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*Review article*

# Molecular mechanisms of fungal signaling

**Stefan Jacob** [1,*], **Sri Bühring** [1] **and Katharina Bersching** [1]

[1] Institute of Biotechnology and Drug Research gGmbH, Hanns-Dieter-Hüsch-Weg 17, 55128 Mainz;
* Correspondence: jacob@ibwf.de

**Definition:** Biochemical signaling is the key mechanism 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 activates multiple effectors, a distinct effector can be activated by numerous stimuli and signals triggered by different stimuli are often transduced via shared network components. This very compact and concise review sheds light on the most important molecular mechanisms of cellular signaling in fungi.

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

## 1. Introduction or History

Adaptation and resilience to environmental changes is a prerequisite for cells and organisms to live, survive and evolve. The propagation of signaling systems in three kingdoms – Bacteria, Archaea and Eukarya – occurs by the horizontal transfer of bacterial genes and the coevolution of the components of the respective systems [1][2][3][4]. 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 prokaryotes 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 sensor (receptor), which specifically recognizes a signal molecule; ii) a signal transducer/transport, which is linked 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. 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 [5][6]. 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 [7][8][9][5].

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 [10]. 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) [11][12] (Figure 1).

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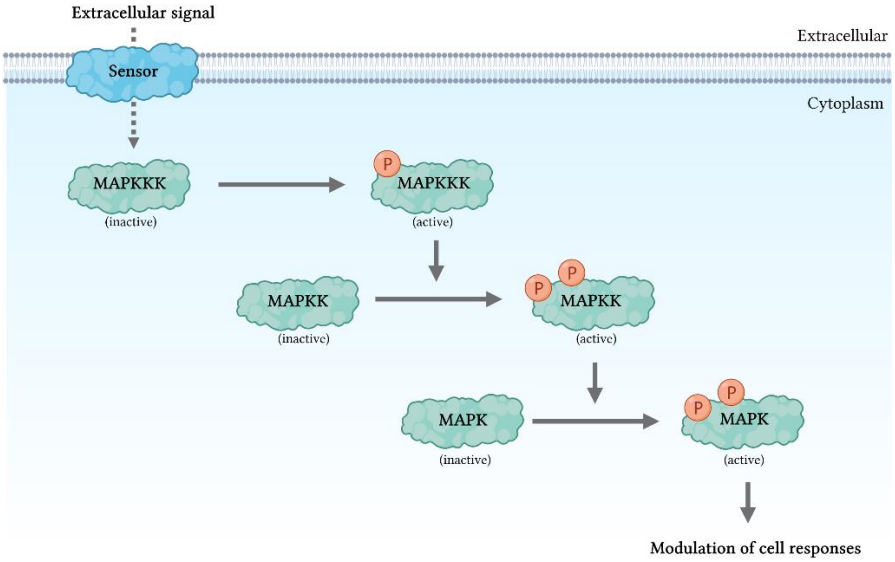


**Fig.1: Schematic representation of MAPK signal transduction cascade.** An extracellular signal is received by a membrane-located sensor. The activation of the MAP kinase module (MAPKKK activates MAPKK, activates MAPK) by the sensor may take place via intermediate steps and by different routes. The modulation of cell responses by the active MAPK may activate other protein kinases, phosphorylate cytoskeletal components or the MAPK translocate to the nucleus and activate 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 [13] [9] [14]. The MAPK suffers conformational rearrangements upon phosphorylation that strongly enhance the catalytic activity and a 1,000–50,000-fold increase in activity is not uncommon [15] [6]. 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 αC-helix [16] [17]. 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 [15].

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 [18] [19] [20] [21]. 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 [22] [23] [18] [24] [25]. 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 [26] [27]. 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 [28][29][30] [31] [32]. 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 [33]. 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 TGFβ-activated protein kinase (TAK)-1 mediated signaling than at Tyr182 [30]. These observations point to a complex but only partially understood imagination of regulatory

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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 [34]. The cAMP regulates a variety of physiological processes in eukaryotic cells and is produced in response to extracellular stimuli, such as hormones [35][36] [37].

The best defined target of cAMP in mammalian cells and the eukaryotic model organism budding yeast *Saccharomyces cerevisiae* is the cAMP-dependent protein kinase A (PKA), which mediates most, if not all, physiological effects of cAMP in fungi and other multicellular eukaryotes [38] [39] [40]. In a classical cAMP signaling pathway, a specific extracellular signal is sensed by a transmembrane cell surface receptor and transmitted into cells via heterotrimeric G-proteins composed of $\alpha$, $\beta$ and $\gamma$ subunits [41] [42] (Figure 2).

