

Review

Recent Advances in Research on Molecular Mechanisms of Fungal Signaling

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Abstract: Biochemical signaling is one of the key mechanisms to coordinate a living organism in all aspects of its life. It is still enigmatic how exactly cells and organisms deal with environmental signals and irritations precisely because of the limited number of signaling proteins and a multitude of transitions inside and outside the cell. Many components of signaling pathways are functionally pleiotropic, which means they have several functions. A single stimulus often results in multiple responses, a distinct response can be triggered by numerous stimuli and signals initiated by different stimuli are often transduced via commonly used network components. This review sheds light on the most important molecular mechanisms of cellular signaling in fungi and consequently provides a comprehensive overview about the current state of research on the road to understand the impact of signal transduction in eukaryotic microorganisms.

Keywords: cAMP signaling; quorum sensing; alternative splicing; lipid signaling; MAPK cascade; multistep phosphorelay; pheromone signaling; glucose signaling; light signaling; fungal signaling; fungi



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1. Introduction or History

Adaptation and resilience to environmental changes is a prerequisite for cells and organisms to live, survive and evolve. The expansion of signaling pathways in three kingdoms—Archaea, Bacteria and Eukarya—came about through the horizontal transfer of bacterial genes and the coevolution of the components of the respective systems [1–3]. Consequently, in terms of their functional properties and molecular architecture, signaling systems in unicellular eukaryotes represent an intermediate stage in the evolution of signaling systems between pro- and higher eukaryotes [2]. All living cells have in common that the functional organization of fundamental processes of the cell—growth, metabolism, differentiation and apoptosis—includes four basic components: (i) a signal receptor, which specifically recognizes a signal molecule; (ii) a signal transport, which is associated to the receptor; (iii) a signal amplifier, which is an ion channel or an enzyme producing second messengers; and (iv) an effector (signal receiver), which initiates single or multiple intracellular signal cascades, resulting in the response to the external changes [1].

Here, we aim to map the great diversity of molecular signal transduction processes in fungi to show how signaling proteins encrypt information, coordinate different transmission routes and deploy response to various environmental stimuli. Therefore, we present an overview of the most important mechanisms of molecular cellular signal transduction by showing selected and prominent examples.

2. Mitogen-Activated Protein Kinase Signaling

Mitogen-activated protein kinase (MAPK) signaling pathways represent one of the most important cellular architectures for the perception and transition of extracellular information ubiquitous in all eukaryotic organisms [4,5]. They have a myriad of cell functions in

all species of fungi, for example, mating, cell cycle control, differentiation, stress-response and -resistance, resilience, adaptation, cell wall assembly and integrity, autophagy and apoptosis, virulence, cell–cell communication and plant–fungus interaction [4,6].

In contrast to metabolic enzymes, which are known to be efficient for catalytic chemistry reactions within and outside of the cell, MAPK evolved to be dynamic molecular switches for signal transduction that can be controlled by membrane recruitment, dimerization and phosphorylation [7]. The signal propagation in the MAPK cascade follows a multistage process in which the amplification of signals by sequential events of phosphorylation make this system sensitive to the lowest stimulation patterns. The MAPKs are serine/threonine kinases, activated by a MAPK kinase (MAPKK), which is a ‘dual-specific’ kinase that phosphorylates its substrates at both Ser/Thr and Tyr motifs, i.e., targeting a Thr/x/Tyr motif at the MAPK (x represents glycine, proline or glutamate) [8,9] (Figure 1).

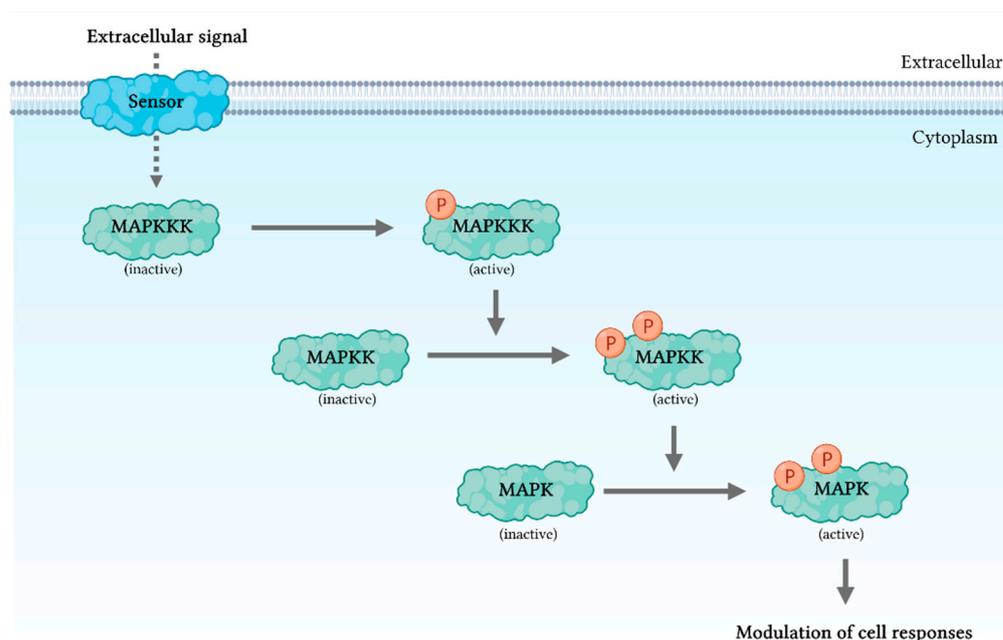


Figure 1. Schematic representation of MAPK signal transduction cascade. A membrane receptor perceives an extracellular signal. The sensor then activates the MAP kinase module (MAPKKK activates MAPKK, which in turn activates the MAPK) by phosphorylation. That may occur via different routes and intermediate steps. The modulation of cell responses by the active MAPK may activate different protein kinases or cytosolic components. Furthermore, the activated MAPK may translocate to the nucleus and regulates transcription factors. Arrows indicate activation.

The MAPKK is, in turn, activated by a MAPKK kinase that transmits signals from stimulus-activated upstream effectors, i.e., response regulators, GTP-binding proteins, other kinases, respectively, so-called pattern-recognition receptors [10,11]. The MAPK suffers conformational changes upon phosphorylation that subsequently increases the activity about 1000–50,000-fold [5,12]. Consequently, MAPKs are not really active unless phosphorylated by their respective upstream kinases. The molecular conformational change, i.e., involves the movement of the phosphorylated loop toward the active site and the rotation of the whole C-terminal lobe. The activation involves the opening of the A-loop, the relative alignment of the N-lobe and C-lobe and the rotation of the α C-helix [13]. In other words, phosphorylation in the activation loop area triggers the reorganization of the flexible C-terminal lobe, which rotates to the N-terminal lobe, thereby forming the ATP-binding active site for catalysis [12].

The most prominent example of MAPK signaling is the eukaryotic p38 MAPK pathway, which is well conserved in all eukaryotes. This signaling cascade is assumed to be a key player in a wide array of cellular processes associated with ageing, inflammatory diseases

and tumor development in mammals or differentiation, virulence and environmental stress signaling in fungi [14–17]. In the latter, the respective signaling cascade is called the high osmolarity glycerol (HOG) pathway with the p38 MAPK Hog1p. Signal transduction at the central MAPK Hog1p is achieved by phosphorylation of the dual Thr/x/Tyr phosphorylation motif. Apart from osmoregulation, Hog1p activation in fungi is addressed by many stimuli, including ultraviolet light, heat, fungicides and reactive oxygen species [14,18–21]. There are very few studies with statements about the molecular function of single amino acids (aas) in the Thr/x/Tyr motif of a Hog1/p38 MAPK. The studies concerning phosphorylation of p38 MAPKs are based mostly on immunoblot analysis using antibodies targeting the doubly phosphorylated Thr/x/Tyr motif of MAPK (null)mutant strains [22,23]. These methods are not suitable to distinguish or individually quantify Thr and Tyr phosphorylation and particularly their relationship to each other. Some rare studies with statements on single Thr or Tyr functionality are also based exclusively on immunoblot techniques [24–27]. In one of them, the role of Thr174 and Tyr176 phosphorylation in the yeast MAPK Hog1p is only addressed by the examination of the vegetative growth of hyperactive mutants [28]. The authors conclude that Tyr176 is required mainly for enhancing the catalytic activity following osmostress, whereas Thr174 is essential for the biological and catalytic activity, although not necessarily as a phosphor-acceptor. This is in line with results in cell culture assays and in vitro experiments with human p38, which postulate that phosphorylation at Thr180 might be more important for TGF β -activated protein kinase (TAK)-1 mediated signaling than at Tyr182 [26]. These observations point to a complex but only partially understood imagination of regulatory molecular mechanisms that present putative functions of MAPK, but this does not reflect anything about the mechanisms of signal coding or signal encryption.

