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Research Article

An *In Silico* Study to Explore the Role of EGFR in Ovarian Cancer

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ABSTRACT

EGFR is a tyrosine kinase receptor that has a role in the tumorigenesis of many types of solid tumors. Aberrantly phosphorylated or overexpressed EGFR is associated with cellular proliferation, prevention of apoptosis, activation of invasion and metastasis, and stimulation of tumor-induced neovascularization. EGFR's hyperactivity has been observed in ovarian cancer. Although conventional chemotherapy and surgery for advanced ovarian cancer have improved over the years, still there is a critical need for the development of molecular targeted therapies. The major challenge for this approach is the complete understanding of the protein structure of this mega receptor. In this study, we explored this receptor using *in silico* tools. The protein structure of the EGFR kinase domain (PDB ID: 1M17) and co-crystal containing EGFR and PTP1B kinase domain fragment (PDB ID: 3I7Z) were obtained from the RCSB Protein Data Bank. We performed protein-protein docking using BioLuminate. It was found in this study that the DADEYL segment of EGFR (position 988-993) which includes autophosphorylated tyrosine at position 992, is the segment that is responsible for the overexpression of this receptor in ovarian cancer. There are currently two main classes of clinically-approved drugs which downregulate EGFR activity; tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (Mabs). However, treatment with both type of therapies has been met with shortcomings. Therefore, there is a need for further studies to explore the suitable ligands that can downregulate its activity.

Key words: EGFR, Protein-protein docking, *In silico* study, Tyrosine kinases

INTRODUCTION

Ovarian cancer is one of the main causes of death from gynecologic malignancies. Although conventional chemotherapy and surgery for advanced ovarian cancer have improved over the years with better outcomes, the majority of women still die with drug-resistant disease and as such, there is a critical need for the development of molecular targeted therapies.[1-7]

The ERbB family of receptor tyrosine kinases have a role in the tumorigenesis of many types of solid tumors and consists of the epidermal growth factor receptor (EGFR) (also known as HER1/ErbB1), human EGFR2 (HER2/*neu*)/ERbB2, HER3/ErbB3 and HER4/ErbB4.[7] These all four HER receptors have a significant role in cancer and promote tumorigenesis *via* cell proliferation, survival, migration, adhesion, and differentiation. Post receptor signaling by activated HERs include four representative pathways: The Ras-Raf/mitogen activated protein kinase (MAPK) and signal transducer and activation of transcription (STAT) pathways, the Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, and the phospholipase Cγ (PLCγ) pathway. Mutations, gene amplifications, and protein overexpression of the EGFR as well as other HER family members are linked to carcinogenesis. Overexpression and/or mutations of EGFR and HER2 are evident in a variety of solid tumors, including ovarian cancer, and have therapeutic implications.

Through the Raf/MEK/ERK and PI3K/Akt signaling transduction pathways, aberrantly phosphorylated or overexpressed EGFR in certain cancers is associated with cellular proliferation, prevention of apoptosis, activation of invasion and metastasis, and stimulation of tumor-induced neovascularization.[8] Cancers in which EGFR hyperactivity has been observed include ovarian cancer, head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), colorectal cancer, and pancreatic cancer, and thus downregulation of EGFR activity by EGFR inhibitors in these cancers, has been shown to be favorable in a clinical setting. Six endogenous ligands are known to stimulate EGFR: epidermal growth factor (EGF), transforming growth factor alpha (TGF-α), amphiregulin, heparin-binding EGF-like growth factor, betacellulin and epiregulin. Upon stimulation, EGFR undergoes oligomerization where it dimerizes with another ErbB1 receptor or another receptor from the ErbB family to form homodimers or heterodimers, respectively. At this stage, each binding partner phosphorylates the other by a process known as transphosphorylation. Activation of EGFR signaling is terminated primarily through endocytosis of the ligand-receptor complex, where the receptor is subsequently recycled or degraded.[9,10]

The Epidermal Growth Factor Receptor (EGFR) family

The EGFR family of Receptor Tyrosine Kinases (RTKs) consists of 4 members (collectively referred to as the ErbB or HER family): EGFR itself, ErbB2 (HER2/Neu), ErbB3 (HER3) and ErbB4 (HER4). Like all RTKs, each ErbB receptor comprises a large extracellular region, a single spanning trans-membrane (TM) domain, an intracellular