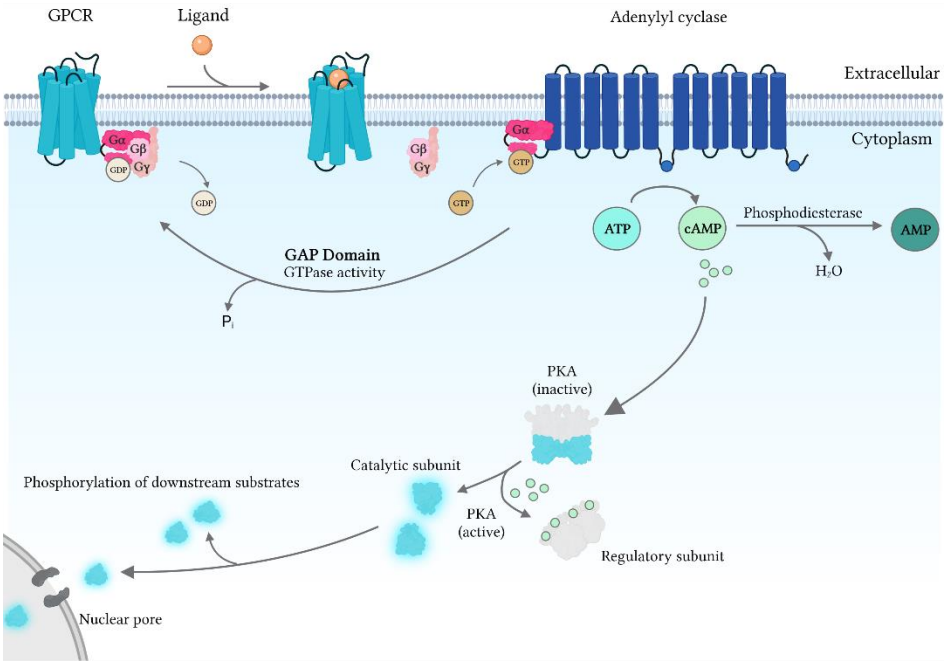


**Fig.2: Schematic representation of cAMP and PKA signaling pathway in *Saccharomyces cerevisiae*.** Activation of the G-protein-coupled receptor (GPCR) by the ligand leads to the activation of adenylyl cyclase which in turn triggers GTPase-activating proteins (GAPs) with GTP hydrolysis activity to stimulate 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 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 [41] [43] [44] [45] [46]. Subsequently, either the G$\alpha$ or 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 [47] [48] [49]. The relative activities of the biosynthetic enzyme adenylyl cyclase and the degradative enzyme phosphodiesterase influences the cellular 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 holoenzyme is a tetramer comprised of two regulatory and two catalytic subunits in the inactive state under non-inducing conditions when the cAMP level is low. Both subunits are highly conserved among eukaryotes and fungi [42]. Upon inducing conditions, when

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cAMP levels increase, the binding of cAMP to the two PKA regulatory subunits results in a conformational change that triggers dissociation of the tetramer and release of the catalytic subunits. Consequently, these catalytic subunits start to freely phosphorylate target substrates, including transcription factors or metabolic enzymes. Although the cAMP signaling cascade is remarkably conserved in different fungi, PKA can either activate or inhibit transcriptional activators or repressors to regulate or control downstream events [50][51][37].

The cAMP pathway in filamentous saprophytes appears to play an integral role in vegetative growth and sporulation, with possible connections to mating. Infection-related morphogenesis includes the formation of appressoria, invasive hyphae, sclerotia differentiation and sporulation [42]. Thus, cAMP regulates virulence and morphogenesis in a wide variety of fungi, including the plant pathogens. The cAMP signaling in saprophytic yeasts, such as *S. cerevisiae*, is involved in nutrient sensing and regulates pseudohyphal differentiation in response to nitrogen-limiting conditions [52] [37] [53] [54] [55]. The cAMP mediates the effects of glucose on gluconeogenesis and spore germination in *Saccharomyces pombe*, and regulates mating in response to either glucose or nitrogen starvation [37] [37] [56]. It regulates hyphal growth polarity and morphogenesis, conidiation and spore germination in the model filamentous fungi, such as *Neurospora crassa* and *Aspergillus* species [57] [58] [59] [60] [61].

## 4. Quorum sensing

Microorganisms living together in high numbers need to communicate with each other. Quorum sensing (QS) is a mechanism of microbial communication dependent on the cell density that governs highly important developmental decisions. In order to achieve cell-cell communication, microorganisms release and monitor molecules called QS molecules (QSMs) that control their biological activities and behaviors [62]. The concentration of these molecules increases proportionally to the population and, after reaching a critical threshold, a regulatory response is triggered, leading to the coordinated expression or repression of QS-dependent target genes [63]. 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 [64]. Subsequently, QS was found in many bacteria regulating important processes, including biofilm formation, secretion of virulence factors, sporulation and biosynthesis of antibiotics [65] [66] [67] [68] [69] [70] [71].

