Review

Tumor Microenvironment: An Emerging Landscape for Lung Cancer Therapy

S M Sohag , Sharmin Nur Toma , Md. Al-Imran Imon , Maiweilan Maihemuti , Famim Ahmed , Mst. Afsana Mimi , Imran Mahmud * , Md. Mahmudul Hasan *

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Review

Tumor Microenvironment: An Emerging Landscape for Lung Cancer Therapy

S M Sohag [1], Sharmin Nur Toma [2], Md. Al-Imran Imon [1], Maiweilan Maihemuti [3], Famim Ahmed [1], Mst. Afsana Mimi [3], Imran Mahmud [1,*,†] and Md. Mahmudul Hasan [4,*,†]

[1] Department of Pharmacy, Khwaja Yunus Ali University, Sirajganj-6751, Bangladesh; sohag.shafin75@gmail.com (S.M.S.); alimranimon23@gmail.com (M.A.-I.I.); famimahmed.kyau@gmail.com (F.A.)
[2] Department of Pharmacy, Islamic University, Kushtia, Bangladesh; sharmintoma77@gmail.com
[3] Graduate School of Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan; maiweilan6@gmail.com (M.M.); afsana.mimichem@gmail.com (M.A.M.)
[4] Earth-Life Science Institute, Institute of Science Tokyo, Tokyo 152-8550, Japan
* Correspondence: imran.mahmud.pharm@kyau.edu.bd (I.M.); m.hasan@elsi.jp; hasan.mahmudbio@gmail.com (M.M.H.)
† These authors corresponded equally to this work.

Abstract: The tumor microenvironment (TME) plays a pivotal role in the initiation, progression, and therapeutic resistance of lung cancer. Comprising a complex network of immune cells, fibroblasts, endothelial cells, extracellular matrix components, and signaling molecules, the TME supports tumor survival and metastasis while suppressing anti-tumor immunity. In lung cancer, tumor-associated macrophages, cancer-associated fibroblasts, mast cells, and dendritic cells interact through cytokines, chemokines, growth factors, and matrix metalloproteinases to shape an immunosuppressive and pro-angiogenic milieu. Hypoxic conditions within the TME further enhance cancer cell adaptability through hypoxia-inducible factors (HIFs), promoting epithelial-mesenchymal transition, immune evasion, and metastatic potential. Moreover, microRNAs have emerged as key regulators of gene expression within the TME, offering novel insights into tumor behavior and potential targets for therapy. Targeting the dynamic interactions within the TME—especially through modulation of immune responses, angiogenesis, and stromal remodeling—offers promising avenues for precision pharmacology. This review summarizes current knowledge of the lung TME, highlighting its impact on cancer pathophysiology and treatment strategies. Understanding and therapeutically reprogramming the TME may pave the way for personalized and more effective interventions in lung cancer management.

Keywords: tumor microenvironment; lung cancer; matrix metalloproteinase; hypoxia

1. Introduction

The cellular environment in which the tumor exists is called the tumor microenvironment (TME) [1]. The tumor microenvironment (TME) comprises various cell types, including stromal, mesenchymal, endothelial, cancer-associated fibroblasts, and cancer cells with specific phenotypic and genetic characteristics [2]. In the lung tumor microenvironment, cellular elements (inflammatory cells, tumor cells, fibroblasts, vascular, structural, and vascular smooth muscle cells, and pericytic cells, among others), soluble (proteases, cytokines, and hormones, among others), are the main components [1]. Genetic alteration shifts in the tumour in oncogenes that modulate tumor growth and invasion into the surrounding tissue orchestrate the entity of anti-inflammatory infiltrates, which vary by size and form in diverse tumour types and different stages of tumor development. Within the tumors, features of the complex inflammatory cells have revealed cells involved in both the intrinsic and adaptive branches of the immunologic response among the infiltrate of lung cancer will help to find their role in tumour progression. This understanding will be vital to finding novel anticancer therapies, though the data gathered will take us nearer to individualized medicine, and give particular treatment to reprogram the tumor microenvironment to control disease [3]. Lung cancer remains the leading cause of cancer-related fatalities worldwide [4]. NSCLC accounts for approximately 85% of lung cancer cases [5]. Lung cancer is divided into two types: non-small cell lung cancer (NSCLC, 80-85%) and small cell lung cancer (10-15%). Adenocarcinoma (45-60%), squamous cell carcinoma (20-25%), and neuroendocrine carcinoma (10-15%) are all types of non-small cell lung cancer. These subgroups

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differ in treatment and prognosis: NSCLC is treated with targeted medicines and has a 5-year overall survival rate of 23%, whereas SCLC is treated mostly with platinum-based chemotherapy and has a median survival of less than one year [6]. Immune checkpoint blockade (ICB) immunotherapy is the first-line treatment for advanced non-small cell lung cancer (NSCLC) with no known driver-gene mutation [7]. Chemokines have emerged as important participants in cancer immunotherapy, coordinating immune cell signaling inside the TME and aiding their recruitment to cancer cells [8]. Coherent with their capability to react to local environmental cues, proinflammatory interleukins, and chemokines are present at high levels in the microenvironment of epithelial tumors [9,10]. The tumor microenvironment also contains T and B lymphocytes of adaptive immunity, and these phenotypes of the T and B subsets are regulatory and weaken the immunologic response against the tumor and evoke a chronic inflammatory state of the tumor microenvironment [11]. Several stimuli-responsive materials that degrade in the pathological tumor microenvironment (TME) have been produced and investigated for drug delivery applications employing nanotechnological methods [12]. In the setting of lung cancer and its complex tumor microenvironment (TME), where conventional treatments frequently confront problems such as drug resistance and immune evasion, traditional plant-based medicines are gaining popularity. Artocarpus chaplasha, a traditional medicine herb, has demonstrated promising antioxidant and cytotoxic activities [13]. Despite substantial research, the role of the tumor microenvironment (TME) in immunotherapy resistance is still unknown. Variable responses in NSCLC can be attributed to variables such as low MHC-I expression, inadequate neoantigen release, and restricted CD8+ T cell infiltration. Understanding these mechanisms is crucial for overcoming resistance [14]. In recent years, a growing study has highlighted the tumor microenvironment (TME), Riera-Domingo et al. offering a complete overview of its metabolic features and hypoxia, as well as their impact on immune function and response to immunotherapies [15]. Understanding the complicated interactions between tumor cells and TME components, such as immune and stromal cells, may lead to novel ways for better lung cancer management and therapy [16]. Therefore, it is crucial to understand the cellular and molecular interplay in the tumor microenvironment to develop therapeutic strategies. In this review, we focused on the cellular and molecular interplay in the lung tumor-microenvironment and discussed several cellular and molecular components that can be focused on while developing any therapeutics.

2. Tumor-Infiltrating Immune Cells

Tumor-infiltrating immune cells are surrounded by infiltrating inflammatory cells, especially macrophages and lymphocytes [17]. Evidence suggests that cancer malignancy is caused by both tumor-intrinsic characteristics and TME factors, particularly invading immune cells. Lung cancer avoids immunosurveillance by low antigenicity, decreased MHC I/II/non-classical expression, a lack of costimulatory signals, and dysregulated immune cell infiltration [18]. The development of tumor-specific adaptive immune responses is particularly driven by tumor antigens [19]. The main components of tumor-specific cellular adaptive immunity are two types of T lymphocytes (CD4+ and CD8+). In which tumor cells are attacked by the CD8+ T lymphocytes, introducing tumor-associated antigen peptide with histocompatibility complex class I (MHC I) by producing interferon-g on their surface. Mechanisms of Interferon-g-dependent tumor cell cytostasis and killing constitute cell cycle prohibition, angiostasis, apoptosis, and also induction of antitumorigenic activity of macrophages [20].

Table 1. Major Tumor-infiltrating immune cells observed in the lung cancer tumor microenvironment, their main roles, and their relationships with clinical outcomes.

Immune cell type	Main Function in TME	Clinical/Prognostic Association
CD8+ T cells	Cytotoxic killing of tumor cells	Improved survival, better ICI response[21],[22]
CD4+ T cells	Helper/regulatory roles; coordinate immune responses	Variable; subset-dependent [22,23]
Regulatory T cells (Tregs)	Suppress anti-tumor immunity	Poorer prognosis [22,24]
B cells	Antibody production, antigen presentation	Mixed; high density may predict HPD [21,25]
Macrophages (M1/M2)	M1: pro-inflammatory/anti-tumor; M2: immunosuppressive	M1: favorable; M2: poor prognosis [22–24]
Myeloid-derived suppressor cells (MDSCs)	Suppress T cell function, promote tumor growth	Poorer prognosis [22]

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Natural Killer (NK) cells	Direct killing of tumor cells (innate immunity)	Generally favorable [23]
Dendritic cells (DCs)	Antigen presentation, T cell activation	It can be immunosuppressive in TME [24]
Mast cells	Modulate inflammation, angiogenesis	Prognostic value in LUAD [23]

2.1. Tumor-Infiltrating Lymphocytes (TIL)

TIL density, distribution, and phenotypic characteristics are important indicators of responsiveness to immune checkpoint inhibitors in lung cancer. TIL subsets ($CD4^+$, $CD8^+$, and $CD19/20^+$) have both effector (anti-tumor) and suppressive (pro-tumor) roles that are influenced by the tumor environment. Their balance ultimately determines disease progression and immunological status.

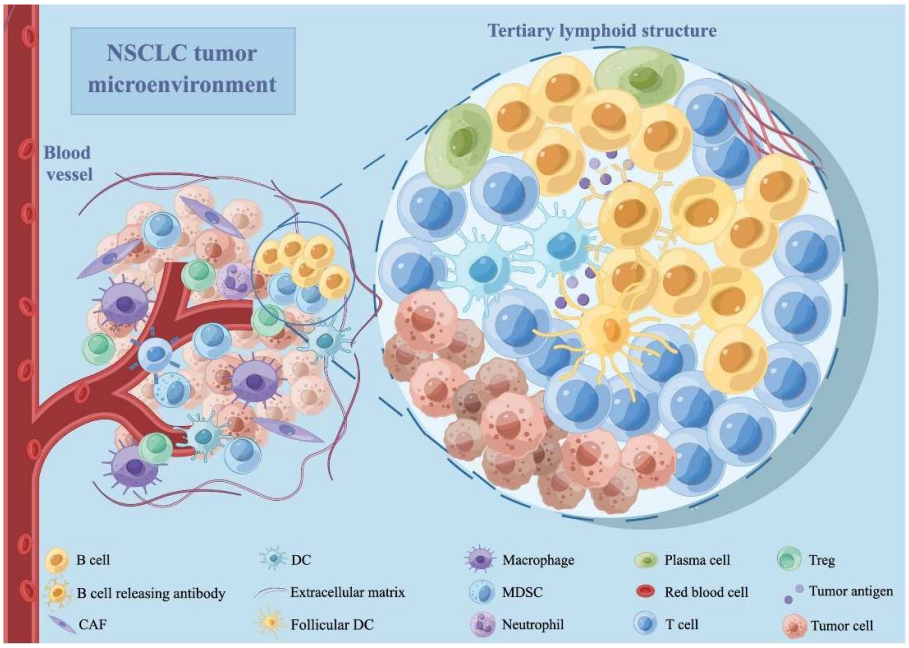

Figure 1. The tumor microenvironment of NSCLC. CAF stands for cancer-associated fibroblast; DC is a dendritic cell; MDSC is a myeloid-derived suppressor cell; NSCLC is a non-small cell lung cancer; and Treg is a regulatory T cell. The figure is reprinted from Wang, Fen, et al. 2022 with free reuse permission [26].

