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Fungal cell death: The beginning of the end

Adriana M. Rico-Ramírez [a], A. Pedro Gonçalves [b], N. Louise Glass [a,*]

[a] Department of Plant and Microbial Biology, University of California, Berkeley, Berkeley, CA 94720, United States
[b] Department of Cell Biology and Anatomy, College of Medicine, National Cheng Kung University, Tainan City 701, Taiwan

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ABSTRACT

Death is an important part of an organism's existence and also marks the end of life. On a cellular level, death involves the execution of complex processes, which can be classified into different types depending on their characteristics. Despite their "simple" lifestyle, fungi carry out highly specialized and sophisticated mechanisms to regulate the way their cells die, and the pathways underlying these mechanisms are comparable with those of plants and metazoans. This review focuses on regulated cell death in fungi and discusses the evidence for the occurrence of apoptotic-like, necroptosis-like, pyroptosis-like death, and the role of the NLR proteins in fungal cell death. We also describe recent data on meiotic drive elements involved in "spore killing" and the molecular basis of allorecognition-related cell death during cell fusion of genetically dissimilar cells. Finally, we discuss how fungal regulated cell death can be relevant in developing strategies to avoid resistance and tolerance to antifungal agents.

1. Introduction

1.1. The 'regulated' nature of fungal cell death

The kingdom Fungi, which diverged from animals approximately 1 billion years ago (Taylor and Berbee, 2006), boasts an astounding biodiversity encompassing an estimated 2–6 million species (Baldrian et al., 2021; Hawksworth and Lücking, 2017). Fungi include molds, mushrooms, yeasts, smuts, rusts, mildews, amongst many others, being also one of the components of the mutualistic structures known as lichens (Willis, 2018). Fungi have been involved in many of the greatest events in our planet's evolutionary history. For instance, arbuscular mycorrhizal fungi were instrumental in facilitating the colonization of land by plants approximately 500 million years ago (Remy et al., 1994). Fungi display lifestyles that are relatively simple in comparison with plants and metazoans. Yet, these remarkable microbes undergo all the basic cellular processes, including cell division, cell differentiation and cell death; the present review is dedicated to the occurrence of cell death in fungal organisms.

Regulated cell death (RCD) with similarities to apoptosis was first described in a cell cycle *cdc48* temperature-sensitive mutant in the budding yeast *Saccharomyces cerevisiae*, including exposure of phosphatidylserine on the outer leaflet of the plasma membrane, DNA fragmentation, and chromatin condensation (Madeo et al., 1997). This work promoted further investigations on RCD in fungi, particularly since most of the genes involved in mammalian apoptotic cell death appeared to lack homologs in *S. cerevisiae* (Fedorova et al., 2005; Madeo et al., 1997). More recently, it has been demonstrated that fungal cell death occurs during a number of developmental processes in fungi. For example, appressorium formation in *Magnaporthe oryzae*, which is necessary for plant infection, requires the occurrence of autophagy-related cell death (Veneault-Fourrey et al., 2006). During sexual development in *Coniochaeta tetrasperma,* the number of sexual spores is reduced by RCD (Raju and Perkins, 2000), and in *Aspergillus nidulans*, cell death is associated with asexual sporulation (Thrane et al., 2004). In the mushroom-forming *Agaricus bisporus,* regulated cell death takes place during basidial differentiation (Umar and Van Griensven, 1997), analogous to organ sculpting during embryonic maturation in mammals (Suzanne and Steller, 2013). In unicellular fungi, RCD leads to the death of the whole organism ('phenoptosis' (Skulachev, 1999)), thus lacking a developmental significance. Nevertheless, the occurrence of RCD appears to have played an instrumental role in the unicellular-to-multicellular transition (Durand et al., 2016; Kulkarni et al., 2019; Ratcliff et al., 2012).

This article features recent data on cell death in the context of nonself recognition (allorecognition), one of the most remarkable demonstrations of fungal cell death and the most well characterized in terms of molecular mechanisms. Allorecognition in fungi, where cell fusion

* Corresponding author.
E-mail address: Lglass@berkeley.edu (N. Louise Glass).

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between germinated asexual spores (germlings) or colonies that differ in allelic specificity at allorecognition loci rapidly triggers cell death (Glass and Dementhon, 2006; Gonçalves et al., 2020; Saupe, 2000). Although germling/hyphal fusion is common within a colony and between genetically identical germlings/hyphae (Fischer and Glass, 2019), successful heterokaryon formation between genetically different germlings/colonies is rare (Gonçalves and Glass, 2020; Muirhead et al., 2002). These multilocus allorecognition systems include those that function prior to contact of hyphae or germlings (Heller et al., 2016), upon contact, but prior to cell wall dissolution (Gonçalves et al., 2019), and after contact and cell fusion (see reviews (Gonçalves et al., 2020; Gonçalves and Glass, 2020). Remarkably, some of the proteins that mediate allorecognition and trigger cell death in filamentous fungi share similarity to proteins associated with innate immunity in mammalian cells, and which we highlight in this review.

2. Fungal cell death

2.1. Apoptotic-like fungal RCD

In animal cells, the first described RCD pathway was a caspase-dependent pathway termed apoptosis, which can be triggered by extrinsic or intrinsic cellular stimuli (Minina et al., 2017). The extrinsic pathway is activated when cells sense extracellular ligands via binding to cell surface death receptors, resulting in the formation of a death-inducing signaling complex (DISC) (Yang, 2015), which triggers cellular suicide. The intrinsic apoptotic pathway relies on the pore-forming BAX and BAK proteins from the BCL-2 family (Kale et al., 2018). Activated BAX/BAK proteins oligomerize into the mitochondrial outer membrane (Salvador-Gallego et al., 2016), which disrupts its integrity and leads to release of cytochrome *c*, which triggers activation of pro-apoptotic caspases (Li and Yuan, 2008). Cellular alterations associated with apoptosis include nuclear and DNA fragmentation, chromatin condensation, cell shrinkage and alteration in the membrane, including the inappropriate presence of phosphatidylserine on the outer leaflet of the cell membrane.

