Applied Microbiology Open Access

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Review Article

Arrestin Regulation in Fungi, from Yeast to Filamentous Fungi

Liang Zhou[1,2], **Xin Wang**[1,2*]

[1]*State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, Yunnan University, Kunming, China;*[2]*Key Laboratory for Microbial Resources of the Ministry of Education, Yunnan University, Kunming, China*

ABSTRACT

Arrestins are a family of scaffold proteins that can be divided into α-arrestins and β-arrestins, which play critical roles in the regulation of numerous cellular processes such as GPCR signaling. Compared with mammals, the research on fungus-related arrestin is not deep enough, and the research on fungal arrestin is mainly carried out around yeast. The main functions of arrestin revolve around GPCRs, and are also involved in pH regulation, related epigenetics, and endocytosis. This review mainly focuses on the above aspects, and focuses on the research of filamentous fungi in recent years.

Keywords: Arrestin; Rsp5; Art; Nutrient aquisition; Ubiquitination

INTRODUCTION

G Protein-Coupled Receptors (GPCRs) are the largest family of cell surface receptors known so far, and they transmit various signals from outside the cell into the cell [1]. After GPCRs are activated by agonists, their connected G protein α subunits and β, γ subunits dissociate, and the activated G protein subunits regulate adenylate cyclase, phospholipase and ion channels, etc., thereby amplifying and transmitting cells internal signal [2]. β-arrestin is an important negative regulator of GPCRs signaling pathway, and its combined action with G-protein-coupled Receptor Kinases (GRK) can reduce the sensitivity of GPCRs to agonists, resulting in receptor desensitization, regulating receptor endocytosis, signal transduction and apoptosis, etc [3].

Arrestins were first discovered as negative regulators of G protein-mediated signaling by GPCRs: they bind GRK-phosphorylated active receptors and preclude their further coupling to cognate G proteins [4]. Vertebrates have only four arrestin subtypes, two of which are specifically expressed in photoreceptors in the retina, whereas the two non-visual arrestins are ubiquitously expressed and apparently regulate hundreds of different GPCRs [5,6]. Later studies showed that, in addition to receptors, non-visual arrestins interact with dozens of other signaling proteins. Current view is that arrestins are versatile regulators organizing multi-protein signaling complexes and localizing them to particular subcellular compartments. Arrestins can exist in several distinct conformations, the best-studied being basal and receptor-bound (often termed "active"), which differentially engage various partners [7,8]. Identification of the arrestin elements engaged by each partner and construction of signaling-biased arrestins where individual functions are selectively disrupted or enhanced helps us to elucidate their biological roles in the cell [6].

Alpha-arrestins, also known as Arrestin-Associated Trafficking Adapters (ARTs), constitute a large class of proteins from yeast to humans [9,10]. Although their evolution takes precedence over their widely studied relatives in the β-arrestin family, α-arrestins are only recently discovered, so their properties are mostly unexplored. The main function of α-arrestins is to selectively recognize membrane proteins for ubiquitination and degradation, which are important factors in maintaining membrane protein homeostasis as well as global cellular metabolism [11,12]. Among members of the arrestin family, only α-arrestins have a PY motif that allows canonical binding to the WW domain of the Rsp5/NEDD4 ubiquitin ligase, followed by ubiquitination of membrane proteins leading to their vacuolar/lysosomal degradation [12,13]. The molecular mechanisms underlying the targeting, function, and regulation of α-arrestins by selective substrates remain incompletely understood. Several functions of α-arrestins in animal models have recently been characterized, including regulation of redox homeostasis, modulation of innate immune responses, and tumor suppression [14]. However, the molecular mechanisms of α-arrestin regulation and substrate interactions are mainly based on observations in the yeast *Saccharomyces cerevisiae* model [15].

G Protein-Coupled Receptors (GPCRs) are important drug targets. The latest statistics show that 33% of clinical drugs act directly on GPCRs. Therefore, GPCR research has always been an international hotspot. Since Robert Lefkowitz and Brian Kobilka,

Correspondence to: Xin Wang, State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, Key Laboratory for Microbial Resources of the Ministry of Education, Yunnan University, Kunming, China ,Tel: 0086-15812045227; E-mail: xinwang2@ynu.edu.cn

Received: 04-Aug-2022, Manuscript No. AMOA-22-18213; **Editor assigned:** 08-Aug-2022, Pre QC No. AMOA-22-18213 (PQ); **Reviewed:** 23-Aug-2022, QC No. AMOA-22-18213; **Revised:** 01-Sep-2022, Manuscript No. AMOA-22-18213 (R); **Published:** 08-Sep-2022, DOI: 10.35284/2471-9315.22.8.235

Citation: Zhou L, Wang X (2022) Arrestin Regulation in Fungi, from Yeast to Filamentous Fungi. Appli Microbiol Open Access. 8: 235.

