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Compounds identified by virtual docking to a tetrameric EGFR extracellular domain can modulate Grb2 internalization

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Abstract

© Ramirez et al. 2015. Background: Overexpression or mutation of the epidermal growth factor receptor (EGFR) potently enhances the growth of many solid tumors. Tumor cells frequently display resistance to mechanistically-distinct EGFR-directed therapeutic agents, making it valuable to develop therapeutics that work by additional mechanisms. Current EGFR-targeting therapeutics include antibodies targeting the extracellular domains, and small molecules inhibiting the intracellular kinase domain. Recent studies have identified a novel prone extracellular tetrameric EGFR configuration, which we identify as a potential target for drug discovery. Methods: Our focus is on the prone EGFR tetramer, which contains a novel protein-protein interface involving extracellular domain III. This EGFR tetramer is computationally targeted for stabilization by small molecule ligand binding. This study performed virtual screening of a Life Chemicals, Inc. small molecule library of 345,232 drug-like compounds against a molecular dynamics simulation of protein-protein interfaces distinct to the novel tetramer. One hundred nine chemically diverse candidate molecules were selected and evaluated using a cell-based high-content imaging screen that directly assessed induced internalization of the EGFR effector protein Grb2. Positive hits were further evaluated for influence on phosphorylation of EGFR and its effector ERK1/2. Results: Fourteen hit compounds affected internalization of Grb2, an adaptor responsive to EGFR activation. Most hits had limited effect on cell viability, and minimally influenced EGFR and ERK1/2 phosphorylation. Docked hit compound poses generally include Arg270 or neighboring residues, which are also involved in binding the effective therapeutic cetuximab, guiding further chemical optimization. Conclusions: These data suggest that the EGFR tetrameric configuration offers a novel cancer drug target.

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Keywords

Epidermal growth factor receptor, Extracellular domain, Grb2, Protein multimerization