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Review

The potential role of COVID-19 in progression, chemo-resistance, and tumor recurrence of oral squamous cell carcinoma (OSCC)

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ABSTRACT

Numerous studies have revealed that cancer patients are more likely to develop severe Coronavirus disease-2019 (COVID-19), which can cause mortality, as well as cancer progression and treatment failure. Among these patients who may be particularly vulnerable to severe COVID-19 and COVID-19-associated cancer progression are those with oral squamous cell carcinoma (OSCC). In this regard, therapeutic approaches must be developed to lower the risk of cancer development, chemo-resistance, tumor recurrence, and death in OSCC patients with COVID-19. It may be helpful to comprehend the cellular and molecular mechanisms by which the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contributes to these problems. In this line, in this review, we described the potential cellular and molecular mechanisms that SARS-CoV-2 can exert its role and based on them pharmacological targeted therapies were suggested. However, in this study, we encourage more investigations in the future to uncover other cellular and molecular mechanisms of action of SARS-CoV-2 to develop beneficial therapeutic strategies for such patients.

Introduction

A major concern in recent years has been the global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused Coronavirus disease-2019 (COVID-19) pandemic [1–3]. One of the main populations at risk for severe COVID-19 courses, death, negative effects on the prognosis and progression of cancer patients, and failure to respond to various anti-cancer chemotherapy regimens are patients with multiple cancers [4–12]. However, a small number of research, have focused on the cellular and molecular processes underlying the effects of SARS-CoV-2 on cancer development, chemo-resistance, and tumor recurrence. For instance, it is unclear how SARS-CoV-2 might contribute to the development of oral squamous cell carcinoma (OSCC) in patients. Hence, in this article, we decided to suggest some cellular and molecular mechanisms of action of SARS-CoV-2 which potentially can contribute to cancer progression, chemo-resistance, and tumor recurrence in OSCC patients.

One of the most prevalent cancers globally is OSCC, ranking fifth in frequency [13]. It can be caused or prolonged by substances that induce cancer, such as alcohol, tobacco, betel quid, or microbiota [13].

Abbreviations: OSCC, oral squamous cell carcinoma; NRP-1, Neuropilin-1; NF-κB, nuclear factor kappa B; JAK, Janus kinase; STAT, signal transducers and activators of transcription; HIF-1α, hypoxia-inducible factor-1 alpha; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; EMT, epithelial-mesenchymal transition; VEGF, vascular endothelial growth factor; ATP, adenosine triphosphate; NLRP3, NLR family pyrin domain containing 3.

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Annually, over 300,000 individuals across the world receive a diagnosis of OSCC, and nearly half of these patients succumb to the disease. Multimodality therapy is necessary for treating advanced oral cavity cancer [14]. This approach involves resection followed by postoperative radiation therapy, along with adjuvant chemotherapy containing platinum-based agents for patients who show pathologic features indicating a high risk of treatment failure [14].

It has been demonstrated that SARS-CoV-2 spike (S) protein can bind to ephrin receptor (Eph), Neuropilin-1 (NRP-1), CD147 as its receptors on host cell. SARS-CoV-2 not only can use these cells for interring to the host cells but also by stimulating their pathological downstream signaling pathways can contribute to progression of cancers and other diseases. These signaling pathways are including NLR family pyrin domain containing 3 (NLRP3) inflammasome, nuclear factor kappa B (NF-κB), janus kinase/signal transducers and activators of transcription (JAK/STAT), phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (AKT), mammalian target of rapamycin (mTOR), hypoxia-inducible factor-1 alpha (HIF-1α), *etc.* [4,6,10,15,16].

In this line, Eph (ephrin) receptors, NRP-1, and P2X7 receptor presented on OSCC cells can be targets of SARS-CoV-2 for these complications in OSCC patients.

Thus, we suggest that pharmacological targeting these receptors could be a promising potential therapeutic and prophylactic approach for cancer progression, chemo-resistance, and tumor recurrence in OSCC patients with COVID-19 (Figure 1).

