Non-Small Cell Lung Cancer and Pre-Metastatic Niches: A Survey

Abstract

Non-small cell lung cancer (NSCLC) is a leading cause of cancer mortality, characterized by complex pathophysiology involving pre-metastatic niches, organ tropism, and the tumor immune microenvironment (TIME). This survey explores the mechanisms underlying NSCLC progression, emphasizing the role of tumor-derived extracellular vesicles (EVs) in pre-metastatic niche formation, organ-specific metastasis, and immune evasion. The TIME, composed of various immune and stromal cells, facilitates immune evasion and therapeutic resistance, complicating treatment strategies. The survey highlights the significance of understanding the interactions between cancer cells and the TIME, which are crucial for developing targeted therapies. Recent advancements in molecularly targeted therapies and immunotherapy focus on manipulating the TIME to enhance anti-tumor immunity. The paper underscores the importance of identifying biomarkers for patient stratification and personalizing treatment approaches. It also discusses the challenges in diagnosing and treating organ-specific metastases, advocating for a multidisciplinary approach to improve patient outcomes. Future directions include exploring the roles of EVs, lipid metabolism, and advanced computational models in understanding NSCLC metastasis. By targeting the complex interactions within the tumor microenvironment, novel therapeutic strategies can be developed to impede metastatic progression and improve clinical outcomes. This comprehensive examination of NSCLC underscores the need for continued research to unravel its complexities and enhance patient survival rates.

1 Introduction

1.1 Significance of NSCLC in Cancer Research

Non-small cell lung cancer (NSCLC) presents a significant challenge in oncology, being the leading cause of cancer-related mortality worldwide. As the most common subtype of lung cancer, NSCLC accounts for a substantial proportion of cancer morbidity and mortality [1]. Despite advancements in treatment, it remains a primary contributor to cancer deaths, underscoring the urgent need for continued research into its complex pathophysiology and therapeutic strategies.

The biology of NSCLC is characterized by tumor progression and immune evasion, particularly in lymph nodes, which are crucial for improving patient outcomes [2]. The tumor microenvironment (TME) significantly influences tumor behavior and resistance to therapy, making it essential for understanding NSCLC metastasis and treatment challenges. Alterations in the TME and extracellular matrix are key to forming pre-metastatic and metastatic niches, which are vital for grasping the metastatic cascade in NSCLC [3].

Predicting cancer prognosis and survival is critical for developing targeted therapies and stratifying patients for appropriate treatments, highlighting the importance of NSCLC research in enhancing patient care [4]. Cancer stage, a primary prognostic factor, is typically evaluated using medical imaging, emphasizing the need for accurate diagnostic tools in NSCLC management [5]. The

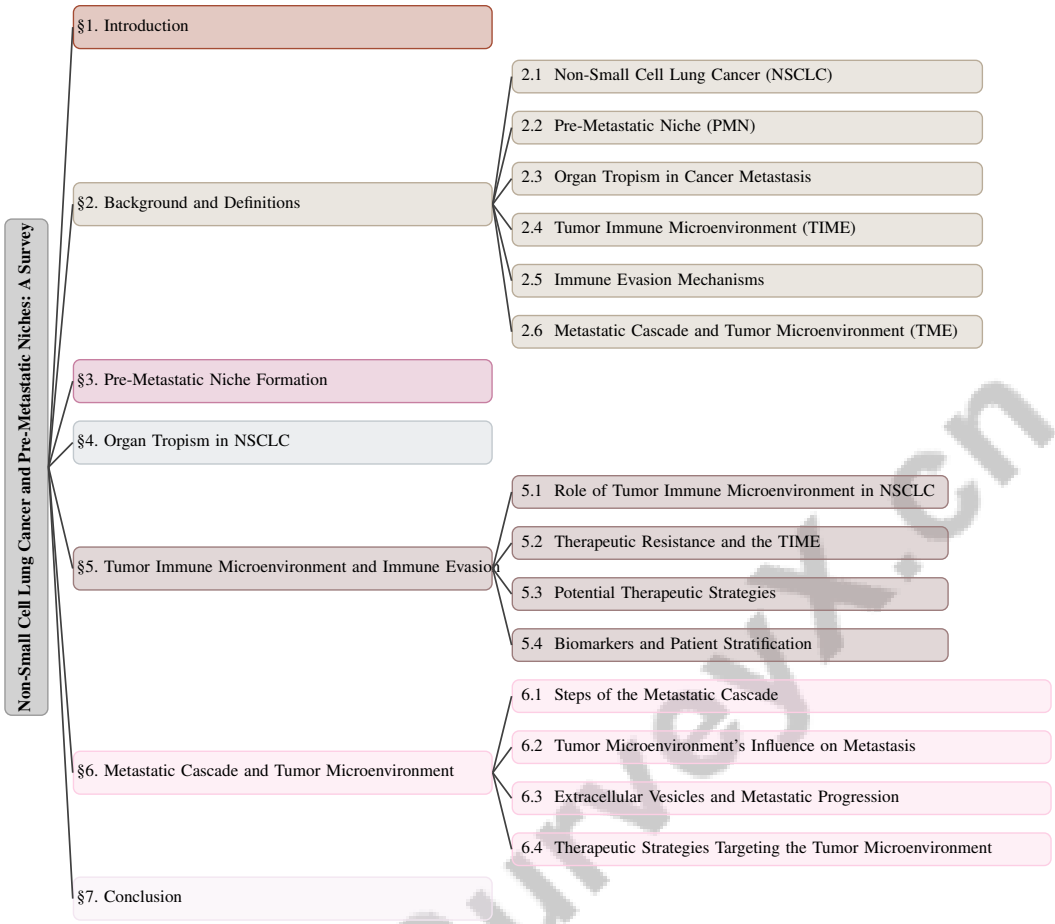


Figure 1: chapter structure

integration of novel anticancer agents, including tyrosine kinase inhibitors and immunotherapy, reflects the evolving landscape of NSCLC therapies. Together, these factors underscore the necessity of focusing on NSCLC within cancer research to unravel its complexities and improve patient survival rates.

1.2 Focus on Pre-Metastatic Niches, Organ Tropism, and Tumor Immune Microenvironment

The progression of NSCLC is significantly influenced by the interplay among pre-metastatic niches (PMNs), organ tropism, and the tumor immune microenvironment (TIME), collectively orchestrating the metastatic cascade. PMNs are essential for creating an environment conducive to metastatic colonization, with tumor-derived extracellular vesicles (EVs) modulating vascular permeability and preparing distant sites for tumor invasion. Liquid biopsy has emerged as a promising tool for understanding and exploiting these niches, offering insights into cancer metastasis dynamics [6].

Organ tropism, the preference of cancer cells to metastasize to specific organs, is governed by intricate molecular signaling pathways and microenvironmental conditions that direct tumor cells to optimal metastatic sites [7]. Understanding the molecular cues and cellular interactions facilitating organ-specific metastasis is crucial for developing targeted therapeutic interventions [8].

The TIME plays a vital role in modulating immune responses and therapeutic outcomes in NSCLC. The interactions between cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) within the TME highlight the complex network of cells contributing to immune evasion and tumor progression [9]. Exosomal PDL1 is particularly significant in tumor immune evasion, complicating the NSCLC progression landscape [10].

AI-generated, for reference only.

Recent advancements in NSCLC management emphasize the potential of molecularly targeted therapies and immunotherapy, focusing on manipulating the TIME to enhance anti-tumor immunity. These therapies aim to dismantle established immune evasion mechanisms, such as exosomal PDL1's role in inhibiting antitumor immune responses, thereby improving patient outcomes in various cancers, especially concerning metastasis and immune surveillance [11, 10]. Understanding these interconnected themes is vital for advancing NSCLC research and improving therapeutic interventions.

1.3 Importance of Understanding Immune Evasion and Metastatic Cascade

Immune evasion and the metastatic cascade are crucial processes in the progression of NSCLC. Immune evasion enables tumor cells to evade immune surveillance, facilitating their dissemination and colonization in distant organs. Within the TME, immune suppressive factors, including lipid metabolism, play a pivotal role in weakening immune responses, thus promoting tumor progression [12]. Somatic copy number alterations (SCNAs) contribute to an immunosuppressive TME, correlating with reduced immune infiltration and lower survival rates post-immunotherapy, suggesting their potential as biomarkers for treatment response prediction [13].

