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POINT OF VIEW

LncRNAs: Bridging environmental sensing and gene expression

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ABSTRACT
The survival of all organisms is dependent on complex, coordinated responses to environmental cues. Non-coding RNAs have been identified as major players in regulation of gene expression, with recent evidence supporting roles for long non-coding (lnc)RNAs in both transcriptional and post-transcriptional control. Evidence from our laboratory shows that lncRNAs have the ability to form hybridized structures called R-loops with specific DNA target sequences in *S. cerevisiae*, thereby modulating gene expression. In this Point of View, we provide an overview of the nature of lncRNA-mediated control of gene expression in the context of our studies using the *GAL* gene cluster as a model for controlling the timing of transcription.

Abbreviations: DRIP, DNA/RNA immunoprecipitation; lncRNA, long non-coding RNA; mRNA, mRNA; ncRNA, non-coding RNA; lncRNA, long non-coding RNA; RNP, ribonucleoprotein complex

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Non-coding RNAs (ncRNAs) are a family of RNAs that display a wide range of biochemically distinct roles.[1] Over the past 50 years, many different classes of ncRNAs have been described, including microRNAs (miRNAs),[2,3] small nucleolar RNAs (snoRNAs),[4,5] small nuclear RNAs (snRNAs),[6] small Cajal body-specific RNAs (scaRNAs),[7] enhancer RNAs (eRNAs),[8] and long non-coding RNAs (lncRNAs).[9] LncRNAs are a diverse class of ncRNAs found in all eukaryotes from mammals[10] to unicellular organisms, such as *Trichomonas vaginalis*,[11] *Plasmodium falciparum*,[12] and the budding yeast *Saccharomyces cerevisiae*.[13] The generally accepted definition of a lncRNA is a transcript that lacks a long or conserved open reading frame and is greater than 200 nucleotides in length.[1,14] Initially theorized to be the result of spontaneous, aberrant transcription initiation, lncRNAs were first dismissed as spurious "sloppy" transcription.[15] However, the characterization of gene regulatory functions by mammalian lncRNAs, such as XIST[16] and HOTAIR,[17] made it clear that many of these transcripts are much more than extraneous transcriptional products.

Upwards of 30,000 lncRNAs have been identified in mammalian cells to date.[18] Thus far, many lncRNAs have been shown to control the expression of protein-coding genes by recruiting chromatin remodeling factors to specific gene loci.[19] Histone modifying enzymes and nucleosome remodeling proteins that interact with lncRNAs include G9a,[20] LSD1,[21] PRC2,[21,22] SWI/SNF,[23] and MLL,[24] indicating a diversity of interactions. LncRNAs have also been described as miRNA sponges,[25] facilitators of cytoplasmic mRNA decay,[26] and remodelers of the 3D chromatin architecture,[27] indicating a broad array of activities. In addition to biochemical diversity, a common theme for lncRNA function is temporal control of gene expression, regulating cellular programs that require highly specific and well timed responses to extracellular stimuli.[28–30] Unsurprisingly, misregulation of lncRNAs has been linked to the development of a multitude of human diseases including cancer[31] and heart failure.[32]

The budding yeast *Saccharomyces cerevisiae* has been a robust system for genetic and molecular investigation of gene expression steps since its introduction as a model organism almost 30 y ago.[33] Thus far, ~2,000 lncRNAs have been identified in budding yeast, which vary both in presence and abundance depending on growth conditions.[34–36] To survive in the wild, yeasts must rapidly adapt to changing environmental conditions, such as heat and osmotic stress and nutrient availability. The natural habitat for *S. cerevisiae* is fresh and decaying fruit where carbon sources are abundant and diverse.[37,38] These yeast preferentially use glucose as a carbon source, however, they have the ability to switch their metabolic profile to use alternative sugars, a response which is essential to environmental adaptation.[39] This switch involves reprogramming of upwards of 40% of the yeast transcriptome as a result of derepression and transcriptional activation of genes necessary for metabolism of sugars other than glucose.[40,41]

