

RNA Interference in Fungi

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RNA interference (RNAi) was discovered at the end of last millennium, changing the way scientists understood regulation of gene expression. Within the following two decades, a variety of different RNAi mechanisms were found in eukaryotes, reflecting the evolutive diversity that RNAi entails. The essential silencing mechanism consists of an RNase III enzyme called Dicer that cleaves double-stranded RNA (dsRNA) generating small interfering RNAs (siRNAs), a hallmark of RNAi. These siRNAs are loaded into the RNA-induced silencing complex (RISC) triggering the cleavage of complementary messenger RNAs by the Argonaute protein, the main component of the complex. Consequently, the expression of target genes is silenced. This mechanism has been thoroughly studied in fungi due to their proximity to the animal phylum and the conservation of the RNAi mechanism from lower to higher eukaryotes. However, the role and even the presence of RNAi differ across the fungal kingdom, as it has evolved adapting to the particularities and needs of each species. Fungi have exploited RNAi to regulate a variety of cell activities as different as defense against exogenous and potentially harmful DNA, genome integrity, development, drug tolerance, or virulence. This pathway has offered versatility to fungi through evolution, favoring the enormous diversity this kingdom comprises.

Keywords: RNA Interference ; RNAi ; fungi

1. Introduction

RNA interference (RNAi) or RNA silencing has been deeply studied in the last two decades, as its discovery entailed a revolution in the understanding of the regulation of gene expression. This RNAi pathway, broadly conserved in eukaryotes, uses small interfering RNAs (siRNAs) to suppress gene expression of homologous sequences. These siRNAs, of 20–30 nucleotides (nt) long, are produced from double-stranded RNA (dsRNA) by an RNase III called Dicer (Dcr) and loaded into an RNA-induced silencing complex (RISC), which contains an Argonaute protein (Ago) that drives the selective degradation of homologous messenger RNAs (mRNA), as well as translational or transcriptional repression of target sequences. Moreover, in fungi and other organisms, an RNA-dependent RNA polymerase (Rdp or RdRP) generates dsRNA from certain single-stranded RNA (ssRNA) or from the target messenger RNA, activating or amplifying the silencing response, respectively^{[1][2]}.

Fungi have proven to be excellent model organisms for the study of the RNAi pathway, since many of the discoveries accomplished in these organisms were later extended to higher eukaryotes. In fact, one of the first RNA silencing phenomena reported was found in *Neurospora crassa*, which is an essential model organism to study modern genetics. *N. crassa* has developed different RNAi mechanisms, but the two that were originally found are the best described. The first is called quelling, a post-transcriptional gene silencing (PTGS) guided by siRNAs^[3], which suppresses transposons and virus infections^[4]. Quelling is triggered by the introduction of transgenes homologous to an endogenous gene. After the transgene is transcribed, it follows a canonical pathway to activate silencing, carried out by an Rdp protein (QDE-1), two Dicer-like proteins (Dcl1 or Dcl2), and an Argonaute (QDE-2). The second mechanism is called meiotic silencing of unpaired DNA (MSUD) and is involved in silencing genes that are not paired with their partner on the homologous chromosome during meiosis^[5]. This mechanism is present not only in *N. crassa* but also in other ascomycetes, such as *Gibberella zeae*, and operates during prophase I^{[6][7]}. Some of the elements involved in the canonical RNAi pathway, such as Dcl1, are necessary for this other mechanism, as well as a MSUD-specific Rdp (SAD-1), a second Argonaute (SMS-2), and the helicase SAD-3. These proteins form a multiprotein complex located at the perinuclear region that acts generating MSUD-associated siRNAs (masiRNAs)^[8]. After these first discoveries in *N. crassa*, the RNAi mechanism was found in several other fungi, such as *Schizosaccharomyces pombe*^[9], *Cryptococcus*^[10], or *Mucor*^[11].

When RNAi was discovered, it was thought to be a defense system against exogenous and potentially harmful DNA, including transposons, virus, and transgenes. However, very soon, its involvement in other cellular functions, such as genome integrity or gene regulation, was found. Recent studies in fungal pathogens stated that the RNAi pathway is also implicated in development, drug tolerance, and virulence. Thus, fungi have exploited RNAi to tune their cellular processes, reaching unsuspected limits.

2. Defense against Viruses

The first predicted function of RNAi as a defense against viral infections would explain the conservation of the pathway through the evolution of eukaryotes, since viral infections affect every phylum on the tree of life. This mechanism has been widely explored in the ascomycete filamentous fungus *Cryphonectria parasitica*^{[12][13]}. In *Aspergillus nidulans* RNAi also acts as a defense mechanism against virus^[14].

