Microreview

Post-transcriptional gene regulation in the biology and virulence of *Candida albicans*

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Summary

In the human fungal pathogen *Candida albicans*, remodelling of gene expression drives host adaptation and virulence. Recent studies revealed that in addition to transcription, post-transcriptional mRNA control plays important roles in virulence-related pathways. Hyphal morphogenesis, biofilm formation, stress responses, antifungal drug susceptibility and virulence in animal models require post-transcriptional regulators. This includes RNA binding proteins that control mRNA localization, decay and translation, as well as the cytoplasmic mRNA decay pathway. Comprehensive understanding of how modulation of gene expression networks drives *C. albicans* virulence will necessitate integration of our knowledge on transcriptional and post-transcriptional mRNA control.

Introduction

The human commensal yeast *Candida albicans* causes oral and vaginal infections, and disseminated disease in severely ill hosts (Brown *et al*., 2012). Screens of transcription factor mutant libraries have revealed functions for gene expression networks in pathogenesis-related biology of *C. albicans* (Nobile and Mitchell, 2005; Homann *et al*., 2009; Pukkila-Worley *et al*., 2009; Finkel *et al*., 2012; Nobile *et al*., 2012; Perez *et al*., 2013). Further to transcription, proper spatio-temporal expression of genes necessitates regulation of the subcellular localization, translation and turnover of mRNAs by RNA binding proteins and post-transcriptional mechanisms. Studies in baker’s yeast *Saccharomyces cerevisiae* and other eukaryotic models have illuminated the functions of multiple RNA binding proteins, and the importance of post-transcriptional mRNA networks in dictating cellular physiology, for example (Hogan *et al*., 2008; Freeberg *et al*., 2013), reviewed in (Keene, 2007; Quenault *et al*., 2011; Blackinton and Keene, 2014). How post-transcriptional regulation controls *C. albicans* biology and pathogenicity is a major knowledge gap. Excitingly, recent publications have focussed on this question, laying the foundation for understanding post-transcriptional mRNA networks in this pathogen.

Post-transcriptional regulation of hyphal morphogenesis

The yeast to hyphae transition is central to *C. albicans* virulence through functions including tissue invasion, cell adhesion, evasion of macrophages and development of clinically relevant biofilm communities. In response to stimuli such as temperature, nutrients or serum, signal transduction pathways and transcription factors induce the hyphal gene expression programme and filamentous growth (Sudbery, 2011). Significant evidence for post-transcriptional mRNA regulation being important in hyphal growth of *C. albicans* is (Fig. 1).

*Mutations in the cytoplasmic mRNA decay pathway impair hyphal morphogenesis*

The major eukaryotic mRNA decay pathway consists of poly(A) tail degradation by the mRNA deadenylase Ccr4-Not, hydrolysis of the 5’ cap (decapping) and mRNA digestion by Xrn1/Kem1, reviewed in Goldstrohm and Wickens (2008) (Fig. 1a). RNA binding proteins modulate these processes by recruiting deadenylation and decapping factors, reviewed in Goldstrohm *et al.* (2008) and Quenault *et al.* (2011). *C. albicans* mutants in the deadenylase subunits CCR4 and POP2, the decapping activators DHH1 and EDC3 and the exonuclease XRN1/KEM1 are defective in hyphal morphogenesis (Richard *et al*., 2005; Dagley *et al*., 2011; Jung and Kim, 2014; Shively *et al*., 2015). Hyphal defects are not seen in all conditions. For example, *ccr4* and *pop2* can filament in...
Post-transcriptional regulation in hyphal morphogenesis.

(a) mRNA decay factors required for hyphal morphogenesis. The pathway is shown as understood in S. cerevisiae. For simplicity, not all known protein–protein interactions are depicted, and the mRNA is shown linear instead of circular with 5’ and 3’ ends in proximity. The roles of the Dcp1/Dcp2 decapping enzyme in filamentation are yet to be studied.

(b) Possible mechanisms of 5’ UTR-dependent repression of UME6 through secondary structure formation, or binding of RNA binding protein(s) (orange circle) to inhibit ribosome association or target to P-bodies, as proposed by (Childers et al., 2014).

