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EDITORIAL

Lung DC-T immunity hub in immune surveillance: new concepts and future directions

1 | INTRODUCTION

An effective coordination of immune and non-immune cells is essential for generating optimal regional immunity to combat tumorigenesis and infection at barrier tissues such as lung. Regional immune structures such as inducible bronchus-associated lymphoid tissue (iBALT) and tertiary lymphoid structure (TLS) play essential roles in modulating lung local immune responses. While the identification of iBALTs or TLS is generally dependent on conventional histology, it remains poorly understood how immune cells are spatiotemporally coordinated in the lung at single-cell resolution to effectively eliminate malignant cells and invading pathogens. Recently studies have revealed the presence of dendritic cell (DC)-T immunity hubs in human lung with close association with tumor immunotherapy response [1], antiviral immunity [2], and inflammation resolution [3]. The identification of DC-T immunity hubs spatiotemporally delineates the pulmonary multicellular networks at single-cell level in modulating antitumor and antiviral immune response, and will have profound implications for the diagnosis and treatment of lung cancer and infection.

List of abbreviations: C1Q, complement component 1, q subcomponent; CC, cervical cancer; CCL19, C-C motif chemokine ligand 19; CCR7, C-C motif chemokine receptor 7; cDC, conventional DC; COVID-19, Corona Virus Disease 2019; CST7, Cystatin F; CXCL13, C-X-C motif chemokine ligand 13; DC, dendritic cell; dLN, draining lymph node; FBP1, fructose-bisphosphatase 1; FPP, farnesyl pyrophosphate; GALT, gut-associated lymphoid tissue; iBALT, inducible bronchus-associated lymphoid tissue; IDO1, indoleamine 2,3-dioxygenase 1; IL-10, interleukin 10; ISG, interferon-stimulated gene; ISG12, interferon-stimulated gene 12; LAMP3, lysosomal-associated membrane protein 3; MARCO, macrophage receptor with collagenous structure; mregDC, mature DCs enriched with regulatory molecules; PASC, Post-acute sequelae of COVID-19; PD1, programmed cell death 1; PECAM, platelet and endothelial cell adhesion molecule; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; scRNA-seq, single-cell RNA sequencing; SLAMF9, SLAM family member 9; SREBP2, sterol regulatory element binding transcription factor 2; Stereo-seq, Spatial enhanced resolution omics-sequencing; TCF7, transcription factor 7; TLS, tertiary lymphoid structure; TME, tumor microenvironment; TNF, tumor necrosis factor; TNFRSF4, tumor necrosis factor receptor superfamily, member 4; Treg, regulatory T cell; TREM2, triggering receptor expressed on myeloid cells 2.

2 | DC-T IMMUNITY HUB MODULATES TUMOR IMMUNOTHERAPY RESPONSE

The integration of single-cell technologies with high-resolution spatial imaging methods has been applied to reveal the spatial landscapes of lung tumor microenvironment (TME) in relevance to caner development, clinical outcome, and therapy responsiveness [4]. Multicellular immunity hubs of C-X-C motif chemokine ligand 13-positive ($CXCL13^+$) T cells with interferon-stimulated gene (ISG)-expressing myeloid cells and malignant cells are detected in the luminal surface of human colorectal cancer [5]. The same group further revealed the existence of DC-T immunity hub in lung cancer [1]. This lung DC-T immunity hub is composed of activated $CCR7^+$ lysosomal-associated membrane protein 3-positive ($LAMP3^+$) DCs (also termed as mature DCs enriched with regulatory molecules, mregDCs), stem-like transcription factor 7-positive ($TCF7^+$) programmed cell death 1-positive ($PD\text{-}1^+$) $CD8^+$ T cells, and C-C motif chemokine ligand 19-positive ($CCL19^+$) fibroblasts, and strongly associate with beneficial outcome of PD-1 blockade therapy. Chemokine and adhesion pathways are essential for the stability and spatial organization of DC-T hub, in consistence with the report that activated leukocyte cell adhesion molecule, ligand of CD6 (ALCAM/CD166) stabilizes DC-CD8 T cell interactions at early tumor stages against immune evasion [6]. An intratumoral niche consisting of mregDCs, $CXCL13^+CD4^+$ T helper cells and progenitor $CD8^+$ T cells is also present in hepatocellular carcinoma and associates with response to PD-1 blockade [7].

