IN BRIEF

ALTERNATIVE SPLICING

Retaining introns to sculpt gene expression

Intron retention is a common form of alternative splicing in plants and unicellular eukaryotes; however, its prevalence in mammals was unclear. Braunschweig *et al.* carried out high-throughput RNA sequencing from ~40 human and mouse cell types and found evidence for intron retention in transcripts from up to 75% of genes. In addition, they identified sequence features in the mRNAs that control intron retention. With this approach the team showed that intron retention seems to be a mechanism to minimize the expression of tissue-inappropriate genes; for example, stop codons in the retained introns result in premature translational termination and nonsense-mediated mRNA decay.

ORIGINAL RESEARCH PAPER Braunschweig, U. *et al.* Widespread intron retention in mammals functionally tunes transcriptomes. *Genome Res.* http://dx.doi.org/10.1101/gr.177790.114 (2014)

CANCER

Up and down for DNA methylation inhibitors

Tumour suppressor genes in cancer cells are frequently silenced by promoter CpG methylation, which has led to the pursuit of DNA methylation inhibitors as potential cancer therapeutics to reactivate these genes. However, DNA methylation in gene bodies is associated with the opposite effect (that is, gene activation). Yang *et al.* carried out a genome-scale analysis of DNA methylation and gene expression changes in colon cancer cells in response to treatment with DNA methylation inhibitors. Treatment led to widespread gene-body demethylation and transcriptional downregulation. Furthermore, many of the genes affected were overexpressed in colon cancer tissue samples and were regulated by the MYC oncoprotein. Thus, antiproliferative effects of DNA methylation inhibitors are likely to be mediated, in part, through the downregulation of overexpressed oncogenes.

ORIGINAL RESEARCH PAPER Yang, X. *et al.* Gene body methylation can alter gene expression and is a therapeutic target in cancer. *Cancer Cell* http://dx.doi.org/10.1016/j.ccr.2014.07.028 (2014)

RNA

Dissecting circular RNA biogenesis

Circular RNAs are thought to arise from non-canonical splicing of linear pre-mRNAs, as they frequently harbour the 3′ end of one exon joined to an upstream (rather than downstream) 5′ end of an exon. Zhang *et al.* used bioinformatic analyses on human transcriptome data and the functional testing of reporter constructs to dissect the sequence features underlying circularization. They found that exons joined during circularization are preferentially flanked by intronic inverted repeat elements (such as species-specific *Alu* repeats), which potentially cross-hybridize to bring these exon ends into proximity before splicing. In a separate study, Ashwal-Fluss *et al.* studied circular RNAs from flies and human cells. They found that RNA circularization occurs co-transcriptionally (as circular RNAs are also found in nascent transcriptomes). The second study also highlights the importance of flanking intronic sequences and additionally shows that RNA circularization may compete with canonical linear splicing. Both studies uncovered multiple alternatively circularized transcript isoforms for some genes, thus highlighting the complexity of RNA circularization.

ORIGINAL RESEARCH PAPERS Zhang, X.-O. *et al.* Complementary sequence-mediated exon circularization. *Cell* **159**, 134–147 (2014) | Ashwal-Fluss, R. *et al.* circRNA biogenesis competes with pre-mRNA splicing. *Mol. Cell* **56**, 55–66 (2014)

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