In fact, these studies show a limited ‘on/off’ mapping without the possibility of distinguishing between the intensity and dynamic of phosphorylation at the single aas. Thus, gaining specific insights about the molecular programming of the Thr/x/Tyr motif by temporal site-specific quantification of phosphorylation and its contribution to (dis)regulation of cellular processes is absolutely mandatory.

3. cAMP Signaling

It is widely accepted that the secondary messenger cyclic adenosine monophosphate (cAMP) plays an extraordinary role in cellular signaling, and the spatial regulation of the cAMP level is critical for faithful signal transduction. However, our knowledge of how receptors, cAMP signaling enzymes, effectors or other key proteins regulate specific cell responses is limited [29]. The cAMP regulates a variety of physiological processes in eukaryotic cells and is produced in response to extracellular stimuli, such as hormones [30,31].

The most studied target of cAMP in eukaryotic cells, and in particular in the model fungus *Saccharomyces cerevisiae*, is the cAMP-dependent protein kinase A (PKA). The PKA mediates almost all physiological effects of cAMP in fungi, and this is also valid for other multicellular eukaryotes [32,33]. In a classical cAMP signaling pathway, a specific extracellular signal is perceived by a transmembrane receptor and transmitted into the cells through heterotrimeric G-proteins structured of α , β and γ subunits [34] (Figure 2).

The G-proteins are activated through the binding of an inducing ligand under GDP-to-GTP exchange of the guanine nucleotide, which is bound to the $G\alpha$ subunit. After that, the $G\alpha$ subunit is released from the $G\beta\gamma$ dimer [35]. Subsequently, the $G\alpha$ or the $G\beta\gamma$ subunit transfers the signal by stimulation of effectors, such as the adenylyl cyclase, which, in turn, starts to synthesize the second messenger cAMP [36,37]. The activities of the synthesizing adenylyl cyclase and the degrading phosphodiesterase affects the intracellular cAMP level. The cAMP biosynthesis occurs as a consequence of various extracellular stimuli, such as light, temperature, nutrients and hormones, thereby regulating a high number of physiological processes. The PKA is a tetramer consisting of two catalytic and regulatory subunits, which rest in the inactive state under non-inducing conditions when the cAMP level is low. Both subunits are highly conserved among eukaryotes and

fungi [34]. Upon inducing conditions, when cAMP levels increase, the interaction of cAMP with the two regulatory subunits results in a conformational rearrangement that triggers disaggregation of the tetramer and consequently the release of the catalytic subunits. These catalytic subunits start the phosphorylation of downstream substrates in the cytosol or translocate into the nucleus (Figure 2). Within the nucleus, the PKA catalytic subunits can either activate or inhibit transcription factors or transcriptional repressors thereby regulating cellular functions [38,39].

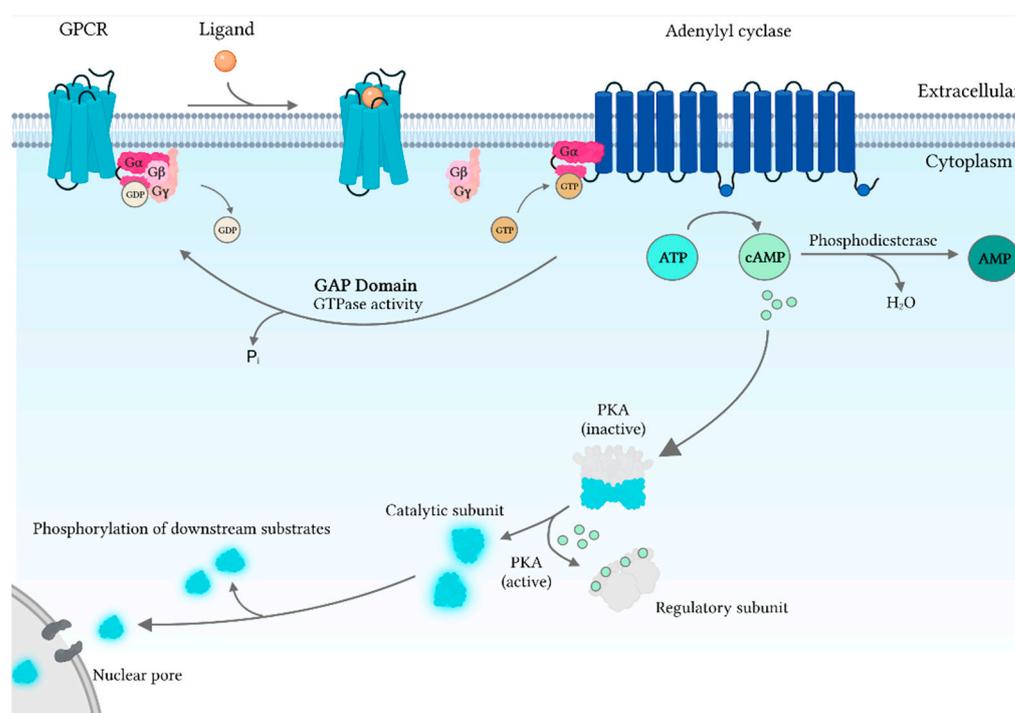


Figure 2. Schematic representation of cAMP and PKA signaling pathway in *S. cerevisiae*. Activation of the G-protein-coupled receptor (GPCR) by the ligand leads to the activation of adenylyl cyclase, which in turn triggers GTPase-activating proteins (GAPs) with GTP hydrolysis activity to stimulate formation of the inactive, GDP-bound protein and the release of free phosphate (Pi). Additionally, adenylyl cyclase synthesizes cAMP from ATP. When cAMP binds to the regulatory subunits of the inactive PKA, the catalytic subunits will be released and phosphorylate downstream substrates in the cytosol or translocate into the nucleus.

The cAMP pathway in filamentous saprophytes is very important for vegetative growth and sporulation and mating. That also includes the formation of appressoria, invasive hyphae, sclerotia differentiation and sporulation [34]. Thus, cAMP regulates virulence and morphogenesis in a wide range in various fungi, including the plant pathogens. The cAMP signaling pathway in *S. cerevisiae* mediates nutrient sensing and controls pseudohyphal differentiation upon nitrogen-limiting conditions [40–43]. In *Saccharomyces pombe*, the cAMP is responsible for the effects of glucose on spore germination and gluconeogenesis and regulates mating [44]. It furthermore regulates hyphal growth and morphogenesis, conidiation and spore germination in model filamentous fungi, such as *Aspergillus* sp. and *Neurospora* sp. [45–48].

4. Quorum Sensing

Microorganisms living close together in high numbers need to communicate with each other. Quorum sensing (QS) is a mechanism of microbial communication reliant on cell density that regulates highly important developmental processes. In order to achieve this communication, microorganisms release and detect small molecules known as QS molecules (QSMs) able to control their biological activities and behaviors [49]. The concentration

of QSMs increases pro rata to the population and a regulatory response is started after a critical threshold is achieved. Consequently, that leads to the coordinated expression or repression of QS-dependent genes [50]. Quorum sensing as a mechanism of signaling and communication was first observed in bacteria in studies on genetic competence in *Streptococcus pneumoniae* and bioluminescence in marine *Vibrio* species about 50 years ago [51]. Subsequently, QS was found in many bacteria regulating important processes, including biofilm formation, secretion of virulence factors, sporulation and biosynthesis of antibiotics [52–54].

