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Cytokine Storms in Cancer and COVID-19

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During the COVID-19 pandemic, research on "cytokine storms" has been reinvigorated in the field of infectious disease, but it also has particular relevance to cancer research. Interleukin-6 (IL-6) has emerged as a key component of the immune response to SARS-CoV-2, such that the repurposing of anti-IL-6 therapeutics for COVID-19 is now a major line of investigation, with several ongoing clinical trials. We lay a framework for understanding the role of IL-6 in the context of cancer research and COVID-19 and suggest how lessons learned from cancer research may impact SARS-CoV-2 research and vice versa.

SARS-CoV-2 is the fifth betacoronavirus to infect humans and has led to the current COVID-19 pandemic. Over 30 million people have been infected worldwide, and mortality continues to rise to over 1 million. Cancer remains a worldwide disease, causing an estimated of 9.8 million deaths per year. "Cytokine storm" or "cytokine release syndrome" is a feature of both SARS-CoV-2 infection and cancer (Figure 1A). The term "cytokine storm" was originally used to describe the uncontrolled systemic inflammatory response in graft versus host disease. More recently, "cytokine storm" has been used widely in the field of infectious disease and beyond to describe the unchecked systemic overproduction of cytokines that precipitates a wide variety of pathologies, including non-infectious, neurodegenerative, and neoplastic diseases. The systemic hyperactivated immune status in "cytokine storm" can lead to vascular leakage, coagulopathy, organ dysfunction, transaminitis, and death.

While many cytokines are implicated in this uncontrolled systemic inflammatory response, IL-6 has emerged as a key player in its pathophysiology and signaling pathways. IL-6 signaling is reviewed extensively elsewhere (Choy et al., 2020). In summary, IL-6 accumulates via other cytokines, including IL-1β and TNF-α, prostaglandins, and toll-like receptors (Figure 1A). IL-6 signals through both classic and trans-signaling pathways, which is dependent on the patterns of expression of the IL-6 receptor (IL-6R) and gp130 on the cell surface. Regardless of whether IL-6 binds the soluble or membrane IL-6R through gp130, it activates JAK-STAT3 signaling. Subsequently, activation of the IL-6-STAT3-NF-κB pathway augments IL-6-regulated gene expression by inducing a pro-inflammatory arsenal including MCP-1 and IL-18. IL-6 is produced by multiple types of stromal cells, immune cells, and tumor cells (Figure 1A).

Over the last 10 years of cancer research, IL-6 has also revealed itself as a driver of tumorigenesis and anti-apoptosis signaling and as a key biomarker of cancer risk, diagnosis, and prognosis (Vargas and Harris, 2016). In this commentary, we review studies demonstrating the role of IL-6 in the inflammatory prodrome leading to malignant change and tumorigenesis with a focus on lung cancer. We then review examples of therapeutic approaches to block IL-6 signaling that are currently being applied to the COVID-19 pandemic. Finally, we reflect on how the current pandemic may influence cancer research and additionally how lessons learned from cancer research may impact the direction of SARS-CoV-2 research.

Inflammatory Storms in Cancer

The relationship between inflammation and cancer was first suggested by Virchow in 1863 with the observation of "lymphoreticular infiltrates," which, to him, suggested that the origin of cancer may lay in areas of chronic inflammation. The term "cytokine storm" has been applied to prodromal inflammation that, if not cleared, develops into "smoldering inflammation" that drives tumorigenesis

(Balkwill et al., 2005). There are many examples of this phenomenon, such as tobacco smoking leading to lung cancer, pancreatitis driving pancreatic cancer, viral hepatitis leading to liver cancer, and AIDS driving Kaposi's sarcoma. In these examples, a chronic inflammatory environment contributes to the neoplastic change. To understand how to interrupt this process, it is key to understand what factor or factors drive this transition and how this might be inhibited. Many studies point to IL-6 as a main mediator responsible for malignant change. The role of IL-6 in driving malignancy has been extensively investigated in lung cancer; thus the following section will focus on this cancer subtype to illustrate the central role of IL-6 in cancer risk tumorigenesis and prognosis.