The metastatic cascade involves a sequence of events, starting with the detachment of cancer cells from the primary tumor, intravasation into the bloodstream, survival in circulation, extravasation, and eventual colonization of distant sites. Key players, including integrins and adhesion molecules, facilitate extravasation and the establishment of metastatic lesions [14]. The formation of PMNs in organs like the brain underscores the necessity of immune evasion in preparing these sites for metastasis. Studies indicate that the predictive power of deep neural networks (DNNs) for brain metastasis is significantly influenced by cellular and tissue-scale features, achieving optimal accuracy at specific feature length scales [15].

Oncogenes such as MYC drive tumorigenesis and immune evasion, complicating the management of MYC-driven cancers [16]. Moreover, immune evasion mechanisms employed by cancer cells metastasizing to lymph nodes can lead to diminished antitumor immunity and poorer prognoses, necessitating a comprehensive understanding of these processes [2].

The high mortality rate associated with NSCLC is largely due to late-stage diagnosis and treatment resistance complexities [17]. Addressing these challenges requires an in-depth understanding of the metastatic cascade and the immune evasion strategies utilized by tumor cells. Recent advancements in immunotherapy aim to enhance immune responses by overcoming these evasion tactics; however, the low response rate to immune checkpoint inhibitors presents a significant hurdle [18]. Furthermore, the emergence of drug resistance to targeted therapies underscores the need for personalized treatment strategies based on genetic mutations [19].

Elucidating the complex interactions between cancer cells and the immune system is essential for advancing NSCLC research and improving clinical outcomes. Ongoing investigations into immune evasion mechanisms and the metastatic cascade are critical, as they hold promise for developing more effective therapeutic strategies to combat metastasis, the leading cause of cancer-related mortality. Recent findings emphasize the unique biology of metastasis-initiating cells, which not only facilitate tumor growth in distant organs but also enable cancer cells to evade immune detection and exploit supportive microenvironments. This research highlights the importance of understanding these processes to enhance treatment options and improve patient outcomes, particularly through advancements in immunotherapy and targeted therapies [11, 2, 20].

1.4 Structure of the Survey

This survey is organized to provide a comprehensive examination of NSCLC, focusing on pre-metastatic niches, organ tropism, and the tumor immune microenvironment. The paper begins with an **Introduction** that emphasizes the significance of NSCLC in cancer research and highlights critical themes such as pre-metastatic niches, organ tropism, and immune evasion. Following this, the **Background and Definitions** section clarifies key concepts including NSCLC, pre-metastatic niche, organ tropism, tumor immune microenvironment, immune evasion, and the metastatic cascade, establishing a foundational understanding for subsequent discussions.

The survey then explores the **Pre-Metastatic Niche Formation** section, detailing mechanisms involved in niche formation, including extracellular vesicles, immune cells, and stromal interactions.

This section also highlights recent findings and ongoing research, providing insights into the preparation of distant organs for metastasis. The subsequent section on **Organ Tropism in NSCLC** examines the preferential metastasis of cancer cells to specific organs, discussing the molecular signaling and microenvironmental conditions influencing organ-specific metastasis.

The **Tumor Immune Microenvironment and Immune Evasion** section analyzes the role of the tumor immune microenvironment in NSCLC, detailing how cancer cells evade immune surveillance and the implications for metastasis, followed by potential therapeutic strategies targeting the immune microenvironment. The **Metastatic Cascade and Tumor Microenvironment** section outlines the steps involved in the metastatic cascade, emphasizing the TME's influence on each step and the role of extracellular vesicles in metastatic progression.

Finally, the survey concludes with a **Conclusion** synthesizing the key points discussed and reflecting on the implications of understanding pre-metastatic niches, organ tropism, and the tumor immune microenvironment in NSCLC. The paper suggests future research directions and potential clinical applications, highlighting the ongoing need for advancements in NSCLC research and treatment.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and is primarily classified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [8]. Its heterogeneity, marked by diverse molecular and histopathological characteristics, demands personalized therapeutic strategies [21]. Genetic mutations in NSCLC significantly influence treatment responses and prognostic outcomes [1]. Despite advancements, prognosis for advanced-stage NSCLC remains poor, compounded by limited systemic therapies for non-metastatic stages [22]. Accurate survival prediction requires integrating multimodal data, including imaging and genomics, as late diagnosis remains a challenge [5].

Research on automated pipelines for evaluating tumor-infiltrating lymphocytes (TILs) in whole slide images (WSIs) has demonstrated enhanced prognostic capabilities [23]. The adaptation of metastatic tumor cells to specific microenvironments, like the brain, presents unique treatment challenges due to selective pressures [24]. Current treatment paradigms integrate data from radiology, pathology, genomics, and clinical sources to improve outcomes [1]. The rise of immune checkpoint inhibitors (ICIs) underscores the need to identify patients likely to benefit, although predicting responses remains challenging due to the complex immune cell composition in NSCLC tumors [25]. Evaluating NSCLC therapies involves understanding resistance mechanisms, tumor biology complexity, and developing effective combination therapies to enhance outcomes [19]. A cohort study of 158 treatment-naive patients with early-stage NSCLC highlights efforts to refine strategies and improve outcomes [15]. The integration of targeted therapies, immunotherapies, and chemotherapy aims to address challenges posed by the immune landscape characterized by neutrophils [18, 19].

2.2 Pre-Metastatic Niche (PMN)

The pre-metastatic niche (PMN) concept is essential for understanding NSCLC metastasis, representing preparatory microenvironments in distant organs that facilitate tumor cell engraftment and proliferation. PMNs are established through interactions between tumor-derived factors and host tissues, modifying the local microenvironment to support metastatic colonization [26]. Extracellular vesicles (EVs) play a pivotal role by altering vascular permeability and promoting the recruitment of bone marrow-derived cells, enhancing PMN establishment. Myeloid-derived suppressor cells (MDSCs) contribute significantly to PMN formation, creating an immunosuppressive environment that supports tumor cell survival [27]. Concurrently, extracellular matrix (ECM) remodeling during PMN formation facilitates tumor cell adhesion and invasion [3].

Recent studies highlight non-coding RNAs (ncRNAs) from EVs in PMN formation, modulating gene expression to support metastatic growth [28]. Fibroblasts are critical in PMN structural and functional remodeling [29]. Specific proteins, such as Caveolin-1 (Cav-1), influence PMN formation, particularly in lung metastasis, by modulating the microenvironment [30]. PMN formation in the brain illustrates organ-specific adaptations during metastatic dissemination [7]. Liquid biopsy provides

valuable insights into PMN dynamics and cancer metastasis, offering potential for early detection and therapeutic intervention [6]. Understanding PMN formation and function, including the roles of EVs, MDSCs, and fibroblasts, is crucial for advancing knowledge of cancer metastasis and developing effective therapeutic strategies [31].

2.3 Organ Tropism in Cancer Metastasis

Organ tropism, the selective tendency of cancer cells to metastasize to specific organs, significantly influences NSCLC clinical management and treatment strategies. This preferential metastasis is facilitated by PMN formation in target organs, characterized by increased vascular permeability and ECM remodeling, often mediated by tumor-derived EVs [26, 31, 32]. Understanding these mechanisms is critical for developing effective therapeutic approaches that impact the efficacy of systemic therapies, including immunotherapy and targeted treatments. The mechanisms underlying organ tropism involve complex interactions between tumor cells and endothelial cells of target organs, mediated by adhesion molecules and chemokine receptors that facilitate extravasation and colonization [14]. For instance, the expression of specific integrins on tumor cells can determine their affinity for ECM components of particular organs, influencing metastatic patterns [30].

The implications of organ tropism are significant, as metastatic sites, such as the brain, present unique microenvironmental challenges affecting prognosis and therapeutic strategies. Understanding the pre-metastatic niche and biological interactions at these sites is crucial for developing targeted treatments and improving outcomes for patients with metastatic disease [5, 7, 24]. Brain metastases from NSCLC are associated with poor outcomes and unique treatment challenges due to the blood-brain barrier and the central nervous system's distinct microenvironment. Addressing organ tropism therapeutically involves targeting molecular pathways that facilitate organ-specific metastasis, including inhibitors that block adhesion molecules or chemokine receptors involved in the homing of cancer cells [19]. Identifying biomarkers associated with organ-specific metastasis can aid early detection and patient stratification, allowing for more personalized treatment regimens [13].

