Meiotic, cryptic, and stable unannotated transcripts: Noncoding RNAs add to the epigenetic tool box controlling meiotic development

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Less than 2% of the genome codes for the ≈20,000 genes found in humans. Rather than representing a genetic desert as originally thought, high-resolution expression profiling has found that these noncoding regions of the chromosome are actively transcribed, producing several types of noncoding RNAs (ncRNAs). Recent studies have found that these ncRNAs can be divided into several groups based on origin and/or function (1). For example, small ncRNAs (e.g., small interfering RNAs or microRNAs) negatively regulate gene expression by targeting specific mRNAs for destruction or preventing their translation. However, ncRNAs have also been shown to stimulate gene transcription by inducing changes in chromatin structure (2–4). In addition, ncRNAs regulate diverse processes, including chromosome segregation, cell cycle progression, and cellular differentiation (5, 6). In particular, several aspects of germ cell development are regulated by ncRNAs [reviewed in (7)]. For example, ablation of the small ncRNA processing pathway disrupts oocyte development (8, 9) whereas small ncRNAs (e.g., miR-122a) can target individual genes for silencing (10).

Previous studies in budding yeast have uncovered stable unannotated transcripts (SUTs) (11) and cryptic unstable transcripts (CUTs) in vegetative cells (12). In a report in PNAS, Lardenois et al. (13) identify and characterize ncRNAs produced during meiotic development in budding yeast. In this study, a unique class of ncRNAs, meiotic unannotated transcripts (MUTs), that accumulate only during meiotic development was discovered. These findings are remarkable in several ways. First, their exquisite timing, coupled with their genomic location, suggests a role for the MUTs in meiotic gene regulation. For example, MUTs were identified whose accumulation inversely mirrored that of a coding gene but were transcribed on the complementary strand, suggesting an antisense function (Fig. 1*A*). In other instances, MUT expression occurred on the same strand, with the potential to interfere with transcription (Fig. 1*B*). In addition, MUTs were observed that transverse DNA replication origins (Fig. 1*C*). This observation is interesting because previous studies have found that active transcription can interfere with the binding and/or function of proteins required for DNA replication (14, 15). Meiotic S-phase (meiS) possesses several characteristics that distinguish it from mitotic DNA replication. For example, meiS rereplication must be prevented both following normal meiS phase and between the two meiotic nuclear divisions. Genetic studies have found that the system controlling this block to rereplication is different in these two systems (16). Preventing origin firing via MUTs represents an interesting possibility to deliver a meiosis-specific answer to this meiotic problem. Finally, a large number of MUTs were found that are transcribed in regions of the chromosome without identifiable features (Fig. 1*D*). Potential regulatory roles for these transcripts are not known.

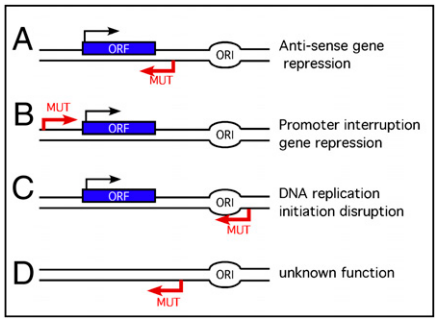

Fig. 1. Proposed roles for ncRNA control of meiotic development. (*A*) Antisense MUT transcription contemporaneously with a meiotic ORF. (*B*) MUT transcription on the same strand as the ORF has the ability to disrupt promoter function. (*C*) Inactivation of a DNA replication origin (ORI) by MUT transcription. (*D*) MUT transcription in a featureless region of a chromosome. Potential functions of this transcript are unknown.

How Is the Regulator Regulated?

Rrp6p is an RNase that is a component of the conserved exosome complex required for many RNA processing tasks, including rRNA processing (17) and degrading CUTs (12). Lardenois et al. (13) find that Rrp6p levels are reduced early in meiotic progression coincident with the accumulation of MUTs. This led the authors to speculate that Rrp6p destruction is a potential mechanism for controlling MUT levels. This model is supported by the finding that deleting *RRP6* resulted in constitutive expression of MUTs in vegetative cells and throughout meiosis. Rrp6p regulation mirrors that observed for the transcriptional repressor Ume6p, a negative regulator of early meiotic gene transcription (18). Entry into meiosis induces the destruction of Ume6p mediated by the anaphase promoting complex/cyclosome ubiquitin ligase (19). Taken together, these findings suggest a common regulatory theme for controlling meiotic induction and progression in that protein destruction is used to inhibit the inhibitors. Why use destruction rather than some other method to inactivate Rrp6p and Ume6p? Inactivation by destroying the proteins may more fully commit the cell to its decision to exit the cell cycle and induce meiotic development.