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 [65]. The discovery of filamentation control in the pathogenic fungus *Candida albicans* by the QSM farnesol promoted the phenomenon of QS in fungi as well [72]. Farnesol was the first QSM isolated from a eukaryotic microorganism [73] [74], but it was rapidly followed by the identification of the QSMs phenylethanol, tyrosol and tryptophol [63] [75] [76]. Since then, the role of QSMs in fungi has been widely studied in both yeasts and filamentous fungi, for example, *Saccharomyces cerevisiae*, *Candida albicans*, *Candida dubliniensis*, *Aspergillus niger*, *Aspergillus nidulans* and *Fusarium graminearum* [73] [63] [77] [78].

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 [79]. 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 [80]. 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 [81] [80]. 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 [82] [83] [84]. Consequently, yeast cells at a high population density produce more aromatic alcohols per cell than yeast cells at a low population density [82] [80]. 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 [65] [80]. The glycosylphosphatidylinositol-anchored cell surface flocculin protein Flo11p is essential for filamentous growth [85] [86] [87]. *S. cerevisiae* strains with inactivation of either FLO8 or TPK2 do

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not form filaments upon the presence of PheOH and TrpOH [80]. 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 [88]. 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 [89]. 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 [90] [91] [92] [93]. 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 snRNPs contain one snRNA (small nuclear RNA) and several proteins [94]. The molecular splicing process is a two-step transesterification reaction that removes introns as lariat intermediates (looped structures) and ligates the remaining exons [95] [96].

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).

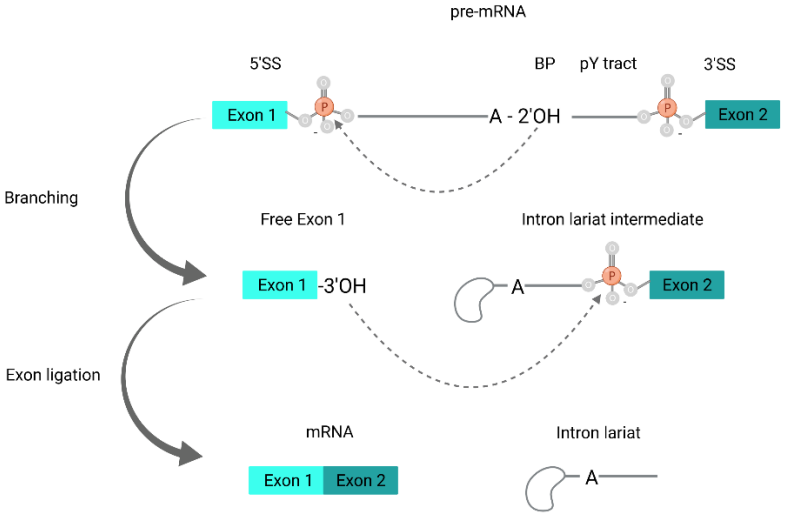


**Fig.3: Two-step transesterification mechanism of pre-mRNA splicing.** In the branching step, the 2′-OH of the branch point (BP) adenine of exon 2 attacks the phosphate of the guanine at the 5′ end of the 5′ splice site (5′SS) of exon 1. During exon ligation, the 3′-OH of the free exon attacks the phosphate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

The first step of the splicing process is called branching and entails the nucleophile 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) [97] [98] [99] [100]. Thereby, the spliceosome assembles the different exons in a stepwise manner (overview in Figure 4).

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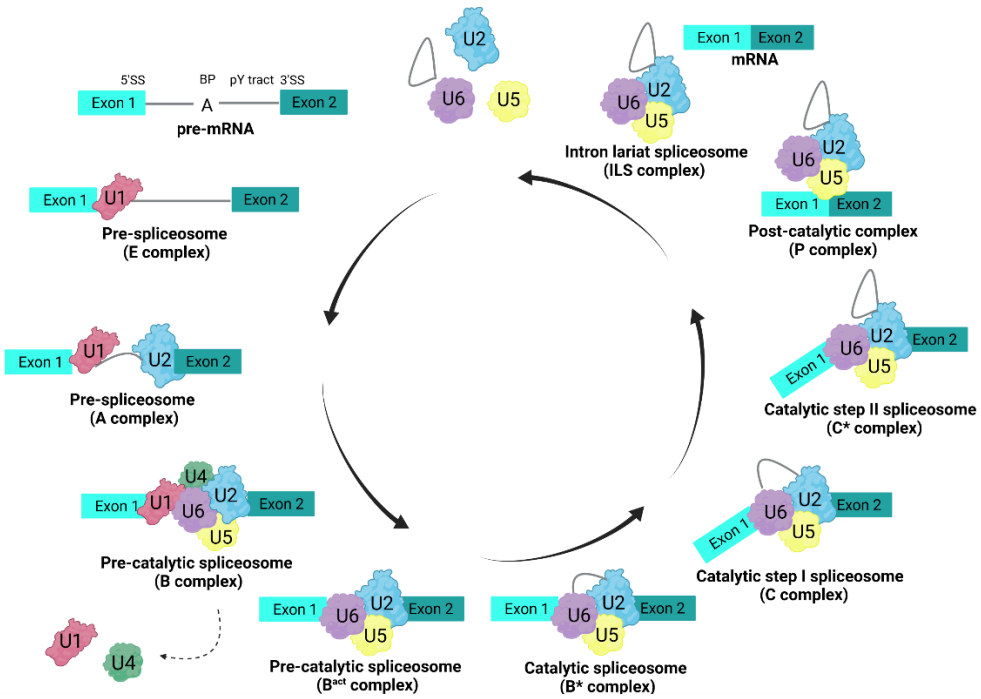


