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Review

RNA metabolism and regulation of virulence programs in fungi

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ABSTRACT

The development of RNA imaging techniques and the establishment of systems biology approaches, together with the improvement of large-scale RNA-protein crosslinking immunoprecipitation protocols have enormously expanded our knowledge of RNA networks and the function of RNA-binding proteins in metazoans and model yeasts. In pathogenic fungi, the biological role of the vast majority of RNA-binding proteins and non-coding RNAs is still largely unknown. However, many RNA-dependent mechanisms which shape fungal pathogenicity have been defined. Here, advances made in this field are reviewed and further theories of biological significance are discussed in the light of latest findings.

Contents

1. Introduction

In a multicellular organism, the expression of genes is tightly coordinated to carry out complex functions such as cell growth and differentiation. This enables the production of proteins with housekeeping functions and with tissue-, developmental- or niche-specific functions. Such synchronized expression of gene networks is regulated at multiple levels, from chromatin organisation to de novo transcription, pre-mRNA maturation, export, localisation, protein translation and degradation (Fig. 1).

Why post-transcriptional regulation matters? Compared to transcriptional control, posttranscriptional mechanisms regulate mRNA half-life and translation rates and as such, are responsible for more rapid and permanent changes in the physiological status of the cell by adjusting cellular concentrations of required proteins [1,2]. In the context of host-pathogen interactions, early contact with the host induces in the pathogen the transcription of genes required for its adaptation to the host cell. Post-transcriptional regulatory mechanisms are potentially more important in later stages when sustained growth in an adverse environment, such

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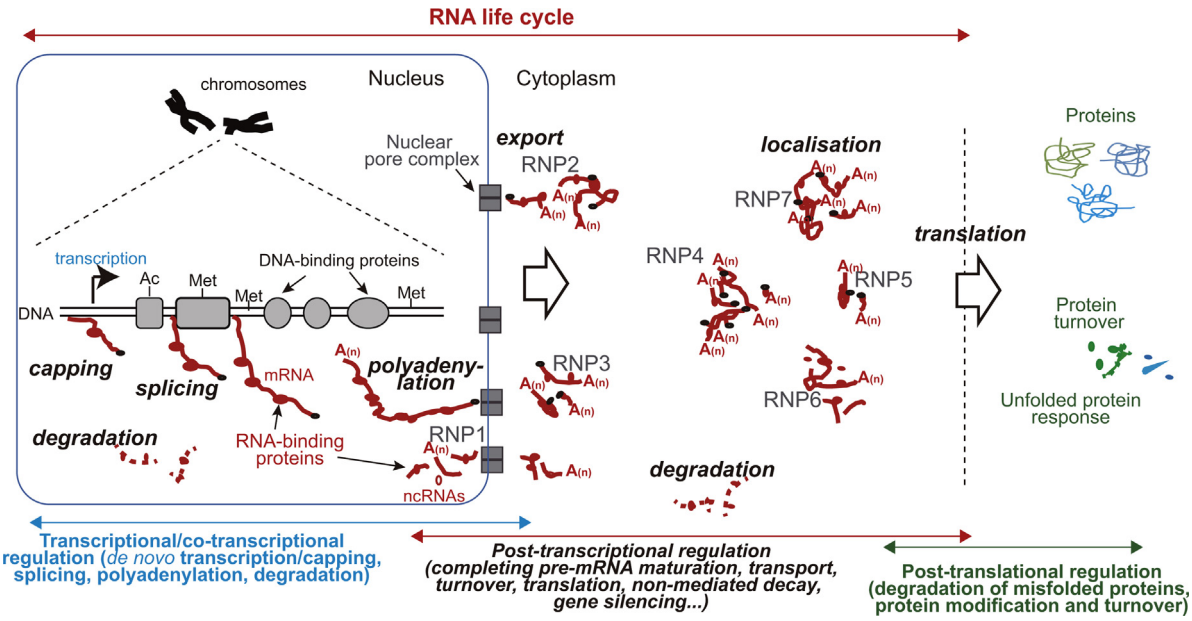

Fig. 1. Multiple steps regulate RNA life cycle. Messenger RNA is controlled by RNA-binding proteins, which play a crucial role at a number of steps between *de novo* transcription and protein synthesis, i.e. capping, splicing, polyadenylation, export, localisation, nuclear/cytoplasmic degradation and translation. Some non-coding RNAs are also polyadenylated and need to be transported to the cytoplasm where they carry out their functions. RNA-binding proteins and RNAs form ribonucleoprotein complexes (RNPs), which control the intricate RNA networks of the cell.

as a host cell defending itself from a foreign invasion, is essential for pathogen survival and reproduction.

