COVID-19–Induced Modifications in the Tumor Microenvironment: Do They Affect Cancer Reawakening and Metastatic Relapse?

Federica Francescangeli†, Maria Laura De Angelis†, Marta Baiocchi†, Rachele Rossi, Mauro Biffoni and Ann Zeuner*

Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy

Severe coronavirus disease 2019 (COVID-19) causes an uncontrolled activation of the innate immune response, resulting in acute respiratory distress syndrome and systemic inflammation. The effects of COVID-19–induced inflammation on cancer cells and their microenvironment are yet to be elucidated. Here, we formulate the hypothesis that COVID-19–associated inflammation may generate a microenvironment favorable to tumor cell proliferation and particularly to the reawakening of dormant cancer cells (DCCs). DCCs often survive treatment of primary tumors and populate premetastatic niches in the lungs and other organs, retaining the potential for metastatic outgrowth. DCCs reawakening may be promoted by several events associated to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including activation of neutrophils and monocytes/macrophages, lymphopenia and an uncontrolled production of pro-inflammatory cytokines. Among pro-inflammatory factors produced during COVID-19, neutrophil extracellular traps (NETs) released by activated neutrophils have been specifically shown to activate premetastatic cancer cells disseminated in the lungs, suggesting they may be involved in DCCs reawakening in COVID-19 patients. If confirmed by further studies, the links between COVID-19, DCCs reactivation and tumor relapse may support the use of specific anti-inflammatory and anti-metastatic therapies in patients with COVID-19 and an active or previous cancer.

Keywords: coronavirus disease 2019, cancer, dormancy, relapse, inflammation, disseminated tumor cells, tumor microenvironment

INTRODUCTION

Since the beginning of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, several studies have investigated the susceptibility and mortality of COVID-19 in cancer patients. A recent meta-analysis reported a high mortality in patients with COVID-19 and cancer (1), with a worse prognosis in case of progressive cancer, hematological cancer, recent antineoplastic therapies or surgical interventions (2–5). While the impact of cancer and anticancer therapies on COVID-19 mortality is beginning to be understood, several questions concerning the pathophysiology of SARS-
CoV-2 infection in cancer patients remain unanswered. Among these, potential long-term effects of COVID-19 on cancer outcome have not yet been explored. In this Perspective, we formulate the hypothesis that severe COVID-19 may increase the risk of subsequent cancer recurrence by inducing the reactivation of dormant cancer cells (DCCs). According to this viewpoint, the major events occurring during severe COVID-19 such as immune-mediated tissue inflammation, impairment of T-cell and natural killer (NK) cell activity, neutrophil hyperactivation and thrombocytosis may collectively generate a temporary pro-tumorigenic microenvironment favorable to DCCs reawakening. Understanding the effects of COVID-19–induced inflammation on tumor cells and their microenvironment will be crucial for a thorough evaluation of the potential long-term risks of COVID-19 in cancer patients and for the implementation of anti-inflammatory and anti-metastatic therapeutic schedules.

**ROLE OF ACE2 IN COVID-19 AND IN THE REGULATION OF INFLAMMATORY PATHWAYS**

Shortly after the beginning of the COVID-19 pandemic, ACE2 was identified as the entry receptor for SARS-CoV-2 and the serine protease TMPRSS2 as the responsible for spike (S) protein priming (17). Following entry, the S protein is cleaved by endosomal acid proteases, thereby releasing the viral genome. Subsequent steps of viral replication, assembly and release have been described in detail for SARS-CoV (18). ACE2 downregulation upon viral infection triggers a cascade of events that contribute to the catastrophic consequences of severe COVID-19 (19). Since ACE2 has been reported to exert multiple anti-tumor effects including inhibition of cancer angiogenesis and metastasis, its downregulation may per se promote tumor progression (20–22). Second, ACE2 is responsible for the conversion of angiotensin II (AngII) to angiotensin 1–7, a process that plays an important role in the control of inflammation and cardiovascular homeostasis by the renin-angiotensin system (RAS) (23). An alteration in the respective levels of AngII/Ang(1–7) can result in vasoconstrictive, proinflammatory, and prothrombotic effects, possibly contributing to the renal and cardiovascular complications observed in COVID-19 patients (24). RAS imbalance that follows SARS-CoV-2 infection has been also proposed to be responsible for an increased expression of TGF-β and pro-inflammatory cytokines that collectively promote lung fibrosis (25). Importantly, the AngII/AT1R axis acts on a variety of non-immune cells to activate nuclear factor-kB (NF-kB), a transcription factor essential for inflammatory responses (26). Moreover, AngII stimulates the release of soluble IL-6 and the subsequent activation of STAT3 (27), contributing to activate the IL-6 amplifier (Figure 1). NF-kB hyperactivation consequent to ACE2 downregulation cumulates with NF-kB activation induced by MyD88 and pattern recognition receptors activated by viral particles, thus becoming a central molecular event in coronavirus clinical picture (28). NF-kB is the most important molecule linking inflammation to cancer. NF-kB activation in cancer cells promotes proliferation, chemoresistance, epithelial-to-mesenchymal transition, stemness and invasion, while in the tumor microenvironment (TME) it stimulates angiogenesis and immune suppression, collectively supporting the metastatic process (29).

