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How Smoking-Induced Immune Reprogramming Drives the Speed and Progression of Lung Cancer Tumors and Treatment Considerations

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ABSTRACT

Lung cancer is the most common and fatal malignant tumor, mostly driven by chronic inflammation in tobacco smoking. Although genetic mutations initiate tumorigenesis, the tumor microenvironment (TME), a recent discovery, is related to the development of lung cancer tumors and their progression. This literature review discusses how chronic inflammation, specifically smoking-induced inflammation, affects specific adaptive and innate immune responses. This process is known as immune cell reprogramming. Recent literature was analyzed to learn how these immune cells reprogram towards tumor-promoting phenotypes. Macrophages and T cells shift from anti-tumor roles to immunosuppressive, tumor-promoting states that accelerate progression and enable immune evasion. Cigarette smoke and nicotine drive macrophage polarization toward immunosuppressive M2 states and disrupt innate immune signaling. Simultaneously, T cells transition from protective antitumor effectors to dysfunctional, exhausted, or regulatory states that facilitate immune evasion. This literature review highlights immune cell reprogramming as an active driver of lung cancer progression rather than a secondary consequence of tumor growth. Ultimately, these findings suggest that further research is essential in order to close a critical knowledge gap regarding how immune dynamics influence the rate of tumor progression in order to improve patient outcomes.

INTRODUCTION

Cancer

In the US and across the whole world, cancer greatly affects our society, becoming the most dreaded disease of the 20th-21st century. This situation is so alarming that approximately 38.0% of men and women in the United States will receive a cancer diagnosis at some point in their lives (National Cancer Institute). Additionally, nearly one in four individuals faces a lifetime risk of developing cancer (R. Zheng

et al., 2023). Due to cancer becoming the most crucial aspect for the leading cause of death, this has enhanced our understanding of cancer development and progression in recent decades. This knowledge ultimately leads to improvements in treatment and in screenings.

Cancer is a disease characterized by the abnormal proliferation of cells, resulting in uncontrollable cell division. Unlike normal cells, cancer cells fail to respond to the signals in the cell environment. Cancer cells grow and divide in an uncontrolled manner, destroying normal tissues and organs that ultimately spread throughout the body. This is driven by a gene mutation that disrupts cellular regulation. A tumor develops in this process when there is any abnormal proliferation of cells, which may be either benign or malignant. Only malignant tumors are labeled as cancerous as they invade and metastasize into dangerous cancer cells (G. Cooper, 2000).

Humans are constantly exposed to cancer-causing agents, also known as carcinogens, which could be physical, chemical, or biological. Physical carcinogens include ultraviolet and ionizing radiation. Biological carcinogens include viral infections, such as hepatitis B, bacterial infections, and parasitic infections. Examples of chemical carcinogens include tobacco smoke, alcohol, asbestos, polycyclic hydrocarbons, aflatoxin (grain contamination), and arsenic (drinking water contaminant). These different types of factors allow the cell to undergo irreversible genetic changes, ultimately leading to the proliferation of cells (Koyal and Ibrahim 2024). Different carcinogens are associated with various cancers, depending on how and where they interact within the body. One of the most well-known chemical carcinogens is tobacco smoke, which is the primary cause of lung cancer (G. Cooper, 2000).

Lung Cancer

Among all cancers, lung cancer is one of the most common cancers in the world and remains the leading cause of cancer-related morbidity globally (Thandra et al., 2023). Statistics show that lung cancer is on the rise globally. In 2025, the American Cancer Society estimates 226,650 new cases of lung cancer, with 110,680 in men and 115,970 in women. This makes lung cancer at risk 51.2% in women and 48.8% in men. (American Cancer Society) Tobacco smoke is the biggest risk factor for lung cancer, as cigarette smoking accounts for almost 90% of cancer risk for men and 80% in women. Overall, compared with nonsmokers, smokers have up to a 30-fold increased risk of developing cancer (NCCDPHP., 2025).

Lung cancers are classified into two historical types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (Toh et al., 2007). SCLC cancers are aggressive lung cancers often caused by smoking and encompass. NSCLC is the most common type of lung cancer, where lung cells change and grow out of control slowly. This type of lung cancer, NSCLC, could be categorized by four subtypes: lung adenocarcinoma, lung squamous cell carcinoma, large-cell carcinoma, and bronchiolar carcinoid tumor (Q. Li et al., 2022). Again, smoking tobacco is the leading risk factor for SCLC, accounting for 98% of all cases. 2% of those cases include exposure to secondhand smoke, workplace carcinogens, radiation, environmental pollution, or a history of Lung Cancer (Office on Smoking and Health, 2020).

