PERSPECTIVE

RNAi in fission yeast finds new targets and new ways of targeting at the nuclear periphery

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RNAi in *Schizosaccharomyces pombe* is critical for centromeric heterochromatin formation. It has remained unclear, however, whether RNAi also regulates the expression of protein-coding loci. In the April 1, 2012, issue of *Genes & Development*, Woolcock and colleagues (pp. 683–667) reported an elegant mechanism for the conditional RNAi-mediated repression of stress response genes involving association with Dcr1 at the nuclear pore. Unexpectedly, the initial targeting of RNAi components to these genes does not require small RNA guides.

Not long after it was discovered as a mechanism of dsRNA-mediated post-transcriptional gene silencing (Fire et al. 1998), it became evident that RNAi also regulates the genome at the level of transcription and chromatin structure in a wide range of organisms. Roles for RNAi have been identified in DNA elimination in *Tetrahymena thermophila*, RNA-directed DNA methylation in plants, and transcriptional gene silencing in *Drosophila melanogaster*, *Caenorhabditis elegans*, and the fission yeast *Schizosaccharomyces pombe* (Moazed 2009). In principle, RNAi could identify target loci through direct base-pairing between its small RNA guides and DNA, but to date, only targeting via complementary RNA transcripts has been described. Consequently, RNAi-based regulation at the chromatin level is thought to involve the interaction of silencing proteins with nascent transcripts (Bühler and Moazed 2007; Lejeune and Allshire 2011). First described in *S. pombe*, this nascent transcript model is strongly supported by the finding that small RNAs can cause gene-specific arrest of elongating RNA polymerase II in *C. elegans* and RNA polymerase IV- and polymerase V-dependent DNA methylation in *Arabidopsis thaliana* (Wierzbicki et al. 2009; Guang et al. 2010).

Extensive evidence that nascent transcripts serve as targets of nuclear RNAi comes from studies in *S. pombe*, in which the genes encoding a Dicer dsRNA nuclease

(*dcr1*⁺), an Argonaute protein (*ago1*⁺), and an RNA-directed RNA polymerase (*rdp1*⁺) are each required for establishment and maintenance of centromeric heterochromatin (Volpe et al. 2002). Biochemical purifications showed that Ago1 acts within a chromatin-bound RNA-induced transcriptional silencing (RITS) complex (Verdel et al. 2004). Subsequent studies revealed that RITS interacts with noncoding centromeric transcripts and that artificially enforcing its binding to a nascent euchromatic RNA is sufficient to induce heterochromatic silencing of the corresponding locus (Motamedi et al. 2004; Bühler et al. 2006). Together, these results gave rise to the view that RNAi is recruited cotranscriptionally to its nuclear targets (Fig. 1A). Also consistent with this model are the observations that centromeric siRNA accumulation is disrupted in mutants of RNA polymerase II subunits or splicing factors (Djupedal et al. 2005; Bayne et al. 2008).

Although *S. pombe* has proved a uniquely powerful system for understanding RNAi-based silencing in the nucleus, the cotranscriptional gene silencing (CTGS) mechanism, suggested by the above studies, still presents several mysteries. Here, we focus in particular on two of them. First, in contrast to many other RNAi systems, it has been observed that *S. pombe* small RNAs alone do not robustly recruit the RNAi machinery to targeted loci, suggesting they must instead act in concert with other molecular signals (Fig. 1B). Second, the physiological regulation of protein-coding genes by RNAi in *S. pombe* has only recently begun to be appreciated.

A new study by Bühler and colleagues (Woolcock et al. 2012) offers exciting new insights into both of these questions. By probing the genome-wide localization of RNAi factors using the highly sensitive DNA adenine methyltransferase identification (DamID) technique, they uncover a role for RNAi in the regulation of a class of stress response genes associated with the DNA-binding protein Atf1 and nuclear pores. They present surprising and compelling evidence for small RNA-independent recruitment of RNAi components to their targets. Finally, they propose an attractive model that provides a structural basis for the conditional relocation of Dcr1 and concomitant derepression of stress-inducible genes.