**IL-6 AND IL-1 SIGNALING IN COVID-19 AND CANCER**

COVID-19 patients admitted to intensive care units usually develop acute respiratory distress and cytokine release syndrome (CRS), a life-threatening toxicity that may lead to sustained fever, edema, neurologic symptoms, organ failure and shock (26). Cytokines found to be elevated in the plasma of patients with severe COVID-19 include interleukin-1β (IL-1β), IL-6, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating

**INFLAMMATION, METASTATIC REAWAKENING, AND CANCER RECURRENCE**

Cancer recurrence can occur after the apparently successful treatment of solid tumors, due to the presence of residual neoplastic cells in the primary tumor area or at metastatic sites. Metastatic recurrence is responsible for over 90% of cancer deaths and depends on the ability of tumor cells to migrate, seed other organs and restart to proliferate, often after an asymptomatic period named metastatic dormancy (6). During this period, pre-metastatic cells implement an array of strategies to ensure their survival and escape from immune surveillance (7). Among such strategies, adopting a non-proliferative state allows DCCs to persist for long time at metastatic sites, giving rise to tumor recurrence years or even decades after diagnosis. The events responsible for DCCs reactivation are only partly understood. Although it cannot be excluded that cell-intrinsic signals such as additional oncogenic mutations may cause DCCs reawakening, several studies have linked metastatic reactivation to microenvironmental cues such as inflammatory or immune-mediated signals (8). Metastatic reawakening has been reported to be triggered by disruption of tissue homeostasis that usually occurs during acute or chronic inflammation (8, 9). Inflammation has been linked to metastatic recurrence in a variety of conditions including obesity (10) or surgical removal of primary tumors (11). Also pathogen-induced infection has been reported to promote the migration of cancer cells to metastatic sites (12) and the reactivation of dormant metastatic cells (13–15). In addition to metastatic reawakening, acute infection by respiratory viruses has been shown to induce an exhaustion of CD8+ T cells that may contribute to release pre-metastatic cells from immune-mediated control (16). Altogether, these evidences indicate that inflammation plays an important role in dictating cancer recurrence and suggest that a defined pro-inflammatory event such as pathogen-induced inflammation seems sufficient to promote DCCs reawakening and metastasis (13–15).
A mechanistic insight between IL-6 and DCCs by inducing the stabilization of programmed death-ligand 1 and resistance to therapies reactivation is still missing, but elevated levels of IL-6 have been correlated with increased rates of tumor relapse in breast cancer and head and neck cancer (49, 50) while inhibition of IL-6/STAT3 signaling reduced cancer recurrence in preclinical models of breast, head and neck and hepatocellular carcinoma (51–54). IL-6 signaling is characterized by an extreme complexity, which derives at least in part by the promiscuous utilization of signaling components by multiple family members (55). In addition to its pro-tumorigenic effects, IL-6 has also been shown to exert anti-tumor effects by increasing T cell trafficking and adhesiveness to the tumor endothelium (56). Altogether, IL-6 may play multiple roles in patients with cancer and COVID-19, which will need to be addressed by future studies. Besides IL-6, also IL-1β has been reported to be elevated in COVID-19 patients as compared to controls (30). High doses of the recombinant IL-1R antagonist anakinra provided clinical improvement in COVID-19 patients (57). Similar to IL-6, also IL-1β has been reported to play a complex role in inflammation and cancer. The pro-tumorigenic role of IL-1β seems to be prevalent, as this cytokine drives chronic inflammation, recruits myeloid-derived suppressor cells (MDSCs), enhances neoangiogenesis and promotes invasion and metastasis (58). However, some anti-tumor effects of IL-1β have been reported (59). A mechanistic insight between IL-1β, inflammation and cancer was recently provided by Wellenstein and coworkers by showing that IL-1β is responsible for neutrophil expansion and neutrophilic inflammation that potentiates the metastatic progression of breast cancer (60). Future investigations will be essential to clarify whether IL-6,
IL-1β, and other pro-inflammatory cytokines produced during COVID-19 may affect tumor cells and the TME, possibly supporting the use of anti-cytokine therapies in cancer patients with COVID-19.

