MINI REVIEW ARTICLE

SARS-COV-2 infection and lung tumor microenvironment

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Abstract
Coronavirus Disease 2019 (COVID-19) is an acute respiratory syndrome, reported at the end of 2019 in China originally and immediately spread affecting over ten million world population to date. This pandemic is more lethal for the older population and those who previously suffered from other ailments such as cardiovascular diseases, respiratory disorders, and other immune system affecting abnormalities including cancers. Lung cancer is an important comorbidity of COVID-19. In this review, we emphasized the impact of lung tumor microenvironment (TME) on the possibility of enhanced severity of infection caused by the SARS-Co-V2. The compromised lung TME is further susceptible to the attack of viruses. The lung cells are also abundant in the virus entry receptors. Several SARS-Co-V2 proteins can modulate the lung TME by disrupting the fragile immune mechanisms contributing to cytokine storming and cellular metabolic variations. We also discussed the impact of medication used for lung cancer in the scenario of this infection. Since other respiratory infections can be a risk factor for lung cancer, COVID-19 recovered patients should be monitored for tumor development, especially if there is genetic susceptibility or it involves exposure to other risk factors.

Keywords Covid-19 · Lung cancer · Tumor microenvironment · Cytokines · Risk factors

Lung cancer

Lung cancer is the most frequent malignancy worldwide, affecting 2.09 million new cancer cases, and 1.76 million deaths annually, thereby the leading cause of cancer-related deaths [1]. Predisposing factors for the lung cancer development include tobacco smoking, genetic polymorphisms, family history, alcohol, dietary preferences, carcinogen exposure (asbestos, silica, and polycyclic aromatic hydrocarbons), air pollution, radiations, chronic inflammation because of infections like tuberculosis and pneumonia [2].

Lung cancer is of two major types; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC accounts for 15% of all lung cancer cases and more common in men. It is an aggressive form which originates in the bronchi and metastasizes to other body organs. NSCLC is the most common lung cancer and accounts for 80–85% cases of lung cancer cases. It originates in the mucus, squamous, or any other cell in the lungs [3]. The dilemma with lung cancer is that the symptoms rarely appear until the situation gets complicated and the cancer is already at a progressive stage. The symptoms like persistent coughing, chest pain and fatigue are mistaken for other causes, such as smoking effects or any other infection. This may delay the diagnosis, which should be within 2–4 weeks after the presentation of symptoms, hence leading to metastasis [4].

Metastasis of lung cancer occurs to the contralateral lung, adjacent lymph nodes, adrenal glands, bones, brain, and liver [5]. The process of metastasis starts with the migration of tumor cells through blood or lymphatic system to a distinct site. Upon extravasation, the tumor cell ends up in any adjacent or distant organ and starts growing there upon finding a suitable environment [6]. Different signaling pathways and epigenetic factors regulate tumor metastasis [7]. A successful metastasis depends on the imbalance between cell survival and apoptotic signals.

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Tumor microenvironment in lung cancer

The effective development of tumors at primary and metastatic sites depends on the surrounding environment called tumor microenvironment (TME). A variety of stromal cells including T-cells, B-cells, Natural Killer (NK) cells, fibroblasts, adipocytes, vascular endothelial cells, and pericyte surround the growing tumor. These cells secrete signals involved in tumor survival, growth, invasion, migration, and change the behavior of cancer cells, also called oncomodulation [8]. Oncomodulation is induced by the effect of various factors that change the components of TME and alter the mechanisms acting on cancer cells and associated stromal cells such as suppressing immunity, halting normal apoptosis mechanisms, altering metabolic pathways, triggering inflammation, inducing angiogenesis, proliferation, invasion, and migration signals in cancer cells [9].