[Keywords: RNAi; CTGS; NPC; stress response; thermoswitch; Atf1 transcription factor]

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Figure 1. Models for target recognition by the *S. pombe* RNAi machinery. (A) At the robustly silenced centromeric repeats, siRNAs bound to the Ago1 subunit guide the RITS complex to complementary nascent RNA targets and corresponding sites on chromatin. RITS then promotes the recruitment of the RNA-dependent RNA polymerase complex (RDRC), containing Rdp1, and Dcr1. Small RNA guides are thus necessary for all targeting of the RNAi machinery to the centromeres. (B) Expression of *ura4⁺* hairpin transcripts or tethering of RITS to *ura4⁺* RNA yields large pools of Dcr1-dependent *ura4⁺* siRNAs that bind to the RITS complex, but the native *ura4⁺* locus is not targeted. Thus, small RNAs are not sufficient to trigger recruitment of the RNAi machinery to this gene. (C) The novel case of the Atf1-bound genes identified by Woolcock et al. (2012). Here, deletion of Ago1, the mediator of small RNA-guided sequence specificity, does not inhibit Dcr1 and Rdp1 recruitment to chromatin. Therefore, small RNAs are not necessary for the initial targeting of these loci.

Small RNAs and the recruitment of the RNAi machinery

In most organisms endowed with RNAi, short dsRNA molecules of ~20–25 nucleotides (nt) in length, often the products of a Dicer ribonuclease acting on endogenous or exogenous dsRNA substrates, are sufficient to trigger a sequence-specific silencing response (Meister and Tuschl 2004). Intriguingly, RNAi-mediated chromatin silencing in

S. pombe stands in stark contrast to this rule. For example, high levels of hairpin-derived, Dcr1-dependent siRNAs directed against the *ura4⁺* gene are unable to elicit repression of the corresponding sequence in its native locus, despite being loaded into the RITS complex (Iida et al. 2008; Simmer et al. 2010). Instead, one or more other events are required to achieve hairpin-mediated silencing (see below). Similarly, when *ura4⁺* siRNAs are generated

by tethering RITS to *ura4* nascent transcripts, they fail to guide RITS to a second allele of *ura4* introduced on another chromosome unless the gene encoding the Eri1 ribonuclease is deleted (Bühler et al. 2006). Together, these results imply that siRNAs are not the only necessary determinants of RNAi targeting in *S. pombe*.

There are currently several clues as to what, in addition to small RNAs themselves, might trigger the initial recruitment of RNAi components (Fig. 1B). One possibility is that a minimal level of methylation of histone H3 on Lys 9 (H3K9me), a key heterochromatic signature, is obligatory to stabilize RITS for de novo silencing (Iida et al. 2008; Schalch et al. 2009). Such a requirement, and possibly other features, could make certain genomic loci more susceptible than others to small RNA-guided targeting of RNAi factors. Consistent with this notion are independent observations that displacing *ura4*⁺ from its native locus can potentiate it for hairpin-mediated silencing (Iida et al. 2008; Simmer et al. 2010). Importantly, hairpin-programmed silencing seems to be favored by the presence of antisense transcription or pre-existing H3K9me at the targeted locus (Iida et al. 2008). A role for bidirectional transcription in targeting the RNAi machinery might also help explain why centromeric repeats are so robustly silenced. Indeed, the widespread presence of complementary transcripts appears to allow the repeats to be targeted by Ago1-bound primal RNAs even in the absence of Dcr1 (Halic and Moazed 2010).

The work of Woolcock et al. (2012) represents a sea change in our understanding of RNAi recruitment to chromatin. Extending previous DamID analyses that uncovered for the first time a physical association between Dcr1 and the genome (Woolcock et al. 2011), the new results show that, remarkably, binding of Dcr1 to both heterochromatin and euchromatin is unchanged in cells lacking Ago1 or Rdp1. Likewise, although Rdp1 association with heterochromatin requires Ago1 and Dcr1, consistent with previous chromatin immunoprecipitation data (Sugiyama et al. 2005), its euchromatic binding profile is very similar to that of Dcr1 and is also unchanged when Ago1 or Dcr1 is deleted. These findings reveal the existence of a mechanism for targeting components of the RNAi machinery to chromatin that is entirely distinct from previous models in that it does not rely on Ago1 or its small RNA guides (Fig. 1C). Until now, it has been taken for granted that small RNAs are indispensable, because deletion of Dcr1 abrogates the interactions of RITS and Rdp1 with one another and with centromeric repeats (Motamedi et al. 2004; Verdel et al. 2004; Sugiyama et al. 2005), but the DamID results from Woolcock et al. (2012) build a very different case for the euchromatic targets of RNAi and raise a host of new questions.