Organ tropism emphasizes the need for a comprehensive understanding of the metastatic process, involving specific interactions between cancer cells and the unique microenvironments of target organs. This complexity highlights the critical need for therapeutic strategies tailored to the organ-specific characteristics of tumor spread, including ECM alterations, immune modulation, and vascular changes that facilitate the formation of PMNs and metastatic niches. Addressing these factors can improve treatment outcomes for patients [33, 3, 26, 7, 34].

2.4 Tumor Immune Microenvironment (TIME)

The tumor immune microenvironment (TIME) in NSCLC is a complex entity influencing tumor progression, immune evasion, and therapeutic resistance. It comprises a network of cellular and acellular components, including tumor cells, immune cells, cancer-associated fibroblasts (CAFs), mesenchymal stem cells, adipocytes, and the ECM, each contributing uniquely to cancer dynamics [35]. Within the TIME, immune cells such as tumor-associated macrophages (TAMs) and MDSCs play crucial roles in modulating immune responses and facilitating immune evasion by creating an immunosuppressive environment that hampers effective antitumor immunity [9]. Interactions between CAFs and TAMs are significant, as they establish a niche that supports tumor proliferation and metastasis. CAFs can enhance TAM pro-tumorigenic activities, promoting immune evasion [9]. ECM remodeling within the TIME aids tumor cell invasion and acts as a barrier to effective drug delivery, complicating therapeutic interventions [36].

Lipid metabolism in the TIME is critical, as it maintains the immunosuppressive milieu characteristic of many tumors. Targeting lipid metabolism pathways may enhance immunotherapy efficacy by reversing suppressive effects and restoring immune surveillance [12]. This aspect of metabolic reprogramming highlights tumor cells' adaptive capabilities in evading immune detection and sustaining growth. Exosomes and EVs facilitate intercellular communication within the TIME, modulating recipient cell behavior and promoting tumor proliferation and immune evasion [37]. These vesicles can carry oncogenic signals and immune-modulatory molecules, complicating the tumor microenvironment's immune landscape.

Cancer immunoediting within the TIME involves a dynamic interplay of immune surveillance and escape mechanisms. Initially, immune cells recognize and eliminate tumor cells, but over time, tumor

cells that evade detection emerge, leading to immune escape and tumor progression. This adaptive process underscores the evolutionary arms race between tumor cells and the immune system [38]. A comprehensive understanding of the TIME's complex interactions is crucial for advancing NSCLC research and developing innovative therapies. These therapies aim to effectively modulate the TIME, characterized by dynamic interplay among immune cells, cytokines, and tumor cells influencing immune suppression and anti-tumor responses. Targeting specific components of the TIME can enhance anti-tumor immunity and improve clinical outcomes for NSCLC patients, particularly through RNA-based therapies and immunotherapeutic strategies that restore immune surveillance capabilities [18, 19, 39, 40]. The diverse components and their interactions present both challenges and opportunities for therapeutic interventions aimed at reprogramming the tumor microenvironment to favor immune-mediated tumor eradication.

2.5 Immune Evasion Mechanisms

NSCLC employs various strategies to circumvent immune detection, a critical factor in its progression and metastatic potential. The tumor microenvironment (TME) is central to this immune evasion, where cancer cells manipulate its complexity to suppress immune responses effectively. A significant mechanism is metabolic competition, where cancer cells outcompete cytotoxic T lymphocytes (CTLs) for nutrients like glucose, impairing immune response and facilitating immune escape [41]. This metabolic reprogramming is enhanced by the cystine/glutamate antiporter xCT, which maintains redox balance and provides resistance against oxidative stress, supporting tumor cell survival [28].

The TME's heterogeneity in NSCLC poses substantial challenges in understanding its role in cancer progression and developing effective treatments [35]. This heterogeneity affects cancer cell states across different tumor types, impacting progression and treatment outcomes [21]. The complex interactions within the TME influence tumor initiation, progression, metastasis, and response to therapies, necessitating targeted approaches to manipulate the TME effectively [42]. Current methodologies struggle to accurately capture architectural differences between healthy and tumor-associated vasculature, complicating drug delivery and treatment efficacy [43].

Exosomal PD-L1 plays a pivotal role in immune evasion by inhibiting T cell responses and contributing to cancer progression through immune escape [10]. Oncogenes such as MYC regulate immune checkpoints, influencing PD-L1 and CD47 expression, thereby facilitating immune evasion [16]. Neutrophils exhibit dual roles in cancer metastasis, either promoting or inhibiting metastasis by modulating the pre-metastatic niche [44]. MDSCs contribute to an immunosuppressive environment, aiding tumor cell survival while suppressing immune responses [2]. Inflammasomes also exhibit dual roles in tumor biology, potentially promoting or inhibiting tumor progression depending on context [45]. These dynamics underscore the complexity of tumor-immune interactions and the challenges in predicting effective treatment combinations [46].

Addressing these challenges requires a comprehensive approach to improve therapeutic strategies and enhance patient outcomes. Current treatments predominantly target cancer cells, often overlooking normal cells' roles in the metastatic process [47]. A deeper understanding of the interplay between TME components and the immune system is essential for developing therapies that effectively target and modulate the immune evasion mechanisms employed by NSCLC cells.

2.6 Metastatic Cascade and Tumor Microenvironment (TME)

The metastatic cascade in NSCLC encompasses several distinct stages: local invasion, intravasation, survival in circulation, extravasation, and colonization of distant sites [14]. Each stage is critically influenced by the tumor microenvironment (TME), which provides structural and biochemical support to migrating cancer cells [48]. The TME's complexity arises from interactions between tumor cells and local stromal components, significantly impacting cancer progression and metastasis [3].

Local invasion initiates metastasis, where cancer cells detach from the primary tumor and invade adjacent tissues, facilitated by epithelial-to-mesenchymal transition (EMT) that enhances migratory and invasive capabilities [49]. Integrins mediate cell-ECM interactions, influencing cancer cell behavior and facilitating invasion [50]. Following invasion, cancer cells undergo intravasation, entering the bloodstream or lymphatic system through intricate interactions with endothelial cells mediated by adhesion molecules that facilitate transendothelial migration [14]. Once in circulation,

cancer cells must survive hostile conditions, including shear stress and immune surveillance, with metabolic adaptations, such as altered nutrient uptake, being crucial for their survival [51].

Circulating tumor cells (CTCs) often travel as clusters, enhancing their metastatic potential by providing protection against immune attacks and mechanical stress [49]. Upon reaching distant sites, cancer cells extravasate by breaching the vascular wall, a process influenced by the TME's modulation of vascular permeability and ECM composition [52]. The final stage, colonization, involves establishing secondary tumors in new organ sites, heavily dependent on the pre-metastatic niche, a supportive microenvironment prepared by the primary tumor through the release of extracellular vesicles and other factors [52]. The systemic nature of metastasis poses significant treatment challenges, as metastatic lesions often exhibit distinct metabolic and phenotypic profiles compared to primary tumors [19].

3 Pre-Metastatic Niche Formation

Category	Feature	Method
Role of Extracellular Vesicles in Pre-Metastatic Niche Formation	Immune System Influence	SITGM[51], EV-NET[53]
Metabolic Adaptations in Pre-Metastatic Niche Formation	Metabolic Adaptation Mechanisms	xCT-T[54]
Molecular Mechanisms and Biomarker Identification	Cancer Therapeutics	CIA[55], CYP4AIM[56]
	Biomarker Analysis	XGBoost[57], QuanTAV[43]
	Machine Learning Techniques	ATIL-EP[23], PT[58]

Table 1: This table summarizes the various methods and features associated with the formation of pre-metastatic niches (PMNs) in non-small cell lung cancer (NSCLC). It categorizes the roles of extracellular vesicles, metabolic adaptations, and molecular mechanisms, highlighting specific techniques and models used to study these processes. The table serves as a comprehensive overview of the methodological approaches employed in understanding early metastatic events and potential therapeutic targets.

The formation of pre-metastatic niches (PMNs) involves intricate biological processes crucial for metastasis in non-small cell lung cancer (NSCLC). This section explores the pivotal role of extracellular vesicles (EVs) in intercellular communication and their impact on PMN establishment, shedding light on early metastatic events. Table 1 provides a detailed overview of the methods and features involved in pre-metastatic niche formation in non-small cell lung cancer, emphasizing the roles of extracellular vesicles, metabolic adaptations, and molecular mechanisms. Table 2 provides a comprehensive overview of the methods and features involved in pre-metastatic niche formation in non-small cell lung cancer, focusing on the roles of extracellular vesicles, stromal and extracellular matrix interactions, and metabolic adaptations. As illustrated in Figure 2, the hierarchical structure of PMN formation in NSCLC emphasizes the multifaceted roles of extracellular vesicles, stromal and extracellular matrix interactions, metabolic adaptations, and various molecular mechanisms and biomarkers. Each of these categories highlights specific functions and impacts, thereby revealing the complexity of early metastatic events and identifying potential therapeutic targets.