Association between COVID-19 and oral squamous cell carcinoma (OSCC)

Currently, the terrible pandemic of COVID-19 is focusing the attention of the entire world. However, other conditions continue to exist, such as OSCC, which has a significant death and morbidity rate [17]. Due to the severity of the pandemic, the public's concern about catching COVID-19 may cause them to underestimate the warning signs and symptoms of dangerous illnesses and stop them from seeking health, medical, or dental care. As a result, the COVID-19 pandemic may be a contributing and exacerbating factor for the delayed diagnosis of life-threatening diseases, like OSCC, which increases morbidity and worsens prognosis [18]. So, the COVID-19 pandemic can alter the prognosis of oral cavity cancer since it delays the detection and diagnosis of the patients [19]. In the Scott study, it was discovered that 53% of patients with possibly malignant oral symptoms put off getting help and 37% visited a doctor in a time interval of more than 3 months. Since we are in the COVID-19 pandemic, these statistics can be even worse [20]. An analysis of the impact of COVID-19 on OSCC patients revealed an increase in morbidity and mortality rates [21]. Two research focused

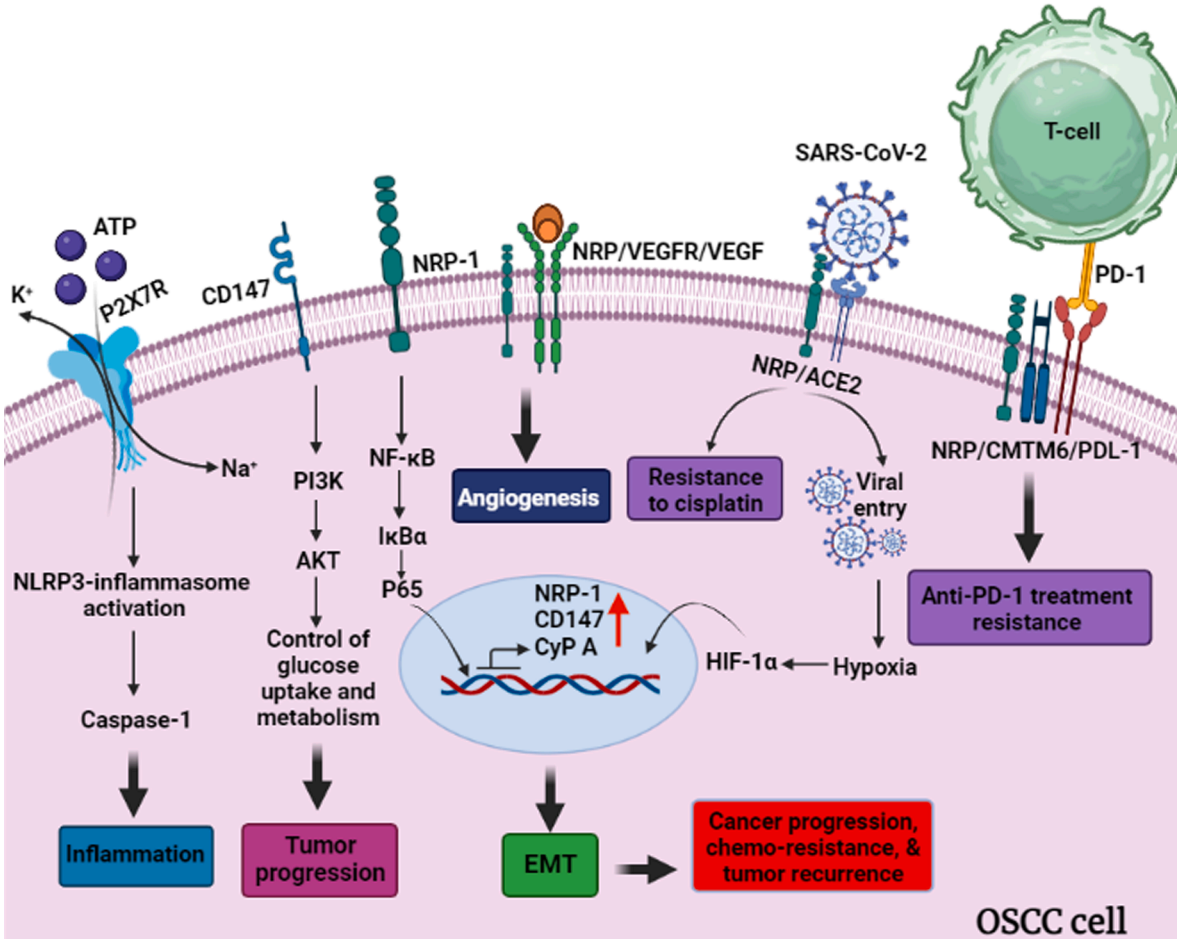

Figure 1. The illustration indicates cellular events of oral-squamous cell carcinoma and its communication with COVID-19 infection: evaluation of neuropilin (NRP) on tumor cells and its interaction with CMTM6 and PDL-1 leads to "resistance to anti-PD-1 treatment". Interaction of NRP with ACE2 causes resistance to cisplatin and facilitation of viral entry (hypoxia caused by covid-19 infection leads to NRP-1 expression). NRP facilitates angiogenesis activity of the VRGF/VEGFR axis. On the other hand, NRP-1 singly evaluates EMT in tumor cells through NF-κB/IκBα/P65. Regulation of glucose uptake and metabolism is a crucial factor in tumor progression. CD147 on the tumor cell membrane helps tumor cells to control this event through PI3K/AKT signaling pathway. P2X7R is one of the receptors that are elevated on the tumor membrane; the activity of P2X7R leads to NLRP3-inflammasome and caspase-1 activation which results in inflammation.

on the malignancy under the pressure of SARS-CoV-2 infection indicated the same, increasingly aggressive behavior on OSSC and oropharyngeal SSC respectively [22,23].

Possible link between Eph receptor stimulated by COVID-19 and OSCC

Eph receptor and COVID-19

Infections with SARS-CoV-2, SARS-CoV, and Middle East respiratory disease (MERS) have been linked to the Eph receptor and ephrin ligand, proteins in the cell signaling pathway that may serve as a different coreceptor for viral entry or to modulate signaling pathways [24]. Eph receptors and ephrin ligands have been identified as binding partners for various viruses that utilize membrane fusion and endocytosis to invade host cells. These viral infections exploit Eph and ephrin proteins to facilitate viral replication, persistence, and transmission by vectors. Notably, the nervous system can be adversely affected by viruses such as Hendra virus (HeV), Nipah virus (NiV), and Epstein-Barr virus (EBV) [24].

