Review article

The role of calcium ions and the calcineurin route in fungal virulence: a review

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SUMMARY

Introduction: Calcium ions (Ca^{2+}) play a fundamental role in regulating various cellular processes and are present in all living organisms. In microorganisms such as fungi, the Ca^{2+} signaling pathway supports essential functions for survival, including stress resistance, apoptosis, growth, reproduction, and virulence. **Objective:** This review aims to explore the importance of Ca^{2+} and the calcineurin pathway in the development and maintenance of fungal virulence. **Method:** This is a narrative review based on literature available in the PubMed and ScienceDirect databases, focusing on articles published between 2015 and 2024. **Results:** The findings reveal that the calcineurin pathway is crucial for several processes contributing to fungal virulence. Calcineurin becomes active through calmodulin, a protein that requires calcium ions for its activation. The main processes regulated by calcium and calcineurin include the formation and maintenance of cell walls, hyphae, and biofilms. Moreover, these components are involved in conidia formation and increase thermotolerance in certain pathogenic fungi. It is worth noting that calcineurin inhibitors, such as cyclosporine A and tacrolimus, have shown synergistic effects when combined with antifungal agents like fluconazole and micafungin. **Conclusions:** These findings highlight the potential of Ca^{2+} and the calcineurin pathway as promising pharmacological targets for the development of new antifungal strategies.

Keywords: Calcium; calcineurin; fungi; virulence.

RESUMEN

El papel de los iones de calcio y de la vía de calcineurina en la virulencia fúngica: una revisión

Introducción: Los iones de calcio (Ca^{2+}) desempeñan un papel fundamental en la regulación de diversos procesos celulares y están presentes en todos los organismos vivos. En microorganismos como los hongos, la vía de señalización del Ca^{2+} sostiene funciones esenciales para la supervivencia, incluyendo la resistencia al estrés, la apoptosis, el crecimiento, la reproducción y la virulencia. **Objetivo:** Esta revisión tiene como objetivo explorar la importancia del Ca^{2+} y de la vía de la calcineurina en el desarrollo y mantenimiento de la virulencia fúngica. **Metodología:** Se trata de una revisión narrativa basada en la literatura disponible en las bases de datos PubMed y ScienceDirect, con énfasis en artículos publicados entre 2015 y 2024. **Resultados:** Los resultados revelan que la vía de la calcineurina es crucial para diver-

sos procesos que contribuyen a la virulencia fúngica. La calcineurina se activa a través de la calmodulina, una proteína que requiere iones de calcio para su activación. Los principales procesos regulados por el calcio y la calcineurina incluyen la formación y el mantenimiento de las paredes celulares, las hifas y el biofilm. Además, estos componentes participan en la formación de conidios y aumentan la termotolerancia en ciertos hongos patógenos. Cabe destacar que los inhibidores de la calcineurina, como la ciclosporina A y el tacrolimus, han demostrado efectos sinérgicos cuando se combinan con agentes antifúngicos como el fluconazol y la micafungina. **Conclusiones:** Estos hallazgos destacan el potencial del Ca^{2+} y de la vía de la calcineurina como objetivos farmacológicos prometedores para el desarrollo de nuevas estrategias antifúngicas.

Palabras-clave: Calcio; calcineurina; hongos; virulencia.

RESUMO

O papel dos íons de cálcio e da via de calcineurina na virulência fúngica: uma revisão