In lung cancer, the TME is significantly active. Invading cancer cells can reprogram the components of lung TME promoting carcinogenesis. Different TME components like cancer activated fibroblast, extracellular matrix, endothelial cells, immune cells that include myeloid cells (macrophages, neutrophils, dendritic cells, natural killer cells) and lymphoid cells (T and B lymphocytes) get modulated under the effect of signals from infiltrating tumor cells and further activate the cascades leading to survival and growth of tumor cell [10]. Figure 1 depicts the remodulation of the surrounding environment in lung cancer.

Upon prolonged exposure to risk factors, the redesigned lung TME becomes more supportive of tumor growth. Persistent exposure to smoking leads to hypoxic conditions

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**Fig. 1** Tumor microenvironment (TME) in lung cancer. The TME components support the tumor growth and secrete signals and initiate cascades that facilitate the proliferation, growth, migration, invasion, and stabilization of tumor cells. They also suppress immune responses and confer drug resistance. IGF2 (insulin-like growth factor-2), CXCL1 (C-X-C Motif Chemokine Ligand 1), STAT (Signal Transducer And Activator Of Transcription), TGF-β (Transforming Growth Factor Beta), IL-6 (Interleukin-6), FASL (Fas Ligand), PDIL1/L2 (Programmed cell death protein ligand 1 and 2), EGF (Epidermal growth factor), MMP14 (Matrix metalloproteinase 14), HIF1A1α (Hypoxia-inducible factor 1A1alpha), HMMR (Hyaluronan mediated motility receptor), mTOR (mammalian target of rapamycin), IL-1β (Interleukin-1beta), sRAGE (soluble Advanced Glycosylation End-Product Specific Receptor), CXCR2 (C-X-C Motif Chemokine Receptor 2), VEGF (Vascular endothelial growth factor), PIGF (Placental growth factor), IFN-γ (Interferon-gamma), TNF-α (Tumor necrosis factor-alpha)
in the blood and other organs, including lungs leading to impaired gaseous exchange and increased inflammation [11]. This hypoxic environment induces Hypoxia-inducible factor-1 (HIF-1) expression and aggravates the malignant potential of the tumor. Increased HIF-1 expression leads to the overexpression of the genes associated with angiogenesis, cell survival, and migration in cancer cells [12, 13]. Hypoxia also causes resistance in the lung cancer cells of NSCLC against chemotherapeutic drugs such as gefitinib [14].

Lung infections cause chronic inflammation and further lead to accumulating pro-inflammatory cytokines, changing TME, and resulting in metastasis. The macrophages secrete pro-inflammatory cytokines (such as TGF-β, IL-6, IL-10, and TNF-α) and further induce stem cell like characteristics in the tumor cells, which enable them to initiate growth and sustainability [15]. The chronic exposure of these cytokines further activate several inflammatory pathways in lung malignancies such as NF-κB pathway activation by TNF-α [16], STAT3 pathway by over-expressed IL-6 [17] and enhanced TGF-β signaling pathway [18]. Prolonged inflammation also increases the E-selectin expression, which promotes hyper-permeability supporting extravasation and facilitates the homing of lung tumor cells in an unfamiliar environment [6]. Another important candidate in the lung TME cross talk is the chemokine receptor CXCR4, which creates a “pro TME” and promotes distant metastasis [19]. CXCR4 antagonists are being considered as an important therapeutic target in NSCLC [20].

Taken together, this information suggests that TME plays an important factor in tumor initiation and progression. Several factors such as smoking, inflammation mediators, and infections can modulate the TME and make it more tumor friendly. Here we discuss different scenarios that COVID-19 infection can influence lung cancer patients because of TME modification.

Impact of Covid-19 on lung cancer: how TME support this infection

What is Covid-19 infection

COVID-19 is an outbreak reported in China at the end of 2019. World Health Organization (WHO) on 11 February 2020 named the novel coronavirus-induced pneumonia as Coronavirus Disease 2019 (COVID-19). The disease causative agent was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Virus Classification Commission [21].

