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Fungi sensing environmental stress

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Abstract

Cells need to adapt to the external environment in order to survive. Signal transduction pathways are crucial mechanisms that allow cells to sense and respond to extracellular stimuli. Among the signal transduction pathways, we point out the cascades mediated by mitogen-activated protein kinases (MAPKs). The MAPKs are conserved from yeast to human and play relevant roles in the physiology of the cell. In pathogenic fungi these MAPK pathways control virulence factors. This review describes the MAPK cascades described in *Candida albicans*, the most frequently isolated fungus, from fungal systemic infections among individuals in developed countries.

Keywords: *Candida albicans*, fungi, mitogen–activated protein kinase, signal transduction

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Eukaryotic cells respond and adapt to external stimuli mainly through signal transduction pathways mediated by mitogen-activated protein kinases (MAPKs). These pathways are well conserved, from the simplest to the most complex organisms, and maintain a similar structure [1]. There is a central MAPK core formed by three MAPKs (MAPK, MAPK kinase and MAPK kinase kinase) that sequentially activate each other by phosphorylation. The signals are sensed by specific receptors that trigger the central module directly or through intermediate proteins. The final effectors of the cascade are, mainly, transcription factors that adjust the transcriptional response, allowing adaptation to environmental change.

Responses to external stresses or vegetative growth are among the processes regulated by MAPK pathways. Therefore, MAPKs are central to a network of pathways that integrate, amplify and modulate protective and adaptive responses. Remarkably, MAPK signalling pathways control virulence in pathogenic fungi. In recent decades, the numbers of infections caused by opportunistic fungi have increased enormously, principally in developed countries. This increase is the consequence of factors such as the immunosuppression linked to organ transplants, cancer, chemotherapy, etc., or the increase in numbers and complexity of invasive techniques (parenteral feeding, catheters, etc.). The most frequently isolated fungal species involved in these infections are *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*, but others have also been identified with increasing frequency. *C. albicans* is still the fungus most frequently isolated from systemic infections. This microbe bases part of its successful strategy of colonization of the host on its ability to assume different morphologies, depending on the growth conditions [2]. They range from unicellular forms (yeast-like forms) to hyphae, but pseudohyphae or thick-walled spores (chlamydospores) are also found. *Cryptococcus neoformans* is a basidiomycetous fungal pathogen that causes human infections after inhalation of small, desiccated yeast cells or spores that pass into the alveoli of the lung [3]. It is the most common cause of fungal infections of the central nervous system, causing fatal meningoencephalitis if untreated. Over the past decade, invasive aspergillosis, which is most often caused by *A. fumigatus*, has emerged as the most serious life-threatening infectious complication of intensive remission–induction chemotherapy and allogeneic bone marrow transplants, and in patients with various haematological malignancies [4].

At least five cascades have been described in *Saccharomyces cerevisiae*, and they are involved in mating, adaptation to hyperosmotic conditions, cell wall integrity, invasive or pseudohyphal growth, vegetative growth, and ascospore wall formation. Several orthologues of signal transduction genes present in these non-pathogenic yeasts have been found in pathogenic fungi. In general, the MAPK pathways conserve similar functional structure and organization; nevertheless, important differences exist that reflect the specialization of the cascades and, in turn, also influence their role in virulence.

Four MAPKs have been identified and characterized in *C. albicans*: Mkc1, Hog1, Cek1, and Cek2 (Fig. 1). Remarkably, Mkc1 and Hog1 are involved in the response to oxida-