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juxtamembrane (JM) region, a tyrosine kinase domain and a C-terminal regulatory region. The ligands that regulate ErbB receptors can be separated into two main groups: the 'EGF agonists' that activate EGFR, and the neuregulins (NRG) that bind ErbB3 and ErbB4.[11] There are at least 7 different EGF agonists: EGF, transforming growth factor α (TGFα), amphiregulin (AR), betacellulin (BTC), epigen (EPN), epiregulin (EPR) and heparin binding EGF-like growth factor (HB-EGF).[12] The extracellular regions of EGFR family members contain two homologous ligand binding domains (domains I and III) and two cystine rich domains (domains II and IV). Although high-resolution structural studies of intact RTKs pose technical challenges that have not yet been overcome, there is a wealth of structural data on both the extra- and intra-cellular regions of the EGFR family. X-ray crystal structures have been determined for the extracellular regions of all four ErbB receptors (sErbBs) in their unliganded state.[13] The structure of the EGFR extracellular region (sEGFR) has also been determined in a dimeric – presumably activated – state induced by binding of EGF or TGFα. The structure of the intracellular kinase domain of EGFR has also been extensively studied in different activation states. Despite this wealth of structural information, there are important regions of EGFR for which relatively little data are available. For example, little is known about the structure of the first ~30 amino acids of the intracellular JM region, which may play an important regulatory role. Moreover, the most C-terminal ~190 amino acids of EGFR that contains multiple tyrosine phosphorylation sites is poorly characterized, but is clearly implicated in regulation of receptor activation.[14]

Protein structure of EGFR

EGFR consists of an extracellular ligand-binding domain, a single membrane-spanning (transmembrane) domain and a cytoplasmic protein tyrosine kinase domain, where the juxta-membrane region and EGFR kinase domain is located. The latter is the most conserved region among the EGFR protein family (excluding ErbB3) and mediates the autophosphorylation of the six tyrosine residues (at positions 992, 1045, 1068, 1086, 1148 and 1173) of the carboxyl-terminal tail. Upon ligand binding, the activation loop (A-loop) of EGFR forms a "closed" conformation that leads further phosphorylation of in intracellular domain, which is situated between the kinase domain and the carboxyl terminal phosphorylation sites.[15]

Current treatments targeting EGFR

There are currently two main classes of clinically-approved drugs which downregulate EGFR activity; tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (Mabs). TKIs (including erlotinib and gefitinib) are competitive inhibitors which target the tyrosine kinase domain, and have been approved for clinical use against cancers such as NSCLC.[17] However there is evidence of intrinsic and acquired resistance to these EGFR antagonists and significant skin toxicity. Mabs (such as cetuximab) bind to the extracellular domain of EGFR with great affinity and subsequently prevents binding and activation by native ligands (*i.e.* EGF, TGF-α, amphiregulin, heparin-binding EGF-like growth factor, betacellulin and epiregulin), and are approved for cancers such as colorectal cancer. However, treatment with this type of therapy has also been met with shortcomings.[18] Mabs are given intravenously and are therefore inconvenient to administer, and some are notoriously known for their immunogenicity, and to cause cutaneous toxicity similar to TKIs.

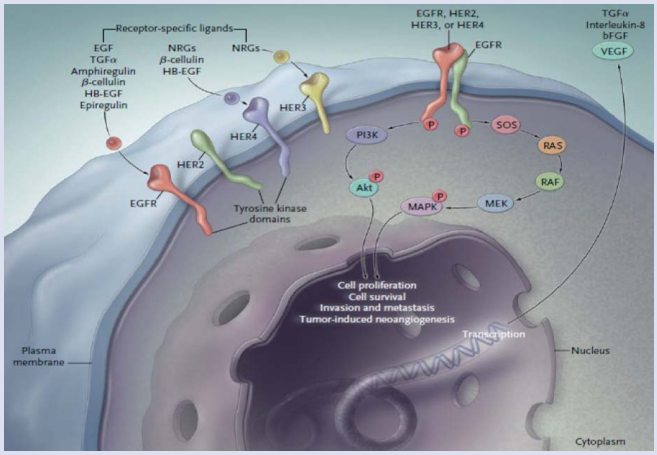

Figure 1: Illustration describing endogenous ligands of EGFR and other receptors from the ErbB family (HER2, HER3, HER4) activating the PI3K/Akt and Raf/MEK/ERK signalling cascades, which in turn regulate cell proliferation, cell survival, invasion and metastasis.[16]

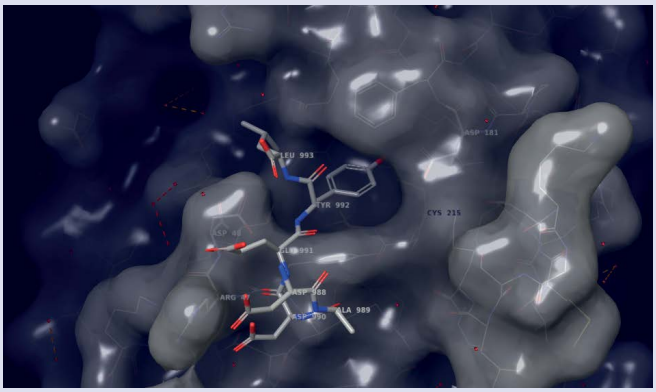

Figure 2: 3D visualization of EGFR fragment (DADEYL).

