CELL CYCLE
2017, VOL. 16, NO. 3, 235–236
http://dx.doi.org/10.1080/15384101.2016.1242962

Taylor & Francis
Taylor & Francis Group

EDITORIALS: CELL CYCLE FEATURES

# Transcription brings the complex(ity) to the centromere

Andrew W. Grenfell, Magdalena Strzelecka, and Rebecca Heald

Department of Molecular and Cell Biology, University of California Berkeley, Berkeley, CA, USA

**ARTICLE HISTORY** Received 26 September 2016; Accepted 29 September 2016

**KEYWORDS** CENP-A; CENP-C; centromere; kinetochore; mitosis; noncoding RNAs; RNA polymerase II; RNA processing; splicing factors; transcription

Mitosis is a dramatic event in the life of a cell. Chromosomes condense, organelles vesiculate, and the microtubule cytoskeleton rearranges into a bipolar spindle that segregates a complete set of chromosomes to each daughter cell. These changes in cellular physiology lead to the global disruption of many interphase processes such as protein trafficking and gene expression. However, many interphase factors are repurposed during mitosis, and play critical roles in the execution of cell division.

There is a growing body of work showing that transcription of repetitive centromeric DNA sequences by RNA Polymerase II contributes to assembly of the kinetochore, a centromere-localized complex that attaches chromosomes to the spindle. Centromeric transcription is important for the localization of the histone H3 variant CENP-A as well as the inner kinetochore protein CENP-C.[1] However, very little is known about the RNA biogenesis pathway at centromeres, and it is unclear exactly how centromeric transcription contributes to chromosome segregation.

In the simplest case, centromeric transcription could lead to the synthesis of noncoding RNAs of a defined sequence that are themselves important for centromere and kinetochore assembly. Consistent with this idea, we recently showed using the *Xenopus* egg extract system that centromeric RNAs are processed during mitosis, and that recruitment of the splicing machinery to these transcripts is important for kinetochore assembly.[2] However, we also found that neither inhibition of transcription elongation (over short time courses) nor complete destruction of cytoplasmic RNAs during mitosis using RNase A (A.W.G and R.H. unpublished) led to impaired kinetochore assembly. In total, our findings suggest, paradoxically, that recruitment of the RNA processing machinery to the centromere, but not the persistence or even complete synthesis of mature centromeric RNAs, is important for kinetochore assembly. We believe that these seemingly contradictory findings can be reconciled if we amend the assumption that centromeric transcription is important because it produces a specific RNA product. Below we outline an alternative model explaining how promiscuous RNA binding by CENP-C and the recruitment of the RNA processing machinery to nascent centromeric transcripts could both contribute to chromosome segregation (Fig. 1).

Previous work showed that both CENP-A and CENP-C exist in RNA-containing complexes, which are important for their localization (e.g.[3,4]). However, there is only limited evidence that these complexes form exclusively with centromeric RNAs. In fact, RNAs derived from retrotransposons within a human neocentromere were required for its maintenance.[3] This suggests that other RNAs originating from abundant DNA elements can substitute for centromeric transcripts and drive centromere assembly and perhaps points to transcript proximity as being more important than transcript identity when it comes to centromere specification. Similarly, work in maize showed that CENP-C does not display a significant binding preference for centromeric RNAs.[5] It seems likely that CENP-C is a promiscuous RNA binding protein that recognizes a short/abundant sequence or structural motif, since *Drosophila* CENP-C appears to have some sequence specificity.[4] It will be interesting to see whether CENP-C orthologs possess similar RNA binding characteristics given the diversity of centromere sequences and divergence of CENP-C across eukaryotes.

While a specific RNA does not appear to be important, CENP-C RNA binding does contribute to inner kinetochore assembly in many systems.[1] Therefore, we propose that transient, promiscuous RNA binding by CENP-C helps stabilize the inner kinetochore at the centromere during mitosis, which promotes kinetochore assembly and ultimately chromosome segregation. This mechanism could help reinforce the centromere as the site for kinetochore assembly given that CENP-A is also distributed throughout non-centromeric chromatin.[6] In addition to CENP-C stabilization, centromeric transcription recruits the RNA processing machinery to the centromere during mitosis. The large number of enzymatic activities associated with the splicing machinery could play regulatory roles in kinetochore assembly, function, or maintenance. For example, Prp4, a kinase involved in splicing, localizes to the kinetochore during mitosis where it is required for spindle assembly checkpoint signaling.[7]

**CONTACT** Rebecca Heald bheald@berkeley.edu

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/kccy.

