

# Promotion Mechanisms of Stromal Cell-Mediated Lung Cancer Development Within Tumor Microenvironment

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**Abstract:** Lung cancer, with its high incidence and mortality rates, has garnered significant attention in the medical community. The tumor microenvironment (TME), composed of tumor cells, stromal cells, extracellular matrix, surrounding blood vessels, and other signaling molecules, plays a pivotal role in the development of lung cancer. Stromal cells within the TME hold potential as therapeutic targets for lung cancer treatment. However, the precise and comprehensive mechanisms by which stromal cells contribute to lung cancer progression have not been fully elucidated. This review aims to explore the mechanisms through which stromal cells in the tumor microenvironment promote lung cancer development, with a particular focus on how immune cells, tumor-associated fibroblasts, and endothelial cells contribute to immune suppression, inflammation, and angiogenesis. The goal is to provide new insights and potential strategies for the diagnosis and treatment of lung cancer.

**Keywords:** tumor microenvironment, lung cancer, stromal cells, immune cells, cancer-associated fibroblasts, endothelial cells

Lung cancer is one of the most burdensome malignancies worldwide, marked by its high incidence, mortality rate, and propensity for metastasis. As of 2020, it ranks second only to breast cancer in incidence, with approximately 2.2 million new cases annually, accounting for 11.4% of all cancer diagnoses. It remains the leading cause of cancer-related deaths, representing 18% of global cancer mortality.<sup>1</sup> Furthermore, the prognosis for lung cancer is poor, with a five-year survival rate of less than 16%.<sup>2</sup> Given these alarming statistics, it is critical to elucidate the pathogenesis of lung cancer and identify effective strategies for its prevention and treatment.

The tumor microenvironment (TME) is the “soil” in which tumor cells thrive, serving as a complex ecosystem that regulates tumor growth, invasion, and metastasis. Immune suppression, inflammation, and angiogenesis are well-established as key pro-cancer factors within the TME.<sup>3</sup> The TME is highly structured, consisting primarily of stromal cells, extracellular matrix (ECM), and various cytokines and growth factors. Stromal cells reside within a complex network of ECM macromolecules, which includes, but is not limited to, immune cells (ICs), cancer-associated fibroblasts (CAFs), and endothelial cells (ECs). These components interact to shape tumor progression and modulate response to therapy.<sup>4</sup> Stromal cells play a pivotal role in various processes such as cancer cell proliferation and invasion, ECM remodeling, immune evasion, and the initiation of angiogenesis and inflammation, all of which contribute to tumor formation and metastasis.<sup>5</sup> By interacting with tumor cells, immune cells, and the ECM, stromal cells foster a supportive microenvironment that enables cancer cells to thrive and spread.<sup>6,7</sup> Recent advances in single-cell and spatial transcriptomics have revealed the diverse characteristics of stromal cells in the TME, further highlighting their potential as therapeutic targets in cancer treatment.<sup>8</sup> Therefore, understanding the intricate interplay between stromal cells and lung cancer development is paramount.

Despite these insights, the precise mechanisms by which stromal cells contribute to lung cancer development remain poorly understood. To address this gap, this review provides a comprehensive classification of stromal cells within the TME. It then explores the relationships between key TME components, including immune suppression, inflammation,

and angiogenesis, in driving lung cancer progression. Ultimately, this review aims to enhance our understanding of stromal cell function in lung cancer and offer new perspectives for diagnosis and treatment (Figure 1).

## Stromal Cells in the TME

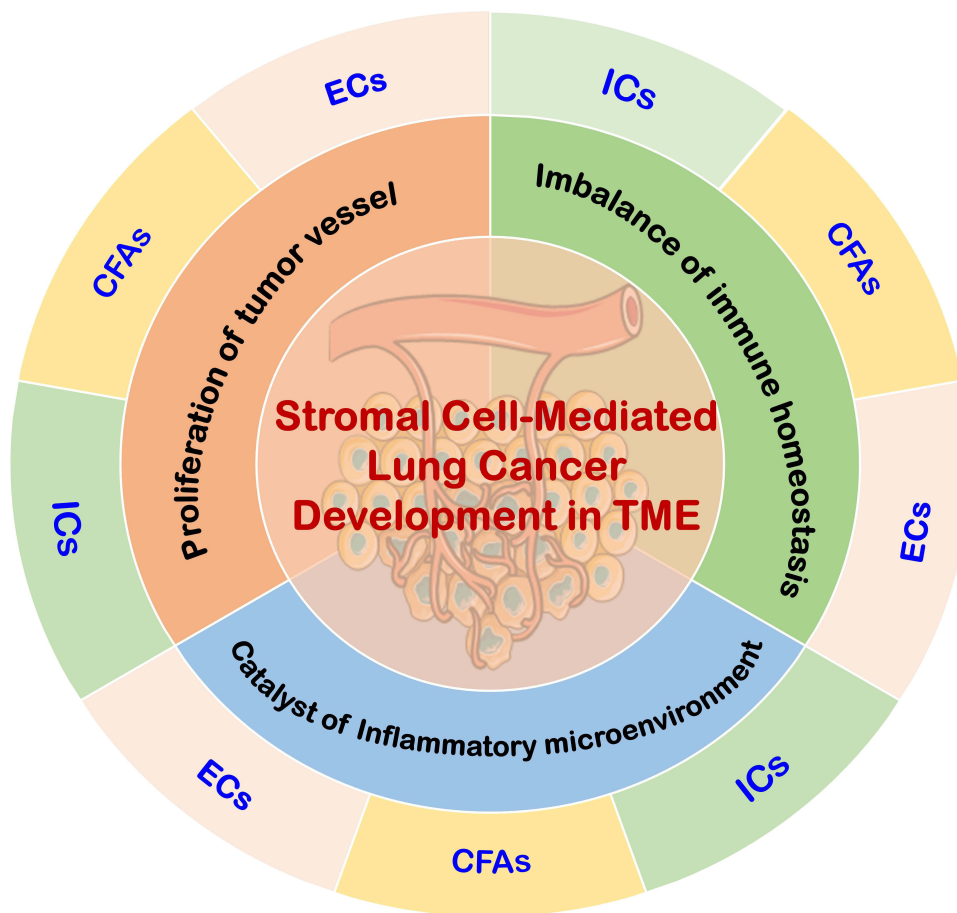
The TME is a complex, highly structured system composed of surrounding blood vessels, stromal cells, extracellular matrix (ECM), and various signaling molecules. Stromal cells, as components of connective tissue, primarily include immune cells, fibroblasts, endothelial cells, and others. These cells play critical roles in biological processes such as immune suppression, inflammation, and angiogenesis, significantly influencing tumor initiation and progression (Figure 2). Below is an overview of the key stromal cell types within the TME.

