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Review

Virulence-specific cell cycle and morphogenesis connections in pathogenic fungi

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ABSTRACT

To initiate pathogenic development, pathogenic fungi respond to a set of inductive cues. Some of them are of an extracellular nature (environmental signals), while others are intracellular (developmental signals). These signals must be integrated into a single response whose major outcome is changes in the morphogenesis of the fungus. The regulation of the cell cycle is pivotal during these cellular differentiation steps; therefore, cell cycle regulation would likely provide control points for infectious development by fungal pathogens. Here, we provide clues to understanding how the control of the cell cycle is integrated with the morphogenesis program in pathogenic fungi, and we review current examples that support these connections.

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1. Introduction

In metazoans, cell division and cell differentiations are intimately intertwined [1]. These processes substantially overlap during the development of any pluricellular organism. By controlling the cell cycle, developmental signals determine cellular morphogenesis, which defines new cell types. However, sometimes it is cell cycle regulation that determines whether a cell is able to perceive the developmental signals for differentiation. In addition, terminal differentiation at the end of a particular developmental program is often characterized by permanent withdrawal from the cell cycle, and therefore pathways controlling exit or entry into the cell cycle have dramatic consequences on the ability of a cell to differentiate.

In contrast, it was thought for many years that cell cycle regulation had a little effect on the ability of a fungal cell to differentiate [2]. There were several reasons for this belief. One important reason was that, with the exception of terminal quiescent spores, cell cycle withdrawal is rare during the morphogenesis of specialized structures in fungal cells. In addition, primary studies of fungal cell cycle regulation were performed in budding and fission yeasts, both with very limited developmental options. Today, this scenario is changing, and recent studies of the influence of cell cycle regulation on the ability of pathogenic fungi to infect their hosts are paving the way for new understanding [3–6].

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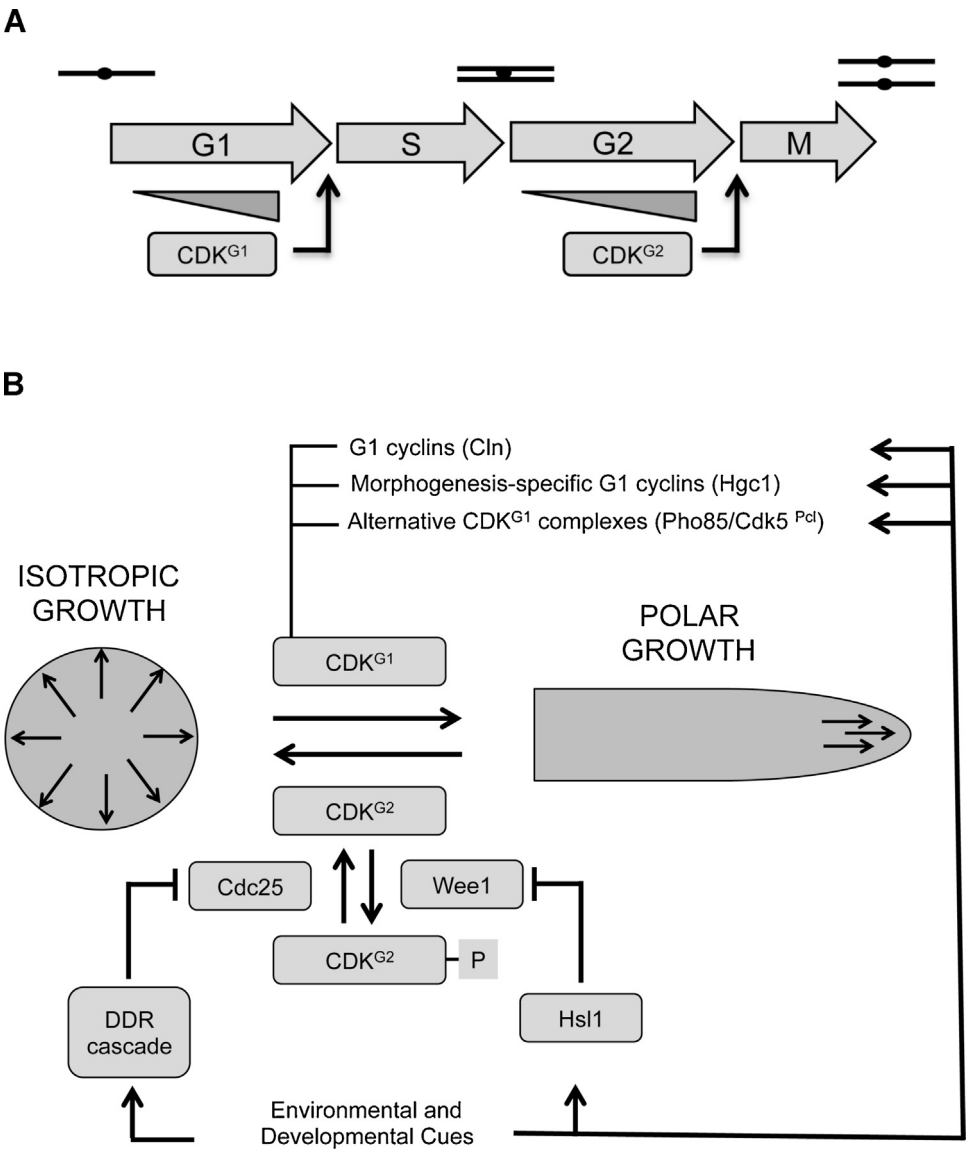