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who won the Nobel Prize in 2012, proposed the concept of GPCR as a superfamily in 1986, a series of important progress has been made in the research on GPCR signal transduction mechanism. For example, the 1994 Nobel laureate Alfred Gilman identified the effector in the tertiary complex of GPCRs as G protein lines. Parallel to the G protein pathway, Prof. Lefkowitz found that arrestin can mediate GPCRs to perform another part of their independent functions. Therefore, G protein and arrestin are two important signaling pathways for GPCR to function. At present, the mechanism of arrestin-mediated GPCR signal transduction is still not very clear, so it brings many difficulties for the development of drugs that precisely target GPCR [16]. The existing traditional view holds that arrestin binds to phosphorylated receptors, and "graps" the phosphorylated receptors with downstream signal transduction proteins to form a complex, acting as an "adapter protein" [17].

The team carried out research work on the phosphorylation coding mechanism of receptor-arrestin interaction, discovered the phosphorylation coding mechanism of GPCR, and proposed the "flute model" theory of receptor phosphorylation [18]. However, this traditional concept often limits our cognition. Yang et al. found that arrestin not only plays a recruitment role, but also plays an important catalytic role. On the one hand, after interacting with the receptor, arrestin can activate downstream proteins through a distal conformational change. At this time, arrestin has an allosteric effect; on the other hand, arrestin can allosterically activate the downstream kinase activity, thereby act as a catalyst [19]. Further, the collaborative team combined crystallography, DeSiPher and BRET to detect that a single GPCR phosphorylation site defect can cause different conformational changes in the distal functional domain of arrestin. Finally, they found that there is a certain correlation between it and the biological function of arrestin [20].

LITERATURE REVIEW

pH regulation

Current models assume that PalF, an α-arrestin protein member, is involved in pH signaling pathway. Furthermore, the importance of the Pal/Rim pathway for fungal adaptation to environmental pH has been demonstrated in *Beauveria bassiana*, *Aspergillus nidulans*, and *Saccharomyces cerevisiae*. Seven proteins are involved in this pathway: PalH, PalI, PalF, PalC, PalA, PalB, and PacC [21,22]. Similarly, we found that deletion of the arrestin-encoded protein Arc2 in *Arthrobotrys oligospora* greatly reduced the pH tolerance of the strain [23]. Following sensing of extracellular alkaline pH, the membrane proteins PalH and PalI, which provide pH-sensing activity, bind to the arrestin-associated protein PalF. PalF is phosphorylated and ubiquitinated in a PalH-dependent manner, suggesting a possible link between PalF and environmental pH sensors. These cascades mediate the adaptation of fungi to environmental pH [21,24]. Yeast Rim8/Art9 α-arrestin mediates the recruitment of the Endosomal Sorting Complex Required for Transport (ESCRT) to the seven-transmembrane protein Rim21 in the environmental pH signaling RIM pathway. Phosphorylation of Rim8 prevents its accumulation at the plasma membrane at acidic pH, thereby inhibiting RIM signaling [25].

Regulatory effects of arrestin on GPCRs

In the biological process, numerous modifications make related proteins more powerful. Arrestin, as the "linker" molecule of related proteins, plays an important role in the biological modifications involved [26].

Ubiquitination: Nedd4/Rsp5 family E3 ligases mediate many cellular processes, many of which require E3 ligases to interact with adaptor protein-containing PY motifs. Zhu et al. found that Art1, Art4, and Art5 undergo K63-linked diubiquitination *via* Rsp5. Furthermore, they found that an exosite homologous to the E6AP C-Terminal (HECT) domain protects the K63-linked diubiquitin on the linker from cleavage by the deubiquitinase Ubp2 [27]. Members of the ART protein family consist of an arrestin fold with interspersed disordered loops. Using Art1 as a model, result showed that these looping and tail regions, although not essential for function, regulate their activity through two independent mechanisms [28].

