Acta Scientific Biotechnology

Volume 4 Issue 5 October 2023

Research Article

Cancer's Covert Culprits: Unraveling the Intricate Interplay Between Pathogens and the Oncogenic Landscape

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Received: November 29, 2023

Published: December 08, 2023

Abstract

Lung carcinoma stands as the preeminent contributor to cancer-related fatalities on a global scale. From the inception of the 20th century, a myriad of infectious entities linked to pulmonary malignancy has come to light. Elucidating mechanisms encompassing systemic inflammatory pathways, arising as a consequence of microbial persistence within the pulmonary milieu, emerges as a pivotal determinant in propelling the trajectory of lung carcinogenesis. The chronic inflammation entwined with infections instigating lung cancer is acknowledged to precede the genesis of tumors, exercising a formidable influence on therapeutic responses. Emanating from both viral and bacterial origins, infections orchestrate the activation of inflammatory cells and pathways, thereby orchestrating a complex interplay within the landscape of lung cancer development. Within the confines of this review, an expansive survey of recent scholarly investigations is undertaken, delving into the intricate associations between viral and bacterial pathogens and lung carcinoma. Special emphasis is placed on delineating the disruptive potential of infectious organisms throughout the spectrum of oncogenic processes, permeating the very fabric of immunity. Furthermore, a nuanced exploration unfolds, navigating the intricate interdependence between the evolution of lung tumors and the orchestration of inflammatory cascades.

Keywords: Lung Carcinoma; Global Scale; Lung Cancer

Introduction

Lung carcinoma as a global concern:

- Lung carcinoma is a leading cause of global cancer-related fatalities.

Historical context:

- Since the 20th century, various infectious entities linked to pulmonary malignancy have been identified.

Mechanisms of carcinogenesis:

- Systemic inflammatory pathways result from microbial persistence within the pulmonary milieu.
- This phenomenon is a crucial determinant in the trajectory of lung carcinogenesis.

Chronic inflammation and tumor genesis:

- Chronic inflammation associated with lung-cancer-related infections precedes the development of tumors.
- It significantly influences responses to therapeutic interventions.

Infectious origins and inflammatory activation:

- Infections, both viral and bacterial, emanate as sources.
- They activate inflammatory cells and pathways, creating a complex interplay in lung cancer development.

Survey of scholarly investigations:

- A comprehensive review of recent scholarly studies is conducted.

Associations between pathogens and lung carcinoma:

- Emphasis on intricate associations between viral/bacterial pathogens and lung carcinoma.

Disruptive potential of infectious organisms:

- Special attention is given to delineating how infectious organisms disrupt oncogenic processes.

Impact on immunity:

- Infectious organisms have a profound impact on the immune system.

Nuanced exploration:

- A nuanced exploration unfolds, examining the interdependence between the evolution of lung tumors and the orchestration of inflammatory cascades.

Implications:

- The study underscores the pivotal role of chronic inflammation in lung carcinogenesis.
- It highlights the disruptive potential of infectious agents on oncogenic processes.
- The interplay between infections, inflammatory pathways, and tumor development is a complex and significant aspect.
- Understanding these relationships is crucial for developing effective therapeutic strategies.

Introduction

Based on GLOBOCAN 2018 data, 11.6% of global cancer cases are identified as lung cancer, the foremost contributor to cancer-related fatalities across genders, constituting 18.4% of total cancer deaths. Beyond dietary factors and smoking, infectious diseases stand as the third primary instigators of cancer worldwide, attributing 16.1% of cases to pathogenic microorganisms. For instance, it is widely acknowledged that pulmonary infections significantly contribute to complications in lung cancer. Furthermore, post-obstructive pneumonia demonstrates an adverse correlation with lung cancer therapy, impacting the overall survival rates of cancer patients. The genesis of lung cancer has been associated with persistent inflammation, characterized by the infiltration of inflammatory cells and the accrual of proinflammatory factors like cytokines, prostaglandins, and chemokines. These elements, stimulating processes such as cell proliferation, angiogenesis, and metastasis, have been implicated in cancer development. Recent investigations indicate that membrane receptors, including Toll-like receptors, pattern recognition receptors, and clusters of differentiation, possess the capacity to recognize various entities such as microorganisms, their products, and proinflammatory cytokines. Notably, alterations in the tumor microenvironment (TME) and the onset of metastasis have been documented, with direct exposure to microbial oncogenes, toxins, and reactive oxygen species contributing to mutations. Furthermore, dysregulation in apoptosis, cell cycle control, and cell proliferation mechanisms play a crucial role in carcinogenesis. Enhancing our comprehension of microbial involvement in inflammation-induced cancer could pave the way for the development of antimicrobial therapies targeting cancer initiation and progression.(Figure 1)

