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were linked to the cell cycle and DNA replication. Interestingly, the increase in cell type-specific transcripts was generally observed at later timepoints (towards mitotic exit), suggesting that genes regulating basic cell functions and cell growth are prioritized over genes with more specialized functions.

Overall, low-level transcription persists in mitosis and high-level transcription is gradually reactivated during progression through mitosis and into G1. The biological significance of mitotic transcription remains to be determined, although it is plausible that the maintenance of gene expression during mitosis supports daughter cell integration into the surrounding extracellular space following division and primes them for the robust gene expression necessary for their growth and basic functions.

Paulina Strzyz

ORIGINAL ARTICLE Palozola, K. C. *et al.* Mitotic transcription and waves of gene reactivation during mitotic exit. *Science* http://dx.doi.org/10.1126/science.aal4671 (2017)

> pro-survival BCL-2 proteins can establish a positive feedback loop

the interactions of pro-survival and pro-apoptotic BCL-2 proteins. Wu *et al.* demonstrated that BH3 mimetics also interfered with the interactions of pro-survival BCL-2 proteins with SUFU, resulting in increased SUFU levels and phosphorylation. Importantly, the application of BH3 mimetics reduced the levels of pro-survival BCL-2 proteins and restricted the growth of tumours induced by overactive Hedgehog signalling.

Overall, pro-survival BCL-2 proteins can reinforce their anti-apoptotic effects by driving their own expression through the Hedgehog effector GLI. This finding sheds new light on the complexity of apoptosis regulation and on the mechanisms of action of BH3 mimetics and their utility for cancer therapy.

Paulina Strzyz

ORIGINAL ARTICLE Wu, X. *et al.* Extra-mitochondrial prosurvival BCL-2 proteins regulate gene transcription by inhibiting the SUFU tumour suppressor. *Nat. Cell Biol.* **19**, 1226–1236 (2017)
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Journal club

THE DISCOVERY OF CATALYTIC RNA

In 1978, Tom Cech started his lab at the University of Colorado and the project he set out on was to study the processing of ribosomal RNA (rRNA) in the ciliated protozoa, *Tetrahymena*. *Tetrahymena* was chosen because its rRNA genes are amplified about 10,000 times, so it is likely to provide a ready source of rRNA precursors. Of note is that the 26S rRNA gene in *Tetrahymena* is interrupted by an intron of 400 nucleotides.

A nuclear extract was developed to produce radioactive precursors (Zaug and Cech, 1980). A distinct 9S RNA molecule was evident in the gels and this turned out to be the 400-nucleotide intron. The appearance of this internal sequence indicated that RNA splicing was occurring in the nuclear extracts.

> The *in vitro* transcribed RNA still underwent the self-splicing reaction

The obvious next thing was to characterize the splicing of the intron. To produce a ^{32}P-labelled RNA substrate, labelled RNA was phenol extracted from nuclei and characterized by gel electrophoresis. In a wonderfully understated paragraph the discovery of RNA catalysis is reported (Cech *et al.*, 1981):

"We hoped to use the unspliced pre-rRNA … as a substrate to assay for splicing activity in nuclear extracts. This approach proved to be impossible, however, because excision of the intervening sequence occurred when the isolated RNA was incubated in transcription cocktail at normal salt concentration in the absence of a nuclear extract."

Papers rarely describe the actual circumstance of a discovery. In this case Art Zaug had carried out an *in vitro* splicing assay with a control lane containing no extract. The splicing reaction still took place. Exhaustive efforts to remove any protein still bound to the RNA after phenol extraction did not affect the reaction but this was not considered definite proof of the absence of a protein.

In a later paper, however, Kruger *et al.* (1982) described the cloning of a portion of the *Tetrahymena* rRNA gene containing the intron into an *Escherichia coli* plasmid. The *in vitro* transcribed RNA still underwent the self-splicing reaction, thereby proving that no protein is necessary.

Quite remarkably, Cech *et al.* (1981) also reported the correct mechanism of the reaction. GTP was found to be a required co-factor in the reaction, in which it forms a standard 3′–5′ linkage with the 5′ end of the intron, suggesting that the 3′-OH of GTP initiates the reaction by attacking the phosphodiester bond at the 5′ splice site.

In addition to the revolutionary implications this result has for biochemistry, there are two additional points to be made. First, the paper by Cech *et al.* (1981) is science at its best. A bound protein catalyst would have been interesting but not revolutionary. Everything possible to prove or disprove the bound protein hypothesis was done. Second, that RNA can be a catalyst has profound implications for the origin of life. Protein enzymes might have appeared but they could not replicate, so there must have been a ribozyme that could catalyse its own replication. Such ribozymes were soon discovered (Doudna and Sjostak, 1989).

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