In the study by Mendoza R. et al. [25], Ephrin A1 expression was found to be significantly increased following SARS-CoV-2 infection. However, recent research has indicated that the ephrin ligand may function as a possible receptor for the regulation of signaling cascades during SARS-CoV-2 infection [26]. These studies demonstrate that Eph receptor tyrosine kinases and their ligands, ephrins, regulate synaptic plasticity, synaptic maturation, and dendritic spine morphogenesis [6]. Therefore, it appears that during COVID-19, SARS-CoV-2 may trigger signaling pathways that culminate in the onset or exacerbation of neurodegenerative disorders [6].

In response to Ephrin-A1, the Eph receptor is activated, and this, in turn, can activate MAPK and PI3K/AKT [27]. Numerous studies have demonstrated that reducing NF-κB and AP-1 and, consequently, inflammation-related cytokines like IL-6 and TNF-α, decreases PI3K/AKT signaling [28,29]. Ephrin-A1 and ADAM12 levels in patients with COVID-19 are higher than those in healthy individuals, according to a subsequent study by Mendoza R. et al. [25], demonstrating that ephrin-A1 and ADAM12 play a significant role in COVID-19 disease. The relevance of ephrin-A1-mediated inflammatory signaling over TNF-α-mediated inflammatory signaling in the progression of COVID-19 was established by the small subset of cases that had high TNF-α levels [4]. Therefore, it would appear that ephrin-A1 could be used as a possible therapeutic target for COVID-19 [4].

Eph receptor and OSCC

The role of Ephs/ephs signaling in a variety of developmental mechanisms, such as cellular adhesion, migration or chemo-repulsion, and the formation of tissue/cell boundaries, was first discovered [30]. The importance of Eph receptors and their ligands as crucial regulators of vasculature remodeling during embryogenesis and tumor neovascularization has recently been further shown. Therefore, in addition to their primary function, the Ephs/ephs system has been linked to a wide range of activities that are directly associated with cancer and metastasis, such as cell attachment and morphology, angiogenesis, and migration [30]. Eph receptors also mediate cell-to-cell interactions in tumor cells and the tumor microenvironment (TME), specifically the tumor stroma, and vasculature, in contrast to traditional oncogenes, which frequently function only in tumor cells. For these reasons, Eph receptors are thought to be appealing targets for drug development [30,31].