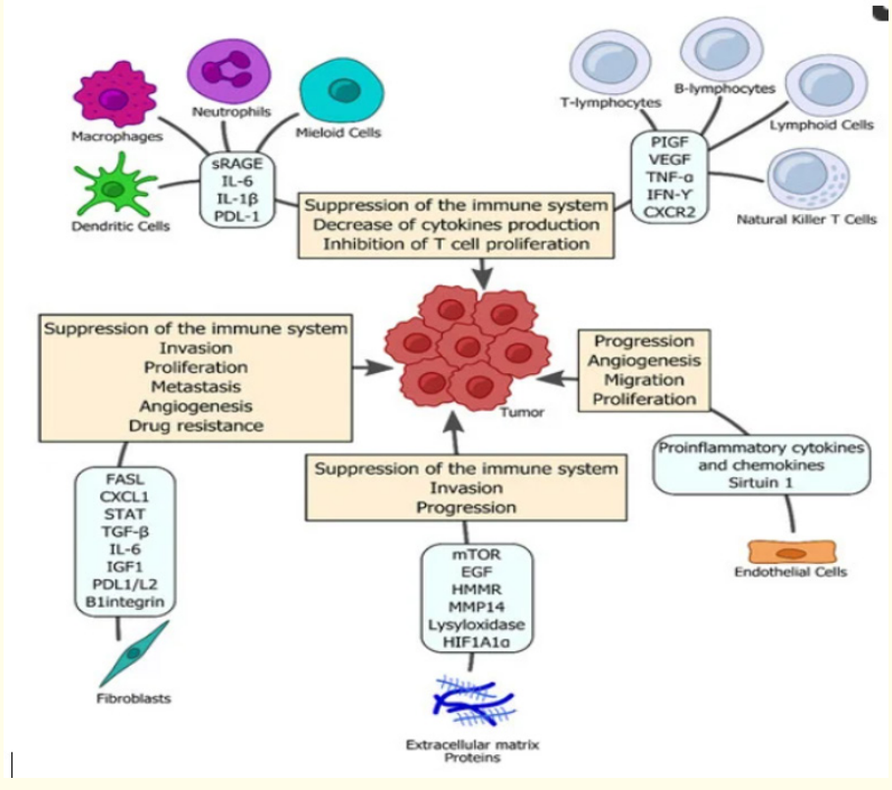

Figure 1

Tumor Microenvironment in Lung Cancer: Key Points

- **Crucial Determinant:** Effective tumor development at primary and metastatic sites hinges on the intricacies of the tumor microenvironment.
- **Diverse Stromal Cells:** A range of stromal cells, including T cells, B cells, NK cells, fibroblasts, adipocytes, vascular endothelial cells, and pericytes, envelop the evolving tumor.
- **Signaling Cascade:** These cells release signals pivotal in tumor survival, growth, invasion, and migration, altering cancer cell behavior through oncomodulation.
- **Essential Signaling Molecules:** TNF-α, mTOR, FASL, PDL1/L2, TGF-β, STAT, IL-1β, EGF, IL-6, sRAGE, IFN-γ, HIF1A1α, IGF2, MMP14, VEGF, CXCL1, HMMR, CXCR2, and PlGF are critical signaling molecules influencing the tumor microenvironment.
- **Potential for Intervention:** Understanding these complex interactions holds promise for developing targeted interventions against cancer initiation and progression.

