TRANSCRIPTION

Dial S for silence

Somewhere between early S phase and G2/M lies a cell-cycle switch that allows gene expression to be silenced. In response to this event, the chromatin adopts an altered form — heterochromatin — that prevents the transcriptional machinery from reaching its target genes. DNA replication has long been thought to flick this switch, but two reports in *Science* suggest that it might not be required after all.

Both groups studied the budding yeast *HMRa* mating-type locus, which is silenced through the formation of heterochromatin. Silencing requires the binding of several proteins to *cis*-acting elements called silencers. Among these proteins is the origin-recognition complex (ORC), which is involved in the initiation of DNA replication (although this function is separable from its role in silencing). ORC then recruits a Sir (silent information regulator) protein called Sir1, and this, in turn, facilitates the incorporation of further Sir proteins into the heterochromatin.

To find out whether replication through the *HMRa* locus is needed to establish silencing, the two groups adopted a similar strategy — they compared the formation of heterochromatin at chromosomal *HMRa* with the same process on a non-replicating, extrachromosomal DNA ring. The extrachromosomal DNA (which was excised by site-specific recombination) could not replicate because it lacked the ORC-binding site. And, to circumvent the need for ORC in silencing, the authors had engineered either Gal4 (Kirchmaier and Rine) or LexA (Li and colleagues) DNA-binding sites into the extrachromosomal ring. Expression of Gal4–Sir1 or LexA–Sir1 fusion proteins then provided all the ingredients required for silencing.

Using this system, both groups saw little difference in silencing of the two *HMRa* loci, with the startling implication that replication is not required to initiate this process. An obvious concern is whether the extrachromosomal ring can, in fact, replicate, but the authors did a number of controls to show that this was not the case. They also showed, consistent with previous dogma, that passage through S phase is required for silencing.

But if replication is not the switch, then what is? Just one of the many theories is that the activity of a silencing component — perhaps a Sir protein — is controlled in a cell-cycle-dependent manner, possibly by regulated synthesis of cofactors or degradation of inhibitors.

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References and links

ORIGINAL RESEARCH PAPERS Kirchmaier, A. & Rine, J. DNA replication-independent silencing in *S. cerevisiae*. *Science* **291**, 646–650 (2001) | Li, Y.-C., Cheng, T.-H. & Gartenberg, M. R. Establishment of transcriptional silencing in the absence of DNA replication. *Science* **291**, 650–653 (2001)

FURTHER READING Smith, J. S. & Boeke, J. D. Is S phase important for transcriptional silencing? *Science* **291**, 608–609 (2001)

WEB SITE Chromatin structure and function page

TELOMERES

Double delivery

For long-term survival a cell must take care of its telomeres. It needs to protect them from the DNA-repair apparatus — which might otherwise view them as double-stranded breaks — while making sure that they are completely replicated during cell division. Reports in *Cell* and *Genes and Development* by Vicki Lundblad and colleagues now show that these two functions are reconciled in yeast through a telomere-binding protein called Cdc13.

Lundblad's group previously showed that Cdc13 can positively regulate telomere replication by recruiting the enzyme responsible — telomerase — to chromosome ends. But Cdc13 also negatively modulates telomere replication — an effect that occurs after the recruitment of telomerase, and depends on a protein known as Stn1.

One explanation for this negative regulation is the recruitment, by Cdc13, of an end-protecting activity. The obvious candidate is Stn1, so the authors fused the DNA-binding domain of Cdc13 to Stn1. Expression of this construct rescued the lethality of a *cdc13* null strain, suggesting that Stn1 is the arbiter of end protection and that it is delivered to telomeres by Cdc13.

The association of Cdc13 with both telomerase and Stn1 is blocked by a single mutation (*cdc13-2*), leading Lundblad and colleagues to describe how Cdc13 might regulate telomere replication. According to their model, telomerase is delivered to the DNA end in the first (positive) step. Then, in the second (negative) step, Stn1 binds an overlapping site on Cdc13, allowing it, in turn, to be recruited to the telomere.

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References and links

ORIGINAL RESEARCH PAPERS Pennock, E., Buckley, K. & Lundblad, V. *Cell* **104**, 387–396 (2001) | Chandra, A. *et al*. Cdc13 both positively and negatively regulates telomere replication. *Genes Dev*. **15**, 404–414 (2001)

WEB WATCH

First among equals

Bio Online™, which began life as the Biological Research Network, International (BRNI) in 1992, claims to be recognized as "the first life sciences web site". Almost ten years on, and the site shows few signs of old age.

At the heart of Bio Online is a fresh-looking home page fronting links to a variety of sections. For the corporate-minded, the 'Industry news' and 'Industry reports and analyses' cover company reports and business issues in the biotechnology sector. 'Research news', on the other hand, gives short summaries of recent research. Although the papers highlighted reflect the site's slant towards biotechnology and medicine, the articles are readable and up to date, with links to useful web sites.

Each month, 'In focus' describes a cutting-edge technology, including a round-up of hot papers in the area and short transcripts of online discussions with leaders in the field. Proteomics and bioinformatics are featured in February and March, respectively, although some of the previous topics are a little more off-beat.

Right on track, however, is the 'Research and education' section, with extensive links to lab protocols and research tools. The 'Career centre' is also useful, featuring careers advice and a moderated career forum. Only the jobs database disappoints — most adverts are placed by US companies, few specific positions are offered, and a high proportion of those seem to be in sales rather than research.

Those behind Bio Online claim that it is used by "researchers … from academia and from pharmaceutical and biotechnology companies". This is a commercial site, though, and we suspect that researchers in industry will gain most from it.

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