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LETTER TO THE EDITOR

# Ephrin (Eph) receptor and downstream signaling pathways: a promising potential targeted therapy for COVID-19 and associated cancers and diseases

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Dear Editor,

Currently, the coronavirus disease 2019 (COVID-19) pandemic has become a serious concern to the worldwide healthcare system. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for COVID-19 and the emergence of new SARS-CoV-2 variants such as Omicron with higher potency for spread and infectivity, as well as immune scape characteristics toward vaccines can encourage us to provide new therapeutic insights for this disease. Recently, in a study, we described Ephrin (Eph) receptors as a possible SARS-CoV-2 entry receptor for human host cells in the central nervous system (CNS) and the potential roles of SARS-CoV-2 spike protein in stimulating the Eph receptor downstream signaling pathway for COVID-19-associated neurodegenerative diseases [1]. In addition, studies have shown that Eph receptors express in a variety of tissues and organs such as the lung, liver, colon, small intestine, prostate, kidney, heart, etc. [2]. Thus, their cells could be potential host cells for SARS-CoV-2 to enter and/or stimulate downstream signaling pathways.

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The SARS-CoV-2 receptor-binding motif (RBM) was discovered in another study by Beaudoin. Ch et al. to mimic ephrin-A5 and ephrin-B2 that bind to the ephrin type 4a receptor (EphA4). Accordingly, docking data indicated similar affinity values between the SARS-CoV-2 RBM–EphA4, ephrin-A5–EphA4, and experimental (PDB: 4m4r) complexes of -1.41, -3.32, and -0.45 kJ/mol, respectively [3].

In addition, researchers discovered that EphA2 promotes the intracellular fusion and internalization of Epstein–Barr Virus (EBV) by interacting with its encoded proteins gH/gL and gB, and the Ephrin ligand-binding domain and Ephrin fibronectin domain are necessary for EphA2-mediated EBV infection. Based on these results, EphA2 is necessary for EBV entry into epithelial cells. Furthermore, EphA2 may act as a co-receptors for hepatitis C virus (HCV) entry and tyrosine kinase inhibitors appear to have significant antiviral properties. The Eph receptor pathway is nearly entirely responsible for Ross River virus (RRV) entry into B cells and endothelial cells, whereas the Eph receptor is not necessary for RRV entry into fibroblasts and epithelial cells [4].

Here, we discussed other possible signaling pathways of Eph receptors that could be stimulated by SARS-CoV-2 spike protein in other diseases (especially cancer progression) as potential promising targeted therapy (Fig. 1).

There are six parts to Eph receptors (Ephs): a ligand-binding domain (LBD), a cysteine-rich region (Cys), two fibronectin III repeats (FNIII), a transmembrane region (TM), a juxtamembrane region (JM), a tyrosine kinase domain (TK), and a PSD95/DLG/ZO-1 subunit. Ephrin-A stimulates activation of FYN and ERK and directly stimulates Src and RHOA through focal adhesion kinase (FAK). It can activate JAK2 by signal transducer and activator of transcription 3 (STAT3). It is known that EphA2 activates AKT in pancreatic cancer cells. Ephrin-Bs promotes endothelial-mesenchymal transition (EMT) and invasion by