Optimally, the immune system can detect and eliminate cancerous cells. To elude immune scrutiny, tumors employ strategies like elevating inhibitory immune checkpoints, creating immunosuppressive microenvironments, and inducing faulty T-cell signaling. Notably, macrophages release proinflammatory cytokines (TGF-β, IL-6, IL-10, TNF-α), fostering stem cell-like traits in tumors, promoting persistent growth.

Immune system responses to infectious factors leading to tumorigenesis

Equilibrium disruption:

The immune system significantly influences tumorigenesis by perturbing immune homeostasis, either promoting or inhibiting cancer cell proliferation.

Infectious agents and oncogenic links:

- Numerous studies identify infectious agents directly linked to cancer incidence, considered oncogenic.
- Inflammation induced by bacteria and viruses amplifies cancer risk.

Immune system development in newborns:

- Newborn immunity exhibits reduced T-helper (Th)1 activity and an excess of Th2 activity.
- Post-birth exposure to infections transforms Th2-biased immunity into a balanced Th1/Th2 immunity with immunological memory development.

Inflammation in children and adults:

- Chronic inflammation linked to infections precedes tumor development.
- Contributes to carcinogenesis via oncogenic mutations and increased angiogenesis.

Cytokines' dual role

- Specific cytokines (IL-6, IL-17, IL-23) either promote or inhibit cancer cell proliferation.
- Others (IL-12, TRAIL, IFN-γ) contribute to tumor development and progression.

Antitumoral response initiation:

- Tumor-associated antigens (TAAs) recognition by immune system required for an antitumoral response.
- Receptors transport TAAs to Th lymphocytes for T cell and macrophage activation to kill cancer cells.

Environmental factors and immune disorders:

- Chronic low-grade inflammation induced by prolonged antigen exposure contributes to immune disorders.
- Can lead to cancer cell accumulation in older individuals.

Respiratory tract infections and cancer risk:

- Later-life respiratory tract infections critical in immune system's capacity to control tumorigenesis.
- Exposure to specific environmental factors, like endotoxins, may offer protection against lung cancer.

Influenza viruses and cancer immunosurveillance:

- *In vi*vo studies show influenza viruses produce TAAs, inducing immune memory and lifelong immunosurveillance.
- Respiratory tract infections associated with increased risk of chronic lymphocytic leukemia.

Type 2 inflammatory dendritic cells (infcDC2s) in infections

- *In vivo* studies identify infcDC2s involved in respiratory viral infections, promoting optimal CD4+ and CD8+ T-cell immunity.
- Tumor microenvironment inflammation leads to strong antigen and T-cell activation, developing tumor-specific CD8+ T cells and long-term antitumor memory responses.
- Proinflammatory γδ T cells secrete cytokines critical for microbial infection response in the lungs.

Numerous bacteria have demonstrated the ability to modify various pathways and moleculeswithin host cells to ensure their intracellular survival. While traditionally considered a sterilespace,

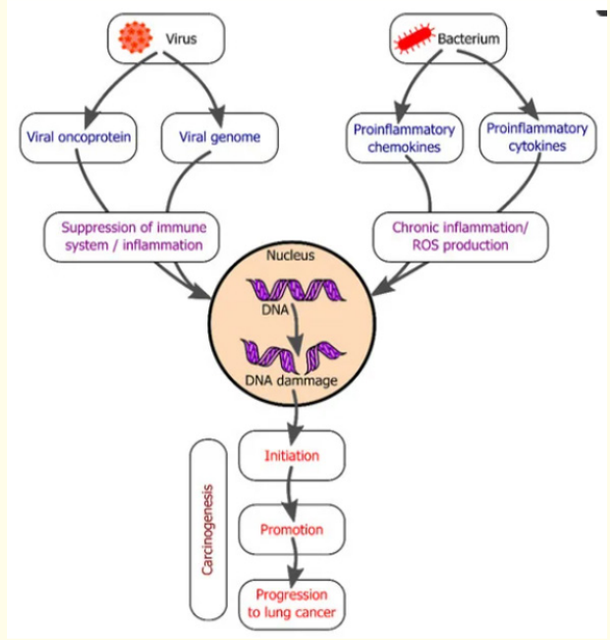

Figure 2: Overview of the role of bacteria and viruses in the development of lung cancer.