3.1 Role of Extracellular Vesicles in Pre-Metastatic Niche Formation

Extracellular vesicles (EVs) are central to PMN formation in NSCLC, facilitating intercellular communication essential for metastasis. EVs transport bioactive molecules, including proteins, lipids, and nucleic acids, that modulate the tumor immune microenvironment and support cancer cell dissemination [59]. They promote lymphangiogenesis, angiogenesis, and stromal cell education, preparing distant sites for tumor colonization [59].

The recruitment of bone marrow-derived cells and modulation of vascular permeability by exosomal proteins are critical for niche establishment [59]. EVs also facilitate neutrophil infiltration and neutrophil extracellular trap (NET) deposition in lymph nodes, enhancing cancer cell entrapment and progression [53]. This highlights EVs' role in modulating immune cell dynamics within the PMN, offering potential therapeutic targets [53].

Advanced models integrating chemotaxis and differential nutrient uptake enhance our understanding of PMN development [51]. This underscores the need to unravel the complex interplay between EV-mediated processes and the tumor microenvironment for effective therapeutic interventions [51].

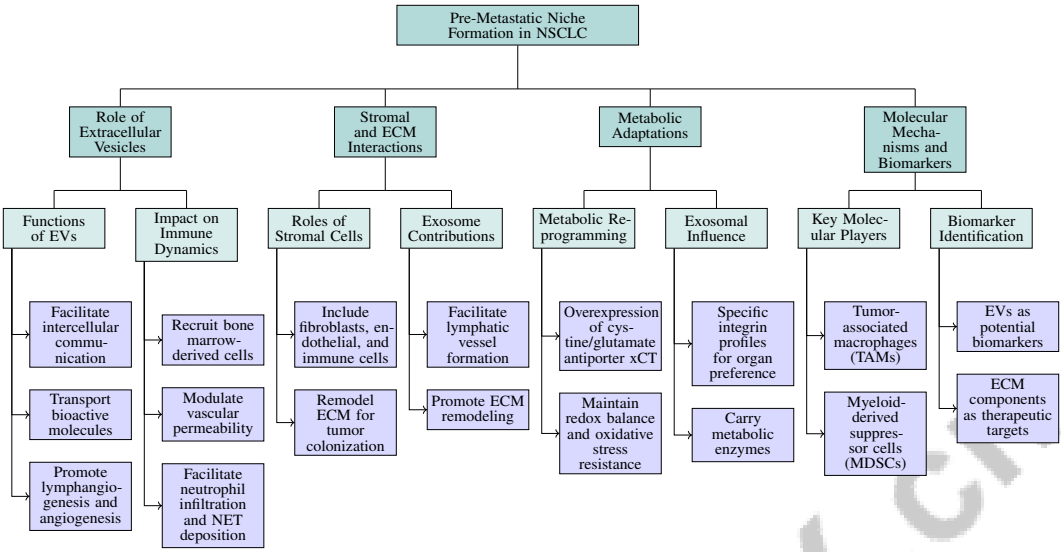


Figure 2: This figure illustrates the hierarchical structure of pre-metastatic niche formation in non-small cell lung cancer (NSCLC), emphasizing the roles of extracellular vesicles, stromal and extracellular matrix interactions, metabolic adaptations, and molecular mechanisms and biomarkers. Each category highlights specific functions and impacts, revealing the complexity of early metastatic events and potential therapeutic targets.

Emerging frameworks categorize fibroblasts by origin and role, emphasizing their heterogeneity and plasticity in EV-mediated niche formation [29]. The interplay between mathematical modeling and biological discovery in cancer immunotherapy offers promising avenues for addressing EV-related challenges in PMN formation [46].

A comprehensive understanding of EVs' roles in PMN formation is crucial for developing strategies to disrupt early metastatic steps. Future research should focus on innovative combinations of immunotherapies and other modalities targeting EV-mediated processes, optimizing treatment durations, and identifying robust biomarkers for patient selection, ultimately aiming to inhibit metastatic progression and improve clinical outcomes in NSCLC. Additionally, incorporating injective pooling functions in multiple instance learning models can enhance metastatic cancer outcome predictions [5].

3.2 Stromal and Extracellular Matrix Interactions

Stromal and extracellular matrix (ECM) interactions are vital in PMN formation in NSCLC, facilitating structural and functional modifications necessary for metastatic progression. Stromal cells, including fibroblasts, endothelial cells, and immune cells, remodel the ECM, creating a microenvironment conducive to tumor cell colonization and growth [60].

The ECM serves as both a structural scaffold and a participant in signaling processes that regulate cell behavior, proliferation, and migration. Research identifies several ECM components as biomarkers, enhancing our understanding of tumor biology and offering new therapeutic intervention avenues [61]. These biomarkers highlight dynamic changes within the tumor microenvironment and PMN establishment.

Exosomes secreted by tumor and stromal cells play a crucial role in stromal-ECM interactions, contributing to lymphatic vessel formation and aiding metastatic spread [62]. By transferring bioactive molecules, exosomes facilitate communication between tumor cells and the surrounding stromal environment, promoting ECM remodeling and niche formation.

As illustrated in Figure 3, the hierarchical structure of stromal and ECM interactions in NSCLC categorizes stromal cells, ECM components, and exosomal roles, emphasizing their contributions to tumor progression and PMN formation. This visual representation reinforces the complexity of the tumor microenvironment and the intricate interplay of its components.

Categorizing stromal cells based on their tumor promotion and suppression roles underscores the tumor microenvironment's complexity [60]. Understanding these dual roles is essential for developing targeted therapies that modulate stromal and ECM interactions, thereby impeding the metastatic cascade. A nuanced understanding of stromal cell functions and their ECM interactions is critical for advancing therapeutic strategies aimed at disrupting PMN formation and maintenance in NSCLC.

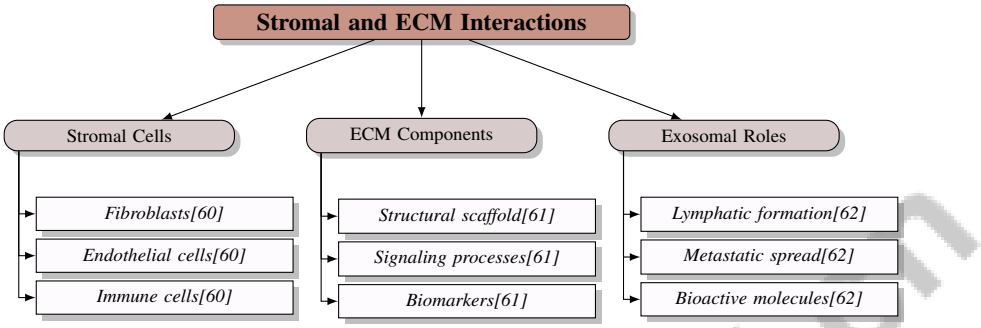


Figure 3: This figure illustrates the hierarchical structure of stromal and extracellular matrix (ECM) interactions in non-small cell lung cancer (NSCLC). It categorizes stromal cells, ECM components, and exosomal roles, highlighting their contributions to tumor progression and pre-metastatic niche (PMN) formation.

3.3 Metabolic Adaptations in Pre-Metastatic Niche Formation

Metabolic adaptations are crucial in forming PMNs and supporting cancer cell survival in NSCLC. These adaptations occur at various cancer progression stages, including the primary tumor site, intravasation into vessels, and colonization of distant organs [63]. Metabolic reprogramming is a hallmark of tumor progression, allowing cancer cells to thrive in diverse, often hostile microenvironments.

A significant metabolic change in NSCLC is the overexpression of the cystine/glutamate antiporter xCT, which supports niche formation by maintaining redox balance and providing resistance against oxidative stress, enhancing cancer cell survival [54]. This adaptation is pivotal for establishing a conducive microenvironment for tumor cell growth and metastasis.

Exosomes, integral to tumor cell and microenvironment communication, exhibit specific integrin profiles dictating metastatic organ preferences [62]. These vesicles carry metabolic enzymes and bioactive molecules, contributing to recipient cells' metabolic reprogramming, thereby promoting PMN establishment and maintenance.

