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Review

Cytokine Signaling Pathways are involved in Lung Cancer and COVID-19

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Abstract: It has long been believed that cytokines mediate the intricate relationships between cells, such as hematopoietic cells, lymphoid cells, and various pro- and anti-inflammatory cells. To create a coherent immunological response, the immune system's intercellular messengers, or cytokines, combine the actions of multiple cell types in different physiological compartments. These include TNF family members, interleukins, mesenchymal growth factors, adipokines, and interferons. Notably, there are some parallels between the symptoms of cancer and COVID-19. For example, both the COVID-19 infection and cancer share the characteristic of cytokine storm, which is an unchecked overproduction of cytokines. People with COVID-19 and/or cancer additionally experience immunosuppression because IFN-I responses are known to be necessary for the pertinent immune responses against the infectious disease or diseases and the cancer. Based on a mechanistic understanding of cytokine, IFN, androgen receptor, and immune checkpoint signaling, COVID-19 has therapeutic potential for cancer. Understanding the biological underpinnings of the link between COVID-19 and cancer may help patients and healthcare professionals recalculate the advantages and disadvantages of different treatments and choose the best courses of action and timing for medication administration. The functions of cytokine signaling pathways and the connection between COVID-19 and lung cancer have been investigated. Since the inflammatory system and/or cytokine signaling pathways are important in these two disorders, the primary goal of this study was to provide more recent information about them.

Keywords: Cytokines; signaling pathways; potential genes; lung cancer; COVID-19

1. Introduction

A single cell type releases cytokines, a class of proteins that regulate an organism's response to infection or inflammation. By binding to particular receptors, cytokines affect the activity of other cells[1-5]. Cytokines carry signals from one cell to another in an organism. Their interactions with receptors, which either inhibit or stimulate the activity of particular genes within the cell, result in secondary signals. The majority of cytokines are specific to the cells that created them, in contrast to endocrine hormones, which have a broad variety of effects. Glycoproteins known as cytokines act as intercellular mediators, promoting the growth, differentiation, proliferation, or death of target cells. They function by engaging with specific receptors on the target cells' cell surface and initiating an intracellular signalling cascade based on phosphotyrosine, which is initiated by kinases and then spread and impacted by transcription factors with SH2 domains. The intensity and duration of cytokine signalling are strictly limited due to its proliferative and often inflammatory nature. By modifying pertinent signalling processes like proliferation, apoptosis, metastasis, and growth (anti-tumor cytokines), cytokines can either increase tumour growth (oncogenic cytokines) or inhibit tumour growth (anti-oncogenic cytokines). The majority of cytokines are small, 150–200 amino acid helical tubular proteins that fall into one of two groups based on receptor patterns. The arrangement of Class I cytokines' four helices is up-up-down-down. While their shape is sustained, some of them, such as IL5, are dimers. Two lengthy loops are anticipated to assemble the up-up and down-down sets because of the peculiar up-up-and-down-down layout. In class II cytokines, one or both of these loops are modified by an extra helix, producing roughly five to six antiparallel helices. A variety of cell types produce cytokines, which have a major impact on the body's reaction to cellular damage or invasive infections[6-8]. The production of TH1 cytokines occurs via two important pathways. STAT4 activation through its receptor in response to IL-12 stimulation triggers IFN-gamma transcription. IFN-gamma stimulates Stat1 to upregulate T-bet, the most

significant TH1 transcription factor, which in turn increases IFN-gamma production.