First, in addition to asking why siRNAs are not sufficient to recruit RNAi, we now are prompted to ask why they are not always necessary. In other words, if not siRNAs, what brings Dcr1 and Rdp1 to specific chromatin sites? The investigators attribute this phenomenon to the subnuclear colocalization of these proteins with targeted loci near the nuclear pore complex (NPC) (discussed

below). It remains to be seen whether small RNA-independent targeting also occurs at loci not bound to nuclear pores. A second question regards the adaptive significance of this recruitment mechanism. Are Dcr1 and Rdp1 maintained at certain sites in order to keep the cell poised to preferentially amplify specific small RNA pools, or is the early timing of association prior to small RNA generation not critical for silencing itself? The investigators have uncovered an ideal system in which to study how physical targeting of RNAi might be uncoupled from repression and small RNA amplification.

The role of subcellular localization in regulating the activity of RNAi

Trafficking between the nucleus and cytoplasm has long been known to be instrumental in the cell's execution of RNAi. In the microRNA (miRNA) pathway, natively synthesized hairpin miRNA precursors undergo two successive processing steps in the nucleus and cytoplasm. The karyopherin Exportin 5 mediates their transport across the nuclear envelope and is essential for miRNA-dependent repression (Yi et al. 2003), and overexpression experiments suggest that it may be a limiting component of the pathway (Yi et al. 2005). In human cells, the Argonaute Ago2 has been shown to localize to the nucleus in an Importin 8-dependent manner, an activity that influences its ability to repress many targets, although the mechanism is not yet well defined (Weinmann et al. 2009). Not surprisingly, RNAi silencing pathways that operate specifically in the nucleus have also evolved ways of directing components to this compartment (for a review, see Ketting 2011). A notable example is the *C. elegans* Argonaute NRDE-3, which binds siRNAs in the cytoplasm and transports them to the nucleus, where it can silence corresponding genes undergoing transcription elongation (Guang et al. 2008, 2010). Analogously, the *Tetrahymena* Argonaute Twi1p binds to siRNAs in the cytoplasm and carries them into the nucleus with essential help from the binding protein Giw1p, which appears to sense successful conversion of siRNAs from a duplex to single-stranded form (Noto et al. 2010).

In *S. pombe* cells, siRNAs are currently only known to be generated and function within the nucleus. Nevertheless, Bühler and colleagues (Emmerth et al. 2010; Barraud et al. 2011) have reported that Dcr1 has the potential to shuttle between the nucleus and cytoplasm and that a C-terminal zinc coordination motif and a dsRNA-binding domain (dsRBD) orchestrate its nuclear retention. Within the nucleus, overexpressed Dcr1 resides in NPC-proximal foci, and deletion of the C terminus suggests that this localization is critical for heterochromatic silencing of the centromeric repeats (Emmerth et al. 2010). It has remained unclear, however, whether the nuclear retention mechanism is actively exploited by the cell to regulate Dcr1 activity or whether the apparent association of Dcr1 with the NPC is physiologically relevant.

In their new study, Woolcock et al. (2012) present significant advances on both of these fronts. First, their genome-wide DamID analyses reveal a very strong cor-

relation between the genomic sites bound by Dcr1 and the nucleoporin Nup85, but not Amol, a perinuclear protein not associated with the NPC. The average Dcr1- and Nup85-binding positions relative to ORF start sites also match exquisitely well, with association occurring preferentially upstream. Together, these observations argue that the NPC-proximal localization of Dcr1 may guide it specifically to Nup85-bound target loci, bypassing Ago1 and small RNAs as determinants of sequence specificity (see above). A second major insight into Dcr1 subcellular localization comes from differential scanning fluorimetry experiments in which the dsRBD critical for nuclear retention unfolds at high temperatures. Consistent with a previous mutational analysis of the dsRBD (Barraud et al. 2011), subjecting live cells to the temperatures that compromised the dsRBD structure also abrogated nuclear retention of overexpressed Dcr1. Although indirect effects are not ruled out, the data support an elegant model in which the effects of heat shock on Dcr1 structure tip the balance toward cytoplasmic localization, with important consequences for silencing. In addition to the regulation of stress-inducible genes associated with NPCs (see below), this might also help explain an old observation that the canonical centromeric targets of Dcr1 are derepressed at high temperatures (Allshire et al. 1994).