Several regulatory mechanisms control the fate of an mRNA molecule. These regulatory mechanisms begin during pre-mRNA processing by regulating capping, splicing and polyadenylation, and last the entire life of a mature mRNA molecule controlling stability/turnover, export, localisation and translation. Key players in these post-transcriptional regulatory pathways are RNA-binding proteins and non-coding RNAs (ncRNAs) [3]. Typically, RNA-binding proteins associate with RNAs and other RNA-binding proteins to form ribonucleoprotein complexes (RNPs) due to their ability to recognise *cis*-acting elements present in their RNA targets (*e.g.* primary sequence and/or secondary structures) and their ability to interact with other proteins [4]. Consequently, the functional diversity of RNPs present in the cell depends on the inherent functionality of the constituent RNAs and the RNA-binding proteins. The RNPs ability to assemble-disassemble and their RNA/protein composition decide how, when, and where to translate functionally related subpopulations of mRNAs. In addition to RNA-binding proteins, ncRNAs, including small RNAs (sRNAs) play a critical role in the post-transcriptional control of gene expression by regulating transcription, mRNA stability, localisation or translation rates [3,5,6]. sRNAs can also be mobile and mediate crosskingdom RNA interference. This discovery has opened exciting avenues leading to an understanding of the role of RNA interference pathways in host-pathogen interactions [7–9].

This review discusses the post-transcriptional/translational regulatory pathways in pathogenic fungi and the recent progress towards understanding the involvement of RNA-binding proteins, ncRNAs and sRNA pathways in fungal virulence programs. Findings are presented in accordance with the maturation process of an mRNA molecule, starting with pre-mRNA processing (splicing and polyadenylation), followed by what we know about mRNA transport, translation regulation, degradation and RNA interference pathways in fungal-host interactions, and concluding with evidence of a class of secreted proteins with RNase-like folding in cereal powdery mildews.

2. Splicing and mRNA decay regulation

The spliceosome is a multimegadalton complex composed of five small nuclear RNAs (snRNAs U1, U2, U4, U5, and U6) and more than 100 core proteins [10]. This macromolecular complex is in charge of removing the introns during splicing [11], a process that occurs co-transcriptionally with the recruitment of splicing factors by the carboxy terminal domain (CTD) of the RNA polymerase II during transcription elongation [12].

Intron-containing genes are abundant among fungal species, with the exception of budding yeast which contains an intron-poor genome (253 introns) [13,14]. Splicing has been extensively studied in this model organism because of its simplicity, although it is not a frequent event in this organism. The chemical reactions of splicing (two sequential transesterifications) are identical in all eukaryotes although the gene architecture and splicing machinery can differ substantially [11]. The percentage of genes containing introns varies considerably among fungal genomes, being low in Baker's yeast (4%) and *Candida albicans* (6%) compared to other fungi such as *Cryptoccocus neoformans* (98%), *Aspergillus fumigatus* (78%), *M. oryzae* (76%), *Schizosaccharomyces pombe* (45%) or *Ustilago maydis* (38%) [15,16].

Several studies have demonstrated the importance of splicing regulation during pathogenic processes in fungal pathogens. Reversible phosphorylation modulates the activity of both core spliceosomal components and accessory splicing factors. In the wheat scab pathogen *Fusarium graminearum*, the *FgPRP4* gene encodes a protein kinase required for full virulence and splicing efficiency [17]. In *S. pombe*, Prp4p kinase activity is required for pre-mRNA splicing in vivo and G1–S and G2–M progression in the cell cycle [18], suggesting that the deficiencies found in *F. graminearum prp4* mutants may be related with the regulation of cell cycle progression.

Alternative splicing is an important source of genetic diversity in eukaryotes [19,20], as it has been shown in the corn smut fungus *U. maydis* [21]. Two key enzymes involved in glycolysis, the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the 3-