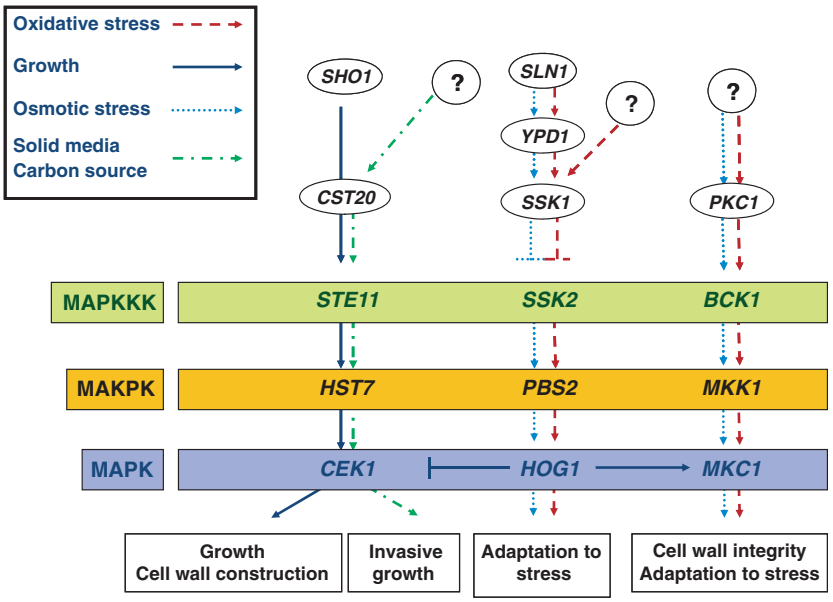

Fig. 1. A scheme of the mitogen-activated protein kinase (MAPK) signalling pathways identified in the pathogenic fungus *Candida albicans*.

tive stress, triggered by phagocytes to fight pathogenic microorganisms. The Hog1-mediated MAPK pathway is involved in resistance to osmotic stress and, interestingly, also to oxidative stress, heavy metals, and thermal shocks [5,6]. In addition, it seems to play an essential role in the regulation of cell wall construction, as shown by the differential behaviour against some antifungals that interfere with its assembly, such as Nikkomycin Z and Congo red [7]. It also plays a role in the dimorphic transition, negatively regulating this process, as Hog1 mutants show an increased ability to filament in sub-inducing media. The MAPK of the HOG pathway, Pbs2 [8], is responsible for the activation of Hog1, and pbs2 mutants display phenotypes that overlap with the phenotypes observed in hog1 mutants, having an enhanced ability to filament and showing cell wall alterations. The transmembrane protein Sho1, first placed on one of the branches of the HOG pathway, mediates the activation of the Cek1 MAPK, which is involved in *C. albicans* growth [9] and in the sensitivity to stress and cell wall biogenesis in this fungal pathogen [10]. Oxidative stress is sensed mainly through Ssk1, which is one member of a two-component system that belongs to the second branch identified in the HOG pathway [11]. The Ssk1 regulator also determines an enhanced killing by human neutrophils [12]. Remarkably, the Hog1 mutant is avirulent in a systemic infection model in the mouse [7], and, moreover, this mutant strain displays reduced viability in the presence of phagocytes [13].

The Mkc1 MAPK, a homologue of *S. cerevisiae* Slt2, the cell integrity pathway MAPK, is essential for growth at elevated temperatures and contributes to the biogenesis of the cell wall. It is also involved in the dimorphic transition and in the biogenesis of the cell wall, as determined by the increased susceptibility of Mkc1 mutants to cell wall lytic enzymes and alterations of the cell wall surface [14,15]. Recent data indicate that this MAPK is also activated by oxidative and nitrosative stress, under different stress situations (ionic, temperature, and certain antifungals) [16] and by contact with surfaces under specific conditions such as those that occur within fungal cells, to initiate invasive growth on solid surfaces [17]. Mkc1 is also a virulence factor, and *mkc1* mutants have reduced virulence in a mouse model of systemic infection [18]. This strain is also more susceptible to nitric oxide [19], in close agreement with previous data and data obtained by our group using *C. albicans* mutants altered in the morphological transition [20].

MAPK cascades control most of the virulence factors characterized in *C. albicans*: cell morphology, superficial antigen (cell wall biogenesis), and response to different stresses, among them oxidative and nitrosative stress. These cascades allow opportunistic pathogens to recognize changes in their environment and take advantage of an impaired immunological system to cause infection. A deeper knowledge of the mechanism and regulation of these MAPK cascades could help in the control of candidiasis as well as in the development of effective vaccines against these severe infections.

Transparency Declaration

The authors declare no conflicts of interests.

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