Tyrosine kinase EphA1 has recently been found to be overexpressed in head and neck malignancies, including certain oral cancers and pharyngeal, hypopharyngeal, tonsillar, and supraglottic cancers [32]. One of the most crucial aspects of solid tumors is hypoxia. Hypoxia-inducible factors (HIFs) are crucial in the adaptive cellular response to the hypoxic microenvironment of tumors [33]. The most significant component in hypoxia that activates transcriptional responses and can cause the development of a number of pro-angiogenic factors is HIF-1α [34]. TT Ma et al. discovered that HIF-1α expression was often positive in OSCC cases and significantly linked with tumor angiogenesis [35]. According to research, MMPs mediate the release of ephrinA1 from glioblastoma cells into the culture medium [36]. Through matrix modification, MMPs play a key role in cancer invasion and angiogenesis [37]. They are prominently expressed in a variety of human cancers. The most effective ones among them for starting collagen breakdown are MMP-2 and MMP-9, which can also successfully cleave ephrinA1 in glioblastoma cells [36]. According to TT Ma et al., MMP-2 up-regulation is responsible for the hypoxia-induced ephrin A1 release in OSCC angiogenesis [35]. They also provided evidence that MMP-9 might not function as a critical signaling molecule in the same mechanism [35]. According to their findings, substantial levels of MMP-2 expression and activation have been found in human pancreatic cancer tissues, and these levels show a strong correlation with tumor invasion and metastasis. These findings demonstrate the role of an MMP2-dependent signaling pathway in the hypoxia-induced regulation of angiogenesis in OSCCs via raising soluble ephrinA1 [35]. The HIF-1α/MMP-2 signaling cascade, which may function in a paracrine way to play an important role in OSCC neovascularization, mediates the release of ephrinA1 [35]. Angiogenesis is a crucial step in the development and spread of tumors [38,39]. Important members of the Eph family who play crucial roles in tumor angiogenic processes are EphrinA1 and EphA2, its main receptor [35,40]. Additional research revealed that ephrinA1/EphA2 overexpression in adenoid cystic carcinoma may be a unique therapeutic target and contribute to tumor angiogenesis [35]. Notwithstanding this, a research conducted by Wang. H et al. indicated that the exosomes secreted by OSCC cells have the ability to enhance miR-210-3p expression and diminish ephrinA3 expression in HUVECs, and boost tube formation through the PI3K/AKT signaling pathway [37]. Similarly, another investigation demonstrated that EPHA10 sustains in vivo tumor growth and lymphatic metastasis of OSCC cells. EPHA10 regulates OSCC cell migration, epithelial-mesenchymal transition (EMT), and sphere formation, and propels the expression of some EMT- and stemness-associated transcription factors [38]. Robust ephrin-B2-positive tumor cells were present in clinical specimens from patients with OSCC, and the ephrin-B2 protein level was linked with clinical stage, lymph node metastasis, and poor survival outcomes. We also observed that the ephrin-B2 protein level was raised in OSCC cell lines relative to normal human oral keratinocytes, and that its levels were correlated with the migratory and invasive potential of OSCC cell lines [39].

Taken together, we hypothesize that SARS-CoV-2 by triggering Eph receptors and ephrin ligands downstream signaling pathways can lead to OSCC progression, chemo-resistance, and tumor recurrence.

Possible link between neuropilin-1 (NRP-1) stimulated by COVID-19 and OSCC

NRP-1 can be a therapeutic target in many cancers. According to studies, the expression of this glycoprotein in the tumor specimen of people with oral cancer is much higher than in the oral cavity of normal people. Accordingly, W. Chu et al. have shown that NRP-1 can promote OSCC in different ways. For example, this group has proven that NRP-1 can induce EMT in OSCC cells through NF-κB overactivation. activation of NF-κB causes IκBα phosphorylation and p65 translocation to the nucleus which leads to EMT [41]. Also, NRP-1 can be a promoter of CSC-like properties in mesenchymal cells, which induces proliferation and chemo-resistance in OSCC [41]. In addition, resistance to cisplatin in CAL27, HN4, and HN6 cells related to OSCC is the result of increased expression of this glycoprotein [42]. According to recent studies, NRP-1 as a co-receptor for vascular endothelial growth factor (VEGF) can cause tube formation and angiogenesis in endothelial cells and proliferation,

migration, and survival in cancer cells. Y.-Y. Wu et al. have proven that the level of expression of NRP-1, like VEGF, increases in hypoxia [43]. This group found that the combination of miR-320 as an inhibitor of NRP-1 with anti-angiogenic drugs can generally reduce tumorgenesis in OSCC [43]. It is interesting to note that, in addition to directly causing tumorigenesis, NRP-1 can re-balance immunity to the detriment of tumor clearance by the expression on OSCC tumor cells. Expression of NRP-1 together with CMTM6 (as a PD-1 acetylator) on tumor cells suppresses anti-tumor immunity and disrupts anti-PD-1 treatment [44] (Fig 1.).

