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

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Tyrosine-kinase inhibitors (TKI) are novel agents in the treatment of lung cancer, the commonest cancer killer worldwide. However, their efficacy is impaired by the rapid development of drug-resistance through various mechanisms. Here, we will discuss resistance to first-generation EGFR inhibitors (e.g. Erlotinib) and SRC inhibitors (e.g. 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. Increasing GSH levels in resistant cells re-sensitizes these to first-generation EGFR inhibitors in vitro and in vivo. As compounds exist in the clinic to achieve this, our finding may have profound therapeutic implications. Src family kinases (SFK) are commonly overexpressed or hyperactivated in lung cancer cell lines and clinical samples. However, despite their on-target efficacy, SRC inhibitors have failed to prevent tumor 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 cell death. 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.

Biography

Olivier E Pardo graduated from the Faculty of Pharmacy Paris-V, France where he was awarded a Doctorate in Industrial Pharmacy (1997). He then completed his PhD in Biochemistry and Molecular Biology at Imperial College-London (2002). He obtained 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. In 2006, he created the Cellular Regulatory Networks lab at Imperial College, Department of Surgery and Cancer. His team focuses on understanding the molecular mechanisms underlying chemo-resistance and metastasis in lung and other cancers.

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