At the molecular level, tobacco smoke doesn't just cause mutation in lung cells, but promotes chronic inflammation in the tumor microenvironment (TME), ultimately leading to critical lung cancer tumors (B. Bade aC., 2020).

Tumor Microenvironment

The tumor microenvironment is defined as the highly structured ecosystem containing cancer cells surrounded by diverse non-malignant cell types in an extracellular matrix. The extracellular matrix is a network of proteins and other molecules that support cells in multicellular organisms. The TME includes diverse cell types such as cancer-associated fibroblasts (CAFs), endothelial cells (ECs), immune cells, pericytes, and additional tissue-resident cells. Together, these cells communicate through direct and indirect mechanisms to ultimately play a critical role in tumor growth and the cancer pathway. This includes metabolic demands to support the time, contact-dependent communication, paracrine signalling, and the involvement of the extracellular matrix. The tumor microenvironment's functions across each cell play a vital role in tumor development, including changing its function. These cells include cancer cells, immune cells, stroma cells, endothelial cells, and perineural cells. Additional non-cellular components of the TME consist of the extracellular matrix, signalling molecules, and physical niches. All these factors of the TME influence tumor progression, growth rate, and response to therapy (Visser and Joyce, 2023).

There are diverse characteristics in the tumor microenvironment, including hypoxia, abnormal vasculature, extracellular matrix remodeling, metabolic alterations, and the recruitment and reprogramming of immune cells, inflammation, all of which collectively influence tumor growth and progression. Specifically, inflammation is one of those factors that is a conserved response to potential insults, affecting tissue repair, regeneration, and homeostasis by stimulating cytokine production, mobilizing innate and adaptive immune systems, and protecting the integrity of tissue to respond to injury. In the tumor-initiating stage, inflammation in the tumor microenvironment and its smoking factors not only induce mutations but also contribute to mutational signatures and promote clonal expansion from immune cells. This means that specific mutation patterns help immune cells in the environment support the growth of those early tumors. Inflammation is a general catalyst for tumor progression in lung cancer. However, while acute inflammation aims to repair damage and has tumor-suppressive effects, chronic inflammation is a well-known tumor risk factor and is considered an enabling hallmark of cancer. Chronic inflammation is the result of pro-inflammatory cytokines from immune-related cells and the chronic activation of the innate immune system. Smoking is one of these factors that is central to the pathogenesis of chronic inflammation. Smoking systemically increases inflammatory markers and induces the expression of adhesion molecules and cytokines in various tissues (Visser and Joyce, 2023). A key component of the TME is the reprogramming of immune cells.

Immune Cell Reprogramming

Immune cell reprogramming is a process in which an immune cell is modified to give it a new, enhanced function in response to external triggers. This process of immune cell function starts with the immune

system detecting and eliminating invading pathogens and foreign particles. To maintain homeostasis, immune cells can reprogram themselves in the tumor microenvironment (TME), but in this context, cancer cells can reprogram immune cells in the TME to constrain their antitumor capacity by creating an immunosuppressive milieu and competing for metabolic resources (Binnewies et al., 2018). This means the immune cells create an environment hostile to immune attacks, creating a function where immune cells can't do their job due to the external characteristics of the TME. When these immune cells are reprogrammed, innate immune cells (macrophages, neutrophils, natural killer cells, dendritic cells, and bone marrow-derived suppressor cells) shape the tumor microenvironment by secreting various cytokines and chemokines, affecting the tumor survival and development. Additionally, innate immune cells and adaptive immune cells (T cells and B cells) are important to the oncogenesis process and tumor progression, which could either have a positive or negative outcome caused by different circumstances and characteristics of the tumor microenvironment (Pires et al., 2019).

Chronic inflammation plays a vital role in immune cell reprogramming that ultimately evades the immune defense and promotes progression. Tumor cells promote chronic inflammation and inflammatory cytokines production (e.g., G-CSF, IL6, and CXCL1) through regulation of NF-κB signaling, a cellular pathway that regulates gene expression involved in immune responses, inflammation, cell survival, and proliferation. Chronic inflammation is moderated by p53 activation, which promotes the activation of immune myeloid-derived suppressor cells like macrophages, T cell response, and precursors of dendritic cells. This shifts the nature of the TME towards a pro-tumorigenic phenotype, ultimately leading to enhanced tumor growth and immune evasion, especially for lung cancer (Visser, Joyce, 2023).

