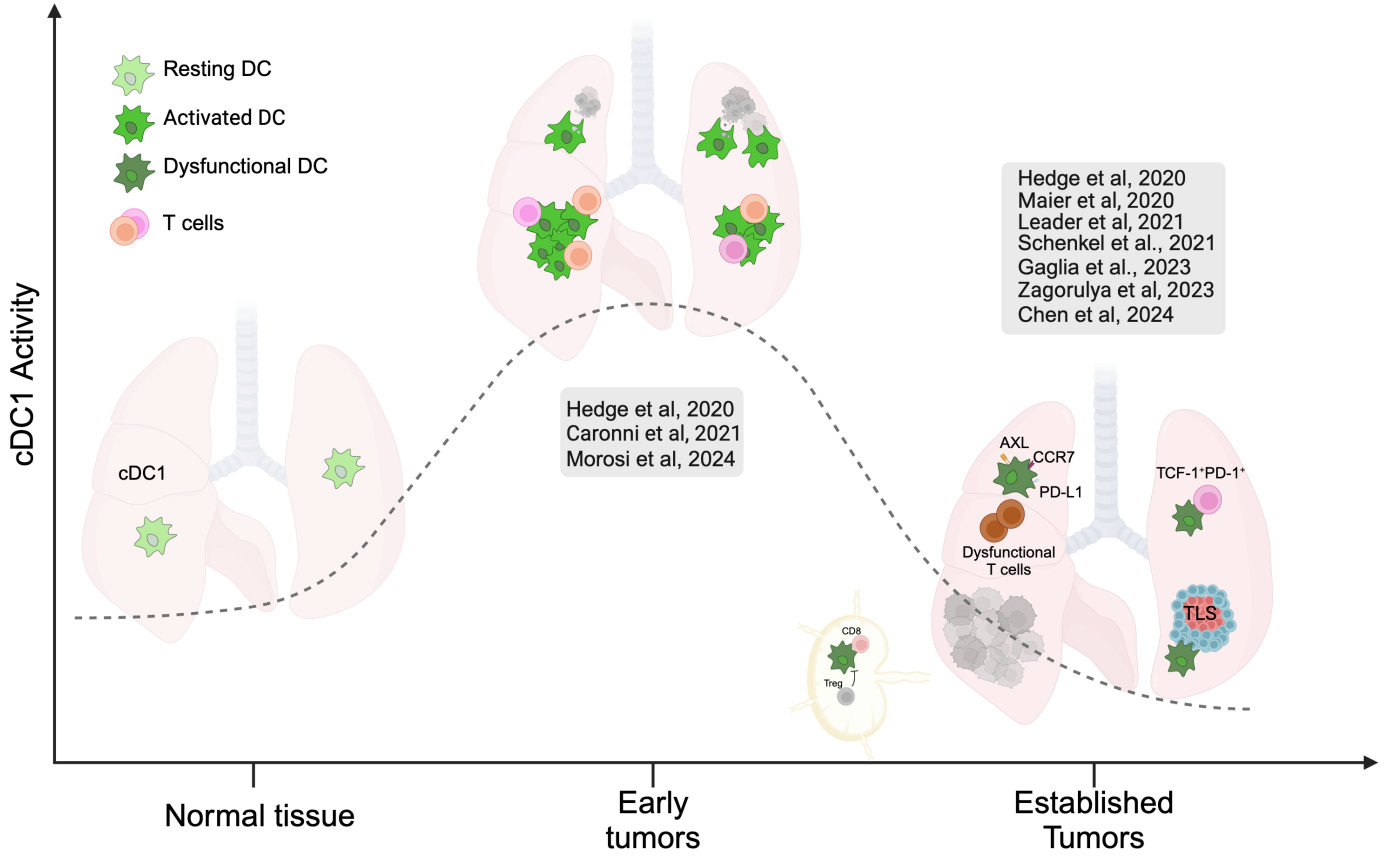

Figure 3 Spatiotemporal changes in cDC1 during non-small cell lung cancer (NSCLC) progression. The cartoon depicts cDC1 evolution during tumor progression, as it emerges from recent data. At tumor inception, the cDC1 compartment is enlarged and shows signs of activation as compared with resting lungs. cDC1 actively captures debris of dying cancer for cross-presentation and induction of antitumoral CD8 T cells and forms stable clusters with $CD8^+$ T cells. In advanced tumors, cDCs acquire regulatory markers, fail to cross-present tumor antigens and inefficiently interact with T cells in lung tissues. Moreover, a suppressive environment is established in tumor-draining lymph nodes whereby Tregs blunt the ability of cDC1 to induce CD8 T cell priming.

to deconvolve at higher resolution the gradual adaptation of the cDC1 compartment to transforming tissues (figure 3).

CROSS-PRESENTATION OF TUMOR NEOANTIGENS BY CDC1

As anticipated, cross-presentation of tumor antigens is the hallmark of cDC1 activity in tumors. The principle has been established primarily by studying ex vivo differentiated cDCs and by validation in vivo using cDC1 deficient strains or deletion of genes controlling cross-presentation in cDC1.[36 112] Invariably, these studies employed model antigens to facilitate the detection of pMHC complexes and tracking of tumor-specific T cells. However, in human cancers, T-cell responses are directed against a range of diverse and heterogeneous neoantigens.[6 113 114] Indirect evidence suggests that cDCs contribute to expanding the diversity of the CD8 T cell responses.[103 115] Moreover, two clonal neoantigens need to be presented by the same cDC1 to induce effective responses against both.[116] Of interest, cDC1 can "select" the antigens to be cross-presented, depending on their subcellular localization.[117] Recent efforts to generate experimental cancers that model the neoantigen content of human tumors include the manipulation by cancer mutagenic agents, expression of APOBEC3B or deletion of DNA repair proteins. These tools have been useful for addressing the evolution of cancer cell clones, the interplay with neoantigen-specific CD8 T cells and the efficacy of immunotherapy as a function of the mutational load.[81 82 118] The role of cDC1 in the context of multiple bona fide neoAgs has been directly addressed using a hypermutated KP variant (KP^{neo}) depleted in the DNA repair regulator Mlh1.[24] De novo-generated MHC class-I epitopes were identified and functionally tested by ELISPOT in tumor-bearing mice. The results suggest that depleting cDC1 reduces the diversity and magnitude of CD8 T cell reactivity, whereas boosting the DC compartment by Flt3L promotes responses to suboptimal neoAgs, expanding the overall T cell repertoire and improving tumor control.[24]

