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Novel Therapeutic Strategy for EGFR-Targeted Therapies in Cancer and Other Diseases

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Background

Epidermal growth factor receptor (EGFR) plays an important role in promoting cancer cell survival. Overexpression of EGFR is observed in the majority of human epithelial cancers and is correlated with poor prognosis. These factors make EGFR a major target for cancer therapy.

Currently, two classes of EGFR antagonists are in clinical use: anti-EGFR antibodies and small-molecule EGFR tyrosine kinase inhibitors (EGFR TKIs). Anti-EGFR antibodies compete with ligand to bind the extracellular domain of EGFR, and they thereby inhibit ligand-induced EGFR tyrosine kinase activation. EGFR TKIs compete with ATP to bind the intracellular EGFR tyrosine kinase domain and thus inhibit EGFR activation and downstream signalling. EGFR TKIs can effectively block EGFR signalling on tumours bearing cancer-related mutations on human EGFR but cannot effectively block EGFR signalling on tumours overexpressing wild-type EGFR. Moreover, all cancer patients who initially benefit from EGFR-targeted therapies eventually develop resistance within a short period. Thus it is essential to develop a novel strategy to overcome resistance and enhance the efficiency of EGFR-targeted therapies. One of the major causes of resistance to EGFR-targeted therapy lies in the fact that tumour cells acquire additional mutations in EGFR that weaken the interaction between EGFR and the drug. Currently, apart from the third generation of EGFR TKIs that target the T790M mutation on human EGFR, there is no drug that can effectively overcome drug resistance. In addition, there are no effective therapies targeting wild-type EGFR in tumours such as head and neck squamous cell carcinoma (HNSCC). To overcome drug resistance, it is essential to explore a novel strategy that inhibits the activity of EGFR by an entirely different mechanism.

Technology Overview

Newly synthesised wild type EGFR has to be delivered to the cell surface so that EGFR can perform its function. Our results indicate that blocking the surface delivery of EGFR blocks EGF-induced EGFR phosphorylation, indicating that blocking the surface delivery of EGFR is an effective way to inhibit EGFR signalling, so this method will be an effective therapeutic strategy to overcome resistance. We found that surface delivery of EGFR depends on the COPII coat subunit, SAR1A. In addition, we revealed that EGFR directly binds SAR1A. The D198 residue in SAR1A was identified as critical for SAR1A to bind EGFR and mutating this residue blocks EGFR surface delivery. In addition, the KKIK motif at the position of 713-716 on human EGFR is important for its ER export. Furthermore, we found that the Arginine residues at the position of 669-681 on human EGFR are also

important for its ER export. Our invention is the strategy of blocking the interaction between SAR1A and EGFR, either by mutating the D198 residue on SAR1A, or mutating the KKIK motif on human EGFR, or mutating the key residues within the juxtamembrane area of human EGFR, or a polypeptide containing the D198 residue and surrounding amino acids on SAR1A, or a polypeptide that contains the KKIK motif at the position of 713-716 on human EGFR, or a polypeptide that contains the Arginine residues at the position of 669-681 on human EGFR, or small chemical molecules that block the interaction between EGFR and SAR1A. This is an effective way to inhibit EGFR surface delivery and thereby inhibit EGFR signalling. This strategy will significantly improve EGFR-targeted cancer therapy.

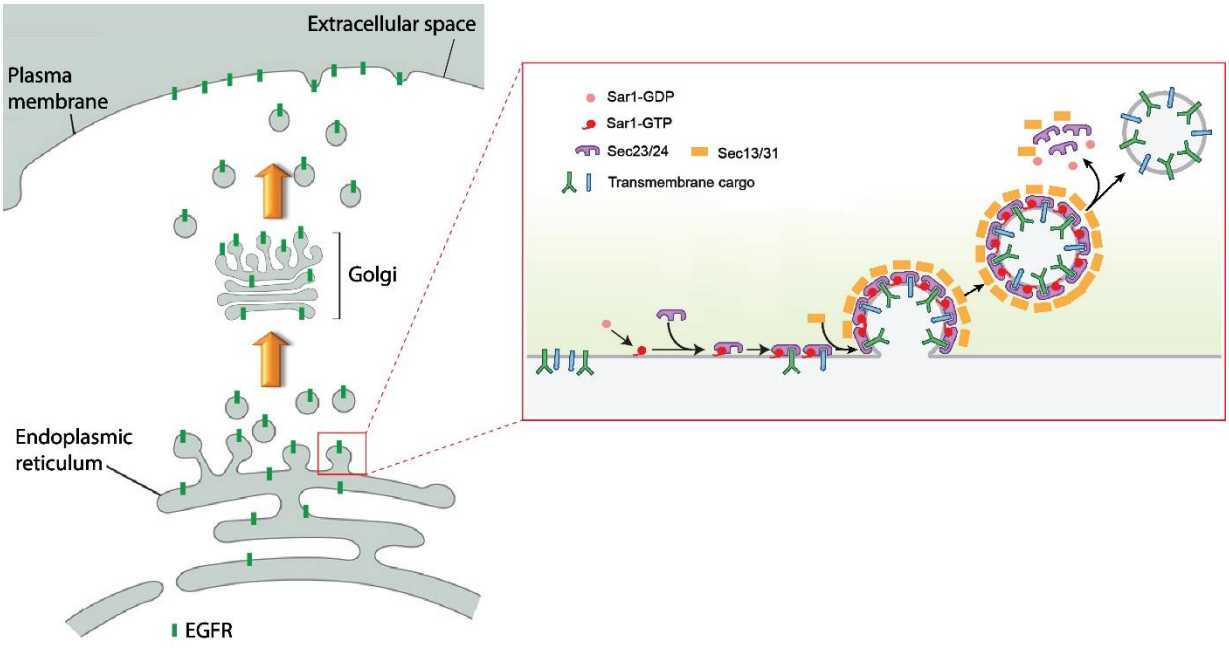
Applications

- Development of drugs for potential cancer or other EGFR-related disease treatments
- Use in research and drug screening as a tool to screen for potential inhibitors of EGFR delivery

Patents

- US Patent no.: 16/254287

Figures



Surface delivery of newly synthesised EGFR along the secretory transport pathway.