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LETTER

CD147 inhibitors as a treatment for melanoma: Promising agents against SARS-CoV-2 infection

Dear Editor,

Many people worldwide are struggling with the coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First reported in China in December 2019, the disease soon became a pandemic. During the COVID-19 pandemic, scientists have conducted many research projects to discover optimal treatment options.[1]

The CD147 protein (known as basigin) is a transmembrane protein that has recently been suggested as a potential receptor for SARS-CoV-2. This protein interacts with several extracellular and intracellular proteins such as cyclophilins A and B and matrix metallopeptidases (MMPs).[2] Recent studies have reported that the spike protein of SARS-CoV-2 attaches to host cells via angiotensin-converting enzyme-2 (ACE-2) and CD147 receptors. CD147 is expressed in different tissues such as epithelia, as well as lymphoid and myeloid cells. Notably, CD147 plays an essential role in the pathogenesis of several diseases, including certain infectious/inflammatory conditions and cancers.[3] In fact, recent studies have suggested CD147 as a novel tumor marker in the early diagnosis of some cancers such as head and neck squamous cell carcinoma and hepatocellular carcinoma.[4] In melanoma, CD147 overexpression fulfills important roles in the proliferation, metastasis, invasiveness, and angiogenesis of malignant melanoma cells. It has been shown that melanoma cell proliferation, migration, and metastasis decrease secondary to CD147 silencing via the regulation of MMP-2, MMP-9, and vascular endothelial growth factor.[5]

Hatanaka et al. used a combination therapy of epidermal growth factor receptor and CD147 inhibitors to treat BRAF-mutated malignant melanoma.[6] On the other hand, Zhao et al. found that CD147 downregulation leads to the apoptosis of melanoma cells via the regulation of IGFBP2 expression in the phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, and suggested CD147 as a potential target for melanoma treatment.[7] Su et al. found that CD147 knockdown inhibited tumor growth by preventing glucose transport via GLUT-1 in melanoma.[8]

Due to the role of CD147 in the aforementioned diseases like melanoma, CD147 inhibition via different mechanisms offers promising treatment outcomes.[4] Therefore, because of the possible role of this protein in the pathogenesis of COVID-19, such targeted therapies could be effective therapeutic options for this infectious disease.

A study conducted by Bian et al. investigated meplazumab (a humanized IgG2 monoclonal anti-CD147 antibody) as a promising treatment for SARS-CoV-2 infection.[9]

Recent studies have corroborated the potential role of different agents such as azithromycin, atorvastatin, doxycycline, and ivermectin in the treatment of COVID-19 infection, with CD147 contributing significantly to their mechanisms of action.[2,3,10,11] For instance, doxycycline as a drug with antimalarial effects possesses in vitro anti-SARS-CoV-2 activity and causes a reduction in CD147 level in some cancers. In addition, Yates et al. offered doxycycline as an anti-COVID-19 treatment through inhibition of CD147 expression, which may be crucial for SARS-CoV-2 to bind to host cells.[11] Moreover, Ulrich et al. reported diminished expression of MMP-9 in monocytes and peripheral blood mononuclear cells besides reduced expression of MMP-3 and MMP-1 in respiratory epithelial cells treated with azithromycin. Furthermore, blockage of the CD147 receptor following azithromycin treatment leads to the inhibition of *Plasmodium falciparum* invasion of host cells; a similar mechanism is propounded for COVID-19 pathogenesis.[3] Also, Rodrigues-Diez et al. described that the pretreatment of monocytes with statins (atorvastatin and pravastatin) led to reduced MMP activity and CD147 cell surface expression. Therefore, the researchers proposed statins as potential therapeutic agents for SARS-CoV-2 infection, acting through the downregulation of CD147 in pulmonary cells.[2] Li et al. also reported ivermectin as a potential treatment for COVID-19 therapy through affecting the SARS-CoV-2 spike protein that binds to the CD147 and ACE-2 receptors.[12]

In conclusion, considering the possible role of CD147 in the pathogenesis of COVID-19, CD147 inhibitors may be considered as promising treatments for SARS-CoV-2 infection. However, the risks/benefits of anti-CD147 agents as a COVID-19 treatment option should be appraised. High-quality studies concerning this therapeutic target are warranted.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Fahimeh Abdollahimajd, Mohammad Reza Pourani, and Sayyed Mojtaba Nekooghadam contributed to the conception of the work. Mohammad Reza Pourani drafted the manuscript. Fahimeh Abdollahimajd, Hassan Vahidnezhad, and Leila Youssefian critically revised the manuscript. All authors gave final approval and agreed to

be accountable for all aspects of the work ensuring integrity and accuracy.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: the reality and challenges. *J Microbiol Immunol Infect*. 2020;53:436-443.
2. Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: could an old friend help the fight against COVID-19? *Br J Pharmacol*. 2020;177:4873-4886.
3. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. *Stem Cell Rev Rep*. 2020;1-7. https://doi.org/10.1007/s12015-020-09976-7. [Epub online ahead of print].
4. Lian C, Guo Y, Zhang J, Chen X, Peng C, . Targeting CD147 is a novel strategy for antitumor therapy. *Curr Pharm Des*. 2017;23(29):4410-4421.
5. Peng C, Chen X. CD147 is a novel chemotherapy or prevention target in melanoma. *J Investig Dermatol Symp Proc*. 2018;19(2):S91-S93.
6. Hatanaka M, Higashi Y, Kawai K, et al. CD147-targeted siRNA in A375 malignant melanoma cells induces the phosphorylation of EGFR and downregulates cdc25C and MEK phosphorylation. *Oncol Lett*. 2016;11(4):2424-2428.
7. Zhao S, Wu L, Kuang Y, et al. Downregulation of CD147 induces malignant melanoma cell apoptosis via the regulation of IGFBP2 expression. *Int J Oncol*. 2018;53(6):2397-2408.
8. Su J, Gao T, Jiang M, et al. CD147 silencing inhibits tumor growth by suppressing glucose transport in melanoma. *Oncotarget*. 2016;7(40):64778–64784.
9. Bian H, Zheng Z-H, Wei D, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. *MedRxiv*. 2020. https://doi.org/10.1101/2020.03.21.20040691. [Epub online ahead of print].
10. Drożdżal S, Rosik J, Lechowicz K, et al. FDA approved drugs with pharmacotherapeutic potential for SARS CoV-2 (COVID-19) therapy. *Drug Resist Updat*. 2020;53:100719.
11. Yates PA, Leone AM, Reichel E. A proposed randomized, double blind, placebo controlled study evaluating doxycycline for the prevention of COVID-19 infection and disease in healthcare workers with ongoing high risk exposure to COVID-19. *medRxiv*. 2020. https://doi.org/10.1101/2020.05.11.20098525. [Epub online ahead of print].
12. Li N, Zhao L, Zhan X. Quantitative proteomics reveals a broad-spectrum antiviral property of ivermectin, benefiting for COVID-19 treatment. *J Cell Physiol*. 2020. https://doi.org/10.1002/jcp.30055. [Epub online ahead of print].