Apart from bacteria, studies have revealed that many population-density behaviors in fungi, such as biofilm formation or virulence and pathogenesis, are regulated by QS [52]. The discovery of filamentation control in the pathogenic fungus *Candida albicans* by the QSM farnesol promoted the phenomenon of QS in fungi as well [55]. Farnesol was the first QSM isolated from a eukaryotic microorganism [56,57], but it was rapidly followed by the identification of the QSMs phenylethanol, tyrosol and tryptophol [50,58,59]. Since then, the role of QSMs in fungi has been widely studied in both yeasts and filamentous fungi, for example, *S. cerevisiae*, *C. albicans*, *Candida dubliniensis*, *Aspergillus niger*, *Aspergillus nidulans* and *Fusarium graminearum* [50,56,60].

The signaling molecules are not generally strain-specific and a huge diversity of those molecules has been reported in fungi. In more detail, among the most important examples of QSM in fungi are lipids (oxylipins), peptides (pheromones), alcohols (tyrosol, farnesol, tryptophol and 1-phenylethanol), acetaldehydes and some volatile compounds [61]. These compounds are actively involved in fungal QS, regulating diverse key functions, such as pathogenesis, morphogenesis and filamentation. It was documented for the first time in 2006 that the cell culture supernatant of the stationary phase from a culture of *S. cerevisiae* strain induced filamentation [62]. In this study, two aromatic alcohols were identified, phenylethanol (PheOH) and tryptophol (TrpOH), as the active principle of QS inducing filamentation. The production of these two molecules was shown to be dependent on the cell density. A high cell density results in an increase of the expression level of the ARO9 and ARO10 genes and subsequently stimulated the production of the aromatic alcohols [62,63]. The aromatic aminotransferase Aro9p and decarboxylase Aro10p are required for their synthesis outgoing from the metabolism of the aa phenylalanine and tryptophan. This aromatic alcohol production can also be stimulated by tryptophol itself. The latter activates the transcription factor Aro80p in a positive feedback loop resulting in the expression of the transaminase and decarboxylase genes ARO9 and ARO10 [64]. Consequently, yeast cells at a high population density produce more aromatic alcohols per cell than yeast cells at a low population density [62,64]. PheOH and TrpOH appear to trigger the upregulation of the FLO11 gene synergistically via the cAMP-dependent PKA subunit Tpk2p and the transcription factor Flo8p [52,62]. The glycosylphosphatidylinositol-anchored cell surface flocculin protein Flo11p is essential for filamentous growth [65–67]. *S. cerevisiae* strains with inactivation of either FLO8 or TPK2 do not form filaments upon the presence of PheOH and TrpOH [62]. Apart from cell density, it is known that the key morphogenesis-inducing stimulus in *S. cerevisiae*, nitrogen starvation, strongly induces the production of PheOH and TrpOH. In the end, the signaling sensors and signal transport mechanisms of QS in fungi have not yet been sufficiently elucidated. There is also evidence for strain differences in QS, which requires more research [68]. The importance of understanding the molecular mechanisms by which microorganisms interact is key to assessing how they might affect biofilms, cause diseases, influence the quality and safety of fermented food and behave in biotechnological applications.

5. Alternative Splicing

Alternative splicing (AS) is a pervasive mechanism in eukaryotic organisms that generates multiple different transcript and protein isoforms from one single gene sequence [69–72]. During gene expression, the spliceosome, a multi-protein complex of five snRNP (small nuclear ribonucleoprotein: U1, U2, U4, U5 and U6), orchestrates the removal of noncoding

sequences (introns) of the primary mRNA and assembles different combinations of coding sequences (exons) into mature mRNA. Each snRNP contains one snRNA (small nuclear RNA) and several proteins [73]. The molecular splicing process is a two-step transesterification reaction that removes introns as lariat intermediates (looped structures) and ligates the remaining exons [74].

Introns are defined by a 5'-splice site (5'SS), an adenosine branch point (BP), the polypyrimidine tract (pY tract) and the 3'SS (Figure 3, top).

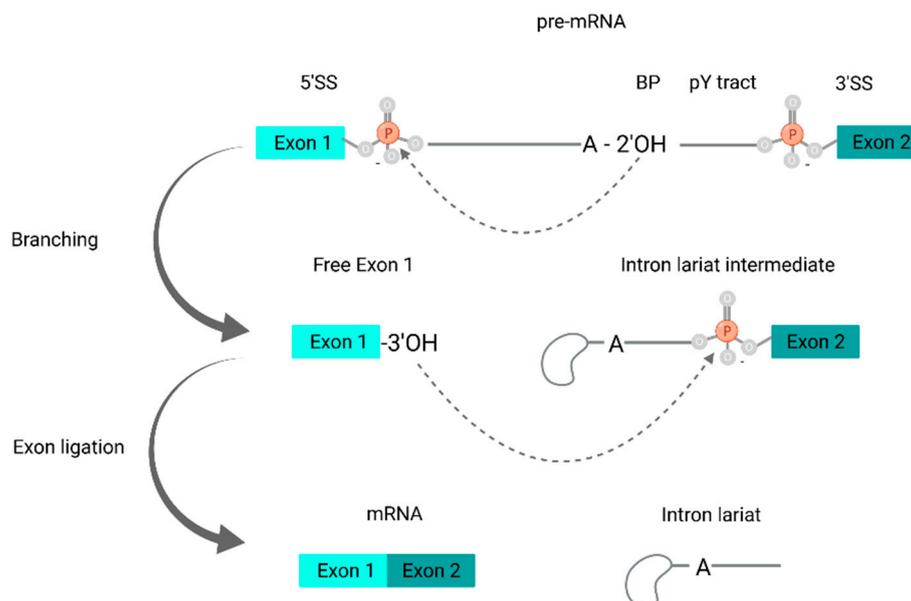


Figure 3. Two-step transesterification mechanism of pre-mRNA splicing. In the branching step, the 2'-OH of the branch point (BP) adenine of exon 2 attacks the phosphate of the guanine at the 5' end of the 5' splice site (5'SS) of exon 1. During exon ligation, the 3'-OH of the free exon attacks the phosphate of the 5' end of the intron lariat intermediate.

The first step of the splicing process is called branching and entails the nucleophilic attack by the 2'-OH group of the BP adenosine on the phosphate at the 5'SS. As a result, the 5'-2' phosphodiester linkage between the 5' end of the intron and the BP adenosine forms an intron-lariat-3'exon intermediate and a free 5'exon with a 3'OH group (Figure 3, middle). In the following exon ligation, the 3'-OH group of the 5'exon attacks a phosphate at the 3'SS, resulting in the ligation of the 5' and 3'exons and the excision of the lariat intron (Figure 3, bottom) [75–77]. Thereby, the spliceosome assembles the different exons in a stepwise manner (overview in Figure 4).

Initially, the intron is recognized by its 5'SS, BS and 3'SS of U1 snRNP and splicing factors, forming the pre-spliceosome (E complex) [78]. In subsequent steps, the E complex recruits U2 snRNP to generate the pre-spliceosome (A complex), which assembles with the tri-snRNP (U4, U5 and U6) into the pre-catalytic spliceosome (B complex). The dissociation of U1 and U4 snRNP results in the activation of the spliceosome (B^{act} complex), which is then converted into the catalytically activated complex (B*) (Figure 4, bottom). The first step of the transesterification reaction occurs in B*, resulting in the catalytic step I spliceosome (C complex) and then remodeling into the step II-activated spliceosome (C* complex). Next, the second step of the transesterification reaction is catalyzed in the complex C*, followed by its conversion into the post-catalytic complex. Ligated exons (mRNA) were found in the post-catalytic complex for the first time and the excised lariat intron could be identified. The newly formed mRNA is then released, resulting in the intron lariat spliceosome. After the latter dissociates, all snRNPs can be recycled for additional rounds of splicing [75,79–82]).