NRP-1 as a binding agent of furin cleaved site of S protein in SARS-CoV-2 virus together with AEC2 causes the virus to enter the cell and increases the percentage of cell infection. Cantuti-Castelvetri et al. have concluded that infection of cells by SARS-CoV-2 virus increases the expression of NRP-1 protein [45]. On the other hand, SARS-CoV-2 virus induces hypoxia and inflammation, which can cause NRP-1 over-expression (Fig 1.). For example, hypoxia can increase the expression of the NRP-1 by inducing VEGF [45]. In addition, Benedicto A et al. have concluded that the cytokine storm caused by the SARS-CoV-2 virus infection can increase the expression of NRP-1 in liver cells [46]. For example, IL-6 can increase the expression of this protein by inducing STAT3 activity. Probably, inflammation increases the expression of NRP-1 in other organs as well, which requires more investigation [46].

Taken together, we hypothesize that SARS-CoV-2 by triggering NRP-1 downstream signaling pathways can lead to OSCC progression, chemo-resistance, and tumor recurrence.

Possible link between COVID-19 hyper-activated P2X7 receptor and OSCC

Increasing extracellular adenosine triphosphate (ATP) can over-express the P2X7 receptor (P2X7R) family. P2X7R is one of the most important ones that sends calcium into the cell by consuming ATP and directs potassium ions out of the cell. It has been demonstrated that elevated levels of extracellular ATP induced by SARS-CoV-2 infection can lead to induction of P2X7 receptor hyperactivity [47–49]. Many studies have linked the increased expression of this receptor with the progression of various cancers [10,50]. Accordingly, J.-Y. Bae et al. have reported that the expression of this receptor has increased in OSCC cells, and perhaps the increase in the expression of this receptor is related to cancer progression, so the increase in the expression of P2X7R indicates the increase in tumor mass, and its decrease prevents tumor cells recurrence [50]. Remarkably, in inflammatory diseases, the inflammasome and P2X7R consistently contribute to the function. Thus, P2X7R causes the efflux of K^+ to the outside of the cell and the reduction of intracellular K^+ causes the activation of the NLRP3 inflammasome. The activation of NLRP3 inflammasome inside the cell causes the activation of caspase-1, which leads to the breakdown of pro-inflammatory cytokines (Fig. 1). This breakdown activates pro-inflammatory cytokines such as IL-1β and causes inflammation. On the other hand, IL-1β causes pyroptosis (a type of inflammation-related cell death that causes the release of inflammatory substances inside the cell to the environment). It seems that all these activities increase extracellular ATP, which causes the overactivation of P2X7R [51].

Consequently, based on our hypothesis, we propose that COVID-19′s hyperactivation of the P2X7R may not only increase the severity of COVID-19 in patients with OSCC but also facilitate cancer progression in these individuals.

