Computational platform for modelling, analysis, and prediction of anti-EGFR drug resistance for lung cancer

H Yan *, GY Zhu, M Wong, V Lee

KEY MESSAGES

1. Epidermal growth factor receptor (EGFR) mutation is an important cause of drug resistance in non-small cell lung cancer (NSCLC). We conducted computational modelling of EGFR mutants and analysis of EGFR-drug interaction patterns.
2. Any observed EGFR mutation can be modelled mathematically, and its 3D structure can be predicted computationally. The fundamental cause of drug resistance can be found at the atomic level.
3. Different drugs can be analysed. Based on our computer model, the binding strength between an EGFR mutant and a drug can be calculated.
4. Drug resistance can be evaluated for each mutation and each drug. Thus, a comprehensive database of EGFR mutation and drug effectiveness is established and is available online. The database provides a useful reference to medical doctors.
5. Our computational framework is less expensive than wet-lab experiments. It can also be used to study drug resistance related to other diseases.

Hong Kong Med J 2019;25(Suppl 9):S40-2
HMRF project number: 01121986

[1] H Yan, [2] GY Zhu, [3] M Wong, [4] V Lee

[1] *Department of Electrical Engineering, City University of Hong Kong*
[2] *Department of Chemistry, City University of Hong Kong*
[3] *Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong*
[4] *Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong*

* Principal applicant and corresponding author: h.yan@cityu.edu.hk

Introduction

Lung cancer has the highest mortality rate among all cancer types and results in 1.6 million deaths each year worldwide.[1] In Hong Kong, lung, liver, and colorectal cancers are the three leading causes of cancer deaths. Lung cancer accounts for more deaths than liver and colorectal cancers combined. About 85% of lung cancer patients have non-small cell lung cancer (NSCLC); many NSCLC cases are caused by a mutation of the epidermal growth factor receptor (EGFR), especially in Asia.[2] Several commercially available drugs are effective to shrink the tumour initially, but almost all patients develop drug resistance over time owing to mutations of EGFR.[2-5]

We studied EGFR mutations at the molecular and atomic levels. We collected EGFR mutations from research publications and from clinical cases at Queen Mary Hospital. Some of the mutations observed locally were rare and had never been reported. Based on computational models, we analysed how the 3D structure of EGFR changed secondary to a mutation. We then computed the binding strength of each drug with EGFR before and after the secondary mutation. The reduction in the binding strength reflected the degradation of the drug effectiveness. We built a 3D structural database of EGFR mutants and analysed the characteristics of all known EGFR mutations at the atomic level. Our work can provide a useful reference to medical doctors for assessment of drug resistance level and planning personalised treatment.

Results

Computational platform and EGFR mutant structural database

Our outcomes are summarised in the website http://bcc.ee.cityu.edu.hk/SFBG/. Under 'Computational Platform', all known EGFR mutations that cause NSCLC and drug resistance are listed. Each mutant is displayed interactively; users can adjust its rotation and scale, and download the PDB file of the mutant. Users can report any new EGFR mutation to us for analysis by clicking 'Report New EGFR Mutations'. Summaries of all these mutants are shown in 'EGFR Mutant Structural Database: Computationally predicted 3D structures and the corresponding binding free energies with gefitinib and erlotinib' under 'Research and Publications' at http://bcc.ee.cityu.edu.hk/SFBG/research_and_publications.html.

Personalised prediction of NSCLC drug resistance

The effectiveness of a cancer drug can be measured

based on the patient survival time and the response level. We built a prediction model based on the extreme learning machines. Leave-one-out was used for cross-validation. Training data included personal attributes (such as the physical condition and smoke history) of 168 patients from Hong Kong hospitals. We also used the binding free energy, which was computed based on the computer predicted 3D structures of EGFR mutants and molecular dynamics simulations. The prediction model was then applied to unseen testing data. We have achieved about 90% accuracy for testing samples.

EGFR mutant surface characteristics

We developed a 3D alpha shape–based model to characterise the surface structure of a biomolecule or the interaction complex of two biomolecules. We can determine the convexity or concavity of a molecular surface. We used the alpha shapes to analyse all known EGFR mutants and found that four types of surface curvature changes can result in weaker EGFR mutant-inhibitor binding and drug resistance (Fig 1). Our analysis provided physical reasons for drug resistance secondary to EGFR mutations.