TYPE 1 DCS CONTROL ANTITUMORAL IMMUNITY LOCALLY IN TISSUES

Increasing evidence points to the critical importance of a local cancer immunity cycle that supports the activation of antitumoral T cells within organized subtissular niches. Spatial technologies identified clusters of precursor-exhausted CD8 T cells interacting with mature cDCs and CXCL13 T helper cells enriched in tissues of patients with hepatocellular carcinoma responding to immunotherapy.[119] Consistently, stem-immunity hubs enriched in TCF-1^+PD-1^+ precursors T cells in contact with activated CCR7^+LAMP3^+ DCs, distinct from tertiary lymphoid structures, correlated strongly with responses to checkpoint inhibitors in NSCLC, highlighting the relevance of local tissue immunity in orchestrating antitumoral responses[21] (figure 3). In a context different from cancer, a recent study showed that CD8 T cell priming by cDC1 in the lung occurs before priming in the lymph node.[120] Furthermore, spatial analysis in experimental melanoma described triads of cDC1-CD4-CD8 as a platform to induce antitumoral immunity[121] (figure 3), which remains to be investigated in lung tissues. A detailed analysis of the spatial distribution of immune cells in established autochthonous KP identified clusters of TCF-1^+PD1^+ lymphocytes near CD103^+ cells.[122] More precise visualization of cDC1 in tumor tissues by the XCR1-Venus reporter in genetic models of breast cancer identified clusters of interacting cDC1 and CD8 T, negatively regulated by Tim3 expression.[123] More recently, expression of the XCR1-venus reporter in the KP genetic strain (KP-$XCR1^{venus}$) facilitated unequivocal identification of cDC1 in lung cancer tissues.[108] This approach unveiled abundant clusters of cDC1-CD8 T cells in incipient KP tumor that fade substantially in advanced tumors. cDC1-CD8 contacts were found to depend on the adhesion molecule ALCAM1, which becomes downregulated in late tumors, suggesting that cDC1 dysfunction includes loss of adhesion molecules and diminished capacity to interact with T cells[108] (figure 3). Of note, ALCAM was recently shown to control cytotoxic synapses between T cells and cancer cells.[124] Of note, the latest findings uncovered a prominent role for cDC1 in promoting the formation and maintenance of tertiary lymphoid structures in lung cancer tissues.[125]

Overall, while the presence of cDC1 in lung tissues correlates to better prognosis and response to therapy,[11 24] the determinants underlying their reduction and deactivation in advanced tumors[13 22 101] remain poorly defined. A fibrotic stroma and specific matrix components like versican have been proposed as potential mechanisms to account for diminished infiltration.[126 127] Conversely, cancer intrinsic expression of CCL7 has been proposed as a mechanism to induce DC recruitment in lung cancer tissues.[128] Other major axes such as CCL5-NK governing the attraction of cDC1s in melanoma and pancreatic tumors await validation in the lung.[11 12 14] Further ongoing research will help to determine the role and status of cDC1 in orchestrating the composition and function of immune clusters across lung cancer stages.

PRECLINICAL MODELS OF LUNG CANCER FOR IMMUNOTHERAPY TESTING

Several studies consistently reported the refractoriness of KP models to standard ICB immunotherapy.[16 75 129 130] Hence, KP recapitulates ICB-resistant NSCLC, which makes the model extremely useful to assess the efficacy of novel therapies as alternatives or complementary to ICB. For instance, immunogenic chemotherapy including oxaliplatin and cyclophosphamide was shown to