Feature to: Grenfell AW, et al. Mitotic noncoding RNA processing promotes kinetochore and spindle assembly in Xenopus. J Cell Biol; 214(2):133-41; PMID: 27402954; http://dx.doi.org/10.1083/jcb.201604029.

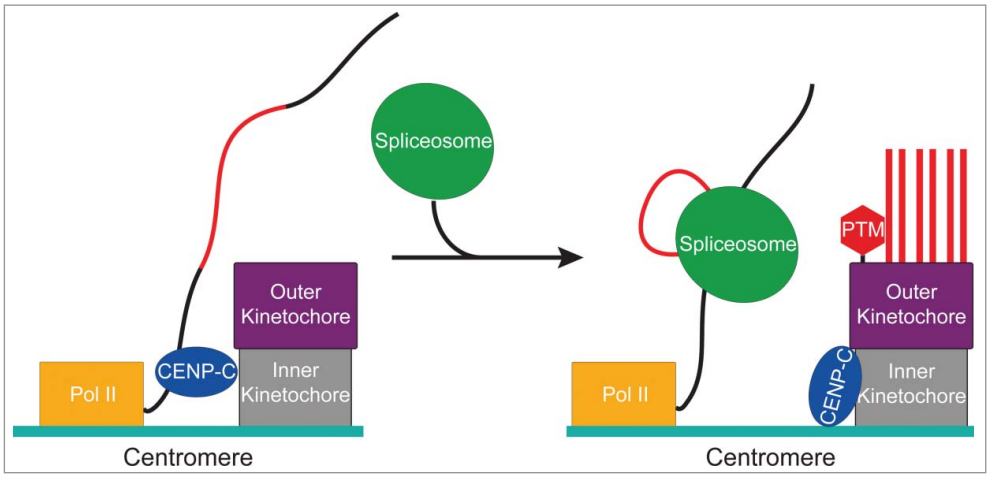


**Figure 1.** Model for the role(s) of centromeric transcription in kinetochore assembly. Nascent RNA Polymerase II (Pol II) transcripts stabilize CENP-C at the centromere, which promotes kinetochore assembly leading to spindle microtubule attachment. Active Pol II also recruits splicing factors that process nascent centromeric RNAs and could catalyze functionally important post-translational modifications (PTM) of kinetochore proteins.

Centromeric transcription adds yet another layer of complexity to centromere and kinetochore assembly. Uncovering the functional aspects of this process will require a quantitative understanding of the RNA-binding characteristics of centromere and kinetochore factors, including knowledge of the sequence and/or structural determinants of RNA-binding, and a more complete picture of the noncanonical kinetochore components recruited by mitotic transcription.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## References

[1] Gent JI, Dawe RK. RNA as a structural and regulatory component of the centromere. Annual review of genetics 2012; 46:443-53; PMID:22974300; http://dx.doi.org/10.1146/annurev-genet-110711-155419

[2] Grenfell AW, Heald R, Strzelecka M. Mitotic noncoding RNA processing promotes kinetochore and spindle assembly in Xenopus. J Cell Biol 2016; 214:133-41; PMID:27402954; http://dx.doi.org/10.1083/jcb.201604029

[3] Chueh AC, Northrop EL, Brettingham-Moore KH, Choo KH, Wong LH. LINE retrotransposon RNA is an essential structural and functional epigenetic component of a core neocentromeric chromatin. PLoS Genet 2009; 5:e1000354; PMID:19180186; http://dx.doi.org/10.1371/journal.pgen.1000354

[4] Rosic S, Kohler F, Erhardt S. Repetitive centromeric satellite RNA is essential for kinetochore formation and cell division. J Cell Biol 2014; 207:335-49; PMID:25365994; http://dx.doi.org/10.1083/jcb.201404097

[5] Du Y, Topp CN, Dawe RK. DNA binding of centromere protein C (CENPC) is stabilized by single-stranded RNA. PLoS Genet 2010; 6: e1000835; PMID:20140237; http://dx.doi.org/10.1371/journal.pgen.1000835

[6] Bodor DL, Mata JF, Sergeev M, David AF, Salimian KJ, Panchenko T, Cleveland DW, Black BE, Shah JV, Jansen LE. The quantitative architecture of centromeric chromatin. Elife 2014; 3: e02137; PMID:25027692; http://dx.doi.org/10.7554/eLife.02137

[7] Montembault E, Dutertre S, Prigent C, Giet R. PRP4 is a spindle assembly checkpoint protein required for MPS1, MAD1, and MAD2 localization to the kinetochores. J Cell Biol 2007; 179:601-9; PMID:17998396; http://dx.doi.org/10.1083/jcb.200703133