(c) mRNA trafficking to the hyphal tip by She3. The precise architecture of the C. albicans She3 complex is not known. The homolog of She3 is lacking, and the myosin is likely Myo2 (Elson et al., 2009). Whether C. albicans She3 interacts directly with mRNAs is unknown, but RNA binding activity can be predicted based on S. cerevisiae (Muller et al., 2011). Based on studies in S. cerevisiae, particularly ASH1 trafficking, mRNA localization elements can be in the open reading frame and 3’ UTR, and the She3 complex is multimeric (Shi et al., 2014). Therefore, our cartoon is a greatly simplified version of the likely protein-RNA complex. En route, mRNAs is repressed and activated at the destined location. The mechanism of translational repression–derepression has not been studied in C. albicans.

The expression of key transcriptional regulators of the yeast-hyphae transition is regulated post-transcriptionally

Evidence for this comes from studies of the hyphal transcriptional activator UME6 and the transcriptional repressor of the hyphal programme NRG1 (Cleary et al., 2012; Childers et al., 2014; Lee et al., 2015b). The 5’ UTR of UME6 dictates Ume6 protein levels, without impacting on mRNA level or induction by hyphal signals (Childers et al., 2014). Polysome association data are consistent with the effect being on mRNA translation (Childers et al., 2014). The mechanism(s) are not defined, but the authors proposed that secondary structure formation by the 5’ UTR could inhibit translation, or alternatively binding of RNA binding proteins could impair
ribosome association or target the *UME6* mRNA to a translationally silent location, such as P-bodies (Childers et al., 2014). Given abundance of Ume6 alone determines whether *C. albicans* exists as yeast or hyphal form (Carlisle et al., 2009), translational regulation might enable fast, reversible yeast–hyphae–yeast morphogenesis that could be important for disease.

To lift repression of the hyphal programme, the mRNA and protein levels of the repressor Nrg1 drop rapidly upon hyphal induction, and *NRG1* is regulated translationally (Braun et al., 2001; Murad et al., 2001; Sellam et al., 2010; Lassak et al., 2011; Lu et al., 2011; Childers and Kadosh, 2015). Further to this, the stability of the *NRG1* mRNA is controlled by the transcription factor Brg1, via production of an anti-sense transcript located in the *NRG1* open reading frame (Cleary et al., 2012). The exact mechanism of this regulation remains to be elucidated. Nrg1 protein levels are further controlled by the RNA binding protein Ssd1 (Lee et al., 2015b). In *S. cerevisiae* Ssd1 interacts with, and regulates the translation and subcellular localization of, a suite of mRNAs encoding cell wall remodelling factors (Hogan et al., 2008; Jansen et al., 2009; Kurischko et al., 2011). The translational repressor activity of Ssd1 is negatively regulated through phosphorylation by the RAM (regulation of Ace2 and morphogenesis) network kinase Cbk1, and this process is important for cell wall remodelling during cell division (Jansen et al., 2009). In *C. albicans* the RAM network is required for hyphal morphogenesis (Song et al., 2008). The *cbk1* mutant does not reduce Nrg1 protein levels upon hyphal signalling, but this can be rescued by deletion of *SSD1* (Lee et al., 2015b). This indicates that in the absence of Cbk1, Ssd1 promotes *NRG1* translation even when hyphal signalling is ‘on’. This, together with the *C. albicans* *ssd1* mutant not being compromised for hyphal morphogenesis (Song et al., 2008), suggests that Ssd1 is a repressor of filamentation.

**mRNA trafficking via She3 impacts on hyphal morphogenesis**

In *S. cerevisiae*, the She3-system transports mRNAs to the site of bud growth and repress their translation in route, reviewed in Haag et al. (2015). The RNA binding proteins She2 and She3 interact together and with localization sites in the mRNA, and form a complex with the myosin V motor Myo4 that enables mRNA trafficking along actin cables (Haag et al., 2015). As shown by the prototypical example of the *ASH1* mRNA, two further RNA binding proteins, Puf6 and Khd1, bind mRNA and are required for translational repression (Paquin et al., 2007; Deng et al., 2008). Three of the RNA binding proteins (She3, Puf6 and Khd1) have orthologues in *C. albicans*, but only She3 has been characterized. *C. albicans* She3 interacts with 31 and 38 mRNAs during yeast and hyphal growth respectively (Elson et al., 2009). The targets represent several functions, including cell wall, hypha-induced genes and transcription factors, and She3 is required for asymmetric mRNA localization (Elson et al., 2009). The *she3* mutant is defective in invasive filamentation on solid media and is further defective in causing damage to epithelial cells (Elson et al., 2009). However, *she3* could initiate hyphal morphogenesis in liquid media (Elson et al., 2009), suggesting that mRNA targeting by She3 is dispensable for hyphal initiation, but important for long-term filamentous growth and invasion.

