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Transcriptional control of microRNA expression in *C. elegans*: Promoting better understanding

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Abstract

Transcriptional regulation of microRNA (miRNA) expression is one of the least understood aspects of miRNA biogenesis. In *C. elegans* the list of miRNAs whose transcriptional control has been described in some detail is currently limited to four: *let-7*, *lin-4*, *lsy-6*, and *mir-61*. Each of these genes has been shown experimentally to be transcriptionaly regulated by *cis*- and/or *trans*-acting factors that either promote or inhibit expression. Additionally, computational methods based on conservation among miRNA genes have yielded predicted regulatory sequences in *C. elegans* that may function to regulate miRNA expression on a genome-wide scale.

Keywords

microRNA; miRNA; pri-miRNA; transcription; promoter; Pol II

Transcription/miRNA Transcription

Of the three known RNA polymerases in eukaryotic cells, RNA polymerase II (Pol II) is primarily responsible for transcribing protein-coding genes into messenger RNAs (mRNAs). However, recent findings indicate that Pol II is also responsible for the transcription of some non-protein-coding genes, including microRNAs (miRNAs).[1] While several aspects of Pol-II-mediated transcription are well understood, the mechanisms that underlie Pol-II mediated transcription of miRNAs, and the cofactors that participate with it, remain largely unknown.

The core transcriptional machinery for protein-coding genes in *C. elegans* is highly similar to that of higher organisms, consisting of Pol II and many Pol-II-associated transcription factors (TF's). Less conserved from *C. elegans* to human are the *cis*-acting regulatory regions that specify when and how transcription is regulated from each gene locus. These *cis*-acting elements work in combinatorial fashion to provide a specific "fingerprint" of expression. Like a key used to unlock a door, *cis*-elements are analogous to the bumps and indents etched into the metal skeleton of the key; their sequence, position, and arrangement on the DNA backbone define a distinct signature able to "unlock" transcription from a

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specific location at a specific time, but not from another "unauthorized" site (for reviews see refs. 2–5).

miRNA Promoters

For Pol II, the best-understood *cis*-acting regulatory elements that make up the core promoter (sequence within about 50 nucleotides of the transcriptional start site, or TSS) include a TATA box and/or an initiator (Inr).[6–8] Though common, these elements are not absolutely necessary for recruitment of the basal transcriptional machinery, as core promoter motifs do exist that are active and independent of TATA and Inr motifs.[2,9] However, the ways in which these elements recruit the basal transcription machinery are poorly understood. While at one time a majority of protein-coding genes were believed to use a TATA motif located between 30 and 35 nucleotides from the TSS to initiate transcription, more recent findings have begun to question that conclusion.[10]

miRNAs have been shown to be products of Pol II, though mature miRNAs are known to be produced from transgenic constructs driven by Pol II- and Pol III-specific promoters.[1,11–13] The evidence implicating Pol II as the polymerase of miRNA transcription includes the discovery of primary-miRNA (pri-miRNA) transcripts that are capped and polyadenylated, signature processing characteristics of Pol II transcription products (Fig. 1).[1] Furthermore pri-miRNA expression levels are greatly reduced by α-amanitin at concentrations that specifically inhibit Pol II.[1]

Strangely, it has been noted that while *C. elegans* miRNA promoters can be comprised of many Pol-II-associated cis-acting elements, motifs like the TATA box are often absent from their promoters.[14,15] Zhou et al. found that in *C. elegans* only half (47%) of putative miRNA promoters contained the canonical TATA box motif.[15] However, 69 out of 73 putative promoters contained a conserved sequence that matches the consensus sequence recognized by TF's and Inr-dependent co-factors. This suggests that known miRNA promoters in *C. elegans* are biased toward Inr-mediated recruitment of basal transcription machinery.