In lung cancer, IL-6 acts directly on lung epithelial cells via the NF-κB signaling pathway under conditions of inflammation and carcinogen exposure, such as tobacco smoking. Tobacco smoking accounts for about 87% of lung cancer cases, which is known to induce *KRAS* mutations and in turn induce expression of IL-6 in lung epithelium (Hecht, 2002). IL-6 in turn promotes lung cancer proliferation and migration through STAT3 signaling (Yeh et al., 2006). An additional source of IL-6 in lung cancer is exhausted tumor-associated CD8+ T lymphocytes (Mondal et al., 2013). Particularly in squamous cell and small-cell carcinoma, elevated levels of circulating IL-6 in ever smokers predicts lung cancer risk more than 5 years before diagnosis in a prospective cohort study. In addition to
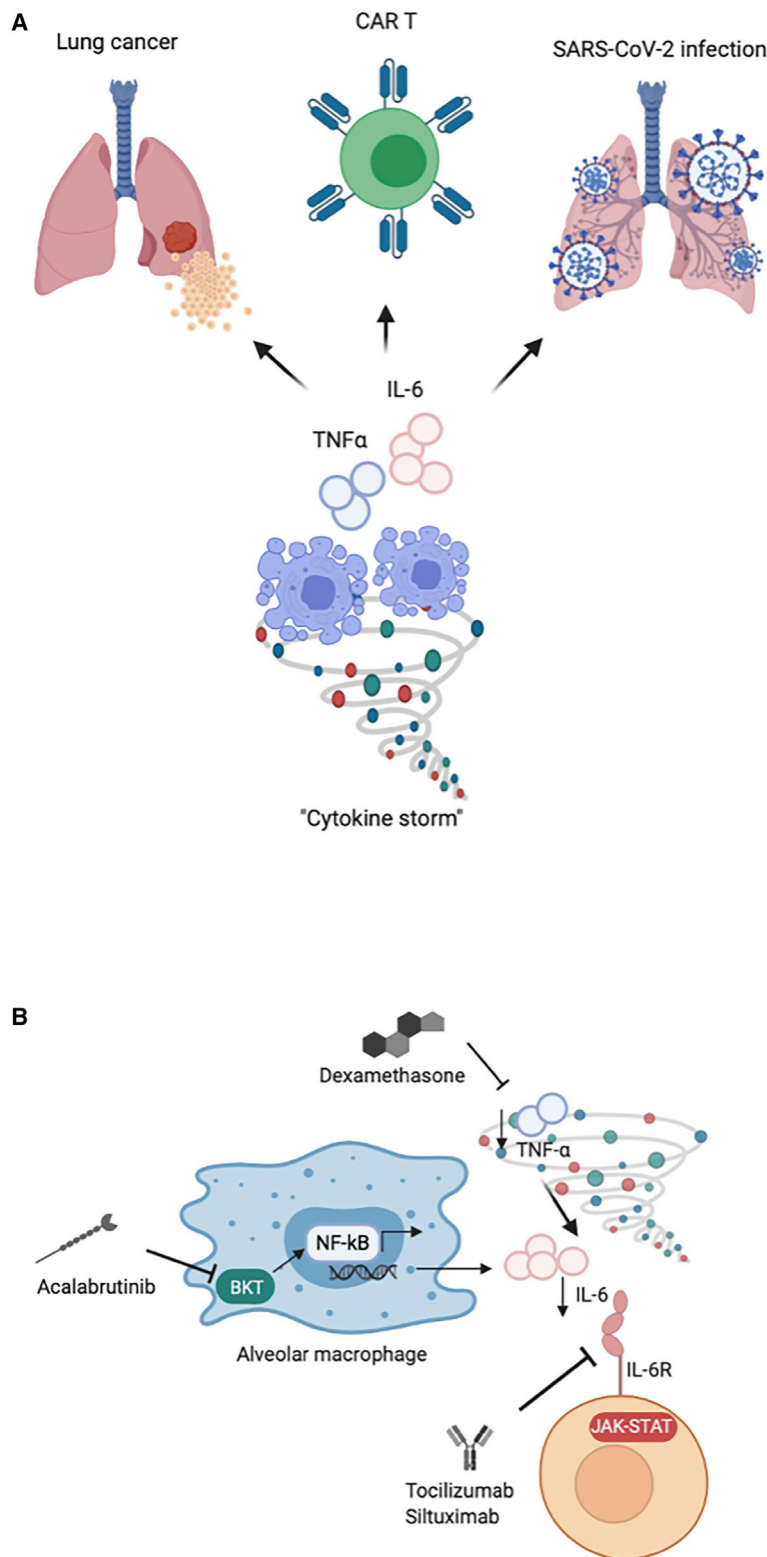
A