Epigenetics and Developmental Control

Similar to other differentiation programs, expression of the genes required for yeast meiosis is controlled by a transient transcription program. The importance of this program is underscored by the finding that many of the factors required for this process are essential for normal meiosis. For example, factors that control chromatin modifications, such as histone acetylation (Gcn5p), histone deacetylation (Rpd3p), and recruiters of these factors (Ume6p), are all essential for meiosis but are dispensable for mitotic cell division (18, 20, 21). Similarly, Rrp6p is necessary for meiotic progression but not for viability (22). These findings indicate a different requirement for epigenetic control when cells are differentiating as opposed to proliferating. Although many exist, one potential reason for this higher reliance on epigenetic control is that the execution of developmental programs requires an increase in regulatory complexity that is afforded by the expansion of ncRNA-dependent regulation (23). Such a model is supported by the increased ratio of ncRNA to total genome size observed as organisms become more complex even though the total number of genes remains similar (23). The ncRNA control of gene expression, DNA synthesis, and chromosome segregation (as well as other

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unknown processes) may add layers of control on a developmental process without requiring more regulators. Studies in model organisms, such as budding or fission yeasts, may provide insight into these questions.

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1. Costa FF (2010) Non-coding RNAs: Meet thy masters. *BioEssays* 32:599–608.
2. Uhler JP, Hertel C, Svejstrup JQ (2007) A role for noncoding transcription in activation of the yeast PHO5 gene. *Proc Natl Acad Sci USA* 104:8011–8016.
3. Sanchez-Elsner T, Gou D, Kremmer E, Sauer F (2006) Noncoding RNAs of trithorax response elements recruit Drosophila Ash1 to Ultrabithorax. *Science* 311:1118–1123.
4. Schmitt S, Prestel M, Paro R (2005) Intergenic transcription through a polycomb group response element counteracts silencing. *Genes Dev* 19:697–708.
5. Fomproix N, Hernandez-Verdun D (1999) Effects of anti-PM-Scl 100 (Rrp6p exonuclease) antibodies on prenucleolar body dynamics at the end of mitosis. *Exp Cell Res* 251:452–464.
6. Ohkura H, et al. (1988) Cold-sensitive and caffeine-supersensitive mutants of the Schizosaccharomyces pombe dis genes implicated in sister chromatid separation during mitosis. *EMBO J* 7:1465–1473.
7. McFarlane L, Wilhelm D (2009) Non-coding RNAs in mammalian sexual development. *Sex Dev* 3:302–316.
8. Tam OH, et al. (2008) Pseudogene-derived small interfering RNAs regulate gene expression in mouse oocytes. *Nature* 453:534–538.
9. Watanabe T, et al. (2008) Endogenous siRNAs from naturally formed dsRNAs regulate transcripts in mouse oocytes. *Nature* 453:539–543.
10. Yu Z, Raabe T, Hecht NB (2005) MicroRNA Mirn122a reduces expression of the posttranscriptionally regulated germ cell transition protein 2 (Tnp2) messenger RNA (mRNA) by mRNA cleavage. *Biol Reprod* 73:427–433.
11. Xu Z, et al. (2009) Bidirectional promoters generate pervasive transcription in yeast. *Nature* 457:1033–1037.
12. Davis CA, Ares M Jr. (2006) Accumulation of unstable promoter-associated transcripts upon loss of the nuclear exosome subunit Rrp6p in Saccharomyces cerevisiae. *Proc Natl Acad Sci USA* 103:3262–3267.
13. Lardenois A, et al. (2011) Execution of the meiotic noncoding RNA expression program and the onset of gametogenesis in yeast require the conserved exosome subunit Rrp6. *Proc Natl Acad Sci USA* 108:1058–1063.
14. Mori S, Shirahige K (2007) Perturbation of the activity of replication origin by meiosis-specific transcription. *J Biol Chem* 282:4447–4452.
15. Snyder M, Sapolsky RJ, Davis RW (1988) Transcription interferes with elements important for chromosome maintenance in Saccharomyces cerevisiae. *Mol Cell Biol* 8:2184–2194.
16. Strich R, Mallory MJ, Jarnik M, Cooper KF (2004) Cyclin B-cdk activity stimulates meiotic rereplication in budding yeast. *Genetics* 167:1621–1628.
17. Allmang C, et al. (1999) The yeast exosome and human PM-Scl are related complexes of 3′ → 5′ exonucleases. *Genes Dev* 13:2148–2158.
18. Strich R, et al. (1994) UME6 is a key regulator of nitrogen repression and meiotic development. *Genes Dev* 8:796–810.
19. Mallory MJ, Cooper KF, Strich R (2007) Meiosis-specific destruction of the Ume6p repressor by the Cdc20-directed APC/C. *Mol Cell* 27:951–961.
20. Vidal M, Gaber RF (1991) *RPD3* encodes a second factor required to achieve maximum positive and negative transcriptional states in *Saccharomyces cerevisiae*. *Mol Cell Biol* 11:6317–6327.
21. Burgess SM, Ajimura M, Kleckner N (1999) *GCN5*-dependent histone H3 acetylation and *RPD3*-dependent histone H4 deacetylation have distinct, opposing effects on *IME2* transcription, during meiosis and during vegetative growth, in budding yeast. *Proc Natl Acad Sci USA* 96:6835–6840.
22. Briggs MW, Burkard KT, Butler JS (1998) Rrp6p, the yeast homologue of the human PM-Scl 100-kDa autoantigen, is essential for efficient 5.8 S rRNA 3′ end formation. *J Biol Chem* 273:13255–13263.
23. Taft RJ, Pheasant M, Mattick JS (2007) The relationship between non-protein-coding DNA and eukaryotic complexity. *BioEssays* 29:288–299.