In terms of amino acid metabolism, Ryoga et al. found that Tat2 (a high-affinity tryptophan permease) rapidly increased in a Rsp5-Bul1-dependent manner after the addition of tryptophan, phenylalanine or tyrosine in *Saccharomyces cerevisiae* degradation, while Tat1 (low-affinity tryptophan permease) was not affected [29]. It has been shown that arginine inhibits proline utilization by specifically inducing endocytosis of the high-affinity proline transporter Put4. Nishimura et al. found that the ubiquitination activity of Rsp5 is critical for arginine-induced Put4 endocytosis. What's more, they found that deletion of Art3 significantly abolished the inhibitory effect of arginine on proline utilization [30]. In *Saccharomyces cerevisiae*, endocytosis of sugar and Amino Acid Transporters (AATs) extensively reconfigures nutrient transporters on the plasma membrane in response to amino acid availability. Amino acid excess or starvation activates the complementary α-arrestin-Rsp5-complex to control selective endocytosis and accommodate nutrient acquisition [31]. In *A. nidulans*, an Rsp5 protein homologue was identified and the gene encoding this HECT ubiquitin ligase was named hulA. The final results indicated the interaction between CreD (Contains an arrestin domain and a PY motif)-ApyA (A protein containing arrestin and a PY motif)-HulA [32].

At present, there are related drugs, mostly around membrane proteins, and their pharmacological effects have been proven. Bap2, an amino acid transporter located on the plasma membrane, is endocytosed when yeast cells are treated with isoflurane, an anesthetic. Depletion of Rsp5, an E3 ligase, prevents this endocytosis, and Bap2 is ubiquitinated in response to isoflurane, suggesting a ubiquitin-dependent process. Screening of all Rsp5-binding adapters suggests that Art2 plays a central role in this process. These results suggest that isoflurane affects Bap2 through an Art2-Rsp5-dependent ubiquitination system [33].

Phosphorylation: Many plasma membrane proteins in yeast are ubiquitinated and endocytosed, which involves complex regulation. When yeast is exposed to cadmium ions, the manganese transporter Smf1 is endocytosed, which relies on Rsp5-dependent ubiquitination of specific lysines, and it also requires phosphorylation at nearby sites. Efficient ubiquitination requires Ecm21 or Csr2, two members of a family of arrestin-like yeast proteins that contain multiple PY motifs and bind to Rsp5. Ecm21 also binds to phosphorylated Smf1, providing a link between Rsp5 and its substrates [34].

To prevent spurious removal of membrane proteins, α-arrestin-mediated endocytosis was controlled by phospho-inhibition. Due to the complexity of the numerous phosphorylation sites on a single α-arrestin and the kinase/phosphatase targeting α-arrestin. To better define the signaling pathways that control the

paralogous α-arrestins, Aly1 and Aly2, Bowman et al. screened a kinase and phosphatase deletion (KinDel) library and found that TORC1 and its signaling effector Sit4 protein phosphatase and Npr1 kinase regulate phosphorylation and stability of Alys. Alys is hyperphosphorylated and destabilized in an Npr1-dependent manner when Sit4 is lost [35]. Analysis of the fission yeast high-affinity hexose transporter Ght5 by Toyoda et al., they found that it must be transcriptionally upregulated and localized to the cell surface for cell division under limited glucose. They also identified a gene encoding the uncharacterized α-arrestin-like protein Aly3/SPCC584.15c. Alpha-arrestins are thought to recruit ubiquitin ligases to membrane-associated proteins. Consistently, Ght5 is ubiquitinated in TORC2-deficient cells, and this ubiquitination is Aly3-dependent [36].

Interaction of arrestin with receptors: Receptor desensitization is found in most GPCRs. First, GPCRs activated by agonists bind to GRK and phosphorylate, which promotes the transformation of β-arrestins from an inactive crystal structure to a structure with high affinity for the receptor. Continued interaction between the body and the G protein results in the release of the C-terminus of activated β-arrestins molecules, leading to receptor endocytosis by binding to endocytic proteins (such as clathrin, Adapter Protein 2 (AP2), etc.) [37]. For most receptors, a prerequisite for the action of β-arrestin is the phosphorylation state of activated GPCRs, so if mutagenesis of key serine/threonine residues impairs receptor phosphorylation, the resulting in decreased binding of β-arrestin. In addition, enhanced phosphorylation of receptors by overexpression of GRKs can promote the recruitment of GFP-β-arrestin complexes to some receptors [38].