NEUTROPHILS AND NEUTROPHIL EXTRACELLULAR TRAPS: DOUBLE PLAYERS IN COVID-19 AND TUMOR REAWAKENING

Among cells of the innate immune system, neutrophils play a prominent role in fighting microbial infections but also in inflicting tissue damage. Furthermore, neutrophils are involved in a network of inflammatory reactions that promote all the stages of tumor initiation, progression, angiogenesis and metastasis (61, 62). Neutrophils generate reactive oxygen and nitrogen species, release proteases, arginase, ectonucleotidases, matrix metalloproteinases, prostaglandin E2, cyclooxygenases, IL-10 and TGFβ1 (62) and express Fas-ligand and PD-L1, which induce lymphocyte apoptosis and immune suppression (63, 64). Once they reach the tumor microenvironment, neutrophils may undergo transition to MDSCs that inhibit CD4+ and CD8+ T cells (66). Subsequently, the presence of NETs and of NET-specific components have been detected in the sera of COVID-19 patients, being higher in cases requiring mechanical ventilation (67). Importantly, NETs have been proposed a role for NETs in COVID-19 (65). Lately, NETs have been shown to release the brakes from DCCs leading to metastatic outgrowth (75, 76). Latent cancer cells were also shown to persist long time by evading NK-mediated immune surveillance through downregulation of cell surface innate immune receptors (77). Therefore, lymphopenia may contribute, together with inflammation-related factors, to create a microenvironment favorable to metastatic reawakening.

POTENTIAL ROLES OF IMPAIRED T-CELL RESPONSES IN COVID-19 AND DCCs REAWAKENING

Lymphopenia with drastically reduced numbers of circulating T cells (particularly striking for CD8+ T cells in patients requiring intensive care) and a functional impairment of NK cells have been consistently detected in severe COVID-19 cases (73). COVID-19–associated lymphopenia can be more severe and persistent as compared with other viral infections and seems to be more selective for T cell lineages (74). It appears to impact prevalently CD8+ T cells, although also CD4+ T cells are affected (74). It is possible that the peripheral lymphopenia observed in COVID-19 patients reflects the recruitment of lymphocytes to the inflamed lungs. However, autopsy studies and single-cell RNA sequencing of bronchoalveolar lavage fluid did not highlight an excessive lymphocytic infiltration, suggesting that pulmonary sequestration of lymphocytes is not the main cause of lymphopenia in COVID-19 patients. More likely, the causes of lymphopenia during COVID-19 are multifactorial, possibly include extensive lymphocyte death, inhibition by the inflammatory cytokine milieu and indirect effects exerted by other cell types such as dendritic cells and neutrophils (73, 74). The impact of COVID-19–associated T cell and NK cell alterations on tumor cells is still unknown and will likely depend by context-specific and tumor-specific factors. However, both CD8+ T cells and NK cells have a crucial function in immune-mediated dormancy and their depletion has been shown to release the brakes from DCCs leading to metastatic outgrowth (75, 76). Latent cancer cells were also shown to persist long time by evading NK-mediated immune surveillance through downregulation of cell surface innate immune sensors (77). Therefore, lymphopenia may contribute, together with inflammation-related factors, to create a microenvironment favorable to metastatic reawakening.