A key component of the glucose to galactose metabolic switch is the *GAL* gene cluster consisting of *GAL1, GAL10*, and *GAL7*. These genes exist in 3 distinct transcriptional states depending on the carbon source in the media. In the presence of glucose, the *GAL* cluster is repressed via association of glucose-dependent transcription factors, Mig1 and Nrg1, and the associated Tup1/Cyc8 (Tup1/Ssn6) co-repressor complex.[42,43] In the presence of galactose, the Gal4 transcriptional activator

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associates with *GAL* genes and facilitates transcriptional activation by promoting recruitment of co-activators and RNA polymerase II (RNA P II).[44] The third transcriptional state, called the "derepressed" or "non-induced" state, occurs when yeast are grown in the presence of raffinose. In this condition, the *GAL* genes are neither actively repressed nor are they induced.[45] This ability to control the transcriptional states by manipulation of carbon sources has made the *GAL* cluster an exceptional model gene locus for studying transcription initiation, termination, and chromatin remodeling events for decades.[44,46]

In addition to regulatory proteins, the *GAL* cluster also contains 2 lncRNAs, the GAL10 and GAL10s lncRNAs, which originate from a bidirectional promoter within the 3′ end of the *GAL10* open reading frame.[47] The GAL10 lncRNA is transcribed in an antisense orientation with respect to the *GAL10* protein-coding gene and overlaps both *GAL10* and *GAL1*, whereas the GAL10s lncRNA is expressed in the opposite orientation and runs through the downstream *GAL7* promoter region.[34,47] Initial studies of the GAL10 antisense lncRNA showed that expression of this non-coding molecule correlates with repression of *GAL10* and *GAL1* transcription when low levels of glucose are available in a complex sugar mixture, similar to conditions in the wild.[47] This repressive role was later supported by single transcript microscopy studies which demonstrated suppression of leaky transcription of the *GAL* cluster genes in the absence of GAL10 antisense lncRNA expression.[48] Repression occurs in *cis*[47] consistent with a transcriptional interference mode of action, whereby the process of transcription, rather than the lncRNA, regulates expression of an overlapped, protein-coding gene. This type of lncRNA-dependent regulation has been demonstrated for other genes in budding yeast as well as mammalian cells.[28,49]

The first discovery of transcriptional interference by a ncRNA was regulation of the *SER3* gene, which encodes 3-phosphoglycerate dehydrogenase, an enzyme integral to glycolysis and serine biosynthesis. In 2004, it was reported that serine-dependent transcription of the SRG1 lncRNA disrupts binding of general transcription factors to the downstream *SER3* gene promoter, thereby regulating transcription of this protein-coding gene.[28] Interestingly, *SRG1* transcription is activated by the presence of serine in the media, suggesting direct regulation of an lncRNA by nutrient availability. Repression of *SER3* is mediated by changes in nucleosome occupancy within the *SER3* promoter that occur during transcription of *SRG1*.[50] When cells become serine-deprived, *SRG1* is no longer transcribed and *SER3* repression is released.[51] These studies demonstrated that lncRNAs can regulate gene expression via multiple modalities in response to extracellular nutrient status.

Interestingly, the same lncRNA can also have more than one biochemical function *in vivo*. In addition to transcriptional repression, our group discovered that the GAL10 and GAL10s lncRNAs also function in transcriptional activation from transcriptionally repressive (+glucose) to activating (−galactose) conditions.[52] During this switch, the *GAL* lncRNAs enhance induction of the *GAL* protein coding genes from a repressed state by interfering with binding of the Tup1/Cyc8-corepressor complex. This occurs, presumably, by physical occlusion of the complex and results in derepression of the glucose-repressed *GAL* genes and allows for faster transcriptional activation in the presence of galactose (Fig. 1). Consistently, the GAL lncRNAs have no effect on induction from the derepressed (+raffinose) state, but rather confer a specific fitness advantage to yeast cells over those lacking the GAL lncRNAs during a glucose to galactose switch.[48,53] GAL lncRNA-dependent induction occurs when the GAL lncRNAs are encoded in *trans*, indicating that lncRNA-dependent transcriptional induction and repression are mechanistically distinct. This result is reminiscent of Air (Airn), which also functions in mechanistically distinct *cis* and *trans* roles to regulate gene expression.[54,55]