Additional *cis*-acting regulatory sequences exist outside of the core promoter (Fig. 1). These elements recruit *trans*-acting factors that work to tailor the expression of a given gene to the specific needs of the cell by either enhancing or silencing transcription. Martinez et al. have shown that this is as true for miRNA promoters as it is for the promoters of protein-coding genes.[16] They defined putative miRNA promoters as the sequence between annotated, intergenic miRNA genes and the nearest upstream genes, and used these sequences to drive expression of green fluorescent protein (GFP).[16] Their results showed that 90% (63/70) of these sequences were sufficient to drive GFP with temporal and spatial specificity.[16]

Despite great diversity among *cis*-acting regulatory elements, there are common, canonical motifs highly conserved in the sequences flanking Pol-II-transcribed genes. These motifs include enhancers like the CCAAT box,[17] and the GC box,[18] as well as silencers like the ANCCTCTCT motif[19] and other transcription inhibitors.[5] To date, few canonical enhancers/repressors have been shown to be involved in regulating miRNA transcription in *C. elegans*.

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Validated *cis*-Acting Regulatory Elements in *C. elegans*

Until recently, only a few *cis*-acting regulatory regions specific to a miRNA gene had been successfully identified in *C. elegans*. In these studies, and other computation-based studies that analyze the *C. elegans* genome, miRNA promoters are found to be diverse, like protein-coding targets of Pol II transcription.[14,15,20–23] Recent work by the Walhout and Ambros laboratories confirms this diversity.[16,24] Martinez et al. used three yeast one-hybrid (Y1H) screens to test 71 putative *C. elegans* miRNA promoters against a *C. elegans* TF library.[24,25] Their results show that 116 TF's interact with 63 putative promoters in a total of 347 interactions. Like protein-coding genes, miRNA promoters seem to consist of both very specific, non-conserved elements that only regulate one, or a few, miRNAs,[20,21,24] as well as more common transcription factor binding sites, the regulation of which is linked to well-studied signaling cascades.[22–24] In either scenario, scientists are just beginning to understand the mechanisms involved in regulating miRNA expression at the level of transcription (Fig. 2). The findings of the Walhout and Ambros laboratories greatly expand the current miRNA promoter/TF interactome, which up until their work was limited to just a few cases, documented below.

The *let-7* miRNA is temporally expressed in *C. elegans* development, and is required for stem cell development. In the first analysis of its kind, Johnson et al. used sequence upstream of the *let-7* miRNA containing the putative promoter to drive expression of GFP.[20] This sequence drove GFP expression in a pattern consistent with the known function of *let-7*. Truncations and deletions within this promoter region revealed that a short, inverted repeat (IR) was necessary and sufficient for GFP expression. Bracht et al. showed that *let-7* initiates transcription from two sites located upstream of the *let-7* mature miRNA sequence in the genome.[26] While the IR sequence was shown by electrophoresis mobility shift assays to be bound by a protein, the identity of that factor remains to be discovered (Fig. 2). Genetic studies place a transcription factor, DAF-12, immediately upstream of *let-7* in its gene pathway.[20] However, DAF-12-mediated regulation could be indirect, and not necessarily limited to transcription of *let-7*. The Y1H screens reported by Martinez et al. did not detect DAF-12 interactions with the *let-7* promoter, supporting this hypothesis.[24] The *let-7* promoter was found to interact with 14 other TFs.[24]

mir-61 is expressed in vulval precursor cells (VPC's) P5.p and P7.p, and is believed to be required for specifying their "2°" VPC fate.[22] Yoo et al. showed that the LIN-12/LAG-1 transcription factor complex regulates transcription of *miR-61*.[22] These binding partners are canonical participants in the NOTCH signaling pathway, and downstream targets are often identified as having LAG-1 binding sites. Two such sites exist in the 500 nucleotides that precede the mature *miR-61* sequence in the genome (Fig. 2). Mutational analysis proved that these sites are necessary for transcription of *miR-61*, as well as provided evidence of direct regulation of *miR-61* by LIN-12/LAG-1.[22] Martinez et al. did not detect any protein interaction with the *miR-61* promoter.[24] It is possible that this is because their pool of TF's tested, though extensive, did not include LAG-1 and/or LIN-12.

lsy-6 is a miRNA required for proper asymmetric development of *C. elegans* ASE chemoreceptor neurons and is expressed specifically in ASE-left (ASEL), but not in ASE-