Introdução: Os íons de cálcio (Ca^{2+}) desempenham um papel fundamental na regulação de diversos processos celulares e estão presentes em todos os organismos vivos. Em microrganismos como os fungos, a via de sinalização do Ca^{2+} apoia funções essenciais para a sobrevivência, incluindo resistência ao estresse, apoptose, crescimento, reprodução e virulência. **Objetivo:** Esta revisão tem como objetivo explorar a importância do Ca^{2+} e da via de calcineurina no desenvolvimento e manutenção da virulência fúngica. **Método:** Trata-se de uma revisão narrativa realizada com base na literatura disponível nas bases de dados *PubMed* e *ScienceDirect*, com foco em artigos publicados entre 2015 e 2024. **Resultados:** Os resultados revelam que a via de calcineurina é crucial para diversos processos que contribuem para a virulência fúngica. A calcineurina torna-se ativa por meio da calmodulina, uma proteína que necessita de íons de cálcio para sua ativação. Os principais processos regulados pelo cálcio e pela calcineurina incluem a formação e manutenção das paredes celulares, das hifas e do biofilme. Além disso, esses componentes estão envolvidos na formação de conídios e aumentam a termotolerância em certos fungos patogênicos. Vale destacar que os inibidores de calcineurina, como a ciclosporina A e o tacrolimo, demonstraram efeitos sinérgicos quando combinados com agentes antifúngicos como fluconazol e micafungina. **Conclusões**: Esses achados destacam o potencial do Ca^{2+} e da via de calcineurina como alvos farmacológicos promissores para o desenvolvimento de novas estratégias antifúngicas.

Palavras-chave: Cálcio; calcineurina; fungos; virulência.

1. INTRODUCTION

Fungi are considered eukaryotic beings. These microorganisms, called saprophytes, play a fundamental role in the decomposition of organic matter and in the process of photosynthesis for the production of carbon dioxide. They can promote pathogenic activity causing diseases in humans, animals and plants [1, 2].

These microorganisms can present in yeast or filamentous form. Yeasts are classified as single-celled fungi with vegetative growth through budding or fission, developing as a fruitful body through asexual reproduction. These microorganisms are tolerant of low levels of pH, temperature, nutritional conditions (carbohydrates) and oxygen [3]. While filamentous fungi, structurally, have interconnected tubular units called hyphae that adhere to cell surfaces and facilitate penetration through the cell wall, favoring pathogenicity in host cells from the activation of different signaling pathways involved with molecules signaling, such as calcium ions [4].

Calcium ions participate in essential cellular processes in the most diverse types of living beings [5]. Ca^{2+} signaling is conserved evolutionarily from prokaryotes and eukaryotes [6]. In fungi, they can regulate resistance to stress, apoptosis, growth, reproduction and virulence [7-11].

Virulence, is the capacity that the pathogenic microorganism has to invade the host's defenses and create favorable conditions for its colonization, growth and development, causing illness [12, 13]. The morphological change to the parasitic phase requires great transitions in the patterns of gene expression, which promotes the adaptation of the fungus to the host environment with consequent remodeling of the cell wall and metabolism, in order to favor its survival and virulence [14].

The participation of Ca^{2+} in the fungal virulence process occurs at different stages. In the morphological transition, the calcineurin pathway has been shown to be important, with the action of calcium being indispensable [15, 16]. In addition, during the germination of conidia, structures that participate in host recognition and infection, the calcineurin pathway is one of the main routes, confirming the importance of Ca^{2+} [17-19].

In general, in fungi, exist six types of Ca^{2+} transporters have been identified, including Ca^{2+}-ATPase, Ca^{2+}/H^{+} exchange [10], high-affinity calcium uptake system (HACS), low-affinity calcium uptake system (LACS), Transient receptor potential (TRP) and mitochondrial calcium uniporter (MCU) [10, 20, 21].

In the vacuole, the main intracellular calcium reserve in fungi, the transient receptor potential (TRP) channel, *TRPY1* (previously named *YVC1*), was found. Which has been shown to act in the virulence of pathogenic fungi, such as *Candida albicans*, *Aspergillus fumigatus* and *Magnaporthe oryzae* [20, 22-24]. Similarly, the plasma membrane Ca^{2+}-ATPase 1 (Pmc1) regulates cytosolic calcium levels by transporting them into the vacuole. A study in which Pmc1 was subjected to mutation, changing its functionality, found a reduction in virulence, with reduced fungal loads in the lungs and no evidence of brain infection [25].

In this context, the focus of the review involves the description of cellular components, functions and molecular mechanisms of the calcium-calcineurin signaling pathway, highlighting the attributions of this pathway and of calcium ions in fungal virulence.