Lung cancer

CAR T

SARS-CoV-2 infection

IL-6

TNFα

"Cytokine storm"

B

Dexamethasone

TNF-α

Acalabrutinib

BKT

NF-kB

IL-6

Alveolar macrophage

IL-6R

JAK-STAT

Tocilizumab
Siltuximab

Figure 1. "Cytokine Storms" in Lung Cancer Tumorigenesis, CAR T Therapy, and SARS-CoV-2 Infection and Repurposed Anti-IL-6 Therapeutics for COVID-19
(A) IL-6 plays a key role in the detrimental systemic hyperactivated immune status characteristic of "cytokine storms." IL-6 accumulates via other cytokines, including TNF-α. In lung cancer, it is produced by lung epithelial cells and exhausted tumor-associated CD8+ T lymphocytes. IL-6 acts on lung epithelial

cancer risk, increasing circulating levels of IL-6 are a biomarker of poor survival among lung cancer patients (Vargas and Harris, 2016).

Beyond its role in tumorigenesis, "cytokine storm" is a toxic side effect of chimeric antigen receptor (CAR) T cell therapy used for chemorefractory hematological malignancies and some solid tumors. Again IL-6 has emerged as a main driver of CAR T-induced "cytokine storm" (Fraietta et al., 2018). Interestingly, while cell-autonomous IL-6 appears beneficial, exogenous IL-6 from monocytes and macrophages induces "cytokine storm" in response to CAR T therapy (Figure 1A). These findings point to IL-6-STAT3 pathway as a key determinant of CAR T therapy success.

IL-6 in COVID-19
The relevance of this research became apparent early in the COVID-19 pandemic as elevated levels of IL-6 were observed to be associated with disease severity and to contribute to complications such as acute respiratory distress syndrome (ARDS) (Figure 1A). IL-6 is also correlated with increased viral load, and elevated levels are found in severe disease (Del Valle et al., 2020). Mechanistically, SARS-CoV-2 uses angiotensin converting enzyme-related carboxypeptidase 2 (ACE2) to gain entry to cells. High expression of ACE2 is found in alveolar type II pneumocytes, monocytes, and macrophages. An *in vitro* model of 2D lung organoids borrowed from the field of lung cancer research suggests that IL-6 is produced by alveolar type II pneumocytes early on in infection but is later produced by macrophages contributing to

cells in inflammatory environments such as tobacco smoking. IL-6 is also a driver of CAR T-induced "cytokine storm" as a toxic therapy side effect and is associated with disease severity in COVID-19, where it is produced by monocyte-derived and recruited macrophages. In all of these settings, IL-6 is key to disease pathogenesis and a hallmark of poor prognosis.
(B) BKT inhibition (Acalabrutinib) inhibits NF-κB signaling and results in decreased IL-6 production. Corticosteroids (Dexamethasone) inhibit TNF-α-mediated IL-6 mRNA expression and protein secretion by decreasing IL-6 mRNA stability. IL-6R monoclonal antibodies (Tocilizumab, Siltuximab) dampen both the classic and the trans-signaling IL-6 pathways to suppress IL-6-JAK-STAT signaling. All of these approaches are currently under investigation in clinical trials to treat COVID-19. Figures were created using biorender.com.

severe disease phenotypes (Huang et al., 2020). Another study supports this hypothesis by showing that increased IL-6 is a shift from alveolar resident macrophages to IL-6-producing monocyte-derived and recruited macrophages, which are found in bronchoalveolar-lavage samples from patients with severe disease (Bost et al., 2020). Immune dysregulation driven by IL-6 is a major feature of SARS-CoV-2 infection characterized by overproduction of pro-inflammatory cytokines downstream of IL-6 by monocytes and also by lymphocytic dysregulation with CD4 lymphopenia (Giamarellos-Bourboulis et al., 2020).