Possible link between CD147 stimulated by COVID-19 and OSCC

CD147 also known as EMMPRIN belongs to the immunoglobulin superfamily in humans. By promoting the release of matrix metalloproteinases (MMPs) and cytokines, it is extensively expressed in human malignancies and plays a significant role in the development of many cancers [52]. It is greatly associated with cancer progression and different cancer cells extremely express it. Studies have demonstrated that CD147 exerts key roles in metastasis, increasing cell glycolysis, invasiveness of tumors, cell proliferation, and multiple drug resistance [53]. A study conducted about “increased CD147 expression during oral carcinogenesis” revealed that overexpression of CD147 appears extremely early in the development of oral cancer and contributes to the growth of OSCC tumors [54]. Studies suggest that CD147 is a potential pathway for SARS-CoV-2 invasion [15,55]. Hence, the viral invasion could be inhibited by medications that disrupt the interaction between the spike protein and CD147 or CD147 expression. It is also found that azithromycin has favorable effects in lowering viral loads in hospitalized patients, presumably by interfering with interactions between ligands and CD147 receptors. Additionally, Azithromycin lowers certain metalloproteinases’ expression (downstream to CD147) reduces rhinovirus multiplication and release by inducing antiviral responses in primary human bronchial epithelial cells [55]. Numerous membranous, extracellular, and intracellular companion of CD147 have been discovered, but cyclophilin A (CypA) is the best-researched and serves as both an external and intracellular companions of CD147 [56,57]. Circulating or extracellular CypA is a crucial mediator for the pathogens SARS-CoV-2, HIV-1, neisseria meningitides, plasmodium, and cytomegalovirus (CMV) to connect with CD147 and undergo endocytosis. It is effective to stop the invasion of these microbes by blocking CD147 or CypA. What is more intriguing is that CypA is a crucial intracellular companion of CD147, which is essential for T cell activation and coronavirus replication [56]. So, CyPA is thought to be a potential drug target for CoVs, and studies have shown that its inhibitory ligand, cyclosporine A (CsA), can stop some CoVs from replicating. Nevertheless, CsA’s adverse effects in clinical uses cannot be disregarded as an immunosuppressant inhibitor. As a solution to this issue Several non-immunosuppressive cyclophilin inhibitors, including alisporivir, SCY-635, and NIM811 are being created right now [58]. Compared to normal cells, tumor cells need more energy because of their greater rates of metabolism, proliferation, and migration [59]. A novel in vitro research found that the PI3K/AKT pathway was activated by the transmembrane glycoprotein CD147, which controlled glucose uptake and metabolism in OSCC cells. Inhibition of glucose metabolism caused by inhibiting CD147 in human OSCC cells led to decreased glucose uptake and lactate production in comparison to normal cells [60]. Additionally, OSCC cell migration was greatly reduced when CD147 was inhibited [60]. The survival of cancer cells is increased by the activation of protein kinase B (AKT) mediated by CD147. As a result, cancer spreads and metastasizes, tumor cells survive anoikis and making them more resistant to chemotherapy and radiation treatment. So it could be concluded that inhibiting AKT phosphorylation inhibits OSCC cell growth and causes them to undergo apoptosis [61].

For recurrent or metastatic OSCC of the head and neck, paclitaxel has been used extensively in chemotherapy as induction therapy or as a subsequent treatment [62]. A study revealed that RNA-based suppression of the CD147 gene reduces tumor cell invasion and tumorigenicity, and also enhances paclitaxel chemo-sensitivity in ovarian cancer cells [63]. Thus, this method can be examined in OSCC cells and CD147 could be a potential target to prevent chemo-resistance in OSCC patients treated with paclitaxel.

Taken together, we hypothesize that SARS-CoV-2 by triggering CD147 downstream signaling pathways can lead to OSCC progression, chemo-resistance, and tumor recurrence.

Therapeutic perspectives

The mentioned factors/receptors should be better understood in OSCC tissue to develop new anticancer treatments [64] (See Table 1). In clinical settings, it is difficult to determine whether EPH receptor inhibitors are helpful since these receptors promote and suppress tumor growth. Although pharmaceuticals have been developed that target various Eph receptors, including mall molecules, antibodies or nanobodies, peptides, and kinase inhibitors, there has been no significant

Table 1
Therapeutic perspectives against progression, chemo-resistance, and tumor recurrence of oral squamous cell carcinoma (OSCC) during SARS-CoV-2 infection.

Drug	Target	Mechanism/ Description	Ref
2,5-dimethylpyrrolyl benzoic acid	EphA4	Binds to the receptor with IC50 of 9—13 M	[66]
76D10	EphA5	Inhibit EphrinA5 binding by EphA4 binding through HT22 neuronal cells with IC50 of 3 mM	[67]
UniPR1331	EphA1-EphA8 and EphB1-EphB6	A D5-cholenoyl-amino acid derivative	[68]
NVP-BHG712	EphB4 and EphA2	HEK293 T cells inhibition with IC50 of 50 nM	[69]
GLPG1790		Inhibited MDA-MB-231 cells growth with 8 nM	[69]
Doxazosin	EphA2	Has an IC50 of 0.74 nM in MDA-MB-231 cells	[69]
IG25		Stimulates the degradation of EphA2 receptors	[70]
NB39 and Nb53	Eph 4	Novel anti-Eph 4 nanobodies	[71]
SWL	EphA2	Promotes EphA2 tyrosine phosphorylation in vitro with an IC50 of 0.31 mM	[72]
MGCD516	PDFGR, VEGFR1, EphA2, EphA3, EphA4, EphB2, EphB4, and EphB3	Targets a wide variety of kinases in sarcoma	[74]
Oxidized ATP, anti-P2X7 receptor antibodies, and AZ11645373	P2X7 receptor	Inhibited the expression of P2X7 and PYD domain-containing protein 3 (NLRP3) inflammasomes	[50]
Acriflavine (ACF), 161-Ab, 059–053, CNTO3899, 1B3, 3B3 and HAb18 (Licartin) antibodies	CD147 and MCT-4 interaction	Inhibiting the growth of several cancer types	[77]
VEGF-A, Sema3B, DLPR and 3F	NRP-1	Compete for NRP-1 binding, thereby inhibiting cancer cell proliferation and inducing apoptosis	[80]