### Immune Cells

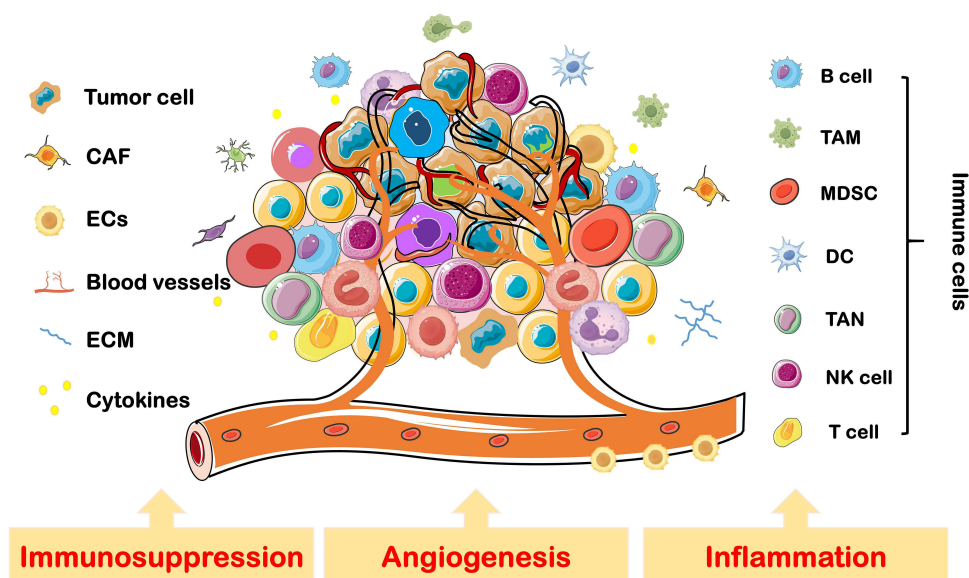
Immune cells and their associated factors are fundamental components of the TME.<sup>9</sup> These cells act as “warriors” that eliminate cancer cells through immune surveillance and clearance. However, cancer cells can also manipulate immune cells to aid in immune evasion, creating a “fertile soil” that fosters tumor growth. Immune cells in the TME are primarily divided into innate and adaptive immune cells.<sup>10</sup>

#### Innate Immune Cells

Innate immune cells form the body’s first line of defense, providing broad and rapid initial protection against pathogens and abnormal cells. These cells include macrophages, neutrophils, natural killer cells, dendritic cells, and eosinophils,



**Figure 1** Mechanisms of stromal cell action in TME. The stromal cells in TME mainly include ICs, CAFs, and ECs, with immune suppression, inflammation, and angiogenesis being the key biological processes that promote cancer in the TME. Various stromal cells can initiate lung cancer by recruiting immune-suppressive cells and creating an immune-suppressive microenvironment. They can also induce inflammation to form an inflammatory microenvironment that catalyzes lung cancer development, and promote tumor angiogenesis to drive the progression of lung cancer.



**Figure 2** Stromal cells in TME. TME is a complex and highly structured milieu, consisting of stromal cells including, but not limited to, ICs, CAFs, and ECs. Immune suppression, inflammation, and angiogenesis are key factors driving tumor initiation and progression within the TME.

**Abbreviations:** DC, dendritic cells; TAM, tumor-associated macrophages; TAN, tumor-associated neutrophils; MDSC, myeloid-derived suppressor cells; NK cell, natural killer cell.

among others. Each type of immune cell has specific surface markers and secreted factors that enable them to perform distinct roles in the immune response (see Table 1).

### Adaptive Immune Cells

Adaptive immune cells are highly specific and possess long-term memory. They are activated upon exposure to specific antigens and mount an immune response by “assessing” the threat using immunological memory. These cells mainly consist of T cells and B cells. T cells exhibit different subtypes and are key regulators of both cellular and humoral immunity (see Table 2).

**Table 1** Classification, Markers, Secreted Factors, and Functions of Innate Immune Cells

Category		Surface Marker	Secreted Factor	Function
Macrophage	M1	CD14 <sup>+</sup> , CD80 <sup>+</sup> , CD64 <sup>+</sup> , CD68 <sup>+</sup>	IL-12, IL-23, TNF- $\alpha$	Activate T lymphocyte immune responses and are key players in the destruction of cancer cells Induce tumor cell growth and migration
	M2	CD163 <sup>+</sup> , CD206 <sup>+</sup> , CD204 <sup>+</sup>	IL-1, IL-10, TGF- $\beta$	
Neutrophil	N1	Siglec8 <sup>+</sup> , CD193 <sup>+</sup> , CD11b <sup>+</sup> , CD14, CD62L <sup>+</sup>	ICAM1, TNF-A	Promote angiogenesis, matrix remodeling, immunosuppression, and mediate toxicity
	N2		VEGF, MMP9	
Natural killer cell		CD3 <sup>-</sup> , CD56 <sup>+</sup>	GM-CSF, IL5, IL-8, IL-10, IL-13, CCL2, CCL3, CCL4, CCL5, CXCL10	Directly promotes complement and antibody activation, kills cancer cells, and maintains immune balance
Myeloid derived suppressive cells		CD11b <sup>+</sup> , CD33 <sup>+</sup> , CD14 <sup>+</sup> , CD15 <sup>+</sup> , CD16 <sup>+</sup> , HLA-DR <sup>-</sup>	NO, ROS, iNOS, PD-L1, MMP9	Inhibit the function and activity of T lymphocytes and natural killer cells by consuming amino acids or expressing immunosuppressive ligands, thus hindering the normal immune response of the body

(Continued)

**Table 1** (Continued).

Category	Surface Marker	Secreted Factor	Function
Dendritic cell	HLA <sup>-</sup> , DR <sup>+</sup> , lineage <sup>-</sup>	IFNs	Capture and process antigens and present them to T cells, bridging the innate and adaptive immune systems
Mastocyte	CD117 <sup>+</sup> , CD203 <sup>+</sup>	VEGF, FGF-2	Support tumor growth and metastasis by secreting growth factors, promoting angiogenesis, regulating the immune environment and matrix remodeling
Eosinophils	CD11b <sup>+</sup> , CD15 <sup>+</sup> , CD16 <sup>+</sup> , CD62L <sup>+</sup> , CD66b <sup>+</sup>	TNF-A, granzyme, IL-18	Secrete growth factors and angiogenic factors that catalyze inflammation to promote tumor growth

**Table 2** Classification, Markers, Secreted Factors, and Functions of T Cells

Category	Surface Marker	Secreted Factor	Function
Th, Helper T cell	Th1	CD4 <sup>+</sup>	IFN- $\gamma$ , IL-2, TNF
	Th2		IL-4, IL-5, IL-13, IL-10, IL-13
	Th9		IL-9, IL-10
	Th17		IL-17, IL-21, IL-22, CCL20
	Tfh		IL-21
CTL, Cytotoxic T cell	CD8 <sup>+</sup> , $\alpha\beta$ TCR, CD3,	EOMES, T-bet, BLIMP1	Secrete perforin and granzyme and kill both infected and mutant cells
Treg, Regulatory T cell	CD4 <sup>+</sup> , CD25 <sup>+</sup> , FoxP3	IL-10, TGF- $\beta$ , IL-35	Regulate the body's immune response, maintains its own tolerance, and prevents excessive immunity
Tm, Memory T cell	Tcm	CD45RO, CCR7, CD62L, CD27	IL-2, CD40L, BCL-6, BCL-6B, MBD2
	Tem		BLIMP1
Natural Killer T cell	CD3, CD8, CD4, CD56	IFN- $\gamma$ , TNF, IL-2, IL-4, IL-10	Exhibit characteristics of T cells and natural killer cells and are involved in immune regulation and anti-tumor responses
Exhausted T cell	CD3, CD8, PD1, TIM3	BLIMP1	chronically exposed to persistent antigens and inflammation, and T cells are continuously stimulated and gradually lose their function to produce effector cytokines

B cells are diverse (see [Table 3](#)) and can produce high-affinity antibodies, playing an important role in immune regulation and working in collaboration with T cells in the TME.