EGFR mutations in cancer

The importance of EGFR-TK autoinhibition is underscored by the growing numbers of somatic EGFR mutations reported in certain cancers, particularly in non-small cell lung cancer (NSCLC). In clinical NSCLC trials with EGFR-targeted tyrosine kinase inhibitors (TKIs), a small subset of patients showed dramatic initial responses, and this response correlated with the occurrence of somatic mutations in exons 18 to 21 in the EGFR kinase domain.[19] Point mutations in the nucleotide binding loop (the P-loop; exon 18) or in the activation loop (exon 21), and deletions immediately preceding the catalytically important C-helix all lead to enhanced sensitivity to TKIs. The initial patient response to TKIs therefore appears to reflect inhibition of constitutive, oncogenic, signaling by EGFR in their tumors.[20] Each class of EGFR-TK mutations found in NSCLC is likely to destabilize the inactive conformation of the EGFR kinase domain. For example, the L834R substitution (L858R in kinase mutation literature) disrupts interactions between the helical turn in the activation loop and the C-helix in the inactive conformation. L834 is relatively surface exposed in the active state. Similarly, deletions in the region preceding the C-helix also remove interactions likely to stabilize the inactive conformation of the activation loop. The occurrence and properties of these cancer mutations thus strongly argue that in inactive EGFR, as for most other RTKs, the kinase domain adopts an auto inhibited state. Normal activation requires ligand-induced dimerization that promotes allosteric activation of EGFRTK. The cancer mutations circumvent the need for ligand activation by disrupting interactions that maintain the kinase in its auto inhibited inactive state.[21]

MATERIALS AND METHODS

In Silico protein preparation

Prior to undergoing protein-protein docking, protein structures for PTP1B (PDB ID: 1SUG), EGFR kinase domain (PDB ID: 1M17) and co-

crystal containing EGFR and PTP1B kinase domain fragment (PDB ID: 3I7Z) were obtained from the RCSB Protein Data Bank (www.rcsb.org) and prepared using the Protein Preparation Wizard (Schrödinger Suite 2016 Protein Preparation Wizard) accessed *via* Maestro. A typical PDB structures normally only contain heavy atoms, waters, cofactors and metal ions, possibly unaligned terminal amide groups, and unassigned tautomeric and ionization states. Neglecting proper preparation steps has been associated with a systematic degradation in virtual screening enrichment. Hence, proteins were pre-processed by assigning bond orders, adding missing hydrogens and filling missing loops and side chains using Prime. Proteins were refined by optimizing hydrogen bonds and sampling water orientations. Imperf-minimization was performed using the OPLS force field with a maximum RMSD of 0.3 Å allowed. Waters beyond 5 Å from het groups were deleted. Het groups are everything that is not a water or protein residue, and include ligands, metal ions, and cofactors.

Protein-Protein docking using BioLuminate

To predict the structural complex formed by the EGFR-PTP1B PPI to be used as our target we generated potential models from individual crystal structures available for PTP1B (PDB ID: 1SUG) and EGFR kinase domain (PDB ID: 1M17) using protein docking program, BioLuminate. PDB structure files usually only contain heavy atoms, waters, cofactors, metal ions and can be multimeric. However, the structure generally has no information on bond orders, topologies, or formal atomic charges, possible contain misaligned terminal amide groups, and unassigned ionization states tautomeric state. Hence, crystal structures were prepared for docking using the Protein Preparation Wizard from the Maestro interface of the Schrödinger Suite 2016. This included assigning bond orders, adding hydrogens, creating disulfide bonds, filling in missing side chains and loops.

Molecular docking

Molecular docking is a study of how two or more molecular structures, for example drug and enzyme or receptor fit together. Molecular docking can be divided into two separate problems. The search algorithm should create an optimum number of configurations that include the experimentally determined binding modes. These configurations are evaluated using scoring functions to find the best binding configuration.[21,22] The docking algorithms are as:

Genetic algorithms

Genetic algorithms and evolutionary programming are quite suitable for solving docking problems because of their usefulness in solving complex optimization problems. Some programs using genetic algorithms are GOLD, Auto Dock.