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right (ASER).[21] Johnston et al. reported a novel zinc-finger transcription factor, LSY-2, required for the expression of *lsy-6*.[21] Discovered from a genetic screen for disruption of left-right neuronal asymmetry in the *C. elegans* nervous system, LSY-2 was subsequently identified as an ortholog of the mammalian SP1/KLF family transcription factors. While no evidence for direct regulation of *lsy-6* transcription was reported, strong genetic evidence showed that LSY-2 is required for *lsy-6* expression (Fig. 2A).[21] In the absence of biochemical evidence, one cannot rule out that this interaction could also be indirect, possibly affecting post-transcriptional processing steps. In fact the Y1H screens preformed by Martinez et al. did not detect LSY-2 as a direct binder of the *lsy-6* promoter.[24] LSY-2 was, however, found to interact with the promoters of *miRs -48*, *-76*, *-228*, *-242*, and *-243*.[24] The *lsy-6* promoter was found to interact with 7 different TFs directly.[24]

Most recently, Ow et al. reported that transcription of the *lin-4* miRNA is regulated by the FLYWCH transcription factors.[23] *lin-4* is required for the transition from larval stages 1 to 2 (L1 to L2) in *C. elegans* development, and *lin-4*(*lf*) mutants reiterate L1-specific cell fates.[27] Ow et al. utilized a Y1H screen, with different regions of the putative *lin-4* promoter for bait, to identify protein factors important for regulating *lin-4* transcription. These protein factors included *C. elegans* FLYWCH proteins FLH-1 and -2. While all other known *trans*-acting factors that regulate miRNA transcription in *C. elegans* act as transcriptional activators, the *C. elegans* FLYWCH proteins FLH-1,-2,-3 work with some redundancy to inhibit transcription from the *lin-4* locus, as well as least six additional miRNA loci, by directly binding to a conserved element in the promoter.[23] Presumably, this binding event blocks transcription until the FLH proteins release the site and allow for transcription to proceed (Fig. 2A). In addition to the FLH-1 and -2 genes, Martinez et al. reported 13 proteins that directly interact with the *lin-4* promoter.[24]

Predicted *cis*-Acting Regulatory Elements

The reports by Ow et al.[23] and Martinez et al.[16,24] provide experimental evidence of *cis*-acting elements being shared by many miRNA promoters. However, other common motifs shared across miRNA promoters have also been computationally predicted on the genomic scale. Ohler et al.[14] and Zhou et al.[15] independently employed computational methods to discover two short, conserved sequences that lie within 200 bases of the predicted hairpin structure of most known intergenic *C. elegans* miRNAs.[14,15] The most significant of these was referred to as “motif A” (mA), which was found upstream of almost all known *C. elegans* intergenic miRNAs.[14] Interestingly, mA is absent from the promoters of protein-coding genes, including those that harbor miRNAs within their introns.[14] Furthermore the authors reported that mA was also absent from intronic sequence upstream of intronic miRNAs. However, recent studies have identified at least three examples of exceptions to this pattern. In the case of the miRNA *lin-4*, for example, which was previously believed to reside in intergenic space, new EST evidence suggests that *lin-4* actually lies within a large intron of a protein-coding gene. The intronic sequence upstream of *lin-4* does indeed contain a sequence homologous with the mA motif (Fig. 2B). Two additional miRNAs, miR-2 and miR-82, are found in introns that contain the conserved mA sequence (Fig. 2B). In each of these three examples, the intronic, mA-containing sequence upstream of the miRNA is sufficient to drive expression of GFP in a cell-specific manner.[16,23,28] It is therefore possible

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that intronic miRNAs driven by independent, internal promoters that initiate transcription from alternative start sites do sit downstream of an mA, and that this motif is a general regulatory motif marking miRNAs whose transcription is independent of neighboring and host genes.

Zhou et al. reported two additional miRNA promoter motifs that are semi-conserved across multiple organisms from nematodes to mammals.[15] A more recent report by Heikkinen et al. described a *C. elegans* motif (GANNNNGA) common to many sequences upstream of miRNAs, regardless of their placement in introns or intergenic space.[29] Versions of this motif in plant and mammal miRNA promoters were reported earlier by Zhou et al.[15] The regulatory capacity of all of these motifs, as well as the motifs reported by Ohler et al. has not been fully elucidated experimentally.