Human diseases that are spread worldwide Numerous studies have shown that COVID-19 is associated with higher levels of pro-inflammatory cytokines, specifically interleukin-6 (IL-6), in seriously ill people than in those who are only mildly ill. Cancer patients are believed to be far more susceptible to viral infections, which have long been believed to be caused by weakened immune responses. Numerous cytokines, such as interleukin (IL)-6, IL-1ß, tumour necrosis factor-a (TNF-α), and interferons, were increased early in the COVID-19 infection[1-3]. The microtumor environment may profit from the virus protein's ability to activate significant inflammatory pathways by triggering a variety of signals. Metabolic alterations, immunosuppression, decreased apoptosis, altered cellular communications, and increased angiogenesis will all occur from the disruption of the signalling pathways. Viral proteins and inflammatory mediators onco-modulate the tumour microenvironment, increasing the likelihood of cancer survival and progression. Changes at various levels in human diseases, including genetic changes, abnormalities in signalling pathways, and epigenetic modifications, can lead to changes in cell destiny. Cellular signalling and connectivity may be impacted by changes in proteomics and epigenomics. Cytokines are released by host cells as a defensive reaction to internal processes that cause stress, such as cancer or microbial infection, and are essential for cell metabolic reprogramming. The source could be squamous cells, mucus, or any other lung cell. Tumour spread is controlled by several signalling channels and epigenetic mechanisms (Figure 1). Chronic inflammation brought on by lung infections causes pro-inflammatory cytokines to build up, tumor microenvironment (TME) to change, and cancer to spread. Macrophages release pro-inflammatory cytokines (including TGF-ß, IL-6, IL-10, and TNF-α) that help tumour cells proliferate and survive by giving them characteristics of stem cells[9-15]. In lung malignancies, prolonged exposure to all of these cytokines triggers several inflammatory pathways, such as TNF, enhanced TGF-ß signalling network activation, and STAT3 pathway stimulation through overexpression of IL-6. The systemic weakened immune responses of the cancer patients or the anticancer treatment they are undergoing may be the cause of this. Since lung cancer patients already have chronic pulmonary inflammation due to the underlying TME and lung pathophysiology, they may be in a more difficult condition. The impact of the tumour microenvironment may be clarified by a systematic list of the genes whose expression varies in response to infection. Lung cancer and COVID-19 infection both have mutations in a number of genes or proteins that may inhibit or activate different signalling pathways and epigenetic mechanisms that promote tumour growth[11,16,17].

Numerous studies demonstrate that pro-inflammatory cytokines, especially interleukin (IL-6), are more prevalent in individuals with severe COVID-19 infection than in those with merely moderate illness. A contagious human illness that has spread globally is COVID-19. Pro-inflammatory cytokines accumulate in the body as a result of systemic inflammation induced by lung infections. The hyperproduction of primarily pro-inflammatory cytokines, including IL-1, IL-6, IL-12, IFN, and TNF, which specifically target lung tissue, might significantly affect the prognosis in the most severe instances. The risk of contracting COVID-19 is higher in older adults and those who have already experienced heart disease, respiratory disorders, or other immune system-related conditions such tumours. By modifying associated signalling pathways such proliferation, growth, metastasis, and apoptosis, cytokines can either promote tumour growth (oncogenic cytokines) or inhibit tumour growth (anti-tumor cytokines). According to several epidemiological research, people with lung cancer have a significantly higher risk of contracting COVID-19 infections. In human diseases, changes (genetic changes, abnormalities in signalling pathways, and epigenetic modifications) at various levels can lead to changes in cell destiny. Changes at the proteome and epigenomics levels may affect cellular connections and signalling. Numerous genes or proteins are altered in lung cancer and COVID-19 infection, which may inhibit or activate several signalling pathways and epigenetic factors that control tumour spread. Given the tumour microenvironment, inflammation plays a major role in the development of tumours. The tumour microenvironment regulates inflammation, immunological activation or suppression, and the epithelial-to-mesenchymal transition[18-20]. The tumour microenvironment is unaffected by viral proteins and

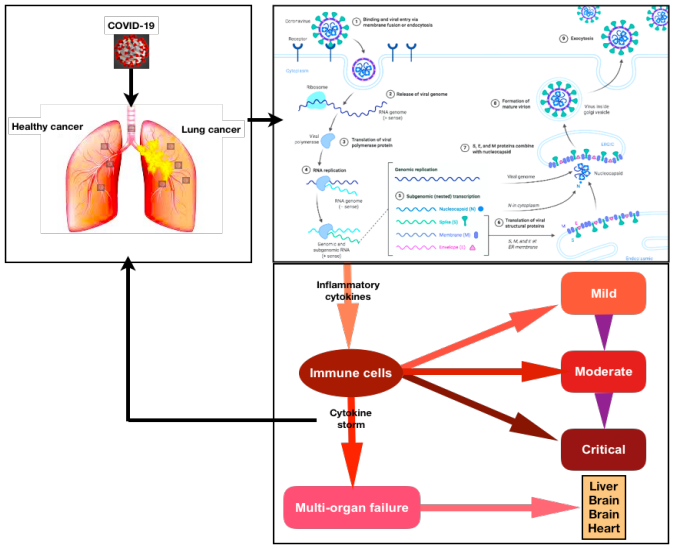

Figure 1.A summarized presentation of COVID-19 and lung cancer mediated by cyto-kines signaling.

