Qeios

Peer Review

Review of: "Structural Biophysics-Guided Computational Design of Semaglutide Analogues to Enhance GLP-1R Activation"

Sarfaraz K. Niazi[1]

1. University of Illinois Urbana-Champaign, Urbana, United States

Wei Li's paper "Structural Biophysics-Guided Computational Design of Semaglutide Analogues to Enhance GLP-1R Activation" presents a computer-based approach to increase how well semaglutide connects to the extracellular domain (ECD) of the GLP-1 receptor, which makes the molecule work better. The reason for this is that the semaglutide-based combination therapy CagriSema did not perform well in a recent Phase III study. Changing semaglutide to enhance its interaction with GLP-1R should lead to better treatment outcomes; this idea is supported by previous successes in improving insulin analogs. With an eye toward electrostatic interactions like salt bridges and hydrogen bonds, the work used Modeler's homology modeling and binding affinity estimation with Prodigy. The author introduces a fast computer process called "Modigy" that ranks specific changes to the site based on predicted binding strengths, resulting in the creation of 564 similar versions.

With considerable computational rigor shown by modeling more than 10,000 structures for top variants, the approach is technically sound and precisely defined. Conceptually, the creative aspect is identifying an "electrostatic scaffold" based on recently developed salt bridges. However, a major limitation of the study is that it relies on fixed homology models and calculated affinities without using molecular dynamics or experimental validation. GLP-1R is especially sensitive to such simplifications because of its GPCR character, which experiences complicated conformational changes. Also, not having negative controls or weakly binding analogs makes it hard to understand the data; plus, there is no comparison of Prodigy's predictions with tested Kd values.

Generally speaking, the paper is well-cited; a thorough and pertinent bibliography covering structural biology, GLP-1R agonists, and insulin analogs is included. However, it relies too much on self-citation. It suffers from too frequent repetition of some references—most notably, reference 24, which runs through

 doi.org/10.32388/8L56SD

the manuscript to quote the same PDB structure. This duplicity compromises the objectivity of the scientific story. More precise mapping of residue alterations between native and mutant counterparts would help the article, especially in visual images or in a summary table instead of being buried in the additional data.

To improve the work, the author should consider using molecular dynamics simulations to validate important conclusions regarding aqueous interactions and receptor flexibility. Furthermore, benchmarking Prodigy forecasts with known experimental evidence for GLP-1 analogs would improve confidence. Additionally, the study should incorporate other energetic interactions, such as hydrophobic and van der Waals interactions, to facilitate binding beyond just salt bridges. Clearing the structural mapping of mutations and naming rules might help readers unfamiliar with the modeling system. Reducing citation repetition and controlling self-citation would help improve academic objectivity.

Even if the work presents a convincing computational hypothesis and a technically exact design methodology, its present form is more exploratory than final. The results offer a basis for further experimental validation rather than instantaneous translational conclusions. With changes, this work might be an excellent candidate for publication in a computational or structural biology magazine, advancing the field of rational GLP-1R agonist design.

Declarations

Potential competing interests: No potential competing interests to declare.