3. Control of Transposable Elements

Transposable elements (TEs) are described as DNA sequences that have the ability to change their position within a genome. Although TEs were initially considered junk DNA, they have been associated with several important activities since their discovery, including centromere function, genome reorganization, and gene expression regulation^{[15][16][17]}. TEs are also considered “selfish” DNA because they try to be perpetuated whilst the host tries to curtail their spread and, thus, their consequences on genome integrity. As a result, many organisms have developed mechanisms to ensure the control of TE activity^{[18][19]}. Some of those mechanisms are well described in the literature and include DNA methylation^[20], histone methylation^[21], and heterochromatin-inducing protein^[22]. Another mechanism that controls TE spread, probably the most ancient of all mentioned, is RNAi. Small RNAs associated with proteins can act at the transcriptional or post-transcriptional level against TE activity. The role of RNAi in TE repression has been well characterized in the plant kingdom^[23] and other organisms, such as *Drosophila melanogaster* and *Caenorhabditis elegans*^{[24][25]}. Studies on the RNAi role in TE control in fungi, such as *Neurospora crassa*^[26], *Schizosaccharomyces pombe*^[27], *Magnaporthe oryzae*^[28], *Mucor lusitanicus*^[29], or *Cryptococcus neoformans*^{[30][31]} have served to further understand these mechanisms.

4. Regulation of Endogenous Genes

As described above, the development of RNAi mechanisms represents an evolutive advantage regarding the defense against exogenous nucleic acids. However, specialization of those RNAi mechanisms has led to the establishment of novel post-transcriptional regulation networks of endogenous genes according to the use of Rdp, Dicer, and Argonaute proteins. The human pathogenic fungus *M. lusitanicus*, for instance, shows an intricate RNAi mechanism as a function the interplay of the silencing proteins in three different pathways, named the canonical, epimutational, and noncanonical RNAi pathways. The crosstalk of the RNAi pathways creates a complex network that regulates both basic cellular activities, such as metabolism or vegetative growth, and elaborated mechanisms, including sexual reproduction and pathogenesis^{[11][32][33]}. *N. crassa*^[34], *Coprinopsis cinerea*^[35], *Fusarium graminearum*^[35] and *Magnaporthe oryzae*^{[28][36]}, also produce sRNAs that regulate endogenous genes.

5. Heterochromatin Formation

Heterochromatin constitutes a highly condensed state of DNA. It is considered to have no transcriptional activity due to the limited access of the regulatory proteins to the promoter regions^[37]. Generally, heterochromatin is concentrated in the telomeric, centromeric, ribosomal, and mating type regions of the eukaryotic chromosome^[38]. Heterochromatin assembly is strictly regulated for accurate chromosome segregation, maintenance of telomere integrity, transcriptional silencing, and transposon control^{[37][39]}. Heterochromatin formation in *S. pombe* is triggered by the production of siRNAs derived from centromeric regions with numerous repeats^{[40][41]}. Remarkably, heterochromatin formation and the RNAi pathway can also regulate the epigenetic inheritance of gene silencing in *S. pombe*^[42].

6. Adaptation to Stressful Conditions

The epimutational pathway in *M. lusitanicus* was discovered after the emergence of isolates resistant to the antifungal drug FK506 with no apparent mutations in the target genes^[43]. The isolates, called epimutants, produced siRNAs from the mature mRNA of *fkbA* gene, which encodes FKBP12, the FK506-interacting protein^{[43][44]}. Epimutants developing resistance to other antifungal agents, such as 5-fluoroorotic acid (5-FOA), have also been isolated^[44]. Therefore, the epimutation process does not appear to occur at a specific gene locus, suggesting it might constitute a general mechanism that generates phenotypic plasticity in *Mucor* by silencing key genes and allowing rapid and reversible adaptation to environmental stresses^{[45][46]}.

7. Pathogenesis

RNAi has also been found to play an important role in pathogenesis, more thoroughly studied in plant pathogens. Many crops with worldwide importance are susceptible to being infected by pathogenic fungi, which translates into economic losses. Thus, alternative methods of infection control have been investigated, allowing a deeper understanding of fungal pathogenesis and the involvement of RNAi. Some of those pathogenic fungi, such as *Colletotrichum gloeosporioides*^[47], *M. oryzae*^[48], *Sclerotinia sclerotiorum*^[49] have active RNAi pathways which influences their pathogenicity. RNAi is also involved in virulence of animal pathogens, such as *M. lusitanicus*^[50].

An important feature of fungal pathogenesis is the mechanism called cross-kingdom RNAi, which has evolved to regulate the host–pathogen interaction. The existence of sRNA trafficking between the host and the pathogen and silencing target genes of the counterparty in trans was first discovered in plants, but afterward extended to mammal systems. Some fungal pathogens, such as *Phytophthora sojae*^[51] or *Botrytis cinerea*^[52], have been found to produce sRNAs that function as RNA effectors to suppress host immunity.

8. Loss of RNAi

In essence, RNAi has crucial regulatory and defense roles in eukaryotes, suggesting that this key mechanism has been positively selected through evolution in plants, nematodes, animals, and fungi. Yet, some members of the fungal kingdom have lost key components of the RNAi pathway^[53], resulting in its inactivation. A hypothesis to explain this contradiction could be that those species may have other defensive mechanisms more advantageous than RNAi. Alternatively, perhaps, this RNA-based mechanism constitutes a disadvantage for them, forcing the survival of the RNAi-deficient species.

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