recent studies challenge the notion of the lungs as devoid of microbial influence. Emerging research suggests that alterations in the lung microbiome may contribute to the exacerbation of chronic obstructive pulmonary disease (COPD). Notably, disruptions in lung microbiota, known as dysbiosis, have been linked to the onset of lung cancer. For instance, specific oral taxa like Streptococcus and Veillonella have been associated with the heightenedactivation of inflammatory signaling pathways such as extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K). Consequently, a comprehensive understandingof key pathogenic organisms connected to or implicated in lung cancer development becomesimperative.

Bacteria

Chlamydophila pneumoniae

Chlamydophila pneumoniae, a bacterial pathogen, has been linked to lung cancer, with various proposed mechanisms explaining this association. One suggested mechanism involves the generation of reactive oxygen species (ROS) during inflammation, leading to DNA damage. Lung inflammation is reported to elevate cell division rates, increasing the riskof mutations and promoting cancer development through a consistent rate of DNA damage. Effector molecules from *C. pneumoniae* induce immunosuppression, chronic inflammation,inhibit tumor suppressor mechanisms, and transform cells via oncogene transfer. During chronic lung infection, *C. pneumoniae* proteins produced within host cells migrate to different organelles, influencing crucial biological activities and contributing to cancer development.

C. pneumoniae is particularly concerning for smokers, easily infecting their lungs and heightening the risk of lung cancer. Smoking, known to decrease lung immunity and increase IL-4 secretion, coupled with *C. pneumoniae*'s ability to downregulate apoptosis by inducing IL-10, leads to chronic infection. Additionally, chronic *C. pneumoniae* infection may release an endotoxin-like protein, chlamydial heat shock protein-60 (CHSP-60), playing a significantrole in lung carcinoma pathogenesis. Despite various proteins released during *C. pneumoniae*infection contributing to lung cancer, competitive inhibition between target and host proteinsfor substrate binding further complicates the scenario. Moreover, *C. pneumoniae* infection induces nitric oxide production, adding another layer to its potential role in lung cancer pathogenesis.

Mycobacterium tuberculosis

The heightened incidence of lung cancer is intricately linked to the immunosuppression induced by Mycobacterium tuberculosis (MTB) infection. Recent investigations underscore inflammation and pulmonary fibrosis, consequences of tuberculosis, as pivotal factors in lungcancer development. Infections, notably tuberculosis, are recognized to instigate inflammation that fosters carcinogenesis, disrupting host tissue, prompting fibrosis, and instigating genetic alterations. Mycobacterium tuberculosis triggers the activation of neutrophils, generating reactive oxygen species (ROS) that bind to DNA, resulting in geneticdamage and contributing to lung carcinogenesis.

Tuberculosis is associated with both lung squamous cell carcinoma and adenocarcinoma, releasing inflammatory mediators such as IL-1, IL-2, IL-12, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), inducing inflammation in lung tissues. On one hand,extracellular matrix (ECM) components are produced, participating in tissue repair characterized by heightened fibroblast activity and increased levels of various cytokines, including transforming growth factor-beta (TGF-β), IL-4, IL-10, IL-3, and IL-13. On the other hand, inhibitory mechanisms such as immune evasion and immune checkpoint inhibition play roles in latent M. tuberculosis infections. Type 1 T-helper cells (Th1) and the production of IFN-γ and TNF-α are activated in a T-cell-mediated immune response to protect tissues/organs against M. tuberculosis infections. Recent evidence suggests that blocking the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD- L1) signaling pathway can prevent lung cancer development in patients with tuberculosis.

While the timely and accurate diagnosis of lung cancer is crucial, clinical symptoms and radiological imaging can resemble those of tuberculosis. Apoptosis and necrosis induction,along with tuberculosis reactivation, contribute to higher levels of IL-17 and THF-α in immunodeficient patients. These elevated levels may reduce p53 activity or increase Bcl-2expression, decreasing Bax-T and inhibiting caspase-3 due to lower mitochondrial cytochrome C oxidase expression. Evidence suggests that the Bacillus Calmette–Guérin (BCG) vaccine significantly enhances the immune system response, along with increased levels of gamma interferon, nitric oxide, and interleukin-2.