Dbp2 is a co-transcriptional RNA chaperone and *bona fide* RNA helicase whose activity is necessary for assembly of RNA-binding proteins, Yra1, Mex67, and Nab2 onto poly(A)$^+$ RNAs.[56,57] During transcription, both messenger and long non-coding RNAs are co-transcriptionally bound with a set of RNA-binding proteins to form a ribonucleoprotein complex (RNP), which then undergoes a variety of processing steps, including capping, splicing, termination, and polyadenylation. Loss of *DBP2* also results in over-accumulation and 3′ extension of the GAL10s lncRNA,[58] suggesting a connection between Dbp2 and proper biogenesis of the GAL lncRNAs. Interestingly, we found that cells lacking *DBP2* display a much more rapid lncRNA-dependent transcriptional induction of the *GAL* genes, as well as reduced association of the Cyc8 corepressor.[52] This suggested that Dbp2 and/or its role in RNP assembly, antagonizes the transcriptionally activating role of the GAL lncRNAs and that *dbp2Δ* cells could be used as a tool to decipher the mechanism of transcriptional induction by these non-coding molecules.

Seminal studies from the Aguilera lab demonstrated that mutations in genes needed for mRNA export, transcription elongation, and termination result in formation of R-loops.[59,60] R-loops are structures that form when an RNA base pairs with one strand of a DNA double helix, resulting in formation of an RNA:DNA hybrid and a displaced stretch of single-stranded DNA. R-loops can be both biologically beneficial as well as etiological agents of DNA damage. Aberrant formation and/or stabilization of R-loops results in genomic instability as a result of prolonged exposure of a single-stranded DNA to the environment and/or by interfering with DNA replication machinery.[61,62] In contrast, R-loops play beneficial roles by mediating CRISPR interference,[63,64] promoting IgG class switching,[65,66] and by regulating transcription.[67,68] These structures can form in *cis*[60] or *trans*[69] in vivo, either by "threading back" of nascent RNAs during transcription by RNA Pol II, through the action of the homologous recombination machinery, or associated RNA-binding proteins as in the case of CRISPR.[60,70,71]

Given that RNP assembly defects cause R-loops,[60,70] we speculated that loss of *DBP2* might promote formation of these structures between the GAL lncRNAs and *GAL* gene promoters. To test this, we asked if ectopic expression of human RNAse H1 in *dbp2Δ* cells would prevent rapid induction of the *GAL* genes by the GAL lncRNAs. Strikingly, this was the case, suggesting that RNA-DNA hybrids were involved in lncRNA-dependent induction of the *GAL* genes in *dbp2Δ* cells.[72] To determine if GAL lncRNA R-loops formed at the *GAL* cluster, we conducted DNA:RNA immunoprecipitation (DRIP) using the S9.6 RNA:DNA hybrid antibody. DRIP revealed that loss of

