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Post-transcriptional regulation in budding yeast meiosis

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Abstract

The precise regulation of gene expression is essential for developmental processes in eukaryotic organisms. As an important post-transcriptional regulatory point, translational control is complementary to transcriptional regulation. Sporulation in the budding yeast *Saccharomyces cerevisiae* is a developmental process controlled by a well-studied transcriptional cascade that drives the cell through the events of DNA replication, meiotic chromosome segregation, and spore assembly. Recent studies have revealed that as cells begin the meiotic divisions, translational regulation of gene expression fine-tunes this transcriptional cascade. The significance and mechanisms of this translational regulation are beginning to emerge. These studies may also provide insights into translational regulation in germ cell development of multicellular organisms.

Keywords

translational control; sporulation; mRNA localization; gene expression; development program

When diploids cells of the yeast *Saccharomyces cerevisiae* are starved for nitrogen in the presence of a poor carbon source they enter the developmental program of meiosis and sporulation (Neiman 2011). In this process, a single diploid cell gives rise to four haploid daughter cells. This program is driven by a transcriptional cascade initiated when the integration of mating-type and nutritional signals leads to induction of ‘early’ genes. These early gene products drive the cell through pre-meiotic DNA replication and the chromosomal events of meiotic prophase. In addition, early gene expression results in induction of a transcription factor encoded by *NDT80* (Chu and Herskowitz 1998). Ndt80 then induces the expression of ~300 genes important for progression into the meiotic nuclear divisions and spore formation (Chu, et al. 1998). While microarray studies have indicated that induction of transcripts in the Ndt80-regulon is largely synchronous, it has recently emerged that post-transcriptional regulation of these transcripts plays an important role in fine-tuning their expression.

An early hint of post-transcriptional regulation was the delayed appearance of the Clb3 protein (Carlile and Amon 2008). Although the related cyclins *CLB1* and *CLB3* are co-induced by Ndt80, Clb1 protein appears immediately after transcriptional induction whereas the accumulation of Clb3 protein is delayed until the onset of the second meiotic division. Eliminating this delay, so that Clb3 appears coincident with transcription leads to mis-

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segregation of chromosomes in Meiosis I, demonstrating the functional significance of proper timing of *CLB3* expression (Carlile and Amon 2008).

The full extent of post-transcriptional regulation in meiosis was revealed by a groundbreaking study using ribosomal footprinting, which demonstrated that translational timing of different transcripts in the *NDT80* regulon varies greatly (Brar, et al. 2012). Though the messages are induced synchronously, their translation is spread out across the ~3hr period required for cells to complete meiosis and spore formation. Broadly, Ndt80-induced transcripts can be divided into those messages that reach peak translation as soon as they are induced, transcripts whose peak translation is delayed until the end of Meiosis I, such as *CLB3*, and transcripts whose translation is delayed until the end of Meiosis II.

Recent studies of one of these genes translated at the end of Meiosis II, *SSP2*, provide another example of the functional significance of this regulation (Tio, et al. 2015, Whinston, et al. 2013). *SSP2* encodes a peripheral membrane protein important for the last phase of sporulation, spore wall development (Coluccio, et al. 2004, Li, et al. 2007, Sarkar, et al. 2002). *SSP2* influences spore wall development by regulating the activation of the protein kinase Smk1 (Whinston, et al. 2013). *SMK1* itself is induced by Ndt80 and translated as soon as it is expressed (Brar, et al. 2012). However the Smk1 protein, which is translated early in meiosis is only partially active. Full activation of Smk1 requires Ssp2, which associates with Smk1 and induces its autophosphorylation (Tio, et al. 2015, Whinston, et al. 2013). Failure to fully activate Smk1 results in defective spore walls. Thus, the translational delay of *SSP2* allows the cell to regulate the timing of activation of Smk1 and promote proper spore wall assembly.