2.1.1. Cytotoxic CD8+ T Lymphocytes

CD8+ T cell density is associated with increased overall survival (OS) in lung cancer. $CD8^+$ T cells play a crucial role in lung cancer immunology, and increased intertumoral concentrations correspond with improved survival rates [27]. However, cancers avoid these cytotoxic cells by:

1. MHC-I downregulation inhibits antigen presentation [28].
2. Tregs and myeloid cells produce immunosuppressive cytokines such as TGF-β, IL-10, and IL-4 [28].
3. Metabolic competition through IDO-mediated tryptophan/arginine depletion and excessive glycolysis starves T cells of glucose [29].
4. Upregulated immunological checkpoints (PD-1, CTLA-4, TIM-3, LAG-3) cause T cell "burnout" despite activation signals [30,31].

Exhausted $CD8^+$ TILs expressing multiple checkpoints resist ICI therapy. However, tumors rich in $PD\text{-}1^+CD8^+$ cells ("hot" TMEs) frequently respond better to PD-1 blocking [32]. Responders have enhanced gene expression profiles with memory/effector signatures, while non-responders have dysfunction-related genes.

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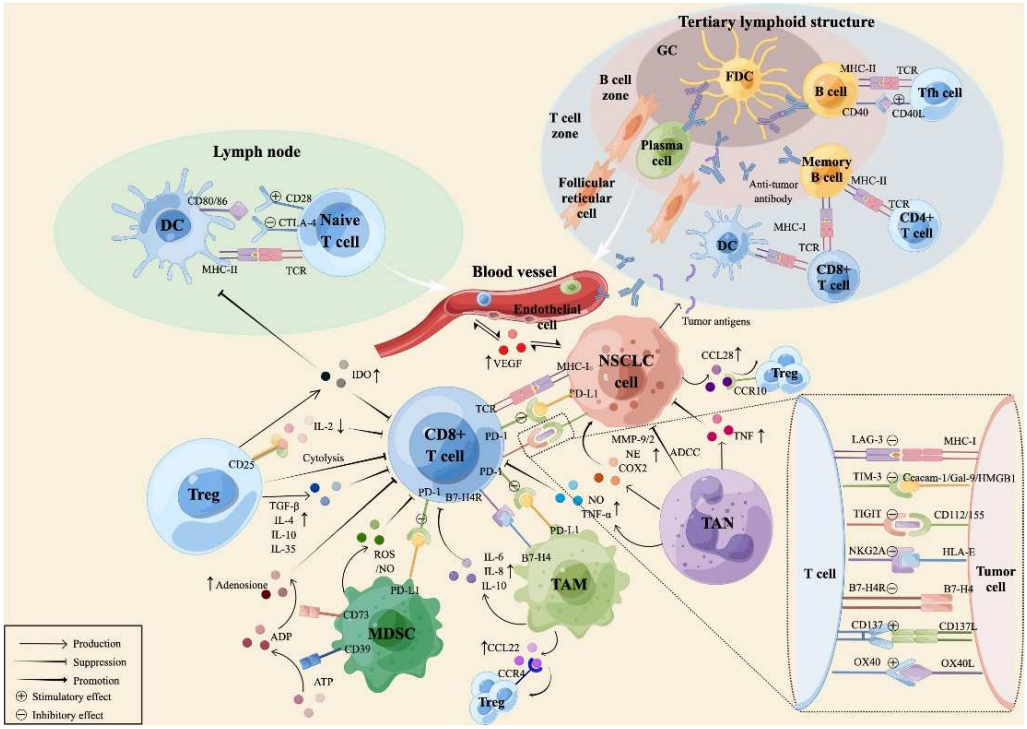

Figure 2. The tumor microenvironment of NSCLC. CAF stands for cancer-associated fibroblast; DC is a dendritic cell; MDSC is a myeloid-derived suppressor cell; NSCLC is a non-small cell lung cancer; and Treg is a regulatory T cell. The figure is reprinted from Wang, Fen, et al. 2022 with free reuse permission.

3. Tumor Expressing Cytokines

Cytokines—membrane-bound or released proteins produced by innate and adaptive immune cells in response to tumor antigens and pathogens—are responsible for immunological homeostasis. Their activities are dependent on local concentration, receptor expression, and pathway integration. Cytokines have an important role in tumor immunity, as evidenced by higher tumor incidence in animals lacking type I or II interferon receptors or downstream signaling components [33]. Cytokines signal through a series of common and shared receptors, there are seven types of Cytokines signal through a series of common and shared receptors, of which Type I and II, Type III cytokine receptor families have the most promising clinical potential. Type I includes IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; they initiate intracellular signals through the coordinated activity of signal transducers of activated T molecule and Janus kinases 1 and 3 [34].

Table 2. Basic characteristics and function of Cytokines [33,35].

Cytokine	Primary Source	Target Cells	Primary Function
IL-1	Monocytes, macrophages, fibroblasts	T/B cells, endothelium, hypothalamus	Co-stimulation, inflammation, fever
IL-2	T cells, NK cells	T/B/NK cells, monocytes	Growth and activation of immune cells
IL-4	T cells	T/B cells	Th2 differentiation, IgE switching
IL-6	T cells, macrophages	T/B cells, liver	Acute phase response, inflammation
IL-10	Th2 cells	Macrophages, T cells	Anti-inflammatory, suppresses APCs
IL-12	Macrophages, NK cells	T cells	Promotes Th1 differentiation
IL-17	NKT cells, ILCs	Epithelial, endothelial cells	Inflammation, infection control
IL-21	CD4+ T cells, NKT cells	T/B/NK cells	Enhances immune responses
IL-23	APCs	T cells, NK cells	Promotes chronic inflammation via Th17

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IFN-γ	T, NK, NKT cells	Monocytes, endothelial cells	MHC upregulation, macrophage activation
TNF-α	Macrophages, T cells	Immune, endothelial, liver cells	Inflammation, fever, acute-phase response
TGF-β	T cells, macrophages	T cells	Suppresses immune activation
IL-35	Tregs	T cells	Immunosuppressive, induces iTr35
IL-37	Monocytes, DCs	Macrophages, B cells	Dampens excessive inflammation

Contributions of oncostatin receptor and leukemia inhibitory factor receptor to signal transduction in heterodimeric complexes with glycoprotein 130. *Type II Cytokine Receptors include* IFN-α/β, IFN-γ, IL-10, IL-20, IL-22, IL-28; they mediate a signaling chain and a ligand binding chain[36]. Recently-discovered type III family contains IFN-1, IFN-2, and IFN-3 that activate an IL-10 receptor 2 and IL-28 receptor subunit complex[37]. This may be a vital subgroup in the future, but at this time, there are no established therapeutic uses for Type III IFNs. JAK-STAT pathways lead to the development of malignant cell growth, survival, and death and occur by different combinations of JAK kinases and their substrate [38].

4. Lung Tumor Microenvironment

Lung cancer is identified and characterized by uncontrolled proliferation of cells inside the lung; most commonly, epithelial cells are known as carcinomas. Metastasis is responsible for >70% of deaths in Europe and the USA, whereas lung cancer is placed in the leading position of cancer-related death. Most patients with last-stage lung cancer die within 18 months of diagnosis [39]. The lung tumor microenvironment is characterized by vascularization and oxygenation. Cigarette smoking is treated as a significant risk factor for the growth of lung cancer. Cigarette smoke results in an inflammatory reaction within the alveolar inflammatory cells of the lungs, and the changed secretion of cytokines predisposes towards lung cancer [40]. The development of lung cancer and tissue preferences for metastasis result from the interaction between tumor cells and stroma and reflect the migration of cancer cells to release chemoattractants instead of propagating cancer cells that may have the power to last in specific tissue microenvironments. Several stages are involved in the metastasis of epithelial cancers [41], First local tumor invasion through the cellar membrane and stroma [42], Intravasation into the lymphatic system [43], then the tumor cells survive within the circulation [44], Grab at the detached tumor site [45], speed up the development of circulating tumor cell microemboli [46], extravasation into the detached tissue microenvironment which is facilitated by tumor-cell secreted factors [47], tumor cells initially survive in the detached tumor stromal environment, responsible for the formation of a ‘‘pre-metastatic niche’’[48,49], modifying growth of cancer-cell intrinsic events at distant sites, and the development of macro metastases [32,50]. The above steps exist as a barrier to dissemination, making the overall metastatic process inefficient. The substantial latency period between primary diagnosis and subsequent formation of distant metastasis is a general observation within epithelial carcinomas. It is proposed that cells that depart the primary tumor are sufficiently well adapted to survive at distinct metastatic sites so that the latency period of the lung does not exhibit [51]. This may also be considered the relatively late stage of almost all types of lung cancer diagnosis.

5. Cells of the Stroma

5.1. Fibroblast Cells

In the late 19th century, based on the location and the microscopic appearance, fibroblasts were first described [52]. Fibroblasts are prolonged cells with extensive cell processes that show a fusiform or spindle-like shape in visibility. Deposition of extracellular matrix (ECM), regulation of epithelial differentiation, and regulation of inflammation are the crucial functions of fibroblasts [53,54]. Many of the constituents of the fibrillar ECM, such as type I, type III, and type V collagen, and fibronectin synthesized by fibroblasts [55]. These cells have a well-perceived role in the carcinogenic process. Stromal fibroblasts dominate tumor biology, but the exact mechanisms involved are still unclear. Fibroblasts in mammals are highly disparate, different sites reflect a substantial topographic diversity disjunct from those cells [56]. A particular type of stromal cells known as cancer-associated fibroblasts

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(CAFs) are myofibroblasts that express α-smooth muscle actin (α-SMA) and produce collagen and other ECM proteins. CAFs are now recognized for their function in epithelial tumor progression, growth, and metastasis by secreting substances that promote angiogenesis, cancer cell proliferation and invasion, macrophage recruitment, and T-cell-mediated immune suppression [57,58]. The functions of immune cells, tumor cells, and endothelial cells are regulated by CAFs, a poly-functionality that could be affected by the entity of multiple CAF lineages with distinguished intra-tumoral functions. In support of this decision, lung cancer patient prognosis is improved by the presence of PDGFR-α/β+ CAFs and aggravated by extracellular matrix (ECM) proteins commonly released by myofibroblastic CAFs. Because elements released by CAFs can increase tumor cell proliferation and invasion, encourage angiogenesis, and inhibit anti-tumor immunity, CAFs are a promising target for cancer prevention and treatment [59]. Immunotherapy is typically ineffective in some NSCLC patients, owing to a lack of CD8+ T cell penetration into tumors. CAF-rich tumors contribute to this by forming a physical barrier and promoting an immunologically cool milieu. CAFs also decrease CD8+ and CD4+ T cell activity, promote Treg differentiation, and recruit MDSCs, all of which aid in tumor growth and resistance to treatment. Thus, targeting CAFs has potential in improving immunotherapy responses in solid malignancies [60].