inflammatory cytokines, which increases the likelihood that the tumour will proliferate and survive. The effects of the microenvironment on the tumour can be better understood by looking at a well-organised list of the genes whose expression varies in response to infection. Although there are many different signalling routes, during COVID-19 infection and lung cancer, cytokine signalling networks interact with other cell signalling networks. Numerous viral entrance receptors are found in lung cells. By influencing the sensitive defence mechanisms that lead to cytokine storming and alterations in cellular metabolism, certain COVID-19 infection proteins can modify the lung TME. Using publicly available databases, we have examined gene expression profiling for COVID-19 infection and lung cancer. In order to investigate the networks of genes with fluctuating expression and the pathways that connect them, we used the previously published computational technique work in this study[12, 21-24].

2. Lung cancer

One of the main causes of death globally, cancer caused more than 14.1 million new cases of the disease in 2012, or 14.6% of all deaths. Breast, prostate, lung, and colorectal cancers are the most prevalent types of cancer. One of the most common diseases, pulmonary carcinoma, often known as lung cancer, is characterised by unchecked cell proliferation in the lung tissues. Lung cancer, which causes around 22% of all cancer-related deaths worldwide, is primarily caused by tobacco use. Globally, 2.2 million individuals will be diagnosed with lung cancer in 2020, and 1.8 million will die from the illness, according to GLOBOCAN. According to Cancer Statistics, 2020: Report from National Cancer Registry Program, the estimated incidence of cancer patients in India for 2020 was 679,421 (94.1 per 100,000) for men and 712,758 (103.6 per 100,000) for women. When normal cell division and development processes are interfered with, abnormal, uncontrollable growth results, which leads to lung cancer. A tumour is formed when the cells grow into a mass. It has been demonstrated that pulmonary carcinoma, one of the most aggressive cancers, has a very high potential for tumour metastases. Lung epithelial cell lines are responsible for producing the carcinomas in most primary lung cancer types. Lung cancer is one of the most common and fatal illnesses. The transformation of normal cells into tumour cells causes lung cancer, a multi-stage process that frequently progresses from a precancerous lesion to a malignant tumour. Lung cells develop and divide abnormally in a variety of diseases known as lung cancer[25-28].

2.1. Tumor progression and microenvironment: In addition to specialized cellular mechanisms that allow host defense against infections, cytokines are molecules that control a range of normal processes that result in cellular proliferation, differentiation, and survival. Cytokines, which are released in reaction to infection, inflammation, or immune response, can also prevent the development and spread of cancer. The JAK-STAT (signal transducer and activator of transcription) pathway is the main intracellular signaling mechanism that cytokines activate. Clinical research in people and knockout mice has shown that JAK-STAT proteins maintain immunological tolerance, control the immune system, and monitor the growth of tumors. Unquestionably harmful, aberrant stimulation of the JAK-STAT pathways is the cause of several malignant malignancies. These findings all suggest that JAK-STAT proteins could be used as targets for the therapy of cancer in human[29-31].

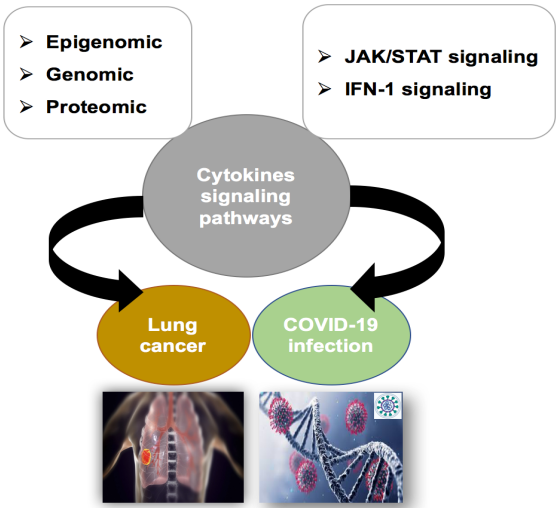

Figure 2. Approach for the study of cytokine signaling between COVID-19 and lung cancer.