How the timing of translation of these different transcripts is controlled remains to be determined, but a picture has begun to emerge. Berchowitz et al (2013) identified a regulatory pathway involving the kinase Ime2 and the RNA binding protein Rim4 that controls the delay in translation of *CLB3* and other transcripts delayed to the end of Meiosis I. Rim4 binds to the Clb3 message and loss of *RIM4* results in earlier translation of *CLB3*, suggesting that Rim4 binding creates the translational delay. Interestingly, the ability of Rim4 to cause translational delay also requires self association of Rim4 into amyloid-like structures (Berchowitz, et al. 2015). Ime2 kinase activity is low early in meiotic prophase and rises during the meiotic divisions (Benjamin, et al. 2003). Premature activation of the Ime2 kinase leads to inappropriately early translation of *CLB3* (Berchowitz, et al. 2013). Moreover, Rim4 is a substrate of Ime2. These observations suggest that Ime2 promotes translation by negatively regulating Rim4.

Interestingly, many of the messages translated at the end of Meiosis II, such as *SSP2*, are also enriched in Rim4 precipitates (Berchowitz, et al. 2013). Consistent with this, the translational delay of these messages is regulated by Ime2 and Rim4 in the same manner as they control the messages translated at the end of Meiosis I: activation of Ime2 or deletion of Rim4 lead to early translation of these messages (Jin, et al. 2015). Despite having the same regulators, however, messages such as *SSP2* are distinct from *CLB3* in their timing of translation. These later translated messages are also distinct in displaying protection from nutrient-induced degradation.

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As *S. cerevisiae* cells progress into meiosis, they become 'committed' to the process. That is, even if nutrients are reintroduced into the medium, the cells do not return immediately to mitotic growth, but first complete meiosis and sporulation (Simchen, et al. 1972). Microarray studies of cells returned to growth medium revealed that, although committed cells progress through meiosis and sporulation, they do respond to the nutrients at the level of gene expression (Friedlander, et al. 2006). In particular, the transcripts of *NDT80* and most of its targets are rapidly depleted upon nutrient addition. However, a subset of *NDT80* targets remains at high levels. Most of the genes translated at the end of Meiosis II display this protection; however transcripts delayed only until the end of Meiosis I do not (Jin, et al. 2015).

Protection involves the same regulatory apparatus as translational delay. Either loss of *RIM4* or constitutive activation of Ime2 leads to loss of protection, suggesting that translational delay and protection are mechanistically linked (Jin, et al. 2015). But how does the Ime2/Rim4 regulatory pathway distinguish between transcripts delayed to the end of Meiosis I and ones that are delayed until the end of Meiosis II and subject to protection? The answer to this question may lie in differential localization of the transcripts. Localization of different mRNAs in sporulating cells reveal that for several protected genes the transcripts are localized in discrete foci, whereas transcripts that have no delay in translation or delay until the end of Meiosis I are found diffusely throughout the cytosol. Activation of Ime2 caused disappearance of the foci, suggesting that the localization is relevant to translational delay and/or protection (Jin, et al. 2015). These results suggest a model in which Rim4 can antagonize translation, resulting in a translational delay, but sequestration of the transcripts results in both a further delay and protection of the sequestered transcripts from nutrient-induced degradation.

As association with Rim4 is not sufficient for sequestration, this model implies the existence of additional RNA binding proteins necessary to localize the later translated mRNAs into foci. The identity of these proteins, as well as many other questions: e.g., how does Rim4 delay translation? How is the timing of Ime2 activation controlled? remain to be determined. Nonetheless, these studies make clear that translational regulation is a pervasive and important aspect of gene expression during meiosis and sporulation in budding yeast.

Translational regulation by RNA localization is a widespread phenomenon (Besse and Ephrussi 2008, Gonsalvez and Long 2012), but a particularly striking parallel to these yeast studies is seen in male germ cell development in mammalian species (Kotaja and Sassone-Corsi 2007, Parvinen 2005). The chromatoid body (CB) is a cytoplasmic structure that first appears during meiotic prophase in spermatocytes (Fawcett, et al. 1970). The CB is a ribonucleoprotein particle consisting of multiple RNA binding proteins as well as both coding and non-coding RNAs (Kotaja, et al. 2006a, Kotaja, et al. 2006b, Meikar, et al. 2014, Walt and Armbruster 1984). Studies of the RNA and protein composition of CBs suggest that association of mRNAs with the CB leads to their translational repression, and it has also been proposed that the CB provides a site of storage for messages that are translated later in spermatogenesis after transcription has been repressed (Braun 1998, Kotaja, et al. 2006a, Meikar, et al. 2014). Thus similar modes of translational regulation may be present during meiosis in both yeast and multicellular organisms.

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