The COVID-19 transmission is reported by both symptomatic and asymptomatic individuals, according to WHO. The origin of this virus is zoonotic as bats are reported as the reservoir hosts of this virus [22]. The primary mode of transmission is by close contact with the infected individual and contaminated areas [23]. The infection primarily affects the respiratory system of the human host. The incubation period of this virus is approximately five days. At this time the viral load in the upper respiratory tract is very high. The symptoms may appear after 14 days of infection [24]. Because of which SARS-CoV-2 has the potential to spread massively before being detected symptomatically.

SARS-CoV-2 belongs to the genus Betacoronavirus and structurally comprises the RNA genome of 29.8 kb which encodes 29 proteins including structural (n = 4), non-structural (n = 16) and accessory (n = 9) proteins. Structural proteins maintain the virus physical characters and include spike (S) protein, envelop (E) protein, membrane (M) and nucleocapsid (N) protein (Fig. 2a). S protein (YP 009724390.1) is a 141 kilo Dalton (kDa) protein and binds to the surface receptors of the host cell, mediates the entry of virus inside the host cell and starts its life-cycle by taking control of the host system. E protein (YP 009724392.1) is an 8.4 kDa hydrophobic protein and forms the outer covering of virus and essential for virus assembly or release. M protein (YP 009724393.1) is a 25 kDa highly expressed protein of SARS-CoV-2 and associated with the production of viral particles and mediate inflammatory pathways. N protein (YP 009724397.2) is a 45.6 kDa highly expressed protein in the host at the early stages of infection [25]. It binds to RNA of the virus and forms ribonucleoprotein, which facilitates in interaction with cellular processes after the entry of virus into the host. Figure 2b illustrates various regions in the genome of SARS-CoV-2 encoding 29 important proteins.

Along with the four structural proteins, 16 non-structural proteins (NSP) degrade the host RNA and take hold of its transcription machinery. These proteins are synthesized as two long polypeptides, one of which is auto-protelytically processed into 16 proteins (NSP1-NSP16; with a molecular weight ranging from 1.3 to 217 kDa). Of these proteins, RNA polymerase (NSP12; YP 009725307.1) and the main protease (NSP3; YP 009725299.1) are the significant proteins which are involved in virus replication processes, promote cytokine expression, and block innate immune responses [26].

The remaining nine accessory proteins aid in the inflammation, induce apoptosis and halt antiviral responses of the host. These accessory proteins include ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c and ORF10; with a molecular weight ranging from 4.4 to 31 kDa.

SARS-CoV-2 gets entry into the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptors through its S protein [27, 28]. These receptors are abundantly present on the alveolar type II (AT2) epithelial cells of the respiratory tract [29]. The AT2 cells abundance is also the hallmark of lung tumor. SARS-CoV-2 infects the lower respiratory
tract and can cause severe respiratory failure that may lead to a high death rate among lung cancer patients [30]. ACE2 knockout mouse model has strongly supported this idea for SARS-CoV-2 entry in pulmonary cells [31]. Another protein, TMPRSS2, involved in propagation of several viruses, including influenza virus, as previously reported, and can also mediate the SARS-CoV-2 entry [32]. The respiratory tract except the alveolar epithelium significantly expresses TMPRSS2 [33] and Matsuyama et al., [32] have shown its vulnerability towards SARS-CoV-2 entry. Recently, Meng et al. [34] have showed that the co-expression of ACE2 and TMPRSS2 and has a propensity for development of SARS-CoV-2 infection. Another preliminary study reported that the elevated expression of CD147 in tumor cells facilitates virus entry by binding to S protein [35]. Moreover, integrins are being investigated for its role in SARS-CoV-2 entry, but a solid confirmation is still lacking [36]. Following the binding of host receptor to virus S protein, the proteolytic activity in S-protein by host proteases fuses the virus envelope to the host membrane. Once inside, the virus gets hold of the cell translation machinery and starts translating its replicase gene and other non-structural components. This translation is followed by the synthesis of genomic and sub-genomic virus RNA. Sub-genomic RNA translates into the structural proteins and going through host cytoplasmic compartments leads to the assembly of the mature virus, which are then transported to host cell surface and are exocytosed (Fig. 3) [37, 38]. SARS-CoV-2 genome like other coronaviruses has a tendency for recombination and this makes it excessively adaptable to different conditions [39]. In two independent studies, SARS-CoV-2 is shown to use neuropilin-1 (NRP1) for getting entry into the host cell by binding through spike protein.