Metastatic cells display distinct metabolic traits compared to primary tumor counterparts, reflecting the need for flexibility in energy production and nutrient utilization during the metastatic cascade [33]. These adaptations are critical for cancer cell survival as they navigate various microenvironments.

Understanding metabolic adaptations provides insights into PMN formation mechanisms and potential therapeutic targets for disrupting metastatic cancer cells' metabolic dependencies. By targeting specific metabolic pathways integral to the metastatic cascade, it may be feasible to disrupt processes such as epithelial-mesenchymal transition (EMT), cancer cell survival in circulation, and metastatic colonization. This approach could ultimately improve clinical outcomes in NSCLC, as recent studies highlight tumor-derived metabolites' role in promoting metastasis and suggest novel molecular therapeutic targets [11, 54, 64].

3.4 Molecular Mechanisms and Biomarker Identification

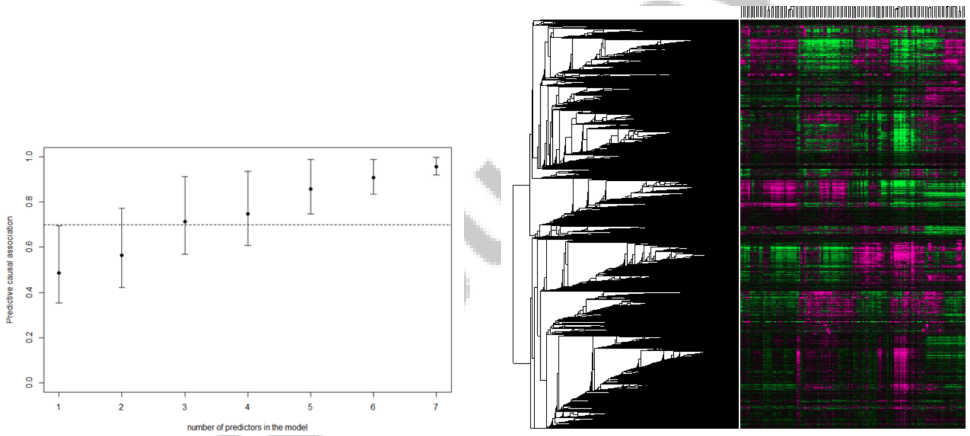
Elucidating molecular mechanisms and identifying biomarkers associated with PMNs are critical for advancing therapeutic strategies in NSCLC. Tumor-associated macrophages (TAMs) play a key role in PMN formation, with CYP4A expression essential for lung PMN formation and metastasis, indicating its potential as a therapeutic target [56]. Myeloid-derived suppressor cells (MDSCs) also significantly contribute to an immunosuppressive environment that facilitates PMN establishment, suggesting that targeting their functions could offer new therapeutic avenues [27].

EVs mediate intercellular communication within the tumor microenvironment, influencing cancer metabolism and promoting PMN formation [52]. These vesicles carry diverse bioactive molecules, including proteins and metabolites, instrumental in establishing PMNs. EVs' potential as biomarkers for early metastasis detection is underscored by their dual role in promoting dormancy and awakening tumor cells [52].

The ECM plays a critical role in tumor progression and metastasis, with specific components identified as PMN facilitators, offering potential therapeutic targets to inhibit metastatic spread [3]. Advanced methodologies, such as the NaroNet framework combining weakly-supervised deep learning with single-cell analysis, enhance the interpretability and adaptability of biomarker discovery processes [58]. This approach is particularly valuable for identifying and categorizing biomarkers predicting responses to immune checkpoint inhibitors (ICIs), addressing resistance mechanisms observed in NSCLC.

Recent advancements in computational imaging have led to a new category of biomarkers, termed quantitative tumor-associated vasculature (QuanTAV) features, aimed at characterizing tumor vasculature morphology and predicting treatment response [43]. Additionally, an automated pipeline for tumor-infiltrating lymphocyte (TIL) estimation integrates semi-stochastic patch sampling with machine learning, offering improved prognostic power [23].

The identification of key molecular mechanisms and robust biomarkers associated with PMNs is crucial for advancing therapeutic strategies and improving patient outcomes in NSCLC. Continued research promises to enhance our understanding of metastasis and inform clinical management of lung cancer [3].



(a) Predictive causal association across different numbers of predictors in the model[55]

(b) Gene Expression Profiling of Different Cell Types[57]

Figure 4: Examples of Molecular Mechanisms and Biomarker Identification

As shown in Figure 4, the concept of pre-metastatic niche formation is critical in understanding cancer metastasis, focusing on molecular mechanisms and biomarker identification preceding the spread of cancer cells to distant organs. The first image illustrates a scatter plot evaluating predictive causal associations of variables across different predictors in a model, providing insights into how well these models forecast causal effects, crucial for identifying potential biomarkers. The second image offers a comparative analysis of gene expression profiles between two different cell types, utilizing a dendrogram and heatmap to visualize relationships and expression patterns. Together, these visual representations underscore the complexity and importance of molecular mechanisms and biomarker identification in pre-metastatic niche formation, paving the way for more targeted therapeutic strategies in cancer treatment [55, 57].

4 Organ Tropism in NSCLC

Understanding organ tropism in NSCLC involves exploring mechanisms that direct cancer cells to specific organs, highlighting the roles of pre-metastatic and metastatic niches in tumor cell infiltration,

Feature	Role of Extracellular Vesicles in Pre-Metastatic Niche Formation	Stromal and Extracellular Matrix Interactions	Metabolic Adaptations in Pre-Metastatic Niche Formation
Role	Intercellular Communication	Structural Modifications	Cancer Cell Survival
Key Processes	Lymphangiogenesis, Angiogenesis	Ecm Remodeling	Metabolic Reprogramming
Potential Targets	Neutrophil Infiltration	Ecm Components	Xct Antiporter

Table 2: Overview of the roles of extracellular vesicles, stromal interactions, and metabolic adaptations in the formation of pre-metastatic niches in non-small cell lung cancer. The table delineates the primary functions, key processes, and potential therapeutic targets associated with each feature, highlighting the complexity of early metastatic events and the multifaceted roles of these biological components.

survival, and colonization. Insights into these mechanisms are crucial for devising diagnostic and therapeutic strategies to combat the lethal spread of cancer [3, 34, 7, 24].

4.1 Conceptual Framework of Organ Tropism

Organ tropism in NSCLC describes the selective metastasis to specific organs, significantly influencing disease progression and treatment strategies. This phenomenon results from molecular signals and microenvironmental factors guiding tumor cells to establish secondary growths in targeted tissues. Integrins are crucial in this process, promoting cancer cell survival and proliferation at distant sites, thereby contributing to organ-specific metastasis [50]. The framework encompasses tumor cell interactions with the microenvironment, essential for establishing pre-metastatic and metastatic niches, providing a novel perspective on metastasis [3]. Engineered models incorporating patient-specific traits enhance the translational potential of organ tropism research [65]. Understanding these mechanisms is vital for developing targeted therapies that disrupt specific interactions, preventing metastatic spread and informing early detection strategies [11, 66, 57, 19].

4.2 Molecular Signaling in Organ-Specific Metastasis

Molecular signaling pathways in organ-specific metastasis of NSCLC are intricate, directing cancer cells to specific organs. These pathways include lymphangiogenesis, tumor cell migration, and immune cell interactions, each contributing to secondary tumor establishment [2]. Lymphangiogenesis is critical for tumor cell dissemination, enhancing NSCLC's metastatic potential by providing routes for tumor cells to enter circulation. Tumor cells interact with lymphatic endothelial cells through growth factors like VEGF-C, promoting lymphatic vessel formation [2]. Tumor cell migration, driven by specific integrins and chemokine receptors, facilitates adhesion to endothelial cells of target organs, enabling extravasation and colonization [2]. Immune cell interactions significantly modulate metastatic signaling pathways. The immune response elicited by NSCLC cells can promote or inhibit metastasis, influenced by the balance of pro-tumorigenic and anti-tumorigenic immune cells. TAMs and MDSCs contribute to an immunosuppressive environment, facilitating tumor progression and metastasis [2]. Therapeutic strategies targeting these pathways aim to prevent organ-specific metastasis by disrupting pre-metastatic niche formation and EMT, enhancing treatment efficacy and improving patient outcomes [67, 14, 19, 11, 31].