Fig. 1. Connections between cell cycle and morphogenesis: clues.
(A) Scheme of a core eukaryotic cell cycle. It comprises four phases: the synthesis (S) phase, the mitotic (M) phase, and the two intervening gap phases, G1 and G2. During S phase, the DNA (schematized as a single chromosome) is replicated, whereas during M phase, the replicated genetic material is segregated into the two equivalent DNA copies. The core engines that drive the progression through the eukaryotic cell cycle are the CDK complexes, which accumulate during the respective gap phases and triggers the G1/S and G2/M transitions.
(B) Effects of the distinct CDK complexes with respect to the choice of growth. Different regulators of the distinct CDK complexes are also included. See text for more explanations.

Pathogenic fungi are excellent systems in which to study developmental choices in simple eukaryotes. The activation of the virulence program requires the integration of both environmental signals (nutrient availability, temperature, host signals and others) as well as internal cues (metabolic status, mating types and others). One of the major outcomes of the activation of the virulence program is the morphogenesis of the fungus to produce specific structures that help the process of infection [7]. To date, the primary experimental approaches used to define and study the regulation of the pathogenic developmental programs in fungi have been focused on studying signal transduction and transcriptional changes. However, during the last decade, novel opportunities have become available to investigate the molecular basis of fungal pathogenicity from a novel point of view that is complementary to previous approaches in the field [8]. The main premise of these studies was to assume that there are novel roles for cell cycle and morphogenetic regulators in pathogenic fungi: roles that may help adapt the cell to the virulence program. Clearly, the cell cycle and morphogenesis machineries are attractive targets through which signaling may coordinately regulate fungal morphogenesis and cell-cell interactions, and thereby virulence [6].

In this review, we will examine the connections between cell cycle regulation and morphogenesis in fungi, as well as summarize recent studies that have investigated these connections during the induction of the virulence program in pathogenic fungi.

2. Cell cycle and morphogenesis: clues

A complete eukaryotic cell cycle is composed of four phases: the synthesis (S) phase, the mitotic (M) phase, and the two intervening gap phases, G1 and G2. The engine that drives the switch-like transitions between the distinct phases consists of a protein heterodimer complex containing a cyclin and an associated kinase moiety. This group of kinases is referred to as the cyclin-dependent kinases