TUMORIGENESIS

Converging paths

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children, yet little is known about the molecular events that are associated with tumorigenesis and progression. Lack of a mouse model of this cancer has been a significant obstacle to this research. In the November issue of *Nature Medicine*, Glenn Merlino and colleagues report that defects in several different pathways need to converge to form these tumours, as mice with disruptions in the *Cdkn2*a locus and activation of the c-Met signalling pathway develop RMS.

The c-*MET* oncogene encodes a receptor tyrosine kinase that binds to hepatocyte growth factor/scatter factor (HGF/SF). Activation of this signalling pathway regulates cell proliferation, motility, survival, extracellular-matrix degradation and angiogenesis, and has been associated with various human cancers — including RMS. Sarcoma development has also been associated with the *CDKN2A* locus, which encodes two tumour-suppressor transcipts, INK4A and ARF. These gene products regulate cell-cycle progression, apoptosis and senescence.

To investigate a possible interaction between the c-MET and INK4A/ARF signalling pathways in sarcoma development, Sharp *et al.* overexpressed an *Hgf/Sf* transgene in *Cdkn2a*-null mice. They found that by four months after birth, nearly all of the mice had developed multifocal sarcomatous malignanices in trunk or limb skeletal muscle. Overexpression of *Hgf/Sf* in *Cdkn2a*$^{+/-}$ mice caused RMS by 8.8 months. These tumours had many features in common with human embryonal RMS. The defects in these two signalling pathways had a synergistic effect, as less than 10% of mice that overexpressed *Hgf/Sf*, or those that carried only a homozygous or heterozygous deletion in *Cdkn2a*, developed RMS-like tumours.

To determine the nature of the synergy by which c-Met activation and *Cdkn2a* inactivation promote RMS, Sharp *et al.* studied skeletal muscle cells from mutant mice. They found that myogenesis was suppressed, as differentiation — but not proliferation — of *Cdkn2a*-null myoblasts was blocked after Hgf/Sf exposure. The authors suggest that constitutive activation of c-Met in the absence of Ink4a/Arf creates an expanded premalignant population of myogenic precursors that are incapable of undergoing cell-cycle arrest or apoptosis. Therapeutics designed to target both of these pathways might be useful in treating this childhood cancer.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Sharp, R. *et al*. Synergism between INK4A/ARF inactivation and aberrant HGF/SF signaling in rhabdomyosarcomagenesis. *Nature Med*. 7 Oct 2002 (doi:10.1038/nm787).

FURTHER READING Trusolino, L. & Comoglio, P. M. Scatter-factor and semaphorin receptors: cell signalling for invasive growth. *Nature Rev. Cancer* **2**, 289–300 (2002)

WEB SITE

Glenn Merlino's lab: http://ccr.cancer.gov/Staff/Staff.asp?StaffID=671

IN BRIEF

TUMOUR SUPPRESSORS

DBC2, a candidate for a tumor suppressor gene involved in breast cancer.

Hamaguchi, M. *et al. Proc. Natl Acad. Sci. USA* **99**, 13647–13652 (2002)

Tumour suppressors such as *BRCA1* and *BRCA2*, which are mutated in familial breast cancer, have previously been identified, but what of those that are responsible for sporadic breast cancer? The gene *deleted in breast cancer* (*DBC2*) was cloned from chromosome 8p21, following the discovery that this region is deleted in some breast cancers. It is homozygously deleted in 3.5% of breast tumours analysed. Expression of wild-type, but not mutated, *DBC2* in breast cancer cells inhibits their growth.

PROSTATE CANCER

The polycomb group protein EZH2 is involved in progression of prostate cancer.

Varambally, S. *et al. Nature* **419**, 624–629 (2002)

Metastatic prostate cancer is essentially incurable, so the identification of genes that are involved in its progression to this stage is an important task. Gene-expression profiling has revealed that the polycomb protein EZH2 — a transcriptional repressor — is overexpressed in hormone-refractory metastatic prostate cancer. Its overexpression in localized prostate cancer also indicates a poorer prognosis, so it might be involved in the progression of prostate cancer, as well as being a marker of metastatic cancer.

ANGIOGENESIS

PPARγ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis.

Panigrahy, D. *et al. J. Clin. Invest.* **110**, 923–932 (2002)

The PPARγ nuclear receptor is known to inhibit growth and/or induce differentiation in cancer cells, and Dipak Panigrahy *et al.* now report that it is highly expressed by the endothelial cells that surround the tumour. The PPARγ ligand rosiglitazone was shown to suppress both primary tumour growth and metastasis by inhibiting angiogenesis — it decreases production of VEGF. By inhibiting angiogenesis, PPARγ ligands could therefore be a useful anticancer therapeutic strategy.

APOPTOSIS

BID regulation by p53 contributes to chemosensitivity.

Sax, J. K. *et al. Nature Cell Biol.* **4**, 842–849 (2002)

Chemotherapy acts against cancer cells by damaging their DNA to such an extent that the cells undergo apoptosis. This response is mediated by the transcriptional regulator and tumour suppressor p53, but the target genes that are involved have not been fully elucidated. Wafik El-Deiry and colleagues show that the pro-apoptotic gene *BID* — a member of the BCL2 family — is upregulated in response to γ-irradiation, and that mice deficient for Bid are resistant to the chemotherapeutic adriamycin. *BID* is therefore a p53-responsive chemosensitivity gene.