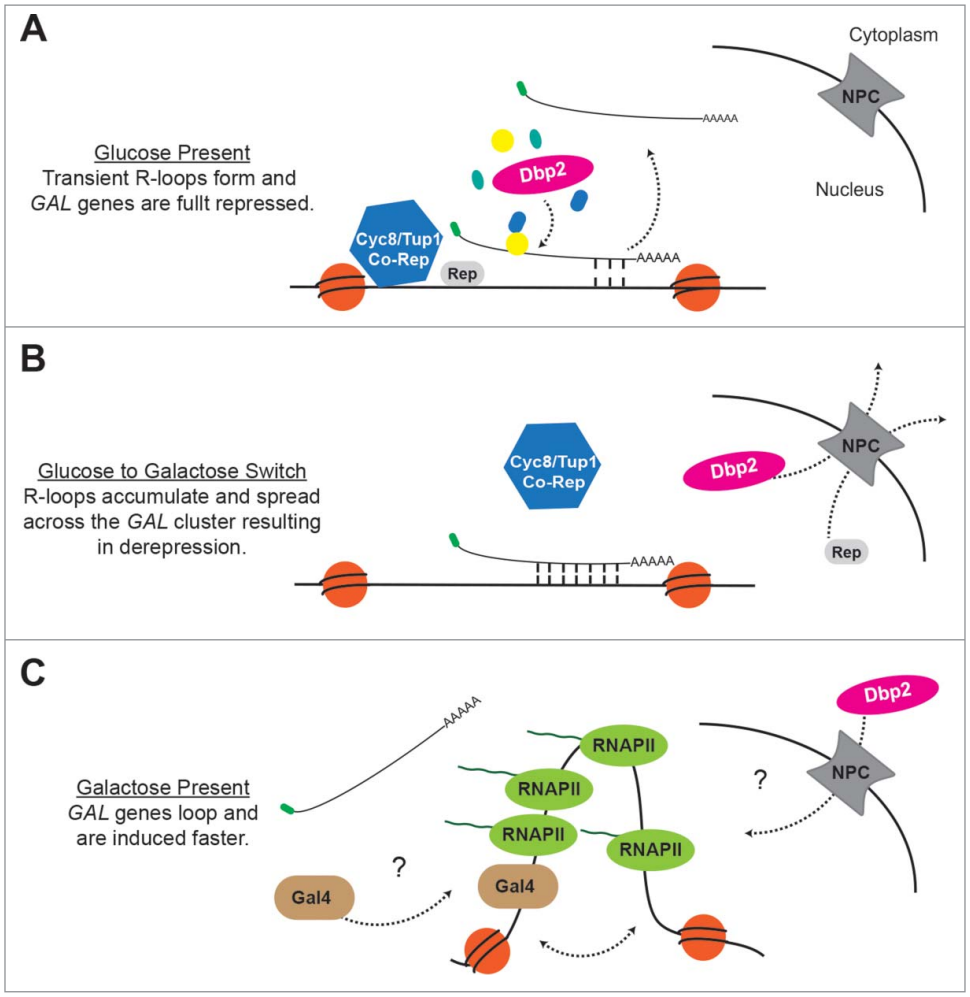

Figure 1. *A model for regulation of the GAL cluster by GAL lncRNA R-loops and Dbp2*. (A) *Glucose Repression* When glucose is available, Dbp2 is localized in the nucleus[74] and prevents the accumulation of R-loops at the *GAL* gene cluster[53] via the assembly of Dbp2-dependent lncRNA-protein complexes.[56] This allows the successful docking of the Cyc8/Tup1 co-repressor complex and subsequent repression. (B) *Carbon Source Switch* During a switch from glucose to galactose, Dbp2 is actively relocalized to the cytoplasm via export through the nuclear pore complex (NPC).[74] This may alter lncRNP assembly and cause R-loop formation and spreading across the *GAL* cluster. R-loop formation likely interferes with binding of transcriptional repressors and the Cyc8/Tup1 corepressor complex, causing derepression of the *GAL* genes. (C) *Galactose Induction* In the presence of galactose, the Gal4 transcriptional activator is released from the Gal80 inhibitor (not pictured),[96] enabling recruitment of co-activators and RNA P II.[97] This results in altered chromatin structure, as evidenced by looping of the GAL10 promoter and terminator,[53] which may enhance transcriptional induction. It is currently unknown how the *GAL* lncRNAs are cleared from chromatin or how Dbp2 is re-imported following long-term growth in galactose.

DBP2 results in accumulation of lncRNA-dependent R-loops across all 3 *GAL* cluster genes, consistent with the length of the GAL10 antisense lncRNA and 3′ extended GAL10s lncRNA.[58] Interestingly, the nuclear RNA decay enzyme RRP6 also controls R-loop formation in mammalian cells between eRNAs and enhancers,[73] indicating that RNP assembly and/or processing may dictate the function of numerous lncRNAs. Since simultaneous loss of *DBP2* and *RRP6* is lethal in yeast, indicating functional overlap,[58] it will be interesting to determine if orthologs of Dbp2 (DDX5 in mammals) also controls R-loop formation in multicellular eukaryotes.