Further to the regulators mentioned earlier, the serine-arginine RNA binding protein of *C. albicans* Slr1 is also required for hyphal morphogenesis (Ariyachet et al., 2013). Slr1 could play multiple roles in mRNA physiology, including splicing and translation, but its RNA targets for hyphal morphogenesis remain to be identified.

**Post-transcriptional regulation of biofilm formation**

*Candida albicans* grows drug-resistant biofilms on various substrates and medical devices, seeding life-threatening infections. Given that hyphae are important structural components of biofilms, it can be predicted that post-transcriptional regulators described earlier will play roles in biofilm formation. This is exemplified by the *xmr1* mutant, which was identified as biofilm-defective because of impaired hyphal morphogenesis (Richard et al., 2005).

Transcription factors have been extensively studied for biofilm phenotypes (Nobile et al., 2005, Nobile et al., 2012). How post-transcriptional regulators control the biofilm transcriptome is poorly defined. The first indication that post-transcriptional mRNA regulation might play a role came from a bioinformatics approach performed by our colleagues and us (Verma-Gaur et al., 2015). Thirty six genes related to mitochondria and down-regulated in biofilms (Nobile et al., 2012) are putative targets of the RNA binding protein Puf3 (Verma-Gaur et al., 2015). Puf3 is a PUF family member that in *S. cerevisiae* regulates a network of mRNAs necessary for mitochondrial biogenesis (Gerber et al., 2004). It does so by binding to sequence elements in 3′ UTRs to control mRNA decay, as well as transcript localization to mitochondria (Olivas and Parker, 2000; Gerber et al., 2004; Saint-Georges et al., 2008). Bioinformatics and functional data in *C. albicans* are consistent with regulation of mitochondrial biogenesis being a conserved role, as is the function of Puf3 in promoting mRNA decay (Verma-Gaur et al., 2015). We proposed therefore that Puf3 is involved in controlling mitochondria-related genes, as part of metabolic changes characteristic of *C. albicans* biofilms (Verma-Gaur et al., 2015). However, the *puf3* mutant displayed a normal biofilm phenotype. This could result from redundancy, as studies in *S. cerevisiae* have shown transcripts tend to
interact with several RNA binding proteins (Hogan et al., 2008). For example, although an earlier study reported minimal correspondence between Puf3 targets and those of other PUFs in yeast (Gerber et al., 2004), more recent works found that close to one third (30.5%) of mRNAs bound by Puf3 are also bound by Puf5 (Wilinski et al., 2015). An alternative explanation is that although the mRNA targets of Puf3 are differentially expressed in *C. albicans* biofilms, their proper regulation is not required for biofilm maturation. It could also be that alternative mechanisms compensate when Puf3 targets are disregulated. In contrast to the mechanisms compensate when Puf3 targets are dis-regulated, they act in parallel pathways for wall integrity (Kaeberlein et al., 2002). Ssd1 has an additional role in regulating the susceptibility of *C. albicans* to antimicrobial peptides (Gank et al., 2008; Jung et al., 2013). This might stem from functions in cell surface biogenesis, and a role in the expression of *BCR1*, a transcription factor necessary for antimicrobial peptide resistance (Jung et al., 2013). The *C. albicans* decapping factor Edc3 also has a stress responsive role in oxidative stress and translational regulation of superoxide dismutase Sod1 and the catalase Cat1 (Jung et al., 2014). Collectively, these observations suggest that post-transcriptional regulators could be considered as drug targets, because of requirements for virulence and potential for combinatorial treatment with current antifungal drugs or antimicrobial peptides.

### Evolution of post-transcriptional gene regulation in fungi

Changes to gene expression control are a known mechanism of evolutionary divergence between species. Evolutionary rewiring of transcriptional regulation has been extensively studied in fungi and other eukaryotes. For this, *C. albicans* has served as a useful comparison to *S. cerevisiae* because it is a related, but biologically divergent yeast (e.g. Tsong et al., 2003; Ihmels et al., 2005; Hogues et al., 2008; Brown et al., 2009). As with transcription factors, RNA binding proteins interact with functionally related genes, thereby establishing post-transcriptional RNA networks, reviewed in Keene (2007) and Blackinton et al. (2014). Understanding the evolution of post-transcriptional regulatory networks in fungi is still in its infancy.