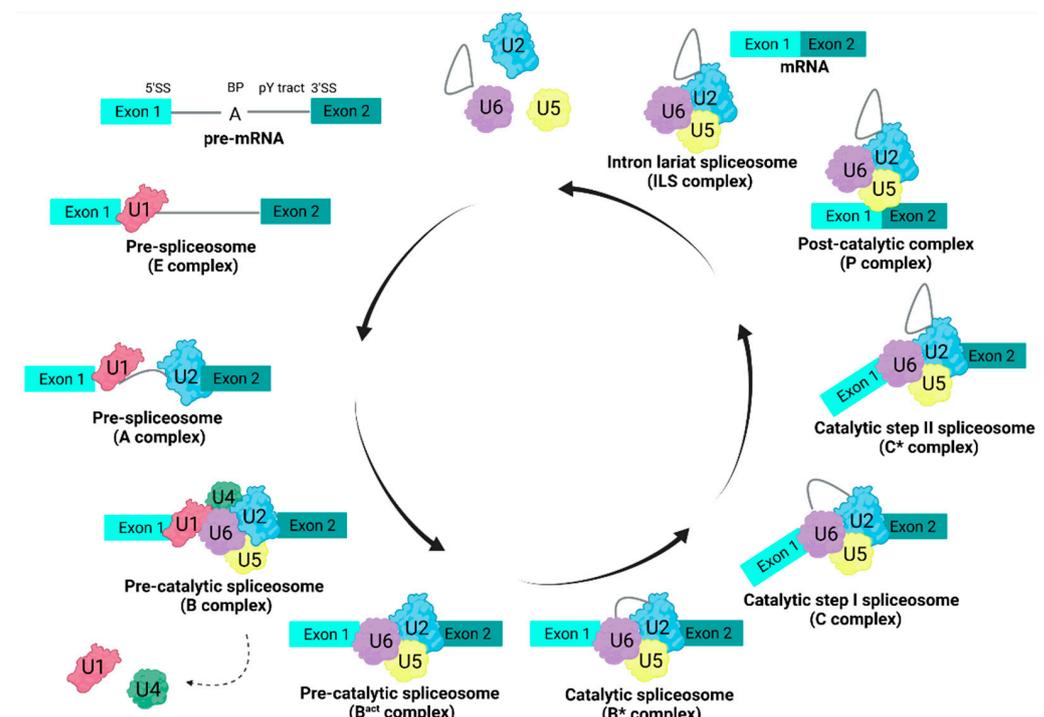


Figure 4. Assembly and the catalytic cycle of the spliceosome. Initially, the 5'SS, BP and 3'SS are first recognized by the U1 small nuclear ribonucleoprotein (snRNP), forming a pre-spliceosome (E complex). The U2 snRNP attaches at exon 2 to subsequently form the A complex, which interacts with the U4, U5, U6 tri-snRNP to assemble into the pre-catalytic spliceosome (B complex). There are at least six additional distinct spliceosome complexes: B^{act}, B*, C, C*, P and the intron lariat spliceosome (ILS complex). Each complex has a unique architecture.

About 95 % of genes containing intron in humans are alternatively spliced, resulting in approximately 100,000 splicing decisions [83,84]. Varying AS events can result in altered protein isoforms with potentially dramatic consequences for the organism. Thus, AS resulting in changed protein interactions or the inhibition of enzymes can induce cancer development or the impairment of drug efficacy [85,86]. The most prominent AS patterns are classified into five categories: exon skipping, intron retention, alternative 5' splice site, alternative 3' splice site and mutually exclusive exons (Figure 5).

Even though AS is widely accepted for increasing transcriptome and proteome diversity in higher eukaryotes, a comprehensive understanding of the molecular mechanisms in fungi and its putative downstream functional effects in signaling is mainly unexplored [87,88]. The fungal kingdom is a species-rich group of organisms with genome sizes ranging from 10 to 90 Mb [89–91]. According to the most recent studies, Ascomycota, Basidiomycota and Deuteromycota have a higher incidence of AS than previously thought [78,90,92–96]. Various physiological processes are affected by AS, such as growth, a pathogenic lifestyle, dimorphic changes and stress adaptation [90,92,94,96–100]. Thereby, numerous precursor messenger RNAs are differently alternatively spliced depending on different environmental conditions, such as changes in extracellular phosphate concentration, temperature and ambient pH [101].

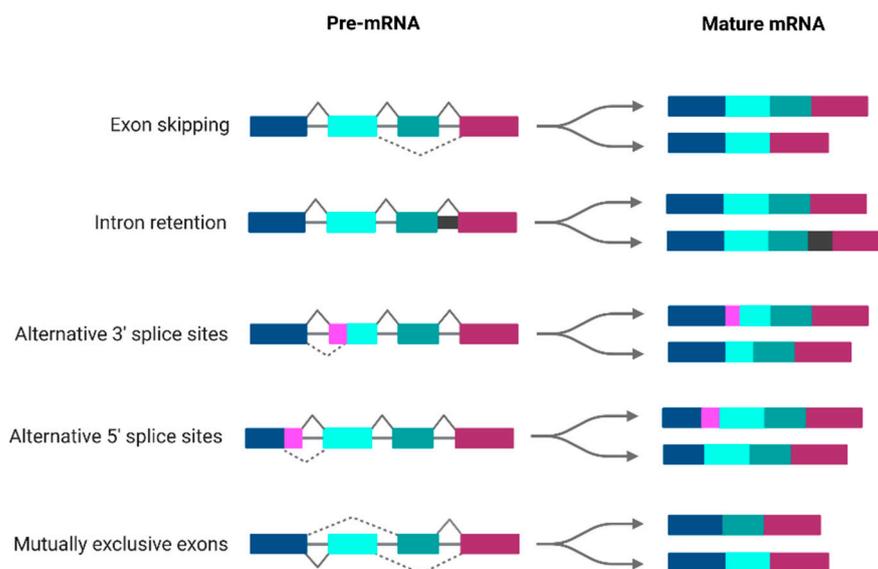


Figure 5. An overview of some of the most prominent types of alternative splicing. Exon skipping: This process removes certain exons and their adjacent introns from mRNA prior to translation. Intron retention: non-coding regions of a gene are retained in the final mRNA transcript. Alternative 5' or 3' splice sites: The exons join at alternative 5' or 3' splice sites. Mutually exclusive exons: two (or more) splicing events are not independent, but are executed or disabled in a coordinated manner.

Interestingly, most genes encoding proteins of nonpathogenic fungi, such as *S. cerevisiae* and *C. albicans*, have a simple gene structure with only one intron, whereas genes of pathogenic fungi, such as *Cryptococcus neoformans*, contain multiple introns [95,102–104]. However, the specific function of fungal introns in pathogenicity or signaling remains unclear. Intron retention is the most common pattern of AS [103,105]. The percentage of genes containing intron ranges from 2.5 % (*Candida glabrata*) to 99 % (*C. neoformans*) [104]. Annotations of fungi in public databases typically include only one or two transcript isoforms per gene [105,106]. Over 20 % of the genes in *Magnaporthe oryzae*, the causal agent of rice blast disease, undergo AS [92]. However, a recent study report has shown that the PTEN gene (*MoPTEN*), a homolog of the human dual-phosphatase tumor suppressor, has two protein isoforms that differ in their lipid and phosphatase activity. One isoform is essential for conidia and appressorium formation, while the other is required for the invasive hyphal growth in rice grains [100]. Consequently, different isoforms of this protein are of use in different stages of the pathogenic life cycle. Host cell invasion by *M. oryzae* starts with conidial development outside plant cells, followed by conidial germination, tube elongation, maturation and differentiation into the dome-shaped appressorium (isoform 1). A successful development of the invasive hypha after penetration will determine the severity of colonization and, thus, the fate of neighboring cells (isoform 2) [107].

In conclusion, the number of reports including AS in fungi are increasing rapidly, consistent with the evidence of the role of AS in essential regulatory mechanisms, as described in higher eukaryotes. However, accurate isoform prediction, identification and biological characterization remains a key issue for a better understanding of the signal diversity in fungi.