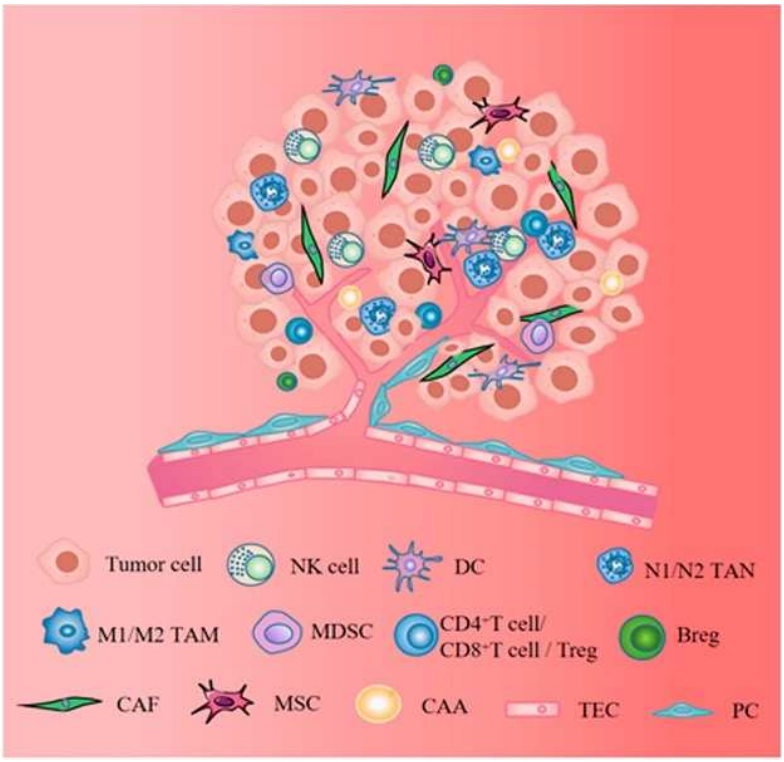

Figure 3. Stromal cells, including CAFs, MSCs, CAAs, TECs, and PCs, establish complex signaling networks that regulate tumor development, growth, and resistance to treatment. The figure is reprinted from Zhao, Yan, et al. 2023 with free reuse permission [61].

5.2. Immune Cells

Tumor cells induce angiogenesis and can increase endothelial cell proliferation, supporting tumor growth. Immune cells play a dual role in tumor progression, initially attacking tumor cells via cytokine production before being co-opted by tumors to boost growth and spread. Infiltrating immune cells are essential components of the tumor microenvironment, which tumor cells can use to cause immunological dysfunction and pro-inflammatory cytokine production. Exosomal miRNAs facilitate intercellular communication, which contributes to these activities [62]. Immune cells play a role in cancer dissemination that was predicted by Ehrlich in 1909; significant research has been conducted to question, re-judge, or approve this theory. In the past century, in vivo and in vitro work has shown that several types of cancer tissues, along with breast cancer, lung cancer, and colorectal

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cancer tissue, hold higher divides of unmarked immune cells than the normal tissue likeness, suggesting that the immune system acts very closely with the tumor microenvironment [63].

5.2.1. T-Cells

The class of immune cells, which represent the key actors of the adaptive immune response, is the T-cells. The tumour microenvironment (TME) can bind antitumoural T cell reactions in respective ways, including immunomodulation and impaired antigen presentation. Several cancer models in mice, antitumoural T cell responses, and T reg cell depletion have been shown to restrain tumour growth can be inhibited by T reg cells. T cell–attained Areg, likely by acting on normal cells in the TME, aided the increase of arising tumors in the lungs. The detected effect on tumor growth was not related to alterations in the number of intratumoral T cells or their capability to produce proinflammatory cytokines, proposing that neither pan–T cell lack in Areg nor its selective loss in T reg cells had immunomodulatory effects on the TME [64]. Regulatory T cells (Tregs) can infiltrate the tumor site and inhibit the function of effector T cells, which identify and destroy cancer cells. Tregs contribute to the formation of an immunosuppressive environment, allowing tumor cells to elude immune surveillance and accelerate tumor development. Inflammatory factors serve crucial roles in disease [65,66].

5.2.2. Macrophages

Macrophages account for the majority of the inflammatory infiltration in malignancies [67]. In inflammatory cells and the wound healing process, macrophages are the main component, which are derived from the monocytes later on, and they go into the tissue from the circulation. Macrophages are a significant part of the body's primary immune response to infection and have also manifested antitumour action under normal conditions. TAM signaling promotes vascularization, invasiveness, growth, cell survival, and immunosuppression, all resulting in continued tumor progression, when an immune injury-healing response is misplaced [68]. The macrophages that infiltrate into the TME are known as TAMs. TAMs are often observed in close proximity to CAFs in various tumor types, proposing interactions between these two cell types. The cleavage of type I collagen by FAP derived from CAFs can activate macrophages [69]. Most malignancies have a high proportion of TAMs with the M2 phenotype, which is associated with a poor prognosis. These M2-like TAMs help tumors survive, grow, and spread by encouraging angiogenesis, epithelial-to-mesenchymal transition, and immune suppression [70,71]. Although M1 macrophage infiltration is uncommon in malignancies, it has been observed in colorectal cancer, where their presence is associated with a better prognosis, even when M2 macrophages are more plentiful. (TAMs) is modified by the tumor's developmental stage as well as the microenvironment. Tumor advancement may result from the interaction of intrinsic (genetic) and extrinsic (microenvironmental) mechanisms, in which one initiates tumorigenesis and then drives the other to advance malignancy [72,73].

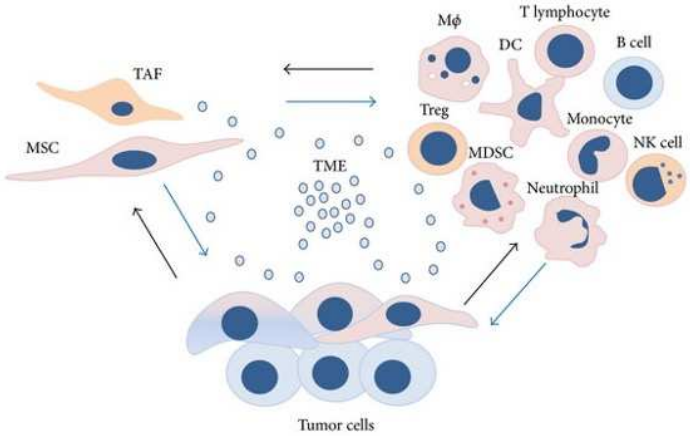

Figure 4. The tumor microenvironment (TME) provides a dynamic and supportive environment in which various cell types constantly modify their phenotypic and functions. It is made up of a complex mix of mesenchymal stromal/stem cells (MSCs), tumor-associated fibroblasts (TAFs), and a variety of immune cells, including macrophages, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), natural killer (NK) cells,

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dendritic cells (DCs), monocytes, neutrophils, T lymphocytes, and B cells, as well as a diverse population of tumor cells. The figure is reprinted from Trivanović, Drenka, et al. 2016 with free reuse permission [74].

5.2.3. Mast Cells

Paul Ehrlich first described mast cells (MCs) as versatile, tissue-homing secretory cells. He reported that MC was enhanced in chronically inflamed tissues, assuming they were providing nutritional aid to damaged cells [75]. Their distribution all over vascularized tissues, revealed to the exterior environment, including the lungs, provides interaction with environmental antigens, invading pathogens, or toxins [76]. Mast cells (MCs) are innate immune cells that reside at tumor edges and in the tumor microenvironment (TME), frequently near blood vessels. MCs, which differ from bone marrow progenitors, circulate in the blood and are guided to certain organs by chemoattractive signals. Several cytokines, including stem cell factor (SCF), CXCL12, IL-3, IL-4, IL-9, IL-10, IL-33, and TGF-β, influence their survival and proliferation. While MCs have generally been examined in the context of allergy reactions, current research has revealed that they can operate as proinflammatory and angiogenic mediators in malignancies. When activated, MCs produce mediators that attract immune cells such as neutrophils, macrophages, eosinophils, and B and T cells, thereby contributing to antitumor immune responses [77]. Mast cells (MCs), with their dual involvement in inducing inflammation and angiogenesis inside the tumor microenvironment (TME), are intriguing targets for adjuvant cancer therapy. Strategies may include suppressing angiogenesis and tissue remodeling, restricting the production of tumor-promoting proteins, and reversing MC-driven immune suppression—all while increasing their ability to produce cytotoxic cytokines, which boosts anticancer effectiveness [78].

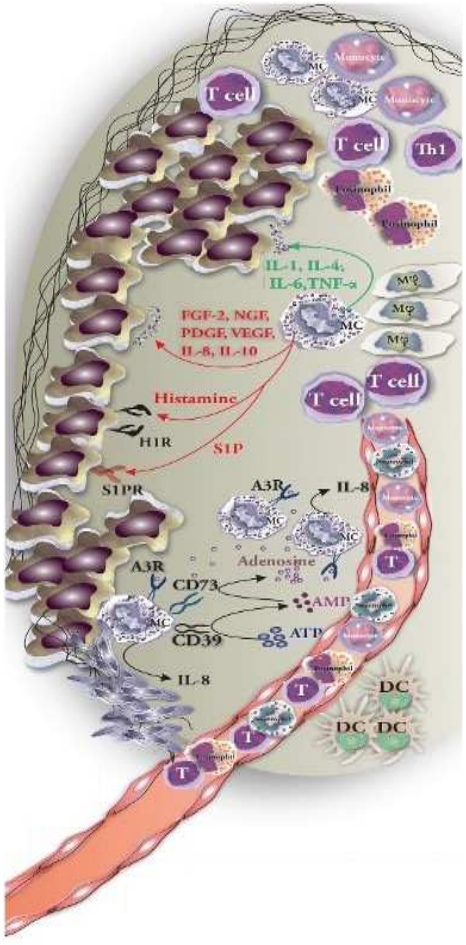

Figure 5. Mast cells (MCs) engage with tumor cells by releasing mediators and making direct cell-to-cell contact. MC-derived mediators can have dual effects: some promote tumor growth (e.g., histamine, VEGF, IL-10—shown in red) while others repress tumors (e.g., TNF-α, IL-1, granzyme B—shown in green). Furthermore, direct interactions with immune and tumor cells can either activate or repress cellular responses, impacting tumor

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development or immunological activation, depending on the situation. The figure is reprinted from Komi & Redegeld et al. 2020 with free reuse permission [77].