Whether apoptosis occurs in fungi has been disputed (Hardwick et al., 2018), although caspase-like protein families named metacaspases (in plants, fungi, protozoans) have been identified (Uren et al., 2000). The first metacaspase assessed for cellular function in fungi was *YCA1/Mca1* in *S. cerevisiae*. When *YCA1* was deleted, hydrogen peroxide treatment did not induce RCD, while overexpression increased RCD (Madeo et al., 2002). However, *YCA1* also protected cells from RCD; over-expression of *YCA1* prevented RCD in response to unfolded proteins and aggregates and increased yeast lifespan. This effect was only partially dependent on the catalytic center of Yca1 (Hill et al., 2014). In the basidiomycete *Ustilago maydis, Mca1,* which shows a 51% homology to *S. cerevisiae YCA1*, inhibited hydrogen peroxide-induced cell death in strains carrying an *Mca1* deletion. However, a strain with N-terminally truncated *Mca1* showed an increase of insoluble protein upon oxidative (H_2O_2) and heat stress treatment compared to the wild type, indicating the importance of the Mca1 both in the RCD and the removal of stress-induced protein aggregates (Mukherjee et al., 2017).

In *Magnaporthe oryzae,* two predicted homologues of yeast *YCA1*, *MoMca1* and *MoMca2* were identified. While *MoMca1* and *MoMca2* conferred a RCD response when over-expressed in *S. cerevisiae*, *M. oryzae* mutants carrying a deletion of both *MoMca1* and *MoMca2* showed an increased growth rate when challenged with oxidative stress, and which led to an accumulation of insoluble protein aggregates (Fernandez et al., 2021). In *Podospora anserina,* deletion of *PaMCA1* and *PaMCA2* increased the lifespan in aging race tube cultures, although growth rate was reduced. In senescent cultures, an increase of metacaspase-dependent protease activity was identified. These data suggested that RCD is induced by oxidative stress in senescent cultures and carried out after metacaspase activation (Hamann et al., 2007). When *Penicillium chrysogenum* was treated with S-ethyl ethanethiosulfinate (ALE), spores underwent morphological aspects associated with apoptosis, including propidium iodide uptake (showing loss of plasma membrane integrity) and Annexin V staining (showing the appearance of phosphatidylserine in the outer leaflet of the plasma membrane). Metacaspase activity could be detected upon treatment of mycelium with ALE, in a reactive oxygen species (ROS)-dependent manner, indicating the involvement of metacaspases in the apoptotic process (Qi et al., 2019).

In filamentous fungi, such as *Neurospora crassa* and *P. anserina*, the stability of heterokaryons is regulated by genetic differences at allorecognition (*het*) loci (Gonçalves et al., 2020, 2017; Saupe, 2000). If individuals that differ in *het* allelic specificity undergo hyphal fusion, the fusion cell is rapidly compartmentalized by septal plugging and undergoes a rapid hyphal death, so called "heterokaryon incompatibility" (HI). In *N. crassa*, fusion between germinated asexual spores (germlings) often results in death of both cells (Daskalov et al., 2019; Gonçalves et al., 2020; Heller et al., 2018). Allorecognition systems, such as HI, provide protection to cells/colony by preventing genome exploitation, resource plundering, the spread of deleterious senescence plasmids and mycoviruses (Bastiaans et al., 2016; Debets and Griffiths, 1998; Laird et al., 2005). Similar to apoptotic processes, HI in *N. crassa* is associated with the production of ROS, propidium iodide uptake and Annexin V staining, suggesting that allorecognition activates an apoptotic-like process to trigger cell death (Hutchison et al., 2009; Marek et al., 2003). However, *N. crassa* strains containing deletions of predicted metacaspase genes or a strain containing a deletion of a predicted apoptosis-inducing factor (AIF) were not affected for HI-mediated RCD. A transcription factor in the NDT80 (a p53-like) superfamily, *vib-1*, is required for HI-mediated cell death in *N. crassa* (Dementhon et al., 2006) and shows genetic interactions with a kinase (IME-2) (Hutchison et al., 2012). In *P. anserina* HI is associated with autophagy, which is induced upon incompatible fusions (Pinan-Lucarré et al., 2003). However, *idi-7* mutants, which are blocked in autophagy, still undergo HI, suggesting that autophagy is not the death inducing mechanism (Dementhon et al., 2004). Although RCD triggered by ROS, stress or HI is associated with morphological characters associated with apoptosis in mammalian cells, whether it represents a *bona fide* exhibition of a fungal form of apoptosis is unclear at present.

2.2. Necroptosis-like RCD

Necroptosis is a process described in mammalian cells that is a programmed form of necrosis (Newton and Manning, 2016). Necroptosis is triggered by cellular damage or infiltration by pathogens and is dependent on oligomerization and permeabilization of the plasma membrane by the MLKL protein (mixed lineage kinase domain-like) (Samson et al., 2020). Recently, it has shown that amyloid signaling in fungi has similarities to necroptosis (Saupe, 2020). In *P. anserina,* the *het-s* allorecognition locus encodes a prion named [Het-s], which functions in heterokaryon incompatibility (Saupe, 2011). In populations samples of *P. anserina*, two allelic variants of *het-s* occur, *het-s* and *het-S*. Both alleles encode proteins of the same length, 289 amino acids, but differ in the sequence of 13 amino acids. HET-S has two domains, a prion-forming domain, which forms a C- terminal β-solenoid structure (Ritter et al., 2005; Sen et al., 2007; Wasmer et al., 2008), and a N-terminal α-helical globular domain termed the HeLo domain (Saupe, 2011). Remarkably, the HeLo domain shows homology with the N-terminal membrane targeting helical domain of MLKL (Saupe, 2020), the terminal effector domain in mammalian necroptosis.

HET-s can exist as a soluble inactive monomer called [Het-s*] or as amyloid aggregate or prion [Het-s]. Prions are infectious proteins, and form protein polymers with a cross-β amyloid structure (Toyama and Weissman, 2011). *het-s* incompatibility and cell death occurs when a strain with a prion conformation of HET-s undergoes cell fusion with a *het-S* strain, although incompatibility does not occur upon cell fusion between a strain bearing the non-prion form of HET-s [Het-s*] and a *het-S* strain (Saupe, 2011). Cell death is triggered by the activation of HET-S

by HET-s or by the product of a gene linked to *het-S*, NWD2. NWD2 encodes a STAND protein resembling Nod-like receptors (NLRs; see below), with an N-terminal motif bearing homology to the HET-S/s PFD with 21 amino acid repeats of the β-solenoid motif. A NACHT domain is present after the PFD in NWD2 and a C-terminal WD-repeat domain (Daskalov et al., 2012). NWD2 acts as an effector protein whereby the oligomerization of the N-terminal β-solenoid fold in HET-S triggers the cytotoxicity of the pore forming domain (Fig. 1A) (Daskalov et al., 2015, 2012). This process exposes the N -terminal hydrophobic helix, whose change targets HET-S to the plasma membrane where it causes a loss of membrane integrity (Daskalov et al., 2015; Greenwald et al., 2010; Mathur et al., 2012; Saupe, 2011; Seuring et al., 2012).