Possible Regulatory Functions of cis Elements Independent of Transcription

Transcription is not the only step of miRNA biogenesis subject to regulation. Indeed, after transcription, pri-miRNA transcripts are subject to two processing steps, via Drosha/Pasha and Dicer, which take place before and after export to the cytoplasm, respectively (for reviews see refs. 30–33). Each of these steps is susceptible to regulation, the details of which are exciting areas of current research.

Perhaps the best understood example of post-transcriptional regulation of miRNA expression is the regulated maturation of *let-7* via LIN28 in mammalian cells. *let-7* pri-miRNAs are transcribed from the earliest stages of development, but LIN28 inhibits their maturation until later developmental stages.[34–38] It is possible that the conserved *cis* elements identified computationally, including the mA motif, are actually involved in post-transcriptional, rather than transcriptional, regulation. One line of evidence suggesting that the role of the mA is not related to transcription lies in the observation that deleting mA out of the *lsy-6* promoter does not effect expression of a reporter construct.[21] Additionally, mA alone is not sufficient to drive expression when placed upstream of GFP; progressive truncations of the promoter::GFP fusion constructs of *let-7* or *lin-4* eventually results in lack of GFP expression, even when mA remains in the promoter (unpublished data and ref. 20). This evidence would also argue against a role for the mA in post-transcriptional regulation, unless the processing events regulated by the mA were also required for the expression of the GFP transgene.

The lack of data regarding the nature of pri-miRNAs further prevents definitive conclusions from being drawn with regards to the nature of regulation imposed by computationally predicted, as well as validated, motifs. The *let-7* pri-miRNA is one case that emphasizes this point. *let-7* is the only monocistronic *C. elegans* miRNA for which a full pri-miRNA sequence, and therefore the transcriptional start site, has been fully characterized.[26] In this instance, two pri-mRNA transcripts for *let-7* were elucidated by 5′ RACE. The distal transcriptional start site for *let-7* was found to be upstream of the mA motif, and all other motifs mentioned here, with the exception of the IR binding site (Fig. 2A and B). This suggests that the regulatory function of the mA is post-transcriptional in nature. However,

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the proximal start site of the *let-7* pri-miRNA is positioned downstream of the mA, and therefore still subject to potential regulation by mA at the level of transcription.

It is possible that highly conserved motifs upstream of miRNAs are important signals that regulate miRNA expression at one of many processing steps. Most likely these steps would precede Drosha/Pasha processing of the pri-miRNA, though, as the 60–70 nucleotide hairpin product of the Drosha/Pasha microprocessor is separated by cleavage from the conserved *cis* regulatory regions described here. The mA motif, and other conserved *cis*-acting motifs, are potential candidates as master regulators of miRNA biogenesis. However, elucidating complete regulatory networks that coordinate pri-miRNA transcription and further processing requires more empirical research.

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Abbreviations

miRNA	microRNA
mRNA	messenger RNA
pri-miRNA	primary miRNA
TF	transcription factor
Pol II	RNA Polymerase II
Pol III	RNA Polymerase III
TSS	transcriptional start site
Inr	Initiator
GFP	green fluorescent protein
Y1H	yeast one-hybrid
IR	inverted repeat
VPC	vulval precursor cell
ASEL	ASE-left neuron
ASER	ASE-right neuron
L1	larval stage 1
L2	larval stage 2
mA	motif A
EST	expressed sequence tag
RACE	rapid amplification of cDNA ends

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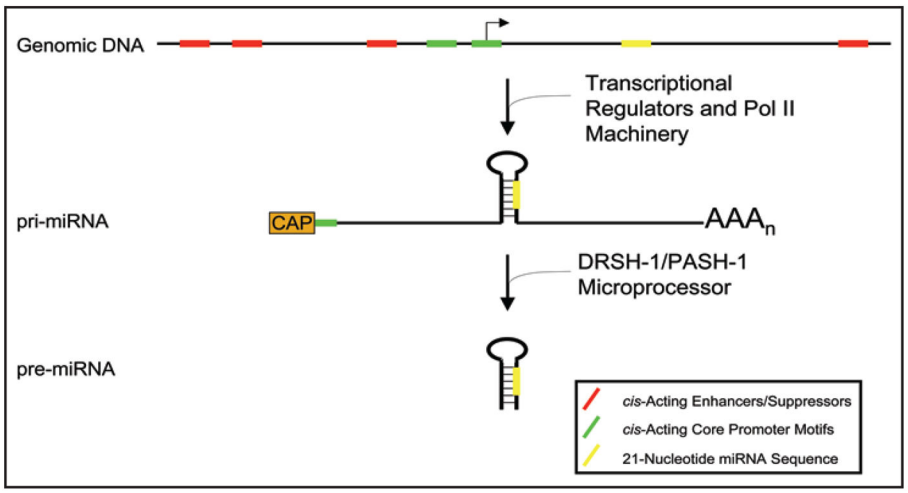