**Fig.4: Assembly and the catalytic cycle of the spliceosome.** Initially, the 5′SS, BP and 3′SS are first recognized by the U1 small nuclear ribonucleoprotein (snRNP), forming a pre-spliceosome (E complex). The U2 snRNP attaches at exon 2 to subsequently form the A complex, which associates with the 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.

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) [101]. 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 [102] [97] [103] [104] [105]).

About 95 % of genes containing intron in humans are alternatively spliced, resulting in approximately 100,000 splicing decisions [106] [107]. 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 [108] [109]. 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).

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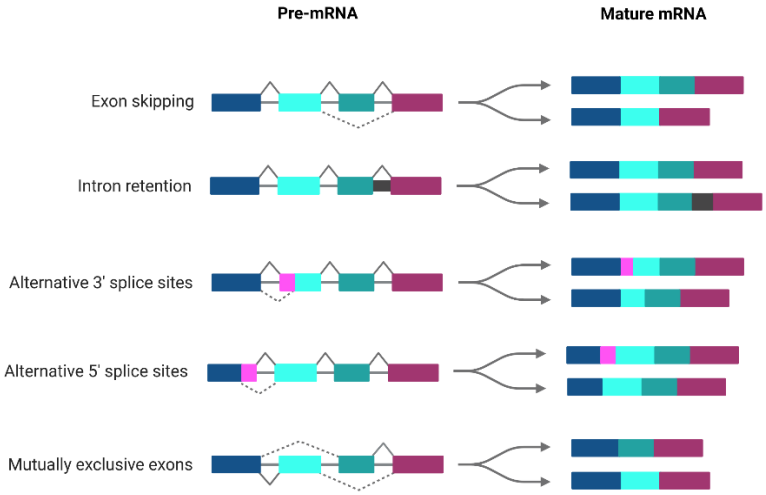


**Fig.5: An overview of some of the most prominent types of alternative splicing.** Exon skipping: This process removes certain exons and their adjacent introns from mRNA prior to translation. Intron retention: non-coding regions of a gene are retained in the final mRNA transcript. Alternative 5' or 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.

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 [110] [111]. The fungal kingdom is a species-rich group of organisms with genome sizes ranging from 10 to 90 Mb [112] [113] [114]. According to the most recent studies, Ascomycota, Basidiomycota, and Deuteromycota have a higher incidence of AS than previously thought [115] [116] [117] [113] [118] [119] [120]. Various physiological processes are affected by AS, such as growth, a pathogenic lifestyle, dimorphic changes and stress adaptation [121] [113] [122] [118] [123] [120] [115] [124] [125]. 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 [125] [126].

Interestingly, most genes encoding proteins of nonpathogenic fungi, such as *Saccharomyces cerevisiae* and *Candida albicans*, have a simple gene structure with only one intron, whereas genes of pathogenic fungi, such as *Cryptococcus neoformans*, contain multiple introns [127] [119] [128] [129]. However, the specific function of fungal introns in pathogenicity or signaling remains unclear. Intron retention is the most common pattern of AS [128] [130]. The percentage of genes containing intron ranges from 2.5 % (*Candida glabrate*) to 99 % (*C. neoformans*) [129]. Annotations of fungi in public databases typically include only one or two transcript isoforms per gene [130] [131]. Over 20 % of the genes in *Magnaporthe oryzae*, the causal agent of rice blast disease, undergo AS [115]. 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 [124]. 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) [132].

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.

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## 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 [133] [134]. Whereas signaling processes in prokaryotic organisms are achieved in a two-component system, eukaryotic organisms have developed a more complex multistep phosphorelay system (MSP) [135]. 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 [136][137] [135] [138]. 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 [139] [140] (Figure 6 [A]).