2.2. Inflammatory cytokines as trivial part in the growth of lung cancer: The molecular mechanisms that lead to the formation of cancer and the signaling pathways that facilitate its proliferation have received a great deal of interest in biomedical research during the last 20 years. Cancer develops as a result of intricate interactions between tumor cells and their environment. Low-molecular-weight proteins and peptides called cytokines facilitate cell-to-cell communication. Cytokines are produced by fibroblasts and endothelial cells to control immune cell activation, cell death, migration, survival, and differentiation[15, 32-33]. Depending on the degree of cytokine receptor expression and the degree of stimulation of the surrounding cells, cytokines during chronic inflammation can cause cell transformation and cancer (Figures 1 and 2).

3. COVID-19 infection: More than 3.8 million people have died worldwide with COVID-19, a highly infectious viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has changed the

world's demographics since the 1918 influenza pandemic. When the first instances of SARS-CoV-2, a mostly respiratory virus, were discovered in Wuhan, Hubei Province, China, in late December 2019, the virus swiftly spread around the world. Consequently, on March 11, 2020, the World Health Organization (WHO) designated it a global pandemic. COVID-19 has ravaged numerous countries and overtaxed numerous healthcare systems since it was deemed a global epidemic. Five SARS-CoV-2 variants have been discovered since the pandemic began, according to a recent epidemiological update from the World Health Organization: alphacoronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. Genomic research indicates that rodents and bats are the most likely source of the genes for both beta and alpha coronaviruses[34-36]. On the other hand, the genes for the gamma and delta coronaviruses seem to have originated in birds.

3.1. Epidemiology of COVID-19 infection: The World Health Organization (WHO) considers the rise in viral infections to be a major threat to public health. Global health has been significantly impacted by several viral epidemics over the last 20 years, including the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The virus that causes COVID-19, SARS-CoV-2, has spread to 223 nations since the WHO designated it a global pandemic. More than 281 million illnesses and 5.4 million deaths have been documented worldwide. People of all ages are at risk from this virus, which can cause severe illness. Individuals with basic symptoms (obesity, cardiovascular illness, chronic kidney disease, diabetes, chronic lung disease, smoking, and cancer) and those over 60 are more likely to have a serious COVID-19 infection[19, 20, 37].

3.2. Pathophysiology of COVID-19 infection: A general description of the coronavirus genome and viral structure is essential for addressing the pathophysiology of SARS-CoV-2. CoVs are nucleocapsid-containing positive-stranded RNA viruses. Among RNA viruses, it has the most genomic structure due to its 5′-cap structure and 3′-poly-A tail. Polyprotein 1a/1ab (pp1a/pp1b) production begins to start viral replication as soon as the viral RNA reaches the host. When the viral RNA enters the host, the replication process begins, resulting in the creation of polyprotein 1a/1ab (pp1a/pp1ab). The replication-transcription complex (RCT), which is organized in double-membrane vesicles, uses synthesized subgenomic RNAs (sgRNAs) to perform transcription. The so-called open reading frames (ORFs), which act as templates for the synthesis of subgenomic mRNAs, are separated from one another by transcription regulatory elements, which stop transcription. An aberrant CoVs genome may contain at least six ORFs. On the outermost layer of the virion, the crown-shaped surface spike glycoprotein is broken down into two subunits: the carboxyl (C)-terminal S2 subunit, which has a fusion peptide, a transmembrane domain, and a cytoplasmic domain that help fuse the virus and cell membranes, and the amino (N)-terminal S1 subunit, which helps integrate the virus into the host cell. The S1 subunit's receptor-binding domain (RBD) and N-terminal domain (NTD) facilitate viral entry into the host cell and are viable targets for neutralization in response to vaccines (Figure 1) [11,13,14,18,38].