While combination of single-cell RNA sequencing (scRNA-seq) and spatial imaging methods has significantly facilitated the identification of cellular and molecular interactions in immunological niches at transcriptional

levels, the multiplexed tissue imaging further allows characterization of spatial molecular interactions at protein levels. One study using multiplexed imaging, quantitative spatial analysis, and machine learning has mapped the landscapes of lung tumors in mice and human, and identified the networks of interacting lymphocytes ("lymphonets") as a distinctive feature of the anti-cancer immune response. Such lymphnets contain $TCF1^+PD\text{-}1^+CD8^+$ T cell progenitors and gain cytotoxic $CD8^+$ T cell populations to enhance anti-tumor responses [8].

It should also be noted that immune cells can be remodeled by TME to promote tumor malignancy and metastasis [9]. One recent study using advanced multiplex imaging techniques discovered that mregDC recruit regulatory T cells (Tregs) form a mregDC-Treg cell niche around lymphatic vessels in the peripheral tumor stroma. This peri-lymphatic niche prevents antigen trafficking to the draining lymph nodes (dLNs), thus inhibits anti-tumor responses and promotes tumor progression [10]. Similarly, $LAMP3^+$ DC expressing indoleamine 2,3-dioxygenase 1 (IDO1) was shown to interact with exhausted $CD8^+$ T cells and $CD4^+$ Treg cells in cervical cancers (CC), and inhibiting IDO1 could enhance the efficacy of immune checkpoint blockade treatment in a mouse model of CC [11]. Further elucidating the mechanisms for education and reprograming of the anti-tumor versus pro-tumor niche in TME will reveal novel targets for cancer screening, diagnosis, and treatment.

3 | DC-T IMMUNITY HUB PROVIDES DEFENSE AGAINST LUNG INFECTION

Although multiple studies have analyzed the immunological mechanisms underlying lung infection such as that caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [12], few has been understood about the tissue immunological niches along the entire process of infection. In a recent study, Cong *et al.* [2] integrated spatial enhanced resolution omics-sequencing (Stereo-seq) and scRNA-seq analysis, and identified specific immunity hub containing three co-localized immune cell subset, $Cd160^+Cd8^+$ T cells, tumor necrosis factor receptor superfamily, member 4 $(Tnfrsf4)^+Cd4^+$ T cells and C-C motif chemokine receptor 7 $(Ccr7)^+Ido1^+$ DCs which dynamically shapes host immunity along the entire process of SARS-CoV-2 infection (Figure 1). Chemokines, co-stimulatory factors and adhesion molecules are critical for the intercellular communication among hub components, emphasizing the active chemotaxis and adhesive responses of DC-T hub after viral infection.

The DC-T hub localizes in the alveoli, and provides the first critical defense against the invading microbial in the alveolar region, which is distinguished from iBALTs or gut-associated lymphoid tissues (GALTs) which only reside at deeper tissues of barrier organs [2] (Supplementary Table S1). The rapid response of DC-T immunity hub to SARS-CoV-2 infection as early as day 2 provides first-line defense against viral infection, challenging the traditional idea that T cell-mediated adaptive immunity requires 5∼7 days to take in place post infection. In addition, the rapid proliferation and potent interaction between $Cd160^+Cd8^+$ T cells and SLAM family member 9 $(Slamf9)^+$ macrophage is important for the clearance of SARS-CoV-2. The virally infected $Slamf9^+$ macrophages highly express tissue remodeling and angiogenesis genes, implying their involvement in inflammation resolution and tissue remodeling.

As late as 14 days post infection, $Slamf9^+$ macrophages differentiate toward triggering receptor expressed on myeloid cells 2 $(Trem2)^+$ and fructose-bisphosphatase 1 $(Fbp1)^+$ alveolar macrophages, accompanied by downregulation of inflammatory genes such as tumor necrosis factor (*Tnf*), complement component 1, q subcomponent (*C1q*), but restoration of inflammation resolution and tissue repair genes such as macrophage receptor with collagenous structure (*Marco*) and *Cd36*, emphasizing the importance of macrophage compartments of DC-T immunity hub in inflammation resolution and tissue repair after SARS-CoV-2 infection [3]. Moreover, $Slamf9^+$ macrophages can interact with distinct neutrophil subpopulations via platelet and endothelial cell adhesion molecule (PECAM), CCL, CD80, and interleukin 10 (IL-10) pathways, contributing to their roles in inflammation resolution and tissue repair (Figure 2). In another study, an immune-epithelial progenitor niche is shown to restrain lung regeneration and drivespost-acute sequelae of corona virus disease 2019 (COVID-19) (PASC), further suggesting important and diverse roles of immunological niche in determining inflammation outcomes and clinal consequences post lung infections [13].