Immune Cells

Macrophages are innate immune cells that represent an important component of the first line of defense against pathogens and tumor cells. They respond to chemokines and growth factors produced by stromal and tumor cells in the tumor microenvironment. An essential component of the first line of defense is the macrophage. They can move to the damaged tissue or inflammatory location in response to chemotactic signals during infection, inflammation, or tissue destruction (Lendeckel, Venz, Wolke, 2022).

Macrophages are also recruited and differentiated into tumor-associated macrophages (TAMS). The interactions of TAMs with either tumor cells or the tumor microenvironment drive macrophage polarization. Polarization is a process where there is an asymmetric distribution of cellular components. When a macrophage polarizes, it changes its functional phenotype. The epigenetic and metabolic pathways are reprogrammed to support the new functions of that polarized state. TAM can be polarized into two types, M1 and M2. During carcinogenesis, macrophages exhibit anti-tumor M1 to eliminate more tumor cells. M1 exerts strong cytotoxic activity to fight against infected cells and remove their pathogens, and mediates resistance to 3 infections. This promotes production and secretion of proinflammatory cytokines, adherence to molecules, chemokine production of oxygen, and cyclooxygenase. When activating cytokines, they change the macrophages' behavior, function, and impact on tumors. M1 macrophages cause inflammation and tissue damage via these mechanisms. In general, during

carcinogenesis, a phase in tumor development, macrophages initially exhibit anti-tumor M1 to eliminate tumor cells. On the other hand, M2-like polarization promotes tumor development, where TAMs are associated with poor prognoses. This decreases a patient's overall survival (C. Lu et al., 2023).

T cells are crucial white blood cells that mature and undergo a positive and negative selection process in the thymus gland (Klein et al., 2014). These cells play a significant role in components of active immunity, ranging from cell-mediated immunity to humoral immunity. They originate in the bone marrow and develop into various types: CD4+ T cells (helper T cells) and CD8+ T Cells (cytotoxic T cells, or killer T cells) (Cleveland Clinic 2022).

Current research has acknowledged T cells as central actors of antitumor immune action, as they are expected to directly kill tumor cells and to be the main final effectors of tumor cell death. However, as T cells could be anti-tumoral cells, T cells can become dysfunctional and harmful to patients, especially those with lung cancer (Zhu & Paul, 2008). Chronic inflammation and tumor-derived signals actively reprogram T cells at transcriptional, metabolic, and functional levels. Rather than functioning as anti-tumor effectors, many of these T cells adopt pro-tumor phenotypes, such as exhausted or regulatory states, that directly suppress cytotoxic responses and indirectly promote tumor progression (G. Kang et al., 2024).

The TME holds diverse immune cells. T cells and macrophages play a critical role in promoting and potentially regulating tumor progression. As they are immune cells that also hold different functions of adaptive and immune, it is important to essentially target these cells to understand tumor growth dynamics in order to develop effective therapies. The knowledge gap of immune cell reprogramming and the tumor microenvironment in relation to lung cancer is still not fully understood, despite immune cell reprogramming becoming popularized. However, chronic inflammation characteristics, such as cigarette smoke, provide a critical context, as they drive chronic immune activation that may accelerate cancer progression and perhaps speed. In response to this, this review mainly focuses on immune cells, specifically macrophages and T cells, and how they progress and advance quickly. By understanding how these specific cells drive lung cancer progression, it may be possible to identify factors that can be considered when developing treatments to slow its progression. Without knowing how immune cells are reprogrammed, treatments may only target the tumor, not the environment that supports it. Targeting these specific cells can ultimately slow its progression, which is important for lung cancer patient survival and reduces the risk of tumor spreading to other organs.

