They studied expression of *CXCR4* and the HIF target genes carbonic anhydrase (*CA9*) and *GLUT1* in RCCs, and mRNA levels of all three were significantly higher in clear-cell RCC than in papillary RCC or normal renal tissue. *CXCR4* expression was investigated in a wide range of RCCs using renal cancer tissue microarrays. Although there was no correlation between high level *CXCR4* expression and tumour stage and/or differentiation grade, there was a strong correlation between *CXCR4* expression and poor survival.

These results provide a mechanism of how RCCs acquire the ability to metastasize. The absence of oxygen — characteristic of highly aggressive tumours — induces expression of *CXCR4*, allowing metastatic RCCs to find their way to distant sites. In addition, tumour cells could be primed to spread early in tumorigenesis by acquiring mutations in *VHL*.

Emma Croager

References and links

ORIGINAL RESEARCH PAPER Staller, P. *et al*. Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL. *Nature* **425**, 307–311 (2003)

FURTHER READING Bernards, R. Cues for migration. *Nature* **425**, 247–248 (2003)

WEB SITE

Wilhelm Krek's lab:
http://www.verw.ethz.ch/cgi-win/whoShow.exe/ws7?ID=1678&lang=engl

model are yet to be determined, but should include identification of contributing genetic lesions and the testing of treatment strategies.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Meuwissen, R. *et al.* Induction of small cell lung cancer by somatic inactivation of both *Trp53* and *Rb1* in a conditional mouse model. *Cancer Cell* **4**, 181–189 (2003)

WEB SITE

Anton Berns's lab:
http://www.nki.nl/nkidep/h5/berns_main.htm

TUMORIGENESIS

Complex catastrophe

Mutations in the CDC42 GTPase that cause it to stay in the active GTP-bound form are oncogenic, and injection of this form into nude mice results in tumour formation. However, the mechanism for this is unknown, as it does not seem to be related to the known ability of CDC42 to regulate the actin cytoskeleton. Now, Richard Cerione and colleagues report in *Cell* that active CDC42 sequesters the c-CBL ubiquitin ligase into a complex with COOL1, so that it is unable to ubiquitylate and downregulate the epidermal growth factor receptor (EGFR).

COOL1 was originally placed in the CDC42 pathway because of its identification following two-hybrid experiments with the CDC42 target PAK. Further two-hybrid and immunoprecipitation experiments showed that COOL1 could, in turn, bind to CBLB. The authors continued with these analyses and found that COOL1 could also bind c-CBL, and that c-CBL and COOL1 could bind CDC42, but only mutated, constitutively active forms. EGF can activate CDC42, and the authors found that addition of EGF stimulated formation of a complex between these three proteins.

Formation of this complex seems to be essential for the transforming ability of CDC42, as removal of 13 amino acids that constitute the RHO-insert region diminished the ability of CDC42 to interact with COOL1 and CDC42-induced colony formation in soft agar — a reliable indicator of malignant transformation. COOL1 mutants that are unable to bind to CDC42, and c-CBL mutants that are unable to bind to COOL1, also failed to induce colony formation in soft agar or growth of fibroblasts in low serum.

So, how does this complex initiate transformation? c-CBL is a ubiquitin ligase that can downregulate EGFR, so perhaps its interaction with CDC42 alters this ability. Indeed, expression of activated CDC42 inhibits c-CBL from ubiquitylating EGFR, and prevents the EGF-dependent phosphorylation of c-CBL that stimulates its ubiquitin-ligase activity. Western blotting confirmed that whereas the EGFR is normally downregulated within 5–45 minutes after addition of EGF, this is not the case when activated CDC42 is also expressed — EGFR could still be detected, albeit at a lower level, after 6 hours.

CDC42 therefore seems to promote transformation by sequestering c-CBL and preventing it from degrading EGFR. This results in the maintenance of the EGF signalling pathway that operates through the mitogen-activated protein kinase (MAPK) cascade. Inhibition of this pathway with inhibitors of either EGFR or MAPK kinase (MEK) prevents cells with activated CDC42 from growing in low serum, and they lose their transformed morphology.

EGFRs are frequently upregulated in breast cancer and glioblastomas; although gene amplification is one mechanism by which this might occur, oncogenic mutations that result in activated CDC42 might well constitute another.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Wu, W. J. *et al.* Activated Cdc42 sequesters c-Cbl and prevents EGF receptor degradation. *Cell* **114**, 715–725 (2003)

WEB SITE

Richard Cerione's lab:
http://web.vet.cornell.edu/public/research/gradEd/cerione.html