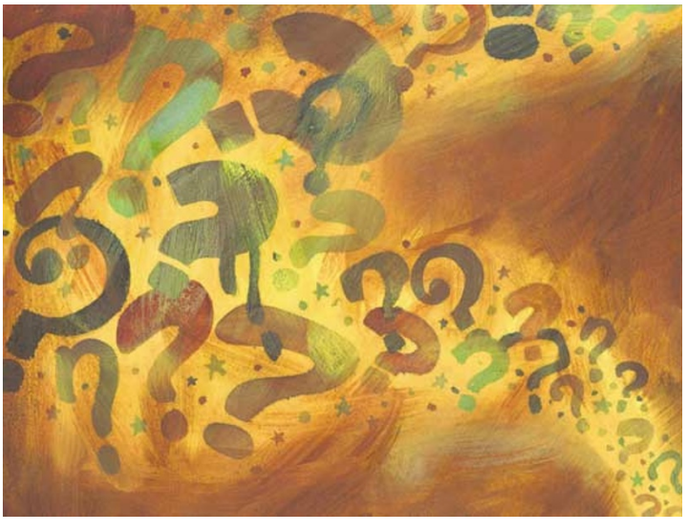
HIGHLIGHTS

TUMOUR SUPPRESSORS

Mystery molecule



Germ-line mutations in *LKB1* are associated with Peutz–Jeghers syndrome (PJS) — a disorder that is characterized by a predisposition to gastrointestinal polyposis and cancer. The pathogenesis of PJS and the role of LKB1 in this process are not well understood, and a new mouse model has only now begun to reveal how complex this disease really is.

PJS is an unusual hereditary cancer syndrome. Although germ-line mutations in *LKB1* are associated with a predisposition to cancer, the gene is rarely mutated or epigenetically silenced in sporadic tumours. The intestinal polyps that develop in PJS patients are not highly malignant, and it is not clear whether they are precursors to the carcinomas that these patients eventually develop. To investigate these paradoxical features of PJS, Bardeesy *et al.* used the Cre-lox system to generate mice that carry a conditional *Lkb1* allele. *Lkb1*-null mice died during embryonic development, whereas $Lkb1^{+/-}$ mice developed intestinal polyps that were identical to those seen in humans with PJS.

So what happens at the cellular level in these mice? *Lkb1* is highly expressed by mouse embryonic fibroblasts. After about nine passages, normal fibroblasts undergo growth arrest, but *Lkb1*-null cells continued growing even after 40 population doublings, indicating a resistance to passage-induced senescence. Although passage-induced senescence is typically attributed to INK4A or p53 activity, these signalling pathways remained intact in *Lkb1*-null fibroblasts.

Lkb1-null fibroblasts were also resistant to transformation by activated Hras. This phenotype is consistent with the low incidence of *Ras* mutations found in PJS polyps. The authors performed transcriptional profiling on *Lkb1*-null cells, and observed alterations in the expression pattern of secreted signalling molecules and regulators of the extracellular matrix, so Lkb1-deficient cells might help create a permissive environment for tumour growth.

On the surface, the resistance to Ras transformation observed in *Lkb1*-null cells seems to contradict the polyposis and carcinoma-prone condition that is associated with *LKB1* deficiency. On the other hand, PJS polyps themselves rarely show features of dysplasia, and *LKB1* mutations are only rarely found in tumours in individuals who do not carry germ-line mutations in this gene. One possible explanation for these seemingly contradictory observations is that although LKB1 loss deregulates growth, there might only be certain oncogenic events that can fully transform these cells. Since PJS patients have a high incidence of carcinomas, the timing of *LKB1* mutation might also affect outcome. The authors propose that loss of *LKB1* in normal cells could result in the formation of benign tumours, whereas loss in advanced neoplasms could promote malignant progression.

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References and links

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FURTHER READING Yoo, L. I., Chung, D. C. & Yuan, J. LKB1 — a master tumour suppressor of the small intestine and beyond. *Nature Rev. Cancer* **2**, 529–535 (2002)
WEB SITE
Ron DePinho's lab:
http://www.hms.harvard.edu/dms/bbs/fac/depinho.html