In the early stage of M. tuberculosis infection, an immune response with type 1 T-helper cells(Th1) secreting IFN-γ and TNF-α helps avoid intracellular mycobacterial death. Inhibitory mechanisms, including immune evasion and checkpoint inhibition, support MTB latent infection. Additionally, tuberculosis mycobacterial cell components activate nitric oxide production and ROS, both contributing to carcinogenesis. The secretion of DNA-damaging reactive oxygen and nitrogen species by tuberculosis-infected macrophages, resulting from chronic tuberculosis infection, leads to the deletion of exon 19 of the epidermal growth factorreceptor, a crucial paracrine growth factor in early carcinogenesis.

Helicobacter pylori

The Gram-negative spiral-shaped bacterium Helicobacter pylori has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) since 1994.Its significance lies in its strong association with various gastrointestinal disorders, includingfunctional dyspepsia, peptic ulceration, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (MALT). Beyond digestive pathologies, H. pylori infection activates immune and inflammatory responses, suggesting potential links to extra-digestive pathologies such as respiratory diseases. The bacterium's involvement in lung cancer is explained through various functional mechanisms, including cytotoxin-associated antigen A (CagA)-associated pathways and Src/p130cas signal cascades.

Evidence from clinical and experimental studies suggests that *H. pylori* may reach the stomach through aspiration, introducing components like bile acids and pepsin into the tracheobronchial segment and causing lung damage. The inflammatory response in the lungsis characterized by the overexpression of pathogen recognition receptors (PRRs) like Toll-like receptors (TLRs) identifying pathogen-associated molecular patterns (PAMPs). Additionally, bacterial DNA recognition occurs through cytoplasmic surveillance receptorssuch as TLR-9 and receptors of advanced glycation end products (RAGE). Recent findingsindicate that TLRs and RAGE influence immune cell responses in the lungs directly by recognizing PAMPs and indirectly through the recognition of damage-associated molecularpatterns (DAMPs) resulting from lung injuries. Notably, H. pylori-derived factors, such as vacuolating cytotoxin (VacA), induce specific responses in lung carcinoma cells and bronchial epithelial cells, further highlighting the bacterium's impact on lung epithelium.

Viruses

Human immunodeficiency virus (HIV)

The role of the human immunodeficiency virus (HIV) in oncogenesis remains unestablished; however, in individuals with HIV-positive status, the prospect of carcinogenesis in lung cancermay arise from the persistent inflammatory milieu induced by concurrent infections. Specifically, HIV patients who engage in smoking face a notable 2.5-fold escalation in their susceptibility to lung cancer. Furthermore, the heightened propensity for lung cancer in those with HIV is intricately linked to diminished CD4 cell count, elevated viral load, and an augmented frequency of bacterial pneumonia occurrences.

Lung cancer stands as the predominant cause of mortality among individuals with HIV, and itsemergence is intricately linked to factors such as immunosuppression, CD4 count, and viral load. Immunosuppression notably contributes to the elevated incidence of lung cancer in this demographic. The risk escalates further due to tobacco smoking, a habit that HIV-positive adults are notably reluctant to abandon. HIV's detrimental impact on the immune system induces chronic inflammation, heightening the vulnerability to coinfections with other virusesand consequently augmenting the likelihood of cancer development. In an extensive clinical investigation spanning from 1988 to May 2018 in Montreal, a substantial proportion of HIV patients with lung cancer were diagnosed at advanced stages, with metastatic disease detectedin 52% of cases.

Human papilloma virus (HPV)

The human papillomavirus (HPV), a member of the DNA virus family Papillomaviridae, exhibits a pronounced predilection for infiltrating epithelial tissues, including squamous epithelium, bronchial regions, and the lungs. The conjecture posits that the virus leverages damage to epithelial tissue to infect undifferentiated cells within the basal layers of a stratifiedsquamous epithelium. Control over the HPV life cycle and gene expression hinges on the differentiation of epithelial cells. HPV infection, contributing to approximately 5% of the global cancer burden, emerges as a recognized risk factor for lung cancer, notably in individualsinfected with high-risk serotypes 16 and 18, nonsmokers, and females.