Figure 1.

Transcription and processing of primary miRNA transcripts. Primary miRNA transcripts are synthesized and processed by DRSH-1/PASH-1in the nucleus. Processed products, 60–70 nucleotide hairpin structures, are exported out of the nucleus and into the cytoplasm where they are further processed by DCR-1/Dicer into mature miRNAs.

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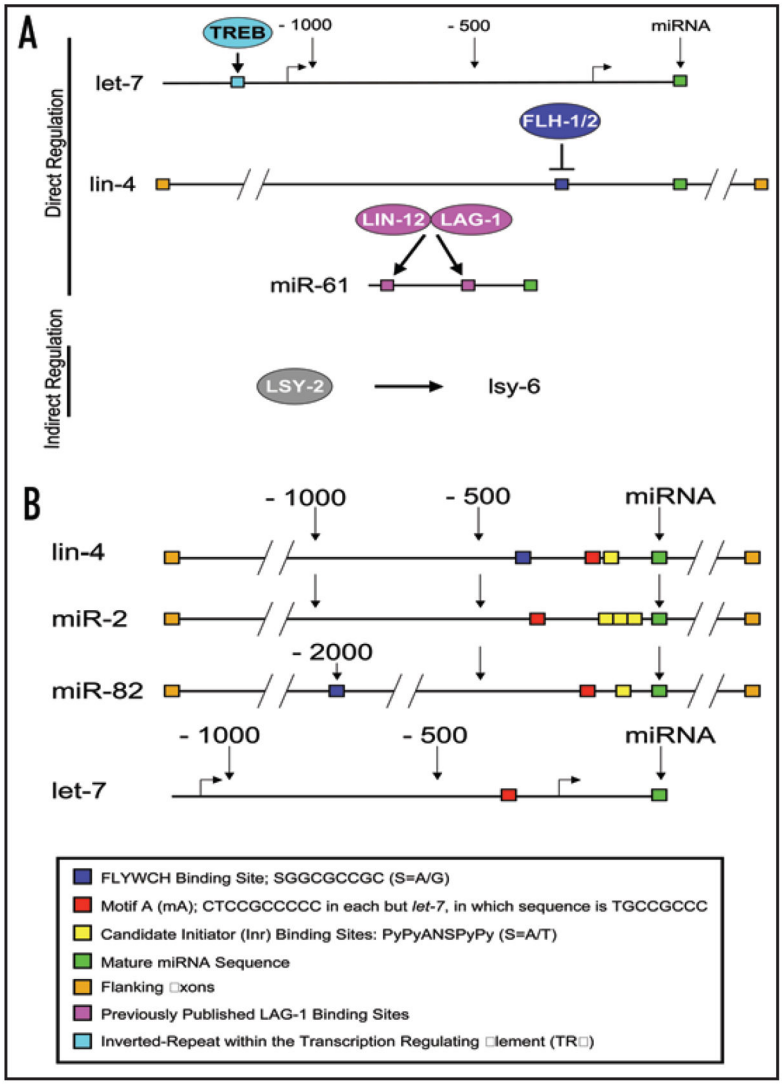

Figure 2.

Known and predicted mechanisms of transcriptional regulation of miRNAs. (A) Schematic of experimentally validated relationships between transcription factors and miRNA promoters. This schematic does not include the 347 promoter/TF interactions recently reported by the Walhout and Ambros groups. (B) Schematic of computationally predicted regulatory motifs within miRNA promoters.