**Possible effects of Covid-19 infection on lung cancer patients**

Cancer patients are more susceptible to COVID-19 infection than individuals without cancer. This could be because

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Fig. 2 Structure of SARS-CoV-2. a A virus particle showing structural proteins and single-stranded RNA genome; b A schematic figure of viral 29.9 kb genome showing 5'UTR, location of the polyprotein, 04 structural proteins, 16 non-structural proteins, 09 accessory proteins, and 3'UTR
of systemic reduced immunity or anticancer therapy being offered to these cancer patients. The situation could be worse in lung cancer patients as they already have chronic pulmonary inflammation because of the underlying TME and lung pathology [40]. The already hostile lung environment may offer suitability for the virus entry, growth, and infection. So, lung cancer can have significant comorbidity for the SARS-CoV-2 infection. The similarity between the symptoms of lung cancer and SARS-CoV-2 infection can also delay the diagnosis of infection in these individuals which can lead to further deterioration of lungs [41]. Overall, cancer patients are more prone to acquire this infection and have poor survival. In a Chinese study, lung cancer was the most reported type of cancer patients carrying COVID-19 infection [42]. A multicenter retrospective study was performed on 205 cancer patients with SARS-CoV-2 infection from China. Lung cancer was one of the most common solid tumors and reported in 12% of all cases [43]. Another multicenter study during the COVID-19 pandemic was performed on 105 cancer patients and 536 age-matched non-cancer patients confirmed with COVID-19 from China [44]. Lung cancer was the most frequent cancer and reported in 21% of all cancer cases. Lung cancer patients reported the highest frequency of severe events including death rate (18.18%), ICU admission rate (27.27%), risks of critical symptoms (50.00%), and the chance of use of invasive mechanical ventilation (18.18%) of reported lung cancer patients. The increased risk of infection in lung cancer can also be because of the abundance of viral spike protein binding receptors to the host cells in the lungs. The ACE2 receptors are expressed on the lung capillaries [45] and can make the situation worse by facilitating infection in such patients. Recently two lung cancer patients with COVID-19 infection underwent lung lobectomies. Pathological examination of lung tissues showed edema, proteinaceous exudate, patchy inflammatory infiltrates, and multinucleated giant cells [46].

The TME in the lung could also be very supportive of the viral proteins, which can act as the signals for activation of several inflammatory pathways. These possibilities are discussed further in this review.

**Oncomodulation due to Covid-19 infection**

Several studies have shown how a virus can alter the processes in the tumor and its surrounding stromal cells. The signaling cascades will be affected and lead to altered metabolism, immunosuppression, decreased apoptosis, transformed cellular communications, and increased

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**Fig. 3** SARS-CoV-2 binds to ACE2 receptors on the host cell surface and gains entry. Once inside it can start its life cycle by using components of the host cell. The virus makes multiple copies that leave by exocytosis to infect other cells.
angiotensin-converting enzyme 2 (ACE2) promotes cytokine production which underlies the cell-to-cell spread of the virus. The SARS-CoV-2 infection activates the host innate immune system through the release of cytokines and chemokines. These cytokines are released in response to infection and further inflammation of lung tissues. Pro-inflammatory chemokines are released in response to infection and recruit immune cells to the site of infection, including macrophages and neutrophils. The increased extracellular glutamine levels also make tumor cells more aggressive, and with lesser survival periods for patients. This increased utilization of glutamine is supported by viral infections [52]. SARS-CoV-2 infected colon cancer cells have shown that a set of genes involved in the metabolic pathways get altered by this infection [49]. Similarly, the TME is usually hypoxic and nutrient deprived which supports suppressed immune response providing a favorable environment for viral growth.