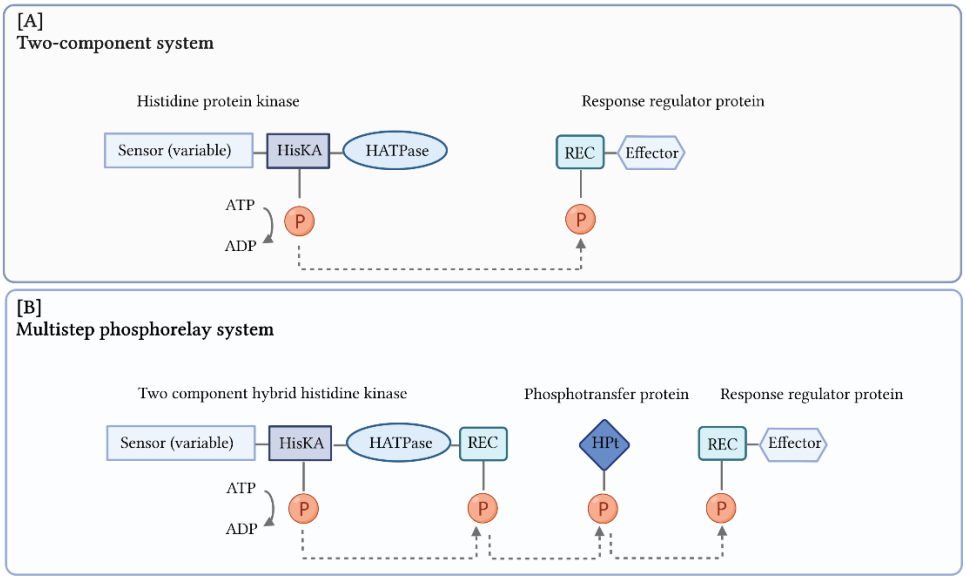


**Fig.6:** **Schematic representation of the prokaryotic two-component system (TCS) and the eukaryotic multistep phosphorelay system (MSP).** The sensor domain (variable sensor), the histidine kinase phosphoacceptor domain (HisKA), the histidine-like ATPase domain (HATPase), the signal receiver domain (REC), the histidine-containing phosphotransfer domain (HPt), and the effector domain (effector) are shown. The phosphoryl group transfer is indicated by arrows. The MSP system includes additional regulatory steps: the phosphoryl group is transferred from the HisKA to a REC domain of the hybrid histidine kinase and, subsequently, transferred via a phosphotransfer protein to the response regulator.

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 [136] [141] [137] (Figure 1 [B]). 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 [142] [143]. Kinases phosphorylate proteins by using ATP as a phosphate donor and are named and categorized based on the aa residue they phosphorylate [144] [143]. These specific aa residues are serine, threonine, tyrosine or histidine [145].

The transfer of the phosphoryl group within the MSP is from His-Asp-His-Asp [144] [143] [146]. 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 [147] [148] [149] and a Histidine similar ATPase catalytic domain (HATPase domain). The C-terminal response regulator domain (REC) within the HHK contains the Asp phosphoacceptor residue [149]. 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) [139]. 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

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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 [146]. The first identification of an MSP in a signaling pathway was documented in the yeast *Saccharomyces cerevisiae*. This MSP, with the HHK Sln1p and the phosphotransfer protein Ypd1p, is known to be part of the HOG pathway [150] [148]. In contrast to the single HHK coding gene *SLN1* in *S. cerevisiae*, the genomes of filamentous pathogenic fungi possess multiple HHK-coding genes [136], where The HHKs are widespread, for example, in *Aspergillus nidulans*, *Botrytis cinerea*, *Candida albicans*, *Cochliobolus heterostrophus*, *Fusarium verticillioides*, *Neurospora crassa* and *Magnaporthe oryzae* [137].

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 [151]. Subsequently, MoHog1p migrates into the nucleus, starting the cellular stress response [152]. 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 [148]. The exact aa positions of the phosphoylation 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 [153] [154]. The His-Asp phosphorylation pattern within a HKK in *M. oryzae* is located at aa position H736 in the HisKA domain [147] [133] [149], and the phosphoryl group is transferred to the phosphoacceptor at position D1153 in the REC domain [155]. 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* [145] [156]. The phosphoryl group is then transferred to the aspartate residue D556 in the REC domain of the response regulator protein in *C. albicans* [157]. Apart from osmoregulation, MSPs regulate key cellular regulatory processes and responses within the fungi when exposed, for example, to osmotic stress [133] [158], oxidative stress [159] [160] or light [161] [162], and plays an important role in the regulation of all aspects of fungal physiology [136] [134] [145].

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. hanseii* 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 [147] [163] [164]. Consequently, research on MSP leads to new opportunities to develop novel antifungal compounds without causing significant toxicity to other organisms in the environment [165] [159] [145] [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 [166]. 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 [167] [168] [169] [170] [171] [172] [173] [174] [175] [176].

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 [177] [178] [179] [180] [181] [182] [183] [184] [185] [186] [187].

Similarly, fungal lipid signaling renders the fungi hypervirulent (e.g. more resistant to cell death by host or environmental stresses, meaning they are more resistant to killing by the host immune responses). The lipid signaling molecules in pathogenic fungi are sphingolipids, farnesol and oxylipins [166]. They trigger and mediate specific cellular processes, such as cell growth, proliferation, apoptosis and senescence. Shedding light on the molecular lipid signaling events in

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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 [188] [189] [190]

Sphingolipids are being studied in detail in the yeast-like fungus *Cryptococcus 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) [191] [192] (Figure 7).