METHODS

A literature search was performed for the development of this paper. From September 2025 to December 2025, Google Scholar and PubMed were the databases queried. Keywords included in the manual search were ‘immune cell reprogramming, ‘progression’, ‘lung cancer, ‘acceleration’, ‘tumor microenvironment’, ‘chronic inflammation, ‘inflammation, ‘T cells’, ‘macrophage’. More recent studies were prioritized because they provided more relevant and up-to-date information on the TME, a relatively

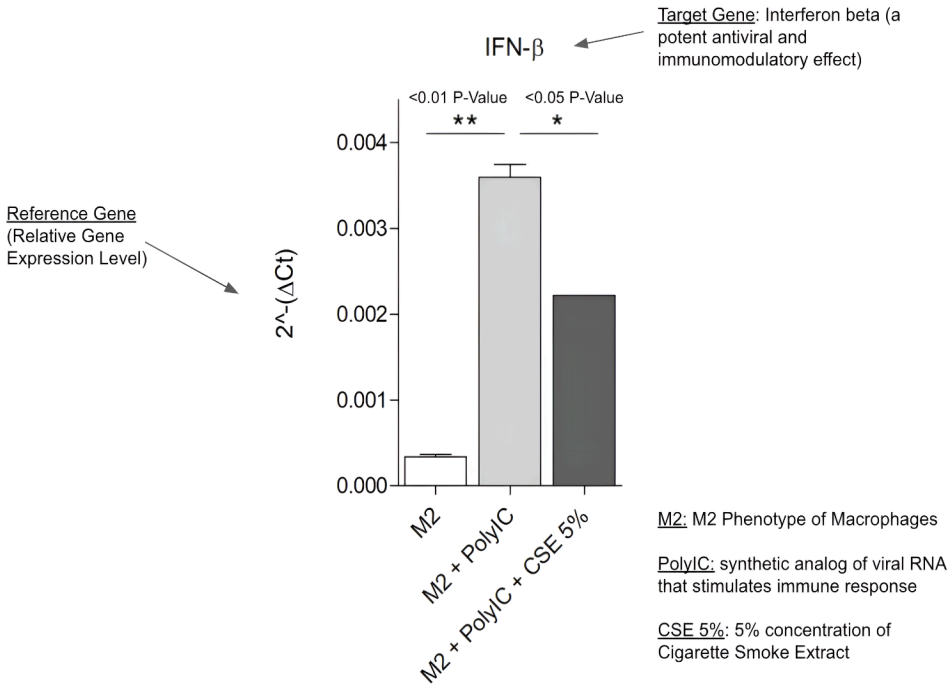
recent discovery. Throughout the paper, the literature included was published between 2015 and 2025. Articles were selected based on relevance to distinguish nonsmoker vs smoker progression in the tumor in relation to immunity. Studies that focused on the tumorigenesis, TME, and specific immune cell relations to lung cancer progression and tumor development were chosen and critically analyzed. Selected studies were analyzed by comparing findings across sources, with attention to consistency, conflicting results, and strength of evidence based on the effectiveness of research methods. Emphasis was placed on identifying patterns in immune cell behavior in TME.

Smoking-Induced Innate Immune Reprogramming

The composition of tumor-associated macrophages differs between smokers and non-smokers, providing insight into how cigarette smoke contributes to immune reprogramming in lung adenocarcinoma. A paper published in 2025, written by Yeqing Tao, disclosed that tumor tissues contained fewer tissue-resident macrophages (TRM) and more monocyte-derived macrophages (MDM) than normal lung tissues (Tao et al., 2025). In smokers with tumors, TRM levels were significantly lower than in normal smokers. Whereas in never-smokers, TRM levels in tumors were similar to those in normal tissues. This pattern was confirmed by sustained patient samples for CD68+FABP4+ cells. In addition, $FABP4^{hi}$ pro macrophages had a distribution pattern similar to TRM, while $SSPP1^{hi}$ pro macrophages mirrored the distribution of MDM across the four tissue types. This suggests that $SPP1^{hi}$ pro cells contribute to production in TME to promote lung adenocarcinosis oncogenesis, especially for never-smokers (Tao et al., 2025). However, these conflicting findings highlight the uncertainty regarding the specific role of $SSPP1^{hi}$ macrophages in smokers versus never-smokers. On the brighter side, this finding supports the idea that the TME in never-smokers is characterized by a distinct composition of immune cells, including a higher prevalence of immunosuppressive macrophages.

In addition, recent studies demonstrate that cigarette smoke and its key component nicotine promote immunosuppressive macrophage reprogramming (Bianchi et al., 2024; Kang et al., 2024). Results from Bianchi et al., (2024) indicated that cigarette smoke weakens the toll-like Receptor 3 (TLR3)-mediated M2 to M1 phenotype shift, thus contributing to the number of M2 macrophages in the lungs of smokers compared to non-smokers. Cigarette smoke directly decreases the expression of TLR3 on macrophages, thereby preventing the immune response and contributing to an anti-inflammatory, M2-rich environment in the lungs. This shift also increases their resistance to smoke-induced cytotoxicity, advising that M2 macrophages are more persistent in a smoker's lung environment, ultimately progressing lung cancer tumors (Bianchi et al., 2024).