RNAi-mediated silencing of protein-coding genes in fission yeast

Although the molecular mechanisms of RNAi are widely conserved, its cellular roles are tremendously varied across species (Ketting 2011). One peculiarity of RNAi in *S. pombe* has been its apparent lack of protein-coding targets. Until recently, RNAi in fission yeast was not known to function outside the assembly of constitutive heterochromatin domains. Interestingly, convergent protein-coding gene pairs have been found to produce overlapping readthrough transcripts specifically in the short G1 stage of the *S. pombe* cell cycle. Transient heterochromatin develops in the corresponding intergenic regions in a manner that requires *ago1*⁺ and *dcr1*⁺, suggesting that dsRNA may form and trigger RNAi-dependent regulation of these loci (Gullerova and Proudfoot 2008). As it turns out, many genes encoding RNAi components belong to convergent gene pairs, and their expression is autoregulated by this mechanism in a manner that is also critical for their role in centromeric silencing (Gullerova et al. 2011). In a distinct mechanism, Woolcock et al. (2012) identify as novel physiological targets of RNAi the class of genes bound by the stress response transcription factor Atf1. DamID shows that these loci are associated with NPCs and, under normal growth conditions, Dcr1, Rdp1, and Ago1. Importantly, expression analysis indicates that Dcr1, Rdp1, and Ago1 are all required for their repression. In at least some cases, RNA polymerase II occupancy is not affected by *dcr1*⁺ deletion, implying that repression occurs by both transcriptional gene silencing and CTGS. As a plausible mechanism for release of these genes from RNAi repression during heat shock, the investigators suggest cytoplasmic export of Dcr1 by temperature-induced structural changes

in its C terminus (see above), and the genes are indeed constitutively derepressed in mutants of the Dcr1 C terminus.

Intriguing differences stand out between the autoregulation of RNAi genes and the RNAi-mediated repression of Atf1-bound genes. First, autoregulated RNAi genes belong to convergent gene pairs; it is therefore their 3' ends that are targeted by the RNAi and heterochromatin components (Gullerova et al. 2011). In contrast, Atf1-bound genes are bound by the RNAi machinery predominantly at their promoters (Woolcock et al. 2012). This suggests that the mechanism repressing the latter genes intervenes earlier in the process of transcription to generate a dsRNA signal. A second, related difference is that silencing at convergent gene pairs relies on Dcr1 and Ago1, but not Rdp1, contrary to Atf1-bound loci (Gullerova et al. 2011; Woolcock et al. 2012). Thus, whereas overlapping transcripts themselves are a sufficient source of dsRNA for regulation of convergent genes, stress-inducible genes seem to require Rdp1 to synthesize the dsRNA trigger, presumably using a nascent transcript as a template. Silencing of the Atf1-bound genes resembles centromeric silencing in this regard, but paradoxically, heterochromatin is absent, as Swi6 is not enriched at these loci, and the H3K9 methyltransferase Clr4 is not required for Dcr1 and Rdp1 binding (Woolcock et al. 2012). However, the Clr4 enzymatic activity was recently shown to contribute to centromeric siRNA generation independently of H3K9 (Gerace et al. 2010), so the possibility remains to be tested that it might participate in euchromatic RNAi as well.

Life beyond post-transcriptional gene silencing

Despite its widespread conservation, the RNAi machinery has been lost in certain organisms such as *Saccharomyces cerevisiae* (Drinnenberg et al. 2009). In the evolution of *S. pombe*, RNAi was retained but acts primarily at the chromatin level. Mechanistically, the *S. pombe* variant of RNAi stands apart from canonical post-transcriptional gene silencing, which potentially targets protein-coding genes for repression with the mere presence of dsRNA. *S. pombe* instead features transcriptional and cotranscriptional silencing pathways with intricate targeting requirements and a role mainly in repressing noncoding repeats. In this context, the regulation of Atf1-bound stress-inducible genes, whose initial physical targeting is surprisingly independent of small RNAs, represents a novel adaptive role for RNAi. In future studies, it will be interesting to see whether silencing within this broad class of genes occurs by a uniform mechanism. The new data (Woolcock et al. 2012) hint at the possibility that both transcriptional gene silencing and CTGS may be at work, depending on the locus. Given the absence of heterochromatin, this suggests the action of another transcriptional repression pathway yet to be determined. Additionally, the noncanonical poly(A) polymerase Cid14, which targets aberrant transcripts for exosomal degradation, is also enriched at these genes (Woolcock et al. 2012), so RNAi-independent RNA processing might also be involved. These and other new

questions raised by this important work await further study.

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