6. Multistep Phosphorelay Systems

It is important to take a deeper look into the perception, transduction and processing of signals within the living cells in order to understand the molecular mechanisms underlying the adaptation of microorganisms toward changes in the environment [108,109]. Whereas signaling processes in prokaryotic organisms are achieved in a two-component system, eukaryotic organisms have developed a more complex multistep phosphorelay system

(MSP) [110]. The detection of environmental changes and the signal transduction in both of these signaling systems occurs by phosphorylation through a phosphoryl group transfer within a signaling cascade [110–113]. External stimuli are perceived by a histidine protein kinase (HK) within the prokaryotic two-component system and are then transmitted to a response regulator protein [114,115] (Figure 6A).

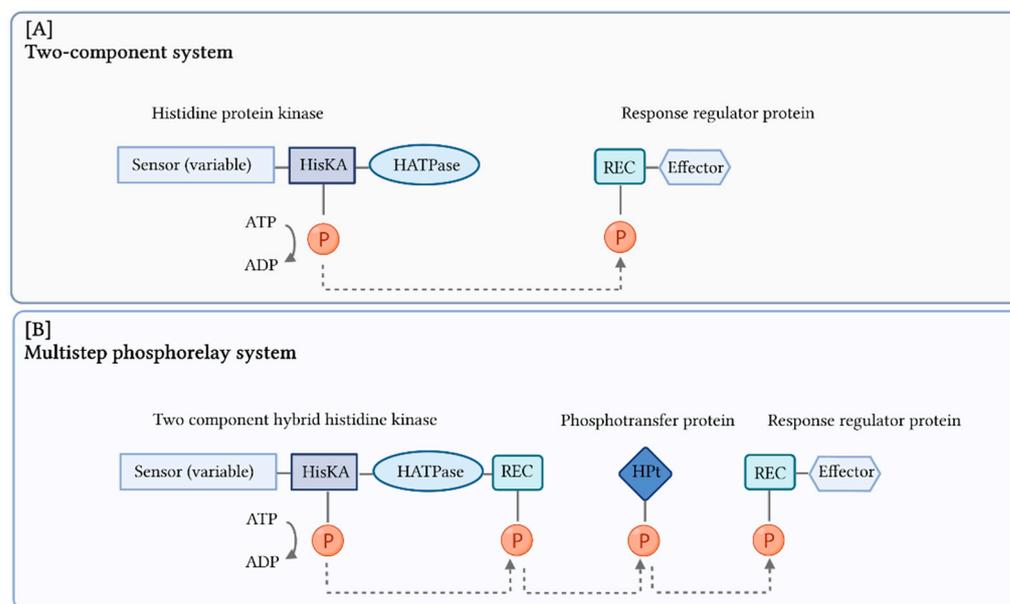


Figure 6. Schematic representation of the prokaryotic two-component system (TCS) and the eukaryotic multistep phosphorelay system (MSP). (A) For the two-component system, the phosphate transport is shown from the histidine kinase phosphoacceptor domain (HisKA) of the histidine protein kinase to the signal receiver domain (REC) of the response regulator protein. (B) The MSP system includes additional regulatory steps: the phosphate is transferred from the HisKA of the two-component hybrid histidine kinase to a REC domain within the same protein and is subsequently transferred via a phosphotransfer protein to the response regulator protein. The phosphate transfer is indicated by arrows.

By contrast, the more complex eukaryotic MSP senses and transmits external changes by the use of different but also more components: a two-component hybrid histidine-kinase (HHK), a phosphotransfer protein and a response regulator protein [111,112,116] (Figure 1). The main difference between the prokaryotic two-component system and the eukaryotic MSP is the HHK containing an additional receiver domain compared to the simpler architecture of the HK from prokaryotes. Additionally, a phosphotransfer protein is working between the HHK and the response regulator, refining but also complicating the signaling process [117,118]. Kinases phosphorylate proteins by using ATP as a phosphate donor and are named and categorized based on the aa residue they phosphorylate [118,119]. These specific aa residues are serine, threonine, tyrosine or histidine [120].

The transfer of the phosphoryl group within the MSP is from His-Asp-His-Asp [118,119,121]. The HHKs are the primary sensor proteins of the signaling cascade, with variable sensory domains at the N-terminus (e.g., HAMP or HAMP-like linker domains (poly-HAMP)), an HK domain with an autophosphorylation site [122–124] and a Histidine similar ATPase catalytic domain (HATPase domain). The C-terminal response regulator domain (REC) within the HHK contains the Asp phosphoacceptor residue [124]. The next step is the transfer of the phosphate group from the Asp to the Histidine residue of the histidine containing phosphotransfer domain (HPT) of the phosphotransfer protein and, in the last step of the phosphorelay system, to the Asp of the REC within a response regulator protein (Figure 6) [114]. The HPTs are attached to HKs at the C-terminal end in prokaryotes. By contrast, eukaryotic HPTs are separated as an individual protein that can communicate

between HK and RR, and shuttle into the nucleus and back to the cytosol. Hence, it serves as a mediator protein between the two units and is responsible for interacting with proteins or signaling pathways in addition to the MSP [121]. The first identification of an MSP in a signaling pathway was documented in the yeast *S. cerevisiae*. This MSP, with the HHK Sln1p and the phosphotransfer protein Ypd1p, is known to be part of the HOG pathway [123]. In contrast to the single HHK coding gene *SLN1* in *S. cerevisiae*, the genomes of filamentous pathogenic fungi possess multiple HHK-coding genes [111], where the HHKs are widespread, for example, in *A. nidulans*, *Botrytis cinerea*, *C. albicans*, *Cochliobolus heterostrophus*, *Fusarium verticillioides*, *Neurospora crassa* and *M. oryzae* [112].

Although the MSP within the HOG pathway is one of the signaling pathways most studied in fungi, the exact molecular mechanisms of phosphotransfer are not yet fully understood and documented. One example is the activation of the HOG pathway within the filamentous fungus *M. oryzae* by osmotic stress, which triggers cytosolic MoHog1p via phosphorylation at T171 and Y173 in the dual phosphorylation motif [125]. Subsequently, MoHog1p migrates into the nucleus, starting the cellular stress response [126]. Whereas some of the details concerning the phosphorylation pattern in the HOG pathway have already been identified in *M. oryzae*, signal perception and transformation of extracellular signals into phosphorylation at the sensor HHK MoHik1p remains unclear [123]. The exact aa positions of the phosphorylation events at the HHK differ slightly between organisms but are comparable on the protein level by blast. An example of different aa position can be illustrated with Nik1p in *C. albicans* and MoHik1p in *M. oryzae*. The phosphotransfer, for example, in the HKK Nik1p in *C. albicans* occurs from aa H510 within the HisKA domain to aa D924 within the REC domain [127,128]. The His-Asp phosphorylation pattern within a HKK in *M. oryzae* is located at aa position H736 in the HisKA domain [108,122,124], and the phosphoryl group is transferred to the phosphoacceptor at position D1153 in the REC domain. The aa position His69 is predicted to play an important role in the phosphoryl transfer activity of the HPt domain within the phosphotransfer protein Ypd1p in *C. albicans* [120,129]. The phosphoryl group is then transferred to the aspartate residue D556 in the REC domain of the response regulator protein in *C. albicans* [130]. Apart from osmoregulation, MSPs regulate key cellular regulatory processes and responses within the fungi when exposed, for example, to osmotic stress [108], oxidative stress [131,132] or light [133], and plays an important role in the regulation of all aspects of fungal physiology [109,111,120].

It is important to focus on the research of MSP in filamentous fungi not only to unravel fundamental basics in order to understand the molecular mechanisms of signaling in fungi, but it is also of high interest due to HOG pathway-specific fungicides. The HHKs MoHik1p in *M. oryzae*, Drk1p in *D. hansenii* or Nik1p in *C. albicans* are group III HHKs and, therefore, specific to filamentous fungi. This means that no homologues have been found in plants or mammals to date. These HHKs are known to be involved in the mode of action of the commercial fungicide fludioxonil [18,122,134]. Consequently, research on MSP leads to new opportunities to develop novel antifungal compounds without causing significant toxicity to other organisms in the environment [110,120,135].