The correlation between HPV infection and lung cancer, though documented in various studies,remains contentious. The involvement of HPV in the pathogenesis of lung cancer in never- smokers is underscored as a significant risk factor, with HPV DNA detected in about 20% of lung cancer cases. Upon entering the lungs, the virus commandeers cellular mechanisms, replicates its genome, evades apoptosis, and instigates tumor genesis. Interactions between estrogen, hypoxia-inducible factor-1α (HIF-1α), and the epidermal growth factor receptor (EGFR) activate mitogenic signaling, contributing to cell survival. Recent research posits thatHPV alters multiple signaling pathways related to lung cancer, exemplified by the regulatory impact of HPV E6 and E7 oncogene proteins on various target genes and proteins, such as p53,IL-6, IL-10, pRb, EGFR, HIF-1α, Mcl-1, Bcl-2VEGF, and cIAP-2, fostering lung cell proliferation, angiogenesis, and tumor progression. Notably, the prevalence of HPV infection is higher in squamous cell carcinoma compared to adenocarcinoma. Furthermore, HPV- induced inflammation and epithelial–mesenchymal transition (EMT) underscore its conceivable role in lung cancer development.

Epstein–barr virus

The Epstein–Barr virus (EBV) has long been conjectured to play a role in various lymphoproliferative and neoplastic disorders, including gastric cancer, Hodgkin's disease, andBurkitt's lymphoma. A pronounced association between EBV and lymphoepithelioma-like carcinoma, an uncommon lung cancer variant, is evident in Asian patients but not in Western counterparts. In a clinical study encompassing 53 lung cancer patients, EBV was discerned inbronchoalveolar fluid, suggesting the lung as a potential reservoir.

Despite this, the link between EBV and lung cancer remains contentious, primarily due to the limitations of conventional viral screening methods and a relatively small sample size. Advanced analyses using microarray and real-time quantitative PCR revealed varied expressions of EBV miRNAs in lung cancer cases. Notably, in situ hybridization identified EBV-encoded RNA in non-small lung cancer cells, coupled with heightened immune cell infiltration in samples with elevated EBV transcripts. Next-generation sequencing unveiled thedirect regulation of tumor pathways by EBV, highlighting its potential role in shaping the molecular landscape of lung cancer.

Cytomegalovirus

Recent evidence suggests that cytomegalovirus (CMV) may exert an oncomodulatory influence by stimulating cell cycle progression and enhancing cell proliferation in certain cancer cells. This effect is attributed to the production of viral proteins that impact DNA replication and gene expression. CMV appears to aid tumor cells in evading immune responses, hindering activated NK and T cells from eliminating cancer cells. Moreover, CMV infection is implicated in heightened tumor invasiveness by facilitating the migration of infected cancer cells. Notably, cancers of the colon, breast, prostate, and lung exhibit elevated expression of cyclo-oxygenase 2 (COX-2), with its inhibition shown to impede CMV replication.

In vivo studies involving xenografted mice injected with HepG2 cells infected with wild-type CMV reveal caspase activation in a p53-independent manner in lung tissues. This implies thatapoptosis induction is not solely confined to the tumor tissues of mice injected with CMV- infected HepG2 cells subcutaneously.

Influenza virus

In a cohort study, it is documented that exposure to influenza is linked to a 1.09-fold elevated risk of lung cancer, escalating to a 25% increase in individuals with recurrent influenza episodes (5 or more). Additionally, administering annual influenza vaccinations to those with chronic obstructive pulmonary disease can induce a TH1 immune response, thereby mitigatingthe risk of lung cancer. Recent investigations have proposed the utility of seasonal influenza vaccines not only in infection prevention but also as a crucial element in cancer immunotherapy. Intratumoral administration of an influenza vaccine is shown to stimulate systemic CD8+ T-cell-mediated antitumor immunity, consequently curtailing tumor growth.

