

Hormone-Independent Active States and Supramolecular Organization of the LH Receptor: Insights from Computational Modeling

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Receptors for glycoprotein hormones (i.e. LH/hCG, FSH and TSH) are particularly susceptible to spontaneous disease-causing mutations. Our study is aimed at understanding, through computational modeling, the molecular mechanism of LH receptor (LHR) functioning either in normal conditions or when hit by gain-of-function or loss-of-function mutations.

Computational models of the LHR were achieved by comparative modeling, followed by Molecular Dynamics (MD) simulations. MD simulations were done on the wild type, on all the naturally occurring mutants known thus far as well as on more than one hundred engineered LHR mutants.¹⁻³

Predictions of the putative architecture of the LHR homo-dimers as well as of the receptor-G protein interface were also done by rigid-body docking, followed by filtering and cluster analysis.

The arginine of the highly conserved E/DRY motif and the cytosolic extensions of helices 3 and 6 are suggested to be amongst the targets of the structural modifications induced by activating mutations and to participate in receptor-G protein interface. An increment, above a threshold value, in the solvent accessibility of the cytosolic ends of these two helices is the main structural feature shared by the active LHR forms. This feature was successfully used for predicting the functionality of novel engineered LHR mutants.¹⁻³

Preliminary simulations of LHR homo-dimerization highlighted helices 4, 5, 6 and 7 as involved in possible intra- and inter-dimeric contacts.

The results of these studies suggest that molecular simulations can be useful for *in silico* screening LHR mutants and for driving novel experiments aimed at gaining insight into LHR function.

References

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