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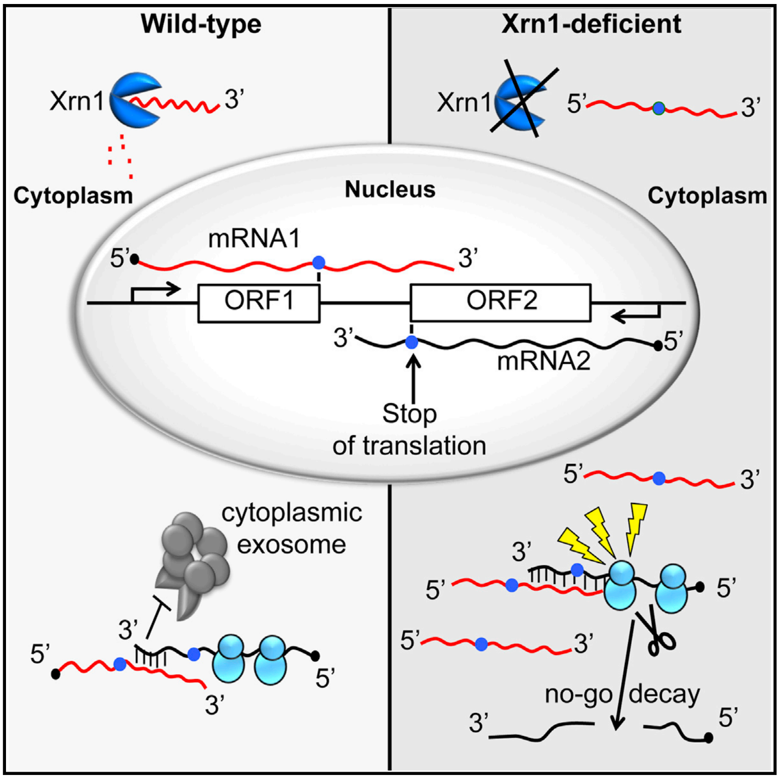
Cytoplasmic Control of Sense-Antisense mRNA Pairs

Graphical Abstract



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In Brief

Sinturel et al. demonstrate that the complementary tails of 3′-overlapping mRNAs can interact in the cytoplasm and promote post-transcriptional regulatory events. They show that hundreds of mRNA-mRNA interactions exist in wild-type cells and are controlled by Xrn1, a conserved 5′-3′ cytoplasmic exoribonuclease in eukaryotes.

Highlights

- Transcription of convergent coding genes can form mRNA-mRNA duplexes
- Cytoplasmic mRNA-mRNA interaction can trigger no-go decay or limit 3′-5′ degradation
- Hundreds of mRNA-mRNA interactions are characterized in wild-type cells
- mRNA-mRNA interactions are subjected to surveillance by Xrn1

Accession Numbers

GSE64090

Sinturel et al., 2015, Cell Reports *12*, 1853–1864
September 22, 2015 ©2015 The Authors
http://dx.doi.org/10.1016/j.celrep.2015.08.016

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Cytoplasmic Control of Sense-Antisense mRNA Pairs

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http://dx.doi.org/10.1016/j.celrep.2015.08.016

SUMMARY

Transcriptome analyses have revealed that convergent gene transcription can produce many 3′-overlapping mRNAs in diverse organisms. Few studies have examined the fate of 3′-complementary mRNAs in double-stranded RNA-dependent nuclear phenomena, and nothing is known about the cytoplasmic destiny of 3′-overlapping messengers or their impact on gene expression. Here, we demonstrate that the complementary tails of 3′-overlapping mRNAs can interact in the cytoplasm and promote post-transcriptional regulatory events including no-go decay (NGD) in *Saccharomyces cerevisiae.* Genome-wide experiments confirm that these messenger-interacting mRNAs (mimRNAs) form RNA duplexes in wild-type cells and thus have potential roles in modulating the mRNA levels of their convergent gene pattern under different growth conditions. We show that the post-transcriptional fate of hundreds of mimRNAs is controlled by Xrn1, revealing the extent to which this conserved 5′-3′ cytoplasmic exoribonuclease plays an unexpected but key role in the post-transcriptional control of convergent gene expression.

INTRODUCTION

In many species of vertebrates, invertebrates, plants, and yeast (Djebali et al., 2012; Kapranov et al., 2007; Katayama et al., 2005; Li et al., 2008; Pelechano et al., 2013; Wang et al., 2005; Zhang et al., 2006), genomic loci produce oppositely oriented transcripts that overlap. Analyses of sense and antisense transcripts produced by convergent transcription have focused on coding/non-coding RNA pairs that are prevalent in databases. This has highlighted the importance of non-coding RNAs (ncRNAs) in the regulation of many biological processes, including siRNA-induced gene silencing, cis-RNA-mediated chromatin modifications, transcriptional interference, or RNA editing (Faghihi and Wahlestedt, 2009; Jacquier, 2009; Ponting et al., 2009; Pelechano and Steinmetz, 2013).

Transcriptome analyses have additionally shown that convergent gene transcription can produce tail-to-tail 3′-overlapping mRNA pairs in eukaryotes (Djebali et al., 2012; Faghihi and Wahlestedt, 2009; Jen et al., 2005; Kapranov et al., 2007; Katayama et al., 2005; Lapidot and Pilpel, 2006; Li et al., 2008; Munroe and Zhu, 2006; Pelechano et al., 2013; Wang et al., 2005; Wilkening et al., 2013; Yelin et al., 2003; Zhang et al., 2006), but surprisingly few examples exist where sense-antisense mRNA pairs have been shown to form mRNA duplexes with regulatory consequences. One precedent for a potential mRNA duplex can be found in *Arabidopsis thaliana* and concerns the SRO5-P5CDH sense-antisense messenger pair, proposed to be processed into natural siRNAs that could participate in the response to salt stress (Borsani et al., 2005). Remarkably, transcriptome analysis of *A. thaliana* reveals the existence of at least 1,000 of convergent and overlapping coding gene pairs, constituting an immense unexplored reservoir of potential mRNA duplexes (Jen et al., 2005). A study in human cells correlated the expression of the RevErb messenger to the regulation of erbAα2 mRNA splicing (Hastings et al., 1997; Salato et al., 2010) via an mRNA-mRNA interaction. In this case, at least 600 additional overlapping coding genes have been identified (Sanna et al., 2008).

We wished to address the question of the fate of 3′-overlapping messengers in the model organism *Saccharomyces cerevisiae*, where hundreds of 3′-overlapping mRNA result from convergent gene transcription and can theoretically form mRNA duplexes (Pelechano et al., 2013; Wilkening et al., 2013). Convergent gene expression has already been shown to lead to transcriptional interference in *S. cerevisiae*. Indeed, using artificial constructs, Prescott and Proudfoot (2002) demonstrated that convergent transcription can result in the collision of RNA polymerases. These collisions led to a reduction in transcription of both genes and limited the production of 3′-overlapping transcripts (Prescott and Proudfoot, 2002). Here, we focus on the post-transcriptional cytoplasmic fate of natural 3′-overlapping mRNAs resulting from convergent gene transcription (Pelechano et al., 2013).

Our first indication of the potential existence of messenger-interacting mRNAs (mimRNAs) came from our previous work demonstrating the importance of Xrn1 for respiration in *S. cerevisiae* (Sinturel et al., 2012). Xrn1 encodes a cytoplasmic