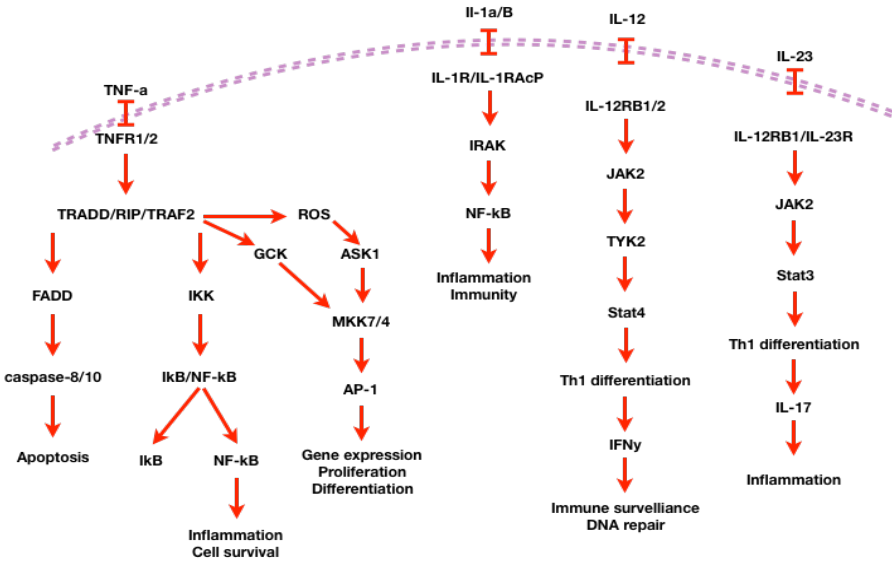

Figure 3. Summarized cytokine signaling. Major cytokine signaling pathways which act as potentially common signaling pathways in COVID-19 and most of the cancers including lung cancer.

4. Major genes and pathways directly associated with cytokine signaling

The immune system's protective response to infectious disease is inflammation, which requires coordination of immune cell activity among many cell types. While chronic inflammation can cause tissue death in autoimmune diseases, neurological disorders, and cardiovascular diseases, acute inflammation is an essential component of the immune response. Secreted cytokine proteins facilitate communication between immune cells and aid in the coordination of the inflammatory response. The mediator protein that cells release when

inflammation occurs is called a cytokine. A single cell type releases cytokines, which are a class of proteins that regulate an organism's response to infection or inflammation. By binding to particular receptors, cytokines affect the activity of other cells. Cytokines carry signals from one cell to another in an organism. Their interactions with receptors, which either inhibit or stimulate the activity of particular genes within the cell, result in secondary signals. The majority of cytokines are specific to the cells that created them, in contrast to endo-crine hormones, which have a broad variety of effects. Cytokines function as intercellular mediators and employ many signalling routes to induce the proliferation, differentiation, development, or death of target cells[2-4, 39-42] (Figure 3).

During SARS-COV-2 infection, type-I interferons and signalling activation are the first reaction that triggers innate immune responses. There are two ways the virus can get inside host cells. The virus's ssRNA will be found in the cytosol by RIG-I and MDA5 if the virus enters the cell by diffusion driven by TMPRSS2. TLR3, 7, and 9 are able to detect ssRNA when a virus enters a cell by endocytosis because CTSL in the lysosome breaks down the spike proteins (PMID 33506952). TLR2, 4, and 6 can also detect the extracellular virus (PMID 33506952). Men may react differently to SARS-CoV-2 infection than women because they produce more TLR4 and have TLR7 on the X chromosome (PMID 33506952). TLR7 MYD88-dependent signalling is inhibited at different stages (red oval) by the SARS-CoV papain-like protease (PLpro) domain of nsp3. The signalling pathway is used by the transcription factors NF-kB, AP-1, and IRF3 to produce type I interferons (INF-I)[12, 14, 23, 43]. The innate immune response is triggered by INF-I's activation of the JAK/STAT pathway, which also causes interferon-stimulated genes (ISGs) including PKR and OAS. For TLR7 and STAT1 to participate in MYD88 recruitment, TREML4 is required. According to the alignment of RefSeq YP 009725299.1 and PDB 3E9S (https://alexanderpico.github.io/SARS-CoV-2_Alignments/#Nsp3_PLpro_domain), there is 100% sequence identity between SARS-CoV and SARS-CoV-2 across all 13 residues of PLpro involved in binding GRL0617 (82.9% identity across 316 amino acids), which supports the theory that GRL0617 inhibits SARS-CoV-2 PLpro. By preventing the activation of several of these similar transcription factors, the antibiotic azithromycin, which is being researched in humans as part of the COVID-19 effort, has been found to lessen inflammation. Chemicals called chemokines, or chemotactic cytokines, attach to a class of G-protein coupled seven-transmembrane receptors to regulate and guide immune cell migration and movement. This technique demonstrates how chemokines cause leukocytes to adhere and migrate, causing tissue infiltration and transcriptional activation that helps draw in more leukocytes. Therefore, inflammatory regions may see decreased leukocyte overproduction by blocking particular chemokines and receptors[32, 33,44].

