سمینار هفتگي ماده چگال نرم

Role of Glycosylation in Developing Anti-cancer Therapeutics

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The epidermal growth factor receptor (EGFR) is a tyrosine kinase protein, overexpressed in several cancers. The extracellular domain of EGFR is known to be heavily glycosylated. Growth factor (mostly epidermal growth factor or EGF) binding activates EGFR. This occurs by inducing the transition from the autoinhibited tethered conformation to an extended conformation of the monomeric form of EGFR and by stabilizing the flexible preformed dimer. Activated EGFR adopts a back-to-back dimeric conformation after binding of another homologous receptor to its extracellular domain as the dimeric partner. Several antibodies inhibit EGFR by targeting the growth factor binding site or the dimeric interfaces. Glycosylation has been shown to be important for modulating the stability and function of EGFR. Here, atomistic MD simulations show that N-glycosylation of the EGFR extracellular domain plays critical roles in the binding of growth factors, monoclonal antibodies, and the dimeric partners to the monomeric EGFR extracellular domain. N-glycosylation results in the formation of several noncovalent interactions between the glycans and EGFR extracellular domain near the EGF binding site. This stabilizes the growth factor binding site, resulting in stronger interactions (electrostatic) between the growth factor and EGFR. N-glycosylation also helps maintain the dimeric interface and plays distinct roles in binding of antibodies to spatially separated epitopes of the EGFR extracellular domain. Analysis of SNP data suggests the possibility of altered glycosylation with functional consequences.

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