progress in this area [65]. The IC50 values of 2,5-dimethylpyrrolyl benzoic acid for binding EphA4 are 13 and 9 M, respectively, according to Noberini et al. [66]. 76D10, a disalicylic acid-furanyl derivative, was shown to inhibit EphrinA5 binding by EphA4 binding through HT22 neuronal cells with IC50 of 3 mM by Noberini et al. [67]. UniPR1331, a D5-cholenoyl-amino acid derivative, inhibits Ephrin ligand binding to all Eph receptors (EphA1-EphA8 and EphB1-EphB6) [68]. A 50 nM IC50 for EphB4 kinase activity and EphA2 was also observed for HEK293 T cells inhibited by NVP-BHG712. NVP-BHG712 is highly affine to other Eph receptors, which has IC50 values ranging from 0.3 to 303 nM [69]. It is shown that GLPG1790 inhibits EphA2 kinase activity in a biochemical assay, while it inhibits EphA2 receptor phosphorylation in a cell study using MDA-MB-231 cells at 8 nM. EphA2 agonist doxazosin has an IC50 of 0.74 nM in MDA-MB-231 cells [64].

Further, monoclonal antibodies that target EphA2 were discovered and developed to inhibit Ephrin A1 binding in the MC38-CEA colon cancer cell line at an IC50 of 0.89 nM. In addition, monoclonal antibodies that target EphA2 include IG25, an agonist that stimulates the degradation of EphA2 receptors, and IG28, an antagonist, which inhibits binding in MC38-CEA cells at an IC50 value of 0.89 [70]. A novel nanobody and a nanobody with a low C50 value of 261 nM, NB39 and Nb53, are also novel anti-Eph 4 nanobodies [71]. The dimer peptide of SWL that Duggineni et al. developed promotes EphA2 tyrosine phosphorylation in vitro with an IC50 of 0.31 mM. In addition to its agonistic properties, SWL peptide might also inhibit pro-oncogenic signaling in EphA2 receptors, which makes it an interesting treatment option in comparison to other EphA2 antagonists [72].

In addition to targeting a wide variety of kinases in sarcoma, MGCD516 also inhibits several Eph receptors: PDFGR (IC50 of 30 nM) and VEGFR1 (IC50 of 6 nM), as well as several other Eph receptors: EphA2, EphA3, EphA4, EphB2, EphB4, and EphB3 with IC50 values of 44, 1, 76, 10, 12 and 249 nM, respectively. The inhibitor inhibits proliferation, which is possibly due to its diverse targets and inhibitory downstream effects on p-Akt. Phase 1 clinical trials have found that MGCD516 (150 mg/day) treatment of solid tumors has limited side effects, mostly gastrointestinal in nature, such as nausea, diarrhea, and weight loss [73,74]. A phase 1 trial is also being conducted with the tyrosine kinase inhibitor JI-10 and the VEGFR2 inhibitor XL647 as well as with the EphA3 receptor inhibitor KB004 (ifabotuzumab) antibody (ifabotuzumab) [73,74].