2. METHODOLOGY

The present research is a narrative literature review [26], in which articles were searched in the databases: PubMed and Science Direct, using the following associated descriptors: "Calcium" AND "Fungal Virulence "," Calcium "AND" Mycelial Growth "," Calcium "AND" Hyphal Growth "," Calcium "and" Thermotolerance "," Calcium "AND" Cell Wall "," Calcium "AND" Biofilm "," Calcineurin "AND" Inhibitors "," Calcineurin "AND" Fungal Virulence "," Calcineurin "AND" Mycelial Growth "," Calcineurin "AND" Hyphal Growth "," Calcineurin "AND" Thermotolerance "," Calcineurin "AND" Cell wall "," Calcineurin " AND "Biofilm".

Articles published between 2015 and 2024, in English, were included, prioritizing the most recent publications that addressed the proposed theme. Works involving bacteria, helminths and protozoa, monographs, dissertations, theses and books, were excluded.

3. LITERATURE REVISION

3.1. General information about calcium in fungi

It has been elucidated that several organelles present in fungi are fundamental for intracellular calcium homeostasis, such as the plasma membrane, vacuoles and endoplasmic reticulum.

The plasma membrane is composed of a lipid bilayer and proteins that form a specialized structure capable of promoting high virulence. In addition, it is responsible for several cellular functions, such as protection barrier, promotion of virulence through the secretion of virulence factors, endocytosis, hyphae production, cell wall synthesis and transport of molecules and nutrients in favor of the concentration gradient [27-30].

On the surface of the plasma membrane, there are calcium channels that will allow the influx of calcium ions and activation of the calcineurin pathway that is involved in several adaptive virulence processes [31].

More specifically in fungi, such as *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*, HACS has been identified. This system is formed by the proteins Cch1, Mid1 and Ecm7, where Cch1 is a homologue of the voltage-gated calcium channel α1 subunit in mammals. Cch1 and Mid1, interact with each other, forming the Cch1-Mid1 complex that acts as a channel for calcium in the plasma membrane, while Ecm7 is involved in the influx of Ca^{2+} mediated by HACS [10, 18, 32-34]. This system presents itself as the main alternative for the influx of Ca^{2+} in fungal cells, being activated by low concentrations of extracellular calcium and inactivated when the concentrations of this cation increase [18, 35].

In addition, LACS was identified in pathogenic fungi, which is activated when there is high availability of calcium in the extracellular environment and is composed of a single member, fig1, formed by four transmembrane domains. This system is directly associated with mycelial growth and conidiation [36-38].

Vacuoles, in its turn, are necessary organelles to maintain homeostasis in fungal cells, being involved in several essential biological processes, including endocytosis, maintenance of pH and salt balance, phosphate degradation, transmembrane transport and are characterized by being the main reserve of intracellular Ca^{2+} in fungi. Therefore, changes in this component can influence cellular functionality [39, 40].

In *Saccharomyces cerevisiae*, about 90% of the calcium ions are stored in the vacuole. Oxalate, phosphate and organic acids present in this organelle chelate a high amount of Ca^{2+}, and only a small portion is available for release in response to different stimuli [4].

Among the mechanisms involved in the capture of Ca^{2+} for vacuoles are the fusion of its membrane with secretory vesicles derived from the Golgi apparatus, the action of Ca^{2+}-ATPase mediated by the vacuole membrane Ca2+-ATPase (PMC1) and H^{+}/Ca^{2+}antiporter (VCX1) [41]. VCX1 has been shown to act by recovering basal $[Ca^{2+}]_c$ after a peak of Ca^{2+} in *S. cerevisiae*, while vacuolar Ca^{2+} _ATPase Pmc1 maintains $[Ca^{2+}]_c$ [10].

In *Cryptococcus neoformans*, VCX1 is believed to have the main function of sequestering high concentrations of Ca^{2+} [25]. While a study carried out in Bauveria bassiana demonstrated that the action of Ca2 + _ATPase is important for the total speed of germination and conidiation, resistance to oxidative stress and cell wall, as well as for virulence [9].

In addition to these, TRPY1 or Yvc1, is a Ca^{2+} channel already identified in the vacuolar membrane of some species of fungi, such as *S. cerevisiae* [42]. This channel participates in the control of intracellular Ca^{2+} concentrations, responses to stress and virulence of pathogenic fungi, such as *Candida albicans*, *Aspergillus fumigatus* and *Magnaporthe oryzae* [20, 22].