More recently, it was shown that death inducing HELLP protein, identified by a genome search of *Chaetomium globosum,* functions to induce death when heterologously expressed in *P. anserina* (Daskalov et al., 2016). HELLP has an N-terminal cell death-inducing domain which is HeLo-like (HELL) and a C-terminal amyloid prion motif termed PP. As with *het-S*, the gene adjacent to HELLP encodes an NLR-like protein, which also contains a PP domain. Similar to HET-S, the HeLo-like domain of HELLP is homologous to the pore-forming domain of MLKL, while the PP domain has similarity to the RIP1/RIP3 (RHIM) amyloid motif in mammalian cells that regulates necroptosis (Li et al., 2012). HELLP, like Het-S, is activated by amyloid templating, with subsequent targeting to the membrane and cell-death induction (Daskalov et al., 2016).

2.3. Pyroptosis-like RCD

Pyroptosis is an effector mechanism of the mammalian inflammasome. The inflammasome is a cytosolic multiprotein complex assembled by members of the NOD-like receptor or protein pyrin and PYHIN protein families in response to pathogens and endogenous danger signals (Von Moltke et al., 2013). The target of inflammasome activation is the cleavage of gasdermin, which is a family of pore-forming proteins that cause cell death (Bergsbaken et al., 2009; Broz et al., 2020; Shi et al., 2017). The activation of gasdermin in mammalian cells occurs upon caspase cleavage of the lipophilic N-terminal domain (NTD) from the inhibitory C-terminal domain (CTD). The liberated N-terminal gasdermin fragment adheres to acidic membrane lipids, inducing oligomerization and insertion into the plasma membrane to form pores (Liu et al., 2016; Ruan et al., 2018). Insertion of the gasdermin NTD results in the release of immune cytokines from cells and triggers cell death (Ding et al., 2016; Liu et al., 2016; Sborgi et al., 2016).

In *N. crassa*, the allorecognition locus *rcd-1* (regulator of cell death) is a distant homolog of the N-terminal pore-forming domain of gasdermin (Daskalov et al., 2020b). Alleles at *rcd-1* are highly polymorphic in population samples, with *rcd-1* alleles falling into two haplogroups (*rcd-1-1* or *rcd-1-2*). Cell fusion between germlings or hyphae harboring antagonistic *rcd-1-1* and *rcd-1-2* alleles is sufficient to trigger vacuolization and death of the fusion cell (Fig. 1B) (Daskalov et al., 2019). Recombinant RCD-1 interacts *in vitro* with negatively charged phospholipids and liposomes with similar lipid specificity as gasdermin (Daskalov et al., 2020b) and forms oligomers of higher molecular weight with architectures similar to a honey comb, suggesting that the RCD-1 could form membrane pores (Daskalov et al., 2020b). In *N. crassa*, RCD-1 targets the plasma membrane causing cell death (Fig. 1B) (Daskalov et al., 2020b). Importantly, the co-expression of incompatible RCD-1-1 and RCD-1-2 proteins in human 293T kidney cells is sufficient to induce pyroptotic-like cell death. These data suggest that the function of RCD-1 and gasdermin have an ancient evolutionary origin, working in a similar manner to cause cell death (Daskalov et al., 2020b). Consistent with this hypothesis, gasdermin homologs have been recently identified in bacteria where they induce cell death via a conserved gasdermin-like pore-forming domain (Johnson et al., 2021). The bacterial gasdermins (bGSDMs) are believed to be involved in anti-phage defense with >50 bacterial gasdermins forming a unique clade different from metazoan and fungal homologs (Johnson et al., 2021). Activation of the bacterial PFD is dependent upon caspase-like proteases, with the membrane-associated oligomerization of bGSDMs resulting in the disruption of membrane integrity (Johnson et al., 2021).

Genome mining of fungal genomes revealed that gasdermin homologs are common in the genomes of members of the Ascomycota phylum, but are variable in number (Daskalov et al., 2019). Interestingly, around 80% of gasdermin homologs in the Ascomycota are in close proximity to genes encoding proteins with a putative protease domain (Clavé et al., 2021), mostly belonging to the subtilisin-like serine proteases (Clavé et al., 2021). *P. anserina, het-Q1* encodes a gasdermin protein (HET-Q1), whose cytotoxic activity is controlled by proteolytic cleavage by a subtilisin-like serine protease named HET-Q2 (Fig. 1C) (Clavé et al., 2021). The regulation of the cytotoxic activity of the gasdermin homolog HET-Q1 by proteolytic activity indicates that some fungal gasdermins could be regulated through proteolytic cleavage, similar to mammalian gasdermins. Analysis of the architecture of the fungal gasdermin-associated proteases also show a similar domain architecture to NLR proteins (see below) (Clavé et al., 2021), with some protease domains fused to repeat domains including leucine-rich repeats, tetratricopeptide repeats and WD40 repeats, or NACHT domains, which are frequently involved in pathogen recognition and inflammasome function in innate immunity in mammals.

2.4. Fungal NLR-like proteins and RCD

The nucleotide-binding domain (NBD), leucine-rich repeat–containing proteins (NLRs) are intracellular proteins that play an important role in the innate immune response in plants and animals (Ting et al., 2008; Jones et al., 2016). NLRs function as a switch, that when activated can result in cellular death, such as pyroptosis in animals, or the hypersensitive response in plants (Jones et al., 2016). NLRs have a unique architecture, with an N-terminal effector domain, a central domain NBD and a C-terminal domain composed of repeat structures such as LRR, WD, HEAT, ANK or TPR motifs. In NLRs there are two types of NBD domains: NACHT type present in animals and NB-ARC (nucleotide-binding, APaf1, Resistance, CED4) found mostly in plants (Jones et al., 2016). NLRs are also members of the family of STAND proteins (signal transduction adenosine triphosphatase (ATPases) with numerous domains) (Danot et al., 2009; Leipe et al., 2004).