4 | METABOLIC CONTROL OF THE DC-T IMMUNITY HUB

Immune metabolic mechanisms play essential roles in modulating immune cell function and behavior in tumor, infection and inflammation, and offer novel opportunities for prevention and treatment of related disorders. The $Ccr7^+Ido1^+$ DCs residing at the center of DC-T hub is phenotypically resembling mregDCs [14], and multiple evidence have identified the metabolic cues in control of the identity and fate of mregDCs. Glycolysis is activated upon CCR7 ligation in DCs and supports CCR7-medited DC migration via maintaining cytoskeleton rearrangement

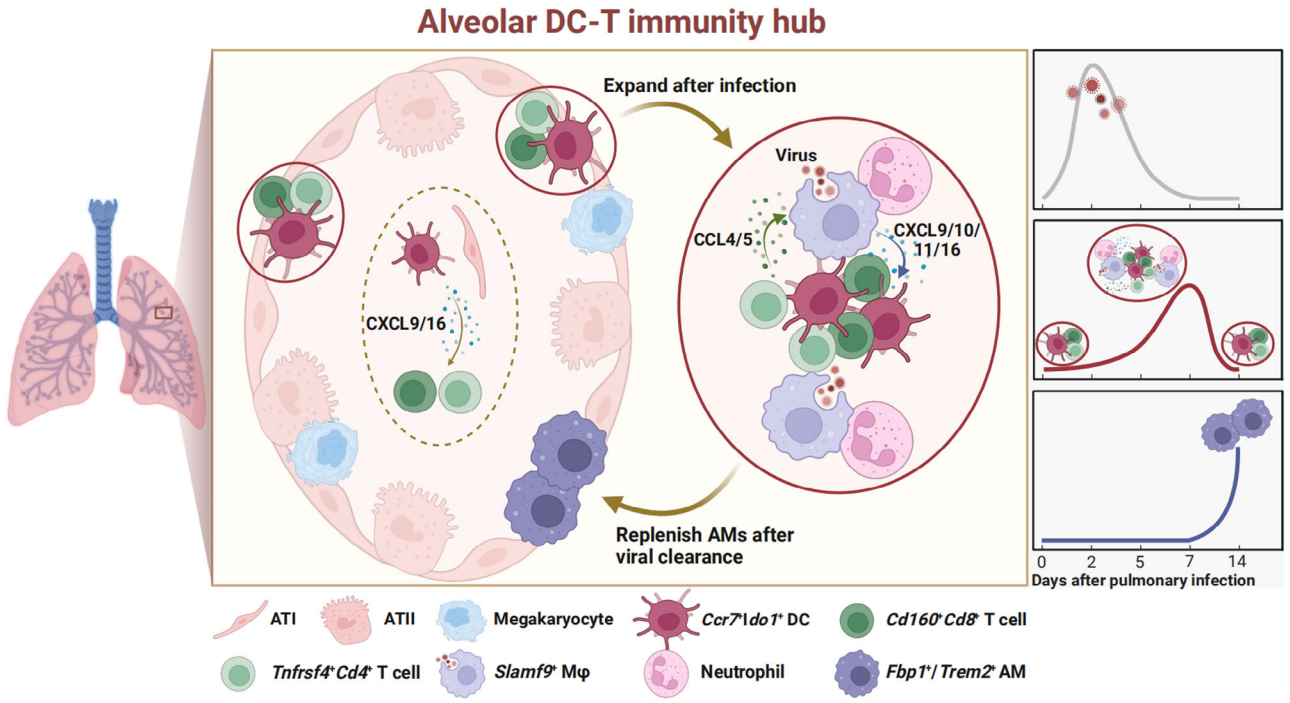

FIGURE 1 The spatiotemporal organization of DC-T immunity hub in the lung. The DC-T immunity hubs are characterized by the spatial co-localization of *Ccr7*$^+$*Ido1*$^+$ DCs, *Cd160*$^+$*Cd8*$^+$ T cells, and *Tnfrsf4*$^+$*Cd4*$^+$ T cells. Such hubs reside in the alveoli at physiological conditions at a low level, and rapidly increase at day2 after SARS-CoV-2 infection, and restores to homeostatic levels at day 14 post infection. DC-T immunity hubs co-localize with multiple antigen-presenting myeloid cells, including a new subpopulation of *Slamf9*$^+$ macrophages, which coordinate for viral clearance. *Slamf9*$^+$ macrophages further recruit *Isg12*$^+$*Cst7*$^+$ neutrophils from blood to the immunity hub, which coordinately clear SARS-CoV-2 and mediate inflammation resolution. As late phase post infection, Slamf9+ macrophages differentiate toward *Trem2*$^+$ and *Fbp1*$^+$ macrophages to mediate inflammation resolution. Created in BioRender. Nk, C. (2024) BioRender.com/y52q320. Abbreviations: AM, alveolar macrophage; ATI, type I alveolar epithelial cell; ATII, type II alveolar epithelial cell; DC, dendritic cell; Mφ, macrophage.

