Review 1: "GRP78 binds SARS-CoV-2 Spike protein and ACE2 and GRP78 depleting antibody blocks viral entry and infection in vitro"

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RR:C19 Evidence Scale rating by reviewer:

- **Strong.** The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

The manuscript by Carlos A.J. *et al.* (<https://doi.org/10.1101/2021.01.20.427368>) discusses an important topic concerning the current pandemic. The present study shows experimental validation of the cell-surface Glucose Regulated Protein 78 (CS-GRP78) recognition to the SARS-CoV-2 spike, which is predicted previously by *in silico* methods by Ibrahim I.M. *et al.* (<https://doi.org/10.1016/j.jinf.2020.02.026>). According to the current experimental study, the GRP78 substrate-binding domain (SBD) is crucial for spike recognition over the cell membrane and in the endoplasmic reticulum (ER). In contrast, both SBD and nucleotide-binding domain (NBD) is contributed to Angiotensin-converting enzyme 2 (ACE2) recognition. The GRP78 T453D mutant variant blocked both spike and ACE2 recognition, while the G227D mutant of GRP78 blocked ACE2 recognition only. These findings agree with previous studies that relate the cross-vaccination of the SARS-CoV-2 and the HKU1, 229E, NL63, and OC43 strains of the human coronaviruses (<https://doi.org/10.1038/s41586-020-2598-9>) and (<https://doi.org/10.1016/j.jinf.2020.09.004>). Additionally, the authors concluded that GRP78 might be crucial for ACE2 trafficking, localization, and stability on the cell surface, which will be of paramount importance not only for COVID-19 treatment but also for cardiovascular diseases.

The authors raised the monoclonal antibody's feasibility (currently under clinical trials) hMAb159 to combat CS-GRP78 in COVID-19 patients to endocytose CS-GRP78 and its associated CS-ACE2, which could dramatically affect the viral attachment and assembly.

Sure this work is an excellent addition to the knowledge about COVID-19 that needs more experimental validation. The work presented in the reviewed manuscript is strong in terms of the experimental methods and hypothesis. This work paves the way to understanding the proposed function of GRP78 in the pathogenesis of COVID-19.

The only debate about this work is the lacking of the GRP78 and the ACE2 in the SARS-CoV-2 protein interaction map of Gordon D.E. et al. (<https://doi.org/10.1038/s41586-020-2286-9>), which needs further studies.

In my opinion, this work is acceptable in its current form.