Through an in vitro exposure of macrophages to cigarette smoke extract, researchers performed flow cytometry and cytofluorimetric analysis to measure M1 vs M2 surface markers. (e.g., CD86 for M1, CD206 for M2). RAW macrophages were treated under different conditions and stained for M1/M2 markers. Particularly, M2-polarized RAW cells were treated with Poly(I: C), which is a synthetic TLR3 agonist, in the presence of 5% of CSE extract. CSE significantly suppressed the Poly(I: C)-induced IFN-β expression, the process by which cells use TLR3 to produce the antiviral cytokine IFN-β in response to



Poly(I: C), indicating that cigarette smoke decreases TLR3-mediated immune activation, creating a viral infection. The results of this experiment were presented in Figure A.

Figure A: **IFN-B Gene Expression under Different Treatment Conditions** (Bianchi et al., 2024): CSE exposure significantly suppressed Poly(I: C)-induced IFN-β expression in M2 macrophages, confirming that cigarette smoke dampens TLR3-mediated immune activation.

Poly(I: C) normally induces IFN-β1 expression in macrophages. Through this analysis, the IFN-B response was blocked because of CSE exposure, indicating that cigarette smoke directly suppresses TLR2-mediated signalling. Cigarette smoke suppresses M1 polarization while promoting the persistence of anti-inflammatory M2 macrophages, creating an immunosuppressive environment that supports tumor growth (Bianchi et al., 2024). As this study uses real-time polymerase chain reaction (PCR) and flow cytometry to quantify immune signaling changes, it provides strong evidence of cigarette smoke-induced suppression of TLR3-mediated macrophage activation and promotion of an M2-dominant immunosuppressive environment.

Moreover, a key component of cigarette smoke, nicotine, promotes lung cancer, specifically lung adenocarcinoma progression and M2 tumor-associated macrophage reprogramming. (G. Kang et al., 2024). Nicotine has a complex role in macrophage regulation in lung adenocarcinoma. Nicotine promotes tumor progression and immune escape of TAMS in LUAD by reprogramming the mutual crosstalk

signaling between tumor cells and macrophages. This is evident by nicotine-related signaling influencing transcriptional regulation. In a recent study, a group of scientists tested the a5 subunit of the nicotinic acetylcholine receptor (a5-nAChR), commonly activated by cigarette exposure, to regulate SOX2 expression through phosphorylated STAT3 (pSTAT3) in LUAD cells. Increased SOX2 expression leads to higher secretion of CSF-1, a cytokine that promotes macrophage polarization towards the m2 phenotype. This activation of SOX2 acts as a messenger that converts nicotine/α5-nAChR/STAT3 activation into a signal, allowing macrophage immune cell reprogramming to support the tumor and suppress the body's anti-tumor immunity (G. Kang et al., 2024). Because of nicotine and a5-nAChR, the a5-nAChR expression of nicotine suppresses ı Figure B, where α5-ı