5.2.4. Dendritic Cells

Dendritic cells (DCs) are responsible for starting, maintaining, and directing anti-tumor immune responses. They detect DAMPs generated by dying tumor cells, which cause cytokine production and T-cell activation [79]. Dendritic cells (DCs) take up antigens and move to lymph nodes to deliver them to $CD8^+$ T lymphocytes. DCs are divided into two types: cDC1s, which deliver antigens to $CD8^+$ T cells, and cDC2s, which trigger $CD4^+$ T cell responses [80,81]. Dendritic cells (DCs) are classified as conventional type 1 (cDC1s) or type 2 (cDC2s). cDC1s promote anti-tumor immunity by delivering antigens to $CD8^+$ T cells, while cDC2s focus on priming $CD4^+$ T cell responses. cDC2s are classed as anti-inflammatory cDC2A (T-bet^+) or pro-inflammatory cDC2B (T-bet^-) based on their transcriptional and chromatin patterns. High cDC1 infiltration correlates with increased T cell presence and better patient outcomes. Tumors may avoid immune recognition by preventing cDC1 penetration into the tumor microenvironment [82,83]. cDC1s use the C-type lectin receptor DNGR-1 to identify F-actin on necrotic cells, which activates $CD8^+$ T lymphocytes by antigen absorption and cross-presentation. However, tumor-secreted gelsolin (sGSN) can disrupt this mechanism by preventing DNGR-1-dependent cross-presentation, reducing the immune response [84,85]. Plasmacytoid dendritic cells (pDCs) produce significant quantities of interferon-α (IFN-α), similar to plasma cells. In breast and ovarian cancer patients, malfunctioning pDCs produce less type I IFN and enhance regulatory T cell (Treg) development, which contributes to tumor progression. Understanding how DCs differentiate in the tumor microenvironment is still an active topic of research, with important implications for future immunotherapies [86].

5.2.5. Vascular Cells

To meet the metabolic and nutritional demands for growth, Tumors require the formation of a complex vascular network. VEGF is the main component involved in the formation of tumor vessels. It is released by the tumor cells directly and by fibroblasts and inflammatory cells in the stroma and is responsible for the ''angiogenic switch'' where new vasculature is shaped to provide the tumor with nutrients. Tumor vessels formed as a result of VEGF are abnormal; they are non-uniformly distributed and irregularly formed, unsuitably branched and tortuous, often terminating blindly. They do not have the classic hierarchical placement of arterioles, venules, and capillaries and often form arteriovenous shunts. These vessels are variably fenestrated and leaky, leading to high interstitial pressures, further exacerbating tissue hypoxia and stimulating additional VEGF production [87,88]. Under the dominance of VEGF, tumour vessels are shaped by one of various mechanisms, including the beginning of being vascular networks, recruitment of vascular progenitor cells to form new vascular channels, or ''vascular mimicry''—a process by which tumor cell-lined channels contribute to the blood tributaries supplying the tumor [89].

6. Extracellular Molecules

6.1. Cytokines

Given the limits of current lung cancer treatments, developing immune-based alternatives is critical. TILs in the tumor microenvironment (TME), including lymphocytes and macrophages, release low-molecular-weight cytokines and chemokines (<30 kDa) that govern cellular activities like metabolism, proliferation, tissue repair, and chemotaxis. These chemicals act on specific cell receptors to facilitate intercellular communication via autocrine, paracrine, and endocrine signaling [90,91]. Not only do cytokines and chemokines orchestrate immune responses, but they also drive local and systemic inflammation. They have a substantial impact on tumor growth, metastasis, and therapeutic resistance in the tumor microenvironment (TME). Several cytokines, including IL-6, IL-10, IL-17, IL-27, IL-35, TNF-α, IFN-γ, and TGF-β, and chemokines, such as CCL-2, CCL-5, CCL-18, CCR4, CXCR4, CX3CL1, CXCL-1, CXCL-5, CXCL-8, and CXCL-13, are extensively explored as therapeutic targets and biomarkers in lung cancer therapy techniques [92]. Lung tumor-derived prostaglandin E2 (PGE2) regulates immunological responses by increasing IL-10 synthesis from lymphocytes and macrophages while decreasing IL-12 production by macrophages. An immunohistochemical examination of human non-small cell lung cancer (NSCLC) tissues showed cytoplasmic COX-2 expression within tumor cells. This is the first report of functional COX-2 expression by NSCLC cells, and it identifies a

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method via which high COX-2 and PGE2 levels affect cytokine balance, changing the immunological landscape of the lung cancer microenvironment [93].

Table 3. Cytokines with their source and functions [94].

Cytokine	Source	Functions
IL-6	T-cells, macrophages, adipocytes	Proinflammatory action, promotes differentiation and cytokine production
IL-8	Epithelial cells, macrophages, endothelial cells	Proinflammatory action, promotes angiogenesis and chemotaxis
IL-10	Monocytes, B-cells, T-cells	Anti-inflammatory action, inhibits proinflammatory cytokines
IL-17	Th17 cells	Proinflammatory action, enhances cytokine and chemokine production, contributes to antitumor immunity
IL-27	Antigen-presenting cells (APCs)	Anti-inflammatory action, induces IL-10 production
IL-35	Regulatory T-cells (Tregs)	Anti-inflammatory action, promotes Treg proliferation, suppresses Th17 cells
IL-37	NK cells, monocytes, epithelial cells, B-cells	Anti-inflammatory, antimicrobial, and contributes to antitumor immunity
TNF-α	Macrophages, CD4+ lymphocytes, adipocytes, NK cells	Proinflammatory action, induces cell proliferation, cytokine production, and apoptosis
IFN-γ	NK cells, T-cells	Antiviral and proinflammatory action
TGF-β	T-cells, macrophages	Anti-inflammatory action, suppresses proinflammatory cytokine production
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T-cells, macrophages, fibroblasts	Proinflammatory action, enhances neutrophil and monocyte function, activates macrophages
Vascular endothelial growth factor (VEGF)	Macrophages, endothelial cells, platelets	Promotes vasculogenesis, angiogenesis, endothelial chemotaxis, and migration

6.2. Growth Factors

Epidermal growth factor is a transmembrane glycoprotein. The growth of cultured benign and malignant cells is promoted by the epidermal growth factor (EGF). Recent studies have manifested that the amount of EGF receptor, when compared with normal epidermal cells, is increased in squamous cell carcinoma cells in tissue culture [95]. Epidermal growth factor (EGFR) is a receptor tyrosine kinase recognized as being highly expressed in cancer cells, including lung cancers. These transmembrane proteins are activated complying binding with peptide growth factors of the EGF-family of proteins. It has been distinguished that mechanisms might contribute to amplifying the signal obstructed by growth factors, as expression of a high number of receptors on the surface of tumour cells can increase their sensitivity to low concentrations of host or tumour-derived growth factors. A direct correlation also exists between growth factors and cellular proto-oncogenes [96]. Many lines of manifest suggest that EGFR has relevance to patients with NSCLC and thus may serve as a potential therapeutic target. Expression of EGFR has been observed by immunohistochemistry testing in from 62% to 93% of resected primary tumors, and EGFR mRNA has been found in 100%. The overexpression of EGFR has been variably correlated with clinical outcomes [97].

6.3. Matrix Metalloproteinase

Growing evidence indicates that extracellular proteinases, notably matrix metalloproteinases (MMPs), play an important role in mediating microenvironmental alterations during tumor growth. These enzymes govern a wide range of physiological activities and signaling pathways, making them critical to the molecular interactions that occur between tumor cells and the stroma [42]. Matrix metalloproteinases (MMPs) are a class of zinc-dependent endopeptidases discovered about 50 years ago. They are required for a variety of physiological activities, including tissue remodeling, wound healing, and organ development, as they degrade extracellular matrix components and modulate cell activity [98,99]. Certain MMPs have tumor-suppressive roles, explaining the limited success of broad-spectrum MMP inhibitors (MPIs) in cancer therapy. For example, MMP-8 deficiency increases cancer risk, and macrophage-derived MMP-12 suppresses lung metastases by modulating tumor

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vasculature. Additionally, MMPs can exert non-proteolytic effects via domains like hemopexin, which are not targeted by typical MPIs, reducing their therapeutic efficacy [42].

7. Immune Regulation by Stroma

Immune system dysfunction is strongly associated with NSCLC, and immune checkpoint inhibitors are currently important second-line treatments following chemotherapy failure. Treatments for lung cancer that target CTLA-4, PD-1, and PD-L1 have demonstrated efficacy. Pembrolizumab increased progression-free and overall survival in NSCLC patients, but TG4010 with chemotherapy improved PFS in advanced cases [100]. Immune cells of a stoma include monocytes/macrophages, neutrophils, and lymphocytes, which enter into and occupy the tumor stroma. Monocytes are actively recruited into tumors along defined chemotactic gradients. Once in the tumor, they differentiate into tumor-associated macrophages (TAMs). TAMs seem to be preferentially pulled to and continued in areas of necrosis and hypoxia, where they become phenotypically changed and upregulate hypoxia-induced transcription factors. Macrophages also release several factors that influence endothelial cell behavior, including VEGF, HGF, MMP2, and IL-8. Neutrophils are distinguished as angiogenesis stimulators by releasing VEGF, HGF, MMP2, and IL-8. Additional immune cell populations have a less well-authenticated part in carcinogenesis and are not consistent occupants of stroma, with their presence limited to specific types of tumors. These include myeloid suppressor cells, which have the phenotypic features of some macrophages and granulocytes and various consequences of immune suppression, a product of MMP9 and VEGF, and the extra power to immediately incorporate into vessel walls [101,102].

8. Hypoxia and Tumour Microenvironment

Hypoxia is a common and significant characteristic of solid tumors. Hypoxic tissue is defined as having an oxygen tension of less than 10 mmHg, as opposed to 40- 60 mmHg in most normal tissue [103]. Cancer-related inflammation contributes to tumor initiation and progression by boosting genomic instability, cell proliferation, angiogenesis, apoptosis resistance, and metastasis. Hypoxia also contributes by allowing tumor cells to evade immune attack and avoid immunosurveillance. Hypoxia-inducible factors (HIFs), which are essential for hypoxic signaling, control genes implicated in tumor immune responses in low-oxygen environments [104]. Often achieved by induction of the hypoxia-inducible factor (HIF) family of transcription factors is the mechanism behind these effects. This family includes three members, HIF-1, -2, and -3, which act to govern cellular processes involved in glucose metabolism, angiogenesis, cell proliferation, and tissue remodeling in response to low oxygen levels. A group of prolyl-4-hydroxylases (PHDs) hydroxylate HIF-1α on two maintained residues, proline 402 and proline 564, under normal oxygen conditions [105–107]. One strategy is to ameliorate drug delivery, thus enhancing drug accumulation within the tumor. Several treatment techniques for hypoxia have been developed. One technique is to directly provide oxygen to the tumor using technologies such as the catalytic breakdown of endogenous hydrogen peroxide (H2O2) and light-triggered water splitting [108]. Several ongoing clinical trials are investigating hypoxia-targeted therapeutics employing a variety of medicines with distinct mechanisms. HIF inhibitors, including PX-478 and LW6, constitute an important class of therapeutic medicines. Studies have revealed that HIF inhibitors, either alone or in conjunction with other therapies, offer promising anti-tumor properties [104].