### Cancer-Associated Fibroblasts

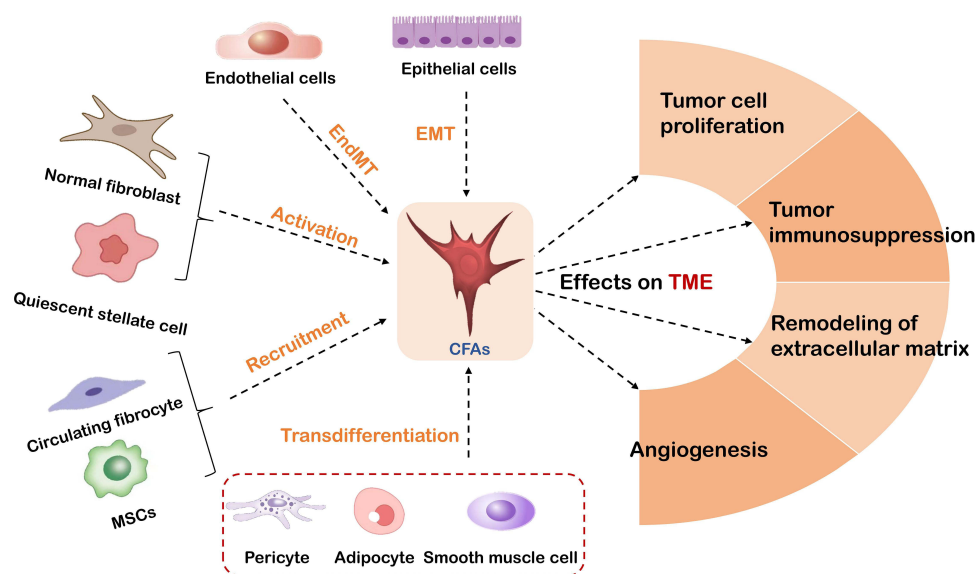
In the TME, cancer-associated fibroblasts are the most abundant stromal cells, constituting approximately 70% of the tumor tissue cells.<sup>11</sup> CAFs act as communication hubs, facilitating extensive cross-talk between cells. They promote the

**Table 3** Classification, Markers, Secreted Factors, and Functions of B Cells

Category	Surface Marker	Secreted Factor	Function
Tumor-infiltrating B cells	CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD22 <sup>+</sup>	Various immunoglobulins (antibodies) and cytokines	Recognize tumor antigens and produce specific antibodies and activate T cells to regulate the immune response in the TME
Ab-producing B cell	CD19 <sup>+</sup> , CD20 <sup>+</sup>	Tumor-specific IgG and IgA	Produce and secrete antibodies that help recognize tumor antigens
Regulatory B cell	CD19 <sup>+</sup> , CD21 <sup>+</sup> , CD24 <sup>+</sup> , CD25 <sup>+</sup> , FOXP3 <sup>+</sup>	IL-10, IL-35, TGF-B	Secrete immunosuppressive factors that help tumors escape the surveillance of the immune system and promote tumor growth and metastasis
Antigen-presenting B cells	CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD21 <sup>+</sup> , CD23 <sup>+</sup> , MHC II	IL-2, IL-6	Support and regulate anti-tumor immune responses by presenting antigens to T cells via MHC class II molecules
Tumor-associated B cells with regulatory functions	CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD27 <sup>+</sup>	Proinflammatory and inhibitory factors	Antagonizes tumors by producing antibodies and activating immune responses, and may also promote tumor growth and immune escape by secreting inhibitory factors and changing the immune microenvironment

formation of a tumor-permissive environment by generating immunosuppression, regulating epithelial-mesenchymal transition (EMT) in tumor cells, continuously remodeling the extracellular matrix (ECM), enhancing cancer stemness, and inducing angiogenesis.<sup>12,13</sup>

CAFs primarily originate from normal fibroblasts and quiescent stellate cells, which acquire the CAF phenotype upon activation.<sup>14</sup> Additionally, epithelial and endothelial cells can contribute to CAFs through phenotypic transitions, while bone marrow-derived mesenchymal stem cells, pericytes, and adipocytes can interact with tumor cells to undergo transdifferentiation and serve as precursors to CAFs<sup>15–18</sup> (see Figure 3 for the sources of fibroblasts).



**Figure 3** The source and function of CAFs. CAFs originate from the activation of normal fibroblasts and quiescent stellate cells, phenotypic transformation of epithelial and endothelial cells, recruitment of bone marrow mesenchymal stem cells, and transdifferentiation provided by interactions between pericytes, adipocytes, and tumor cells. CAFs promote the formation of a tumor-permissive microenvironment by producing immune-suppressive factors, regulating tumor cell proliferation, remodeling the ECM, and inducing angiogenesis.

Beyond their diverse origins, CAFs also exhibit significant heterogeneity, which is mainly reflected in differences in cell phenotype, including temporal and spatial characteristics. Temporally, CAF phenotypes are closely related to tumor progression stages, while spatial heterogeneity refers to variations in CAF phenotypes within different regions of the tumor tissue.<sup>19</sup> Researchers have identified three distinct subtypes of CAFs in lung cancer:<sup>20</sup> 1. CAFs characterized by high expression of growth factors HGF and FGF7, which have a strong protective role. 2. CAFs with high expression of FGF7, providing moderate protection. 3. CAFs that produce inflammatory factors and recruit immune cells, but offer relatively low protective capacity.

## Endothelial Cells

Endothelial cells are a single layer of flattened epithelial cells located on the inner membrane of blood vessels, forming a semipermeable barrier between the vascular compartment and the surrounding tissues. They serve as metabolic interfaces that control the entry and exit of substances and compound exchanges within the blood circulation. Under normal conditions, endothelial cells are polygonal and tightly connected. However, in the tumor microenvironment, tumor-associated endothelial cells (TECs) exhibit abnormal characteristics. Compared to normal endothelial cells, TECs are irregular in shape and size, proliferate and migrate faster, and may even display disordered endothelial networks and disrupted basal membranes.<sup>21,22</sup> TECs, which form the inner layer of the tumor vasculature, have been definitively shown to play a crucial role in cancer development.<sup>23</sup> A population structure map of TECs, constructed using single-cell RNA-seq data from 19 types of tumors, reveals their underestimated functional heterogeneity. These features and spatial characteristics form the basis for responses to anti-angiogenesis therapies and immunotherapies, making TECs a promising target for tumor intervention.<sup>24</sup> According to single-cell sequencing, multiple subtypes of tumor endothelial cells exist in lung cancer, each playing roles in leukocyte recruitment, ECM remodeling, and vascular integrity.<sup>25</sup> This review will further summarize the role of endothelial cells in lung cancer development.

## Initiation of Lung Cancer: Imbalance of Immune Homeostasis

The immune system plays a pivotal role in recognizing, eliminating, and controlling tumor cells, thereby maintaining immune homeostasis. However, insufficient immune clearance and diminished immune surveillance can enable tumor cells to evade recognition and destruction, leading to immune evasion. This disruption of immune homeostasis culminates in the establishment of a tumor immune-suppressive microenvironment. Various stromal cells in the tumor microenvironment (TME) contribute to lung cancer initiation by undermining immune homeostasis, as discussed below.