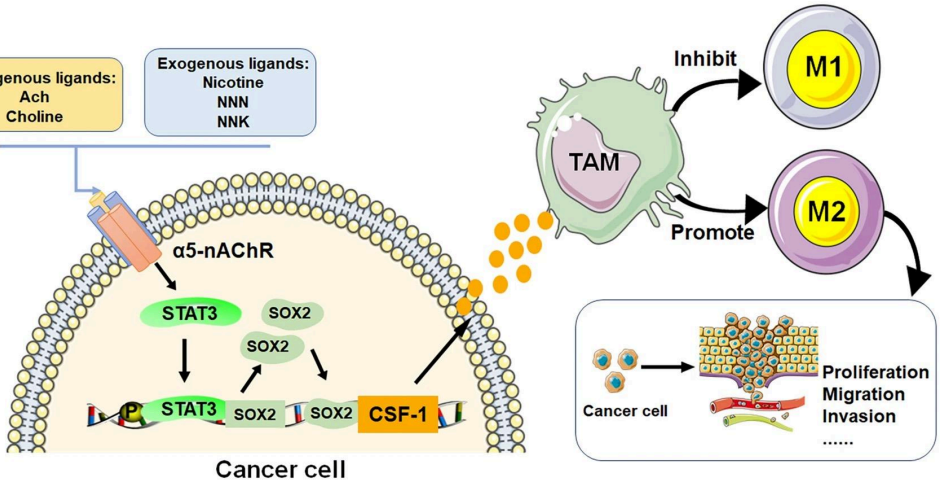


Figure B: **Nicotine activates the α5-nAChR/SOX2/CSF-1 pathway**, which is involved in lung cancer progression and immune escape. The nicotine and cell surface of α5-nAChR connect and interact with the STAT3/SOX2 signalling pathway, promoting macrophage M2 polarization, and overall promoting the metastatic ability of tumor cells (G. Kang et al., 2024).

In this research study, the experiment was properly controlled and used data ranging from patient cases and mice. These experimental methods continue to remain highly effective. However, they used mechanisms of differential expression. Although it provides valuable insight into smoking-associated transcriptional changes, its correlational nature limits conclusions about the direct functional mechanisms. They would need more experimental validation.

Collectively, these studies converge on a conclusion despite differing methodologies that smoking promotes both structural remodeling and functional immunosuppression of macrophages. While Tao et al., (2025) highlight changes in macrophage origin and distribution, Bianchi et al., (2024) and Kang et al. (2024) explain the molecular mechanism underlying polarization and immune suppression. Hence, the

tumor microenvironment is dominated by immunosuppressive macrophages that facilitate lung adenocarcinoma progression.

Smoking-Induced Adaptive Immune Dysfunction

As previously introduced, T cells promote tumor progression through dysregulated immune signaling within the tumor microenvironment. Research conducted by X. Li et al., (2018) showed that cigarette smoking shifts CD4+ memory T cells from resting, protective function to activated pro-tumor states (X. Li et al., 2018). Specific T cells, such as the CD4+ memory, are crucial for long-lived immune cells to remember past infections in order for a faster response to reinfection (MacLeod et al., 2010). This study used CIBERSORT, a skilled computational method for quantifying cell fractions into bulk tissue gene expression profiles, with a refined lung-specific signature matrix to estimate 21 immune cell subtypes in 1,111 lung adenocarcinomas versus 200 normal samples to estimate the compositional differences in immune cells in ever- and never-smokers (Chen et al., 2019). As a result, smokers exhibited reduced proportions of resting mast cells and resting $CD4^+$ memory T cells, both associated with improved survival, while displaying increased proportions of activated $CD4^+$ memory T cells and activated mast cells, which correlated with adverse survival outcomes. Therefore, resting immune cells are more favorable to survival in never-smokers. These findings also indicate that activated CD4+ memory T cells predict poor survival in smokers. Activated CD4+ memory T cells in smokers are associated with pro-tumor activity and poorer survival. Cigarette smoke reprograms from the resting state, which additionally activates state chemokine axes over time through the activated T Cell (X Li et al., 2018). Ultimately, activation reshapes the TME to favor growth and immune evasion. This study compared two sample sizes: 1000+ individuals with lung adenocarcinoma and 200 never-smokers. Although both are considered reasonable minimums for simple quantitative studies, the relatively small sample of never-smokers may limit the generalizability of the findings to broader populations.

Additionally, it is evident that cigarette smoking alters tissue-resident memory T cells (TRM), T cells that reside in non-lymphoid tissues. TRM-like cells are enriched and more activated in ever-smoker lungs and promote tumor immune evasion (Weeden et al., 2023). Although TRM cells are normally protective and help eliminate infected or malignant cells, in the context of chronic smoking, their constant activation can lead to functional exhaustion or dysregulation. Using flow and mass cytometry on non-malignant lung tissue from cancer patients and organ donors, it was proven that TRM-like $CD8^+$ cells are significantly more abundant in ever-smoker lungs than in never-smoker lungs, independent of patient age, sex, or cancer status (Weeden et al., 2023). This altered activation state can paradoxically assist tumor cells in adapting and evading the immune system (Weeden et al., 2023). Thus, smoking itself is associated with more $CD8^+$ TRM-like cells in the lungs, regardless of other variables. Pre-existing TRM-like cells in the lung promote immune evasion, as their high presence drives tumor cells to lose antigen presentation, facilitating immune escape via SIINFEKL-OVA neoantigen and H-2Kb MHC. This study employed high-dimensional single-cell mass cytometry (CyTOF) to characterize immune cell populations in lung cancer patients and control tissues (Weeden et al., 2023). By detailing phenotypic profiling of tumor-infiltrating immune cells, this finding remains highly effective.