THERAPEUTIC STRATEGIES FOR COVID-19 THAT INTERFERE WITH PRO-TUMORIGENIC PATHWAYS

Hyper-inflammation crucially contributes to COVID-19 severity and patient death, and dexamethasone is the first drug shown to improve patient survival (78). Multiple anti-inflammatory agents are thus currently undergoing clinical evaluation for COVID-19, including not only corticosteroids but also biologicals that target inflammatory cytokines, such as anti-IL-6 or anti-IL-1β agents, and other immune-modulatory agents (Table 1). Drugs that
block IL-1β signaling may also inhibit the NET-IL-1β loop and decrease NETs formation (65). Additional drugs that interfere with NETs (although not specifically) are inhibitors of neutrophil elastase, recombinant DNases and colchicine (65). Trials evaluating the blockade of additional myeloid-derived inflammatory cytokines, such as TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) are also being considered and/or initiated (79). Other strategies to reduce hyperinflammation in patients include targeting common downstream mediators of cytokine signaling, such as JAK proteins (downstream of IL-6 receptor and several other cytokine receptors) (80, 81) or IRAK4 (that mediates Toll-like

| Pathway/molecular target | Potential role in COVID-19 | Drug type | Drug name | Clinical trials for COVID-19 (clinicaltrials.gov) |
|--------------------------|---------------------------|-----------|-----------|-----------------------------------------------|
| Inflammatory cells and mediators | Pro-inflammatory | corticosteroid | dexamethasone | 31 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Dexamethasone&cntry=&state=&city=&dist=&Search=Search) |
| | | | hydrocortisone | 11 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Hydrocortisone&cntry=&state=&dist=&Search=Search) |
| IL-6 signaling | Pro-inflammatory | anti-IL-6 receptor | tocilizumab | 63 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Tocilizumab&cntry=&state=&dist=&Search=Search) |
| | | | sarilumab | 16 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Sarilumab&cntry=&state=&dist=&Search=Search) |
| | | | anti-IL-6 | [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Siltuximab&cntry=&state=&dist=&Search=Search) |
| IL-1β signaling | Pro-inflammatory, NET-IL-1β loop | IL-1R antagonist | anakinra | 26 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Anakinra&cntry=&state=&dist=&Search=Search) |
| | Pro-inflammatory | Anti-IL-1β | canakinumab | 6 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Canakinumab&cntry=&state=&dist=&Search=Search) |
| NETs formation | Pro-inflammatory, immune suppression | Neutrophil elastase inhibitors | alvelestat | N/A [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Dornase&cntry=&state=&dist=&Search=Search) |
| NETs structural integrity | Pro-inflammatory, immune suppression | Recombinant DNases | lonodelestat, elafin dornase | 8 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Dornase&cntry=&state=&dist=&Search=Search) |
| IFNγ JAK-STAT signaling | Pro-inflammatory, Cytokine signaling | Anti-IFNγ JAK1/JAK2 inhibitors | emapalumab baricitinib | 14 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Baricitinib&cntry=&state=&dist=&Search=Search) |
| | | | ruxolitinib | 20 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Ruxolitinib&cntry=&state=&dist=&Search=Search) |
| | | | JAK3 inhibitor | 5 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Tofacitinib&cntry=&state=&dist=&Search=Search) |
| GM-CSF CCR2 | Pro-inflammatory, Monocyte recruitment | Anti-GM-CSF Anti-CCR2 | otilimab cenicriviroc | 4 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Acalabrutinib&cntry=&state=&dist=&Search=Search) |
| CCR5 | Monocyte and T-cell recruitment | Anti-CCR5 | lerinlimab | 4 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Acalabrutinib&cntry=&state=&dist=&Search=Search) |
| Bruton tyrosine kinase (BTK) | B-cell receptor signaling, Toll-like receptors activation | anti-BTK | acalabrutinib | 4 studies [link](https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Acalabrutinib&cntry=&state=&dist=&Search=Search) |

Clinical trials are indicated by clinicaltrials.gov identifier (NCT) number. For drugs whose clinical trials exceed three, the total number of trials available at the moment of submission is reported, with links leading to the relative trial list at clinicaltrials.gov. IL-6, interleukin-6; IL-1β, interleukin-1 beta; IL-1R, IL-1β receptor; CCR, CC-chemokine receptor; IFNγ, interferon gamma; JAK, Janus kinase; STAT, signal transducer and activator of transcription; NETs, neutrophil extracellular traps. N/A, not applicable.

