JOURNAL CLUB

GATA2, a novel therapeutic target for RAS-oncogene-addicted NSCLC?

Targeted cancer therapy with Epidermal Growth Factor Receptor (EGFR)-tyrosine kinase inhibitors (TKI), such as Gefitinib and Erlotinib, is revolutionising treatment of non-small cell lung cancer (NSCLC) in patients with activating mutations in EGFR. Another proto-oncogene, KRAS, is mutually exclusive to EGFR mutations and predicts poor response to TKIs, therefore offering an attractive therapeutic target to circumvent intrinsic EGFR-TKI resistance.

However, despite a wealth of data on the RAS signalling pathway, currently there is no effective therapeutic inhibitor. Signalling pathways downstream of RAS, which may be more susceptible to inhibition, are, therefore, an area of great interest. Kumar *et al* consider the role of the GATA2 transcriptional network in RAS-oncogene-addicted NSCLC.

Using gene expression and genome occupancy analysis, the investigators demonstrate that NSCLC cell lines with mutations in KRAS and related RTK/RAS oncogenes depend upon GATA2 for survival through regulation of the proteasome, Interleukin 1 (IL1)/Nuclear Factor Kappa Beta (NFKB) and the Rho-signalling cascade. In vivo, GATA2 loss prevented tumour development and induced tumour regression in established tumours in a KRAS-driven NSCLC murine model. Similar regression was seen with the study of pharmacological inhibitors of downstream pathways.

This work remains to be validated in clinical trials but is an appealing approach: several of the nodes of the GATA2 signalling pathway are amenable to existing approved clinical agents, facilitating translation to clinical therapies. This interesting study describes a new means by which KRAS-mutant NSCLC could be tackled, and offers another step forward in the development of personalised approaches to treating lung cancer.

► Kumar MS, Hancock DC, Molina-Arcas M, *et al*. The GATA2 transcriptional network is requisite for RAS oncogene-driven non-small cell lung cancer. *Cell* 2012;149:642–55.

Richard Lee

Correspondence to Dr Richard Lee, ST4 Specialty Trainee in Respiratory Medicine and General Internal Medicine, Darent Valley Hospital NHS Trust, Kent DA2 8DA, UK; richwlee@gmail.com

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