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LETTER TO THE EDITOR

# Neuropilin-1 may be responsible for retinal findings in patients with COVID-19

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Dear Editor:

Coronavirus Disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has affected more than 120 million people worldwide and caused 2,672,857 deaths in 192 countries as of March 17, 2021, https://coronavirus.jhu.edu/map.html. COVID-19 can attack several body parts in different ways. Recently, Marinho et al. [1] have used non-invasive imaging optical coherence tomography to track the findings of 12 adults with COVID-19. SARS-CoV-2 infection induces hyperreflective lesions in the retinal ganglion cells of both eyes, including the papillomacular bundle. Moreover, fundus examination showed that SARS-CoV-2 triggers retinal arcade microhemorrhages and subtle cotton wool spots[1]. In this study, we would like to shed light a possible theory behind these retinal findings. Several studies reported that neuropilin-1 (NRP-1) facilitates not only the transport and cell entry into the central nervous system to develop ageusia and anosmia but also the transplacental transmission of SARS-CoV-2 [2]. Substantially, we utilized the data of single-cell analysis of retinal bipolar drop-seq [3] to examine the distribution of NRP-1 expression. Interestingly, our analysis demonstrated that NRP-1 presents in amacrine cells, Müller glia (MG), and retinal bipolar neuron cells (BC1A, BC1B, BC2, BC3A, BC3B, BC4, BC5A, BC5C, BC5D, and BC8/9) (Fig. 1). MG cells, the primary source for releasing inflammatory factors and cytokines in several diseases, play essential roles in detecting pathogen and host-derived ligands in retinal innate immunity. In addition, MG cells assist retinal ganglion cells with essential functions, such as the elimination of excess glutamate and the supply of energy sources [4]. Conedera et al. [5] identified the required steps for ophthalmic research to conduct a valid retinal degeneration/regeneration model. This study demonstrated that diode laser-induced hyperreflective lesions appear in the retina of zebrafish via activation of MG cells [5]. Many studies suggested that vascular endothelial growth factor (VEGF) interacts with NRP-1 to ensure the protection and functionality of the vascular system [6]. Clinically, cotton-wool spots are driven by the upregulation of VEGF [7]. Subsequently, this analysis supports the notion that COVID-19 triggers hyperreflective lesions at the retina by activating MG cells via NRP-1. Furthermore, SARS-CoV-2 could promote microhemorrhages and subtle cotton-wool spots through the interaction of NRP-1 and VEGF. Future studies are required to determine the exact role of NRP-1 as a critical mediator for several retinal findings linked with SARS-CoV-2 infection in humans.

**Limitations**: Lack of available animal models that recapitulate the retinal findings found in SARS-CoV-2-infected humans and reliable data to test this hypothesis.

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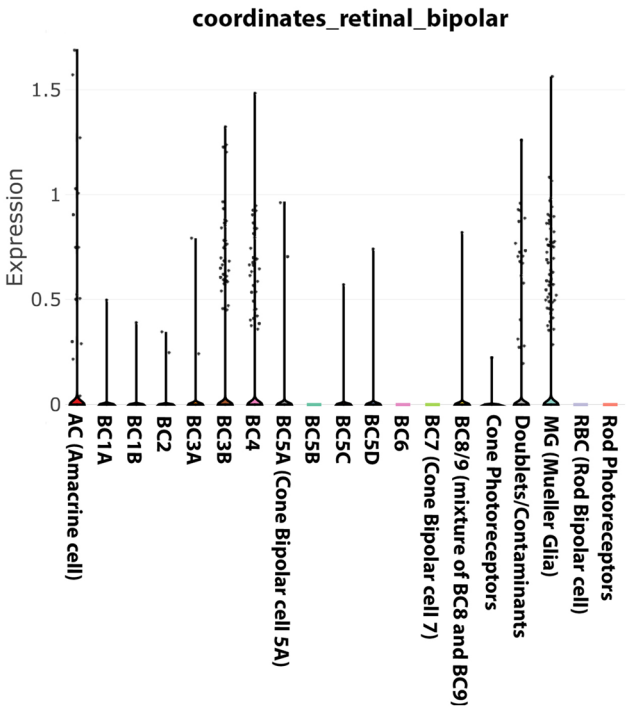


**Fig. 1** Expression of NRP-1 based on single-cell transcriptomics analysis of retina

## References


1. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. Lancet. 2020;395
2. El-Arabey AA, Abdalla M. Transplacental transmission of SARS-CoV-2 infection via NRP1. Travel Med Infect Dis. 2021;40
3. Shekhar K, Lapan SW, Whitney IE, Tran NM, Macosko EZ, Kowalczyk M, et al. Comprehensive classification of retinal bipolar neurons by single-cell transcriptomics. Cell. 2016;166
4. Kumar A, Pandey RK, Miller LJ, Singh PK, Kanwar M. Muller glia in retinal innate immunity: a perspective on their roles in endophthalmitis. Critical Rev Immunol. 2013;33
5. Conedera FM, Arendt P, Trepp C, Tschopp M, Enzmann V. Muller glia cell activation in a laser-induced retinal degeneration and regeneration model in zebrafish. J Vis Exp. 2017; :56249
6. Mayi BS, Leibowitz JA, Woods AT, Ammon KA, Liu AE, Raja A. The role of Neuropilin-1 in COVID-19. PLOS Pathogens. 2021;17
7. Park Y-G, Jee D, Kwon J. Aqueous humor cytokine levels in diabetic macular edema patients with cotton-wool spots. J Diabetes Res. 2019;2019