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LUNG CANCER

Driver-mutation-dependent stratification: learning from STAT3

KRAS and *EGFR* mutations are the most frequent genetic alterations found in lung cancer. While several anti-EGFR therapies have been developed, *KRAS* is still considered an undruggable target.

An alternative strategy to treat *KRAS*-mutated tumours relies on targeting KRAS downstream or parallel pathways, as described in a study led by Emilio Casanova, in which an unexpected tumour-suppressive role of STAT3 in *KRAS*-mutant lung cancer was described.

The investigators used the inducible $KRAS^{G12D/+}$ mouse lung cancer model to analyse tumour development and progression in the presence or absence of STAT3, and performed parallel experiments in a xenograft model with a human lung cancer cell line. "STAT3 has a tumour suppressive function in both lung cancer initiation and progression," says Casanova, and "in the absence of STAT3, enhanced expression of the chemokine IL-8 increased tumour growth via neoangiogenesis and immune cell infiltration." Of note, blockade of the IL-8–CXCR2 pathway reverted the observed phenotype in STAT3-deficient tumours.

"These findings elucidate the importance of stratifying patients according to their driver mutation," highlights Casanova. STAT3 inhibitors are currently being investigated in trials and this study suggests that patients with *KRAS*-mutated lung tumours might not respond to STAT3 inhibition. However, patients with *EGFR*-mutated tumours might still benefit from STAT3 inhibition as increased STAT3 activation levels have been detected in these tumours.

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Original article Grabner, B. *et al.* Disruption of STAT3 signalling promotes KRAS-induced lung tumorigenesis. *Nat. Commun.* doi:10.1038/ncomms7285