9. Role of microRNAs in Regulating Tumor Microenvironment

MicroRNAs (miRNAs) are tiny, noncoding RNAs that control gene expression by degrading mRNA or impeding translation. Dysregulated miRNA expression is associated with cancer initiation, progression, and metastasis. Some upregulated miRNAs serve as oncogenic drivers (oncomiRs), whereas downregulated miRNAs operate as tumor suppressors. Aberrant miRNA expression can interfere with cellular processes such as apoptosis, cell proliferation, invasion, metastasis, and treatment sensitivity, all of which contribute to tumor development [109]. According to studies, a single miRNA can bind to over 200 target genes, altering processes such as transcription, receptor activation, and transport. This intricacy makes it difficult to determine the exact transcripts and pathways controlled by individual miRNAs [110]. MicroRNAs have been depicted to be involved in several cellular processes, including proliferation, development, metabolism, differentiation, and apoptosis. Most importantly, pathological conditions involving cancer have been associated with deregulation of

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microRNA expression and role [111,112]. In cancer, microRNAs have been separated into oncogenic or tumor suppressor miRNAs. In the first instance, microRNAs assume an oncogenic function by post-transcriptionally lowering mRNA and, subsequently, protein levels of molecules with tumor suppressor functions. Despite the enormous quantity of knowledge we already have on microRNAs, new publications continue appearing, depicting yet other novel purposes, making us wonder about the wide-reaching possibility of these small molecules. In summary, microRNAs seem to be a very promising research target; however, the complexity of their activities makes keeping this promise challenging [113].

Table 4. microRNA expression status in lung cancer.

microRNA	Targets	Expression status (Under-expressed/Over-expressed/ Unchanged)	Comments (if any)	Reference
miR-487b	SUZ12,BM11, MYC	Over-expressed	Tumour suppressor	Xi et al, 2013 [114]
miR-449	HDAC1	Over-expressed		AM Rusek et al;2015 [113]
miR-101	EZH2	Over-expressed		AM Rusek et al;2015 [113]
miR-486	IGF1R	Under-expressed	NSCLC-Tumour suppressor	C M. Croce et al;2013 [115]
miR-9	MHC 1 gene	Over-expressed		AM Rusek et al;2015 [113]
miR-124a	CDK6	Over-expressed	Tumour suppressor	A Lujambio et al;2007 [116]
miR-221	TIMP3	Over-expressed		AM Rusek et al;2015 [113]
miR-222	TIMP3	Over-expressed		AM Rusek et al;2015 [113]
miR-429	ZEB1/2	Over-expressed	NSCLC- Oncogenic	Wu CI et al;2018 [117]
miR-128b	EGFR in NSCLC	Under-expressed	Tumour Suppressor	Becker-Santos DD et al 2012 [118]
miR-1827	SK-LU-1, RBX1 in NSCLC	Under-expressed	NSCLC- Tumour suppressor	SM Noor et al;2018 [119]
miR-378	RBX1, CRKL in NSCLC	Over-expressed	NSCLC- Tumour suppressor	SM Noor et al;2018 [119]
miR-630	Mut-Bcl-2-3'-UTR	Unchanged	NSCLC- Tumour suppressor	Huei Lee et al;2018 [120]
miR-31	LATS2/PPP2R2A	Overexpressed	NSCLC -Oncogenic	Liu et al;2010 [121]
miR-221/222	PUMA	Overexpressed	NSCLC -Oncogenic	Zhang et al;2014 [122]
miR-197	PD-L1	Overexpressed	NSCLC -Oncogenic	Fujita et al; 2015 [123]
microRNA-146a	EGFR	Overexpressed	NSCLC- Tumour suppressor	Chen et al; 2013 [124]

10. Targeting the Tumor Microenvironment for Cancer Therapy

The malignant features of cancer cells cannot be proved without a crucial interplay between cancer cells and their local environment. Angiogenic vascular cells, lymphatic endothelial cells, immune cells, and cancer-associated fibroblastic cells are the composition of the tumor infiltrate, which actively leads to cancer progression. The efficiency to alter these surroundings is a crucial feature by which tumor cells are capable of gaining some of the hallmark functions necessary for tumor development and metastatic dissemination. Targeting the tumor microenvironment to encapsulate or destroy cancer cells in their local environment has become compulsory. The difference in stromal cells, the complexity of the molecular elements of the tumor stroma, and the resemblance with normal

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tissue present huge challenges for therapies targeting the tumor microenvironment. Most recent investigations have shed light on the significant role in cancer progression played by the noncellular stromal compartment composed of the extracellular matrix [125].

This TME will influence the therapeutic effect/response and has an impact on the explicit surface receptors and activated or silenced signaling pathways. To deal with troubles such as no response to therapy or tumor resistance, and aiming to attain a personalized medicine in oncology, each tumor must be considered as a complex disease, different in each patient, and thus demanding a different strategy concerning therapeutics, especially centered on combinations. Hence, to formulate new therapeutic strategies towards a more effective targeting of TME, a big attempt has been made, which centers on (i) therapeutic strategies that target TME components and (ii) the development of models that exactly correspond to the TME for bench investigations [126]. It is now progressively accepted that cancer cells interact intimately with the extracellular matrix (ECM) and stromal cells, which together form the major construct of TME, instead of working alone [127].

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Abbreviations

The following abbreviations are used in this manuscript:

NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
TME	Tumor-microenvironment
ICB	Immune checkpoint blockade
MSCs	Mesenchymal stromal/stem cells
TAFs	Tumor-associated fibroblasts
Tregs	Regulatory T-cells
MDSCs	Myeloid-derived suppressor cells
NK	Natural killer cells
DCs	Dendritic cells
ECM	Extracellular matrix
HIFs	Hypoxia-inducible factors
MMPs	Matrix metalloproteinases

References

1. Sica, A.; Bronte, V. Altered macrophage differentiation and immune dysfunction in tumor development. *J. Clin. Investig.* **2007**, *117*, 1155–1166, https://doi.org/10.1172/jci31422.
2. Mimi, M.A.; Hasan, M.; Takanashi, Y.; Waliullah, A.; Mamun, A.; Chi, Z.; Kahyo, T.; Aramaki, S.; Takatsuka, D.; Koizumi, K.; et al. UBL3 overexpression enhances EV-mediated Achilles protein secretion in conditioned media of MDA-MB-231 cells. *Biochem. Biophys. Res. Commun.* **2024**, *738*, 150559, https://doi.org/10.1016/j.bbrc.2024.150559.
3. Biswas S. Tumor Microenvironment and Myelomonocytic Cells. BoD–Books on Demand; 2012.
4. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer J. Clin.* **2021**, *71*, 209–249, https://doi.org/10.3322/caac.21660.
5. Goldstraw P, Ball D, Jett JR, et al. Non-small-cell lung cancer. Lancet. 2011;378(9804):1727-1740.

 doi:10.20944/preprints202505.1025.v1

6. Pirlog, R.; Chiroi, P.; Rusu, I.; Jurj, A.M.; Budisan, L.; Pop-Bica, C.; Braicu, C.; Crisan, D.; Sabourin, J.-C.; Berindan-Neagoe, I. Cellular and Molecular Profiling of Tumor Microenvironment and Early-Stage Lung Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 5346, https://doi.org/10.3390/ijms23105346.
7. Mok, T.S.K.; Wu, Y.-L.; Kudaba, I.; Kowalski, D.M.; Cho, B.C.; Turna, H.Z.; Castro, G., Jr.; Srimuninnimit, V.; Laktionov, K.K.; Bondarenko, I.; et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* **2019**, *393*, 1819–1830, doi:10.1016/s0140-6736(18)32409-7.
8. Jung, H.; Paust, S. Chemokines in the tumor microenvironment: implications for lung cancer and immunotherapy. *Front. Immunol.* **2024**, *15*, 1443366, https://doi.org/10.3389/fimmu.2024.1443366.
9. A Arenberg, D.; Keane, M.P.; DiGiovine, B.; Kunkel, S.L.; Morris, S.B.; Xue, Y.Y.; Burdick, M.D.; Glass, M.C.; Iannettoni, M.D.; Strieter, R.M. Epithelial-neutrophil activating peptide (ENA-78) is an important angiogenic factor in non-small cell lung cancer.. *J. Clin. Investig.* **1998**, *102*, 465–472, https://doi.org/10.1172/jci3145.
10. Huang, M.; Wang, J.; Lee, P.; Sharma, S.; Mao, J.T.; Meissner, H.; Uyemura, K.; Modlin, R.; Wollman, J.; Dubinett, S.M. Human non-small cell lung cancer cells express a type 2 cytokine pattern.. **1995**, *55*, 3847–53.
11. Jover, R.; Nguyen, T.; Pérez–Carbonell, L.; Zapater, P.; Payá, A.; Alenda, C.; Rojas, E.; Cubiella, J.; Balaguer, F.; Morillas, J.D.; et al. 5-Fluorouracil Adjuvant Chemotherapy Does Not Increase Survival in Patients With CpG Island Methylator Phenotype Colorectal Cancer. *Gastroenterology* **2011**, *140*, 1174–1181, https://doi.org/10.1053/j.gastro.2010.12.035.
12. Srinivasarao, D.A.; Shah, S.; Famta, P.; Vambhurkar, G.; Jain, N.; Pindiprolu, S.K.S.; Sharma, A.; Kumar, R.; Padhy, H.P.; Kumari, M.; et al. Unravelling the role of tumor microenvironment responsive nanobiomaterials in spatiotemporal controlled drug delivery for lung cancer therapy. *Drug Deliv. Transl. Res.* **2024**, *15*, 407–435, https://doi.org/10.1007/s13346-024-01673-z.
13. Sohag, S.M.; Toma, S.N.; Morshed, N.; Imon, A.I.; Islam, M.; Piash, I.; Shahria, N.; Mahmud, I. Exploration of analgesic and anthelmintic activities of Artocarpus chaplasha ROXB. leaves supported by in silico molecular docking. *Phytomedicine Plus* **2025**, *5*, https://doi.org/10.1016/j.phyplu.2025.100761.
14. Huang S, Chung JYF, Li C, et al. Cellular dynamics of tumor microenvironment driving immunotherapy resistance in non-small-cell lung carcinoma. Cancer Lett. Published online 2024:217272.
15. Riera-Domingo C, Audigé A, Granja S, et al. Immunity, hypoxia, and metabolism–the Ménage à Trois of cancer: implications for immunotherapy. Physiol Rev. 2020;100(1):1-102.
16. Saeed Issa B, Adhab AH, Salih Mahdi M, et al. Decoding the complex web: cellular and molecular interactions in the lung tumour microenvironment. J Drug Target. 2025;33(5):666-690.
17. Shackleton, M.; Vaillant, F.; Simpson, K.J.; Stingl, J.; Smyth, G.K.; Asselin-Labat, M.-L.; Wu, L.; Lindeman, G.J.; Visvader, J.E. Generation of a functional mammary gland from a single stem cell. *Nature* **2006**, *439*, 84–88, https://doi.org/10.1038/nature04372.
18. Liu, X.; Wu, S.; Yang, Y.; Zhao, M.; Zhu, G.; Hou, Z. The prognostic landscape of tumor-infiltrating immune cell and immunomodulators in lung cancer. *Biomed. Pharmacother.* **2017**, *95*, 55–61, https://doi.org/10.1016/j.biopha.2017.08.003.
19. van der Bruggen P, Van Pel A. Tumor antigens recognized by T lymphocytes. Annu Rev, Immunol. 1994;12:337-365.
20. Dunn, G.P.; Old, L.J.; Schreiber, R.D. The Immunobiology of Cancer Immunosurveillance and Immunoediting. *Immunity* **2004**, *21*, 137–148, doi:10.1016/j.immuni.2004.07.017.
21. Cheng, C.; Nguyen, T.T.; Tang, M.; Wang, X.; Jiang, C.; Liu, Y.; Gorlov, I.; Gorlova, O.; Iafrate, J.; Lanuti, M.; et al. Immune Infiltration in Tumor and Adjacent Non-Neoplastic Regions Codetermines Patient Clinical Outcomes in Early-Stage Lung Cancer. *J. Thorac. Oncol.* **2023**, *18*, 1184–1198, https://doi.org/10.1016/j.jtho.2023.04.022.
22. A Barnes, T.; Amir, E. HYPE or HOPE: the prognostic value of infiltrating immune cells in cancer. *Br. J. Cancer* **2017**, *117*, 451–460, https://doi.org/10.1038/bjc.2017.220.