"Quelling the Storm": Therapeutic Avenues Dampening IL-6

Due to the role of IL-6 in a number of malignancies and rheumatological diseases, therapies that dampen its action have been a major focus of drug development (Choy et al., 2020). During the COVID-19 pandemic, an increasing number of these repurposed drugs are undergoing clinical trials in an effort to find common mechanisms that may also suppress SARS-CoV-2 and provide a shorter timeline to an approved therapy (Figure 1B).

IL-6 Inhibitors

Tocilizumab (Actemra, Roche), a monoclonal antibody against IL-6R, suppresses both the classic and the trans-signaling pathways and is approved for the treatment of rheumatoid arthritis as well as those receiving CAR T cell therapy with "cytokine storm" as a toxic side effect. A retrospective study compared outcomes to patients that did not receive the drug and found reduced mortality in those who received tocilizumab (Biran et al., 2020) (Figure 1B). Interestingly, the drug was most effective in patients with a higher C-reactive protein (CRP) level, which is a marker for a hyperinflammatory state and known to be induced by IL-6. However, a phase III randomized controlled trial, COVACTA (NCT04320615), found no difference in mortality between patients who were treated with tocilizumab compared to controls. These studies may not be comparable, due to different dose regimes and variable patient inclusion criteria; notably, the randomized control trial did not select patients based on inflammatory status, which may be relevant if IL-6 blockade is most effective in the patient

group with higher CRP, as the previous study found. A further trial, EMPACTA (NCT04372186), a double-blind, placebo-controlled phase III trial, found that patients receiving tocilizumab and standard of care were 44% less likely to progress to severe disease requiring mechanical ventilation or causing death, compared to patients receiving placebo with standard of care. At this point in time, only preliminary findings have been released, and further details on inflammatory makers are not available. These studies raise the question of which COVID-19 patients are the most suitable candidates for immunosuppression treatment and which markers are important when assessing inflammatory status.

An IL-6R chimeric mouse-human monoclonal antibody, Siltuximab, is currently the most thoroughly studied clinical agent targeting IL-6 in cancer. In preclinical models, Siltuximab demonstrated antitumor efficacy in several solid tumor subtypes and decreased levels of activated STAT3 and MAPK. However, its efficacy in solid tumor clinical trials is limited, perhaps reflecting the need for patient selection and biomarkers that predict response. In terms of COVID-19, Siltuximab has been evaluated in an observational case-control study involving 25 patients, which found that the majority of patients had improved disease as determined by a decrease in IL-6 and CRP up to 1 week after receiving treatment (Figure 1B). Several randomized control trials are currently underway to further assess the efficacy of Siltuximab for COVID-19 (NCT04486521, NCT04330638, NCT04329650).

BTK Inhibitors

Bruton tyrosine kinase (BTK) inhibitors such as acalabrutinib have previously been used to treat specific B cell malignancies. BTK activation is mediated by toll-like receptors that recognize viral genomes and induce NF-kB signaling which results in cytokine and chemokine production, including IL-6. The antitumor effect of BTK inhibitors is thought to be mediated by decreasing the proliferation and survival of malignant B cells. Studies showing that BTK inhibition in lymphoma resulted in the side effect of aspergillosis infection, which is normally controlled by monocytes, macrophages, and neutrophils, raised the possibility that BTK inhibitors regulate the inflammatory response

of these cell types that are predominant in COVID-19 (Figure 1B). Using these principles, a small observational study was conducted with 19 patients with severe COVID-19 requiring oxygen supplementation, who were administered a selective BTK inhibitor, acalabrutinib (Roschewski et al., 2020). Improved oxygenation of the lung and a decrease in biomarkers of inflammation, including CRP and IL-6, were observed in most patients. In vitro studies revealed that BTK activation was associated with elevated levels of IL-6 in peripheral blood monocytes from patients with severe COVID-19 compared with healthy volunteers. The authors hypothesize that BTK inhibition targets pathological monocyte and macrophage activation to decrease the "cytokine storm," leading to improved outcomes. Further studies, including an international prospective clinical trial and a multisite natural history laboratory study (NCT04394884), are underway to better elucidate the role of BTK activation in COVID-19 and to determine whether BTK inhibitors result in reduced morbidity and mortality in patients with COVID-19.