4.1. Interleukin 6 (IL-6): IL-6 is an inflammatory cytokine that has both pro- and anti-inflammatory properties in humans. Hodge et al. claim that interleukin 6 induces tumour cells to multiply while inhibiting apoptosis via binding to IL-6R and gp130 receptors and activating the JAK/STAT signalling cascade. According to several studies, STAT3 activation found that IL-6 both reduced the onset of lung cancer and sped up its progression. Although it has several uses, the cytokine IL6 is essential for the start of the immune response. The elderly's persistently inflammatory environment seems to be linked to the greater levels of this cytokine in this group. IL-6 is one of the primary signals that cancer cells employ to communicate with their non-cancerous counterparts in the tumour microenvironment. In cancer patients nearing the end of their lives, IL-6 also plays a role in the formation of a premetastatic niche and metabolic changes. In individuals with severe COVID-19, IL-6 plays a significant role in the cytokine storm, which ultimately leads to the disease's death. The treatment of issues related to ageing, cancer, and severe viral infections may benefit from a better knowledge of the function of IL-6 in physiological and pathological contexts as well as the creation of innovative therapeutic manipulation techniques of the IL-6 axis[11-13, 23, 45].

4.2. Interleukin 8 (IL-8): One of the primary inflammatory cytokines, IL-8, is released by macrophages, epithelial cells, and certain smooth muscle cells in the airways. According to the study, interleukin 8 exhibits strong angiogenic and metastatic properties by interacting with the relevant CXCR1 and CXCR2 receptors. It is also necessary for the proliferation of cells. In non-small cell lung cancer, it has been shown that EGFR is activated by IL-8 to stimulate cell proliferation. IL-8 is a potential biomarker candidate for predicting the severity and prognosis of certain illnesses in COVID-19 patients. While blood IL-6 became noticeably raised in individuals with severe symptoms of COVID-19, serum IL-8 was readily recognised in those with minor symptoms. Furthermore, at various points during the trial, IL-8 levels showed a stronger correlation than IL-6 levels with the overall clinical illness assessments of the same COVID-19 participants. According to our research, IL-6 and IL-8 can be utilised as biomarkers for COVID-19 patients who are seriously unwell and to forecast their prognosis, respectively[12, 14, 38, 46].

4.3. Tumor necrosis factor Alpha (TNF-α): Alpha, a cytokine that promotes inflammation, has been shown to play two distinct functions in the emergence of cancer. TNF-α has been demonstrated to be comparatively elevated in advanced tumours and to inhibit the normal death of cancer cells. In the early stages of cancer, there

was a decrease in TNF-α levels, which promote cell death. Through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), TNF-α stimulates the formation of tumours by damaging DNA and so promoting carcinogenesis. TNF encourages the invasion and growth of cancer cells, per some research[14, 46-50].

4.4. Vesicular endothelial growth factor (VEGF): Vesicular endothelial growth factor is the main regulator of pathological angiogenesis, which includes tumour angiogenesis. Both healthy and malignant tissues are impacted by this strong angiogenic agent. It has been shown that VEGF contributes to neovascularisation when other growth factors and inflammatory cytokines are present. VEGF was also found to promote tumour invasion through lymph node metastases in primary lung cancer. The drugs used to treat COVID-19, a dangerous coronavirus condition, have recently attracted more attention. Because of their strong anti-inflammatory properties, anti-VEGF drugs have been suggested as possible treatments for "cyto-kine storm" and susceptible angiogenesis. Therapeutic approaches to treat ARDS may be used with patients. Because there is strong evidence that VEGFs contribute to inflammation and are crucial in the pathophysiology of illness, we highlighted in our research the possible role of VEGF in the cytokine storm exacerbation in COVID-19[12,22,24,38,51].