The role of arrestin in receptor desensitization: Receptor desensitization is a phenomenon in which a receptor loses its responsiveness after continuous stimulation, including allogeneic desensitization (agonist specific) and xenogeneic desensitization (agonist nonspecific). Allogeneic desensitization means that the specific receptor response of the desensitizing ligand is weakened, while the potency of other receptors is not affected; the lead response is weakened. The former may be caused by changes in the receptor itself, such as phosphorylation, endocytosis, etc.; while the latter may be caused by all affected receptors having a common feedback regulation mechanism, or sharing a certain link in the signal transduction pathway. β-arrestin1/2 can inhibit the activity of Guanosine Triphosphatase (GTPase) by 80% under the stimulation of β2AR [39]. Furthermore, in cell lines overexpressing β2AR, receptor desensitization was enhanced if β-arrestin was transfected. In addition, β-arrestin small interfering RNA (siRNA) method and antisense method can effectively confirm that in HEK293 cells, due to the decrease of endogenous β-arrestin expression, stimulation of β2ARs leads to a large amount of cAMP accumulation [37]. Furthermore, the absence of both β-arrestins in mouse embryonic fibroblast cell lines affected both β2AR and angiotensin II receptor type 1A (AT1AR) desensitization. Knockdown of β-arrestin1 or β-arrestin2 alone also causes desensitization disorder of β2AR and AT1AR receptors [40].

Alvaro et al. found that the negative regulation of Rod1 by phosphorylation is mediated by two distinct stress-activated protein kinases Snf1/AMPK and Ypk1/SGK1, and demonstrated *in vitro* and *in vivo* that this phosphorylation hinders Rod1 desensitization. However, in cells lacking a component required for clathrin-independent entry (formin Bni1), Rod1 derivatives that are largely unphosphorylated and unable to bind to Rsp5 still promote efficient adaptation, an alpha-arrestin-promoting pheromone mechanisms of desensitization-reaction pathways [41].

Endocytosis of arrestins: Plasma membrane transporters play an extremely important role in the import of nutrients around fungal cells. Selective removal of these transporters by endocytosis is one of the most important regulatory mechanisms that ensure rapid adaptation of cells to changing environments. A network of proteins plays a key role, including the arrestin-associated transport linker (ART) that links the ubiquitin ligase Rsp5 to nutrient transporters and endocytic factors. The conformational changes of the transporter, as well as the dynamic interactions between its cytoplasmic ends/loops and plasma membrane lipids, are also critical during endocytosis [42]. Selective endocytosis is a major mechanism for downregulation of plasma membrane transporters in response to specific environmental cues. In *Saccharomyces cerevisiae*, this endocytosis is facilitated by ubiquitination catalyzed by the Rsp5 ubiquitin ligase, which targets the transporter *via* α-arrestin family of linkers. Tanahashi et al. found that the amino acid permease Agp1 in *Saccharomyces cerevisiae* undergoes ubiquitination and endocytosis in response to the addition of excess asparagine. Furthermore, substrate-induced Agp1 internalization is dependent on the ubiquitination activity of Rsp5. Since Rsp5 requires α-arrestin family proteins as adaptors for substrate binding, both Rsp5 and Bul1 are required for Agp1 endocytosis [43].

Endocytosis is required not only for receptor desensitization, but also for activated receptor dephosphorylation and resensitization. Phosphorylation of GRK and binding of β-arrestin promote receptor endocytosis. Endocytosis of GPCRs is multi-pathway, including interactions with clathrin-coated bodies, caveolae, and uncoated bodies. Specific receptors and types of cellular expression determine the rate of endocytosis and pathways for reutilization. Generally, most GPCRs are endocytosed by clathrin-coated bodies after binding to β-arrestin [44]. Goodman et al. first demonstrated a clear and direct interaction between β-arrestin1 or β-arrestin2 and clathrin through *in vitro* binding assays. The Leu-Xaa-Glu/Asp sequence at the C-terminus of β-arrestins has high affinity with amino acid residues 89-100 of the clathrin heavy chain. β-arrestins also interact with the clathrin-AP2 complex, and two arginine residues downstream of the Leu-Xaa-Glu/Asp sequence are critical for the binding of β-arrestin2 to AP2. Deletion of these residues by mutation does not affect efficient binding to β2AR, but blocks the targeted movement of the receptor-β-arrestin complex to clathrin-coated bodies. Therefore, β-arrestin becomes an important linker protein during receptor endocytosis by binding to clathrin and AP2 [45].