An analysis of NLR-related proteins in 198 fungal genomes, primarily within the Pezizomycotina (filamentous ascomycete species) identified 5616 NLR candidates. NLR-like proteins in fungi have a tripartite domain distribution with an NACHT or NB-ARC core domain, flanked with diverse N- and C-terminal domains (Fig. 2A) (Daskalov et al., 2020a; Dyrka et al., 2014). The repeated domains in the C-terminal could be WD, ANK or TPR type and lack LRR motifs (Fig. 2A) (Dyrka et al., 2014; Soanes and Talbot, 2010). The N-terminal domain consists of diverse effector domains such as: PNP_UDP, HELO-LIKE, GOODBYE-LIKE, SESB-LIKE, HET, HELO, PATATIN, PFD, C2, PEPTIDASE_S8, RELA-SPOT or PKINASE (Fig. 2A) (Dyrka et al., 2014). The different combinations of the effector domains and the repeated domain together with the core domain show fungal NLR diversity in protein architecture (Fig. 2B).

In filamentous fungi, some NLR-like genes are involved in allorecognition and RCD (Daskalov et al., 2019), including an NLR-like signalosome in *P. anserina* involved in amyloid signaling (Saupe, 2020) (see above). In *N. crassa*, an NLR-like protein, PLP-1, composed of three domains, a patatin-like phospholipase domain, a central nucleotide-binding domain (NB-ARC type) and a C-terminal tetratricopeptide repeat domain (TPR), is involved in allorecognition and cell death in concert with SEC-9. *plp-1* and *sec-9* are closely linked loci, with highly polymorphic alleles that fall into four discrete haplogroups in *N. crassa* populations (Heller et al., 2018). Cell fusion between hyphae or germlings from different *plp-1/sec-9* haplogroups triggers rapid cell death (Fig. 1D) (Heller et al., 2018). *sec-9* encodes an essential SNARE protein