Measles virus (MV)

Measles, an omnipresent RNA virus, has the potential to induce persistent viral infection, possibly attributable to a mutated strain. In lung cancer cells, an overexpression of the ubiquitin E3 ligase Pirh2 is noted, correlating with p53 inactivation. Interestingly, the presence of Pirh2 serves as an indicator of enhanced survival, yet the ubiquitination of Pirh2is hindered by the MV phosphoprotein.

Compellingly, CD46, a cell membrane inhibitory protein acting as an MV receptor, is abundantly expressed in lung cancer cells. Measles virus (MV) exhibits oncolytic properties against non-small

cell lung carcinoma, independently expressing in nectin-4. Moreover, intratumoral injections of carcinoembryonic antigen (MV-CEA) facilitate inhibition of tumorgrowth, coupled with the detection of the viral transgene in mice sera.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

A delayed diagnosis of lung cancer often occurs due to the overlapping symptoms with SARS- CoV-2 infection, resulting in additional harm to lung tissues. The exaggerated inflammatory response to SARS-CoV-2 is associated with elevated circulating cytokine levels, acute lymphopenia, and substantial mononuclear cell infiltration in the lungs. Severe COVID-19 cases exhibit systemic cytokine profiles resembling cytokine release syndromes, characterized by heightened levels of IL-6, IL-7, tumor necrosis factor (TNF), and inflammatory chemokineslike CXCL10, CCL2, and CCL3.

Furthermore, Type I interferons induce the expression of SARS-CoV-2 entry receptors, facilitating viral migration into macrophages' cytoplasm. This process promotes NLRP3 inflammasome activation and the release of mature IL-1β and/or IL-18. IL-1β, in turn, activates monocyte-derived macrophages and suppresses type I interferon production in the lungs. Additionally, the SARS-CoV-2 spike (S) protein binds to angiotensin-converting enzyme 2 (ACE-2), facilitating viral entry into cells with the assistance of host proteases, particularly transmembrane serine protease 2 (TMPRSS2).

Conclusion

Early pathogen detection in clinical practice: Implications

Critical component for clinical success:

- Early detection of pathogens is pivotal for successful clinical practice.
- Particularly crucial for lung cancer patients due to vulnerability to aggressive pathogenic bacteria and viruses.

Interplay with immunotherapy:

- Lung cancer patients reliant on various treatments, including immunotherapy.
- Combined treatments may modulate the systemic immune response.

Infectious agents and lung carcinogenesis:

- While infectious agents may not be primary causes of lung cancer, they can create an inflammatory environment conducive to initiation and progression.
- Infectious agents influence the response to therapy.

Associations between infectious factors and lung cancer:

- Reported associations between infectious factors and lung cancer exist.
- Further studies needed to confirm and comprehend these associations, including molecular mechanisms involved.

Consideration of contributing factors:

- Recognition that smoking habits, air pollution, and other factors contribute to lung cancer.
- Comprehensive understanding necessitates investigation into the intricate interplay of these elements.

Recommendations and open questions:

Research recommendations:

- Investigate the confirmed associations between infectious factors and lung cancer.
- Explore the molecular mechanisms involved in these associations.
- Assess the impact of smoking habits, air pollution, and other factors on lung cancer development.

Clinical considerations:

- Develop early detection strategies tailored to the susceptibility of lung cancer patients.
- Integrate comprehensive treatment plans considering the potential modulation of the systemic immune response.

Future inquiries:

- How can early detection methodologies be optimized for lung cancer patients?
- What specific molecular pathways link infectious agents to lung cancer initiation and progression?
- How do various contributing factors interact in the complex landscape of lung cancer development?

Author Contributions

Sristi Dasgupta spearheaded bacterial literature exploration, crafted the initial manuscript, and played a key role in deliberating on pivotal aspects and the repercussions of this review.

Disha Nayak delivered a comprehensive introduction, offered valuable insights in early drafts, incorporated virus-related literature, and engaged in insightful discussions on crucial points in the conclusion, considering their implications.

Additional Information

The authors declare no conflict of interest.