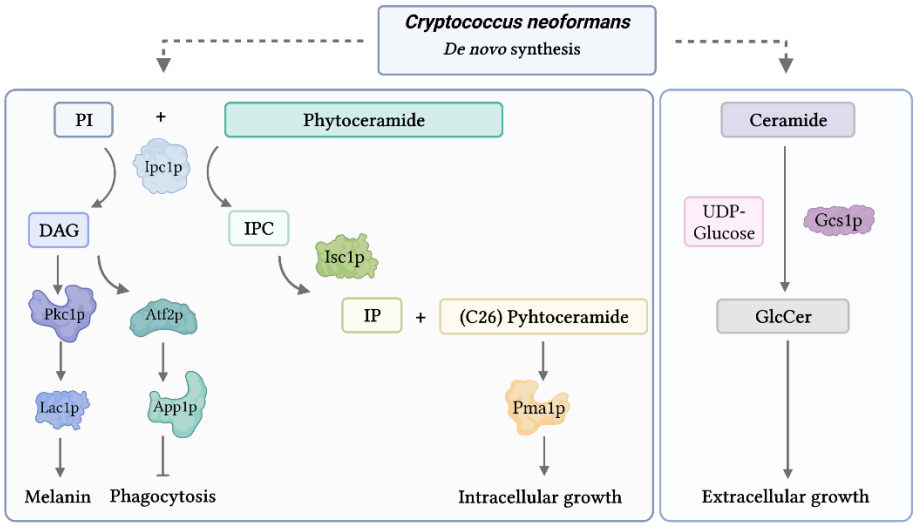


**Fig.7:** **Regulation of lipid pathway in *Cryptococcus neoformans*.** PI = phosphatidylinositol; Ipc1p = inositol phosphoryl ceramide synthase; IPC = inositol phosphoryl ceramide; DAG = diacylglycerol; Pkc1p = protein kinase C1; Lac1p = laccase; Atf2p = activating transcription factor 2; App1p = antiphagocytic 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), to trigger phagocytosis through the transcriptional activation of the antiphagocytic protein 1 (App1p) [193] [194]. Furthermore, they are involved in the regulation of fungal growth in the intracellular and extracellular environments by the activities of inositol phosphosphingolipid phospholipase C1 (Isc1p) and GlcCer synthase (Gcs1p) [192] [191] [195] [196] [197] (Figure 7). These lipid-regulated processes strongly affect the virulence of *C. neoformans* in the lung environment with an important effect on the disease outcome. Interestingly, intra- and extracellular growth of *C. neoformans* appears to be regulated by environment-specific sphingolipids, suggesting 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 [198]. 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 a alkaline or neutral pH to an acidic pH, Ipc1p and Isc1p are required for adaptation towards the changing environment [199]. These observations make complete sense because *C. neoformans* enters the body through the respiratory tract and inhalation, finding a neutral environment in the alveolar spaces and an acidic niche 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 sensed by G-protein-coupled receptors (GPCRs), which comprise the largest family of transmembrane receptors in eukaryotes and are likely to be key mediators of host–microbial interactions [200] [201].

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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 [202]. The GPCRs are crucial conduits for pheromone and nutrient sensing in many fungi [203] [201] [204] [205][206] [207].

The involvement of GPCRs in fungal pheromone sensing has been well studied [208] [209]. The fact that pheromone-binding to a GPCR which is located on the cell surface initiates fungal mating is also documented in detail [210] [211]. Two different pheromones in ascomycetes, such as *Saccharomyces cerevisiae*, are sensed and secreted by opposite mating types by two different GPCRs, Ste2p and Ste3p [212][213] (Figure 8).

