IN BRIEF

MULTIPLE MYELOMA

Destruction of Ikaros

The thalidomide-like drug lenalidomide is used to treat multiple myeloma, but its mechanism of action is not known. Two studies have shown that lenalidomide induces proteasomal degradation of Ikaros family zinc finger protein 1 (IKZF1) and IKZF3 through cereblon (CRBN), a substrate-recognition component of a cullin-dependent ubiquitin ligase. Loss of IKZF1 and IKZF3 was required for the therapeutic effect of lenalidomide. Other studies have shown that inhibition of CRBN and stabilization of its substrates mediates the limb defects observed following *in utero* exposure to thalidomide-like drugs. Therefore, these results in multiple myeloma imply that these drugs do not simply inhibit CRBN, but modify the substrate specificity of CRBN, and that the teratogenic and anticancer effects of thalidomide-like drugs can be uncoupled.

ORIGINAL RESEARCH PAPERS Krönke, J. *et al.* Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* http://dx.doi.org/10.1126/science.1244851 (2013) | Lu, G. *et al.* The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* http://dx.doi.org/10.1126/science.1244917 (2013)

EPIGENETICS

Context-dependent role of SWI/SNF

The SWI/SNF chromatin-remodelling complex suppresses tumours in many tissues. Shi *et al.* found that, in acute leukaemias, SWI/SNF complexes containing the ATPase subunit BRG1 (also known as SMARCA4) have an oncogenic function. BRG1 occupied lineage-specific enhancers clustered 1.7 Mb downstream of *MYC* in leukaemia cells and maintained *MYC* expression by sustaining transcription factor occupancy and allowing long-range interactions with the *MYC* promoter. This enhancer cluster is amplified in ~3% of acute myeloid leukaemias, suggesting that it is functionally relevant in human leukaemias. Loss of BRG1 ATPase activity inhibited leukaemia cell proliferation, indicating that ATPase inhibition would be desirable therapeutically. However, targeting this activity would have to be balanced with the tumour-suppressing effects of BRG1 in other tissues.

ORIGINAL RESEARCH PAPER Shi, J. *et al.* Role of SWI/SNF in acute leukemia maintenance and enhancer-mediated *Myc* regulation. *Genes Dev.* http://dx.doi.org/10.1101/gad.232710.113 (2013)

MICRORNA

Self-regulated transcription

Insulin-like growth factor 2 (IGF2) is often overexpressed in paediatric cancers, including Wilms' tumours and sarcomas. *IGF2* is maternally imprinted, and increased expression is attributed in part to loss of imprinting at fetal promoters. To look for other modes of regulation of *IGF2* expression, Liu *et al.* examined microRNA expression in primary Wilms' tumours and found that miR-483-5p, which is located in an intron of *IGF2*, was overexpressed compared with fetal kidney tissue (from which Wilms' tumours are thought to arise). miR-483-5p upregulated the transcription of *IGF2* mRNA in Ewing's sarcoma cell lines (Wilms' tumour cell lines are scarce), and nuclear miR-483-5p bound the 5′ untranslated region of *IGF2* mRNA and enhanced its transcription. Ectopic expression of miR-483-5p in sarcoma cells increased tumour size in mice, reinforcing the role of this microRNA and positive feedback regulation of its host gene in tumorigenesis.

ORIGINAL RESEARCH PAPER Liu, M. *et al.* The *IGF2* intronic miR-483 selectively enhances transcription from *IGF2* fetal promoters and enhances tumorigenesis. *Genes Dev.* **27**, 2543–2548 (2013)