LUNG CANCER

Expanding the range

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Non-small-cell lung cancer (NSCLC) includes several subtypes that, although different in histology, all have a poor prognosis. A study in *Nature* now shows that inactivation of the tumour-suppressor gene serine/threonine kinase 11 (also known as *LKB1*) underlies some of these variants, and has multiple effects on lung tumorigenesis.

Although *LKB1* inactivation occurs in lung adenocarcinomas along with *KRAS* activation, mouse embryonic fibroblasts lacking *Lkb1* are resistant to transformation with oncogenic Ras. To address this conundrum Nabeel Bardeesy, Norman Sharpless, Kwok-Kin Wong and colleagues studied the effect of *Lkb1* inactivation in a mouse model of *Kras*-induced lung cancer.


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Mice expressing oncogenic *Kras* ($Kras^{G12D}$) in lung cells developed non-metastatic tumours after a long latency. The concomitant loss of the tumour suppressors *Trp53*, *Ink4a* or both *Ink4a* and *Arf*, promoted $Kras^{G12D}$-induced lung tumorigenesis; but, surprisingly, *Lkb1* loss had a stronger effect than any of these tumour suppressors, causing more and larger tumours, which had a shorter latency and more frequently metastasized. In the absence of $Kras^{G12D}$, *Lkb1* inactivation does not cause lung cancer, suggesting that LKB1 is crucial for suppressing $Kras^{G12D}$-induced tumorigenesis.

Interestingly, *Lkb1* inactivation expanded the range of histological tumour variants because, in addition to the adenocarcinomas observed in $Kras^{G12D}$ mice (with or without inactivation of *Trp53*, *Ink4a* or both *Ink4a* and *Arf*), $Kras^{G12D}$;$Lkb1^{-/-}$ mice also developed squamous cell carcinomas (SCCs), adenosquamous carcinomas and large-cell carcinomas (LCCs), indicating that LKB1 has a role in cell differentiation. Consistent with these findings, the authors found inactivating mutations of *LKB1* in all the histological subtypes of human NSCLC.

How does LKB1 exert its anti-tumour activity? LKB1 is known to function through activation of p53 and/or INK4a and ARF, but $Kras^{G12D}$;$Lkb1^{-/-}$ tumours are more aggressive than those lacking p53 or INK4a and ARF, indicating that LKB1 has anti-tumour activity that is independent of these other tumour suppressors. Consistent with this, *LKB1* expression in a human NSCLC cell line that lacks both *LKB1,* and INK4a and ARF function inhibited anchorage-independent growth and metastasis formation in mice after tail-vein injection, without affecting the expression of p53 and its targets.

Gene-expression analysis of $Kras^{G12D}$ mouse tumours and human NSCLC cells with different *LKB1* status identified several metastasis-promoting genes as LKB1 targets. Inactivation of one of these, *NEDD9*, by RNA interference, inhibited migration and invasion of NSCLC cells *in vitro*, indicating that the *NEDD9* upregulation observed following *LKB1* loss could be crucial in promoting metastases.

Altogether these data show that LKB1 suppresses lung cancer by inhibiting tumour initiation, differentiation and metastasis, and therefore LKB1 loss could represent a useful prognostic marker of aggressive disease. It will be important to determine whether LKB1 targets might be exploited for new therapeutic strategies.

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