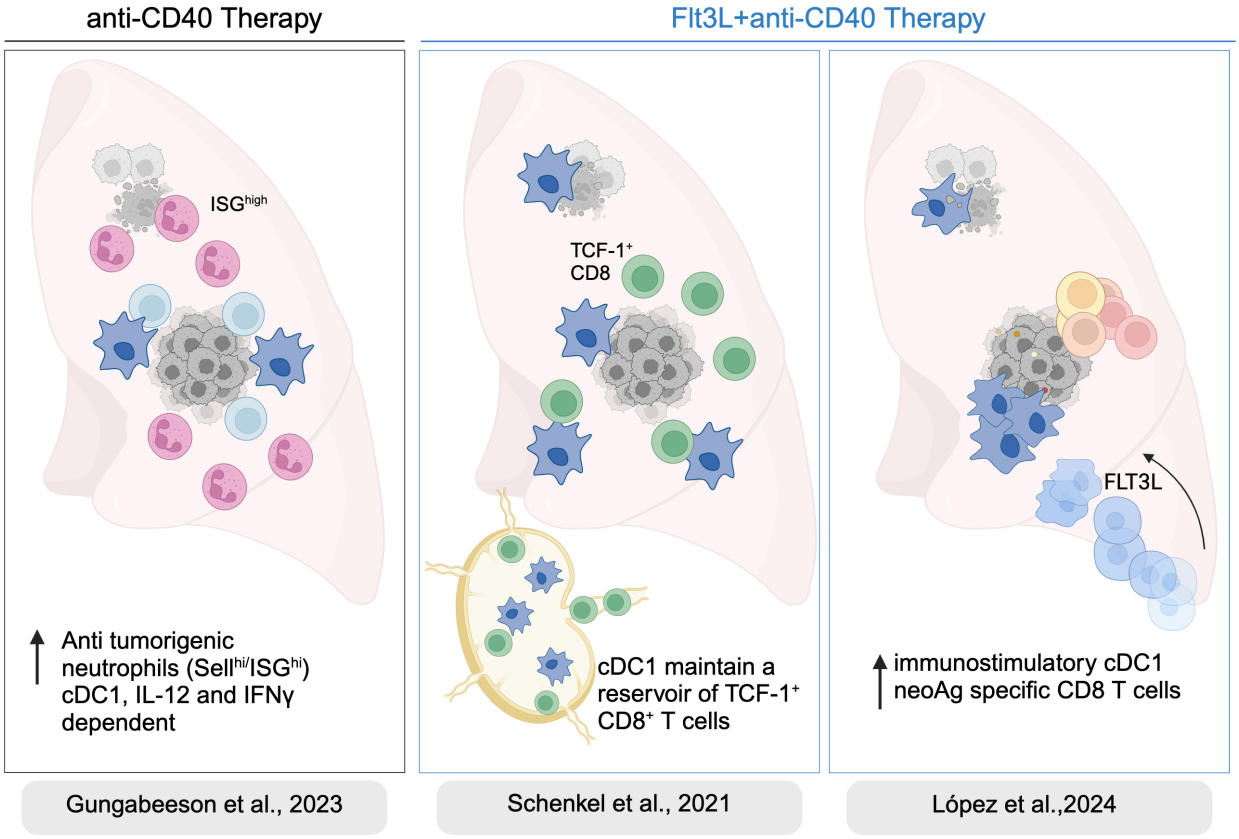

Figure 4 Harnessing cDC1 for immunotherapy in experimental KP. Recent studies unveil the potential of dendritic cell (DC)-based therapies in lung tumors. Gungabeeson *et al* tested anti-CD40 as a single-agent therapy in the KP (Cre-inducible Kras activating mutations combined with p53 loss of function) model, demonstrating that tumor elimination can be achieved through the reprogramming of neutrophils, which acquire an interferon-stimulated gene (ISG) signature. This process is mediated by cDC1s and interferon-γ (IFN-γ). Schenkel *et al* demonstrated that a combination of FLT3 ligand (FLT3L) and anti-CD40 therapy effectively controls tumor progression by expanding a reservoir of TCF-1+CD8+ T cells. López *et al* showed that DC therapy enhances the diversity and magnitude of neoantigen-specific CD8+ T cells and delays the growth of ICB refractory lung tumors.

induce TLR4-mediated activation of myeloid cells and to synergize with ICB to improve the rejection of KP tumors.[75] CSFR1 inhibitors to target tumor-associated macrophages, combined with antiangiogenic immunotherapy and conventional chemotherapy, achieved complete regression of KP endogenous lesions.[129] The dysfunctional phenotype of tumor-specific CD8 T cells induced in transplantable KP tumors could be reverted by the administration of recombinant IL-2 and IL-12, reducing tumor growth.[16] Further studies in KP or KP variants showed that blocking IL4r and Axl can rescue anticancer CD8 T cell responses, blunting tumor progression.[20 110 131] On a different line, blocking glucose intake in tumor-supporting neutrophils enhances the efficacy of radiotherapy and improves tumor rejection.[132] Recently, αCD40 as a single agent was sufficient to reprogram protumorigenic neutrophils and achieve tumor rejection in not-modified, hence poorly immunogenic, autochthonous KP tumors, emphasizing the dominant role of suppressive myeloid cells in the model[19] (figure 4). An additional mechanism of immunotherapy resistance in lung tumors was recently mapped to cancer-associated fibroblasts that drive infiltration of protumorigenic immune cells while precluding access to antitumorigenic cells.[19 92 127]