7. Lipid Signaling

The study of lipid signaling networks has increased significantly in recent years. Lipid signaling, although best studied in mammalian cells, is now also appreciated in microbial cells, particularly in yeasts and molds [136]. Lipids are well characterized in mammalian cells as signaling molecules in pathophysiological processes, such as cancer, autoimmune diseases, inflammation, cardiovascular diseases and neurological disorders. Changes in the network of lipid signaling most probably results in these diseases because of the alteration in cellular homeostasis [137–145].

Lipids perform signaling and regulatory roles in plants, apart from structural roles, in various cellular processes, particularly the sphingolipids as regulatory signaling molecules. These lipids have signaling functions in programmed cell death, cell-to-cell interactions and cell wall formation, endoplasmic reticulum integrity, stomatal closure, membrane

stability, temperature-induced signal transduction, salt and drought tolerance, pollen development, cell division and growth, cell type differentiation and organogenesis, mineral ion homeostasis, cellular organization and plant-microbe interactions [146–155].

Similarly, fungal lipid signaling renders the fungi hypervirulent. That means, lipids help them to get more resistant to cell death by host or environmental stresses, e.g., to the host immune responses. The lipid signaling molecules in pathogenic fungi are mainly sphingolipids, farnesol and oxylipins [136]. They mediate specific cellular processes, such as growth, differentiation and apoptosis. Shedding light on the molecular lipid signaling events in fungi can lead to a significant understanding of the pathophysiological events regulated by lipids and open up the possibility of exploiting new means for the development of novel therapeutic strategies [156,157].

Sphingolipids are being studied in detail in the yeast-like fungus *C. neoformans*. The studies highlight that sphingolipids play a significant role in the regulation of virulence. Sphingolipids were found to regulate many cellular processes in *C. neoformans*, including the production of melanin by the formation of diacylglycerol, which affects protein kinase C1 (Pkc1p) [158,159] (Figure 7).

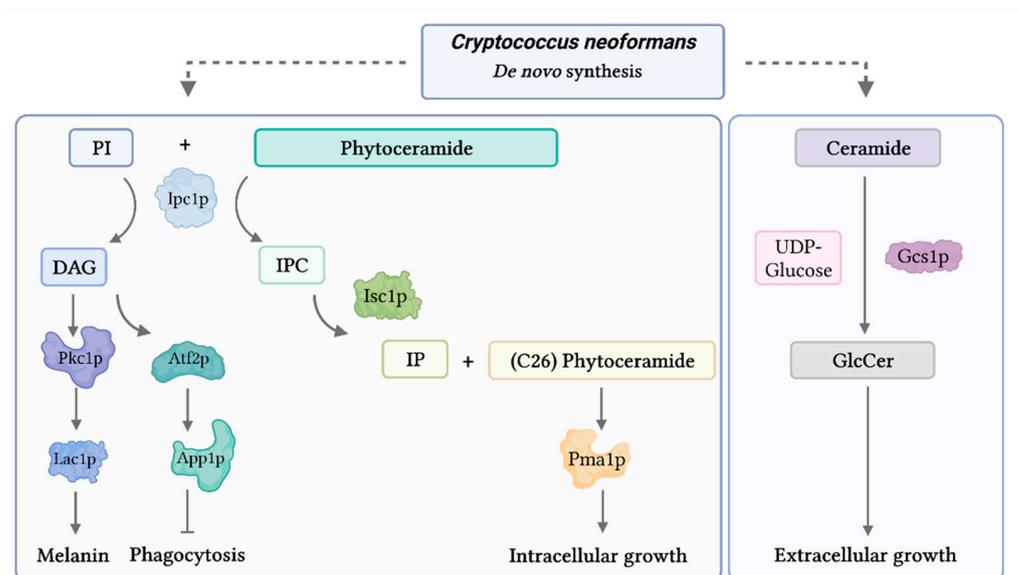


Figure 7. Regulation of lipid pathway in *C. neoformans*. PI = phosphatidylinositol; Ipc1p = inositol phosphoryl ceramide synthase; IPC = inositol phosphoryl ceramide; DAG = diacylglycerol; Pkc1p = protein kinase C1; Lac1p = laccase; Atf2p = activating transcription factor 2; App1p = antiphagocytic protein 1; Isc1p = inositol phosphosphingolipid phospholipase C; IP = inositol phosphate; Pma1p, plasma membrane ATPase 1; Gcs1p = glucosylceramide synthase; UDP = uridine diphosphate; GlcCer = glucosylceramide.

Sphingolipids modulate signaling events by the activation of transcription factor 2 (Atf2p). This process renders phagocytosis through the activation of the antiphagocytic protein 1 (App1p) [160,161]. Furthermore, they are involved in the regulation of fungal growth in the intracellular and extracellular environments by the biochemical performance of inositol phosphosphingolipid phospholipase C1 (Isc1p) and the GlcCer synthase (Gcs1p) [158,159] (Figure 7). These lipid-regulated processes strongly affect the virulence of *C. neoformans* in the lung environment with important impact on the course of the disease. Interestingly, intra- and extracellular growth of *C. neoformans* was found to be regulated by environment-specific sphingolipids, indicating that the fungus has an efficient arsenal of different lipid-molecules that might be used depending on which host cell compartment it is currently in [162]. To explain in more detail, when *C. neoformans* is located within the macrophages of its host, the expression pattern of only some specific sphingolipid-metabolizing enzyme(s) coding genes increase, such as Ipc1p. To further support this

hypothesis, it was found that when the fungal cells are shifted from an alkaline or neutral pH to an acidic pH, Ipc1p and Isc1p are required for adaptation towards the changing environment [163]. These observations make complete sense because *C. neoformans* enters the body through the respiratory tract and inhalation, finding an environment with neutral pH in the alveolar spaces and an acidic pH later on within the phagolysosome of alveolar macrophages. Thus, a better understanding of lipid signaling and how *C. neoformans* adapts to different environments will give us to a better understanding of how the pathogen interacts with the host.

8. Pheromone and Glucose Signaling

Sophisticated molecular mechanisms have evolved in microorganisms sensing the environment to respond to pheromone and nutrient signals. These environmental signals are perceived by G-protein-coupled receptors (GPCRs), which comprise the largest family of transmembrane receptors and are likely to be key mediators of host–microbial interactions in eukaryotes [164,165]. Apart from a conspicuous sequence and functional diversity, all the GPCR family members have a fundamental basic architecture that includes seven transmembrane domains and a common molecular mechanism of signal transduction [166]. The GPCRs are crucial conduits for pheromone and nutrient sensing in many fungi [165,167–170].

The involvement of GPCRs in fungal pheromone sensing has been well studied [171,172]. The fact that binding of pheromones to a GPCR, which is located on the cell surface, initiates fungal mating is also documented in detail [173,174]. Two different pheromones in ascomycetes, such as *S. cerevisiae*, are sensed and secreted by opposite mating types by two different GPCRs, Ste2p and Ste3p [175] (Figure 8).