Incremental construction algorithm

The method involves dividing the ligand into fragments and docking them into active site, finally these fragments are linked together *i.e.* based on incremental construction algorithm. Selection of base fragment has been automated in newer programs such as FlexX and DOCK.

Scoring functions for docking

When the docking is completed the scoring function is used to rank each ligand in the database for which a docking solution has been found. The energy of binding is given by the Gibbs-Helmholtz equation:

$\Delta G=\Delta H-T\Delta S$

The ΔG giving the free energy of binding, ΔH the enthalpy, T is the temperature in Kelvin and ΔS the entropy. Bohn function is the type of scoring function which is most commonly used in docking software. DOCK uses different scoring function. Scoring functions can be grouped as follows:

Empirical scoring functions like LUDI, FlexX, ChemScore, etc.

Force field-based functions like Dock.

Knowledge-based potential of mean force functions like PMF, Drug Score, and BLEEP.

Glide is one of the widely used docking programs. It uses a series of hierarchical filters to search for possible locations in the active site region of the receptor. The properties of a receptor/active site region are represented by a grid that has different set of fields that provide progressively more accurate scoring of the ligand pose. It uses a Glide score (Gscore) for predicting binding affinity and rank ordering of ligands in database screening.

RESULTS AND DISCUSSION

Among the 30 poses, generated by BioLuminate, the poses were sorted out based on the best fit model. BioLuminate has embedded algorithm for sorting out these models based on the best fitting criteria and also take into account the attraction residues that are given as input to it. So, among the poses generated by the docking program we selected pose no. 01. We assumed that it is the best pose obtained by the program based on the attraction residues given by us. We further analyzed the pose no. 01. Table 1 shows the list of all residues that are responsible in the interaction. DADEYL substrate forms extensive interactions with the surface groove adjacent to the active site, including H-bonds between the backbone carbonyl of Asp (at position P-2) with Arg47 backbone amide proton of PTP1B, as well as pTyr and Leu backbone amide protons with Asp48 side chain carboxyl. The pTyr contributes to ~53% of the peptide solvent-accessible surface area that is buried upon binding. The DADEYL segment of EGFR (position 988-993) which include auto phosphorylated tyrosine at position 992 is the segment which is responsible for overexpression of the receptor in cancer.

CONCLUSION

EGFR is a member of tyrosine kinase family. It has a very complex structure. It comprises a large extracellular region, a single spanning trans-membrane (TM) domain, an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and a C-terminal regulatory region. Upon stimulation, EGFR undergoes oligomerization where it dimerizes with another ErbB1 receptor or another receptor from the ErbB family to form homodimers or heterodimers, respectively. In this study we explored its stimulation mechanism using *in silico* approach. The structural analysis of EGFR fragment was carried out using Shrodinger's BioLuminate. The best fit model was selected and it was found that DADEYL segment of EGFR (position 988-993) which include autophosphorylated tyrosine at position 992, is the segment which is responsible for the overexpression of this receptor in ovarian cancer.

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DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

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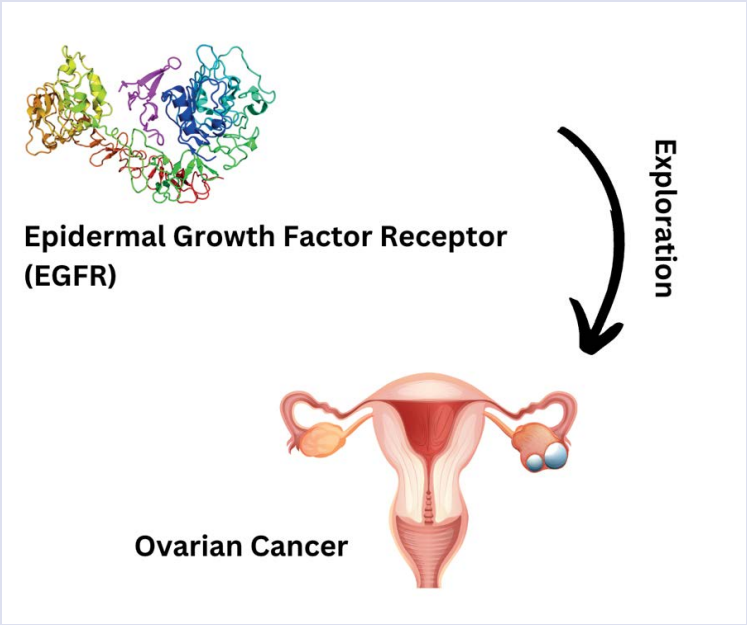
GRAPHICAL ABSTRACT



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