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A Computational Study of Estrogen Affinity for GPER Using Molecular Dynamics and Enhanced Sampling

G-protein coupled estrogen receptors (GPERs) play a critical role in cellular signalling; yet the precise nature of their interaction with estrogen (EST) remains a subject of debate [1–4]. While recent studies have questioned whether EST binds directly to GPER [4], our molecular dynamics (MD) simulations provide compelling evidence in favor of such an interaction. Using MD simulations, we identified a plausible EST-binding pocket within the GPER. Thermodynamic integration–based free energy calculations revealed a notable binding affinity at this site. Notabley, under elevated EST concentrations, EST molecule spontaneously localized to this pocket within microseconds, validating the predictions from our thermodynamic integration analysis. Structural characterization of the binding site uncovered key stabilizing interactions: three strong hydrogen bonds anchoring EST at both sides of the pocket, and a hydrophobic cavity accommodating its central nonpolar core. Together, these computational results strongly support a direct binding interaction between EST and GPER, providing novel insights into the receptor's function in EST-mediated signalling pathways.

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