Nutrient supply influences changes in cellular signaling, which in turn regulate membrane protein trafficking. To better utilize nutrients, cells relocate membrane transporters through selective protein transport. Key to this shuffling are α-arrestins, which bind membrane proteins and control the ubiquitination and endocytosis of many transporters. In *Arthrobotrys oligospora*, we identified a total of 12 proteins encoded by arrestin, and we performed endocytosis staining analysis on some gene knockout strains and found that endocytosis was significantly reduced [23]. N-acetylglucosamine (GlcNAc) is an important amino sugar involved in infection by the fungal pathogen *Candida albicans*, triggering multiple cellular processes. GlcNAc import from the cell surface is mediated by the GlcNAc transporter Ngt1, which appears to play a key role in GlcNAc signaling. Interestingly, analysis of Δsnf1 and ΔRsp5

mutants showed that while Rsp5 promotes Ngt1-GFP endosomal trafficking, Snf1 hinders this process [46]. Megarioti et al. explored the molecular mechanism of the endocytosis of the arginine permease Can1 and showed that cycloheximide promotes Rsp5-dependent Can1 ubiquitination and endocytosis in a Bul1/2 α-arrestins-dependent manner [47].

With regard to the endocytosis of arrestin on GPCRs exoreceptors, the endocytic function of β-arrestin has been extended to other receptor families, such as mutant families of GPCRs. Binding of β-arrestin1 to the activated IGF-1 receptor promotes receptor endocytosis through the clathrin-coated body pathway. β-arrestin2 also regulates the endocytosis of GPCRsFz4 (type 4 mutant). Fz4 is activated by Wnt family glycoproteins, leading to the recruitment of the cytoplasmic protein Dvl, β-arrestins can interact with Dvl, and *in vitro*, after Dvl phosphorylation, the binding capacity of β-arrestin1 and Dvl is enhanced several-fold. Normal GPCRs recruit β-arrestin upon activation by agonists, however, for Fz4, Dvl recruits β-arrestin upon stimulation with Wnt5A. The endocytosis of Fz4-GFP is achieved through the clathrin-coated body pathway, and the use of antisense RNA to interfere with the β-arrestin2 gene prevents the endocytosis of Fz4-GFP, suggesting that activation of the Fz4 receptor can lead to protein kinase C (Protein kinase C, PKC)-mediated Dvl phosphorylation eventually recruits β-arrestin to the receptor-Dvl complex, resulting in the endocytosis of the Fz4 receptor. However, this aspect of fungal research is still in its infancy [48].

Transport and recycling of GPCR receptors: After GPCR receptors are endocytosed, there are two outcomes: Part of the receptors are degraded; the other part is recycled back to the cell membrane in an active state. The intracellular transport mode of endocytosed receptors is related to the sequence of the endocytic region of the receptor, the configuration of the phosphorylation site and the binding of β-arrestin. It has been found that the ubiquitination and deubiquitination of β-arrestin is related to the receptor transport mode. Although β-arrestin can regulate the transport mode of GPCRs after endocytosis, it has only recently been discovered that it plays a specific role in the cycling of GPCRs. The mechanism by which β-arrestin causes receptor cycling of GPCRs is unclear, but it can be inferred to be related to the recruitment of transport regulators, phosphatases, or related molecules that promote the reduction of β-arrestin to an inactive state [49].

Specific fungal species

Magnaporthe oryzae: The conidia produced by the differentiation of the vegetative hyphae of the pathogenic fungi of rice blast play a decisive role in the spread of the disease. So far, the vast majority of studies have focused on the development, penetration, and post-invasion growth of conidia and appressors, and the origin of how germ cells differentiate from vegetative hyphae to produce conidia. No mechanistic studies have been reported yet. Dr. Dong et al. found that the arrestin pathway plays a crucial role in the regulation of germ cell differentiation and conidia production in M. oryzae [50]. Arrestin protein, like G protein, can bind to G-protein coupled receptors. The binding of arrestin protein can inhibit receptor signaling, while the binding of G protein plays a role in transmitting its signal. The two works together to ensure the reasonable release of the signal. Studies have shown that the deletion of the arrestin gene leads to a fundamental change in the germ cell differentiation pattern of *M. oryzae*, that is, the spore pattern changes from coaxial to apical. Further research found that this protein co-localized with autophagic vesicles, and its transport mode was completely consistent with that of autophagic vesicles, which was different from other arrestin proteins associated with the endocytosis process. For the first time, this study clarified the regulatory role of arrestin protein on the germ cell differentiation process of pathogenic fungi, and revealed the connection between alpha-arrestin protein and autophagy process, creating a regulatory network of alpha-arrestin signaling pathway in the pathogenic fungal disease cycle. mode of action study. The research results are conducive to improving people's understanding of the formation mechanism of filamentous fungal germ cells. In conclusion, this study has important scientific significance and guiding value for in-depth research on the signal transduction mediated by the pathogenic fungal arrestin protein and the use of pathogenic genes to develop anti-rice blast drugs.

