BBAMEM-19-314: Final Decision

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Manuscript No.: BBAMEM-19-314
Title: CD4-binding obstacles in the conformational transitions and allosteric communications of HIV gp120
Article Type: Regular Paper
Journal Title: BBA - Biomembranes
Corresponding Author: Dr. Yi Li
All Authors: Yi Li; Lei Deng; Peng Sang; Xiao-Ling Zhang; Li-Quan Yang; Shu-Qun Liu
Submit Date: Sep 13, 2019

Dear Dr. Li:

Thank you for submitting the above-named article to BBA - Biomembranes.

I am sorry to inform you that your paper is not acceptable for publication. We have completed the review of your manuscript and a summary of the comments received from two expert reviewers is appended below. Significant shortcomings were identified in the work, for example, one reviewer points out that simulations with the glycoprotein form of the protein need to be done, to provide data that are physiologically more meaningful. Addressing this issue alone would take more time than what is normally allowed for a major corrections decision in our journal. The second reviewer also has a series of concerns that would need to be addressed. Your manuscript in its present form will therefore not be considered further for publication at this stage. However, the topic is within scope and if you can address at a later date the concerns of both reviewers in an appropriate manner, you may, in the future, resubmit it as a completely new submission (in that case please include a cover
letter describing the history of the manuscript).

Yours sincerely,

Hans J. Vogel, Ph.D.
Executive Editor
BBA - Biomembranes

Please see Reviewers' comments:

Reviewer #1: A manuscript by Li et al. describes simulations study of HIV protein gp120, which plays an essential role in virus entry into a host cell. Authors used a few computational methods and analysis tools, which provide a nice framework for studying protein dynamics. Thus, the manuscript is interesting from a methodological point of view. The manuscript is also well written and nicely illustrated.
There is, however, an essential problem with the biological relevance of the results. Gp120 is essentially glycoprotein; carbohydrates constitute half of the protein mass. Therefore, it is difficult to believe that glycan does not affect protein behavior. My suggestion is that authors extend simulation on glycosylated protein, including at least core glycan (5 first sugars of conserved sequence), which may represent about 30% of carbohydrates. My recommendation to reject the manuscript is based on time limit given for revision which is too short to perform such calculations.

Reviewer #2: The manuscript "CD4-binding obstacles in the conformational transitions and allosteric communications of HIV gp120" by Li et al applies molecular simulations, Markov modeling and network-based analysis to describe conformational states during the HIV-1 Env transitions from Env State 1 (closed conformation) to State 3 (open or CD4-bound conformation). The authors used computational tools and available CD4-bond Env structure as a starting point and analyzed the possible pathways by which gp120 or gp120-CD4 can transition to different states. The in silico methods/analysis provides some theoretical information but the study still needs to show consistency with concepts and experimental data available in numerous publications. Specifically, the mechanism of CD4 binding has been well investigated leading to current understanding that CD4 may bind State 1 or capture and stabilize State 3. There are also experimental data that describe intermediate states. Specific
comments follow.

1. The term "unliganded" and "liganded" are outdated as HIV-1 gp120 is almost always crystalized with antibodies and not unliganded, and "liganded" can be ambiguous as it may represent a complex with CD4 or antibodies. The authors should use the new terms in the HIV-1 Env field that were coined in 2016 (Herschhorn et al. mBIO 2016) after the identification of a new Env intermediate state throughout the manuscript. State 1 (for the closed conformation), State 2 (intermediate conformation), and State 3 (open or CD4-bound conformation).

2. The CD4 receptor can bind to either Env conformational state. Binding to State 1 induces the transition to State 3 and binding to State 3 stabilizes this conformational state. There is not any "different role". Please delete or rephrase the sentence: "However, significant structural rearrangements between these two states and recent biophysical observations suggest that CD4 may play a different role" from the abstract. Also remove

any of these concepts from the discussion section. If the authors believe that capturing State 3 is a dominant mechanism, they should provide strong experimental evidence.

3. The authors should include the relevant references for identified Env intermediate conformations. They should at least add:
a. Herschhorn A. et al mBIO 2016 for the intermediate state;
b. Alsahafi N. et al Cell Host & Microbe 2019 for a new conformational state related to ADCC activity; and
c. Lu M. et al Nature 2019 for discussion on BG505SOSIP state.
The authors should further discuss how these experimental-defined intermediates are related to their in silico Env states.

4. The authors should validate their finding/results using available experimental data in the literature. Changes of residue 193 lead to substantial conformational changes that are consisted with the ability of L193 to form a hydrophobic core maintaining State 1. Changes to more hydrophilic residues correlate with transitions to downstream conformations. The authors should introduce in silico all amino acids to position 193, calculate the most stable conformation for each and show the correlation between opening of the trimer and hydrophobic changes. Similarly, the I423A change should stabilize State 3-like Env conformation.

5. Delete the sentence: "It is doubtful whether such so significant structural change of gp120 between these two states should be attributed to the binding of CD4." Structural rearrangements as the result of CD4 binding are documented in numerous publications using functional, biochemical and biophysical assays.

6. Rephrase "There are about 75% unliganded state and 25% liganded state at 4°C, whereas an inverted distribution of 25% unliganded state and 75% liganded state was observed at 37°C, suggesting from a thermodynamic perspective that gp120 is intrinsically able to sample a variety of conformational states." to reflect that these data is based on one method/structure. smFRET experiments show the primary HIV-1 Env are dominantly in State 1.

7. V3 is not emanating from the bridging sheet but from under the stem of the bridging sheet.

8. Please add that hydrogen-deuterium exchange analysis, which is referenced, was performed with soluble BGSOSIP trimer.

9. The authors used Clade G X1193.c1 SOSIP.664. They should explain why they used this structure and discuss how representative this structure is with regard to different Envs from different HIV-1 strains.

10. Delete or rephrase "the liganded state can be considered as a high free energy state, which can intrinsically transfer into the ground state (i.e. the unliganded state) of gp120