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receptor (TLR) and IL-1β signaling). The Bruton’s tyrosine kinase inhibitor acalabrutinib, used for chronic lymphocytic leukemia (CLL) and involved in the inhibition of TLR7/8, has shown beneficial effects on CLL/COVID-19 patients (82) and is currently undergoing clinical trials for COVID-19. Drugs against chemokine receptors may reduce CRS in COVID-19 patients by inhibiting massive monocyte infiltration in the lungs or other organs. Accordingly, trials with anti-CCR5 (leronlimab) and anti CCR-2 (cenicriviroc) antibodies have been initiated in patients with COVID-19. Modulating the interferon response may also be useful in reducing inflammation during COVID-19. Clinical trials have been initiated testing the administration of type I interferons (IFNαβ) or type III interferon (IFNλ), which are potent activators of the antiviral response. By contrast, IFNγ production likely contributes to macrophage hyperactivation and tissue damage. Therefore, trials to evaluate IFNγ blockade with emapalumab are underway. In addition to short-term therapies aimed at reducing the deleterious consequences of COVID–19–associated hyperinflammation, long-term approaches to reduce the risks of inflammation-related metastasis may be evaluated by future clinical studies in cancer patients with COVID-19. Targeted approaches against critical receptors for metastatic niche components (such as integrin αvβ3) have been proposed as a feasible strategy to prevent DCCs reactivation (83). By contrast, long-term treatment of cancer patients with anti-inflammatory drugs should be carefully evaluated, as corticosteroids have been reported to increase breast cancer metastasis (84) while non-steroidal anti-inflammatory drugs increase the risk of venous thromboembolism (85). In all cases, strict adherence to recurrence monitoring schedules may be recommended for patients with COVID-19 and an ongoing or previous history of cancer.

**DISCUSSION**

The hypothesis that severe COVID-19 may create a microenvironment favorable to cancer recurrence stems from the authors’ observation that several factors activated during coronavirus infection have been previously implicated in tumorigenesis and metastatic relapse. Recent studies on protein–protein interactions during COVID-19 revealed that common cancer pathways were targeted by SARS-CoV-2, including those involved in cell cycle progression, metabolism and epigenetics (86). However, the interactions between SARS-CoV-2, cancer cells and the immune system are currently unknown and will need to be investigated in detail, possibly with the use of complex in vitro models that reproduce multicellular microenvironments (87). By contrast, in vivo studies to explore COVID-19 and cancer recurrence would likely be challenging, as they should employ mice with multiple genetic modifications predisposing to both COVID-19 and cancer (such as mice transgenic for hACE2 and ErbB2/Neu). In parallel to preclinical studies, in our opinion it will be crucial to investigate all the clinical effects of COVID-19 in cancer patients. While the first large studies in this field have focused on the susceptibility and mortality of COVID-19 in cancer patients (3, 88, 89), new studies are investigating the relationships between anticancer therapies/interventions, single cancer types and immunological status. Additionally, it will be important to assess the long-term effects of severe COVID-19 in patients either with an active cancer, in remission or with a previous history of cancer. Understanding the links between COVID-19 and cancer recurrence may be a challenging task. For example, patients with severe COVID-19 often present concomitant clinical conditions predisposing to cancer recurrence (such as obesity or an immune-compromised state) that may complicate the evaluation of individual risk factors. Nevertheless, a recently launched observational study (CAPTURE, COVID-19 antiviral response in a pan-tumor immune monitoring study) (90) will assess long-term SARS-CoV-2 sequelae on cancer patients including the impact on cancer outcomes, helping to reveal potential effects of COVID-19 on cancer recurrence. In case future studies will confirm a link between severe COVID-19 and tumor recurrence, this finding may be used to schedule personalized treatments and follow-up programs for patients with both conditions. For example, prolonged anti-inflammatory therapies may be evaluated for cancer patients that experienced SARS-CoV-2 infection. Also, the use of drugs with double anticancer/anti-inflammatory action such as acalabrutinib (a Bruton’s tyrosine kinase inhibitor) or leronlimab (an antibody against CCR5 with anti-metastatic activity) is currently being evaluated in the COVID-19 setting (Table 1) and in the future may find an increased use the treatment of cancer patients with COVID-19. Altogether, the observations presented in this Perspective suggest a possible link between COVID-19, inflammation and immune-mediated tumor reawakening that, if confirmed by future studies, may have important implications for the treatment and the long-term management of cancer patients.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article-supplementary material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

AZ, FF, MLD, and MBA wrote the manuscript. RR provided essential contribution in editing the manuscript. MBi provided essential expertise. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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