Arthrobotrys oligospora: As a typical Nematophagous Fungus (NTF), our previous study found that *Arthrospora oligospora* contains N- or C-terminal arrestin domains, which are highly conserved proteins in function and structure. We analyzed the roles of seven *AoArc* genes in regulating growth, conidia, trap formation and pathogenicity, endocytic processes, and pH signaling. Our study provides a possible mechanism of SNARE formation in which arrestin-mediated endocytosis regulates SNARE structure biogenesis in NTF. Interestingly, we found that AoArc2 is clearly involved in pH regulation. Furthermore, further studies are required to reveal how arrestin interacts to regulate Plasma Membrane (PM) stability following environmental stimuli [23].

Cryptococcus neoformans: The mechanism by which arrestin regulation processes are involved in fungal virulence remains unexplored, and Telzrow et al. identified a small family of four arrestin proteins in *Cryptococcus*, Ali1, Ali2, Ali3, and Ali4. Among them they defined Ali1 as a new contributor to cytokinesis, a fundamental cell cycle-related process. Arrestin proteins are conserved regulators of adaptive cellular responses in eukaryotes. Studies limited to mammals and model fungi suggest that disruption of arrestin-regulated pathways is detrimental to viability [51].

Aspergillus oryzae: *A. oryzae* produces a large number of amylolytic enzymes, and the major maltose permease, MalP, is required for the expression of amylase-encoding genes. The role of CreD, an arrestin-like protein, in glucose-induced MalP endocytosis and CCR of amylase-encoding genes was examined. Deletion of creD inhibits glucose-induced MalP endocytosis, and CreD shows a physical interaction with HulA (an ortholog of yeast Rsp5). The combination of a phosphorylation deficient mutation of CreD and disruption of creB significantly increases alpha-amylase production. This study provides a new method to improve the production of amylolytic enzymes in *Aspergillus oryzae* [52].

Aspergillus nidulans: The PalH of *Aspergillus nidulans* is mechanistically similar to mammalian GPCRs that signal through arrestin, so the relative positions of individual helices within the seven-helix bundle determine the Pro316-dependent transition between inactive and active PalH conformations, controlled by environmentally exposed regions , including the key Tyr259 may represent the agonist binding site [53]. Transcript level analysis and overexpression studies indicated that inhibition of acid expression of palF, a designated Pal pathway inhibitory protein, may be caused by PacC(27) and/or PacC(53), preventing the escalation of the alkaline pH response [54]. It has also been shown that PalB, like PalA and PalC, localizes to cortical structures in an alkaline pH-

dependent manner. Therefore, signaling through the Pal pathway does not involve endocytosis [55]. A single arrestin-like protein, ArtA, is essential for HulA-Rsp5 dependent ubiquitination and UapA-responsive ammonium or substrate endocytosis. ArtA is essential for the vacuolar turnover of purine (AzgA) or l-proline (PrnB) specific transporters, but not the Aspartate/Glutamate Transporter (AgtA) [56]. Similarly, PalF is ubiquitinated in an alkaline pH and PalH-dependent manner. PalF acts upstream or in concert with the Bro1 domain-containing pH signaling protein PalC, which is normally recruited to cortical structures that may represent pH signaling foci active at neutral/alkaline pH. Thus, PalF ubiquitination is a key, and perhaps the only, molecular trigger required for the transmission of alkaline pH signals to downstream elements of the pathway [57].

Mechanism

Signal transduction by kinases: Although beta-arrestin proteins were discovered in the context of attenuating receptor signaling, it was recently discovered that β-arrestin can also initiate signaling, but only from receptors to be "desensitized". Subsequently, kinases or other regulatory proteins that bind to either or both β-arrestin isoforms are continually being discovered. As a result, β-arrestin has become a regulator of Src family tyrosine kinases, as well as some extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinases (c-Jun N-terminal Kinases, JNK) and p38 Mitogen-Activated Protein Kinase (MAPK) pathway receptor regulatory platform [58].