Selectivity profile of afatinib

Afatinib is a second-generation NSCLC drug that forms covalent binding to an EGFR mutant. We analysed the potency of afatinib for different types of EGFR mutants computationally and experimentally. In clinical studies, the mutation type of each patient was determined before treatment with oral afatinib,[5] and then the disease progression was observed. Fig 2 shows a potency ranking of afatinib for different EGFR mutations.

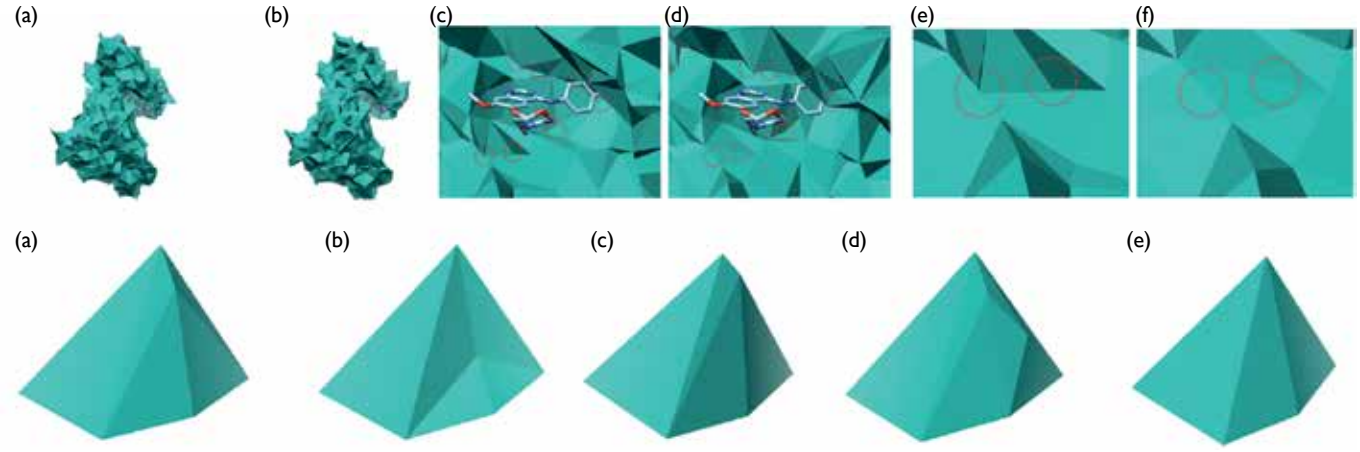

FIG 1. Top: (a and b) 3D alpha shapes, (c and d) surface structures at the drug-binding site, and (e and f) the zoomed version of the site of the wild-type EGFR and the mutant with L858R, respectively. Bottom: different types of local surface curvature changes based on alpha shape analysis: (a) the original surface structure, (b) convexity/concavity change, (c) convexity/concavity degree change, (d) addition of another atom, and (e) disappearance of an atom. [Diagrams are adapted from: Ma L, Wang DD, Huang Y, Wong MP, Lee VH, Yan H, Decoding the EGFR mutation-induced drug resistance in lung cancer treatment by local surface geometric properties. Comput Biol Med 2015;63:293-300.]

