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GENE EXPRESSION

Variety is the splice of strife

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Alternative splicing is a key mechanism for enhancing the variety of RNAs (and therefore proteins) that are encoded by genes. Two new reports add weight to our growing appreciation of splicing disruptions in diseases such as cancer.

To uncover recurrent, potentially driving events in tumorigenesis, Seishi Ogawa and colleagues carried out genome-wide exome sequencing of 29 samples of myelodysplasia, which is a frequent precursor of acute myeloid leukaemia. This pilot study was followed by the focused sequencing of candidate driver genes in nearly 600 samples of myelodysplasia and other myeloid neoplasms. The authors identified recurrent mutations in eight splicing factors. These mutations showed remarkable disease specificity, as they were present in only ~7% of the myelodysplasia-independent acute myeloid leukaemias but present in >85% of two of the subtypes of myelodysplasia.

Overexpression of mutant alleles of one of the splicing factors, U2AF35 (also known as U2AF1), in HeLa cells caused the accumulation of aberrantly spliced transcripts and the upregulation of genes that are involved in the nonsense-mediated decay pathway, which responds to transcripts with premature stop codons. Interestingly, the expression of mutant U2AF35 reduced the proliferation rate in these cells and impaired the ability of haematopoietic stem cells to reconstitute the haematopoietic systems of irradiated mice. Although this defective haematopoiesis is consistent with the pathogenesis of myelodysplasia, how such mutations are compatible with neoplastic evolution is unclear. Other uncertainties include whether the cellular effects of U2AF35 mutations are caused by global transcriptional disruption or through effects on specific transcripts, and whether the transcriptomic effects of mutant U2AF35 *in vitro* are mirrored in myelodysplasia samples.

In a separate study, Luca Cartegni and colleagues investigated the function of specific aberrantly spliced transcripts in glioblastoma. Glioblastoma samples were characterized by deregulated splicing in which two particular genes — MAP-kinase activating death domain (*MADD*) and macrophage stimulating 1 receptor (*MST1R*; also known as *RON*) — have an exon selectively excluded compared with transcripts from normal tissue. Engineered mutation of both of these genes revealed that these splicing events are controlled by an exonic splicing silencer (ESS) sequence that is a characteristic binding site for heterogeneous nuclear ribonucleoprotein H (hnRNPH). Indeed, the authors found hnRNPH to be overexpressed in glioblastoma samples, revealing a potential mechanism for these glioblastoma-specific splicing events. High hnRNPH levels and these splice variants are also found in embryonic stem cells, which may indicate that dedifferentiation accompanies tumorigenesis. Although hnRNPH could have many cellular effects, the expression of the glioblastoma-specific splice variants of *MADD* and *MST1R* partially rescued the detrimental effects of hnRNPH knockdown. Interestingly, this research parallels a recent finding from an independent team that a related splicing factor, hnRNPA2/B1, is also overexpressed in glioblastoma and drives aberrant splicing of various tumour suppressor genes.

These papers reinforce the view that deregulated splicing might be a crucial event during tumorigenesis.

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ORIGINAL RESEARCH PAPERS Yoshida, K. *et al.* Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* 11 Sep 2011 (doi:10.1038/nature10496) | Lefave, C. V. *et al.* Splicing factor hnRNPH drives an oncogenic splicing switch in gliomas. *EMBO J.* 13 Sep 2011 (doi:10.1038/emboj.2011.259)

FURTHER READING Golan-Gerstl, R. *et al.* Splicing factor hnRNP A2/B1 regulates tumor suppressor gene splicing and is an oncogenic driver in glioblastoma. *Cancer Res.* **71**, 4464–4472 (2011)