Cytokines rush is the phenomenon characterized by increased production of cytokines leading to an elevated inflammatory response. It can occur in tumor cells because of several underlying factors and with immune-based therapeutics [53]. SARS-CoV-2 infection can fuel this process, causing the top mortality rates in cancer patients. When the viruses attack the respiratory tract, the cytokine response is triggered in a variety of ways. Pro-inflammatory chemokines are released in response to infection and recruit immune system cells including lymphocytes, macrophages, and neutrophils to the site and increase inflammation and immune suppression. Along with chemokines, interleukins, tumor necrosis factors, and interferon-gamma are rushed to the site to release cytokines. These excessive cytokines which initially affect the TME, get leaked from the site of infection in the respiratory tract and end up in other organs where they produce tumor promoting effects [54]. However, host susceptibility to this storm depends on the underlying genetics of the host innate immune system [55].

SARS-CoV-2, NSP3 affects the host innate immune mechanisms and promotes cytokine production which may lead to the storming of cells with pro-inflammatory cytokines. ORF6 and ORF9b, the accessory peptides in the SARS-CoV-2 genome, act as type I IFNs antagonists. Type I interferon has a protective function for tumor cells as they activate the JAK-STAT pathway leading to the expression of transcription factors and genes with antiviral, antiproliferative, and immunomodulatory functions. These viral peptides (ORF6 and ORF9b) can block IFN and may lead to increased proliferation and tumor survival. SARS-CoV-2 can also modify the host immune system through another accessory peptide, ORF3a which can activate the NLRP3 (nucleotide-binding domain (NOD)-like receptor protein 3) inflammasome. This activation produces excessive IL-1β and IL-18 in response to infection, but increased pro-inflammatory signals can make the situation worse. It is noteworthy that the activity of this inflammasome is regulated by type I IFN which is also affected by other viral proteins discussed before so a shift in type I IFN level has the potential to change the scenario in TME of the lung.

TNF-α mediated NF-κB pathway activation and TGF-β signaling in TME are crucial as these cytokines regulate growth, proliferation and differentiation, and apoptosis [56]. However, the destruction of cellular mRNA by viral proteins (such as NSP1) can lead to the destruction of the inhibitory molecules for these pathways triggering their activation, thus promoting inflammation of lung tissues.

Similarly, ORF7 peptide can induce apoptosis in host cells and NSP2 can bind to a host protein “Prohibitin” which is a regulator of cell proliferation, several transcription factors, and mitochondrial processes. The functions of several other SARS-CoV-2 proteins in the host cells still need to be determined.

Ongoing therapy and fighting COVID-19 infection

As the SARS-CoV-2 dampens down the immune system of the host, a question arises if the individuals are on immune supportive therapy can better fight with this infection than those without such therapy. Because of the symptoms resemblance between lung cancer and COVID-19, it may affect similar mechanisms and cascades. Based on this, we have assessed different chemotherapeutic and immunotherapeutic drugs being administered to lung cancer patients.

The immunotherapy in lung cancer patients targets either the Programmed cell Death-1 receptor and its ligand (PD-1/PDL-1) [57] such as pembrolizumab, nivolumab, atezolizumab, and durvalumab or cytotoxic T-lymphocyte associated protein 4 (CTLA-4) [58] such as Ipilimumab. Conflicting data reported effective, adverse, or with no effect of anti-PD-1/PDL-1 or anti-CTLA-4 therapies to lung cancer patients. This variation can be attributed to the diverse innate immune system of the studied participants. However, a conclusion cannot be drawn from these studies because...
of the small sample size of available data. Also, the hyper-
activation of the immune response in lung cancer patients
or the cytokine storm because of immunotherapy may lead
to injury in other body organs and increase the severity of
damage leading to death.

