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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], Huiru Tang[2] and **Yulan Wang[2]**
[1]Imperial College London, UK
[2]Wuhan Institute of Physic and Mathematics, China
[3]Signal Transduction Laboratory, 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 (e g. 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 demonstrated that increasing GSH levels in ER cells sensitizes 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 synthesizing 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-sensitizes resistant tumors to erlotinib 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 Pardo studied Pharmacy and Pharmacology at the University Paris V, Paris, France, obtaining his Doctorate in Pharmacy in 1997. He then joined Imperial College London, where he completed his PhD in Biochemistry and Molecular Biology in 2002. Following a 4-year postdoctoral fellowship in the laboratory of Prof Julian Downward at the Cancer Research UK London Research Institute, he returned to Imperial College to start his own research team at the Division of Cancer. In addition, Dr Pardo is the course director for the MRes Cancer Biology at Imperial College, where he trains the next generation of Cancer researchers.

o.pardo@imperial.ac.uk

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