 doi:10.20944/preprints202505.1025.v1

23. Tong, Z.; Wang, X.; Liu, H.; Ding, J.; Chu, Y.; Zhou, X. The relationship between tumor infiltrating immune cells and the prognosis of patients with lung adenocarcinoma. *J. Thorac. Dis.* **2023**, *15*, 600–610, https://doi.org/10.21037/jtd-22-1837.
24. Steffens, S.; Kayser, C.; Roesner, A.; Rawluk, J.; Schmid, S.; Gkika, E.; Kayser, G. Low densities of immune cells indicate unfavourable overall survival in patients suffering from squamous cell carcinoma of the lung. *Sci. Rep.* **2024**, *14*, 1–11, https://doi.org/10.1038/s41598-024-64956-y.
25. Ku, B.M.; Kim, Y.; Lee, K.Y.; Kim, S.; Sun, J.; Lee, S.; Ahn, J.S.; Park, K.; Ahn, M. Tumor infiltrated immune cell types support distinct immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *Eur. J. Immunol.* **2021**, *51*, 956–964, https://doi.org/10.1002/eji.202048966.
26. Wang, F.; Yang, M.; Luo, W.; Zhou, Q. Characteristics of tumor microenvironment and novel immunotherapeutic strategies for non-small cell lung cancer. *J. Natl. Cancer Cent.* **2022**, *2*, 243–262, https://doi.org/10.1016/j.jncc.2022.10.002.
27. Geng, Y.; Shao, Y.; He, W.; Hu, W.; Xu, Y.; Chen, J.; Wu, C.; Jiang, J. Prognostic Role of Tumor-Infiltrating Lymphocytes in Lung Cancer: a Meta-Analysis. *Cell. Physiol. Biochem.* **2015**, *37*, 1560–1571, https://doi.org/10.1159/000438523.
28. Vinay, D.S.; Ryan, E.P.; Pawelec, G.; Talib, W.H.; Stagg, J.; Elkord, E.; Lichtor, T.; Decker, W.K.; Whelan, R.L.; Kumara, H.M.C.S.; et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin. Cancer Biol.* **2015**, *35*, S185–S198, doi:10.1016/j.semcancer.2015.03.004.
29. Ye, B.; Stary, C.M.; Gao, Q.; Wang, Q.; Zeng, Z.; Jian, Z.; Gu, L.; Xiong, X. Genetically Modified T-Cell-Based Adoptive Immunotherapy in Hematological Malignancies. *J. Immunol. Res.* **2017**, *2017*, 1–13, https://doi.org/10.1155/2017/5210459.
30. Keenan, T.E.; Burke, K.P.; Van Allen, E.M. Genomic correlates of response to immune checkpoint blockade. *Nat. Med.* **2019**, *25*, 389–402, https://doi.org/10.1038/s41591-019-0382-x.
31. Walunas, T.L.; Lenschow, D.J.; Bakker, C.Y.; Linsley, P.S.; Freeman, G.J.; Green, J.M.; Thompson, C.B.; Bluestone, J.A. CTLA-4 can function as a negative regulator of T cell activation. *Immunity* **1994**, *1*, 405–413, https://doi.org/10.1016/1074-7613(94)90071-x.
32. Zhang, L.; Chen, Y.; Wang, H.; Xu, Z.; Wang, Y.; Li, S.; Liu, J.; Chen, Y.; Luo, H.; Wu, L.; et al. Massive PD-L1 and CD8 double positive TILs characterize an immunosuppressive microenvironment with high mutational burden in lung cancer. *J. Immunother. Cancer* **2021**, *9*, e002356, https://doi.org/10.1136/jitc-2021-002356.
33. Lee S, Margolin K. Cytokines in cancer immunotherapy. Cancers (Basel). 2011;3(4):3856-3893.
34. Rochman, Y.; Spolski, R.; Leonard, W.J. New insights into the regulation of T cells by γc family cytokines. *Nat. Rev. Immunol.* **2009**, *9*, 480–490, https://doi.org/10.1038/nri2580.
35. Essogmo, F.E.; Zhilenkova, A.V.; Tchawe, Y.S.N.; Owoicho, A.M.; Rusanov, A.S.; Boroda, A.; Pirogova, Y.N.; Sangadzhieva, Z.D.; Sanikovich, V.D.; Bagmet, N.N.; et al. Cytokine Profile in Lung Cancer Patients: Anti-Tumor and Oncogenic Cytokines. *Cancers* **2023**, *15*, 5383, https://doi.org/10.3390/cancers15225383.
36. Kotenko, S.V.; Pestka, S. Jak-Stat signal transduction pathway through the eyes of cytokine class II receptor complexes. *Oncogene* **2000**, *19*, 2557–2565, https://doi.org/10.1038/sj.onc.1203524.
37. Vilcek, J. Novel interferons. *Nat. Immunol.* **2003**, *4*, 8–9, https://doi.org/10.1038/ni0103-8.
38. Steen, H.C.; Gamero, A.M. Interferon-Lambda as a Potential Therapeutic Agent in Cancer Treatment. *J. Interf. Cytokine Res.* **2010**, *30*, 597–602, https://doi.org/10.1089/jir.2010.0058.
39. Langer, C.J.; Besse, B.; Gualberto, A.; Brambilla, E.; Soria, J.-C. The Evolving Role of Histology in the Management of Advanced Non–Small-Cell Lung Cancer. *J. Clin. Oncol.* **2010**, *28*, 5311–5320, https://doi.org/10.1200/jco.2010.28.8126.
40. I Grivennikov, S.; Karin, M. Inflammation and oncogenesis: a vicious connection. *Curr. Opin. Genet. Dev.* **2010**, *20*, 65–71, https://doi.org/10.1016/j.gde.2009.11.004.
41. Valastyan, S.; Weinberg, R.A. Tumor Metastasis: Molecular Insights and Evolving Paradigms. *Cell* **2011**, *147*, 275–292, https://doi.org/10.1016/j.cell.2011.09.024.
42. Kessenbrock, K.; Plaks, V.; Werb, Z. Matrix Metalloproteinases: Regulators of the Tumor Microenvironment. *Cell* **2010**, *141*, 52–67, https://doi.org/10.1016/j.cell.2010.03.015.

 doi:10.20944/preprints202505.1025.v1

43. Azzali, G. The modality of transendothelial passage of lymphocytes and tumor cells in the absorbing lymphatic vessel.. **2007**, 73–7.
44. Chunhacha, P.; Chanvorachote, P. Roles of caveolin-1 on anoikis resistance in non small cell lung cancer.. **2012**, *4*, 149–55.
45. Al-Mehdi, A.B.; Tozawa, K.; Fisher, A.B.; Shientag, L.; Lee, A.; Muschel, R.J. Intravascular origin of metastasis from the proliferation of endothelium-attached tumor cells: A new model for metastasis. *Nat. Med.* **2000**, *6*, 100–102, https://doi.org/10.1038/71429.
46. Chambers, A.F.; Groom, A.C.; MacDonald, I.C. Dissemination and growth of cancer cells in metastatic sites. *Nat. Rev. Cancer* **2002**, *2*, 563–572, https://doi.org/10.1038/nrc865.
47. Gupta, G.P.; Nguyen, D.X.; Chiang, A.C.; Bos, P.D.; Kim, J.Y.; Nadal, C.; Gomis, R.R.; Manova-Todorova, K.; Massagué, J. Mediators of vascular remodelling co-opted for sequential steps in lung metastasis. *Nature* **2007**, *446*, 765–770, https://doi.org/10.1038/nature05760.
48. Psaila, B.; Lyden, D. The metastatic niche: adapting the foreign soil. *Nat. Rev. Cancer* **2009**, *9*, 285–293, https://doi.org/10.1038/nrc2621.
49. Erler, J.T.; Bennewith, K.L.; Cox, T.R.; Lang, G.; Bird, D.; Koong, A.; Le, Q.-T.; Giaccia, A.J. Hypoxia-Induced Lysyl Oxidase Is a Critical Mediator of Bone Marrow Cell Recruitment to Form the Premetastatic Niche. *Cancer Cell* **2009**, *15*, 35–44, https://doi.org/10.1016/j.ccr.2008.11.012.
50. Kang, Y.; Siegel, P.M.; Shu, W.; Drobnjak, M.; Kakonen, S.M.; Cordón-Cardo, C.; Guise, T.A.; Massagué, J. A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell* **2003**, *3*, 537–549, https://doi.org/10.1016/s1535-6108(03)00132-6.
51. Nguyen, D.X.; Bos, P.D.; Massague, J. Metastasis: from dissemination to organ-specific colonization. *Nat. Rev. Cancer* **2009**, *9*, 274–284, https://doi.org/10.1038/nrc2622.
52. Bozkurt, A.S. Publication Status of Mouse Embryonic Fibroblast Cells in Scientific Journals. *Eur. J. Ther.* **2021**, *27*, 135–141, https://doi.org/10.5152/eurjther.2021.20111.
53. Tomasek, J.J.; Gabbiani, G.; Hinz, B.; Chaponnier, C.; Brown, R.A. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 349–363, https://doi.org/10.1038/nrm809.
54. Parsonage, G.; Filer, A.D.; Haworth, O.; Nash, G.B.; Rainger, G.E.; Salmon, M.; Buckley, C.D. A stromal address code defined by fibroblasts. *Trends Immunol.* **2005**, *26*, 150–156, https://doi.org/10.1016/j.it.2004.11.014.
55. Rodemann, H.P.; Müller, G.A. Characterization of Human Renal Fibroblasts in Health and Disease: II. In Vitro Growth, Differentiation, and Collagen Synthesis of Fibroblasts From Kidneys With Interstitial Fibrosis. *Am. J. Kidney Dis.* **1991**, *17*, 684–686, https://doi.org/10.1016/s0272-6386(12)80352-0.
56. Chang, H.Y.; Chi, J.-T.; Dudoit, S.; Bondre, C.; van de Rijn, M.; Botstein, D.; Brown, P.O. Diversity, topographic differentiation, and positional memory in human fibroblasts. *Proc. Natl. Acad. Sci.* **2002**, *99*, 12877–12882, https://doi.org/10.1073/pnas.162488599.
57. Desmouliere, A.; Guyot, C.; Gabbiani, G. The stroma reaction myofibroblast: a key player in the control of tumor cell behavior. *Int. J. Dev. Biol.* **2004**, *48*, 509–517, https://doi.org/10.1387/ijdb.041802ad.
58. Erez, N.; Truitt, M.; Olson, P.; Hanahan, D. Cancer-Associated Fibroblasts Are Activated in Incipient Neoplasia to Orchestrate Tumor-Promoting Inflammation in an NF-κB-Dependent Manner. *Cancer Cell* **2010**, *17*, 135–147, https://doi.org/10.1016/j.ccr.2009.12.041.
59. Schliekelman, M.J.; Creighton, C.J.; Baird, B.N.; Chen, Y.; Banerjee, P.; Bota-Rabassedas, N.; Ahn, Y.-H.; Roybal, J.D.; Chen, F.; Zhang, Y.; et al. Thy-1+ Cancer-associated Fibroblasts Adversely Impact Lung Cancer Prognosis. *Sci. Rep.* **2017**, *7*, 6478–6478, https://doi.org/10.1038/s41598-017-06922-5.
60. Shintani, Y.; Kimura, T.; Funaki, S.; Ose, N.; Kanou, T.; Fukui, E. Therapeutic Targeting of Cancer-Associated Fibroblasts in the Non-Small Cell Lung Cancer Tumor Microenvironment. *Cancers* **2023**, *15*, 335, https://doi.org/10.3390/cancers15020335.
61. Zhao Y, Shen M, Wu L, et al. Stromal cells in the tumor microenvironment: accomplices of tumor progression? Cell Death Dis. 2023;14(9):587.
62. Jiang, X.; Hu, S.; Liu, Q.; Qian, C.; Liu, Z.; Luo, D. Exosomal microRNA remodels the tumor microenvironment. *PeerJ* **2017**, *5*, e4196, https://doi.org/10.7717/peerj.4196.