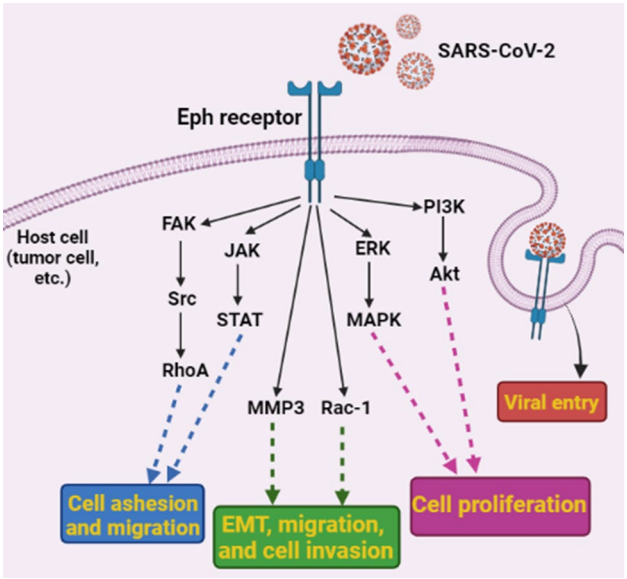


**Fig.1** Potential role of SARS-CoV-2 with using Eph receptor as entry receptor and stimulating downstream signaling pathways of Eph receptor in host cell (especially tumor cells, etc.), leading to progression of cancer or other diseases

stimulating Src, STAT3, MMP8 (matrix metalloproteinase 8), and RAC1. These molecules promote EMT and invasion by stimulating RAC1, RhoA, and CDC42 [5].

The Eph receptor is activated by ephrin-A1, and this can activate the MAPK and PI3K/AKT systems [6]. There has been much research showing that inhibition of PI3K/AKT signaling reduces NF-κB and AP-1 and, therefore, inflammation-related cytokines such as IL-6 and TNF-α [7, 8]. A further study conducted by Mendoza R. et al. [9] showed that patients with COVID-19 have ephrin-A1 and ADAM12 levels which are higher than those found in healthy people, indicating ephrin-A1/ADAM12 plays a key role in COVID-19 disease. However, a small subset of the cases showed elevated TNF-α levels, establishing the importance of ephrin-A1-mediated inflammatory signaling over TNF-α-mediated inflammatory signaling in COVID-19 disease progression. Accordingly, it seems that ephrin-A1 could be served as a potential target of therapy for COVID-19.

Studies have been demonstrated that Eph/ephrin contributes to several prevalent diseases and aging-related conditions. As a consequence of neurodegenerative diseases, such as Alzheimer's disease, the cytotoxic amyloid β (Aβ) peptides generated by presenilin/ Aβ -secretase intramembrane protease complex increase N-methyl-D-aspartate (NMDA) receptor-mediated calcium currents and inhibit synaptic transmission by binding to EphB2 and its proteosomal degradation. Additionally, the Aβ activates EphA4 forward signaling to exert its synaptotoxic effects. As a result, EphA4/ephrin-A1 can also increase the Aβ level [10].

Moreover, Eph/ephrin plays a role in angiogenesis, vascular permeability, and remodeling by regulating endothelial cells and their supporting cells, such as pericytes and smooth muscle cells. Ephrin-B2 is required for VEGF receptor endocytosis and angiogenic signaling, for example, and can be expressed as a consequence of vascular endothelial growth factor (VEGF). Cancer cells are concerned about this issue. As the most overexpressed Eph receptor in tumors, EphA2 facilitates self-renewal and inhibits differentiation of glioblastoma stem cells. Additionally, EphA2 overexpression increases the abnormal growth of cancer cells in lung tumors. Eph/ephrin are associated with heart health/disease and even heart tissue structure. In aging hearts, defective EphA2 signaling reduces the capacity of the progenitor cells to regenerate, resulting in decreased regeneration. In this way, adhesion and transmigration of monocytes and leukocytes to endothelial cells are induced by binding EphA1/EphA2/EphA4 to EphB2 via activation of EphB4, resulting in intimal inflammation and atherosclerotic plaque formation [1, 10].

Therefore, designing agents/molecules that target and modulate the Eph/ephrin system will improve/treat multiple diseases. The ephrin-binding site on Eph receptors can be approached with the help of small molecules, such as polyphenols, doxazosin, and lithocholic acid (LCA) derivatives, kinase inhibitors, peptide analogs, peptide proteins, and specific antibodies (11).

In conclusion, based on this evidence, targeting Eph receptors as a potential SARS-CoV-2 entry receptor for human host cells, as well targeting Eph receptors downstream signaling pathways could be a promising therapeutic strategy for various COVID-19-associated diseases and pathological complications.

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**Data availability** Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Declarations

**Conflict of interest** There is no conflict of interest.

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