Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Cancer metastasis may increase COVID-19 mortality: Suitable targets required to impede cancer metastasis

Coronavirus disease 2019 (COVID-19) is a highly communicable disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This coronavirus was first detected in Wuhan, China, in late 2019, and as of July 19, 2021, this emerging infection has caused 188,655,968 infections and 4,067,517 deaths [2]. Several studies have reported that COVID-19 has severe outcomes in patients with malignant disease [3–5]. Additionally, preliminary studies have claimed that the severity of COVID-19 is linked to cancer metastasis [5–8]; thus, it represents a substantial threat to the healthcare system worldwide. It is therefore urgent to fully elucidate the factors responsible for cancer metastasis and identify suitable targets for inhibiting cancer metastasis during this COVID-19 pandemic.

Cancer treatments can weaken a patient's ability to fight disease. As a result, cancer patients are at an increased risk of serious COVID-19 disease. Several other factors could increase the risk of COVID-19 illness in cancer patients, including comorbidities, higher smoking rates, a weakened immune system, frequent health care exposure, and an older age. A recent study stated that current treatment with chemotherapy or immunotherapy among cancer patients was associated with a 2.2-fold increased risk of testing positive for COVID-19 [9]. Another study reported that cancer patients with critical COVID-19 perform worse than those without cancer [10]. COVID-19-associated inflammation has been reported to generate a microenvironment conducive to tumor cell proliferation and, in particular, the awakening of dormant cancer cells (DCCs) [6]. Therefore, cancer continues to be a risk factor for a severe outcome of COVID-19 infection [11].

Vascular endothelial growth factor (VEGF) and its receptors are involved in carcinogenesis, invasion, and tumor angiogenesis [12]. In cancer patients, the high expression of VEGF is related to metastasis and anti-VEGF treatment (bevacizumab) has clinical effects on tumor metastasis [12]. The VEGF-VEGFR1 signaling pathway has been reported to be crucial for tumor metastasis and the blocking of VEGF-VEGFR1-induced metastasis may provide a novel approach to the prevention and treatment of tumor metastasis [12]. A previous study indicated that VEGF-B promotes cancer metastasis through remodeling of the tumor microcirculation [13]. The knockdown of VEGF-B in tumors resulted in increased perivascular cell coverage and reduced lung metastasis in human melanoma [13]. In contrast, the gain-of-function of VEGF-B in tumors led to pseudo-normalized tumor vessels that were highly permeable and poorly perfused [13]. Tumors expressing high levels of VEGF-B were more metastatic, although primary tumor growth was strongly affected [13]. Similarly, VEGF-B in a VEGF-A-null tumor resulted in attenuated primary tumor growth but substantial lung metastasis [13]. Another study suggested that the VEGF-C/NRP2/GLI axis is a novel and conserved paracrine medium by which epithelial-to-mesenchymal transition (EMT) cells enhance metastasis and provide potential targets for therapeutic intervention in this heterogeneous disease [14]. An interesting study stated that the overexpression of VEGF-C in breast cancer cells potently increased intratumoral lymphangiogenesis, resulting in significantly greater metastasis to regional lymph nodes and lungs [15]. The degree of tumor lymphangiogenesis was highly correlated with the extent of metastasis in the lymph nodes and lungs [15]. One study found that the VEGF-C/Flt-4 axis improves the mobility and invasiveness of cancer cells and contributes to the promotion of cancer cell metastasis [16]. VEGF-C/Flt-4-mediated invasion and metastasis of cancer cells were found to require the upregulation of the neural cell adhesion molecule contactin-1 through the activation of the Src-p38 MAPK-C/EBP-dependent pathway [16]. Therefore, VEGF blockade could be a suitable approach for the prevention of cancer metastasis.

Transforming growth factor (TGF)-β signaling events are well known to control various processes and responses, including cell proliferation, differentiation, apoptosis, and migration [17]. In addition, TGF-β signaling promotes invasion and metastasis in later stages of cancer [17]. A previous study reported that the TGF-β system sends signals through protein kinase receptors and SMAD mediators to regulate a large number of biological processes [18]. Alterations of the TGF-β signaling pathway are implicated in human cancer [18]. Another study stated that both *in vitro* and *in vivo* experiments suggest that TGF-β can promote cancer metastasis through its effects on the tumor microenvironment, enhanced invasive properties, and inhibition of the immune cell function [19]. An interesting study indicated that all human tumors overproduce TGF-β, the autocrine and paracrine actions of which promote invasiveness and metastasis of tumor cells [20]. Consequently, TGF-β induces the epithelial-mesenchymal transition, a differentiation switch that is necessary for the transient invasiveness of carcinoma cells [20]. TGF-β1 has been reported to modulate clonogenicity *in vitro*, protect against stress-induced apoptosis and increase adhesion, spread, lung retention and metastatic growth [21]. The PI3K and MEK1 signaling pathways have been involved in the TGF-β1-mediated stimulation of metastasis [21]. Therefore, the inhibition

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of TGF-β could be a suitable approach to suppress cancer metastasis.