 doi:10.20944/preprints202505.1025.v1

63. Seager, R.J.; Hajal, C.; Spill, F.; Kamm, R.D.; Zaman, M.H. Dynamic interplay between tumour, stroma and immune system can drive or prevent tumour progression. *Converg. Sci. Phys. Oncol.* **2017**, *3*, 034002, https://doi.org/10.1088/2057-1739/aa7e86.
64. Green, J.A.; Arpaia, N.; Schizas, M.; Dobrin, A.; Rudensky, A.Y. A nonimmune function of T cells in promoting lung tumor progression. *J. Exp. Med.* **2017**, *214*, 3565–3575, https://doi.org/10.1084/jem.20170356.
65. Xiao, J.; Huang, K.; Lin, H.; Xia, Z.; Zhang, J.; Li, D.; Jin, J. Mogroside IIE Inhibits Digestive Enzymes via Suppression of Interleukin 9/Interleukin 9 Receptor Signalling in Acute Pancreatitis. *Front. Pharmacol.* **2020**, *11*, 859, https://doi.org/10.3389/fphar.2020.00859.
66. Lim, B.; Lin, Y.; Navin, N. Advancing Cancer Research and Medicine with Single-Cell Genomics. *Cancer Cell* **2020**, *37*, 456–470, https://doi.org/10.1016/j.ccell.2020.03.008.
67. Mantovani, A.; Sozzani, S.; Locati, M.; Allavena, P.; Sica, A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol.* **2002**, *23*, 549–555, https://doi.org/10.1016/s1471-4906(02)02302-5.
68. Ostuni, R.; Kratochvill, F.; Murray, P.J.; Natoli, G. Macrophages and cancer: from mechanisms to therapeutic implications. *Trends Immunol.* **2015**, *36*, 229–239, https://doi.org/10.1016/j.it.2015.02.004.
69. Mazur, A.; Holthoff, E.; Vadali, S.; Kelly, T.; Post, S.R. Cleavage of Type I Collagen by Fibroblast Activation Protein-α Enhances Class A Scavenger Receptor Mediated Macrophage Adhesion. *PLOS ONE* **2016**, *11*, e0150287, https://doi.org/10.1371/journal.pone.0150287.
70. Lewis, C.E.; Pollard, J.W. Distinct Role of Macrophages in Different Tumor Microenvironments. *Cancer Res.* **2006**, *66*, 605–612, https://doi.org/10.1158/0008-5472.can-05-4005.
71. Bingle, L.; Brown, N.; Lewis, C.E. The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J. Pathol.* **2002**, *196*, 254–265, https://doi.org/10.1002/path.1027.
72. Conway EM, Pikor LA, Kung SHY, et al. Macrophages, inflammation, and lung cancer. Am J Respir Crit Care Med. 2016;193(2):116-130.
73. Edin S, Wikberg ML, Oldenborg PA, Palmqvist R. Macrophages: Good guys in colorectal cancer. Oncoimmunology 2, e23038. Artic PubMed PubMed Cent. Published online 2013.
74. Trivanović, D.; Krstić, J.; Djordjević, I.O.; Mojsilović, S.; Santibanez, J.F.; Bugarski, D.; Jauković, A. The Roles of Mesenchymal Stromal/Stem Cells in Tumor Microenvironment Associated with Inflammation. *Mediat. Inflamm.* **2016**, *2016*, 1–14, https://doi.org/10.1155/2016/7314016.
75. Galli, S.J.; Tsai, M. Mast cells in allergy and infection: Versatile effector and regulatory cells in innate and adaptive immunity. *Eur. J. Immunol.* **2010**, *40*, 1843–1851, https://doi.org/10.1002/eji.201040559.
76. Boldrini, L.; Gisfredi, S.; Ursino, S.; Lucchi, M.; Melfi, F.; Mussi, A.; Basolo, F.; Fontanini, G. Tumour necrosis factor-α: prognostic role and relationship with interleukin-8 and endothelin-1 in non-small cell lung cancer. *Int. J. Mol. Med.* **2006**, *17*, 887–892, https://doi.org/10.3892/ijmm.17.5.887.
77. Komi, D.E.A.; Redegeld, F.A. Role of Mast Cells in Shaping the Tumor Microenvironment. *Clin. Rev. Allergy Immunol.* **2020**, *58*, 313–325, https://doi.org/10.1007/s12016-019-08753-w.
78. Cimpean, A.M.; Tamma, R.; Ruggieri, S.; Nico, B.; Toma, A.; Ribatti, D. Mast cells in breast cancer angiogenesis. *Crit. Rev. Oncol.* **2017**, *115*, 23–26, https://doi.org/10.1016/j.critrevonc.2017.04.009.
79. Jang, G.-Y.; Lee, J.W.; Kim, Y.S.; Lee, S.E.; Han, H.D.; Hong, K.-J.; Kang, T.H.; Park, Y.-M. Interactions between tumor-derived proteins and Toll-like receptors. *Exp. Mol. Med.* **2020**, *52*, 1926–1935, https://doi.org/10.1038/s12276-020-00540-4.
80. Dudziak, D.; Kamphorst, A.O.; Heidkamp, G.F.; Buchholz, V.R.; Trumpfheller, C.; Yamazaki, S.; Cheong, C.; Liu, K.; Lee, H.-W.; Park, C.G.; et al. Differential Antigen Processing by Dendritic Cell Subsets in Vivo. *Science* **2007**, *315*, 107–111, doi:10.1126/science.1136080.
81. Roberts EW, Broz ML, Binnewies M, et al. Critical role for CD103+/CD141+ dendritic cells bearing CCR7 for tumor antigen trafficking and priming of T cell immunity in melanoma. Cancer Cell. 2016;30(2):324-336.
82. Böttcher, J.P.; Bonavita, E.; Chakravarty, P.; Blees, H.; Cabeza-Cabrerizo, M.; Sammicheli, S.; Rogers, N.C.; Sahai, E.; Zelenay, S.; e Sousa, C.R. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. *Cell* **2018**, *172*, 1022–1037.e14, https://doi.org/10.1016/j.cell.2018.01.004.

 doi:10.20944/preprints202505.1025.v1

83. Brown, C.C.; Gudjonson, H.; Pritykin, Y.; Deep, D.; Lavallée, V.-P.; Mendoza, A.; Fromme, R.; Mazutis, L.; Ariyan, C.; Leslie, C.; et al. Transcriptional Basis of Mouse and Human Dendritic Cell Heterogeneity. *Cell* **2019**, *179*, 846–863.e24, https://doi.org/10.1016/j.cell.2019.09.035.
84. Canton, J.; Blees, H.; Henry, C.M.; Buck, M.D.; Schulz, O.; Rogers, N.C.; Childs, E.; Zelenay, S.; Rhys, H.; Domart, M.-C.; et al. The receptor DNGR-1 signals for phagosomal rupture to promote cross-presentation of dead-cell-associated antigens. *Nat. Immunol.* **2020**, *22*, 140–153, https://doi.org/10.1038/s41590-020-00824-x.
85. Giampazolias, E.; Schulz, O.; Lim, K.H.J.; Rogers, N.C.; Chakravarty, P.; Srinivasan, N.; Gordon, O.; Cardoso, A.; Buck, M.D.; Poirier, E.Z.; et al. Secreted gelsolin inhibits DNGR-1-dependent cross-presentation and cancer immunity. *Cell* **2021**, *184*, 4016–4031.e22, https://doi.org/10.1016/j.cell.2021.05.021.
86. Ahluwalia, P.; Ahluwalia, M.; Mondal, A.K.; Sahajpal, N.S.; Kota, V.; Rojiani, M.V.; Kolhe, R. Natural Killer Cells and Dendritic Cells: Expanding Clinical Relevance in the Non-Small Cell Lung Cancer (NSCLC) Tumor Microenvironment. *Cancers* **2021**, *13*, 4037, https://doi.org/10.3390/cancers13164037.
87. Carmeliet P. Angiogenesis in life, disease and medicine. Nature. 2005;438(7070):932-936.
88. Dvorak, H.F. Angiogenesis: update 2005. *J. Thromb. Haemost.* **2005**, *3*, 1835–1842, https://doi.org/10.1111/j.1538-7836.2005.01361.x.
89. Ribatti, D.; Ennas, M.G.; Vacca, A.; Ferreli, F.; Nico, B.; Orru, S.; Sirigu, P. Tumor vascularity and tryptase-positive mast cells correlate with a poor prognosis in melanoma. *Eur. J. Clin. Investig.* **2003**, *33*, 420–425, https://doi.org/10.1046/j.1365-2362.2003.01152.x.
90. Hogan, K.A.; Cho, D.S.; Arneson, P.C.; Samani, A.; Palines, P.; Yang, Y.; Doles, J.D. Tumor-derived cytokines impair myogenesis and alter the skeletal muscle immune microenvironment. *Cytokine* **2018**, *107*, 9–17, https://doi.org/10.1016/j.cyto.2017.11.006.
91. Poeta, V.M.; Massara, M.; Capucetti, A.; Bonecchi, R. Chemokines and Chemokine Receptors: New Targets for Cancer Immunotherapy. *Front. Immunol.* **2019**, *10*, 379, https://doi.org/10.3389/fimmu.2019.00379.
92. Sarode, P.; Schaefer, M.B.; Grimminger, F.; Seeger, W.; Savai, R. Macrophage and Tumor Cell Cross-Talk Is Fundamental for Lung Tumor Progression: We Need to Talk. *Front. Oncol.* **2020**, *10*, 324, https://doi.org/10.3389/fonc.2020.00324.
93. Huang, M.; Stolina, M.; Sharma, S.; Mao, J.T.; Zhu, L.; Miller, P.W.; Wollman, J.; Herschman, H.; Dubinett, S.M. Non-small cell lung cancer cyclooxygenase-2-dependent regulation of cytokine balance in lymphocytes and macrophages: up-regulation of interleukin 10 and down-regulation of interleukin 12 production.. **1998**, *58*, 1208–16.
94. Ramachandran, S.; Verma, A.K.; Dev, K.; Goyal, Y.; Bhatt, D.; Alsahli, M.A.; Rahmani, A.H.; Almatroudi, A.; Almatroodi, S.A.; Alrumaihi, F.; et al. Role of Cytokines and Chemokines in NSCLC Immune Navigation and Proliferation. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 5563746, https://doi.org/10.1155/2021/5563746.
95. Hendler, F.J.; Ozanne, B.W. Human squamous cell lung cancers express increased epidermal growth factor receptors.. *J. Clin. Investig.* **1984**, *74*, 647–651, https://doi.org/10.1172/jci111463.
96. Normanno, N.; De Luca, A.; Bianco, C.; Strizzi, L.; Mancino, M.; Maiello, M.R.; Carotenuto, A.; De Feo, G.; Caponigro, F.; Salomon, D.S. Epidermal growth factor receptor (EGFR) signaling in cancer. *Gene* **2006**, *366*, 2–16, https://doi.org/10.1016/j.gene.2005.10.018.
97. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non–small cell lung cancer: a randomized trial. Jama. 2003;290(16):2149-2158.
98. Page-McCaw, A.; Ewald, A.J.; Werb, Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 221–233, https://doi.org/10.1038/nrm2125.
99. Gross, J.; Lapiere, C.M. COLLAGENOLYTIC ACTIVITY IN AMPHIBIAN TISSUES: A TISSUE CULTURE ASSAY. *Proc. Natl. Acad. Sci.* **1962**, *48*, 1014–1022, https://doi.org/10.1073/pnas.48.6.1014.
100. Liu, L.; Xu, S.; Huang, L.; He, J.; Liu, G.; Ma, S.; Weng, Y.; Huang, S. Systemic immune microenvironment and regulatory network analysis in patients with lung adenocarcinoma. *Transl. Cancer Res.* **2021**, *10*, 2859–2872, https://doi.org/10.21037/tcr-20-2275.

