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50 & 100 YEARS AGO

50 YEARS AGO

"The Sun", edited by Prof. Gerard P. Kuiper. — Nothing comparable with this work has appeared since the publication of Vol. 4 of the "Handbuch der Astrophysik" in 1929. A comparison of the two volumes demonstrates impressively the strides solar physics has made in a quarter of a century. The identification of 'coronium', the recognition of H^- absorption, postulation of the carbon–nitrogen cycle, invention of the coronagraph... the discovery of chromospheric flares and their terrestrial effects and of solar radio noise... It is regrettable that the present volume includes no contribution from the U.S.S.R.; but the cause can doubtless not be laid entirely at the door of the editor, who is as well aware as anyone how much solar research carried out in Soviet territories remains a closed book to Western readers.

From *Nature* 2 July 1955.

100 YEARS AGO

It is announced in the *Times* that the Board of Trade and the Trinity House have concluded a contract with Marconi's Wireless Telegraph Company (Limited) providing for the equipment of lightships with Marconi wireless telegraph installations. This arrangement will enable the lightships to communicate with the shore and with one another by wireless telegraphy for the ordinary purposes of the lightship service, and also to report ships in distress.

ALSO

"British Bird Life". By W. Percival Westell. The wearisome procession of books on British birds drags on — a long train of volumes, all of necessity telling the same tale, and for the most part badly... At times Mr. Westell becomes ecstatic, and, blinded by the intensity of his emotions, rushes onwards regardless of obstacles — even of the rules of grammar... This book is profusely illustrated, partly by photographs, some of which are very pleasing, and partly by "original" drawings, all of which are bad.

From *Nature* 29 June 1905.

Gleich and Weizenecker allow only certain locations inside the body to send a signal. They achieve this by placing the object concerned in an inhomogeneous magnetic field which, in most regions, is strong enough to saturate a magnetic particle (Fig. 1a). Only particles situated at sites where the external field is essentially zero are not saturated, and can therefore signal in response to the radio-frequency field. By changing the location of this field-free spot (either mechanically or with auxiliary magnetic fields) the sample can be scanned bit by bit, resulting in a map of the spatial distribution of the magnetic particles.

The images obtained in the initial experiments have a resolution of well below 1 mm. This is surprising, considering that the size of the recording coils (squares with 16-mm sides) and the wavelength of the applied radio-frequency field (around 1 km) are both much larger than the size of the resolved features. MPI can be seen as a form of 'zeugmatography', a term coined by 2003 Nobel laureate Paul Lauterbur[5] in his introduction of MRI as a concept for image formation: when two fields are combined, the first one (here, the radio-frequency field) induces an interaction with the body, and the second one (the inhomogeneous magnetic field) restricts this interaction to a limited region. In this way, there is no imposed wavelength limit and MPI can use harmless radio waves that pass through the body without significant attenuation. Furthermore, the detectors can be much larger than the smallest resolved structure, thereby opening the door to depth resolution and, ultimately, three-dimensional imaging.

Beyond this proof-of-principle demonstration, the practical usefulness of MPI remains unknown. The concept promises to complement existing methods and, in certain applications, to provide a unique internal view. MRI owes much of its versatility to the fact that our bodies (and virtually all materials) are made of nuclei that exhibit weak magnetism. MPI, on the other hand, relies on the detection of magnetic particles with stronger intrinsic magnetism, but in general those particles have to be introduced. Although MPI will reveal fewer details, it will not suffer from any background interference and should resolve structures with excellent contrast.

If the potentially higher sensitivity of MPI can be fully exploited, a fast and powerful imaging technique could be in prospect, as well as relatively cheap mobile scanners, with geometries that can be adapted to particular applications. MRI has continued to astonish us with its ever-increasing sophistication over the past three decades. MPI might offer surprises of its own. ■

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GENE REGULATION

Expression and silencing coupled

Stephen Buratowski and Danesh Moazed

The RNA interference pathway can inhibit the expression of specific genes. It now seems that an essential component of the silencing process is the gene-expression machinery itself.

