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50 & 100 YEARS AGO

50 YEARS AGO

The American Air Force lunar probe attempt on October 11 failed to achieve the full objective of a circum-lunar orbit, but demonstrated that many of the technical problems of launching and accelerating a three-stage rocket to the necessary speed have been solved. Guidance of the rocket into the correct path and precise control of the final cut-off velocity appear to have been the chief problems not yet completely mastered ... In the instrument payload of some 40 lb. were included radiation detectors, which confirmed the earlier measurements on *Explorer* IV of the intense radiation belt surrounding the Earth. Preliminary analyses of the results have shown a significant decrease in intensity beyond several Earth radii, and seem to confirm the idea that the radiation is due to trapping of cosmic particles by the Earth's magnetic field ... No doubt there are some who will not regret the failure to penetrate the mystery of the Moon's unseen face, but it must be only a matter of time until this is done ...

From *Nature* 18 October 1958

100 YEARS AGO

On October 10, in the presence of the leading aëronautical experts of France, Mr. Wilbur Wright, with M. Painlevé as a passenger, accomplished a flight of 1h. 9m. 45.6s in duration, the distance covered being estimated at nearly seventy kilometres. This successful flight is the last demanded of Mr. Wright by the French syndicate which has acquired the local rights in his aëroplane by the payment of 10,000l. at once and 10,000l. in a month's time, after three men have been trained to work the machine ... [O]n November 1 the Société navale des Chantiers de France will begin at Dunkirk the construction of fifty Wright aëroplanes, which are to be sold at the price of 1000l. each.

From *Nature* 15 October 1908

regulated splicing in yeast is intron retention[4]. Nevertheless, the mechanisms underlying these two kinds of regulated splicing may be similar.

In *S. pombe*, regulated splicing occurs in meiosis[5]. Many meiosis-specific proteins are toxic to vegetative (that is, mitotic) cells, and their expression is kept turned off by multiple mechanisms[6]. For many meiosis-specific genes, transcription is repressed in vegetative cells, and furthermore, if and when small amounts of transcript are made, their splicing is repressed; that is, introns are retained, so that no active protein is made. When the cells enter meiosis, transcription is induced, and so is splicing.

Moldón *et al.*[3] have studied the splicing of *rem1*, a meiosis-specific gene of *S. pombe*. Transcription of *rem1* is repressed in vegetative growth, and any transcript that does get made does not get spliced. On entry into meiosis, the *rem1* transcript is induced and spliced[5,7]. The major finding of Moldón *et al.*[3] is both simple and remarkable: the information that specifies meiosis-specific splicing lies entirely inside the promoter, and not in the transcribed region. For example, when the *rem1* transcript is expressed from some other promoter, it is spliced in both vegetative and meiotic cells. Conversely, when the authors used the *rem1* promoter to drive transcription of a normal vegetative gene (*cdc2*, which has four introns, and which is usually spliced in both vegetative and meiotic cells), then splicing occurred only in meiosis, and in the same temporal pattern as for the wild-type *rem1* gene.

In meiosis, the *rem1* promoter is bound by Mei4, a meiosis-specific protein belonging to the forkhead family of transcription factors. *S. pombe* has three other forkhead transcription factors, and Moldón *et al.* suggest that, in vegetative cells, the Mei4-binding sites in the *rem1* promoter are probably occupied by one of these other factors, Fkh2. When the authors deleted the *fkh2* gene from *S. pombe*, vegetative transcription of *rem1* was slightly increased, and some of this transcript was spliced. This suggests that Fkh2 represses both transcription and splicing in vegetative cells. The authors show that Mei4, which is made only in meiosis, binds to *rem1* and turns on both transcription and splicing.

Why would one forkhead transcription factor induce splicing, but not the other? On the basis of co-immunoprecipitation experiments, Moldón *et al.* found that Mei4, but not Fkh2, forms complexes with the spliceosome. The authors therefore suggest that the Mei4 transcription factor actively recruits splicing factors to the *rem1* gene and transcript, whereas Fkh2 does not. They suggest that it is this recruitment of the spliceosome by a meiosis-specific transcription factor that is responsible for meiosis-specific splicing. However, less direct explanations are also possible: transcription factors can affect the conformation of chromatin, the rate of mRNA elongation, and the 5′ capping and 3′ polyadenylation processing of transcripts, and all these are interrelated with splicing[8].

The model proposed for *rem1* is exciting, but still leaves us with a major puzzle. How can Fkh2 at a promoter inhibit splicing of *rem1* and even an unrelated gene such as *cdc2* whose transcript has good splicing signals? Maybe control of RNA processing (5′ capping and 3′ polyadenylation as well as splicing) will be a more general feature of promoters. It now seems that most of the genome is transcribed to at least some degree, so turning gene expression off completely may depend on regulating steps of RNA processing in addition to controlling efficiency of transcription.

These remarkable findings[3] leave some loose ends. First, Fkh2 regulates many vegetative transcripts, and many of these are spliced. Thus, Fkh2 is not repressing vegetative splicing at most of its targets. Second, the *rem1* promoter does not impose its usual temporal pattern of splicing when fused to the *crs1* gene[5], in contrast to the results obtained here with *cdc2* (ref. 3). Third, in the model proposed, the failure of vegetative splicing for the *rem1*-driven *cdc2* transcript seems to suggest little or no ability to splice *rem1*-driven transcripts post-transcriptionally, in contrast to *Saccharomyces cerevisiae*, in which most splicing may be post-transcriptional[9]. It should also be noted that the study of intron retention is complicated by two subtle and nasty artefacts: unlike mRNAs generated by alternative splicing, mRNAs generated by complete intron retention are perfectly co-linear with the DNA. Thus, the polymerase chain reaction following reverse transcription (RT-PCR), which is used to amplify an mRNA with retained introns, can amplify genomic DNA instead, with results that appear identical results (an artefact Moldón *et al.* addressed). Second, if a gene has an antisense transcript, this will never be spliced, but, in RT-PCR, will yield the same product as an unspliced sense transcript.

Still, these issues do not significantly undercut the core result for *rem1*: splicing depends on which transcription factor is bound to the promoter. Understanding exactly how Mei4 turns splicing on, and how Fkh2 keeps splicing turned off, will be interesting investigations for the future. In addition, it is a reminder that efforts to understand splicing by searching for signals inside the transcript have limitations, as some of the information is elsewhere. ■

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