While investigating the role of the GAL lncRNAs, we serendipitously discovered that Dbp2 is transported to the cytoplasm in response to glucose deprivation or a glucose to galactose shift, suggesting that wild type yeast actively export Dbp2 from the nucleus to alter gene expression.[74] Strikingly, nuclear depletion of Dbp2 using the "anchor away" strategy[75] resulted in time-dependent accumulation of R-loops beginning at the 5′ end of *GAL1* and spreading across *GAL1, GAL10* and through the 3′ end of *GAL7*.[53] Removal of the lncRNAs through genomic deletion reduced R-loops at the 5′ end of *GAL1* and abolished detection of these structures across the rest of the *GAL* cluster locus. This suggested that Dbp2 regulates formation of lncRNA R-loops at the *GAL* genes (Fig. 1A-B), thereby controlling lncRNA-dependent transcriptional regulation in response to nutrient availability. Moreover, this suggests that GAL lncRNA R-loops promote induction of the *GAL* genes from transcriptionally repressive conditions. In support of a role for R-loops in depression of the *GAL* cluster, we found that ectopic expression of RNase H1 reduced induction of the *GAL* genes to wild type levels in *dbp2Δ* cells.[53] The fact that *INO1*, an inducible gene without an overlapping, annotated lncRNA, induced at the same rate regardless of the presence of RNAse H1 argues against a general reduction in transcription.[53]

Because we observed R-loop accumulation across the entire *GAL* cluster, this leads one to wonder how these structures could specifically prevent Cyc8 association without impacting subsequent steps of transcriptional activation by Gal4, coactivators, and RNAPII (Fig. 1C). One possibility is that these R-loops are transient, allowing recruitment of transcriptional

activators. Resolution of R-loops *in vivo* would be accomplished by the activity of endogenous RNase H enzymes as well as RNA-DNA helicases such as Sen1/Senataxin.[70,76,77] It is also likely that these R-loops are cleared by transcription of another lncRNA molecule. The latter is supported by the fact that high levels of transcription correlate with the presence of R-loops in wild type cells,[78] which would be predicted to interfere with transcription if these structures were static. If this is the case, one would predict that most chromatin-bound factors would be displaced by these R-loops, irrespective of their role in transcriptional regulation. Cyc8 would be impacted specifically, not necessarily because of the R-loops, but because of the combined action of these structures with regulated export of glucose-dependent transcription factors to the cytoplasm.[79,80] However, very little is known about the dynamics of R-loops *in vivo*.

Another possibility is that the GAL lncRNA R-loops are discontinuous, forming along regions that impact Cyc8 but not Gal4 and RNA P II. It should be noted that DRIP assays depend on chromatin shearing to an average DNA size and is, thus, not at nucleotide resolution. Two new reports have attempted to address this concern by either the addition of S1 nuclease to prevent RNA:DNA hybrid loss or by sequencing the isolated RNA following immunoprecipitation.[81,82] However, a weakness of these studies and of our own investigations of the *GAL* cluster is the reliance on the S9.6 antibody as the sole reagent available for detection of RNA-DNA hybrids. Because this antibody shows both length and sequence bias,[83] new methods will need to be developed to precisely determine the sites of R-loop formation *in vivo*.

The GAL lncRNAs offer a striking example of how non-coding RNA molecules can promote adaptation. While we do not know if the GAL lncRNAs serve as a paradigm for other lncRNAs, because very few have been functionally characterized, the majority of those that have been studied thus far are linked to environmental sensing and stress response (Table 1). This role would be consistent with the emerging theme for mammalian lncRNAs cellular differentiation programs and human disease states. Additionally, 43% of single-nucleotide polymorphisms associated with human disorders are found outside of protein-coding regions [7], suggesting that mutations in the non-coding genome have been underappreciated. *S. cerevisiae* likely offer the perfect model system for mechanistic investigation of lncRNA activities, given recent evolutionary studies showing an increased reliance on antisense RNAs for fine tuning gene expression following loss of the microRNA pathway in this species.[84]