In fungal cells, the endoplasmic reticulum (ER) is a crucial organelle, performing important functions, such as the metabolism of several proteins and sterols [43]. In addition, it is one of the intracellular compartments that participate in the regulation of intracellular Ca^{2+} [44].

In homeostasis, the concentration of cytosolic calcium in these cells remains at low levels, in contrast to the levels in the ER that are about a thousand times higher. This is mainly due to the action of binding proteins that favor their excess accumulation [43].

However, stimuli can trigger an opening of the calcium channels and a rapid increase in the concentration of calcium in the cytosol, which gives a versatile and universally used signal in fungal cell dynamics [44, 45, 46].

It has been shown that the Ca^{2+}-Calmodulin (CaM) signaling pathway depends on the intracellular calcium of the endoplasmic reticulum, the association of the endoplasmic reticulum and the release of calcium from the lumen of the phagosome, which regulate the recruitment of Rubicon, a negative autophagy regulator, for the sustained production of phosphatidylinositol-3-phosphate (PtdIns3P), assembly of NADPH (nicotinamide and adenine dinucleotide phosphate) oxidase and formation of LAPosome [46, 47].

The continuity of the nuclear membrane with the ER has been described. These contact sites, such as MECA (mitochondria-RE-anchor cortex) and ERMES (ER and mitochondrial meeting structures), connect the ER to the mitochondria [48, 49]. They provide a direct and agile transport of metabolites between organelles [50].

The role of ERMES in Ca^{2+} homeostasis has been seen in previous studies, in which imaging techniques have shown that excess Ca^{2+} in ER may be released into mitochondria, acting in the prevention of possible cytotoxic effects and modulating mitochondrial activity [43]. The action of Ca^{2+} present in the ER is also important for the process of cellular apoptosis, especially produced by stress in this organelle [51].

Thus, different fungal structures present themselves as sources of Ca^{2+} that participate in the calcineurin (CN) activation process. Structurally, CN is a heterodimer containing a catalytic subunit called calcineurin A (CnA) and a regulatory subunit, called calcineurin B (CnB) [31, 37].

Once there is an influx of Ca^{2+} by HACS, LACS or unknown calcium channels or its release by vacuoles and endoplasmic reticulum, four of these ions bind to CaM, forming the $4Ca^{2+}$ - Calmodulin (CaM) complex, which in turn, will be able to stimulate calcineurin (CN), increasing the phosphatase activity of CN, allowing dephosphorylation of the calcineurin-dependent transcription factor (CrzA). This will be translocated to the nucleus allowing the transcription of calcium-responsive genes, by binding to the calcineurin-dependent response element (CDRE) [18, 31, 37]. Another important protein is the root clavata-homolog 1 (Rch1) protein, which acts as a negative regulator of calcium uptake when the intracellular concentrations of this cation are high [38]. In a study carried out in *S. cerevisiae*, it was observed that once CDRE is activated, there will be an induction of Rch1 production in the endoplasmic reticulum (ER), which will be transported through the secretory pathway of the ER / Golgi Complex to the membrane, inhibiting the influx of calcium ions (Figure 1) [38].

