GENETICS

Becoming mobile

Mouse models have provided valuable insights into cancer biology, but have been limited in terms of performing unbiased genetic screens. Now an *in vivo* RNA interference screening approach has been used to identify determinants of lymphoma progression, showing that genes involved in cell motility are crucial in this process.

Michael Hemann and colleagues combined the *Eμ-Myc* mouse system, a model of B cell lymphoma, with short hairpin RNA (shRNA) screening using a pool of ~2,250 hairpins that targeted 1,000 genes that have potential or known roles in cancer. They found that 600–900 unique shRNAs could be identified in lymphomas from individual mice, indicating that a large proportion of the original library complexity was retained in this *in vivo* setting.

What genes specifically affect *in vivo* lymphoma growth? The authors selected genes for which two or more shRNAs were depleted by at least tenfold in *Eμ-Myc* mice. They found that the targets were enriched for genes involved in cell motility processes, such as dynamic actin reorganization and cell adhesion. They then validated a subset of these genes, including those that encode RAC2, a Rho GTPase involved in lamellipodia formation during cell migration; CRKL, which is involved in Rac activation; and twinfilin (TWF1), which binds to actin.

Do these proteins affect cancer cell migration? *Eμ-Myc* lymphoma cells in which the expression of RAC2, CRKL or TWF1 was knocked down showed motility defects in Transwell migration assays. In addition, the authors found that suppression of RAC2 was selected against in common sites of lymphoma metastasis, suggesting that RAC2 could be therapeutically targeted. Supporting this idea, mice that were injected with lymphoma cells in which RAC2 or TWF1 had been knocked down using shRNA lived longer than *Eμ-Myc* mice. Moreover, treatment with a RAC1 and RAC2 inhibitor, NSC23766, also improved the survival of *Eμ-Myc* lymphoma-bearing mice. Combinations of shRNAs targeting motility components synergised to inhibit lymphoma growth.

When the authors treated lymphoma-bearing *Eμ-Myc* mice with the front-line chemotherapeutic vincristine and then knocked down *Rac2* or *Twf1* with shRNAs, survival was extended, suggesting that RAC2- and TWF1-dependent tumour cell motility is important in lymphoma relapse after vincristine treatment. Therefore, combining inhibitors of these targets with conventional chemotherapeutics may prove beneficial in lymphoma treatment.

The results of this study indicate that this technique is applicable to the large-scale identification of new cancer genes and can provide insights into tumour progression. The authors suggest that this approach could also be used to dissect genes that affect the therapeutic response or tissue-specific tumour metastasis.

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ORIGINAL RESEARCH PAPER Meacham, C. E. *et al.* *In vivo* RNAi screening identifies regulators of actin dynamics as key deteminants of lymphoma progression. *Nature Genet.* **41**, 1133–1137 (2009)