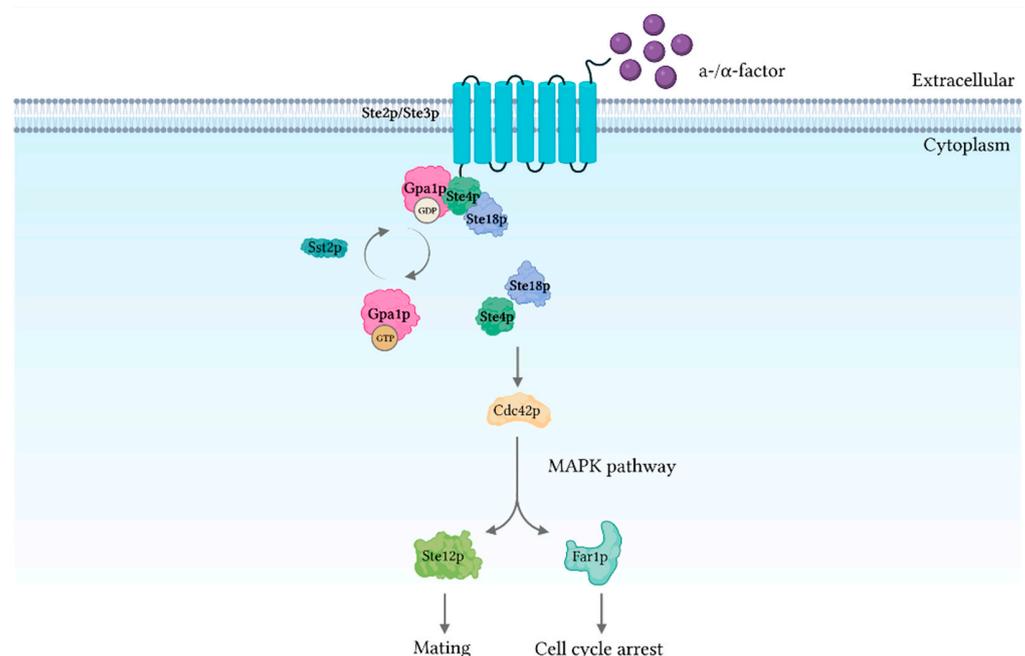


Figure 8. Schematic representation of the pheromone signaling pathway in *S. cerevisiae*. Pheromone signaling relies on the two sensors Ste2p and Ste3p that bind α - and α -factor. The signal is transported to the GPCR consisting of the $G\alpha$ protein Gpa1p and the $\beta\gamma$ subunit Ste4p and Ste18p. Ste4p and Ste18p are released and subsequently stimulate Cdc42p, which results in activation of the mating MAP kinase cascade or in cell cycle arrest.

These pheromones are named the α and α sex peptide pheromones, which trigger Ste2p and Ste3p to activate the $G\alpha$ protein Gpa1p upon GDP-GTP exchange. Gpa1p dissociates from the $\beta\gamma$ dimer of Ste4p and Ste18p and that leads to the activation of the MAPK cascade, resulting in either cell fusion with the opposite mating type or cell cycle arrest [176–178].

The architecture of the GPCRs is well conserved in the ascomycete phylum, including *C. neoformans*, *M. oryzae*, *N. crassa*, *Schizosaccharomyces pombe* or *A. nidulans* [179–181].

Glucose is one of the main carbon energy sources for many organisms and has dramatic effects on the regulation of carbon metabolism and many other properties of cells. Consequently, all organisms have evolved elaborated mechanisms to sense this molecule. Elucidation of the molecular basis of the initial glucose-sensing mechanisms has proven to be very difficult for a long time. This is largely due to the dual function as a signaling and nutrient molecule and the overlapping of the two functions [182]. Fungi have developed multiple strategies to perceive and transport glucose. One example is the GPCR sugar receptor Gpr1p in *S. cerevisiae* that senses glucose and sucrose and, subsequently, triggers Gpa2p. That results in activation of the adenylyl cyclase, the amount of cAMP increases and that activates the PKA [170] (Figure 9).

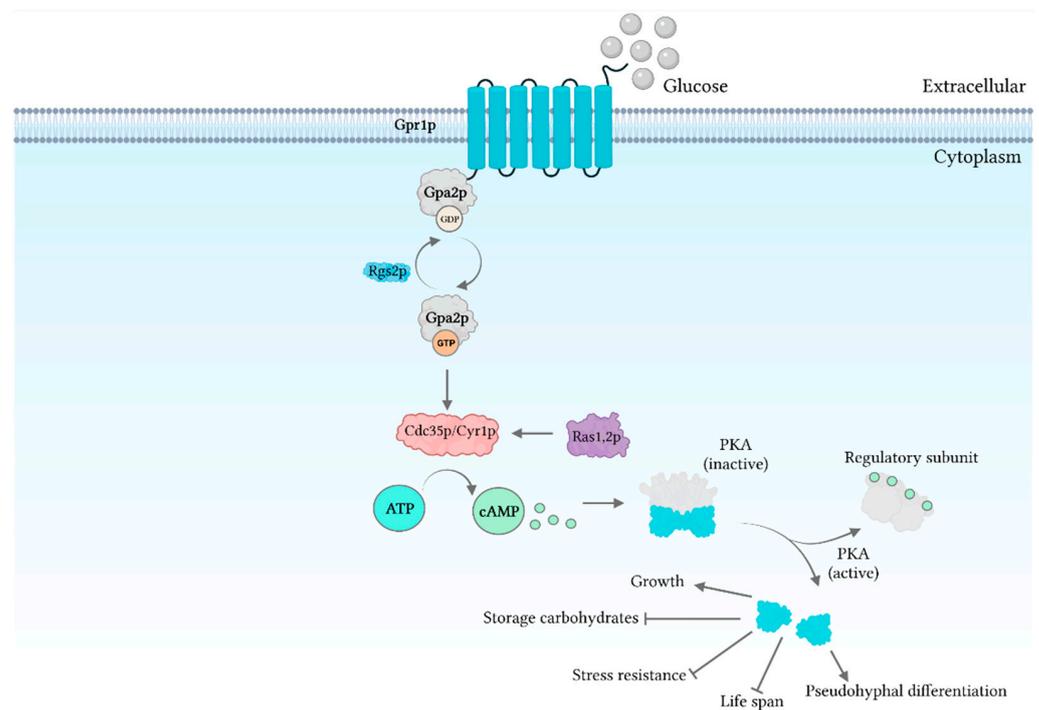


Figure 9. Schematic representation of the glucose signaling pathway in *S. cerevisiae*. The putative glucose receptor Gpr1p activates the G α protein Gpa2p. Rgs2p stimulates the GTPase activity of Gpa2p and inhibits glucose-induced cAMP signaling. Gpa2p in turn activates adenylyl cyclase (Cdc35p/Cyr1p). The function of adenylyl cyclase also depends on the Ras1p and Ras2p. Activation of the PKA by cAMP results in stimulation of growth and differentiation, loss of stress resistance, mobilization of carbohydrates and in reduced life-span.

Similarly, Gpr1p homologues in *S. pombe* (Git3p receptor) and *C. albicans* (CaGpr1p) sense glucose and activate cAMP signaling, regulating morphogenesis and yeast-to-hyphal transition [183,184]. It was documented concerning the Gpr1p homologue Gpr4p in *N. crassa* that a carbon source-dependent interaction with the G α subunit Gna1p influences cAMP production and, consequently, asexual development [185]. Many glucose-induced effects require the metabolization of the glucose molecule. Therefore, it is possible to distinguish between the nutrient function of glucose and its regulatory or signaling function: most glucose-induced signal transduction pathways apparently require no metabolization for their activation [182]. In line with this, apart from the GPCRs, *S. cerevisiae* also possesses a family of hexose transporters (Hxts) that are involved in sugar sensing or transport [186]. The existence of multiple low- and high-affinity Hxts allows cells to adjust their glucose uptake or metabolism in response to changing environmental conditions to adjust cellular physiology and growth [166]. All members of the HXT family contain 12 putative

transmembrane domains and some prominent examples are the sugar transporter-related genes SNF3, RGT2 or HXT1–17, [187]. This also highlights the central role of transport in the glucose-sensing process. Interestingly, Snf3p and Rgt2p, were found to be related to transporters but also function as sensors of extracellular glucose to regulate the expression of HXT genes [188]. That somehow distinguishes these sensors from other common Hxts. The use of transporter-like proteins as nutrient sensors may be a more common strategy in eukaryotic cells and is reviewed in reference [182].

9. Light Sensing

Light covers almost all above-ground areas on earth and represents one major driving force for adaptation and evolution. It can be both a negative and positive stimulus, since it has harmful effects, particularly at ultraviolet wavelengths, but also provides a signal to sense the environment [166]. An indisputable advantage to studying light signaling is that light behaves at light speed; the application is easy and quickly stopped, facilitating the study of stimulus-response relationships. Light sensing is conserved throughout the evolution of all the kingdoms of life, thereby, controlling important physiological and morphological responses [189]. Fungal light sensing is a good example of signal transduction in eukaryotes, and enables fundamental knowledge about the molecular basis of how cells respond and react to environmental stimuli [133]. Fungi use specialized proteins, so-called chromoproteins, to perceive blue, green, red, far-red and near-ultraviolet light. They ‘see’ multiple colors of light by means of different photoreceptors, for example phytochromes for red light, cryptochromes and the prominent White Collar proteins for blue light or opsins for green light [133]. The red light receptor phytochrome is found in the nucleus and cytoplasm and is linked to other signaling proteins [190,191], whereas the blue light photoreceptors reside in the nucleus, directly regulating the transcription of light-dependent genes [192]. The opsin photoreceptor for green light is a transmembrane protein, and it is still unclear how signaling takes place exactly [189,193].

