inhibitors in 3 out of 5 Notch-1-dependent human T-ALL cell lines and, conversely, that expression of ICN1 can rescue the growth of transgenic *MYC*-driven murine T-ALL cells when expression of the human *MYC* transgene is suppressed. Interestingly, the expression of ICN1 in these cells induces the expression of endogenous *Myc* in the absence of transgenic *MYC* expression, which confirms the functional importance of the Notch-1–MYC pathway.

Although the inhibition of Notch 1 decreased the expression of MYC in all cell lines tested, not all human T-ALL cell lines were rescued from Notch 1 inhibition by MYC alone, which indicates that other targets of ICN1 also contribute to T-ALL cell growth. Nevertheless, these findings are important initial steps towards understanding the oncogenic pathways downstream of Notch 1.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Weng, A. P. *et al.* c-Myc is an important target of Notch1 in T cell acute lymphoblastic leukemia/lymphoma. *Genes Dev.* 17 July 2006 (doi: 10.1101/gad.1450406)
FURTHER READING Grabher, C., von Boehmer, H. & Look, A. T. Notch 1 activation in the molecular pathogenesis of T-cell acute lymphoblastic leukaemia. *Nature Rev. Cancer* **6**, 347–359 (2006)

to doxorubicin, and then treated with doxorubicin. Vaccination with pFAP or treatment with doxorubicin suppressed but did not eradicate tumour growth, but vaccination and drug therapy in combination led to complete tumour rejection in 50% of the mice. This experiment was repeated in mice with established metastases, and treatment with pFAP and doxorubicin extended the lifespan of these mice threefold.

As FAP is stably overexpressed in most colon, breast and lung carcinomas, and vaccination increases the intra-tumoral uptake of chemotherapeutic agents, this is an attractive approach to study further.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Loeffler, M. *et al.* Targeting tumour-associated fibroblasts improves cancer chemotherapy by increasing intratumoural drug uptake. *J. Clin. Invest.* **116**, 1955–1962 (2006)
FURTHER READING Kalluri, R. & Zeisberg, M. Fibroblasts in cancer. *Nature Rev. Cancer* **6**, 392–401 (2006)

ONCOGENES

Keeping it in the family

The expression of MITF, a member of the MiT family of transcription factors and a master regulator of melanocytic differentiation, is often seen in clear-cell sarcoma (CCS). However, neither the mechanism of MITF regulation in CCS nor its function were known. Now, David Fisher and colleagues show that the CCS fusion protein Ewing sarcoma breakpoint region 1 (EWS)–activating transcription factor 1 (ATF1) is oncogenic because it regulates MITF expression.

CCS is a soft-tissue malignancy that is molecularly defined by the *EWS–ATF1* translocation. Despite being a sarcoma, CCS contains premelanosomes, expresses markers of melanocytic differentiation and, in some cases, produces melanin.

Fisher and colleagues investigated three human CCS lines that express the melanocyte-specific isoform of MITF (M-MITF). Immunoprecipitation using an EWS-selective antibody revealed that EWS–ATF1 occupied the *M-MITF* promoter in all three cell lines. So, does EWS–ATF1 regulate transcription of *M-MITF*? A reporter gene that directs luciferase expression from the *M-MITF* promoter was constitutively active in all three CCS cell lines. Furthermore, expression of dominant-negative EWS–ATF1 in CCS cells resulted in the selective inhibition of endogenous *M-MITF* expression. So, EWS–ATF1 is a necessary transactivator of the *M-MITF* promoter in CCS.

But what is the role of EWS–ATF1-mediated M-MITF expression in CCS? Dominant-negative inhibition of EWS–ATF1 significantly reduced the expression of the M-MITF-target genes *PMEL17* (which encodes the HMB45 antigen used for the pathological identification of CCS) and *MLANA* (a melanocyte marker). Pigmentation was also diminished in EWS–ATF1-inhibited CCS cells, and this could be rescued by M-MITF expression. Together, these findings indicate that EWS–ATF1 functions through M-MITF to mediate the melanocytic differentiation that is characteristic of CCS. Moreover, M-MITF activity was demonstrated to be necessary for CCS cell survival and proliferation: the inhibition of either EWS–ATF1 or M-MITF abrogated CCS colony formation. Interestingly, the expression of MiT-family members TFEB or TFE3 — oncoproteins that are translocated in alveolar soft-part sarcomas and some papillary renal-cell carcinomas — rescued cell viability in M-MITF-inhibited CCS cells in a dose-dependent manner. This indicates that MiT family members can functionally replace each other.

A xenograft model was used to study CCS tumour growth *in vivo*. RNA inhibition of *EWS–ATF1* potently inhibited *in vivo* tumour growth, which could be rescued by co-expression of M-MITF. The authors conclude that in CCS, the EWS–ATF1 fusion protein functions by targeting *M-MITF* to promote tumour cell survival and proliferation.

They propose that CCS could be grouped with melanoma, paediatric renal-cell carcinoma and alveolar soft-part sarcoma to form a family of MiT-associated human cancers, each showing distinct oncogenic deregulation of MiT-family genes. These 'MiT tumours' are clinically and morphologically distinct malignancies that would not otherwise be co-classified, but share characteristics of particular resistance to traditional chemotherapies and radiation therapy. The recognition of a common oncogene family in these seemingly diverse malignancies might aid the discovery of improved therapeutic approaches.

Rebecca Robey,
Assistant Editor, Oncogene

ORIGINAL RESEARCH PAPER Davis, I. J. *et al.* Oncogenic MITF dysregulation in clear cell sarcoma: defining the MiT family of human cancers. *Cancer Cell* **9**, 473–484 (2006)