Molecular biologists have been amazed in recent years by the discovery of an RNA-mediated mechanism for inhibiting the expression of specific genes — the RNA interference (RNAi) pathway. The 'RNA-induced silencing complex' (RISC) contains small interfering RNAs (siRNAs) whose sequence of nucleotide bases can pair with that of a particular messenger RNA, targeting this mRNA for destruction before it can be translated into protein[1]. However, in many organisms this 'post-transcriptional' gene silencing is only part of the story: production of the mRNA can be shut off by a second siRNA complex called RITS (for 'RNA-induced transcriptional silencing').

Schramke *et al.* (page 1275 of this issue)[2] and Kato *et al.* (writing in *Science*)[3] now show that a gene must first be transcribed if it is subsequently to be silenced. More surprisingly, this transcription must be specifically carried out by RNA polymerase II (RNApII), the enzyme responsible for making mRNAs in eukaryotic organisms.

DNA is packed into nuclei by being wrapped around histone proteins to form nucleosomes. RITS represses transcription by recruiting a histone methyltransferase to the target genes. This enzyme modifies histones so as to make the wrapped DNA inaccessible to the gene-expression machinery, creating a silenced nucleosome configuration known as heterochromatin. RITS requires siRNAs for its

association with chromatin, and, based on its similarity to RISC, it seemed likely that RITS would also be targeted via base-pairing of siRNAs, either to DNA or RNA[1]. The dependence on transcription suggests that the target is RNA.

Schramke *et al.*[2] show that the transcription of the gene targeted for silencing must be carried out specifically by RNApII. Although a polymerase from bacteriophage (a virus that infects only bacteria) can produce transcripts from a eukaryotic chromosome, silencing does not occur. Therefore, although RITS may be targeted via base-pairing to nascent RNA transcripts, an additional mechanism must exist for specifically coupling silencing to RNApII. The two groups[2,3] find that very different mutations in RNApII disrupt the formation of heterochromatin: truncation of the RNApII largest-subunit carboxy-terminal domain (the CTD, normally required for coupling mRNA synthesis to mRNA processing[4]), or a specific point mutation in the RNApII Rpb2 subunit, both lead to loss of silencing, but with an interesting difference. Whereas siRNAs are made normally in the CTD truncation mutant, the Rpb2 mutant seems to be blocked in processing the siRNAs. Therefore, RNApII may have multiple roles in the siRNA pathway.

Perhaps the simplest model to explain the coupling of RNA-induced silencing with transcription (Fig. 1) is that RITS is tethered to some part of the RNApII elongation complex, which produces the target mRNA. Through this interaction, as well as recognition of specific transcript sequences, the histone methyltransferase would be localized to the appropriate target gene and so could modify the histones as the gene is being transcribed. Indeed, molecular-interaction experiments show that RITS is linked to nascent transcripts[2,5] as well as to RNApII (ref. 2). Furthermore, RITS and its associated factors can be chemically crosslinked to genes undergoing silencing, and this requires siRNA and the nascent transcripts[2,5]. There is clear precedent for the coupling of transcription with chromatin modification: two other histone methyltransferases (Set1 and Set2) bind directly to elongating RNApII and modify transcribed regions of genes[6].

However, there are several other models that could explain why only RNApII can mediate RITS-dependent silencing. It is possible that RITS interacts with the transcript not only through base-pairing, but also by recognizing an RNApII-specific modification of mRNA (such as the cap structure or poly(A) tail). In this regard, it is interesting that a screen for factors that promote RNAi in the nematode worm *Caenorhabditis elegans* identified several factors that are required for proper mRNA processing[7]. The mechanisms by which these factors affect RNAi are unknown.