4.3 Microenvironmental Conditions and Metastatic Niches

The microenvironment of distant organs is crucial for supporting metastasis in NSCLC, providing a conducive milieu for disseminated tumor cells to establish secondary growths. This process is regulated by interactions between tumor cells and their surrounding stromal and immune components, contributing to metastatic niche formation [3]. ECM remodeling provides structural support and influences signaling pathways that promote tumor cell survival and proliferation [61]. Stromal cells, including fibroblasts and immune cells, play an active role in creating a supportive microenvironment. Fibroblasts can promote or inhibit tumor progression depending on their activation state and interactions with tumor cells [29]. Tumor-derived factors, including EVs, mediate stromal cell recruitment and activation, enhancing vascular permeability and establishing a pre-metastatic niche [53, 59]. The immune landscape within the metastatic niche is crucial for metastatic success. TAMs and MDSCs create an immunosuppressive environment that facilitates tumor cell colonization and growth [2]. These immune cells interact with the ECM and other stromal components to modulate the inflammatory response, supporting metastatic lesion establishment [3]. Metabolic adaptations within the metastatic niche are essential for tumor cell survival. Reprogramming of metabolic pathways

allows cancer cells to thrive in nutrient-deprived conditions and resist oxidative stress [12]. This metabolic flexibility enables tumor cells to outcompete normal cells and establish dominance in the metastatic site [33]. Understanding these conditions is vital for developing therapies that disrupt metastatic niche formation and maintenance, aiming to impede NSCLC metastatic progression and enhance clinical outcomes [11, 67, 68, 42].

4.4 Therapeutic Strategies Targeting Organ Tropism

Therapeutic strategies targeting organ tropism in NSCLC focus on disrupting pathways facilitating organ-specific metastasis. Identifying osteocytes as critical players in PMN formation opens new avenues for therapeutic intervention, suggesting that targeting osteocyte signaling pathways may effectively inhibit bone metastasis [69]. Recent advancements in sEVs have provided insights into their role in cancer metabolism, positioning them as promising biomarkers and therapeutic targets for disrupting organ-specific metastasis [70]. These vesicles facilitate communication between tumor cells and the microenvironment, modulating processes essential for metastatic colonization. Immunotherapy, particularly immune checkpoint inhibitors like sintilimab, has emerged as a potential strategy to disrupt organ-specific metastasis in NSCLC. Sintilimab enhances anti-tumor immune responses, offering a promising avenue for targeting metastatic lesions, especially in organs with unique immune microenvironments [25]. Integrating immunotherapy with other treatment modalities is crucial for developing comprehensive treatment plans addressing organ tropism complexities. Guidelines emphasize a multidisciplinary approach and personalized treatment plans to improve NSCLC patient outcomes [8]. Emerging therapies targeting specific molecular pathways involved in metastasis offer new intervention opportunities [71]. Developing therapeutic strategies targeting organ tropism in metastatic cancer requires understanding the molecular and cellular mechanisms governing organ-specific metastasis, including PMN formation and metastasis-initiating cell biology, as these factors significantly influence tumor dissemination and treatment resistance in distant organs [11, 29, 34, 7]. Disrupting these pathways may prevent metastatic lesion establishment and progression, improving clinical outcomes for NSCLC patients.

4.5 Challenges in Diagnosing and Treating Organ-Specific Metastasis

Diagnosing and treating organ-specific metastasis in NSCLC presents challenges due to the complex interplay of molecular, cellular, and microenvironmental factors governing metastatic spread. The heterogeneity of NSCLC tumors and distinct microenvironments of metastatic sites complicate the identification and management of organ-specific metastases. This complexity is exacerbated by variability in clinical trial results, limiting the ability to standardize treatment protocols and assess long-term outcomes effectively [32]. A primary challenge is the lack of reliable biomarkers to predict metastatic potential and organ tropism. Identifying specific biomarkers, such as C/EBP-alpha and HIF-1-alpha, is essential for early detection and stratification of patients with stage III NSCLC, particularly among female nonsmokers. These biomarkers facilitate developing personalized treatment strategies targeting distinct metastatic sites, improving patient outcomes and advancing therapeutic approaches against metastasis [72, 66, 7, 57, 11]. However, tumor evolution dynamics and tumor microenvironment influence complicate biomarker discovery and validation. Treating organ-specific metastases is hindered by the need for comprehensive therapeutic strategies addressing each metastatic site's unique characteristics. Treating brain metastases presents challenges due to the blood-brain barrier, which hinders effective therapeutic agent delivery. This barrier, along with the brain's unique microenvironment, including specific cell types and immune dynamics, creates distinct selective pressures on tumor cells, complicating metastatic processes and therapeutic responses. Understanding these complexities is crucial for developing novel treatment strategies and improving clinical outcomes for patients with brain metastases [46, 7, 24]. Similarly, bone metastases require targeted approaches that consider tumor cell interactions with the bone microenvironment. Current therapeutic strategies for managing organ-specific metastases typically involve a multidisciplinary approach combining systemic therapies, such as chemotherapy and immunotherapy, with localized interventions like surgery and radiation therapy. This integrated treatment paradigm aims to enhance patient outcomes by addressing both the systemic nature of metastatic disease and the need for targeted local control. Recent advancements in understanding cancer biology, including tumor microenvironment roles and the emergence of novel agents, have refined these therapeutic options, leading to improved survival rates and treatment efficacy in metastatic cancer patients [11, 73, 74, 32]. However, the efficacy of these treatments is limited by resistance mechanisms and the need for precise

targeting of metastatic lesions. Integrating novel therapeutic modalities, including targeted therapies and immune checkpoint inhibitors, holds promise for improving outcomes, but their implementation requires a thorough understanding of the molecular pathways involved in organ-specific metastasis. Addressing the challenges in diagnosing and treating organ-specific metastasis in NSCLC requires a multidisciplinary approach that combines advances in molecular biology, imaging, and clinical oncology. By tackling the complexities associated with metastasis, including the unique biology of metastasis-initiating cells and their metabolic adaptations, researchers can develop more effective therapeutic strategies targeting both micro- and macrometastases. This approach aims to improve patient survival rates and enhances understanding of the metastatic cascade, ultimately leading to better management of metastatic diseases through personalized medicine and precision oncology. Recent advancements in cancer treatment, particularly in immunotherapy and targeted therapies, have shown promising results in reducing mortality rates from metastatic conditions, underscoring the potential for further progress in this area [11, 5, 65, 33].

5 Tumor Immune Microenvironment and Immune Evasion

The tumor immune microenvironment (TIME) is pivotal in understanding NSCLC progression and therapeutic outcomes. This section delves into the TIME's components and dynamics, highlighting their roles in immune responses and tumor behavior. Insights into these interactions can uncover immune evasion mechanisms and strategies to counteract them. The following subsection specifically addresses the TIME's role in NSCLC, detailing its complex composition and functional implications.

5.1 Role of Tumor Immune Microenvironment in NSCLC

The TIME in NSCLC profoundly influences tumor progression, immune evasion, and therapeutic resistance. Key cellular components such as tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), neutrophils, and T cells intricately interact with cancer cells and the extracellular matrix (ECM). The functional diversity of CAFs and TAMs underscores their importance in modulating immune responses and supporting tumor growth [9]. Vascular heterogeneity and nutrient gradients further complicate the TIME, impacting the tumor's immune landscape and stability [35]. Lipid metabolism is crucial for regulating immune cell functions and maintaining an immunosuppressive environment, which facilitates tumor progression and complicates therapeutic interventions [19]. This metabolic reprogramming aids tumor cells in evading immune detection, presenting challenges for effective treatment development.

Extracellular vesicles (EVs) are vital in intercellular communication within the TIME, enhancing tumor invasiveness and facilitating tumor-stromal interactions [19]. Exosomal PDL1 has emerged as a prognostic biomarker, reflecting the tumor's immune status and indicating the potential of EVs as both biomarkers and therapeutic targets due to their role in promoting therapeutic resistance. Immunotherapy effectiveness is closely tied to TIME characteristics, with radiotherapy (RT) modifying this environment to potentially enhance immune-based treatments. Inflammasomes, which mediate anti-tumor immune responses, have surfaced as promising therapeutic targets. Their activation in cancer and stromal cells can lead to pro-inflammatory cytokine maturation and pyroptosis, inhibiting tumor progression. However, inflammasomes can also recruit immunosuppressive cell types, complicating their therapeutic role. Current research emphasizes targeting inflammasome pathways in both preclinical and clinical settings to improve immunotherapy efficacy [45, 68]. Understanding the immune microenvironment is essential for optimizing treatment strategies.