4.5. Interleukin 10 (IL-10): Tumour cells and nearly every other type of immune cell emit the powerful anti-inflammatory cytokine IL-10 in the tumour microenvironment. There are both pro- and anti-tumorigenic actions of IL-10. Inhibiting NF-kB signalling reduces the generation of pro-inflammatory cytokines and acts as an anti-tumor cytokine, according to research. Subsequent studies have demonstrated that IL-10 activates and phosphorylates STAT3 to stimulate tumour growth. It was also found that interleukin-10 was a predictive factor in patients with advanced non-small cell lung cancer when blood levels of the protein were displayed to be abnormally elevated. We know that IL-10, a pleiotropic cytokine, has strong immunosuppressive and anti-inflammatory properties. A variety of immune cells with lymphoid and myeloid origins that are engaged in both innate and adaptive immunity are now known to produce IL-10. It was once thought that T helper 2 cells produced IL-10. IL-10 reduces immuno-pathology and tissue damage during infection by preventing the immune system from reacting to pathogens and bacteria. IL-10 accomplishes this by preventing excessive T cell activation, proliferation, and antigen presentation in dendritic cells, macrophages, and activated monocytes/macrophages. Additionally, it lowers the synthesis of cytokines that promote inflammation. IL-10 interacts with the IL-10 receptor, which is mostly expressed on monocytes and macrophages, to activate the JAK1-TYK2-STAT3 pathway. The transcription of genes that reduce the inflammatory response is then regulated by STAT3. Its ability to trigger the formation of the SHIP1-STAT3 complex may be the particular mechanism by which IL-10's anti-inflammatory effects differ from those of other cytokines that activate STAT3. Additionally, IL-10's capacity to suppress the expression of pro-inflammatory cytokines depends on the inositol phosphatase SHIP1[11-14].

4.6. Transforming growth factor beta (TGF-β): The developing component of beta possesses immune-suppressive and anti-inflammatory qualities. Depending on the type of cell and the stage of carcinogenesis, TGF- has different effects on tumour cells. By inhibiting cell cycle progression and encouraging apoptosis, TGF- suppresses tumours in their early stages. However, by initiating the epithelial-mesenchymal transition (EMT), it has been discovered to promote invasion and metastasis in their later stages. Furthermore, it was found that TGF-induced Smad and non-Smad signalling pathways enhanced the ability of mice lung adenocarcinomas to disseminate. It has been hypothesised that the pathogenesis of COVID-19 and the features of the cytokine storm are caused by a dysregulated cytokine network because of the increased biological activity of the transforming growth factor (TGF-), which in certain patients causes clinical manifestations like fatigue, fever, dry cough, pneumonia, abatement, and loss of taste and olfactory senses. Understanding the pathogenesis of COVID-19 better through research will enable us to provide individualised treatment. A number of anti-TGF-drugs are potential COVID-19 therapies. This innovative strategy will contribute to lowering the prevalent COVID-19 death rate[14, 52-56].

4.7. JAK-STAT pathway: Interferons and cytokines both activate the JAK-STAT pathway. Fast and direct extracellular signal transduction into the nucleus is made possible by this pathway. Signal transducers and transcription activators (STAT) are triggered by the Janus (JAK) family of tyrosine kinases. Activated STATs proceed to dimerise, enter the nucleus, and control the production of many other gene products. Numerous internal and external stress signals affect the cellu-lar homeostatic mechanisms that regulate DNA replication, chromosomal segregation, and cell division. A network of genes and its byproducts that are designed to react to these signals makes up the p53 pathway. Mdm2 and p53, two crucial proteins, are at the heart of this process. It was found that the p53 tumour suppressor protein is bound to and inhibited by the Mdm2 oncogene. The p53 gene is mutated in 50% of human cancers; nevertheless, in tumours with wild-type p53, lowering Mdm2 activity may trigger p53 tumour suppression, providing a treatment option for cancer treatment. The generation of gastrin is suppressed by the hormone gastrin, which causes the stomach mucosa to release hydrochloric acid. Additionally, this hormone promotes the growth of gastrointestinal epithelial cells. G34 and G17 are two

physiologically active variants of gastrin peptide. The expression of the gastrin gene is elevated by a variety of routes in both pre-malignant states and malignancy. Differential processing of the polypeptide product results in the production of distinct physiologically active peptides depending on the tissue where it is expressed and the amount of expression[12,24,57-61].

One of the most prevalent malignancies, lung cancer has a high death rate. Lung cancer is primarily caused by smoking and genetic factors. Lung cancer growth and metastasis are significantly influenced by the tumour microenvironment. The significance of the production of certain inflammatory cytokines by cancer has been demonstrated by numerous research. The hypothesis that pro-inflammatory cytokines encourage the growth of lung cancer is supported by the fact that the use of non-steroidal anti-inflammatory medicines (NSAIDs) has been demonstrated to slow the course of lung cancer and increase patient satisfaction. Both pro- and anti-inflammatory actions are possible with inflammatory cytokines. Inflammatory cytokines in the tumour microenvironment can cause cancer to start, progress, and even terminate. A few key inflammatory cytokines that were overexpressed as the disease worsened and contributed to the malignancy of lung cancer were covered in this review study. By comprehending the cytokine expression profile, we may develop customised treatment according to the kind of cytokine secreted at a specific stage of lung cancer[15,62-66].