## Immune Cells and Immune Homeostasis Imbalance

Dysfunction of immune cells is a major factor in disrupting immune homeostasis, creating an immune-suppressive microenvironment that facilitates lung cancer initiation. Among these cells, macrophages are the most abundant and functionally significant infiltrating immune cells in the TME. Their polarization from the M1 to the M2 phenotype influences the secretion of immune-related cytokines, promoting lung cancer progression.<sup>26</sup> Multiple mechanisms regulate this polarization, including enhanced secretion of M-CSF,<sup>27</sup> exosome-mediated signaling,<sup>28</sup> induction of reactive oxygen species (ROS),<sup>29</sup> and modulation of the transcription factor STAT6.<sup>30</sup> Recent studies have identified POSTN, a highly mutated gene in lung adenocarcinoma, as a driver of macrophage polarization. By inhibiting lung cancer cell apoptosis and accelerating tumor progression, POSTN opens new avenues for targeted immunotherapy.<sup>31</sup> Additionally, Li et al demonstrated that nanomedicine enhances anti-tumor immunity by modulating tumor-associated macrophages, suggesting that macrophage-targeted nanotherapeutics may offer innovative approaches for lung cancer treatment.<sup>32</sup>

NK cells, critical for the first line of defense against tumor formation, play a key role in improving the TME.<sup>33</sup> However, reduced NK cell infiltration and functional impairment—marked by weakened cytotoxicity, decreased reactivity, and compromised survival—are strongly associated with lung cancer initiation.<sup>34</sup> This dysfunction is driven by inhibited glucose metabolism and elevated levels of transforming growth factors.<sup>34,35</sup> For instance, a decrease in sphingosine-1-phosphate receptor 1 and CX3CR1 expression, alongside an increase in CXCR5 and CXCR6, impairs NK cell migration. Additionally, elevated CTLA-4 and killer cell lectin-like receptor levels further suppress NK cell function within the lung cancer microenvironment.<sup>36</sup> Ouyang et al highlighted that the traditional Chinese medicine



Sophora alopecuroide-Taraxacum Decoction (STD) inhibits NK cell cytotoxicity and abundance, blocking lung cancer progression. These findings position STD as a promising immunotherapeutic target.<sup>37</sup>

Myeloid-derived suppressor cells (MDSCs) play a pivotal role in immune suppression within the TME, accelerating lung cancer progression.<sup>38</sup> Mechanisms include metabolic regulation that inhibits T cell function, suppression of CD4+ and CD8+ T cell proliferation and activation via the STAT3 pathway, exosomal release of pro-inflammatory factors such as IL-13, and production of chemokines like CCL11.<sup>39</sup>

Dendritic cells (DCs), specialized antigen-presenting cells, represent approximately 2.1% of immune cells in the TME. However, their maturation and activation are inhibited in lung cancer, resulting in decreased immune surveillance and increased immune escape.<sup>40</sup> In lung cancer, the exclusion of functional DCs from tumor lesions, downregulation of effector molecules, and induction of immunosuppressive pathways collectively impair immune clearance, disrupt homeostasis, and exacerbate disease progression.<sup>41</sup>

Tumor-infiltrating T lymphocytes, including CD4+ T cells (helper and regulatory subsets) and CD8+ T cells (cytotoxic subsets), are key mediators of anti-tumor immunity. During lung cancer progression, a Th1-to-Th2 immune response shift promotes immunosuppression and tumor immune escape.<sup>42</sup> The Th1-specific transcription factor TBX21 drives lung cancer development by activating the TBX21-IL-4 signaling cascade.<sup>43</sup> Th17 cells further contribute to disease progression by secreting IL-17, which increases extracellular matrix production.<sup>44</sup> Zhang et al confirmed through single-cell transcriptomics and Mendelian randomization that regulatory T cells (Tregs) mediate the causal relationship between COPD and lung cancer, highlighting their potential as early intervention targets.<sup>45</sup>

B lymphocytes, derived from hematopoietic stem cells, play a dual role in immune homeostasis and lung cancer progression. By activating regulatory B cells (Bregs), they negatively regulate immune responses. Bregs secrete inhibitory cytokines like TGF- $\beta$ , helping cancer cells evade immune surveillance.<sup>46</sup> They also recruit CD49+ Tregs and suppress CD8+ T cell activity, promoting tumor growth.<sup>47</sup> Furthermore, inhibiting high-density Bregs has been shown to significantly block lung cancer progression.<sup>48</sup> Tousif et al identified elevated Bregs in lung cancer patients, where IL-10 secretion fosters an immunosuppressive microenvironment. Their study established Trp metabolites, such as L-Kyn, as therapeutic targets for regulating Bregs in lung cancer.<sup>47</sup>

## CAFs and Immune Homeostasis Imbalance

Cancer-associated fibroblasts (CAFs) are pivotal stromal cells in lung cancer that foster an immunosuppressive microenvironment conducive to tumor growth. CAFs achieve this by secreting cytokines and metabolic products, reducing antigen presentation, modulating immune cell function, and inducing the proliferation of immunosuppressive cells.<sup>49</sup>

Recent advances in single-cell and spatial transcriptomics have identified a novel CAF subgroup, POSTN CAFs, which are closely associated with SPP1 macrophages and linked to T cell exhaustion and reduced T cell infiltration in non-small cell lung cancer (NSCLC). This subgroup highlights the significant role of CAFs in immune suppression.<sup>50</sup> Additionally, Cords et al demonstrated that CAF phenotypes, analyzed using single-cell imaging mass spectrometry and flow cytometry (IMC), are strongly correlated with NSCLC prognosis. High-density myofibroblastic CAFs (mCAFs) were associated with low immune infiltration, driving fibrosis and preventing immune cells from reaching the tumor, thereby contributing to poor outcomes in lung cancer.<sup>51</sup>

CAFs also modulate immune responses by producing chemokines such as IL-1, IL-6, and IL-8, which inhibit the activation of T and B lymphocytes and promote tumor progression.<sup>52</sup> Among these, CAF-derived IL-6, which is highly expressed, activates the JAK2/STAT3 pathway in lung cancer cells, upregulating vimentin while suppressing E-cadherin expression. This facilitates epithelial-mesenchymal transition (EMT), further driving tumor cell growth and proliferation.<sup>53</sup>

Another immunosuppressive mechanism involves the expression of tryptophan-2,3-dioxygenase (TDO) by CAFs isolated from lung cancer tissues. TDO degrades tryptophan into kynurenine, inhibiting dendritic cell antigen presentation and blocking T cell-mediated antitumor immunity.<sup>54</sup>

Transforming growth factor- $\beta$  (TGF- $\beta$ ), a key factor in CAF recruitment and activation, is abundantly secreted by activated CAFs. TGF- $\beta$  suppresses CD8+ T cell proliferation and cytotoxicity, weakens NK cell function, and polarizes

macrophages towards the M2 phenotype, thereby reinforcing immune suppression and promoting lung cancer progression. TGF- $\beta$ -dependent pathways have been shown to significantly enhance lung cancer growth and metastasis in preclinical models.<sup>55</sup>