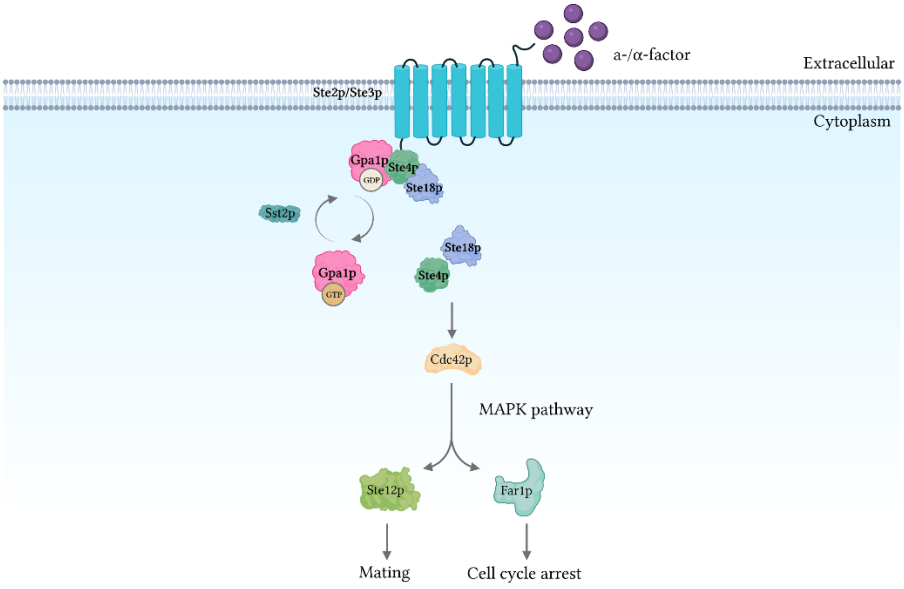


**Fig.8:** **Schematic representation of the pheromone signaling pathway in *Saccharomyces cerevisiae*.** Pheromone sensing depends on the Ste2p and Ste3p sensors that respectively bind α- and a-factor. The signal is transported to the heterotrimeric G-protein consisting of the Gα protein Gpa1p and the βγ subunit Ste4p and Ste18p. Ste4p and Ste18p stimulate Cdc42p which results in activation of the mating MAP kinase cascade or in cell cycle arrest.

These pheromones are named the a and α sex peptide pheromones, which trigger Ste2p and Ste3p to activate the Gα protein Gpa1p upon GDP-GTP exchange. Gpa1p dissociates from the βγ 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 [214] [215] [216]. The architecture of the GPCRs is well conserved in the ascomycete phylum, including *Cryptococcus neoformans*, *Magnaporthe oryzae*, *Neurospora crassa*, *Schizosaccharomyces pombe* or *Aspergillus nidulans* [217] [218] [219] [220] [221].

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 [222]. Fungi, especially yeasts, have developed multiple strategies to sense and transport glucose. One example is the GPCR sugar receptor Gpr1p in *S. cerevisiae* that senses glucose and sucrose and, subsequently, triggers Gpa2p, which, in turn, activates the adenylyl cyclase, resulting in increased amounts of cAMP and that activates the PKA [206] [223] [224] (Figure 9).

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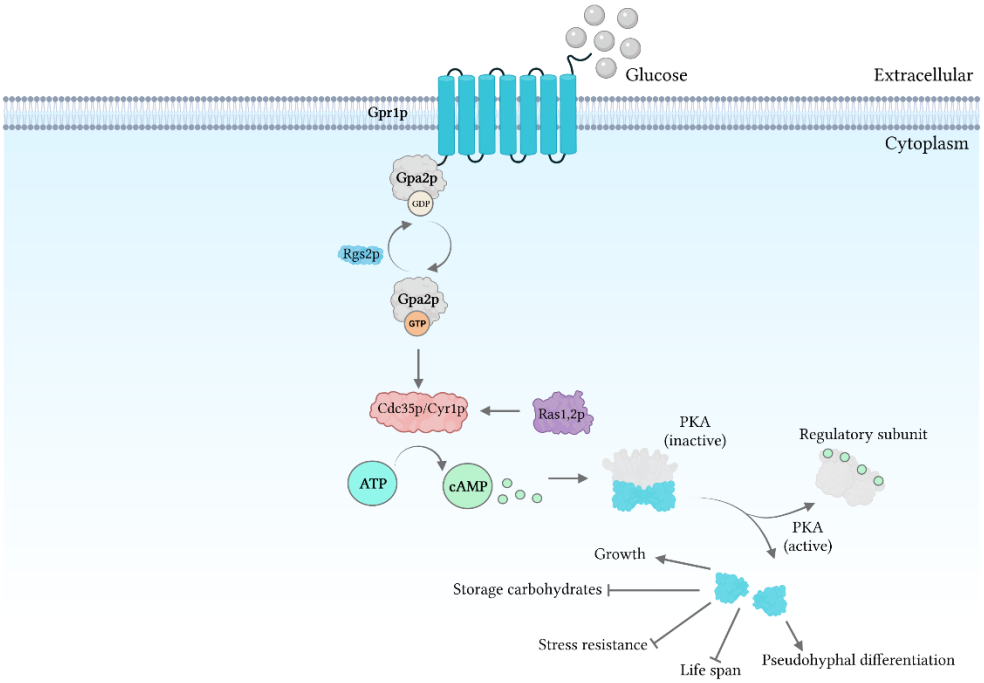


**Fig.9:** **Schematic representation of the glucose signaling pathway in *Saccharomyces cerevisiae*.** The putative glucose receptor Gpr1p activates the G$\alpha$ protein Gpa2p. Rgs2p stimulates the GTPase activity of Gpa2p and inhibits glucose-induced cAMP signaling. Gpa2p in turn activates adenylate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

Similarly, Gpr1p homologues in *S. pombe* (Git3p receptor) and *Candida albicans* (CaGpr1p) sense glucose and activate cAMP signaling, regulating morphogenesis and yeast-to-hyphal transition [225] [207] [226]. It was documented concerning the Gpr1p homologue Gpr4p in *N. crassa* that a carbon source-dependent interaction with the G$\alpha$ subunit Gna1p influences cAMP production and, consequently, asexual development [227]. 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 [222]. 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 [228][229]. 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 optimize cell growth [202]. 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, [230] [231]. 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 [232]. 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 [222].