Examples of differences in post-transcriptional mRNA control have been uncovered between *S. cerevisiae* and *C. albicans*, with orthologous RNA binding proteins displaying distinct regulation of the same mRNA, or having distinct sets of targets in the two species. Within fungi, the PUF family of RNA binding proteins is best reviewed in *S. cerevisiae* (Kaeberlein et al., 2002; Hogan et al., 2008). In *S. cerevisiae*, deletion of *SSD1* and *CCR4* results in a negative genetic interaction, suggesting that they act in parallel pathways for wall integrity (Kaeberlein et al., 2002). Ssd1 has an additional role in regulating the susceptibility of *C. albicans* to antimicrobial peptides (Gank et al., 2008; Jung et al., 2013). This might stem from functions in cell surface biogenesis, and a role in the expression of *BCR1*, a transcription factor necessary for antimicrobial peptide resistance (Jung et al., 2013). The *C. albicans* decapping factor Edc3 also has a stress responsive role in oxidative stress and translational regulation of superoxide dismutase Sod1 and the catalase Cat1 (Jung et al., 2014). Collectively, these observations suggest that post-transcriptional regulators could be considered as drug targets, because of requirements for virulence and potential for combinatorial treatment with current antifungal drugs or antimicrobial peptides.

#### Post-transcriptional regulators in stress responses and virulence

Mutants in several mRNA regulators display reduced virulence in the mouse systemic candidiasis model. *ccr4* (Dagley et al., 2011), *slr1* (Aryachet et al., 2013) and *ssd1* (Gank et al., 2008). In addition, the *xmr1* mutant is less virulent in *Galleria mellonella* (Fuchs et al., 2010). The reasons for reduced virulence are likely multifactorial, including crippled fitness, hyphal defects and altered cell wall integrity. The cell wall is particularly relevant, because its biogenesis is targeted by the echinocandin drugs used to treat *Candida* infections. Given that the *C. albicans ccr4* and *pop2* mutants display changes to cell wall composition and increased susceptibility to the echinocandin drug caspofungin (Dagley et al., 2011), we proposed that inactivation of the deadenylase could be considered for combinatorial therapy (Panepinto et al., 2013). Several cell wall-related genes are dis-regulated in the *ccr4* mutant, but their levels are mostly up-regulated compared with controls suggestive of compensatory activation (Dagley et al., 2011; Verma-Gaur et al., 2015). Ccr4 has further been implicated in regulating cell wall genes in hypoxia (Sellam et al., 2014).

Ssd1 is also required for cell wall integrity in *C. albicans* (Gank et al., 2008; Song et al., 2008), consistent with roles in *S. cerevisiae* (Kaeberlein et al., 2002; Hogan et al., 2008). In *S. cerevisiae*, deletion of *SSD1* and *CCR4* results in a negative genetic interaction, suggesting that they act in parallel pathways for wall integrity (Kaeberlein et al., 2002). Ssd1 has an additional role in regulating the susceptibility of *C. albicans* to antimicrobial peptides (Gank et al., 2008; Jung et al., 2013). This might stem from functions in cell surface biogenesis, and a role in the expression of *BCR1*, a transcription factor necessary for antimicrobial peptide resistance (Jung et al., 2013). The *C. albicans* decapping factor Edc3 also has a stress responsive role in oxidative stress and translational regulation of superoxide dismutase Sod1 and the catalase Cat1 (Jung et al., 2014). Collectively, these observations suggest that post-transcriptional regulators could be considered as drug targets, because of requirements for virulence and potential for combinatorial treatment with current antifungal drugs or antimicrobial peptides.

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functions and identify the mRNA targets of many more RNA binding proteins in this pathogen and decipher how regulation of post-transcriptional mRNA networks mediates the response of \textit{C. albicans} to its environment. Constructing libraries of RNA binding protein mutants, coupled with systems-biology approaches that have been developed in \textit{S. cerevisiae}, will achieve these goals. Ultimately, integrating this knowledge with transcriptional circuits will provide a more accurate picture of how \textit{C. albicans} adapts to host and antifungal drug stresses and might offer new avenues for therapy.

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