The relationship between arrestin and non-receptor tyrosine kinases: Many GPCRs mediate Ras activation-dependent mitogenic signaling pathways that require the recruitment and activation of Src family non-receptor tyrosine kinases. After recruitment to the cell membrane, c-Src tyrosine kinase phosphorylates the adaptor protein Shc, leading to the recruitment of the Ras transforming factor Sos and its adaptor protein Grb2, which activates Ras, Raf-1, MEK1, and ultimately leads to the activation of ERK1/2. β-arrestin acts as a signaling linker in studies demonstrating that c-Src recruitment to the cell membrane is activated by isoproterenol and is dependent on β-arrestin. There are two regions on C-Src that can bind to β-arrestin, the SH3 region (Src homology 3) interacts with the proline-rich region of β-arrestin, and the kinase SH1 region binds to the N-terminal region of β-arrestin. The inactive c-Src mutant (K298M, with a point mutation at the ATP binding site) contains only the SH1 region (residues 250-536) and can bind to β-arrestin, but cannot recruit to the cell membrane. Activation of β2AR by isoproterenol leads to c-Src-mediated tyrosine phosphorylation of two amino acid residues Tyr231 and Tyr597 of dynamin on the cell membrane, which is β2AR endocytosis and isoproterenol-activated ERK-mediated phosphorylation required [59].

The relationship between β-arrestin and MAPK pathway: MAPKs phosphorylate a variety of protein substrates and regulate a wide range of cellular signals, including cell proliferation, gene expression, and apoptosis. MAPKs are serine and threonine kinases that are phosphorylated by upstream MAPKKs (MAPK kinases), which in turn are phosphorylated by their upstream MAPKKKs (MAPKK kinases). Eukaryotic cells have a large number of cascade-activated protein kinases that form the MAPK cascade. In some cases, the same protein kinase may be a component of multiple signaling pathways, potentially leading to some unwanted crossover between signaling pathways. To maintain signal specificity, components of specific pathways are linked by regulatory scaffold proteins. Studies have shown that β-arrestin acts as a scaffold protein in JNK3 and ERK1/2, which prolongs the stay of JNK3 in the cytoplasm, thereby prolonging the lifespan of the activated state of JNK3; making Raf (MAPKKK), MEK (MAPKK) Link with ERK (MAPK). β-arrestin also regulates P38MAPK activated by activated GPCRs [58]. Similarly, Allyson F. O'Donnell's work in yeast revealed a novel role for AMPK to regulate glucose and other carbohydrate fluxes by controlling the endocytosis of transporters [60].

Effects of arrestin on gene transcription

β-arrestins regulate gene expression through at least two pathways: One is to transfer from the cytoplasm to the nucleus, providing a scaffold for transcription factors in the promoter region of the target gene, thereby directly regulating transcription; the other is to bind transcription in the cytoplasm. Regulators of factors, altering their activity and subcellular distribution, thereby indirectly regulating transcription. In the presence of ERK2 recruitment, β-arrestin2 directly interacts with the nuclear receptor RAR-β2 to enhance the transcriptional activity of RAR-β2, thus β-arrestin-mediated activation of MAPKs can induce transcription of some genes. NF-κB affects the transcription of immunity, stress and apoptosis-related genes through the regulation of dimeric transcription factors. In the inactive state, the NF-κB dimer binds to the inhibitory protein IκBα and exists stably in the cytoplasm. The action of β-arrestin2 prevents the phosphorylation and degradation of IκBα, thereby attenuating NF-κB activation and transcription of NF-κB target genes [61]. β-arrestins link the GPCR pathway and the NF-κB pathway and may play an important role in the regulation of immune function. In addition, Wang et al. found that β-arrestins also interact with tumor necrosis factor receptor-associated factor 6 (TRAF6) to regulate transcription mediated by NF-κB and AP-1 [62].

Other biological roles of arrestin

In higher organisms, other biological effects of β-arrestin have also been gradually discovered, such as chemotaxis and apoptosis. Fong et al. found that the directional movement of lymphocytes to cytokines is specifically regulated by GRK6-mediated phosphorylation and binding of β-arrestin2 to the GPCRs CXCR4, a cytokine receptor that is also a co-receptor for HIV [63]. DeFea et al. reported that activation of β-arrestin-dependent phosphorylation of ERK GPCRs, such as PAR2 (a GPCRs abundant in neutrophils, macrophages, and tumor cells), enhanced cellular stretch toward agonists, whereas activation of those that did not β-arrestin-dependent activation of ERK GPCRs, such as PAR1, similar chemotaxis was not found [64]. Wang et al. reported that β-arrestin plays a role in p53-mediated apoptosis through overexpression in p53-deficient human osteosarcoma cells (Saos2 cells). Overexpression of β-arrestin2 reduced Mdm2-induced p53 degradation and enhanced p53-mediated apoptosis. In the same cells, depletion of endogenous β-arrestin expression by RNA interference attenuates p53-mediated apoptosis [65].

DISCUSSION

Fungi are a large group of eukaryotic organisms, ranging from yeast and molds to mushrooms [66,67]. Unlike mammalian cells, fungal cells have a unique cell wall composed of glycoproteins and aggregates of carbohydrates, including chitin, the polysaccharides that define the cell wall [68,69]. Fungi populate many ecological niches, often functioning as decomposers of organic matter.