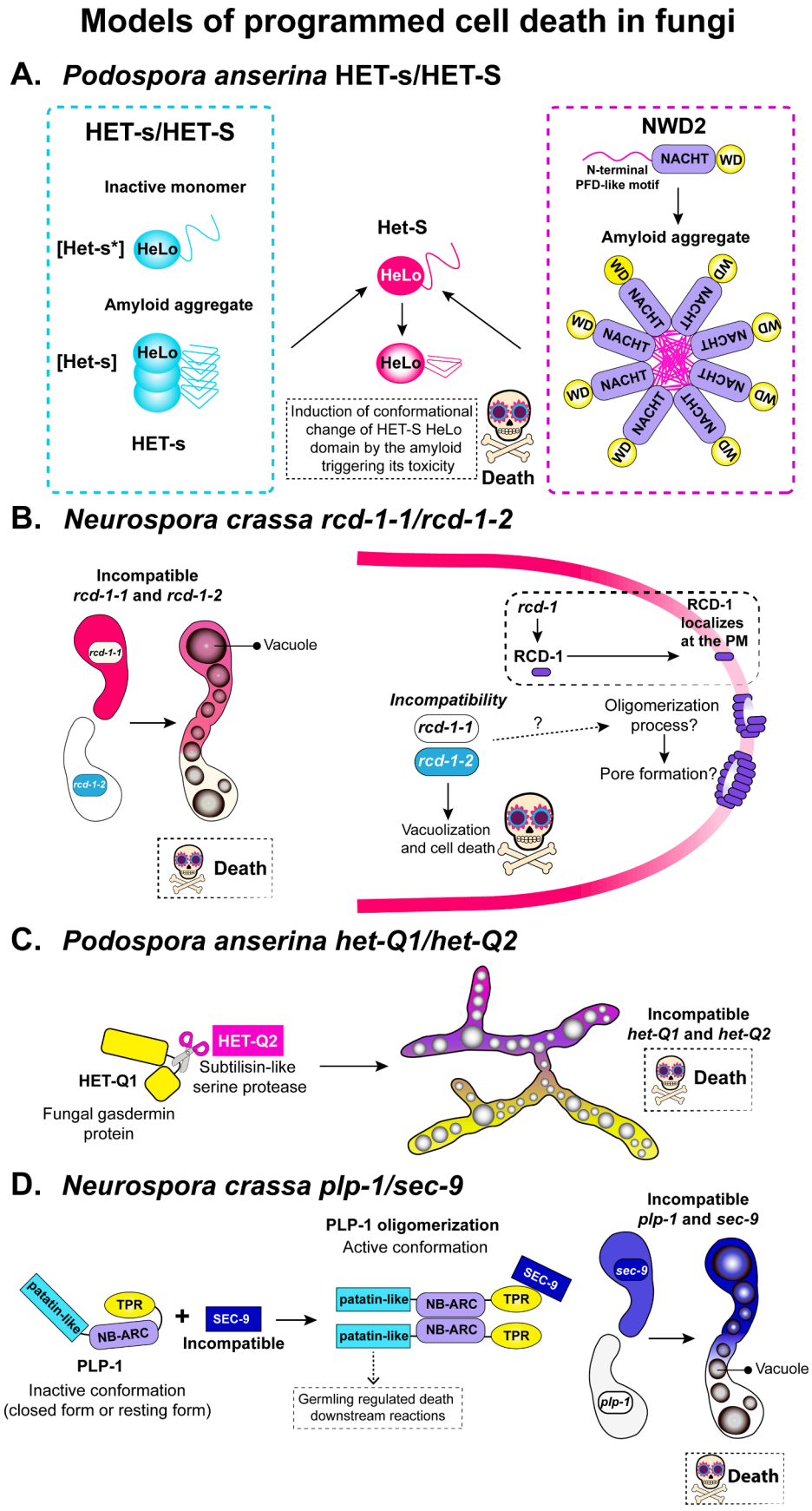

Fig. 1. Models of programmed cell death in fungi. A. Model of activation of HET-S cell death-inducing protein in *Podospora anserina.* The activation of the HeLo toxic domain of HET-S can occur in two ways. Through the conformational change of [Het-s] PFD, which takes the form of β-solenoid structure, or through the effector NWD2, which also has a PFD that when activated induces its conformational change in the β-solenoid structure. The amyloid-like fold (from [Het-s] or NWD2) serves to refold the HET-S PFD into the amyloid fold, which produces the conformational change of HET-S HeLo domain exposing the N-terminal hydrophobic helix, targeting HET-S to the plasma membrane where it causes a loss of membrane integrity. It is not clear if the N-terminal HeLo domain oligomerizes at the plasma membrane (Modified from Daskalov et al., 2012; Saupe, 2011). **B.** The incompatibility of allelic variants *rcd-1-1* and *rcd-1-2* in *N. crassa* causes vacuolization and cell death. RCD-1, which has homology to mammalian gasdermin, localizes at the plasma membrane, and *in vitro* RCD-1 forms oligomers and aggregates. It is unclear how oligomerization and death are activated when RCD-*1*-1 and RCD-*1*-2 are in the same cell. **C.** In *P. anserina, het-Q1* and *het-Q2* induce cell death. HET-Q1 is also a gasdermin homolog. The proposed activation mechanism of HET-Q1 involves proteolytic cleavage of the presumable inhibitor domain by the HET-Q2 subtilisin-like serine protease. The presumption is that the death domain of HET-Q1 functions similar to RCD-1, oligomerizing at the plasma membrane, producing a membrane disruption and causing cell death. **D.** Model for allorecognition by *plp-1/sec-9* of *N. crassa*. The model proposes that PLP-1 maintains an inactive conformation. Following cell fusion, an interaction between incompatible SEC-9 and PLP-1 proteins through the SEC-9 SNARE domain and the PLP-1 TPR domain results in a conformational change in PLP-1, exposing the NB-ARC domain and inducing oligomerization. The N-terminal patatin-like phospholipase activity of PLP-1 is required for cell death (Modified from (Heller et al., 2018)).

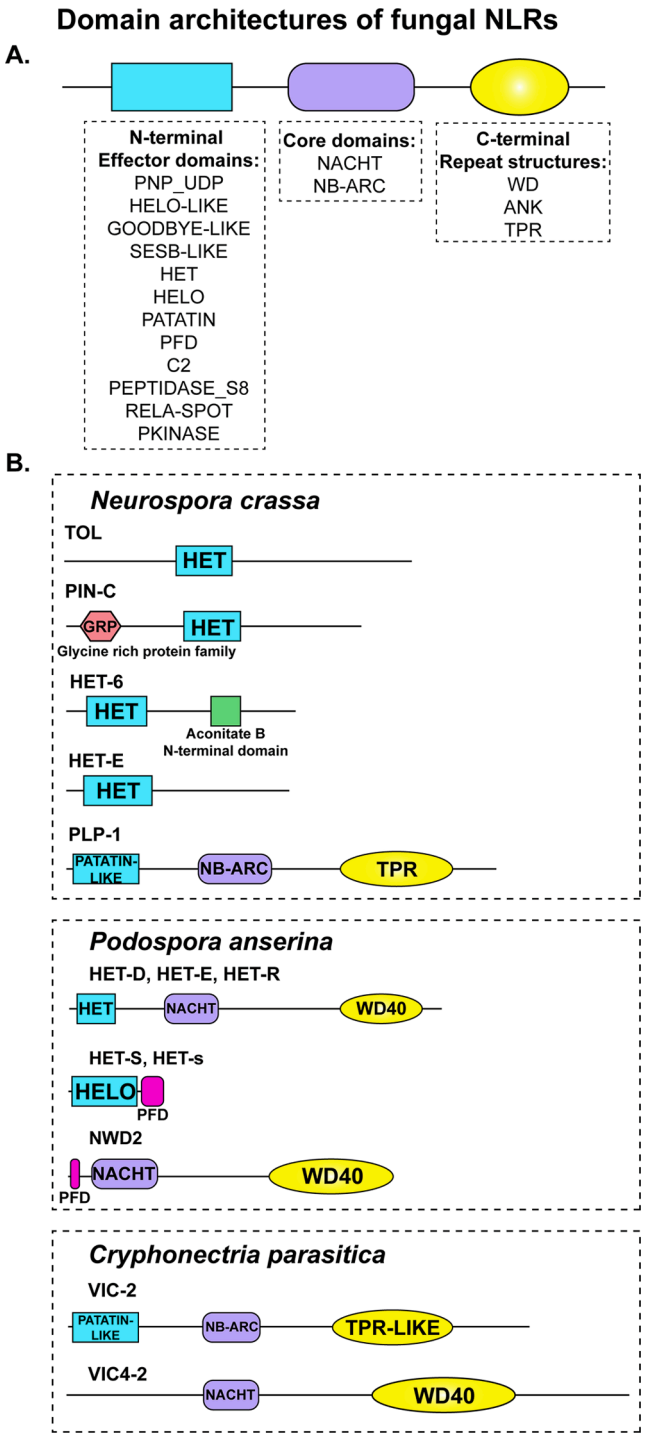

Fig. 2. Domain architectures of fungal NLR-like proteins. A. The architecture of the fungal NLR-like proteins is typically composed of three domains. An N-terminal domain has varied effector domains, the middle region is composed of either a NACHT or NB-ARC domain, and C-terminal domain is composed of repeat structures like WD, ANK, or TPR. **B.** Architecture of different allorecognition proteins identified in *Neurospora crassa*, *Podospora anserina* and *Cryphonectria parasitica* that have domains similar to those found in NLR-like proteins discussed in this review. These proteins are involved in allorecognition and cell death. In some proteins involved in allorecognition and RCD in *N. crassa,* the HET domain is conserved, but these proteins do not have the NLR architecture.

and which is required for post-Golgi transport (Brennwald et al., 1994). Orthologs of *plp-1* and *sec-9* have similar domain structures in the plant pathogenic fungus *Cryphonectria parasitica* (*vic-2* and *vic-2a,* respectively), and *P. anserina* (*het-z1* and *het-z2,* respectively) are also involved in allorecognition and HI (Choi et al., 2012; Heller et al., 2018).