The significance of inflammation and an inflammatory environment in the development of cancer has long been known. The term "immuno-surveillance" describes the host immune system's continuous search for unwanted cells and foreign invaders that the body needs to eliminate. An advantageous reaction to tissue damage, inflammation serves to ward off undesirable organisms. Unchecked inflammation, on the other hand, can linger for a long period and cause nearby tissues to grow cancerous cells. Inflammation may raise the risk of cancer by increasing the amounts of bioactive substances including cytokines, growth hormones, and chemokines in the tumour microenvironment, as well as matrix-modifying enzymes such matrix metalloproteinases. The relationship between inflammation and cancer is demonstrated by a number of medical conditions, such as endometriosis, primary sclerosing cholangitis, chronic gastritis, chronic prostatitis, and inflammatory bowel illnesses. These problems may eventually lead to the development of one or more forms of cancer. This study looks at the role that main inflammatory cytokines play in the development of lung cancer[10,67-71].

5. Future perspectives and conclusions

Numerous people have died as a result of the widespread COVID-19 pandemic, many of them from cancer. The frequency and prevalence of SARS-CoV-2 infection are significantly influenced by the kind, stage, and therapy of cancer. There are currently no conclusive results regarding the mortality rates of COVID-19-infected cancer patients. To ascertain whether cancer is a risk factor for COVID-19 development on its own, more research is necessary. Since it is difficult to treat patients with both cancer and COVID-19 at current moment, there is a pressing need to find a medication that can do both tasks at once. Through our combined work, we have achieved a previously unheard-of understanding of the clinical significance and molecular links driving the occurrence and severity of both conditions. Antiviral cancer therapies that can prevent SARS-CoV-2 infection and lessen COVID-19 symptoms have a lot of promise because cancer biology and SARS-CoV-2 are closely related. Notwithstanding the advantages of repurposing, cancer treatments may exacerbate COVID-19's comorbidities. For example, using immune checkpoint inhibitors to treat COVID-19 has been linked to more hospitalizations and serious respiratory problems. In patients on checkpoint inhibitors, immunotherapy may increase IL-6 production and set off the cytokine storm. Notably, it has been demonstrated that administering tocilizumab, an IL-6R inhibitor, to patients reduces cytokine release while preserving their ability to receive ICI-based therapy. Several investigations have demonstrated that PD-1 and/or PD-L1 expression is also induced by IL-6/JAK/STAT signaling. Because PD-1 and PD-L1 are downregulated when IL-6/JAK/STAT signaling is targeted, the effectiveness of ICIs may be reduced. In animal models of pancreatic and hepatocellular carcinoma, PD-L1 and IL-6 targeting combined showed strong tumor-progression-inhibitory effects. By reducing systemic inflammation in the tumor microenvironment and increasing CTL infiltration and activation to combat anti-PD-1 antibody resistance in pancreatic cancer, the JAK inhibitor ruxolitinib has been demonstrated to dramatically improve the effectiveness of immune checkpoint blockade therapy. Interestingly, a recent study suggested that certain TLR agonists and antagonists might be useful in anti-PD-1 treatment. These other modulators of the innate immune system include. Given the success of combination drugs in the treatment of cancer, future research should focus on creating combination therapies to treat COVID-19 in order to reduce the negative effects of the currently used monotherapies. The non-selectivity of JAK inhibitors is another issue with COVID-19 treatment. Using JAK inhibitors typically results in a decrease in the production of several cytokines. Furthermore, JAK1 and TYK2 are downstream signaling molecules that are shared by IL-6 and IFN-I. Since IFN-I responses are not meant to be reduced because of their beneficial effects in early infection, it is crucial to carefully consider the administration of JAK inhibitors (or TYK2 inhibitors) in the context of reducing IL-6-mediated inflammatory responses. Further research on the clinical interactions between

COVID-19 and cancer will be crucial as this terrible tragedy continues to spread over the world in order to treat cancer patients more effectively during the COVID-19 pandemic. It is uncertain what biological mechanisms underlie the robust association between COVID-19 and cancer. To gain a deeper understanding of the underlying factors that contribute to the susceptibility and death of cancer patients who get COVID-19, more study is necessary. Additionally, the practical applicability of the molecular insights obtained from basic research may lead to the expansion of therapeutic methods against COVID-19.

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