T cell reprogramming operates through two complementary mechanisms. This includes the compositional shifts favoring activated but ineffective $CD4^+$ T cell states and function and dysregulation of tissue-resident $CD8^+$ T cells. While Li et al., (2018) highlight systematic immune composition changes with smoking, Weeden et al., (2023) provide single-cell evidence of localized dysfunction in the TME. Thus, these findings across different methodologies support that smoking impairs adaptive immune surveillance and promotes an immunologically permissive environment for lung tumor progression.

DISCUSSION

This study demonstrates that cigarette smoking fundamentally reshapes the lung tumor microenvironment by reprogramming key immune cell populations, particularly macrophages and T cells. By examining the specific immune cells in this review, we can elucidate that smoking may contribute to immune cell reprogramming, accelerating lung cancer progression and perhaps speeding, ultimately impacting treatment development. Based on the reviewed evidence, we can conclude that smoking reprograms macrophage composition toward immunosuppression (Kang et al., 2024), cigarette smoke and nicotine lock macrophages into a tumor-supportive M2 state (Bianchi et al., 2024; Kang et al., 2024), and smoking shifts T cells from protective to pro-tumor states (Li et al., 2018). Chronic smoking activates TRM-like T cells, which drive immune escape (Weeden et al., 2023*)*. Further research can combine these aspects to target these specific immune cells in the tumor microenvironment to create an effective treatment to ultimately slow tumor progression and speed lung cancer. While several peer reviews show that immune cell reprogramming is effective in lung cancer treatments (Lv et al., 2025), acknowledging the downsides of immune cell reprogramming tells us that when developing treatments, it is crucial to emphasize the importance of carefully designing therapies to avoid unintended immunosuppression or tumor-promoting effects.

In the quickly advancing field of medical science, there are also additional insights into immunosuppression. Given our findings that smoking reprograms macrophages and T cells towards immunosuppressive states, it is critical to understand that the presence of immunosuppression has a positive functional impact on tumor growth dynamics in general, proving that there are pros and cons (Ruiz et al., 2015; Aerts et al., 2014). Therefore, future studies should investigate whether targeting these reprogrammed immune cells gives a clear answer on whether immunosuppression has detrimental or beneficial effects, depending on the context.

In this review, we have discussed how smokers and non-smokers exhibit distinct macrophage profiles in the lung tumor microenvironment. Compared with never-smokers, smoking introduces an additional layer of immune cell reprogramming, not only shifting macrophages but also fueling chronic inflammation that accelerates cancer progression. In never-smokers, immunosuppressive macrophages contribute to tumor growth, yet in ever-smokers, inflammation intensifies this process, which promotes tumor expansion (Luo et al., 2023).

To further understand the complex role of immune cell reprogramming in lung cancer, recent studies have examined additional mechanisms by which macrophages influence tumor progression (Shen et al., 2025). The role of senescent macrophages has recently become a key focus of lung cancer treatment. Senscent macrophages in the TME perform functions such as cell cycle arrest marked by functional decline and altered gene expression, reduce phagocytosis, and antigen presentation. They also secrete the senescence-associated secretory phenotype (SASP) that is composed of pro-inflammatory cytokines and tissue-remodeling factors. Additionally, SASP factors regulate immune responses, being functionally rich in the TME. This means that targeting senescent macrophages or their SASP could modulate immune reprogramming in the tumor microenvironment, providing a potential strategy for lung cancer treatment.

CLINICAL IMPLICATIONS & THERAPY

Immunotherapies, including immune checkpoint inhibitors (ICIs), have recently revolutionized cancer treatments. These immune checkpoints engage with proteins on the surface of T cells, binding to other partner proteins (NCI 2022). ICIs block these inhibitory pathways, preventing T-cell exhaustion and restoring cytotoxic activity against cancer cells. Notably, PD-1, PD-L1, and CTLA-4 inhibitors play a central role in this process. Currently, the US Food and Drug Administration (FDA) has approved ICIs, including Pembrolizumab (Keytruda) and nivolumab (Opdivo), for melanoma, NSCLC, and renal cell carcinoma (RCC) (Liu et al., 2025). Even so, it is important to know that primary resistance and acquired resistance continue to limit ICIs' efficiency for many patients. Primary resistance occurs when tumors fail to respond to immune checkpoint blockade due to intrinsic tumor or microenvironmental factors, while acquired resistance develops after an initial therapeutic response, driven by tumor evolution and adaptive immune escape mechanisms. These resistances result in antigen loss and TAM, T Cell, and Myeloid-Derived Suppressor Cells (MSDC) suppression.