Complex formation between incompatible proteins PLP-1 and SEC-9 is indispensable to the induction of cell death (Fig. 1D) (Heller et al., 2018), with cell death requiring the N-terminal patatin-like phospholipase and NB-ARC activity of PLP-1 (Heller et al., 2018). In the guardian model in plants, the NLRs behave like protective proteins called 'guard' and monitor the status of 'guardee' proteins. The primary function of the 'guardees' is in defense signaling of pathogens, thus making them a target of pathogens. When virulence proteins from the pathogen alter the complex between the 'guard' and the 'guardees', it activates the NLR ('guard') (Jones et al., 2016). In the case of PLP-1 and SEC-9, the 'guard model' occurs differently, as an interaction between SEC-9 ('guardee') and PLP-1 ('guard'), compatible proteins do not occur. However, the interaction between incompatible proteins SEC-9 and PLP-1 is predicted to affect the activity of the "guard and guardee complex", thereby triggering HI (Heller et al., 2018).

2.5. HET incompatibility (HET domain) and RCD

The HET domain was the first domain identified that functions in HI in filamentous fungi (Smith et al., 2000). HET domain loci show high allelic diversity in comparison to genes in the rest of the fungal genome, consistent with their proposed role in allorecognition (Fedorova et al., 2005; Zhao et al., 2015). A number of *het* loci that encode proteins containing a HET domain (Glass and Dementhon, 2006; Saupe, 2000; Zhang et al., 2014), have a protein domain architecture similar to NLR-like proteins in fungi (Dyrka et al., 2014). The HET domain has some similarities with Toll/interleukin-1 receptor domains found in plants and animal immune receptors (Dyrka et al., 2014). However, how the HET domain functions biochemically either as a signaling motif or a death-inducing factor is unknown.

In *N. crassa,* with the exception of *rcd-1* and *sec-9/plp-1*, all the molecularly characterized *het* loci encode proteins containing a HET domain. HI induced by genetic differences at *het* loci cause death of hyphal fusion cells, but do not function in germlings. The linked *pin-c* and *het-c* loci function in non-allelic HI, similar to *sec-9/plp-1*. Non-allelic interaction between alternative haplotypes of *het-c* and *pin-c* (partner for incompatibility with *het-c*) cause incompatibility (Kaneko et al., 2006). *het-c* encodes a plasma membrane protein while *pin-c* encodes a HET-domain protein (Hall et al., 2010; Kaneko et al., 2006). In *N. crassa*, the *tol* locus encodes a protein that triggers HI and cell death when hyphae of opposite mating types (*mat A* and *mat a*) undergo somatic cell fusion (Glass and Dementhon, 2006; Shiu and Glass, 1999). The *het-6* locus consists of the linked *het-6* and *un-24* loci. *het-6* encodes a HET domain protein, while *un-24* encodes an essential ribonucleotide reductase; incompatibility is triggered by non-allelic interactions between *het-6* and *un-24* (Lafontaine and Smith, 2012). *P. anserina* also has non-allelic incompatibility systems involving proteins with HET effector domains, including incompatibility interactions between *het-c/het-d, het-c/het-e, and het-r/het-v* (Chevanne et al., 2009; Glass and Dementhon, 2006; Saupe, 2000). In addition to their N-terminal HET effector domain, these proteins have an architecture with a NACHT core domain and a C-terminal domain with a repeat domain WD40 (hypervariable) (Paoletti and Clavé, 2007; Smith et al., 2000) (Dyrka et al., 2014). Mutations in the HET domain of *tol* or *pin-c* in *N. crassa*, or *het-e* or *het-r* in *P. anserina* abolish HI, highlighting the importance on the HET domain in HI (Chevanne et al., 2009; Kaneko et al., 2006; Paoletti and Clavé, 2007; Shiu and Glass, 1999).

2.6. Meiotic drive elements and RCD

Meiotic drive elements (MDs) are able to manipulate the meiotic

process in order to enhance their own transmission rate (Zimmering et al., 1970) and are present in a large number of eukaryotes (Núñez et al., 2018), including the *S5* locus in rice (Yang et al., 2012) *t*-complex in mice (Lyon, 2003) and the segregation distorter gene complex (SD) in *Drosophila melanogaster* (Larracuente and Presgraves, 2012). In ascomycete species, meiotic drive manifests itself as "spore killing" during meiosis (Turner and Perkins, 1991). When a strain with a meiotic drive element is crossed with a strain that lacks it, the meiotic products (ascospores) that contain the drive element survive, while ascospores that do not have the drive element die. In *Neurospora intermedia,* two meiotic drive elements, *Spore killer-2 (Sk-2)* and *Spore killer-3 (Sk-3)* (Turner and Perkins, 1979), were identified in wild strains (Turner, 2001). *Sk-2* and *Sk-3* are associated with large chromosomal inversions (Campbell and Turner, 1987; Hammond et al., 2012; Harvey et al., 2014; Svedberg et al., 2018; Turner and Perkins, 1979) that have separate origins (Svedberg et al., 2018; Raju, 1979; Turner and Perkins, 1979). *Sk-1* spore killer element was identified in *Neurospora sitophila* and the gene responsible of the spore killing is *Spk-1* (Svedberg et al., 2021). The introgression of these drive elements into *N. crassa* identified a gene that confers resistance to spore killing (*rsk*) (Hammond et al., 2012; Rhoades et al., 2019). The killer neutralization model proposes that *rsk* and spore killer are expressed in the ascus compartment and that ascospores that carry the resistant version of *rsk* ("the antidote") neutralize the drive element ("poison") and thrive, while those who do not bear the *rsk* are killed (Hammond et al., 2012). Recent studies identified a gene required for *sk-2* spore killing termed *rfk-1* (required for killing) (Rhoades et al., 2019). An edited *rfk-1* transcript is predicted to produce a protein of 130 aa expressed in sexual tissues, while an unedited transcript produces a protein of 102 aa in vegetative tissues. These data suggest that the two proteins encoded by *rfk-1* may have different roles in spore killing activity (Rhoades et al., 2019).