The chemotherapeutic drugs given for cancer treatment
may also provide additional benefits against SARS-CoV-2
peptides. Gordon et al., [26] developed an interactome of
human proteins and SARS-CoV-2 peptides. Further, they
sought the ligands interacting with those human proteins and
then used viral peptides as bait to determine their interaction
with the ligands. From the data, several chemotherapeutic
compounds can be spotted, which might be the candidates
against SARS-CoV-2 peptides. The Casein Kinase 2 inhibi-
tor (Silmitasertib), HDAC2 inhibitor (Valproic Acid), RIPK1
inhibitor (Ponatinib), Protein kinase inhibitor MARK1/3
(Midostaurin), Topoisomerase Inhibitor (Daunorubicin)
and NEK9 inhibitor (Dabrafenib) interacted with N protein,
NSP5, NSP12, ORF9b, ORF9c, and NSP9 when used as
baits. However, verifiable data from patients is still missing
and the clinical manifestation for these medications against
COVID-19 infection is also required.

Prospects of COVID-19 leading to lung
cancer

The chances of pulmonary infections to develop into lung
cancer are very high. Pneumonia, tuberculosis, and influ-
enza infections are potential risk factors for developing lung
cancer [2]. As SARS-CoV-2 infects the respiratory tract and
leads to similar symptoms, it might trigger some cascades
which facilitate the modification of the lung environment
for tumor appearance and growth. The situation could be
more alarming for the SARS-CoV-2 infected cases where
 genetic predisposition or other risk factors like smoking are
also involved.

At a later stage in COVID-19 with respiratory distress,
a hyper-activated immune system is observed. This can
cause cytokine rush leading to multiple organ damage. It
is previously shown that acute lung injury (ALI) or acute
respiratory distress syndrome (ARDS) caused by infections
can lead to inflammatory response and can also predispose
for lung cancer development [59]. ALI represents the most
severe outcome of SARS-CoV-2 infection [60]. The pre-
cise mechanism of ARDS/ALI in COVID-19 is still unclear.
The predominant factor noted in several studies is age of
the patient [61]. Two hospital-based studies from China and
Singapore investigated the clinical features of typical ARDS
and COVID-19 related ARDS cases. The lung pathology
was similar in both groups, but thrombosis and mortality
were more common in cases of COVID-19 ARDS [62]. A
similar study from Italy reported the same findings among
COVID-19 related and unrelated ARDS cases [63]. Being
heterogeneous, the management of ARDS is being tailored
in context to the over whelming pressure on health care sys-
tems because of COVID.

The symptoms of ARDS and ALI are overlapping with
the lung cancer and it can be predicted that SARS-CoV-2
infection can lead to cancer. The early players of the inflam-
matory pathway after acute lung damage are TNF-α, IL-1β,
IL-8, and IL-6 which are very active mediators of inflam-
matory pathways, whereas the anti-inflammatory cytokines
appear late [64]. Figure 4 explains the connection between
the lung infections and cancer. The monoclonal anti-IL-6
receptor antibody, tocilizumab emerges to be an effective
treatment choice in COVID-19 patients who are at risk of a
cytokine storm. Significantly improved clinical, biological,
and radiological outcomes are noted within 5–7 days after
tocilizumab treatment [65].

Conclusion

This review summarizes that TME has an important role in
determining the route of tumor development. The lung tumor
environment supports for infectious agents like SARS-
CoV-2 and can expedite infection. We conclude from the
evidence to date, the immune and chemotherapeutic drugs
administered during lung cancer have no convincing evi-
dence of being supportive in case of accompanying SARS-
CoV-2 infection. We propose that the COVID-19 recovered
patients should pay unusual attention to the symptoms of
lung cancer, as the viral infection may have elicited any
tumor initiation mechanisms.
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