TUMOUR SUPPRESSORS

House of cards

Tumour suppressors such as ARF are multifunctional proteins that regulate a range of cell activities. But what then regulates the tumour suppressors? Pier Paolo Pandolfi and colleagues have shown that a transcription factor named Pokemon shuts down expression of ARF, and possibly other tumour-suppressor genes, to promote tumorigenesis.

Pokemon is a member of the POK family of DNA-binding proteins, which recruit histone deacetylases to promote chromatin remodelling. Pokemon has previously been shown to regulate differentiation of haematopoietic cells, and it physically interacts with BCL6, another haematopoietic cell transcription factor. Dysregulated BCL6 activity has been associated with lymphomagenesis. So the authors investigated whether alterations in Pokemon function might also impair cellular differentiation and lead to lymphoma.

They first observed that Pokemon-null fibroblasts were resistant to transformation by combinations of oncogenes that have tumorigenic effects in normal fibroblasts, such as activated *HRAS*, *E1A* or *MYC*. Conversely, fibroblasts that expressed transgenic Pokemon were resistant to apoptosis and senescence. *Pokemon* and *BCL6* seemed to function together as oncogenes, as Pokemon expression was required for the immortalizing and transforming capabilities of BCL6 in fibroblasts.

As Pokemon is a transcription factor, Pandolfi's group set out to find its gene targets. *ARF* seemed like a logical candidate, because its inactivation promotes MYC and RAS-mediated transformation of cells. Indeed, they found several Pokemon-binding sites in the *ARF* promoter, and showed that Pokemon binding at this site was indispensable for repression of *ARF* transcription. Loss of *ARF* rescued the transformability of Pokemon-null cells, so *ARF* suppression seemed to be a key mechanism of Pokemon's oncogenic effect.

What happens *in vivo*? Transgenic mice that expressed Pokemon specifically in the immature T-cell and B-cell lineage developed aggressive T-cell lymphomas, and the authors observed that Pokemon is upregulated in a subset of human T-cell lymphomas. Furthermore, Pokemon was upregulated in diffuse large B-cell lymphoma and follicular lymphoma samples — two human tumour types that also express BCL6. Pandolfi and colleagues showed that lymphomas that expressed both Pokemon and BCL6 had a higher proliferative index than cells that only upregulated one of these factors, supporting the functional cooperation between these two transcription factors in promoting lymphomagenesis. Further studies could identify other Pokemon gene targets involved in tumorigenesis.

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References and links

ORIGINAL RESEARCH PAPER Maeda, T. *et al.* Role of the proto-oncogene *Pokemon* in cellular transformation and *ARF* repression. *Nature* **433**, 278–285 (2005)

FURTHER READING Sherr, C.J. & McCormick, F. The RB and p53 pathways in cancer. *Cancer Cell* **2**, 103–112 (2002).

WEB SITE
Pier Paolo Pandolfi's lab:
http://www.mskcc.org/mskcc/html/10345.cfm