On the other hand, the P2X7 receptor needs to be targeted by drug therapies such as oxidized ATP, anti-P2X7 receptor antibodies, AZ11645373, some P2X7 receptor inhibitors, and some anti-P2X7 receptor monoclonal antibodies (mAb). A study investigating head and neck cancers found that oxidized ATP, an inhibitor of P2X7R, inhibited the expression of P2X7 and PYD domain-containing protein 3 (NLRP3) inflammasomes. NLRP3 expression was significantly decreased in both oATP and ATP-treated groups compared to ATP-only groups. P2X7R is clearly implicated in the increased activity of NLRP3 inflammatory cells in response to oATP by reducing active caspase-1 p20 [50]. The P2X7 in HEK293 cells was inhibited or sensitized by natural compounds and analogues. It was found that sub-micromolar concentrations of teniposide could inhibit human P2X7. All three cell populations responded to ATP in a similar fashion with agelasine (AGL) and garcinolic acid (GA). AGL did not affect YO-PRO-1 intracellular accumulation stimulated by ATP, while GA enhanced this process [75].

Moreover, anti-CD147 therapy combined with EGFR inhibition reduced proliferative and migratory properties of head and neck squamous cell carcinoma (HNSCC) cells [76]. Cells from colon cancer cells and melanoma cells were shown to die from necrosis-like cell death when an antibody was used to block CD147-MCT-1 interaction. A further study showed that MEM-M6/1 inhibited lactate secretion [76]. As a result of a drug screening assay, Acriflavine (ACF) was recently identified as a small molecule that inhibits CD147 and MCT-4 interaction, thereby inhibiting the growth of glioblastoma tumors [77], and 161-Ab, 059–053, CNTO3899, 1B3, 3B3, and HAb18 (Licartin) antibodies have been developed against CD147 in several cancer types [78].

VEGF-A and other growth stimulants are unable to attach to NRP-1 found on tumor cells or normal cells due to the presence of sNRP-1, which serves as a natural bait and obstructs their binding. Previously, various approaches have been employed to counteract the cancer-triggering effects of NRP-1, such as recombinant sNRP-1, class 3 semaphorins, monoclonal antibodies (mAbs), peptides, and peptidomimetics [79]. VEGF-A and Sema3B and 3F, a pair of semaphorins, appear to be in a contest for NRP-1 attachment, consequently suppressing the growth of cancerous cells and promoting programmed cell death [80]. Furthermore, a monoclonal antibody (mAb) with strong affinity towards the coagulation factors domain of NRP-1 (anti-NRP-1B) hinders the movement of human endothelial cells instigated by VEGF-A in animal specimens by obstructing the connection between NRP-1 and VEGF-A [81].

In addition to the protein inhibitor DLPR, another peptidomimetic compound with strong protein resistance is DLPR, a tripeptide produced by replacing d-amino acids with l-amino acids, which reverses the amino acid chain (amino acid retroinversion). This particular peptide engaged with NRP-1 and demonstrated anti-angiogenic properties in various animal models of cancer in vivo [82].

Conclusion and future directions

It has been proposed that individuals diagnosed with cancer, specifically OSCC patients, may be more susceptible to severe COVID-19 symptoms and a higher risk of mortality compared to the general population. Moreover, COVID-19 has the potential to exacerbate cancer progression, resistance to chemotherapy, and tumor reappearance. However, the exact mechanisms by which SARS-CoV-2 contributes to these complications remain incompletely understood. A comprehensive comprehension of the cellular and molecular mechanisms underlying SARS-CoV-2′s role in OSCC cell complications may offer novel opportunities for developing therapeutic interventions that can mitigate disease severity, cancer progression, and mortality risk. In this research, we have outlined the possible impacts of SARS-CoV-2 on OSCC progression. We have proposed that ACE2, Eph receptor, NRP-1, and CD147, which act as entry receptors for SARS-CoV-2, may trigger various intracellular signaling pathways that ultimately result in OSCC progression, chemotherapy resistance, and tumor recurrence. In addition to antiviral treatments, pharmacological targeting of these receptors and their downstream signaling pathways significantly can be beneficial for OSCC patients with COVID-19 or new generations of coronaviruses in the future. However, we encourage researchers to conduct more experimental *in-vitro* and *in-vivo* studies to examine these hypotheses and uncover other SARS-CoV-2 cellular and molecular mechanisms of actions which can play in OSCC progression.

Author contributions

A.N conceived the hypothesis and designed the study. A.N, M.B, M.L, SM.NV, H.Z, and M.N-A searched and wrote the manuscript text. M.B and H.Z created the figures. HZ, M.N-A and T.M supervised the study. All authors read and approved the final manuscript. Ali Norouzi and Mahsa Liaghat had equal contributions as first author.

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Declaration of Competing Interest

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