Furthermore, CAFs recruit immune cells through the secretion of CC chemokine ligands (CCL), CXC chemokine ligands (CXCL), and colony-stimulating factors (CSF). For instance, CXCL2 secretion by CAFs upregulates PD-L1 expression in lung cancer cells, leading to immune system inactivation and reduced T cell functionality, which fosters an immunosuppressive TME.<sup>56</sup> The CCL2-CCR2 signaling axis also contributes to lung cancer progression by recruiting immunosuppressive cells such as MDSCs and tumor-promoting monocytes, which inhibit CD8+ T cell proliferation and IFN- $\gamma$  production.<sup>57</sup>

Recent findings further elucidate the regulatory mechanisms of CAFs. Sun et al reported that PRRX1 promotes CAF activation by recruiting H3K27ac and H3K4me3 to activate OLR1 expression, inducing immune evasion in lung cancer cells and advancing tumor progression.<sup>58</sup> Moreover, Sun et al identified POSTN as a highly variable gene in CAFs. POSTN facilitates EMT, enhances macrophage recruitment, promotes M2 polarization, and inhibits lung cancer cell apoptosis, underscoring its critical role in lung cancer progression. These discoveries highlight the intricate interplay between CAFs and lung cancer cells and provide a foundation for advancing lung cancer immunotherapy.<sup>31</sup>

## ECs and Immune Homeostasis Imbalance

Endothelial cells (ECs) are essential components of the tumor microenvironment (TME), forming tight junctions that act as barriers to restrict tumor cell infiltration and extravasation while preventing immune cells from entering tumor tissues. This structural integrity positions ECs as the first line of defense against effector immune cells.<sup>22</sup> Interestingly, emerging evidence suggests that ECs share an evolutionary origin with traditional immune cells, earning them the designation of “novel immune cells”.<sup>59</sup> Certain EC subtypes exhibit immune-like characteristics, such as recruiting immune cells, modulating immune functions, and presenting antigens in a semi-professional manner.<sup>60</sup>

Recent studies have further elucidated the immunoregulatory roles of ECs. Halima et al demonstrated that ECs influence macrophage phenotype transformation and the establishment of an immune-suppressive microenvironment through the secretion of CCL2. ECs can also present antigens to cytotoxic T cells via MHC class I and II molecules, highlighting their dual roles in immune modulation and antigen presentation. Single-cell RNA sequencing has identified ECs as potential therapeutic targets for optimizing tumor immunotherapy strategies.<sup>61</sup>

In the lungs, specialized ECs not only facilitate gas exchange but also participate in immune responses, protecting lung tissue from pathogens and pollutants.<sup>21</sup> Mass cytometry analyses reveal that healthy lung ECs express high levels of HLA-DRA, comparable to immune cells, suggesting significant roles in immune regulation.<sup>25</sup> Conversely, single-cell RNA sequencing data from non-small cell lung cancer (NSCLC) indicate that ECs suppress immune responses primarily by remodeling processes that reduce antigen presentation and immune activity, as well as diminishing their immune-stimulatory phenotype.<sup>62</sup>

The immune-regulatory functions of ECs are critical in lung cancer progression. Studies show that untreated lung cancer-associated ECs exhibit reduced expression of chemokines such as CCL2 and CCL18, cytokine IL-6, and HLA-I/HLA-II molecules, contributing to an immunosuppressive environment.<sup>63</sup> Furthermore, aberrant ECs express inhibitory receptor molecules, including FasL, PD-L1, and CD73, which play direct roles in immune suppression. Activation of VEGF, PDGF-R, or FGFR pathways results in phosphorylation that suppresses AKT signaling, subsequently upregulating PD-L1 expression in ECs. This cascade reduces CD8+ T cell proliferation and activation while enhancing FoxP3+ Treg cell-mediated immunosuppressive functions. Ultimately, these processes establish an immune-suppressive microenvironment that supports lung cancer growth and progression.<sup>64</sup>

## Inflammation as a Catalyst for Lung Cancer Development

In 1863, Rudolf Virchow first linked inflammation to cancer, initiating the exploration of the “inflammation-cancer” relationship. Chronic, persistent inflammation is now recognized as a major driver of tumorigenesis. With advances in research, inflammation has evolved from a “controllable” factor to an “uncontrollable” participant in tumor



microenvironment (TME) formation, ultimately promoting tumor cell proliferation. As the “seventh hallmark” of cancer, inflammation influences every stage of tumor development.<sup>65</sup>

Inflammatory responses drive lung cancer progression by inducing immunosuppression, evading immune surveillance, causing oxidative stress, and promoting angiogenesis, thereby establishing a TME conducive to tumor growth.<sup>66</sup> Below, we systematically explore how various stromal cells contribute to lung cancer progression through inflammation.

## Immune Cells and Inflammation

Chronic inflammation exposes tissues to hypertonic, hypoxic, low-glucose, and acidic conditions, disrupting homeostasis and creating an inflammatory microenvironment.<sup>67</sup> This environment reshapes the biological behavior of immune cells, accelerating lung cancer initiation and progression.

Neutrophils, which constitute 40–70% of peripheral white blood cells, dominate the inflammatory microenvironment. They play critical roles in infection resistance and homeostasis by balancing pro-apoptotic and anti-apoptotic signals to terminate inflammation.<sup>68</sup> Recent findings by Qian et al reveal that IGF2BP2, an m6A modification regulator, is upregulated in lung cancer tissues and stabilizes LOX1 via m6A modification, facilitating neutrophil-mediated inflammatory responses and promoting lung cancer progression.<sup>69</sup>

In the TME, chronic inflammation induces the formation of neutrophil extracellular traps (NETs). NETs are significantly elevated in the plasma of lung cancer patients, with persistently high levels observed in tumor tissues even post-surgery, suggesting their role in cancer progression.<sup>70</sup> NETs promote lung cancer by secreting neutrophil elastase (NE), which induces mitochondrial biogenesis and maintains mitochondrial homeostasis via the TLR4-p38-PGC-1 $\alpha$  pathway.<sup>71,72</sup> Furthermore, NETs impair the cytotoxic activity of NK cells and drive T cell exhaustion, exacerbating immune suppression in lung cancer.<sup>73</sup> NETs also awaken dormant lung cancer cells by capturing circulating tumor cells, remodeling proteins, and activating integrin signaling pathways.<sup>74</sup> Dimitrov et al demonstrated that prolonged NET exposure activates the Notch 1 signaling pathway, triggering EMT and enhancing lung cancer cell migration and invasion.<sup>75</sup> Complementary research by Lu et al highlighted the anti-inflammatory effects of cryptotanshinone (CPT) and ginsenoside Rg1, which reduce neutrophil infiltration and NET formation in lung tissue, reversing NET-induced tumor-promoting effects.<sup>76</sup>

M2 macrophages play a role in suppressing immune clearance by inducing T cell dysfunction.<sup>77</sup> The transformation of macrophages from the M1 to the M2 phenotype is closely related to inflammation. Inflammatory factors can activate the STAT6 signaling pathway and Toll-like receptor (TLR) signaling pathway, thereby promoting the conversion of M1-type tumor-associated macrophages (TAMs) to M2-type TAMs.<sup>78</sup> Wang et al’s study demonstrated that nervonic acid alleviates lung inflammation and prevents lesions by targeting macrophage activation, underscoring the therapeutic potential of macrophage modulation.<sup>79</sup>