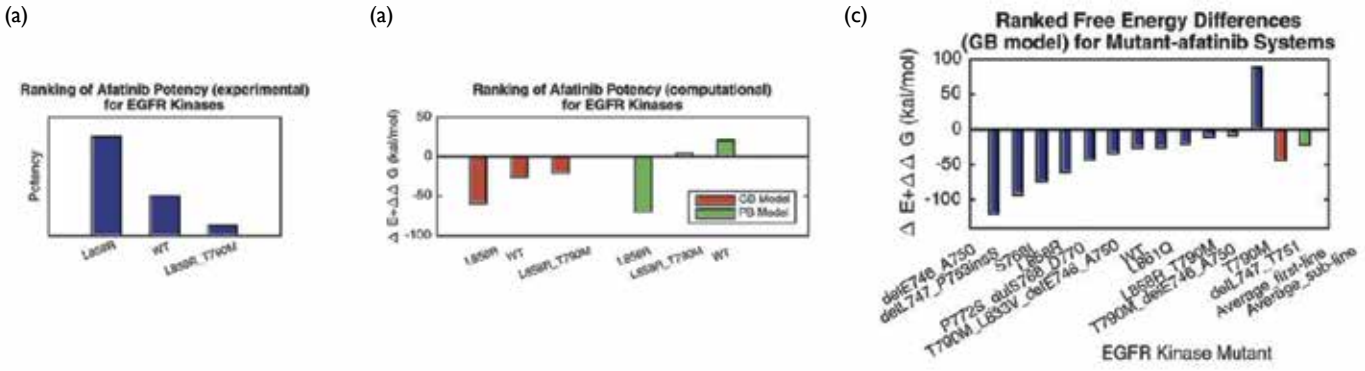

FIG 2. Ranking of afatinib potency for EGFR kinases from (a) experimental and (b and c) computational studies. [Diagrams are adapted from: Wang DD, Lee VH, Zhu G, Zou B, Ma L, Yan H. Selectivity profile of afatinib for EGFR-mutated non-small-cell lung cancer. Mol Biosyst 2016;12:1552-63.].

Characterisation of EGFR and ErbB-3 heterodimerisation

Based on data from 168 NSCLC patients, we characterised the interaction patterns of the EGFR mutants of these patients with three other proteins in the downstream EGFR signalling pathway: ErbB-2, IGF-1R, and c-Met,[3,4] as well as the interaction patterns with NSCLC drug molecules (gefitinib and erlotinib), particularly c-Met and ErbB-3 had a very high binding strength, which implies c-Met plays an important role in regulating ErbB-3.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#01121986). We also thank the staff at the Signal Processing and Biocomputing Lab, City University of Hong Kong, for their help with computer hardware and software and maintenance of our website.

Results from this research have been published in:

(1) Ma L, Wang DD, Huang Y, Yan H, Wong MP, Lee VH. EGFR Mutant Structural Database: computationally predicted 3D structures and the corresponding binding free energies with gefitinib and erlotinib. BMC Bioinformatics 2015;16:85.

(2) Wang DD, Zhou W, Yan H, Wong M, Lee V. Personalized prediction of EGFR mutation-induced drug resistance in lung cancer. Sci Rep 2013;3:2855.

(3) Ma L, Wang DD, Huang Y, Wong MP, Lee VH, Yan H, Decoding the EGFR mutation-induced drug resistance in lung cancer treatment by local surface geometric properties. Comput Biol Med 2015;63:293-300.

(4) Wang DD, Lee VH, Zhu G, Zou B, Ma L, Yan H. Selectivity profile of afatinib for EGFR-mutated non-small-cell lung cancer. Mol Biosyst 2016;12:1552-63.

(5) Wang DD, Ma L, Wong MP, Lee VH, Yan H. Contribution of EGFR and ErbB-3 heterodimerization to the EGFR mutation-induced gefitinib- and erlotinib-resistance in non-small-cell lung carcinoma treatment. PLoS One 2015;10:e0128360.

References

1. Stewart BW, Wild CP, editors. World Cancer Report 2014. WHO Press; 2014. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cancer.
2. Haley JD, Gullick WJ. Cancer Drug Discovery and Development: EGFR Signaling Networks in Cancer Therapy. Springer; 2008.
3. Singh I, Amin H, Rah B, Goswami A. Targeting EGFR and IGF 1R: a promising combination therapy for metastatic cancer. Front Biosci (Schol Ed) 2013;5:231-46.
4. Temraz S, Mukherji D, Shamseddine A. Dual targeting of HER3 and EGFR in colorectal tumors might overcome anti-EGFR resistance. Crit Rev Oncol Hematol 2016;101:151-7.
5. Liao BC, Lin CC, Yang JC. Novel EGFR inhibitors in non-small cell lung cancer: current status of Afatinib. Curr Oncol Rep 2017;19:4.