Light signaling was found to be tightly linked to signal transduction pathways responsible for cellular differentiation, sporulation, primary metabolism, secondary metabolism or the production of hydrolytic enzymes [194–197]. In addition, light regulates developmental differentiation, such as spore germination, vegetative growth or the development of sexual reproductive structures [133].

The molecular mechanisms of fungal light signaling have been studied intensively in the filamentous fungus *N. crassa*, since White Collar-1 (WC-1) was identified as the first fungal photosensor in this fungus [166]. The WC-1 is part of the White Collar complex (WCC), which is composed of WC-1 and WC-2 and essential for light sensing in *N. crassa* [198]. Biochemical characterization of WC-1 revealed in the beginning that this protein is a blue light photoreceptor [199]. Subsequently, it was found that the blue light responses are the induction of sexual development and sporulation, the synthesis of carotenoids and the control of the circadian clock. All these responses are reliant on the products of WC-1 and WC-2. The WCC system has been intensively studied with focus on how the clock protein frequency (FRQ) and interacting factors are controlled and regulated by the WCC [200,201]. The WC-1 features a transactivation (TAD) domain, two classic Per-Arnt-Sim (PAS) domains (required for dimerization), a light-, oxygen- and voltage-sensing (LOV) domain (which was found to be dispensable for clock function), a DNA binding (DBD) domain and a zinc-finger (ZnF) domain required for DNA binding; WC-2 has PAS and ZnF DNA-binding domains [200,202]. A structural change occurs in the WC-1 protein upon blue light perception. In more detail, a connection between the flavin and a nearby cysteine on the molecular level leads to protein structure changes, resulting in photoreceptor activation [203]. The dimer, which is formed by WC-1 (the blue light photosensor) and WC-2 (the transcriptional activator), translocate into the nucleus and is recruited onto the promoter sequences of target genes (LRE: Light Response Elements) in order to activate their expression [204]. In short, WC-1 and WC-2 proteins dimerize at their PAS domains forming the WCC com-

plex [205,206], which, in turn, heterodimerizes upon light and mediates the light responses by starting the transcription of light-inducible genes [189,207] (Figure 10).

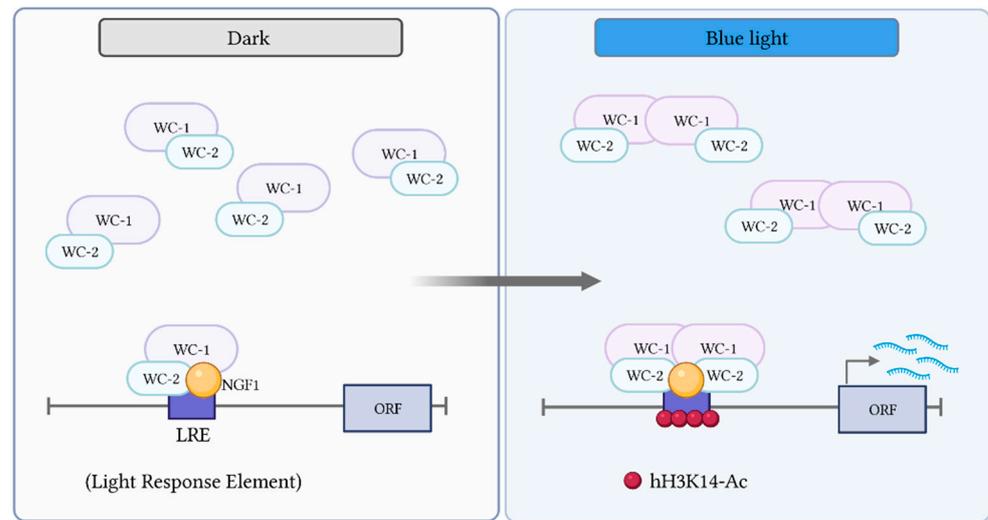


Figure 10. A simplified model for the activation of transcription by light and photoadaptation in *N. crassa*. In the dark, WC-1 and WC-2 are dimers. Light reception by the WC-1/WC-1 dimer should trigger the formation of a WCC-heterodimer, which in turn leads to chromatin remodeling through the histone acetyltransferase NGF-1 at the light response element, and the activation of gene transcription. The acetylated histones hH3K14-Ac are shown by red balls at the site of promoter binding.

Additionally, the DNA motif GATN repeats (N stands for any nucleotide) are known to be consensus sequences within the promoter regions of these light-dependent genes, but the molecular mechanism that controls the transcription during the light/dark transition it is still not understood completely. Chromatin modifications regulated by WCC in response to light are involved in the induction of these light inducible genes. Light induces the acetylation in the promoter region of histone H3-K14, which is essential for the induction of these genes [208]. This K14-acetylation is mediated by the histone acetyltransferase NGF-1. The latter interacts with WC-1 in the dark, and it was found that light promotes the activation of this WCC/NGF-1 complex, resulting in conformational changes in the WCC architecture (converting it to 'on'). Consequently, the acetyltransferase activity of NGF-1 increases [209].

Step by step, homologues of WC-1 have been identified in zygomycetes [210,211], basidiomycetes [212] and other ascomycetes [192,213]. This information extends the function of WC-1 homologues in light signaling across the fungal kingdom.

The question arises: why do fungi evolve so many different photoreceptors? Do fungi need to distinguish different wavelengths, having up to 11 photoreceptors, as described in *B. cinerea*, with 3 phytochromes, 6 blue light receptors and 2 opsins [214]? The major problem of answering this question may be our limited knowledge of the biology of fungi, since most experiments so far have been restricted to laboratory conditions [189]. To explain in more detail, light signals do not only mediate an 'on' or 'off' answer to initiate a biological response. The example of phytochromes illustrates that it is the ratio between the P_{red} and $P_{far-red}$ forms which is used to 'sense' the daytime. The use of different photoreceptors is important in different habitats and, thus, may be essential for competing in nature. It certainly makes sense, since the wavelengths responsible for green light, for example, dominate in forests, whereas these for red light penetrate soil deeper than these for blue light [189].

10. Concluding Remarks and Future Perspective

Signaling receptors and the related signaling pathways in fungi have been increasingly studied in the last years, and the more information was collected, the more questions have opened up. Thus, it is not surprising that actual knowledge does not yet allow us to present an exhaustive review encompassing all aspects of the molecular mechanisms of fungal signaling.

One question that comes up over and over again is about the relevance of the limited number of signaling proteins being present in one fungus with regard to the extremely high number of environmental signals to be processed. One major finding in the last years is functional pleiotropy of many molecular components in signaling networks. A lot of signaling proteins do not have just one function, but are involved in plenty of cellular processes, as explained for the p38 MAPK Hog1p in this review. Molecular mechanisms of fungal signaling should not be seen as a kind of limited ‘on/off’ mapping but rather integrate dynamic time- and intensity-based events to regulate and control cellular processes. Despite the fact that signaling pathways and signaling proteins are very important in the biology of fungi, many of them are still not characterized sufficiently. As a consequence, future research has to focus on this topic in order to close the gaps and lead to a better understanding of how signaling proteins encrypt information, coordinate different transmission routes and deploy response to various environmental stimuli. Apart from the molecular mechanisms of fungal signaling presented in this review, highly interesting signaling processes and (putative) new signaling molecules have been found in the last years. Among the most promising and scientific relevant candidates to be studied are chitosan-sensing [215], nitric oxide sensing [216] and iron–sulfur signaling [217].

In the end, for most if not all of the signaling pathways and components known so far, a dynamic time- and intensity-based comprehensive characterization will pave the way to answer one of the most important questions of cellular signaling: how can the huge number of different signals surrounding living cells be recognized, processed and transmitted by a limited number of signaling proteins?

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