Matrix metalloproteinases (MMPs) are intriguing genes linked to cancer disease progression, the functional promotion of angiogenesis, invasion, metastasis, and the avoidance of immune surveillance [22]. A previous study stated that, *in vitro*, the elimination of MMP-1 reduced the invasiveness of breast cancer cells [23]. Many reports have shown that MMP-1 can promote tumor growth and metastasis by catalyzing the extracellular matrix and promoting angiogenesis [23,24]. Another study reported that MMPs are involved in tumor breakdown, neovascularization, and subsequent metastasis, while tissue inhibitors of metalloproteinases (TIMPs) negatively regulate the activity of these MMPs [25]. It has been reported that the gene expression of most MMPs is consistently increased in all tumors, while the expression of several MMPs is consistently decreased in various tumors [22]. An interesting study stated that P53 positivity was significantly correlated with the expression of MMP-1 in tumor cells, while the expression of HER2 was correlated with MMP-1 in both tumor cells and stromal cells [26]. The expression of MMP-1 in stromal cells showed a significant association with luminal A and luminal B breast cancer subtypes (both HER2 overexpressing and triple-negative) [26]. One study indicated that MMPs are involved from the early stages of the onset of cancer to the creation of a metastatic niche in a second organ [27]. Its role in cancer progression is related to its participation in the degradation of the extracellular matrix (ECM) and in the regulation and processing of adhesion and cytoskeletal proteins, growth factors, chemokines and cytokines [27]. The involvement of MMPs in cancer progression makes them an attractive target for cancer therapy [27]. An earlier study stated that the removal of MMP-19 or -20 also reduced the invasiveness of various ovarian cancer cell lines [28]. Therefore, MMP inhibition could be a suitable approach to hinder cancer metastasis.

Epiregulin (EREG) belongs to the ErbB ligand family [29]. EREG binds to the EGFR and ErbB4 receptors and stimulates the EGFR and ErbB4 homodimers as well as all possible ErbB heterodimeric complexes, with consequent activation of the downstream signaling pathways [29]. EREG is overexpressed in several human cancers and has been implicated in tumor progression and metastasis [29]. The oncogenic activation of the MEK/ERK pathway plays a central role in the regulation of the expression of EREG [29]. A previous study reported that epidermal growth factor receptors (EGFRs) were constitutively activated in metastatic lung subtypes of salivary adenoid cystic carcinoma (SACC) cells and that this activation was induced by the autocrine expression of EREG, a ligand of EGFR [30]. The autocrine expression of EREG was increased in metastatic SACC-LM cells in comparison to non-metastatic parental SACC cells [30]. Importantly, the neutralizing antibody EREG, but not normal IgG, blocked EREG-induced autocrine EGFR phosphorylation and SACC cell migration, suggesting that EREG-induced EGFR activation is essential for the induction of cell migration and invasion by SACC cells [30]. Another study stated that—in oral squamous cell carcinoma (OSCC)—EREG is essential for the NF-CAF transformation required to induce tumor cell EMT in a JAK2-STAT3 and IL-6 dependent manner [31]. EREG has been reported to be predominantly expressed in NSCLC with pleural involvement, lymphatic permeation or vascular invasion and in KRAS mutant adenocarcinomas [32]. An interesting study found that the expression of EREG in gastric cancer (GC) tissues was significantly higher than that in paired adjacent non-cancerous tissues [33]. The elevated expression of EREG protein in gastric cancer (GC) was significantly associated with the tumor, node, metastasis (TNM) stage, including the tumor size, lymph node metastasis, and distant metastasis, as well as poor overall survival [33]. One study stated that the reduction of the individual expression of EREG, COX2, MMP1 and MMP2 by short hairpin RNA interference in a subpopulation of a human breast cancer cell line that has lung metastatic capacity (LM2 cells) had little effect on orthotopic tumor cell growth in nude mice, while silencing of all four genes severely reduced growth [34]. Therefore, the attenuation of EREG will be a suitable approach to the inhibition of cancer metastasis.

Despite significant improvements in diagnostic techniques, surgical techniques, and advances in general patient care, the majority of cancer deaths are caused by metastasis [35]. One study claimed that TGFα-EGFR signaling in colon cancer cells creates a metastasis-friendly microenvironment, providing a rationale for efforts to inhibit epidermal growth factor receptor (EGFR) signaling in TGFα-positive tumors [35]. Diffuse lung metastasis has been reported in non-small cell lung cancer (NSCLC) hosting EGFR mutations [36]. A previous study reported that the number of brain metastases (BMs) in EGFR mutation-positive patients is relatively higher in comparison to wild-type EGFR patients [37]. Another study stated that the overexpression of EGFR alters tumor biology and behavior. EGFR mutations mainly occur in exons 19 and 21 and could pave the way for tumor growth and metastasis [38]. An interesting study indicated that among patients with EGFR mutant NSCLC, the presence of brain metastasis leads to a worse outcome in comparison to extracranial metastasis alone [39]. A meta-analysis suggested that EGFR mutation is an important predictor related to the improvement of overall survival (OS) in NSCLC patients with brain metastasis. It can serve as a useful index in the prognostic evaluation of NSCLC patients with brain metastasis [40]. Therefore, the application of EGFR inhibitors may be useful in the prevention of cancer metastasis.

In conclusion, COVID-19 has created a missive threat to healthcare systems around the world. Regrettably, there are currently no promising cancer treatments available because the COVID-19 pandemic has affected nearly every aspect of cancer care. Due to the limited numbers of preclinical and clinical studies, numerous unknown risk factors related to COVID-19 mortality remain to be clarified. We predict that our findings on the association between the severity of COVID-19 and cancer metastasis in this study will be enormously useful for in-depth studies in the short term. Consequently, the results of our study could help to establish an adequate treatment guide for COVID-19 cancer patients, which could save many lives.

Author contributions

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Competing interests

The authors declare no conflicts of interest in association with the present study.

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