 doi:10.20944/preprints202505.1025.v1

101. Serafini, B.; Rosicarelli, B.; Magliozzi, R.; Stigliano, E.; Aloisi, F. Detection of Ectopic B-cell Follicles with Germinal Centers in the Meninges of Patients with Secondary Progressive Multiple Sclerosis. *Brain Pathol.* **2004**, *14*, 164–174, https://doi.org/10.1111/j.1750-3639.2004.tb00049.x.
102. A Rosenberg, S.; Yang, J.C.; Restifo, N.P. Cancer immunotherapy: moving beyond current vaccines. *Nat. Med.* **2004**, *10*, 909–915, https://doi.org/10.1038/nm1100.
103. Brown, J.M.; Wilson, W.R. Exploiting tumour hypoxia in cancer treatment. *Nat. Rev. Cancer* **2004**, *4*, 437–447, https://doi.org/10.1038/nrc1367.
104. Li Y, Zhao L, Li XF. Hypoxia and the tumor microenvironment. Technol Cancer Res Treat. 2021;20:15330338211036304.
105. Bedogni, B.; Powell, M.B. Hypoxia, melanocytes and melanoma – survival and tumor development in the permissive microenvironment of the skin. *Pigment. Cell Melanoma Res.* **2009**, *22*, 166–174, https://doi.org/10.1111/j.1755-148x.2009.00553.x.
106. Chan, D.A.; Sutphin, P.D.; Denko, N.C.; Giaccia, A.J. Role of Prolyl Hydroxylation in Oncogenically Stabilized Hypoxia-inducible Factor-1α. *J. Biol. Chem.* **2002**, *277*, 40112–40117, https://doi.org/10.1074/jbc.m206922200.
107. Masson, N.; Willam, C.; Maxwell, P.H.; Pugh, C.W.; Ratcliffe, P.J. Independent function of two destruction domains in hypoxia-inducible factor-α chains activated by prolyl hydroxylation. *EMBO J.* **2001**, *20*, 5197–5206, https://doi.org/10.1093/emboj/20.18.5197.
108. Sahu, A.; Kwon, I.; Tae, G. Improving cancer therapy through the nanomaterials-assisted alleviation of hypoxia. *Biomaterials* **2020**, *228*, 119578, https://doi.org/10.1016/j.biomaterials.2019.119578.
109. Otmani, K.; Lewalle, P. Tumor Suppressor miRNA in Cancer Cells and the Tumor Microenvironment: Mechanism of Deregulation and Clinical Implications. *Front. Oncol.* **2021**, *11*, https://doi.org/10.3389/fonc.2021.708765.
110. Palmero, E.I.; de Campos, S.G.P.; Campos, M.; de Souza, N.C.N.; Guerreiro, I.D.C.; Carvalho, A.L.; Marques, M.M.C. Mechanisms and role of microRNA deregulation in cancer onset and progression. *Genet. Mol. Biol.* **2011**, *34*, 363–370, https://doi.org/10.1590/s1415-47572011000300001.
111. Lee YS, Dutta A. MicroRNAs in cancer. Annu Rev Pathol Mech Dis. 2009;4(1):199-227.
112. Garzon R, Calin GA, Croce CM. MicroRNAs in cancer. Annu Rev Med. 2009;60(1):167-179.
113. Rusek, A.M.; Abba, M.; Eljaszewicz, A.; Moniuszko, M.; Niklinski, J.; Allgayer, H. MicroRNA modulators of epigenetic regulation, the tumor microenvironment and the immune system in lung cancer. *Mol. Cancer* **2015**, *14*, 34–34, https://doi.org/10.1186/s12943-015-0302-8.
114. Xi, S.; Xu, H.; Shan, J.; Tao, Y.; Hong, J.A.; Inchauste, S.; Zhang, M.; Kunst, T.F.; Mercedes, L.; Schrump, D.S. Cigarette smoke mediates epigenetic repression of miR-487b during pulmonary carcinogenesis. *J. Clin. Investig.* **2013**, *123*, 1241–1261, https://doi.org/10.1172/jci61271.
115. Peng, Y.; Dai, Y.; Hitchcock, C.; Yang, X.; Kassis, E.S.; Liu, L.; Luo, Z.; Sun, H.-L.; Cui, R.; Wei, H.; et al. Insulin growth factor signaling is regulated by microRNA-486, an underexpressed microRNA in lung cancer. *Proc. Natl. Acad. Sci.* **2013**, *110*, 15043–15048, https://doi.org/10.1073/pnas.1307107110.
116. Lujambio, A.; Ropero, S.; Ballestar, E.; Fraga, M.F.; Cerrato, C.; Setién, F.; Casado, S.; Suarez-Gauthier, A.; Sanchez-Cespedes, M.; Gitt, A.; et al. Genetic Unmasking of an Epigenetically Silenced microRNA in Human Cancer Cells. *Cancer Res.* **2007**, *67*, 1424–1429, https://doi.org/10.1158/0008-5472.can-06-4218.
117. Wu, C.; Ho, J.; Hung, S.; Yu, D. miR-429 expression in bladder cancer and its correlation with tumor behavior and clinical outcome. *Kaohsiung J. Med Sci.* **2018**, *34*, 335–340, https://doi.org/10.1016/j.kjms.2018.01.001.
118. Hubaux R, Becker-Santos DD, Enfield KSS, Lam S, Lam WL, Martinez VD. MicroRNAs As Biomarkers For Clinical Features Of Lung Cancer. Metabolomics open access. 2012;2(3):1000108. doi:10.4172/2153-0769.1000108
119. San Ho C, Noor SM, Nagoor NH. MiR-378 and MiR-1827 regulate tumor invasion, migration and angiogenesis in human lung adenocarcinoma by targeting RBX1 and CRKL, respectively. J Cancer. 2018;9(2):331.
120. Chen, M.-J.; Wu, D.-W.; Wang, G.-C.; Wang, Y.-C.; Chen, C.-Y.; Lee, H. MicroRNA-630 may confer favorable cisplatin-based chemotherapy and clinical outcomes in non-small cell lung cancer by targeting Bcl-2. *Oncotarget* **2018**, *9*, 13758–13767, https://doi.org/10.18632/oncotarget.24474.

 doi:10.20944/preprints202505.1025.v1

121. Liu, X.; Sempere, L.F.; Ouyang, H.; Memoli, V.A.; Andrew, A.S.; Luo, Y.; Demidenko, E.; Korc, M.; Shi, W.; Preis, M.; et al. MicroRNA-31 functions as an oncogenic microRNA in mouse and human lung cancer cells by repressing specific tumor suppressors. *J. Clin. Investig.* **2010**, *120*, 1298–1309, https://doi.org/10.1172/jci39566.
122. Kang, C.; Zhang, C.; Zhang, J.; Zhang, A.; Wang, Y.; Han, L.; You, Y.; Pu, P. PUMA is a novel target of miR-221/222 in human epithelial cancers. *Int. J. Oncol.* **2010**, *37*, 1621–1626, https://doi.org/10.3892/ijo_00000816.
123. Fujita, Y.; Yagishita, S.; Hagiwara, K.; Yoshioka, Y.; Kosaka, N.; Takeshita, F.; Fujiwara, T.; Tsuta, K.; Nokihara, H.; Tamura, T.; et al. The Clinical Relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 Network in Chemoresistant Non-small-cell Lung Cancer. *Mol. Ther.* **2015**, *23*, 717–727, https://doi.org/10.1038/mt.2015.10.
124. Chen, G.; Umelo, I.A.; Lv, S.; Teugels, E.; Fostier, K.; Kronenberger, P.; Dewaele, A.; Sadones, J.; Geers, C.; De Grève, J. miR-146a Inhibits Cell Growth, Cell Migration and Induces Apoptosis in Non-Small Cell Lung Cancer Cells. *PLOS ONE* **2013**, *8*, e60317, https://doi.org/10.1371/journal.pone.0060317.
125. Sounni NE, Noel A. Targeting the tumor microenvironment for cancer therapy. Clin Chem. 2013;59(1):85-93.
126. Roma-Rodrigues C, Mendes R, Baptista P V, Fernandes AR. Targeting tumor microenvironment for cancer therapy. Int J Mol Sci. 2019;20(4):840.
127. Pitt, J.M.; Marabelle, A.; Eggermont, A.; Soria, J.-C.; Kroemer, G.; Zitvogel, L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. *Ann. Oncol.* **2016**, *27*, 1482–1492, https://doi.org/10.1093/annonc/mdw168.