and receptor oligomerization, and thereby supporting tissue inflammation [15]. An intermediate metabolite of mevalonate pathway, farnesyl pyrophosphate (FPP), could enhance mregDC migration to dLNs via remodeling mitochondrial structure and metabolism, and consequently lead to sustained germinal center responses and pathological immune responses [16]. In addition, IDO1 expression in CCR7$^+$ DCs promotes the tolerogenic function of conventional DC2 (cDC2) via producing tryptophan metabolite l-kynurenine, suggesting an indispensable role for tryptophan metabolism in controlling the tolerogenic property of cDCs [17].

Metabolic crosstalk emerges as critical mechanisms for regulating DC-centered immunity during tumor and infection. Intra-tumoral glutamine supplementation could support cDC1-mediated CD8$^+$ T cell immunity to overcome therapeutic resistance to immunotherapies [18]. In addition, melanoma-derived lactate serves as a trigger for sterol regulatory element binding transcription factor 2 (SREBP2)-dependent activation of cholesterol metabolism in mregDCs within TME, forming a lactate-SREBP2 signaling axis driving mregDCs tolerogenic maturation and suppression of antitumor immunity. DC-specific ablation or inhibition of SREBP2 exert anti-tumor therapeutic effects by promoting antitumor CD8$^+$ T cell activation [19]. Moreover, hyperglycaemia inhibit antiviral adaptive immune response via shifting the composition and gene expression of distinct lung DC subsets, most notably cDC1. The increased glucose-to-acetyl-CoA metabolism induced by hyperglycaemia alters global chromatin and key function genes in DCs, suggesting an indispensable role of metabolic-immune pathway in orchestrating DC dysregulation in pulmonary viral infection [20]. It will be intriguing to identify whether glucose and cholesterol metabolism would affect the function of *Ccr7*$^+$*Ido1*$^+$ DC and its communications with T cells and B cells in the immunity hub during pulmonary cancer and infection.

5 | CONCLUSIONS AND PERSPECTIVES

In sum, the lung DC-T immunity hubs exhibit a unique multicellular network of CCR7-expressing DCs and distinct T cell subsets, orchestrating lung immunity during