Moving forward, there are many aspects of lncRNA-dependent gene regulation that remain to be addressed. First, it is currently unknown how many lncRNAs utilize R-loops as a mechanism for gene regulation. It has been speculated for some time that direct hybridization of lncRNAs with genomic DNA could be a mechanism for locus-specific targeting, however, with the exception of RNA:DNA:DNA triplexes,[85–87] this has yet to be broadly demonstrated. Another question is how an RNA invades a DNA duplex, an activity that is thermodynamically unfavorable. Interestingly, evidence from the Koshland laboratory points to direct roles for Rad51 and Rad52, components of the homologous recombination machinery, for promoting R-loop formation in *trans*.[69] However, it is unknown what features of the RNA and/or DNA locus are recognized to mediate RNA:DNA hybridization and how the RNA helicase Dbp2 antagonizes this process. One possibility is that the lncRNA-protein composition and structure dictates the ability of this molecule to form R-loops.

Another question is how many other lncRNAs, in fungi or other species, promote the timing of gene expression. It is likely that many lncRNAs detected to date are spurious, non-functional products of transcription. However, future studies may be informed by analyses of transcription induction or repression kinetics, rather than reliance on lncRNA-dependent changes in steady state transcript levels. Finally, as more efforts are put forth to decipher the role of the non-coding genome, it must be emphasized that some of these long non-coding RNAs have been detected with translating ribosomes.[88] Although no examples of lncRNAs that produce functional peptides have been documented to date, we should continue to view the term

Table 1. Individually characterized lncRNAs of Saccharomyces cerevisiae. 65% of functionally characterized lncRNAs in S. cerevisiae have gene targets that function in pathways associated with metabolism or nutrient sensing/transport. AS = antisense. Us = upstream.

Functionally characterized lncRNAs in *S. cerevisiae*.				
Name	Function	Target Gene	Target gene function	Metabolism/ Nutrition related
MMF1 AS RNA[29]	Promotes induction	*MMF1*	Mitochondrial protein	YES
ASP3 lncRNA[98]	Upregulation	*ASP3*	Asparagine catabolism	YES
PHO84 AS RNA[99-101]	Repression	*PHO84*	Phosphate metabolism	YES
SRG1[28,50,51]	Repression	*SER3*	Serine / glycine biogenesis	YES
PHO5 AS RNA[102]	Promotes induction	*PHO5*	Phosphate metabolism	YES
usURA2.[103]	Repression	*URA2*	Pyrimidine biogenesis	YES
usDCI1.[104]	Repression	*DCI1*	Fatty acid metabolism	YES
GAL10 lncRNA[47,48,105]	Repression	*GAL* genes	Galactose metabolism	YES
GAL10/GAL10s lncRNAs.[52,53]	Promotes induction	*GAL* genes	Galactose metabolism	YES
KCS1 lncRNAs[106]	Translational interference	*KCS1*	Inositol hexa/hepta bisphosphate kinase	YES
SUT719[30,35]	Repression	*SUR7*	Plasma membrane protein	YES
CDC28 AS RNA[29]	Promotes induction	*CDC28*	Cell cycle regulator	NO
RTL.[107]	Repression	*Ty1*	Retrotransposon	NO
ICR1.[108]	Repression	*FLO11*	Cell surface glycoprotein	NO
PWR1.[108]	Upregulation	*FLO11*	Cell surface glycoprotein	NO
IME4 AS RNA[109,110]	Repression	*IME4*	Meiosis regulator	NO
IRT1.[109]	Repression	*IME1*	Meiosis regulator	NO

"non-coding" with caution until a much larger subset of these molecules have been functionally validated.

Aberrant expression of lncRNAs is associated with various diseases such as prostate cancer,[89] breast cancer,[90] HIV,[91] Type-2 diabetes,[92,93] and obesity,[93,94] underscoring a need for understanding the precise roles of lncRNAs. It should be emphasized that, although pioneering discoveries regarding lncRNA scaffolding of chromatin remodeling factors[21] and remodeling of the 3D genome[95] have relied on mammalian systems, transcriptional interference[28] and lncRNA R-loops were initially discovered in budding yeast.[53] As we continue to define biological roles for individual lncRNAs, it is essential to complement our studies of multicellular eukaryotes with simple model organisms, which have provided and continue to provide mechanistic paradigms for gene regulation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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