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Resistance to tyrosine kinase-targeted therapy in lung cancer: Autophagy and metabolic changes

Lung cancer is the commonest cancer killer worldwide. Tyrosine-kinase inhibitors (TKI) are novel agents in the treatment of this cancer. However, their efficacy is impaired by the rapid development of drug-resistance. Here, we discuss resistance to the first-generation EGFR inhibitors (eg. Erlotinib and SRC inhibitors eg. Dasatinib). The principal mechanism of resistance to first-generation EGFR inhibitors is the appearance of the T790M receptor mutation. Our metabolomics analysis revealed that resistance is associated with decreased cellular levels of glutathione (GSH), a direct consequence of the T790M mutation. This occurred because of decreased SQSTM1/NRF2-mediated transcription of GSH synthesizing enzymes in cell lines and clinical samples with T790M-EGFR. Increasing GSH levels in resistant cells re-sensitizes these to first-generation EGFR inhibitors *in vitro* and *in vivo*. As clinically-relevant compounds exist to achieve this, our finding may have profound therapeutic and economic consequences. Src family kinases (SFK) are commonly over-expressed/hyperactivated in lung cancer. However, despite their on-target efficacy, SRC inhibitors have failed to prevent tumour growth and improve patients' survival in multiple clinical trials. Here we show that this failure is associated with the induction of autophagy in treated cells that prevents these compounds from triggering apoptosis. Targeting autophagy, either genetically or using our novel small-molecule inhibitor, C1A, sensitizes lung cancer cell lines to Dasatinib both *in vitro* and *in vivo* by unlocking the apoptotic response. These findings propose new combinational therapeutic strategies that could resurrect the use of SRC inhibitors in the treatment of lung cancer.

Recent Publications

1. Hongde Li, William Stokes, Emily Chater, Rajat Roy, Elza de Bruin, Yili Hu, Egbert F Smit, Guus J J E Heynen, Rene Bernards, Julian Downward, Michael J Seckl, Yulan Wang, Huiru Tang and Olivier E Pardo (2016) Decreased glutathione synthesis mediates EGFR T790M-driven erlotinib resistance. Cell Discov. 2:16031.
2. Ewa Rupniewska, Rajat Roy, Francesco A Mauri, Xinxue Liu, Guido Bellezza, Lucio Cagini, Mattia Barbareschi, Stefano Ferrero, Harriet Taylor, Fränze Progatzky, Anna M Tommasi, Jonathan Lamb, Maggie Dallman, Ana Costa-Pereira, Michael J Seckl and Olivier E Pardo (2018) Targeting autophagy sensitizes lung cancer cells to Src family kinase inhibitors. OncoTarget. 9(44):27346-27362.

Biography

Olivier E Pardo has completed his Graduation from the Faculty of Pharmacy Paris-V, France where he was awarded a Doctorate in Industrial Pharmacy in 1997; PhD in Biochemistry and Molecular Biology at Imperial College-London in 2002 and Post-doctoral experience in the laboratory of Prof. Julian Downward at the CRUK-London Research Institute where he worked on the regulation of apoptotic cell death and cell migration. He created the Cellular Regulatory Networks lab at Imperial College, Department of Surgery and Cancer in 2006. His team focuses on understanding the molecular mechanisms underlying chemo-resistance and metastasis in lung and other cancers.

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