Wild populations of *P. anserina* harbor multiple spore killers, making it an excellent model for investigating the interaction between different meiotic drive elements (Grognet et al., 2014; Hamann and Osiewacz, 2004; Van Der Gaag et al., 2000). The *P. anserina het-s* gene is a spore killer and crosses between *het-s* as a female strain with *het-S* strain results in high percentage of aborted spores that contain the *het-S* variant (Dalstra et al., 2003). Additional spore killer types were identified and characterized from *P. anserina* population samples (Van Der Gaag et al., 2000). The *Spok* (spore killing: *Spok1, Spok2, Spok3* and *Spok4*) genes are a class of selfish genetic elements that constitutes autonomous drive systems (Grognet et al., 2014; Vogan et al., 2019). The *Spok* genes are poison-antidote meiotic drivers (Grognet et al., 2014), resembling the toxin-antitoxin (TA) system of bacteria. In this system, genetic elements encode toxins capable of interfering with the cell growth, while the cognate antitoxins neutralize the toxin (Harms et al., 2018). However, unlike the TA system, the *Spok* system synthesizes a protein with dual activity, functioning as toxin and antitoxin molecule. The predicted SPOK proteins have an N-terminal coiled-coil region, N-terminal domain of an unknown function, a nuclease domain, a cysteine cluster region, and a kinase domain. It is possible that the nuclease SPOK domain is required for the killer function, whereas the predicted kinase activity appears to be involved in resistance activity (Vogan et al., 2019). *Spok-3* and *Spok-4* are associated in a large genomic region named 'the *Spok* block'. It can carry either *Spok3, Spok4,* or both (Vogan et al., 2019). The *Spok* block can be present in four distinct locations within the genome of *P. anserina* (Vogan et al., 2019)*;* recent data suggests the *Spok* block has variable positions because it is capable of transposition (Vogan et al., 2021).

2.7. Antifungal drugs and cell death

While fungal cell death can occur during development or ecological interactions (see previous sections), it may also be induced by exposure to chemical compounds. In this context, antifungal drugs that induce cell death can serve as useful tools to mitigate the consequences of fungal infections of plants and animals, including humans. Some fungal species pose serious challenges as shown by the animal pathogens *Batrachochytrium dendrobatidis* and *Pseudogymnoascus destructans*, which have been driving populations of amphibians (Scheele et al., 2019) and bats (Hoyt et al., 2021), respectively, to the brink of extinction. In the case of plants, a large number of fungal pathogens represent a major threat to agricultural productivity, global food security and stability of forest ecosystems (Fisher et al., 2020, 2018, 2012). While human fungal infections have been largely underappreciated and neglected, recent estimates indicate that fungal infections afflict more than 1 billion people globally and approximately 1.5 million people succumb to fungal diseases every year (Bongomin et al., 2017; Brown et al., 2012; Pendleton and Pearce, 2015). A restricted number of therapeutic drugs against fungal infections of animals and plants are available. These drugs often involve the induction of fungal cell death (Gonçalves et al., 2017; Kulkarni et al., 2019), but the efficacy of these compounds varies greatly (Berman and Krysan, 2020; Brauer et al., 2019; Fisher et al., 2018; Nett and Andes, 2016; Ostrosky-Zeichner et al., 2010). The development of resistance to antifungal drugs has been demonstrated for all licensed systemic antifungals (Fisher et al., 2018), while long term exposure to fungicides and concomitant cellular adaptation is associated with genetic instability and aneuploidy, target modification (due to conformational changes or overexpression), overexpression of efflux pump genes, detoxification by metabolic enzymes, or hot spot amino acid substitutions (Berman and Krysan, 2020; Fisher et al., 2018; Robbins et al., 2017). The evolution of drug-adapted lineages is exacerbated by long periods of prophylactic treatment, excessive usage of over-the-counter medications and incomplete treatment courses in humans (Fisher et al., 2018), monoculture and genetically uniform practices in agriculture (Fisher et al., 2018), and incorrect waste disposal by antimicrobial drug-manufacturing facilities (Larsson, 2014). The dramatic situations observed for *Candida auris* (Casadevall et al., 2019; Lockhart et al., 2017) and, more recently, a dermatophytosis outbreak caused by a new clonal population of *Trichophyton* (Singh et al., 2019), which both display resistance to all major classes of antifungal compounds, underlines the urgent need to understand the molecular basis of antifungal drug resistance and to develop of new antifungal therapies. Thus, the modulation of the pathways underlying fungal RCD is a prominent topic of research in the context of antifungal compound development.

Pathways that regulate antifungal drug resistance and cell death may be closely intertwined. An example of such a crosstalk has been demonstrated in *N. crassa* using the bacterial alkaloid and protein kinase C inhibitor staurosporine as a cell death inducer. Staurosporine has been shown to significantly reduce tolerance to fluconazole in clinical isolates of *C. albicans*, hence improving the antifungal outcome of this azole drug (Rosenberg et al., 2018). Upon treatment with staurosporine, *N. crassa* cells react by dynamically modifying the levels of cytosolic calcium (Gonçalves et al., 2014a) and producing ROS (Gonçalves et al., 2015a) in a phospholipase C signaling-dependent manner, resulting in a rapid cell death (Gonçalves et al., 2014a). Staurosporine-induced cell death shows a mitochondrial involvement, particularly at the level of the mitochondrial complex I of the electron transport chain (Gonçalves et al., 2015a), and is linked to an unbalanced lipid organization at the plasma membrane (Santos et al., 2018). The cell death response to staurosporine is regulated by the Zn_2Cys_6 transcription factor CZT-1 (Cell death-activated Zinc cluster Transcription factor) and the absence of *czt-1* results in hypersensitivity to the drug (Gonçalves et al., 2014b). The increased susceptibility of Δ*czt-1* cells to staurosporine may be attributed to their inability to upregulate *abc-3,* encoding an ATP-binding cassette (ABC)-transporter whose expression is highly induced by staurosporine (Fernandes et al., 2011; Gonçalves et al., 2014b). CZT-1 also regulates genes involved in the detoxification of ROS and cell death, such as *cat-1* (encoding Catalase-1) and *amid-2* (Apoptosis-inducing factor-homologous mitochondrion-associated inducer of death-2) (Fig. 3) (Gonçalves et al., 2014b). The expression of *czt-1* is also increased upon exposure to hydrogen peroxide, phytosphingosine,