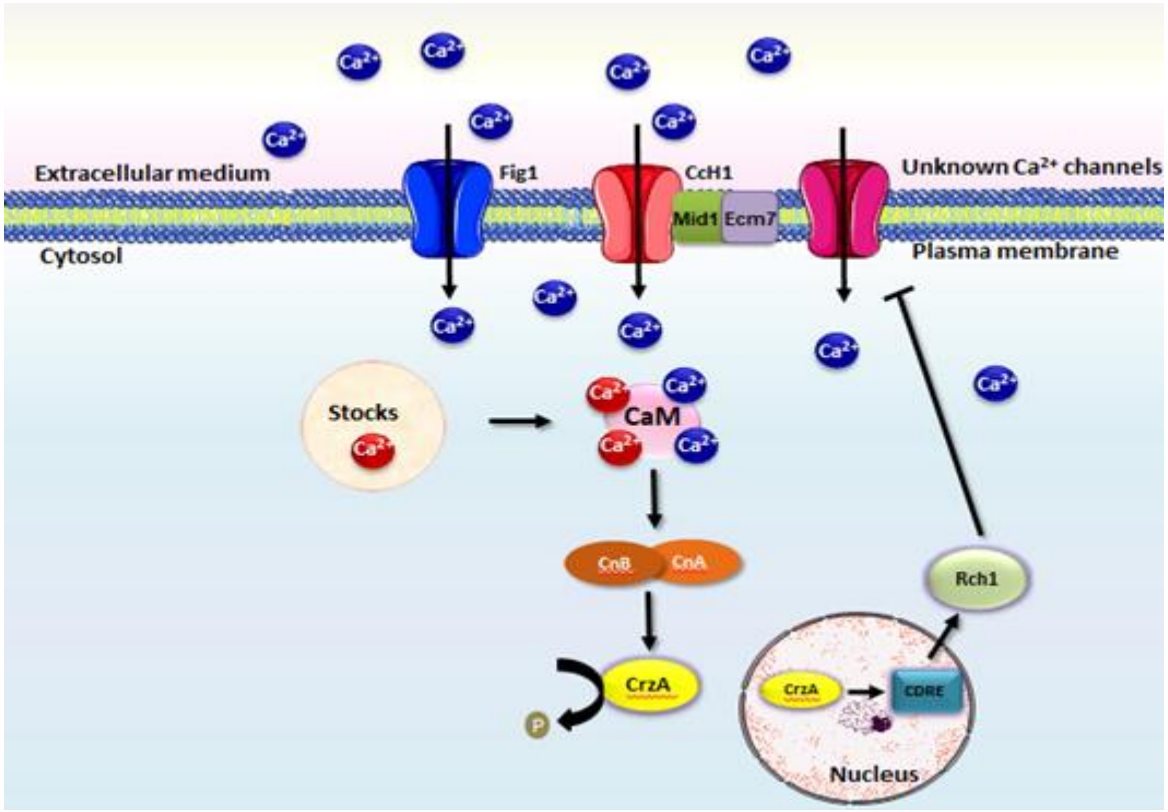

Figure 1. Calcineurin pathway in fungal. Caption: CaM = calmodulin; CDRE = calcineurin-dependent response element; CnA = calcineurin A; CnB = calcineurin B; CrzA = calcineurin-dependent transcription factor; Rch1 = Protein root clavata-homolog 1.

3.2. Cell wall

The fungal cell wall consists of an important structure, being responsible for both protection against stress and the host's immune system. Molecularly, this virulence factor is formed by an internal matrix composed of β-glucans and chitin, which together give the fungal cell rigidity [52].

It has been shown that the deletion of the subunit A of calcineurin has caused a decrease in the ability of strains of *C. albicans* to withstand osmotic stress, indicating that calcium and the calcineurin pathway may influence the plasticity of the cell wall [52].

Studies have indicated that there is participation of the calcineurin pathway in the cell wall integrity pathway (CWI) that is responsible for allowing the formation of specific genes involved in the fungal cell wall biogenesis [53-55].

In *A. fumigatus*, it was evidenced that the deletion of the CnaA gene, responsible for encoding the A subunit of calcineurin, caused a loss of the growth phenotype. This may be associated with the fact that CnaA regulates the phosphorylation of a mitogen activated kinase (MpkA), involved in the CWI pathway. The non-functioning of this kinase results in the absence of expression of genes involved in the synthesis of the cell wall with the emergence of compact colonies and reduced filamentation. In addition, the deletion of CnaA causes in the absence of CrzA that encodes the expression of ChsB (chitin synthase B), responsible for encoding the enzyme chitin synthase involved in the synthesis of chitin, one of the main components of the fungal cell wall [56, 57].

3.3. Conidia

Conidia are specialized structures produced at the end of the asexual life cycle of several filamentous fungi. They have intra and extracellular characteristics that give them the ability to survive in unfavorable conditions such as thermal stress, dehydration, osmotic pressure and variations in pH and temperature. Among its functions, fungi dispersion and environmental persistence stand out [58, 59]. In pathogenic species, they also participate in the host's recognition and infection process, acting as "infectious particles" of fungi [60].