Inflammatory cytokines secreted by immune cells also promote lung cancer progression. For instance, IL-6, produced by activated T cells and macrophages, regulates immune and inflammatory responses and is strongly associated with lung cancer development.<sup>80</sup> The SIRP $\alpha$ /IL-6 axis forms a positive feedback loop via STAT3 signaling, fostering an immunosuppressive environment that supports tumor growth.<sup>81</sup> Moreover, Th22 cells, which increase with lung cancer severity, secrete IL-22. This cytokine activates the JAK-STAT3/MAPK/AKT pathways, further driving the formation of an immunosuppressive microenvironment and promoting lung cancer progression.<sup>82</sup>

## CAFs and Inflammation

Inflammation is characterized by the persistent presence of leukocytes, unable to either repair or resolve. Studies have shown that fibroblasts contribute to leukocyte recruitment and retention by altering the stromal landscape, leading the body from a state of “homeostasis” to persistent inflammatory invasion. Inflammatory CAFs (iCAFs) represent a specific pro-inflammatory subtype, highlighting the critical role CAFs play in remodeling the inflammatory microenvironment within the lung cancer TME.<sup>83</sup>

Firstly, cancer-associated fibroblasts (CAFs), as tissue sentinel cells, engage in an interactive dialogue with inflammatory factors. These inflammatory factors are not only secreted by CAFs but can also activate the inflammatory profile of CAFs, creating a malignant feedback loop that promotes the formation of an inflammatory microenvironment.<sup>84</sup>

According to the study by Koppensteiner et al, IFN $\gamma$  and TNF $\alpha$  can drive the inflammatory profile in CAFs derived from NSCLC, upregulating the secretion of inflammatory cytokines and chemokines, thereby promoting the development of lung cancer. IL-6, highly expressed in lung cancer and secreted by CAFs, cooperates with leukemia inhibitory factor (LIF) to modulate CAF invasion and promote lung cancer cell proliferation.<sup>85</sup>

Furthermore, CAFs induce the formation of immunosuppressive cells, which release inflammatory mediators to reshape the lung cancer inflammatory microenvironment. For instance, CAFs secrete IL-8, IL-6, and CCL2 to recruit and polarize pro-tumorigenic type 2 macrophages (TAM2) and pro-inflammatory Th2-type CD4 T cells, creating an inflammatory state that catalyzes lung cancer progression.<sup>86</sup> Additionally, activated CAFs undergo metabolic reprogramming through glycolysis and lipid metabolism, which leads to the downregulation of caveolin-1 (Cav-1), promoting the remodeling of the lung cancer stroma. This metabolic shift stimulates the secretion of VEGF-A, CCL2, CXCL, and CXCL8, while lactate accumulation renders the lung cancer stroma acidic, further enhancing the inflammatory microenvironment and driving lung cancer development.<sup>87</sup> Nicotinamide N-methyltransferase (NNMT) plays a pro-inflammatory role in cancer, and CAFs are the primary source of NNMT expression in solid tumors. According to a study by Yang et al, in A549 cells, NNMT promotes lung cancer cell proliferation and migration through a pro-inflammatory mechanism mediated by the STAT3/IL1 $\beta$ /PGE2 axis.<sup>88</sup> Recently, the negative regulation of NNMT on genes in CAFs has also been confirmed to promote the occurrence and metastasis of lung adenocarcinoma.<sup>89</sup>

The inflammatory environment forms the basis for the interaction between CAFs and lung cancer, with inflammation signaling pathways exacerbating cancer progression. For example, the COX2 and PGE2-integrin signaling axis plays a key role in promoting lung cancer. Targeting cyclooxygenase-2 (COX2) in lung cancer has been shown to reduce the progression of squamous cell carcinoma, highlighting the therapeutic potential of inhibiting inflammatory pathways.<sup>90</sup> The TLR4/MyD88/NF- $\kappa$ B signaling pathway has been widely reported in inflammatory diseases. Sun et al demonstrated through cellular experiments that exosome-derived miR-3124-5p from CAFs inhibits the expression of TOLLIP, thereby activating the TLR4/MyD88/NF- $\kappa$ B axis to promote malignant processes in NSCLC.<sup>91</sup>

## ECs and Inflammation

ECs, located between blood and lung tissue, serve as a physical barrier, control metabolite exchange, and regulate inflammation.<sup>22</sup> According to recent reports by Baris et al, the activation of nucleic acid sensors in endothelial cells has been shown to drive tumor-related inflammation. Specifically, activation of RIG-I reduces EC survival, angiogenesis, and triggers an inflammatory response. The researchers identified TYMP as a key mediator of RIG-I-induced EC dysfunction, suggesting that targeting TYMP could improve the inflammation driven by RIG-I activation in endothelial cells.<sup>92</sup> Among various cell types, ECs are highly sensitive to hypoxic conditions, a hallmark of the inflammatory-to-cancer transition in the lungs. During this transition, lung tissue experiences sustained hypoxia, which disrupts the tightly connected vascular structures, increasing their permeability. This leads to upregulation of leukocyte adhesion molecules such as ICAM-1 and E-selectin, altering the function of red blood cells and inducing inflammation in lung ECs, ultimately triggering the recruitment and infiltration of inflammatory mediators.<sup>93</sup> Studies suggest that hypoxia and inflammation create a mutually reinforcing environment, perpetuating a “hypoxia-inflammation-hypoxia” vicious cycle that accelerates lung cancer progression.<sup>94</sup> ECs, as key participants and regulators of inflammatory responses, can inhibit the progression of lung cancer by modulating various signaling pathways.<sup>95</sup> Targeting the Wnt/ $\beta$ -catenin signaling pathway may promote endothelial cell self-renewal in inflammation-induced lung injury. R-spondins (RSPOs), a highly conserved family of secreted glycoproteins, can enhance Wnt/ $\beta$ -catenin signaling. Recent studies by Zhang et al have shown that endothelial RSPO3 mediates lung endothelial regeneration after inflammatory vascular injury through  $\beta$ -catenin and ILK signaling pathways in an LGR4-dependent manner.<sup>96</sup> ECs also directly secrete inflammatory factors that can accelerate lung cancer onset, such as IL-6 and IL-8, which foster a microenvironment niche that supports non-small cell lung cancer (NSCLC) cell proliferation and viability.<sup>97</sup> In addition, IL-33, which is highly expressed in the vascular ECs of lung cancer patients, plays a crucial role in the inflammatory microenvironment. IL-33 can bind to the membrane-bound ST2 molecule (ST2L) on the IL-33R complex, inducing a Th2 immune response and promoting the polarization of M2 macrophages. Moreover, IL-33 acts as a transcriptional regulator that enhances the pro-inflammatory microenvironment in lung cancer.<sup>98</sup>

Endothelial inflammation can also be triggered by pyroptosis, a form of programmed cell death. Pyroptosis, initiated by the activation of NLRP3 and caspase-1, leads to cell membrane rupture and the release of intracellular contents, inducing endothelial inflammation. Activated caspase-1 releases active pro-inflammatory cytokines such as IL-1 $\beta$  and IL-18, which recruit inflammatory cells and amplify the inflammatory response.<sup>99</sup> Pyroptosis-driven endothelial inflammation contributes to lung cancer progression through multiple mechanisms.<sup>100</sup>