CDC1 AND IMMUNOTHERAPY OF LUNG CANCER

Harnessing cDC1 for cancer therapy as mono or combinatorial therapy is a fast-evolving field, intensively investigated in preclinical studies and early clinical trials. A new generation of DC-based vaccines that leverages the superior ability of cDC1 to induce anticancer responses is emerging.[97] Primary mouse cDC1 loaded with tumor antigens and transferred in vivo achieved rejection of three different cancer models, at least in the context of strong model antigens and subcutaneous engraftment.[133] Recently, an innovative strategy based on the enforced expression of Flt3L and IL-12 in cDC1 precursors showed the potential to reprogram the microenvironment and induce tumor rejection in different experimental cancer models.[25] Engineered DC expressing Cxcl9/10 showed efficacy in amplifying T cell-responses and controlling the growth of lung cancer cells implanted subcutaneously.[26] A second approach is based on amplification of the cDCs compartment in situ by the growth

factor Flt3L. Administration of recombinant Flt3L has shown beneficial effects in several experimental tumor settings[101 103 134–138] and early clinical trials are beginning to demonstrate the potential of Flt3L-based therapies in patients.[139] A further important area of experimental research relates to the adjuvants that better induce the immunostimulatory potential of cDC1 in situ. The available evidence suggests that STING activity in cDC1 is crucial to induce protective antitumoral immunity.[140 141]

In the context of lung tumors, few reports explored Flt3L-based therapies in NSCLC models. The group of T. Jacks demonstrated that supplying Flt3L plus αCD40 in mice carrying highly immunogenic autochthonous tumors promotes the expansion of a subset of Slamf6^{+}TCF-1^{+} precursor exhausted CD8 T cells in lymph nodes and reduces the progression of established tumors.[23] Our team recently applied the same combination (Flt3L plus αCD40, DC therapy) to mice carrying transplantable KP^{neo} encoding bona fide neoAgs, in parallel to ICB. Interestingly, DC therapy induced CD8 T cell responses that delayed tumor growth, whereas ICB did not provide beneficial effects.[24] The protective effect of the therapy depended on the accumulation of de novo differentiated cDC1 with enhanced immunostimulatory properties and increased cytotoxicity in CD8 T cells (figure 4). In line with our preclinical findings, a recent trial demonstrated the induction of a full spectrum of T cell activation states in patients with NSCLC on neoantigen-based DC vaccination.[142] Future fundamental research in appropriate KP variants will be critical to define the impact of Flt3L on the whole lung immune compartment, the optimal formulation/modality of administration, the efficacy in immunocompromised hosts carrying advanced tumors and the best adjuvant for local activation of lung DCs. In parallel with the results of ongoing clinical trials (NCT02839265, NCT04491084), these efforts will help to refine the strategies for targeting the DC compartment in lung cancer.

CONCLUSIONS

The general features and markers shared by cDC1 across tissues allowed us to establish common cellular principles controlling their antitumoral properties and delineate mechanisms of functional suppressions. It is now time to resolve less obvious context-dependent features of cDC1 in specific cancer tissues to improve the precise design of future approaches. Lung cDC1s possess peculiar properties such as superior abundance, half-life and transcriptional programs related to the control of lung homeostasis, whose implications for anticancer responses are not yet appreciated. At the experimental level, molecular mechanisms controlling cDC1 function and dysfunction have been identified mostly in inflamed tumors and often in ectopic cancer tissues with their validity in the lung still to be demonstrated. Critically, the traits of antitumoral cDC1 operating at tumor inception and the kinetics of their transition toward exhausted/tolerogenic states are still largely elusive. These gaps can only be addressed using lung tumor models slowly developing in situ, which are technically more challenging and time-consuming. Yet future efforts in this direction will be necessary to guide tailored strategies to deploy the lung guardians against transformed cells.

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