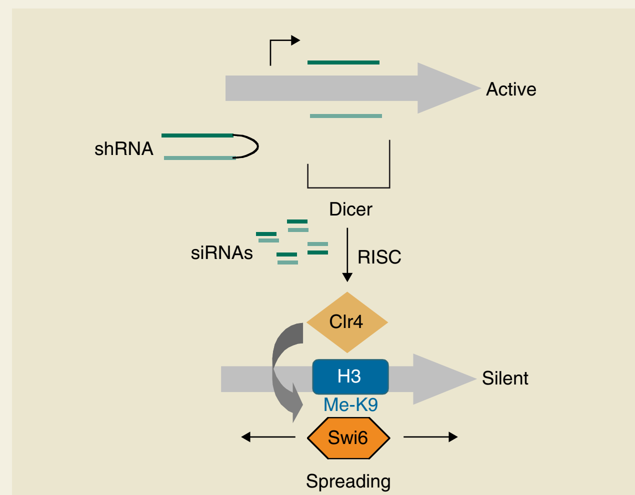
RNA interference: RISCing chromatin silence

In a variety of organisms, small-interfering RNAs (siRNAs) can down-regulate gene expression by targeting specific mRNA transcripts for degradation. Work from Schramke and Allshire published in Science (published online: 17 July 2003; DOI: 10.1126/science.1086870) now shows that in the fission yeast *Schizosaccharomyces pombe*, treatment with siRNAs can cause specific gene silencing by nucleating assembly of repressive heterochromatin.

Previous work has demonstrated that gene silencing at fission yeast centromeres is dependent on components of the cellular RNA interference (RNAi) apparatus, such as Ago1, Dcr1 and Rdp1. These earlier studies suggested that processing into siRNA of the non-coding transcript generated from a centromeric repeat resulted in targeted histone modification and assembly of silent chromatin structures at centromeres.

In this work, Schramke and Allshire set out to determine whether RNAi-mediated chromatin silencing could also occur at non-centromeric loci in fission yeast. They expressed a short-hairpin RNA (shRNA; a substrate for the RNAi machinery) that is homologous to the endogenous *URA4* locus. The authors found that not only was silencing of the endogenous URA4 locus dependent on the RNAi machinery, but the silenced locus bore other hallmarks of centromeric heterochromatin, such as dimethylated K9-histone H3 and binding of the HP1 homologue, Swi6. Both histone modification and Swi6 recruitment were dependent on a functional RNAi apparatus. Thus, even at non-centromeric loci, siRNAs seem to promote gene silencing through heterochromatin formation. Interestingly, silent chromatin nucleated at the site homologous to the shRNA also propagated outwards to nearby sequences in a Swi6-dependent manner.

In other organisms, mobile elements such as retrotransposons are known to be associated with both RNAi and heterochromatin. In an important next step, the authors went on to show that repression of a set of meiosis-specific genes in vegetative fission yeast cells is dependent on nearby retrotransposon long terminal repeats (LTRs) that generate non-coding RNA transcripts. As with the shRNA, LTR-mediated repression of the meiotic genes also required the RNAi apparatus, as well as Swi6 and the histone methyltransferase Clr4. The authors found characteristic features of heterochromatin deposited onto at least two of the LTRs, and could also show that only meiotic genes whose promoters were located in the vicinity of an LTR were silenced by an RNAi dependent mechanism. Both findings can be explained by propagation of a silencing heterochromatic structure from the LTRs.



Double-stranded RNA can be processed into siRNA by Dicer and targeted to endogenous transcripts by the RNAi machinery (RISC). At the target locus, methylation of H3-K9 and binding of Swi6 results in formation of silent chromatin.

Studies in plants and flies have uncovered similar modes of RNAi-based gene silencing, but understanding whether RNAi-mediated chromatin silencing is a widespread phenomenon, and defining the conditions under which particular siRNAs may result in heterochromatin formation, is clearly an important issue for future studies.

SOWMYA SWAMINATHAN

Deconstructing cytokinesis

Amy Shaub Maddox and Karen Oegema

In animal cells, cytokinesis is initiated by assembly and ingression of a cleavage furrow, the position of which is determined by signals from the anaphase spindle. Recent work highlights two specialized microtubule populations that may stimulate furrow assembly: inter-zonal microtubule bundles, and astral microtubules that are stabilized by proximity to chromosomes.

After mitotic chromosome segregation, cytokinesis partitions the cytoplasm and the cell cortex to form two daughter cells. To ensure that each cell receives a single nucleus, placement of the cleavage furrow is coordinated spatially and temporally with chromosome segregation. Furrowing is controlled by a bipartite mechanism that requires both cortical activation and signalling from the anaphase spindle. First, at mitotic exit the cell cortex becomes conducive to cleavage[1,2]. Then, signals from the mitotic apparatus modulate contractility of the cortex to direct assembly of a persistent furrow that bisects the spindle. Here, we discuss insights into this process emerging from two recent papers by Alsop and Zhang[3] and Canman *et al.*[4] that continue the long tradition of manipulating cells, mechanically or molecularly, to define the components of the spindle important for cleavage furrow positioning (reviewed in refs 5, 6). Although the two studies produced differing results, both suggest that furrow formation is directed by specialized subsets of microtubules.

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