However, the most studied species in this large group are unicellular yeasts and filamentous fungi, which are partly animal or plant pathogens and partly include fungi developed for use in industrial processes. Classifying yeast and filamentous fungi as microorganisms can often be compared to bacteria [70]. However, because fungi are eukaryotic organisms, they share many basic cellular physiology and molecular biology features with animals and plants [71]. Most studies on the biosynthesis, composition and function of arrestin have come from mammalian systems [72]. Studies of fungal arrestin, especially the pathogenic yeast arrestin, have revealed multiple mechanisms, including metabolic regulation of proteins, lipids, nucleic acids, carbohydrates, and small molecules [60,73-75]. Arrestin is also a vehicle for the secretion and delivery of key components by fungi. Fungal arrestins are thought to play a role in numerous biological processes, including virulence and cell wall homeostasis, and host-pathogen interactions [76,77]. Arrestin also functions to transmit signals between fungal cells, allowing for a coordinated attack on the host during infection. Research on fungal arrestin is still in its infancy. Research on fungal arrestin has focused on yeast pathogenic to humans, as well as on *Saccharomyces cerevisiae* and *P. pastoris*. The main questions that have arisen to date relate to the biogenesis of arrestin and the pathways involved in the regulation of arrestin [78].

Although the genetic regulation of arrestin production, release, and pathogenesis is an important topic, the most challenging unsolved question in this field may be how to use arrestin to directionally engineer fungi to maximize their effects, based on the breadth of fungal application rate. Current knowledge in this field is mainly limited to basic biological studies of arrestin, but mechanistic investigations are lacking; however, these studies are an important foundation for future molecular biology research [46]. Since the functional study of arrestin is a phenomenon that affects all aspects of fungal physiology, from biofilm formation to secretion and pathogenic mechanisms, we hope this review can provide ideas for fungal arrestin-related research [9,79,80].

CONCLUSION

There is conclusive evidence from many laboratories that the functional studies of arrestin in many species of fungi, such as yeast, mold, filamentous fungi and macrofungi, show relatively high consistency, mainly plays the role in the regulation of GPCRs by binding to Rsp5, using a conserved PY motif. Although the understanding of GPCR signal transduction and function has gradually improved, there are still many orphan receptors in the GPCR family, the ligands of which are unknown, and there may be undiscovered ligands for known receptors. Elucidating the ligands of these receptors and discovering the signal transduction mechanisms mediated by them has important physiological significance and pharmacological value, and requires a lot of research resources. The same GPCR receptor is often activated for a period of time, can couple to several G proteins at the same time, and also interact with other proteins such as arrestin. In terms of structure, although the first complex of G protein and GPCR has been solved, the structure cannot explain the selectivity and recognition of receptor-G protein coupling and conserved sequences that require other GPCRs with more G proteins, structural elucidation of complexes including Gq, Gi, etc. The structure of the receptor and arrestin complex and the receptor endocytosis complex are also expected to be analyzed. The corresponding ligand binding of G protein-coupled receptors will have multiple conformations, and its dynamic conformational changes may also have multiple forms. Research related to GPCRs has won 5 Nobel Prizes, but many important questions remain unresolved. For example: How to design and screen out more efficient drugs with fewer side effects based on the structure and dynamic conformational change information of G-protein coupled receptors? How do G-protein coupled receptors transmit information from outside the membrane to the inside of the membrane through dynamic conformational changes? Collectively, these findings directly implicate arrestin in a number of physiological processes. The regulatory network of Torc1-Npr1-Art-Rsp5 has been widely accepted, but the differences in how they function raise interesting questions about the cellular mechanisms responsible for this phenomenon. Because fungal arrestin research is still on the rise, many of these important questions remain unanswered. Although functional studies of arrestin involvement in molds, filamentous fungi, and macrofungi have intensified, the mechanisms by which endocytosis occurs in these cell wall organisms remain poorly understood.

AUTHOR CONTRIBUTIONS

Conceptualization, XW and LZ; data curation, XW; writing original draft preparation, LZ and XW; writing-review and editing, XW and LZ. All authors have read and agreed to the published version of the manuscript.

FUNDING

This research was jointly supported by the Applied Basic Research Foundation of Yunnan Province (202101AT070266), the Scientific Research Fund Project of Yunnan Provincial Department of Education (2021Y048), and the Postgraduate Research and Innovation Foundation of Yunnan University (2021Z014).

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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