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Unraveling the Structural Role of Glycosylation in Regulation of EGFR-ErbB2 Heterodimers

ارائه دهنده

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چکیده

The ErbB family has four known homologous members including EGFR, ErbB2, ErbB3 and ErbB4. EGFR which is a key member of the ErbB glycoprotein family that triggers cellular processes including proliferation, survival, cell migration and apoptosis. Its overexpression or mutation has been observed in a variety of human cancers. Protein glycosylation is the enzymatic addition of sugar moieties to specific amino acid residues. It has been reported that sorting, stability and protein–protein interactions of the ErbB receptors are affected by glycosylation. The members of ErbB family could form homo and heterodimer with each other in the active form. Herein, we used computational tools to model the heterodimer of EGFR-ErbB2 receptors and investigate its dynamical pattern for the first time. Furthermore, we utilized the phylogenetic tools to investigate the evolutionary relationships of the ErbB family receptors.

We found that the dynamics of the heterodimer is regulated by glycosylation and the glycosylated heterodimer is more stable than the unglycosylated heterodimer. However the ErbB2 monomer is more stable than the EGFR monomer before and after glycosylation. The results of simulations analysis shows that there are three glycosylation sites around the growth factor binding site in ErbB2 and the attached glycans in these places may inhibit ligand binding of the ErbB2 monomer. Investigation of atomic interactions within the heterodimer shows that the hydrophobic cores interactions between two monomer in dimeric interface are affected by glycosylation. To investigate the phylogenetic relationship of vertebrate ErbB family genes, maximum likelihood methods were applied and the tree created by GTR+G+I evolutionary model. The results show that two major duplications had occurred early in the vertebrate lineages. The first duplication led to the emergence of two lineages which evolved into EGFR and ErbB2, and the second duplication, also early in vertebrate evolution, resulted in ErbB3 and ErbB4 but we still don't know that the duplications are orthologues or paralogues. The phylogenetic relationship of *Homo sapiens* ErbB family genes illustrate the ErbB2,ErbB3 and ErbB4 are more similar to each other.

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