In addition to mRNA-processing enzymes, the RNApII elongation complex carries several chromatin-modifying enzymes[6]. Although bacteriophage polymerases and eukaryotic RNA polymerase III can transcribe through chromatin without disrupting nucleosomes[8], passage of the RNApII elongation complex leads to large changes in the chromatin[9]. Histone subunits may be exchanged as the transcription complex passes through a nucleosome. Furthermore, several transcription-dependent modifications of histones, including the methylations described above, have been identified. It may be that one or more of these alterations are prerequisites for the RITS-associated histone methyltransferase to modify its substrate.

Each of these explanations makes some testable predictions, so the process that links RITS-mediated repression specifically to RNApII may soon become clear. However, other questions remain. For example, is transcription required only to initiate silencing, with the repressive chromatin being subsequently propagated by epigenetic mechanisms such as histone methylation? Or is some low level of transcription paradoxically required to maintain repression? Any transcripts made from a 'silenced' gene would be subject to RISC-mediated degradation, so some leakiness of transcriptional silencing may easily be tolerated. An RNA polymerase IV that apparently specializes in synthesizing siRNA precursors has recently been discovered in plants[10]. This suggests another mechanism for simultaneous transcription and silencing: perhaps RNApIV can transcribe through chromatin structures that block RNApII. It will be interesting to see whether transcription by RNApIV is directly coupled to the silencing complex.

Another question is whether siRNAs are themselves generated during transcription, a possibility suggested by the findings of Kato *et al.*[3]. Once targeted by RISC/RITS, the transcript slated for destruction can be used to generate new siRNAs. This requires two enzymes — an RNA-dependent RNA polymerase that generates double-stranded RNA, and the Dicer enzyme that cuts the RNA into siRNA lengths. Both enzymes associate with RITS or RISC complexes and could therefore be present at the site of transcription.

One of the main functions of the RNAi system is probably to suppress expression of the repetitive elements that parasitize eukaryotic genomes. A two-pronged approach to silencing makes good sense. The RISC complex can target any transcripts that manage to reach the cytoplasm from the nucleus, preventing them from being translated. But if this were the only mechanism, considerable cellular energy might still be wasted in making transcripts from the repetitive elements. The nuclear RITS complex can repress expression of those RNAs before they are even made. Because target recognition uses complementary RNA sequences, once a particular element or gene is recognized by the RNAi system, all copies in the cell will be targets for inactivation. Nucleotide sequences provide a high level of specificity, but there must be an opportunity for the target sequences to be recognized. By coupling the RNAi machinery to ongoing transcription, siRNAs can identify target transcripts as they are synthesized, resulting in efficient and almost immediate repression. ■

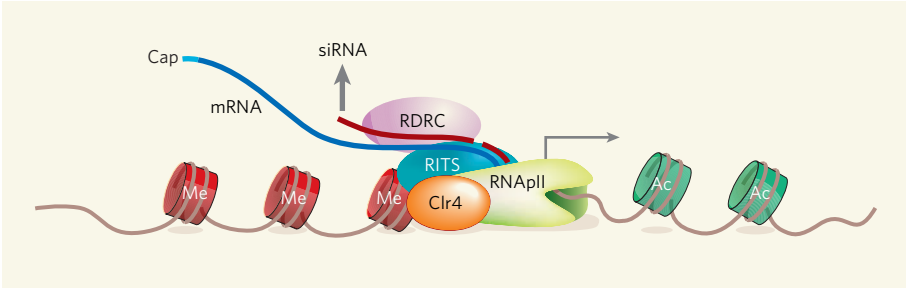

Figure 1 | Transcription-coupled RNA interference. **This speculative model incorporates the results of Schramke *et al.*[2] and Kato *et al.*[3]. As RNA polymerase II synthesizes the RNA transcript, targets to be silenced are recognized by the RITS complex by siRNA–mRNA base-pairing, and possibly through direct contacts with the elongation complex. Formation of repressive heterochromatin, where histones carry a particular methylation pattern (Me) and have lower levels of acetylation (Ac), is initiated by the histone methyltransferase Clr4. At the same time, RITS and an RNA-dependent RNA polymerase complex (RDRC) can generate double-stranded RNA that is processed to become new siRNAs.**

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