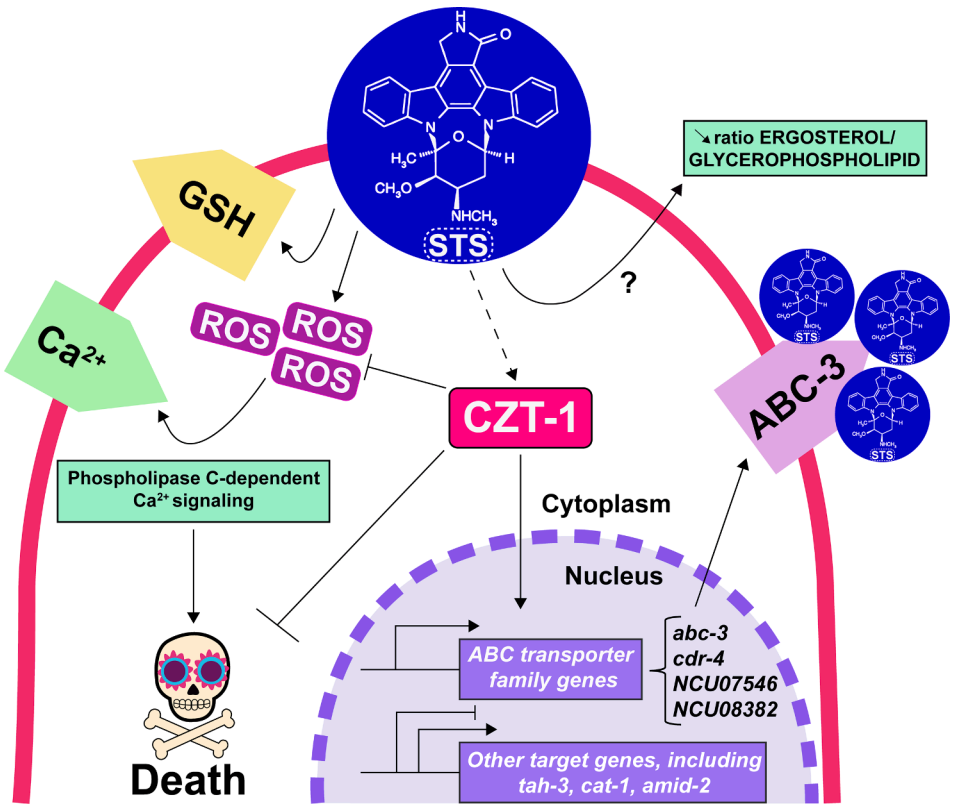

Fig. 3. The role of CZT-1, reactive oxygen species (ROS) and intracellular calcium (Ca^{2+}) during the *N. crassa* response to staurosporine (STS). Upon exposure to STS, *N. crassa* cells respond by rapidly accumulating ROS, which leads to mobilization of Ca^{2+} from the extracellular space and intracellular stores (the latter is not represented). The recruitment of Ca^{2+} to the cytosol depends on phospholipase C-based signaling. STS prevents the ratio of ergosterol/glycerophospholipid at the plasma membrane to become appropriate for mycelial development, causing a developmental arrest. CZT-1 functions as an anti-cell death transcription factor, by regulating the expression of drug efflux pumps of the ABC transporter family, namely ABC-3. CZT-1 controls the expression of multiple other genes that may play a role in antifungal drug resistance and cell death (Data used for the construction of this scheme from Fernandes et al., 2013; Gonçalves et al., 2014b, 2014a; Santos et al., 2018).

amphotericin B (Gonçalves et al., 2014b), menadione (Zhu et al., 2013) and 1-(piperidin-1-yl)-4-propoxy-9H-thioxanthen-9-one (Gonçalves et al., 2015b), suggesting that CZT-1 may play a broader role in antifungal drug resistance/tolerance.

3. Conclusions

In fungi, cell death is of vital importance to carry out different processes such as sexual development, cell differentiation, ecological interactions such as allorecognition, invasion, and colonization of the host cell. Death can also occur in response to toxic agents. However, there are still many open questions about how all these different mechanisms of RCD are controlled and executed, namely the molecular machinery involved in each process, and the commonalities and differences amongst the various cell death-inducing mechanisms. In this regard, although there are notable differences between the different types of RCD, it appears that the destabilization of the plasma membrane is a common mechanism; this is exemplified by the formation of pores at the plasma membrane (see the necroptosis and pyroptosis sections above) or by an imbalance in the homeostasis of the lipid composition of the plasma membrane (see the staurosporine example above; in addition, azole drugs induce cell death by targeting the biosynthesis of ergosterol and disrupting the integrity of the plasma membrane (Nett and Andes, 2016)). These effects ultimately result in fungal cell death. Moreover, some fungal cell death processes activated by allorecognition have effector molecules that have architectures similar to those implicated in innate immunity in plants and animals.

The different types of RCD in fungi seem to be well defined, although the true occurrence of apoptotic death in fungi remains controversial. Although there is data that could support mechanisms very similar to apoptosis in fungi, these are still not conclusive. On the other hand, the existence of necroptosis and pyroptosis in fungi seems to be now well documented. These pathways share the molecular effectors and the functional mechanistic bases similar to those found in mammals. For example, the regulated arrangement of HET-S by amyloid signaling exposes an N-terminal domain homologous to the effector domain of necroptosis in mammals, or the activation of gasdermins through proteolytic cleavage triggering pyroptosis. Death also appears through MDs, whose evolution drove them to use remarkable methods of transmission, giving them an advantage over viable meiotic products that do not inherit the selfish alleles producing their death. MDs could therefore be developed into a powerful molecular tool to be exploited in the future.

Future research on RCD in fungi is important for defining molecular mechanisms to approach arising resistance and tolerance to antifungal drugs used in agriculture and clinical settings. In particular, the relationship between death induced by treatment with drugs, various mutations, developmental aspects (asexual/sexual development and spore killer), infectious agents and allorecognition are still unclear. Could different molecular mechanisms that induce RCD be used interchangeably depending on the selective environment that a particular species finds itself? In aging colonies of *S. cerevisiae,* cell death is induced by oxidative stress that can be ameliorated by ammonia (Váchová and Palková, 2005). How might a particular lifestyle of a fungus (unicellular, dimorphic or strictly hyphal) affect the selection of particular RCD pathways? The relationship of the various cell death mechanisms discussed in this review and rules dictating their evolution and selection are still unclear, making this area fertile ground for future investigations.

Author contributions

A.M.R.-R., A.P.G. and N.L.G. collectively wrote and edited the manuscript. Figs. 1 and 2 drawn by A.M.R.-R. Fig. 3 drawn by A.P.G. and A.M.R.-R. All the authors have read and agreed to the published version of the manuscript.

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CRediT authorship contribution statement

Adriana M. Rico-Ramírez: Conceptualization, Writing – review & editing. **A. Pedro Gonçalves:** Conceptualization, Writing – review & editing. **N. Louise Glass:** Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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