Corticosteroids

Corticosteroids have long been used as part of a regime with cytotoxic agents for hematological malignancies including acute lymphoblastic leukemia, non-Hodgkin's lymphoma, and multiple myeloma. Although their anticancer mechanism remains unclear, glucocorticoids inhibit lymphoid development. The UK RECOVERY trial (Horby et al., 2020) was the first to investigate the use of dexamethasone for severe COVID-19 and found a reduced mortality risk of 20% for patients on oxygen and 35% mortality in patients requiring mechanical ventilation (Figure 1B). As steroids are readily available and inexpensive, this presents a promising approach to combat the pandemic on a global scale. Mechanistically, corticosteroids inhibit IL-6 production, and immediate decreased IL-6 levels were found in patients receiving treatment in the UK RECOVERY trial, while no effect on T lymphocyte count was observed compared with controls. Dexamethasone inhibits TNF-α-mediated IL-6 mRNA expression and protein secretion by decreasing IL-6 mRNA stability. In June 2020, dexamethasone became approved in the UK to treat COVID-19 patients based on results from the

RECOVERY trial (Horby et al., 2020). A recent meta-analysis included seven randomized controlled trials including this study, two additional trials of dexamethasone, three trials of hydrocortisone, and one study of methylprednisolone. Overall, the meta-analysis of approximately 1,700 patients shows reduced mortality in patients receiving corticosteroids within 28 days compared to standard care or placebo (WHO REACT Working Group et al., 2020). Recent approaches are evaluating co-administration of an antiviral agent with corticosteroids, as this regime may benefit patients who are not yet on mechanical ventilation but are brewing a "cytokine storm." Thus, reduction of viral load in addition to suppression of inflammation could be advantageous.

Looking to the Future: COVID-19 and Cancer

The role of IL-6 in cancer biology and anticancer treatments as well as emerging knowledge about the role of IL-6 in COVID-19 has produced a beneficial crosstalk between these two areas of research. For instance, COVID-19 research has benefitted from the adoption of lung cancer in vitro models (Huang et al., 2020), as previously mentioned. Additionally, an understanding of monocyte- and macrophage-mediated IL-6 release as part of the "cytokine storm" has played a role in a greater understanding of CAR T therapy response, tumor progression, and COVID-19.

Shortly after the COVID-19 pandemic began, a plethora of research on the mechanisms by which SARS-CoV-2 attacks the host emerged, and IL-6 was identified as a major driver of disease severity. Given the key role of IL-6 in both COVID-19 and cancer, research on the effects of COVID-19 on cancer patients will be key to understanding if it plays a synergistic role in tumor progression. For instance, if a cancer patient were to become infected with SARS-CoV-2, would the tumor cells be susceptible to a surge of IL-6, which is known to be associated with malignant progression, and result in worse outcomes? Should cancer patients therefore be treated with anti-IL-6 therapeutics, as blunting IL-6 production may be advantageous both to cancer treatment and in attenuating "cytokine storm" from COVID-19? Under the compassionate use protocol, the National

Cancer Institute, along with its clinical trial networks, is making tocilizumab available to patients with lung cancer, who are believed to face an elevated mortality from complications of COVID-19. Data collected from this intervention include blood biomarkers and, although on a small scale and outside the setting of a trial, may lead to a trial in the future. A phase II clinical trial (NCT04370834) is underway to evaluate the use of tocilizumab in patients with COVID-19 and hematopoietic and lymphoid cell malignancies or solid organ malignancies.

Additionally, the question remains if a surge of IL-6 as a result of COVID-19 will impact occult pre-malignant lesions and progression of tumorigenesis before the presentation of cancer. One possibility is that treatment of COVID-19 patients with anti-IL-6 therapeutics could prevent this malignant progression and that patients with known IL-6-mediated malignancy and COVID-19 could be selected for specific IL-6-targeted therapies to combat both diseases.

Despite numerous ongoing avenues being investigated in clinical trials to dampen IL-6 production, the question remains: which COVID-19 patients will most benefit from IL-6 inhibition, and what metrics should be used to assess potential to benefit? Scoring systems such as the H-score used for hemophagocytic lymphohistiocytosis, in which IL-6 inhibition is a mainstay of treatment, have been proposed, but a consensus has yet to be reached and will be important to the success of anti-IL-6 therapies for both cancer and COVID-19.

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