The beginning of the infection process is characterized by the adhesion of the pathogen to the host, being indispensable for growth, persistence and fungal pathogenesis. Studies have shown that conidia preferentially adhere to proteins and carbohydrate fractions, as well as to constituents of the basal lamina. And that, a series of proteins present on the surface of the conidia mediate the adhesion to the cellular components. As examples, we have Lectin A and the extracellular protein of the thaumatin domain AfCalAp (Afu3g09690) [60, 61].

Undoubtedly, conidia formation is of great importance in fungal virulence. Recent studies have reported the influence of calcium ions on a wide range of cellular processes in filamentous fungi, such as production, sporulation and germination of conidia [19, 62].

Magnaporthe oryzae conidia were treated with four Ca^{2+} signaling inhibitors: a Ca^{2+} chelating agent, eghazic acid (EGTA); a calmodulin II kinase (CaMKII) inhibitor, KN-93; a Cch1 calcium channel protein inhibitor, verapamil; and a Ca^{2+}-ATPase inhibitor, CPA. The results showed that all tested inhibitors decreased the germination of conidia. In addition, the elongation of the germ tube was also altered by the inhibitors [19]. Similar results were found by Zhang *et al.* [41] in *Arthrobotrys oligospora*, in which blocking calcium absorption led to a reduction in the rate of vegetative growth, resulting in the absence of conidia.

The involvement of calcineurin in the regulation of the production and germination processes of conidia has been widely described [17]. In *Aspergillus* spp. the CrzA transcription factor acts downstream in order to favor the germination process. The calcineurin signaling pathway is important in morphogenesis/dimorphism and fungal virulence, where its activation is mediated by several other regulatory pathways that depend on stress factors to promote greater transcription [63, 64].

The deletion of the Mid1 and Cch1 genes has been shown to affect HACS and consequently essential processes such as growth and production of conidia, however the importance of HACS for virulence depends directly on the fungal fungal species [10, 41].

The genetic replacement of the CrzA locus in *Aspergillus fumigatus* resulted in a strain with significant problems in the growth of polarized hyphae, in the structure of the cell wall, in asexual development and in the germination of conidia [63].

In the investigation of the heat shock proteins (HSP)-calcineurin pathway, more specifically, in Hsp90 and Hsp70, it was observed that a negative modulation on this pathway, promoting the inhibition of the conidial morphogenesis in *Aspergillus flavus* [11].

3.4. Hyphae

Hyphae and pseudo-hyphae are structures that allow fungi to invade tissues, as well as give these microorganisms resistance to the phagocytosis process. Pseudo-hyphae are morphologically elliptical in shape and long multicellular, with the presence of constriction between the mother cell and the length of the filament, whereas hyphae are multicellular tubular cells, with no constriction between the mother cell and the filament [65-67].

Several factors can contribute to the development of these fungal structures. In the case of pseudo-hyphae, it has been shown that pH 6.0 and temperatures of 35ºC induce growth. Regarding hyphae, growth is benefited from temperatures of 37ºC, N-acetyl glucosamine, hypoxia, hypercapnia and alkaline pH in vitro, in addition to calcium ions [66, 68].

It has been shown that calcium in fungal cells causes the depolymerization of actin, allowing the fusion of secretory vesicles present at the end of the hyphae with consequent secretion of hyphae specific cell wall proteins (CWPs), providing material for the structure of the cell wall, allowing the rapid phases of cell extension. Thus, this process is associated with the rapid growth of these fungal structures. It is believed that the calcium needed to perform this function is derived, mainly from Cch1 and Mid1 and that calcineurin plays a crucial role in this process [69-76].

A study carried out in Aspergillus fumigatus reported that when deleting subunit A or B or both, from the CN, the microorganism showed defects in hyphal growth [71]. Thus, it is evident that mutations or modifications in calcineurin cause inhibition of the extension of hyphae during the invasion process, causing less virulence, lessening the infectious process and consequent decrease in mortality rates [18].