Advancements in computational methodologies, including multimodal data integration, have enhanced treatment response predictability through clinically interpretable biomarkers rooted in cancer biology [15]. These innovations, alongside enhanced CAR-T cell function strategies, reflect a growing understanding of the TIME's complexity and its critical role in cancer progression. The TIME in NSCLC is a key determinant of cancer behavior and treatment response. By focusing on the intricate components and dynamic interactions within the TIME, innovative therapeutic strategies can be developed to significantly enhance treatment efficacy and improve clinical outcomes for NSCLC patients. This approach leverages insights from advancements in molecularly targeted therapies and immunotherapy, transforming the treatment landscape for NSCLC and enabling personalized medicine tailored to the unique genetic and molecular characteristics of each patient's tumor [71, 21, 75, 19, 8].

5.2 Therapeutic Resistance and the TIME

The TIME plays a pivotal role in mediating therapeutic resistance in NSCLC due to its complex composition and dynamic interactions among various cell types. Existing models often overlook TIME heterogeneity, assuming homogeneity and failing to accurately represent intricate cell type interactions, which leads to an incomplete understanding of the tumor immune landscape [76]. This lack of precision contributes to challenges in developing effective therapeutic strategies.

A significant barrier to successful therapy is the immunosuppressive environment created by various cell types within the TIME, which impedes anti-tumor immune responses [77]. This barrier is exacerbated by the complex ECM and abnormal tumor vasculature, hindering the effective delivery of nano-chemotherapeutics and reducing their therapeutic efficacy [36]. Macrophages within the TIME exhibit diverse roles influenced by their polarization states. M1 macrophages, dependent on glycolysis, enhance anti-tumor immunity, while M2 macrophages, reliant on fatty acid oxidation, often promote tumor progression and resistance [78]. This polarization highlights the metabolic adaptations cancer cells undergo to survive in nutrient-deprived and hypoxic conditions, complicating treatment efforts [33].

EVs are crucial mediators within the TIME, facilitating immune evasion and therapeutic resistance by altering tumor-stromal interactions [37]. However, challenges in isolating and characterizing EVs and circulating tumor cells (CTCs) pose significant hurdles in understanding their precise roles and developing standardized diagnostic procedures [6]. Inflammasomes present another layer of complexity, with studies yielding contradictory results regarding their role in cancer progression and therapy resistance, necessitating further investigation to clarify their therapeutic potential [45].

Addressing therapeutic resistance in NSCLC requires a comprehensive understanding of the TIME's influence on treatment outcomes. By targeting metabolic pathways, immune responses, and stromal interactions within the TIME, researchers can develop innovative strategies to overcome resistance mechanisms and enhance clinical outcomes for NSCLC patients. This approach leverages insights from precision oncology, emphasizing the importance of understanding individual tumor molecular characteristics for personalized and effective treatment regimens that combine targeted therapies, immunotherapies, and chemotherapy [54, 21, 19, 11, 68].

5.3 Potential Therapeutic Strategies

Emerging therapeutic strategies for NSCLC increasingly focus on the TIME, encompassing a complex network of cellular and molecular interactions that influence immune responses. These strategies aim to manipulate the balance between immune-suppressive and cytotoxic elements within the TIME to enhance anti-tumor immunity. Recent research underscores the importance of restoring disrupted immune surveillance mechanisms in NSCLC and exploring novel approaches such as RNA-based therapies and combination treatments with immune checkpoint inhibitors and chemotherapy. By addressing the immunosuppressive landscape of the TIME, these innovative therapies seek to improve treatment outcomes for NSCLC patients [79, 80, 39, 40]. Targeting metabolic pathways within the TIME is crucial, as these pathways regulate immune cell functions and sustain an immunosuppressive environment, potentially enhancing immune responses against tumors and improving immunotherapy efficacy.

Reprogramming TAMs from a pro-tumor to an anti-tumor phenotype represents another promising therapeutic avenue. Current research highlights TAMs' critical role in tumor biology and the potential for strategies aimed at altering their polarization to support anti-tumor immunity [81]. Enhanced agent-based models simulating interactions within the TIME can provide insights for developing targeted therapies [79]. RT has been identified as a potential strategy to convert an immunosuppressive TIME into an immunostimulatory environment, improving immunotherapy outcomes [77]. This approach emphasizes the importance of integrating RT with other treatment modalities to enhance overall therapeutic response.

Targeting exosomal PDL1 to inhibit its immunosuppressive effects is another area of interest, with implications for enhancing immune surveillance and reducing tumor progression [10]. Additionally, modulating immune cell interactions within the TIME, such as enhancing CAR-T cell efficacy, shows promise in overcoming immunosuppressive barriers that limit traditional approaches [80]. Current research highlights the TIME's critical role in cancer progression, providing insights into potential therapeutic targets [35]. The strengths of current research include advancements in targeted therapies

and immunotherapies that have improved survival rates in NSCLC patients [71]. These emerging strategies underscore the importance of targeting the TIME to develop more effective and personalized cancer therapies. By addressing metabolic, immune, and stromal interactions within the TIME, novel therapeutic approaches can enhance anti-tumor immunity and improve clinical outcomes for NSCLC patients.

5.4 Biomarkers and Patient Stratification

Identifying biomarkers for stratifying patients based on their immune microenvironment is crucial for advancing personalized therapies in NSCLC. The TIME significantly modulates therapeutic responses and disease progression, necessitating robust biomarkers that can predict patient outcomes and guide treatment decisions [82]. Despite progress, gaps remain in understanding the specific mechanisms through which the microenvironment confers resistance and how to effectively target these interactions [82].

Recent advancements in RNA-based therapies offer promising tools to enhance anti-tumor immunity by targeting TIME components. These therapies may improve patient outcomes by modulating immune responses and overcoming resistance mechanisms [39]. Exploring RNA-based biomarkers could provide insights into dynamic interactions within the TIME and aid in developing personalized treatment strategies. The role of monocytes within the TIME has been elucidated, revealing their potential as therapeutic targets. Identifying specific markers and pathways involved in monocyte differentiation presents promising avenues for enhancing anti-tumor immunity and stratifying patients based on immune profiles [83]. Additionally, targeting neutrophils and other immune suppressive factors offers opportunities to enhance immune checkpoint inhibitor efficacy, warranting further research into combinatorial therapies [18].

Ferroptosis, a regulated form of cell death, has emerged as a potential target in cancer therapies. Future research should elucidate the molecular mechanisms underlying ferroptosis sensitivity and explore its dual role in modulating immune responses, which could lead to novel biomarkers for patient stratification and therapeutic intervention [84]. Macrophage metabolic networks and their systemic effects on the tumor microenvironment represent another area of interest for biomarker discovery. Targeting these pathways may enhance immune responses and improve treatment outcomes [78]. Furthermore, integrating advanced technologies such as nanoparticles and tumor-on-chip models in CAR-T therapy could facilitate personalized immunotherapy approaches, offering insights into the TIME and patient stratification [80].

The interplay between the ECM and immune responses in the pre-metastatic niche (PMN) remains a significant research gap. Understanding how ECM alterations affect immune responses and the reversibility of these changes could inform biomarker development for patient stratification [85]. Additionally, optimizing RT protocols and exploring combinations with various immunotherapies could maximize therapeutic benefits and aid in identifying biomarkers predictive of treatment response [77]. Advancing personalized therapies for NSCLC critically depends on developing biomarkers that effectively stratify patients according to their immune microenvironment characteristics, as this microenvironment plays a pivotal role in tumor progression, immune response, and treatment outcomes. Recent studies have highlighted the complexity of the immune landscape in NSCLC, revealing distinct immune cell compositions, such as the predominance of neutrophils, which differ between subtypes like lung adenocarcinoma and lung squamous cell carcinoma. Understanding these variations is essential for optimizing immunotherapy strategies and improving response rates, which currently stand at only 20

6 Metastatic Cascade and Tumor Microenvironment

6.1 Steps of the Metastatic Cascade

The metastatic cascade in non-small cell lung cancer (NSCLC) involves a sequence of events crucial for cancer spread. It begins with local invasion, where cancer cells detach from the primary tumor and invade surrounding tissues, facilitated by epithelial-to-mesenchymal transition (EMT), which enhances cellular motility [34]. Integrins, often overexpressed in malignancies, play a pivotal role in detachment and invasion, making them potential therapeutic targets [14].