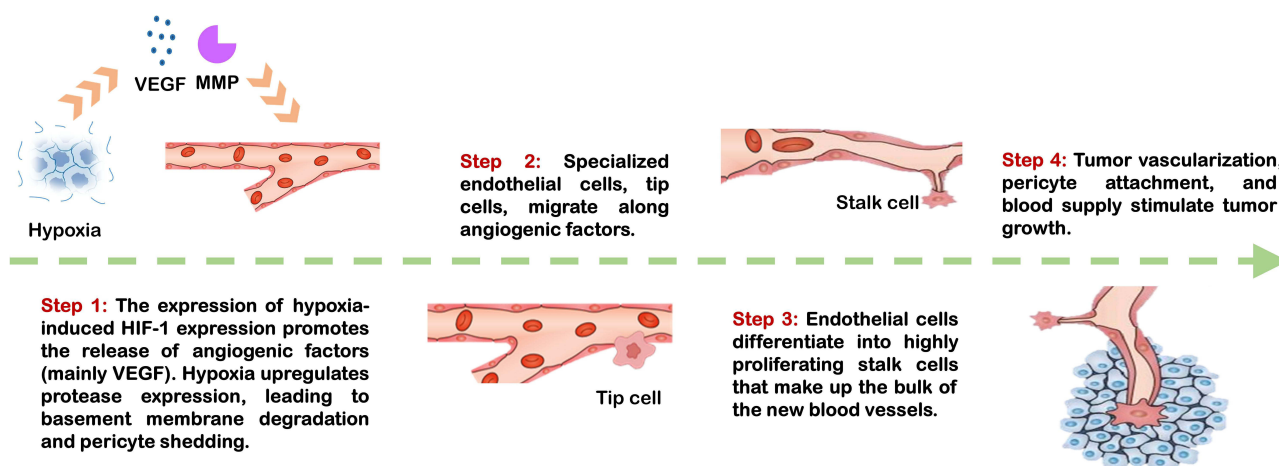
## Promoting Lung Cancer Development: Tumor Angiogenesis

Angiogenesis accompanied by abnormal vasculature is a crucial component of the tumor microenvironment (TME). Angiogenesis is considered a hallmark of cancer formation, playing a key role in tumor proliferation and metastasis.<sup>101</sup> Vascular endothelial growth factor (VEGF) and its receptors (VEGFR) play an essential role in inducing angiogenesis (as shown in Figure 4, the process of tumor vessel formation). The “angiogenesis switch” is a rate-limiting step in tumor development, dependent on the balance between pro-angiogenic and anti-angiogenic factors. Modulating this “angiogenesis switch” is a critical factor in promoting tumor angiogenesis, ensuring that the tumor acquires sufficient oxygen and nutrients for continuous growth within the TME.<sup>102</sup>

Tumor angiogenesis leads to the formation of physical barriers in the TME, where high vascular permeability and increased interstitial pressure induce an immune-suppressive microenvironment. The abnormal tumor vasculature is characterized by loose cell junctions and a low coverage of pericytes, which contributes to a hypoxic and acidic tumor environment.<sup>103</sup> Notably, this immune suppression, hypoxia, and acidity in the TME provide a key setting for driving further angiogenesis. Thus, the TME and tumor angiogenesis interact and complement each other, creating a vicious cycle that promotes tumor progression. In the following, we will systematically review the correlation between various stromal cells in the TME and tumor angiogenesis.

## Immune Cells and Angiogenesis

Angiogenesis is a critical process in lung cancer progression, and vascular endothelial growth factor (VEGF) is a key angiogenic protein that accelerates tumor development. According to recent reports, VEGF promotes lung cancer progression by inhibiting dendritic cell (DC) antigen presentation and the maturation of natural killer (NK) and T cells, while enhancing the immunosuppressive functions of regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). This process fosters the creation of an immune-suppressive microenvironment that facilitates tumor growth and progression.<sup>104</sup>



**Figure 4** The process of tumor angiogenesis. (Step 1: The expression of hypoxia-induced HIF-1 expression promotes the release of angiogenic factors (mainly VEGF). Hypoxia upregulates protease expression, leading to basement membrane degradation and pericyte shedding. Step 2: Specialized endothelial cells, tip cells, migrate along angiogenic factors. Step 3: Endothelial cells differentiate into highly proliferating stalk cells that make up the bulk of the new blood vessels. Step 4: Tumor vascularization, pericyte attachment, and blood supply stimulate tumor growth.)

As one of the most complex cellular populations within TME, immune cells not only contribute to immune surveillance but also actively promote angiogenesis. Macrophages are particularly important in this context, with Tie2-expressing macrophages (a subset of macrophages) secreting angiopoietin-2 (Ang-2) and VEGF to drive the formation of tumor vasculature.<sup>105</sup> Studies have shown that both VEGF and Ang-2 are highly expressed in the serum of NSCLC patients. Together, these molecules synergistically promote endothelial cell differentiation and the formation of new blood vessels, thereby facilitating tumor growth.<sup>106,107</sup>

In addition to VEGF and Ang-2, macrophages secrete a variety of cytokines and pro-angiogenic factors, including TGF- $\beta$ , TNF- $\alpha$ , arachidonic acid, IL-1 $\alpha$ , VEGF-A, EGF, CXCL8, and bFGF2. These factors, along with regulatory molecules like urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMPs), play a pivotal role in the angiogenic switch. They trigger the degradation of the basal membrane and extracellular matrix (ECM), destabilizing tumor vasculature, stimulating endothelial cell proliferation, and ultimately contributing to the formation of malignant tumor blood vessels.<sup>108</sup> Furthermore, IL-37 has been shown to regulate macrophage polarization and enhance angiogenesis in lung cancer patients, further supporting the role of macrophages in shaping the tumor vasculature and driving malignancy.<sup>109</sup>

Myeloid-derived suppressor cells (MDSCs) also contribute to tumor vascularization by secreting MMP-9 and TGF- $\beta$ 1, which increase the bioavailability of VEGF, thereby enhancing vascular density. Additionally, MDSCs promote new blood vessel formation in tumors through activation of the STAT3 signaling pathway.<sup>106</sup> Regulatory T cells (Tregs), critical components of the immunosuppressive landscape, secrete pro-angiogenic factors and cytotoxins that block anti-angiogenic signals from effector cells, regulate vascular permeability, and disrupt the stability and functionality of tumor blood vessels, further supporting angiogenesis and lung cancer progression.<sup>110</sup>

In a recent study, Yuan et al proposed a novel immunotherapy strategy for lung cancer, utilizing a protein targeting integrin  $\alpha\beta$ 3 (ProAgi). This approach reduces the number of CD4+ Tregs and MDSCs, while increasing the ratio of CD8+ T cells to M1/M2 macrophages, effectively depleting tumor angiogenesis. This study provides a promising therapeutic option for lung cancer patients with dense tumor masses and elevated angiogenesis.<sup>111</sup>