Another component responsible for the control of calcium and hyphal growth is SPF1 which presents itself as a P-type ATPase present in the endoplasmic reticulum of fungi. In C. albicans species, the SPF1 deletion has been shown to affect the growth rate of the microorganism. In addition, it was shown that this deletion resulted in increased chitin synthesis, an important component of the fungal wall. The increase in this polysaccharide is directly associated with stress [75]. Thus, it has been identified that the deletion of SPF1 leads to an increase in the abnormal content of cytoplasmic calcium, with a decreased response to stress, as well as attenuation of virulence [75].

3.5. Biofilm

Biofilms are presented as a set of microbial cells protected by a polymeric extracellular matrix, constituted mainly by polysaccharides that have the ability to strongly adhere to biotic and abiotic surfaces, favoring the development of infections, especially hospital infections [77, 78]. Furthermore, this virulence factor is complex, since it is responsible for considerable resistance to antifungals and the host's defenses [79].

The deletion of genes such as MidA, CchA, CrzA or CnaA in Aspergillus niger, has shown a reduction in the concentration of intracellular calcium, causing an inhibition of biofilm formation [56]. Thus, there was the quantification of several groups of genes ags1, ags2 and ags3 that encode α-1,3-glucan, important for mycelial adhesion; genes related to galactosaminogalactane (GAG) (uge3, uge5, agd3, gtb3), which act in adhesion processes; genes responsible for chitin synthesis (chsB, chsD) and β-1-3-glucan synthesis (Fska). Thus, the authors showed that genes related to GAG and α-1,3-glucan had their expression reduced due to decreased concentrations of intracellular Ca^{2+}, causing a reduction in the biofilm's adhesion capacity, in addition, and chsB and Chsd were regulated negatively, with a decrease in chitin production [56]. Furthermore, it has been elucidated that ueg3 is essential for the biofilm formation process and the reduction of intracellular calcium causes its depletion, causing defects in the constitution of biofilm [80].

One of the most important characteristics for biofilm formation is hydrophobicity, due to the fact that microorganisms must be able to adhere to hydrophobic surfaces, due to the secretion of proteins called hydrophobins. The RodA gene, which expresses the hydrophobin

RodA, showed a reduced level in *A. niger* with deletion of MidA, CchA, CrzA or CnaA [56], due to the reduction of intracellular calcium.

3.6. Thermotolerance

It is believed that when fungi such as *C. neoformans* are exposed to about 37 °C, CN activation occurs, which will cause the migration of Crz1 to the nucleus, however, when excluding Crz1 in mutant microorganisms it was shown that the growth continued for 37ºC, but which was totally inhibited at 39 °C [37].

When studying other targets present in the calcineurin pathway in C. neoformans Park et al. [70] showed that blocking RNA-binding proteins such as Lhp1, responsible for adapting to thermal stress, caused greater sensitivity to temperature changes, suggesting that this pathway contributes to the greater thermotolerance and survival of this pathogen [16, 70, 81-84].

3.7. Calcineurin pathway as a pharmacological target

Calcineurin inhibitors associated with antifungal agents have demonstrated synergistic effects, suggesting that calcineurin may present itself as an interesting target for future antifungal drugs [18].

Calcineurin activity can be inhibited by binding FK506 (tacrolimus) and cyclosporin A (CsA) to the heterodimer [85].

Studies have shown that the use of calcineurin inhibitor CsA and tacrolimus associated with fluconazole, caused a decrease in the Minimum Inhibitory Concentration (MIC) in strains of *C. albicans* [86, 87]. While FK506 showed synergism with fluconazole and micafungin against strains of *C. neoformans* and *M. circinelloides* [15, 18].

In addition to calcineurin itself, other targets are interesting within the pathway, such as heat shock protein 90 (HSP90), which is a molecular chaperone preserved in bacteria and fungi of medical importance, stabilizing calcineurin and contributing to resistance mechanisms [88, 89]. Thus, the inhibition of this protein has demonstrated an improvement in antifungal activity. Currently, several natural products such as ansamycin, geldanamycin and radicicol are able to inhibit it [88].

4. CONCLUSIONS

Further studies are needed to understand the influence of the different elements that compose the calcineurin pathway and those responsible for the regulation of intracellular Ca^{2+} in different fungal genera of medical importance, in order to highlight targets that are increasingly specific against these pathogens and that present themselves as possibilities for new therapeutic approaches in antifungal pharmacotherapy.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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