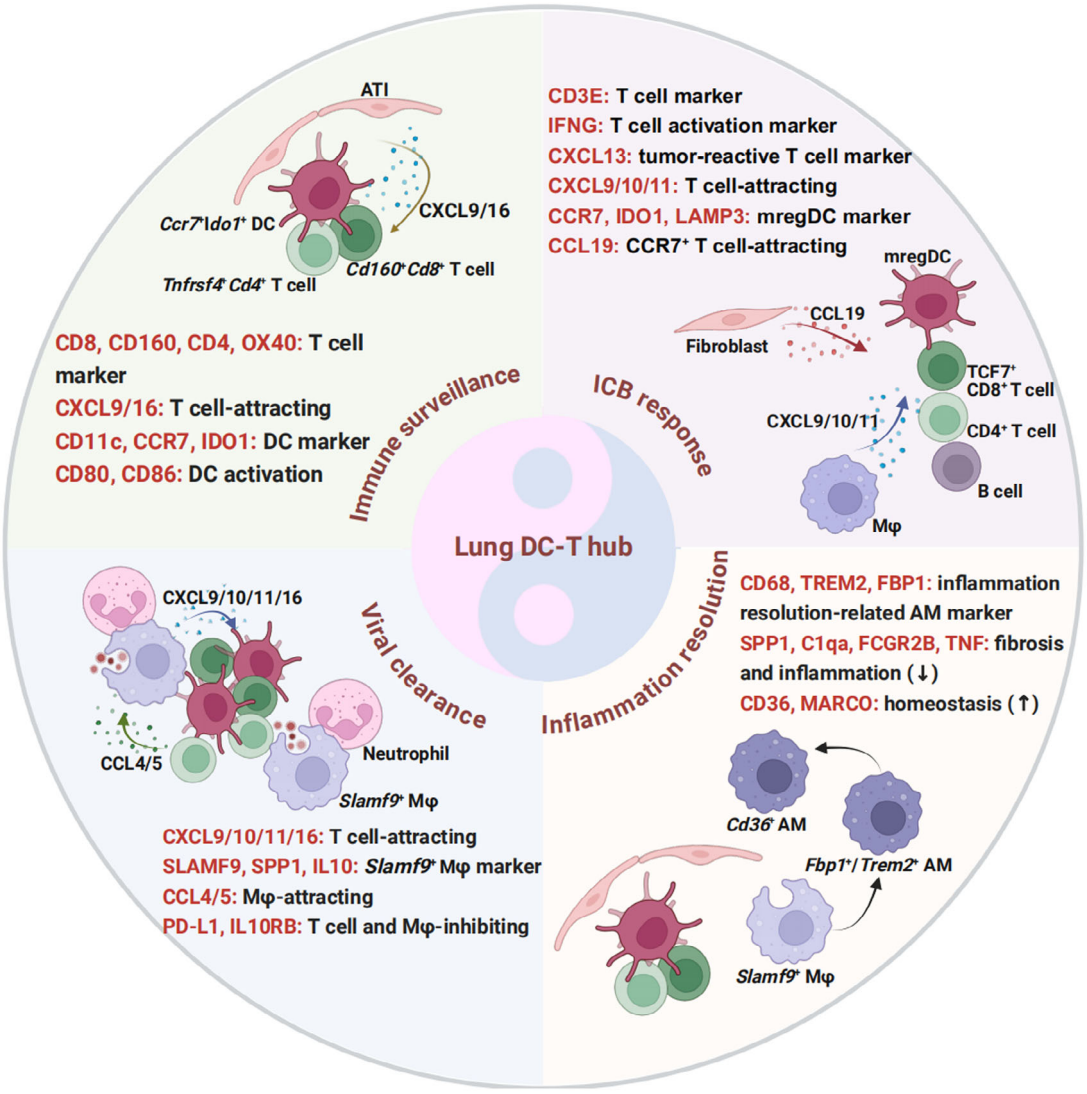

FIGURE 2 Lung DC-T immunity hub empowers immune surveillance in infection and cancer. The lung DC-T immunity hubs dynamically orchestrate host immunity in health, infection and cancer. They can mediate immune surveillance at steady states, viral clearance at early phase of infection, inflammation resolution at late phase of infection, and enhance host response to immune checkpoint blockade during tumor development. The dynamic and versatile roles of DC-T immunity hub depend on a complicated and flexible communications between various cellular, molecular, and metabolic components. Created in BioRender. Nk, C. (2024) BioRender.com/y52q320. Abbreviations: AM, alveolar macrophage; ATI, type I alveolar epithelial cell; DC, dendritic cell; Mφ, macrophage; mregDC, mature DCs enriched in immunoregulatory molecules.

infection and cancer. These immunity hubs represent the previously unrecognized mechanisms for the dynamic intercellular communications to establish host immune surveillance and homeostasis. The key issues of biological function, regulation mechanism, and disease relevance of immunity hub remain largely unanswered and are worthy of further investigations in the future, for examples, (1) the distinct developmental origin, functional specialization and metabolic remodeling of the hub cellular components; (2) the regulatory mechanisms governing the initial formation, expansion, and restoration of the immunity hub; (3) the tissue antigens and niche signals that determine the functional polarization and migratory property of hub CCR7$^+$ DCs; (4) the distribution and characteristic of DC-T immunity hub at other barrier tissues such as gastrointestinal tract, etc. Future exploration of the comprehensive spatiotemporal lung immune landscape will have profound implications in understanding how regional immunity dictates the development of cancer and infection, and will greatly facilitate the development of effective immunotherapies based on key cells or molecules involved in DC-T immunity hub. The integrative multi-omics analysis techniques will also initiate a paradigm-shifting transformation to oncological

and immunological studies and provide a comprehensive resource for the scientific community to understand lung diseases and developing therapies in future.

AUTHOR CONTRIBUTIONS

Xuetao Cao and Juan Liu conceived and conceptualized the concept of this writing and wrote the original draft. Boyi Cong generated the figures and table with supervision from Xuetao Cao and Juan Liu. All authors critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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DATA AVAILABILITY STATEMENT

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