Unravelling the Atomistic Mechanism of EGFR N-glycosylation

Dr Maryam Azimzadeh Irani, Bioinformatics Institute,
A*-STAR, Singapore; School of Biological Sciences, Nanyang Technological University, Singapore

Abstract

Epidermal Growth Factor Receptor (EGFR) is a glycosylated tyrosine kinase receptor associated with several cancers. EGFR plays an important role in cancer therapy and inspired several experimental and computational (molecular dynamics simulation) studies to investigate its function and dynamics. N-glycosylation is a critical aspect of EGFR functioning that was mainly unexplained until recently due to the challenges in obtaining and analysis of the structural data involving the glycan moieties. Latest simulations of glycosylated EGFR suggest atomistic mechanisms underlying the experimentally proposed functions of N-glycans in: EGFR increased ligand binding, reduced flexibility and arrangement within the cell membrane. It was shown that the increase in the ligand binding of glycosylated EGFR is mediated by the interaction between the two glycans attached to the growth factor binding subdomains resulting in stabilization of the growth factor binding site. Persistent hydrogen bonds' formation between the glycans and EGFR contributes to proper folding and reduced flexibly of the glycosylated receptor. Assembly of the cell-integrated EGFR and its relative distance from the membrane are acquired by the lift-up action of the attached glycans. These findings can be used as a framework for implementation of computational techniques to obtain atomistic details of protein glycosylation as one of the most important areas of structural biology.

Image

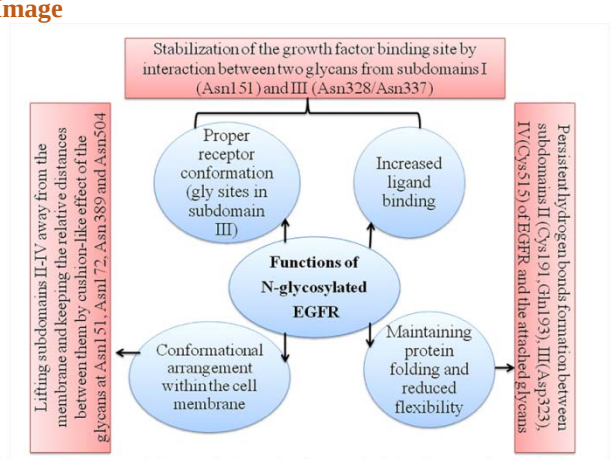


Figure 1. Summary of the atomistic mechanisms underlying the experimental observations. Experimentally indicated and atomistic mechanisms explained by molecular dynamics simulations are shown with blue circles and red boxes, respectively.

Recent Publications

1. Maryam Azimzadeh Irani (2018) Correlation between experimentally indicated and atomistically simulated roles of EGFR N-glycosylation, Molecular Simulation, 44:9, 743-748.
2. Azimzadeh Irani, M. , Kannan, S. and Verma, C. (2017) Role of N-glycosylation in EGFR ectodomain ligand binding. Proteins, 85: 1529-1549.
3. Azimzadeh Irani, M. (2017) Role of glycosylation in EGFR ectodomain interactions : a molecular dynamics study. Doctoral thesis, Nanyang Technological University, Singapore.
4. Taylor, E. S., Pol-Fachin, L. , Lins, R. D. and Lower, S. K (2017) Conformational stability of the epidermal growth factor (EGF) receptor as influenced by glycosylation, dimerization and EGF hormone binding. Proteins, 85: 561-570.
5. Kaszuba K, Grzybek M, Orłowski A, Danne R, Tomasz R, Simons K, Coskun U, Vattulainen I (2015) *N*-Glycosylation regulates EGFR structure. Proceedings of the National Academy of Sciences (14) 4334-4339.
6. Arkhipov A, Shan Y, Kim ET, Shaw DE (2014) Membrane Interaction of Bound Ligands Contributes to the Negative Binding Cooperativity of the EGF Receptor. *PLoS Computational Biology* 10(7):e1003742.



Biography

Dr Maryam Azimzadeh Irani has her expertise in understanding the structural roles of glycoconjugates at the atomic level. By working at the world-leading research groups in Singapore, Germany and Iran, she has gained a reliable background in the field of structural glycobiology. Her current research is mainly focused on the glycosylation of cancer mediated transmembrane receptors for developing anti-cancer therapeutics.

Email: Maryamai1988@gmail.com