This review, "A comprehensive review on targeting diverse immune cells for anticancer therapy: Beyond immune checkpoint inhibitors," written by Dequan Liu et al., (2025), discussed key treatment strategies that target innate and adaptive cells in the tumor immune microenvironment beyond ICIs. This includes treatment specifically targeting immune cells in the TME or combinational therapies with ICIs. In NSCLC, there are combination therapies targeting both macrophages and T cells with ICIs. Inhibition of the CCR2–CCL2 axis limits TAM recruitment, promoting anti–PD-1 efficacy by increasing $CD8^+$ T-cell infiltration and reducing regulatory T-cell populations. As well, clinical evidence supports combination approaches, as pembrolizumab with platinum-based chemotherapy and pemetrexed (KEYNOTE-189) restores exhausted T-cell function via immunogenic cell death, while nivolumab with hypofractionated radiotherapy (FORCE trial) enhances T-cell activation through radiation-induced antigen release and abscopal effects (Liu et al., 2025).

Factors to be considered for treatment in non-small cell lung cancer when focusing on immunotherapy are the immune status. Assessing the T cell exhaustion and the activity of immunosuppressive cells, including TAMS, MDSCs, and neutrophils, is crucial when developing therapies for each patient. The efficacy of

ICIs is variable and may be limited in some patients. Therefore, assessing PD-L1 expression on tumor and immune cells is important to guide therapy and predict response; hence, ensure that PD-L1 is expressed in at least 50% of tumor cells. In addition, different treatments vary based on cancer stage and mutations. In patients with nonsquamous NSCLC without EGFR or ALK mutations, pembrolizumab combined with platinum-based chemotherapy (KEYNOTE-189) improves overall survival compared with chemotherapy alone (1-year OS 69% vs 49%). Monitoring and examining the TME is essential to manage the safety of inhibitors, allowing to assess the potential synergy. This includes biomarkers and chemokine labels that are associated with the treatment pathways. Overall, these factors of integrating tumor immune profiling, biomarker assessment, and patient-specific factors are essential for treatment in each patient with NSCLC (Liu et al., 2025).

LIMITATIONS

Despite extensive research on tumor progression in lung cancer in the TME, a major limitation is the lack of studies that quantitatively look into immune cells and influence the rate of tumor progression. While there are many papers analyzing tumor progression in lung cancer through the tumor microenvironment in various ways, there is almost no existing research about the immune cells affecting the quantitative speed of progression in lung cancer tumors. Hence, because of this gap, it is critical to understand disease dynamics and identify potential therapeutic targets. For example, faster-growing tumors may require more aggressive or immediate interventions, impacting treatment effectiveness. It is important to know that it is hard to develop therapies that target the pace of cancer progression. However, this does not imply that treatments are incapable of reducing tumor aggressiveness or delaying disease progression. Perhaps more publications should focus on quantitatively linking smoking-induced immune cell reprogramming with tumor growth kinetics and treatment responses. This will allow more precise prediction of disease progression and optimization of personalized therapeutic strategies for each patient.

CONCLUSIONS

As our knowledge of TME continues to advance, the reviewed literature suggests that it is essential to understand how chronic inflammation in the TME affects immune cells and how they ultimately result in deadly tumors through reprogramming. Immune cells, such as macrophages, are reprogrammed by cigarette smoke and nicotine since they drive macrophage polarization toward the immunosuppressive M2 state and disrupt innate immune signaling. Disrupting the innate immune signalling triggers the chronic inflammation in the TME, resulting in our body not properly balancing pathogen elimination along with self-protection from cancer. Additionally, T cells transition from protective antitumor effectors to a dysfunctional state that facilitates immune evasion, which may lead to tumor growth. As lung cancer death rates continue to rise, these characteristics of our immune cells in the tumor microenvironment must be acknowledged, as demonstrated in the evidence. As well, these findings suggest that these gaps and limitations provide promising opportunities for future research to decrease lung cancer progression.

Collectively, these factors have the potential to significantly reduce lung cancer mortality and meaningfully improve patient outcomes.

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