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NRF2-mediated changes in glutathione metabolism mediate the resistance of EGFR-T790M mutant lung cancer cells to erlotinib

Olivier E Pardo[1], William B Stokes[1], Hongde Li[2], Emily Chater[1], Rajat Roy[1], Elza De Bruin[3], Julian Downward[3], Michael J Seckl[1] and **Yulan Wang[2]**
[1]Imperial College London, UK
[2]Wuhan Institute of Physic and Mathematics, China
[3]CRUK-LIF, UK

EGFR tyrosine-kinase inhibitors (TKI) such as erlotinib are novel agents in the treatment of lung cancer. However, their efficacy is impaired by the development of drug-resistance through secondary receptor mutations (eg T790M). Although decreased affinity of the mutants for the inhibitors was considered responsible for this, we show that additional factors are at play. Following metabonomics profiling of erlotinib-sensitive/resistant cell pairs we found that the levels of glutathione (GSH) are considerably reduced in erlotinib-resistant (ER) cells. Using RNA interference and pharmacological inhibitors of GSH pathway enzymes, we demonstrate that increasing GSH levels in ER cells sensitises these to erlotinib. Conversely, reducing GSH levels renders sensitive cells resistant to the drug. We show that the reduction in GSH levels in ER cells is associated with the decreased transcription of the GSH synthesising enzymes, GCLC and GSS. This correlates with inhibition of NRF2, through increased KEAP1 levels and/or decreased expression of SQSTM1 and PALB2. We demonstrate these changes to be directly linked to the T790M-EGFR mutation, as introducing this mutant in HEK293 cells reduces GSH levels and decreases expression of SQSTM1 and PALB2. Finally, administration of ethacrynic acid, a GST inhibitor that increases intracellular GSH levels, re-sensitises resistant tumours to erlotininb in a xenograft mouse model. Our data identify a new resistance mechanism to EGFR TKIs and propose a novel therapeutic strategy to tackle this problem in the clinic.

Biography

Olivier E Pardo completed his Biochemistry and his Pharmacy degrees from the University Paris V, France. He then joined Imperial College London, UK where he obtained his PhD in 2002. The same year, he joined the laboratory of Prof. Julian Downward at Cancer Research UK, London Research Institute where he worked as a post-doctoral fellow on a number of both high-throughput/content and biochemistry projects. He now holds a position of team leader at Imperial College London, UK, where his laboratory investigates mechanisms of chemo-resistance and metastasis in lung cancer. He has a number of high-impact publications in the fields of cell signalling, drug resistance and cancer metastasis and is a member of the Lung Target EU FP7 consortium and the London Lung Cancer Alliance.

o.pardo@imperial .ac.uk

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