

Targeting RSK4 prevents both chemoresistance and metastasis in lung cancer

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Abstract

Background

Lung cancer is the primary cause of cancer death worldwide with a 5-year survival rate <5%. Non-small cell lung cancer (NSCLC) accounts for 85% of cases with adenocarcinoma being the major subtype. Patients almost invariably develop metastatic drug-resistant disease and this is responsible for our failure to provide curative therapy. Hence, a better understanding of the mechanisms underlying these biological processes is urgently required to improve clinical outcome.

The 90 kDa ribosomal S6 kinases (RSKs) are downstream effectors of the Ras/MAPK cascade. RSKs are highly conserved serine/threonine protein kinases implicated in diverse cellular processes, including cell survival, proliferation, migration and invasion. Four isoforms exist in humans (RSK1-4) that are uniquely characterised by the presence of two non-identical N- and C-terminus kinase domains.

Method

Two kinome siRNA screens were performed to identify novel regulators of drug response and migration/invasion in lung and bladder cancer cells. RSK4 emerged as a novel regulator of both processes.

Results

We show here that RSK4, contrary to RSK1, promotes both drug resistance and metastasis in lung cancer. This kinase is overexpressed in the majority of NSCLC biopsies and this correlates with poor overall survival in lung adenocarcinoma patients. The knockdown of RSK4 sensitises lung cancer cells to chemotherapy and prevents their migration and invasiveness in vitro and

in vivo. RSK4 downregulation decreases the anti-apoptotic proteins Bcl2 and cIAP1/2 which correlates with increased apoptotic signalling. RSK4 silencing also induces mesenchymal-epithelial transition (MET) through inhibition of NF κ B activity. A small-molecule inhibitor screen identified several floxacins, including trovafloxacin, as potent allosteric inhibitors of RSK4 activation. Trovafloxacin reproduced all effects of RSK4 silencing in vitro and in vivo and is predicted to bind a novel allosteric site revealed by our RSK4 N-terminal kinase domain crystal structure.

Conclusion

Taken together, our data demonstrate that RSK4 represents a promising novel therapeutic target in lung cancer.