## 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 [202]. An indisputable advantage to studying light signaling is that the stimulus light behaves at light speed: It is easily induced and quickly removed, and, consequently, facilitates the study of stimulus-response relationships. Light sensing is evolutionarily conserved throughout all the kingdoms of life, from archaea and fungi to humans, thereby, controlling important physiological and morphological responses [233] [234]. Fungal light sensing is a good example of signal transduction in eukaryotes, and its study offers fundamental knowledge about the molecular basis of how cells respond and react to environmental stimuli [235]. Fungi use specialized proteins, so-called chromoproteins, to sense near-ultraviolet, blue, green, red and far-red light. They ‘see’ light of different colors by using different photoreceptors, such as the White Collar proteins and

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cryptochromes for blue light, opsins for green light and phytochromes for red light [235]. The red light receptor phytochrome is found in the nucleus and cytoplasm and is linked to other signaling proteins [236] [237] [238], whereas the blue light photoreceptors reside in the nucleus, directly regulating gene expression [239]. The opsin photoreceptor for green light is a transmembrane protein, and it is still unclear how signaling occurs exactly [234] [240].

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 [241] [242] [243] [244] [245]. In addition, light regulates developmental transitions, such as the germination of spores or conidia, the growth of vegetative hyphae, or the development of sexual and vegetative reproductive structures [235].

The molecular mechanisms of fungal light signaling have been investigated in most detail in the ascomycete *Neurospora crassa*, since the first fungal photosensor was identified in this fungus, White Collar-1 (WC-1) [202][246]. 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* [247]. Biochemical characterization of WC-1 revealed in the beginning that this protein is a blue light photoreceptor [248] [249]. Subsequently, it was found that the blue light responses in *Neurospora* include the induction of sexual development and sporulation, the synthesis of carotenoids and the regulation of the circadian clock. All these processes require the products of the WC-1 and WC-2 genes. This system has been extensively studied with an emphasis on how the clock protein frequency (FRQ) and interacting factors are regulated by the WC-1 and WC-2 proteins [250] [251] [252]. 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 [250] [253] [254]. 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 [255] [256]. 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 [257]. In short, WC-1 and WC-2 proteins dimerize at their PAS domains forming the WCC complex [254] [258], which, in turn, heterodimerizes upon light and mediates the light responses by starting the transcription of light-inducible genes [234] [259] [260] (Figure 10).

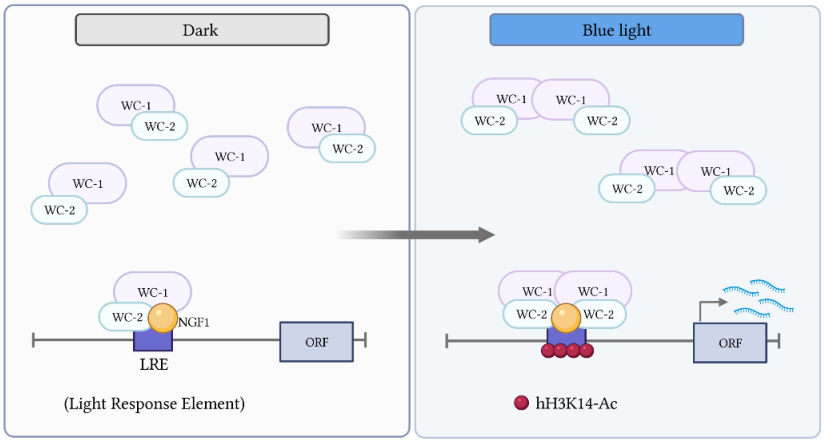


**Fig.10:** **A simplified model for the activation of transcription by light and photoadaptation in *Neurospora crassa*.** In the dark, WC-1 and WC-2 are dimers. Light reception by the WC-1/WC-1 dimer should trigger the formation of a WCC-heterodimer, which in turn leads to chromatin remodeling through 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 [261]. This K14-acetylation is mediated by the histone acetyltransferase NGF-1 (Figure 11). 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 [262].

Step by step, homologues of WC-1 have been identified in zygomycetes [263] [264] [265] [266], basidiomycetes [267] [268] and other ascomycetes [239][269]. 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 of different photoreceptors? Do fungi need to distinguish different colors, having up to 11 photoreceptors, as described in *B. cinerea*, with 3 phytochromes, 6 blue light receptors and 2 opsins [270]? 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 [234]. 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 $P_{far\text{-}red}$ 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 green light, for example, dominates in forests, whereas red light penetrates soil deeper than blue light [234].

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