## CAFs and Angiogenesis

Tumor angiogenesis, a hallmark of vascular-dependent diseases, is a critical factor in the development and progression of lung cancer. CAFs are the most abundant stromal cell component within TME and play a pivotal role in producing key growth factors that promote both tumor angiogenesis and proliferation. One of the first identified vascular growth factors, fibroblast growth factors (FGFs), is highly expressed in the nuclei of lung cancer cells.<sup>112</sup> Recent findings by Lei et al have shown that overexpression of Glioma-associated oncogene 1 (Gli1) in lung cancer can promote angiogenesis. In this context, basic fibroblast growth factor (bFGF) has been identified as a critical regulator of Gli1-mediated angiogenic activity. Gli1 actively modulates bFGF protein levels by enhancing its transcriptional activity and reducing its protein degradation. This suggests that bFGF-based therapies could potentially reverse Gli1-mediated angiogenesis in lung cancer, offering a promising strategy to target tumor vasculature.<sup>113</sup> Binding of FGF to its receptor (FGFR) induces phosphorylation, activating key signaling pathways such as PI3K, MAPK, and JNK, which mediate the growth and angiogenesis of NSCLC. Notably, FGFR fusion proteins have been shown to significantly inhibit angiogenesis.<sup>114</sup>

Moreover, CAF-derived vascular endothelial growth factor (VEGF) plays a crucial role in promoting angiogenesis and is essential for the progression of lung adenocarcinoma.<sup>112,115</sup> According to Fu et al, CAFs secrete stromal cell-derived factor 1 (SDF-1/CXCL12), which recruits endothelial progenitor cells (EPCs) to the TME, remodeling the extracellular matrix (ECM). Additionally, CAFs directly chemotax blood endothelial cells (ECs) and secrete matrix metalloproteinases (MMPs) to degrade the ECM, facilitating the formation of new blood vessels and significantly contributing to tumor angiogenesis and proliferation.<sup>116</sup> Research also indicates that long non-coding RNAs (lncRNAs) promote tumor formation through their vascular-active properties. For instance, lncRNA ZEB1-AS1, which is specifically overexpressed in CAFs, enhances lung adenocarcinoma occurrence and invasion by promoting angiogenesis via the miR-505-3p/VEGFA axis. This promotes the growth of new blood vessel branches and their elongation.<sup>117,118</sup> Furthermore, exosomal microRNA-20a derived from CAFs plays a crucial regulatory role in immune response, angiogenesis, and cancer progression. The upregulation of miR-20a in

NSCLC patients has been linked to enhanced angiogenic activity. Recent studies have shown that CAF-derived exosomal miR-20a inhibits the PTEN/PI3K-AKT pathway, promoting the progression of NSCLC.<sup>119</sup>

Periostin (POSTN), a non-structural ECM protein synthesized by both cancer cells and CAFs, is one of the key factors significantly influencing the process of angiogenesis. Research indicates that the high expression of POSTN promotes NSCLC progression via angiogenesis.<sup>120</sup> Single-cell RNA sequencing of lung cancer has revealed elevated expression of FHL2 in fibroblast subtypes. In surgically resected lung adenocarcinoma specimens, FHL2-positive expression correlated significantly with microvascular density. Further investigation showed that FHL2 expressed by CAFs promotes lung adenocarcinoma progression by enhancing angiogenesis and metastasis.<sup>121</sup>

## ECs and Angiogenesis

In normal physiological conditions, ECs are organized in a structured manner, tightly connected with a high coverage of pericytes and an intact basement membrane, which helps maintain vascular homeostasis by minimizing leakage and sprouting.<sup>122</sup> However, when ECs are activated by local environmental stimuli, metabolic reprogramming occurs, driving tumor angiogenesis. Tumor vascularization is a critical step in tumor development, with tumor angiogenesis being one of the primary forms of this process.<sup>123</sup>

The metabolic reprogramming of ECs involves alterations in the biosynthesis and metabolism of glucose, fatty acids, and amino acids.<sup>124–126</sup> Upregulation of VEGF signaling enhances glycolysis in ECs, leading to excessive lactate accumulation. This lactate is then utilized by ECs, activating hypoxia-inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ), which promotes sprouting and the formation of pathological blood vessels.<sup>127</sup>

As a hallmark of tumor progression, angiogenesis plays a pivotal role in lung cancer development, and increasing evidence suggests that ECs significantly contribute to tumor progression by driving angiogenesis. Recent research identified microRNA-186-5p (miR-186) expression in ECs within non-small cell lung cancer (NSCLC) tissues. Through both *in vitro* and *in vivo* studies, researchers demonstrated that downregulation of miR-186 in ECs led to upregulation of protein kinase  $\text{C}\alpha$ , which mediates angiogenesis in NSCLC.<sup>128</sup>

Moreover, in NSCLC patients, neutrophil extracellular traps (NETs) can damage endothelial cells, converting them into a pro-coagulant phenotype. In collaboration with platelets, this conversion promotes a hypercoagulable state that disrupts vascular function and accelerates lung cancer progression.<sup>129</sup> Further studies by Santio et al uncovered the central role of reactive capillary endothelial cells (rCap) in lung cancer progression and metastasis. rCaps are enriched in angiogenic and inflammatory pathways, with PIM3, activated by the JAK-STAT pathway, acting as a key regulator. Inhibition of PIM3 increases vascular leakage and metastatic colonization while compromising endothelial cell barriers, suggesting PIM3 as a potential therapeutic target for preventing lung cancer metastasis.<sup>130</sup>

VEGF specifically binds to its receptors (VEGFR1, VEGFR2, VEGFR3) on ECs, leading to the downregulation of microRNA-1 (miR-1) in lung ECs, which promotes angiogenesis and contributes to lung cancer progression.<sup>131</sup> In NSCLC, Wnt proteins bind to their receptor Frizzled, activating the Wnt/ $\beta$ -catenin signaling pathway, which regulates endothelial cell proliferation and further drives angiogenesis.<sup>132</sup> Additionally, extracellular vesicles (EVs) transfer YAP from lung adenocarcinoma H1975 cells to ECs, modulating their role in vascular formation.<sup>64</sup>

## Summary and Outlook

Stromal cells infiltrating TME—including ICs, CAFs, and ECs—are active drivers of lung cancer initiation and progression. Immune suppression, inflammation, and angiogenesis are the primary factors within the TME that facilitate the advancement of lung cancer. This review integrates these concepts and delves into the roles and specific mechanisms by which various stromal cells contribute to lung cancer pathogenesis. It highlights how stromal cells initiate lung cancer by recruiting immune-suppressive cells, creating an immunosuppressive microenvironment, and catalyzing tumorigenesis through inflammatory responses, thereby fostering the development of an inflammatory milieu. Furthermore, by promoting tumor angiogenesis, stromal cells enhance tumor progression, thus serving as key contributors to lung cancer development. This review advances our understanding of how stromal cells influence the TME and provides insights into lung cancer pathogenesis, which is crucial for both diagnosis and treatment strategies.



Currently, remodeling the TME to restore homeostasis remains a major focus in medical research. While significant progress has been made in lung cancer therapies, including immune-modulatory therapies, anti-angiogenic treatments, and targeted approaches, challenges persist, including limited therapeutic options, suboptimal efficacy, and poor prognosis. This review underscores the interconnected roles of various stromal cells as critical components of the TME that promote lung cancer progression.

Looking ahead, the development of therapies targeting more specific stromal cell pathways holds promise. For example, immune-modulatory drugs could be designed not only to target immune cells but also CAFs, ECs, and the complex interplay between angiogenesis and immune suppression. Future research into the role of stromal cells, coupled with the development of combination treatment strategies to restore TME homeostasis and inhibit lung cancer initiation, presents an exciting avenue for advancing lung cancer therapies.

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## Disclosure

The authors report no conflicts of interest in this work.

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