Following invasion, cancer cells enter the bloodstream or lymphatic system as circulating tumor cells (CTCs), which must survive immune surveillance despite their low concentration [86]. These CTCs then extravasate to distant tissues, influenced by signaling molecules and interactions with the pre-metastatic niche, which prepares distant sites for colonization [7]. The microenvironment of these sites is critical in supporting secondary tumor formation and growth.

Throughout this cascade, metabolic adaptations are vital for cancer cell survival in diverse microenvironments [33]. Targeting these metabolic vulnerabilities offers promising therapeutic avenues to impede metastasis. Mathematical models provide insights into the invasion-metastasis cascade, enhancing our understanding of cancer spread mechanisms [87]. Identifying prognostic biomarkers at each cascade step aids in understanding cancer progression and supports targeted interventions [57].

A comprehensive understanding of the metastatic cascade's molecular mechanisms is essential for developing targeted therapies to inhibit metastasis and improve clinical outcomes in NSCLC. Leveraging genomic medicine advancements and clinical trials can lead to personalized therapies that address individual tumor characteristics, ultimately enhancing survival rates and quality of life [11, 19].

6.2 Tumor Microenvironment's Influence on Metastasis

The tumor microenvironment (TME) significantly impacts metastasis in NSCLC, acting as a dynamic ecosystem that modulates cancer cell behavior. It comprises various cellular components, such as tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and myeloid-derived suppressor cells (MDSCs), which play critical roles in tumor growth and metastasis [9].

TAMs exhibit plasticity, transitioning between pro-inflammatory and anti-inflammatory states, influenced by metabolic pathways like glycolysis and oxidative phosphorylation [10]. This flexibility fosters an immunosuppressive environment that enhances tumor survival and dissemination. Manipulating macrophage polarization remains challenging due to the TME's capacity to induce changes that promote tumor growth [9].

Integrins facilitate tumor cell motility, survival in circulation, and metastatic colonization by mediating interactions with the extracellular matrix (ECM), which supports invasion and migration [36]. The ECM serves as a structural scaffold and a source of biochemical signals, with CAFs remodeling it to enhance cancer cell invasiveness [9].

Metabolic competition, such as glucose competition between cancer and immune cells, plays a vital role in immune evasion and tumor escape [76]. High immune cell death rates can lead to tumor escape, underscoring the importance of metabolic interactions within the TME [76]. Targeting tumor metabolism may enhance immunotherapy by alleviating metabolic suppression of immune cells, suggesting a dual approach to cancer treatment [67].

Advanced computational models, such as the multitype Fiksel interaction model, provide insights into the complex interactions and feedback loops between immune and tumor cells within the TME [76]. These models enhance understanding of tumor growth and treatment responses, offering potential strategies for therapeutic intervention [76].

Understanding the evolution from normal to pre-metastatic to metastatic niches can inform novel treatment strategies, emphasizing the TME's importance [3]. Targeting the TME's components and dynamics can lead to innovative strategies that impede metastatic progression and improve clinical outcomes for NSCLC patients.

6.3 Extracellular Vesicles and Metastatic Progression

Extracellular vesicles (EVs) are crucial in mediating intercellular communication and influencing the TME, thereby facilitating metastatic progression in NSCLC. These vesicles transport bioactive molecules, including proteins, lipids, and nucleic acids, which modulate recipient cell behavior and promote pre-metastatic niche (PMN) formation [72]. EVs alter recipient cell phenotypes, creating a pro-metastatic environment conducive to tumor colonization and growth [72].

Transglutaminase 2 (TG2) promotes cancer metastasis through interactions with fibronectin (FN) on EVs, facilitating metastatic niche establishment [88]. This interaction highlights the complex

mechanisms through which EVs contribute to metastasis, emphasizing the importance of targeting these pathways for therapeutic intervention.

Caveolin-1 (Cav-1) also influences metastatic progression through its role in PMN formation and interactions with the TME [30]. Cav-1 in EVs modulates the local microenvironment to favor metastatic colonization, illustrating EVs' multifaceted roles in cancer dissemination.

EVs' involvement in metastasis underscores their dual role as therapeutic targets and biomarkers for early metastasis detection. They facilitate PMN formation by transferring bioactive molecules that promote tumor migration and establish a supportive microenvironment. Their presence and specific markers can indicate tumors' metastatic potential, providing critical insights for patient prognosis and guiding therapeutic strategies aimed at inhibiting metastasis [89, 14, 72]. Disrupting EV-mediated communication and PMN establishment may hinder metastatic spread and improve clinical outcomes in NSCLC.

6.4 Therapeutic Strategies Targeting the Tumor Microenvironment

Therapeutic strategies targeting the TME in NSCLC aim to disrupt the interactions between tumor cells and their surrounding stromal and immune components to impede metastasis. The TME is a dynamic entity composed of various cellular and acellular elements, each contributing to tumor progression and therapeutic resistance [90]. Targeting stromal cells, particularly CAFs, which remodel the ECM and support tumor growth, is a key approach [42]. The ECM itself serves as a critical TME component, with its fragments acting as biomarkers for cancer diagnosis and prognosis, offering potential therapeutic implications [90].

EVs are central to the TME's influence on cancer biology, presenting opportunities for novel therapeutic strategies [26]. Targeting EV-mediated communication can disrupt PMN establishment and hinder metastatic progression [31]. Future research should standardize EV isolation methods, explore specific EV cargos contributing to therapy resistance, and investigate strategies to manipulate EV production and content to enhance treatment efficacy [91].

Combination therapies integrating multiple treatment modalities often yield better outcomes than single-agent therapies, emphasizing the need for a multifaceted approach to target the TME [42]. Future research should focus on developing combination therapies, understanding resistance mechanisms, and exploring new therapeutic targets in NSCLC [71]. Efforts should also develop novel therapeutic agents, understand resistance's molecular basis, and explore combination strategies integrating targeted therapies with immunotherapies [19].

Restoring immune surveillance alongside tumor removal is a critical strategy, highlighting the need for personalized treatment plans based on the tumor immune microenvironment (TIME) characteristics [23]. The suppression of natural killer (NK) cell functions by platelet cloaking reveals novel immune evasion mechanisms that could be targeted to enhance anti-tumor immunity in metastatic cancer [47].

Strategies targeting the TME necessitate a comprehensive understanding of the intricate interactions among its diverse components, as these interactions significantly influence tumor progression, metastasis, and anti-cancer therapies' efficacy. Understanding the roles of various TME elements, such as CAFs, immune cells, and the ECM, is crucial for developing effective interventions that can modify the TME to enhance treatment outcomes and mitigate therapy resistance [67, 48, 68, 92, 42]. By addressing the metabolic, immune, and stromal components of the TME, novel therapeutic approaches can effectively impede metastasis and improve clinical outcomes for NSCLC patients.

7 Conclusion

7.1 Future Directions in Metastasis Research

Advancing the study of NSCLC metastasis necessitates a concentrated focus on the roles of extracellular vesicles (EVs) in pre-metastatic niche (PMN) formation, with an emphasis on identifying specific molecular markers that can potentially disrupt these processes. The modulation of immune responses through exosomal PDL1 across various cancers remains a critical area for developing targeted therapies. Furthermore, elucidating lipid metabolic pathways that influence immune responses is vital for enhancing the efficacy of immunotherapy.

The tumor microenvironment (TME) continues to be a central theme, highlighting the need for research into combinatorial therapies that target multiple components within the TME and support personalized treatment approaches tailored to individual tumor profiles. The interactions between cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) offer promising avenues for overcoming drug resistance and improving therapeutic outcomes.

Emerging technologies such as deep learning and radiopathomics hold significant potential for refining predictive models and personalizing treatment strategies in NSCLC. Future research should aim to enhance these methodologies by incorporating diverse datasets and exploring additional loss functions to improve robustness. The integration of clinical variables into predictive models could further refine survival predictions and aid in making informed treatment decisions.

The development of sophisticated delivery systems that adapt to the dynamic TME is crucial for optimizing therapeutic outcomes. Investigating combination therapies targeting various aspects of tumor biology is essential for advancing treatment efficacy. Additionally, refining imaging parameters and exploring new disease contexts could enhance the predictive performance of deep neural networks in metastasis prediction.

These research directions are pivotal in expanding our understanding of NSCLC metastasis and facilitating the development of more effective, personalized therapeutic strategies. By exploring the complex interactions between cancer cells and the TME, future studies can pave the way for innovative treatments that address the intricacies of metastatic disease.

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