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Review

Circadian clocks and the regulation of virulence in fungi: Getting up to speed

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ABSTRACT

You cannot escape time. Therefore, it seems wise to learn how to keep track of it and use it to your advantage. Circadian clocks are molecular circuits that allow organisms to temporally coordinate a plethora of processes, including gene expression, with a close to 24 h rhythm, optimizing cellular function in synchrony with daily environmental cycles. The molecular bases of these clocks have been extensively studied in the fungus *Neurospora crassa*, providing a detailed molecular description. Surprisingly, there is scarce molecular information of clocks in fungi other than *Neurospora*, despite the existence of rhythmic phenomena in many fungal species, including pathogenic ones. This review will comment on the overall importance of clocks, what is known in *Neurospora* and what has been described in other fungi including new insights on the evolution of fungal clock components. The molecular description of the circadian system of the phytopathogenic fungus *Botrytis cinerea* will be revisited, as well as time-of-the-day variation in host-pathogen interaction dynamics, utilizing an Arabidopsis-Botrytis system, including also what is known regarding circadian regulation of defense mechanisms in the *Arabidopsis thaliana* plant model. Finally, this review will mention how little is known about circadian regulation of human pathogenic fungi, commenting on potential future directions and the overall perspective of fungal circadian studies.

Contents

1. Introduction

On planet Earth we are immersed in a highly cyclic environment, exposed to daily oscillations in several factors: light-dark cycles, temperature, solar radiation, and other more subtle fluctuating abiotic variations, like environmental humidity. Even though these daily changes can represent a considerable stress, their iterative

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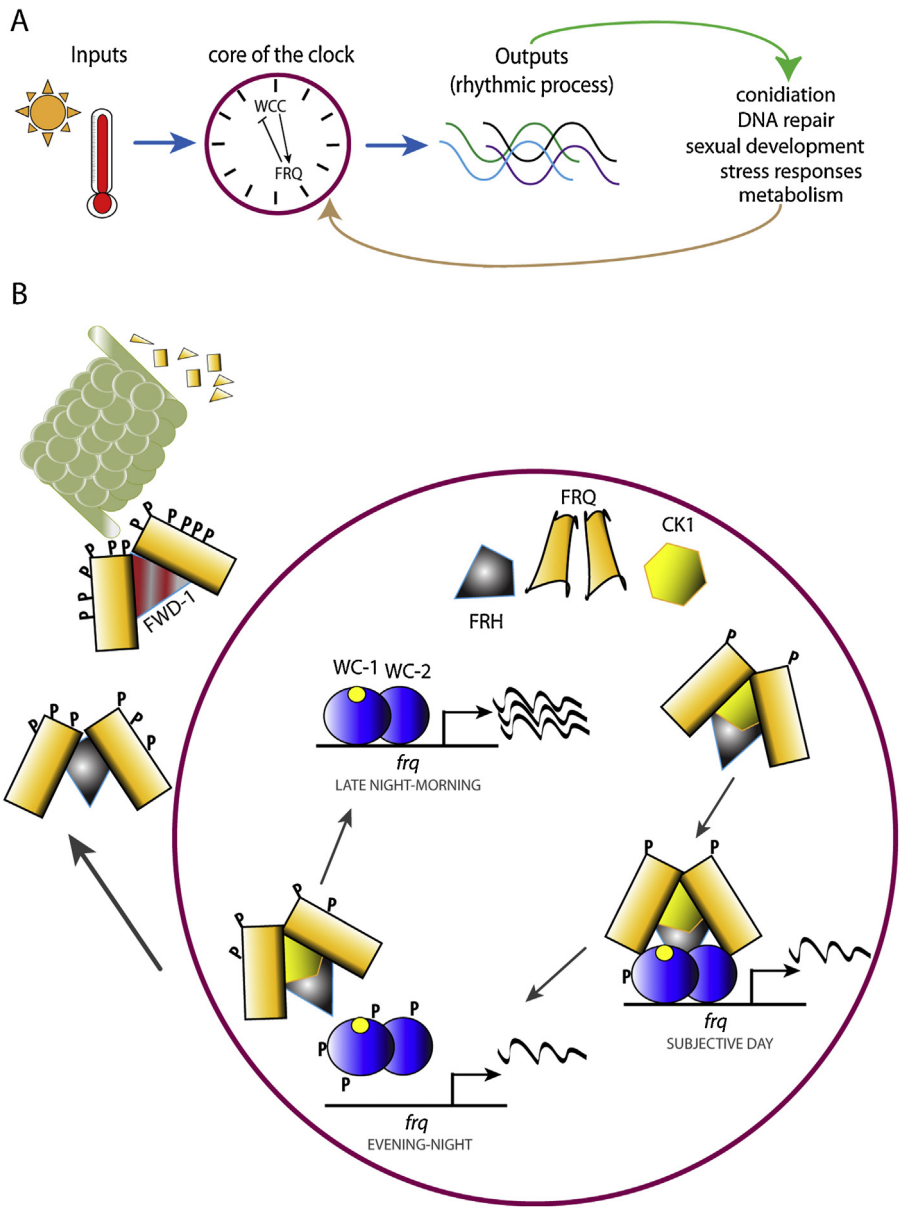

Fig. 1. The *Neurospora crassa* circadian system. (A) Both light and temperature (inputs) feed the clock with temporal information, allowing synchronization, entrainment or resetting. The core oscillator is composed of a transcriptional-translational negative feedback loop, in which FRQ and the WCC act as the negative and positive element, respectively. The clock controls the rhythmic expression of several TFs at different time of the day, which in turn will generate rhythms in physiology, behavior and metabolism (output). It is important to highlight that metabolism can also act as an input to the clock, causing a bidirectional control. (B) In the late night, the WCC binds to the clock box in the *frq* promoter, activating its transcription. As FRQ is synthesized it homodimerizes and binds to the RNA helicase FRH and also to CK1. The latter, plus other kinases, progressively turn FRQ from a hypophosphorylated to a hyperphosphorylated state (represented with P letters), being these posttranslational modifications essential to determine the speed of the clock. During the subjective day, the FRQ-FRH-CK1 complex promotes WCC phosphorylation, leading to a decrease in *frq* expression. During the night FRQ becomes hyperphosphorylated, leading to its dissociation from WCC and CK1, which will allow a new cycle to start again. Meanwhile, hyperphosphorylated FRQ is recognized by FWD-1, which promotes FRQ ubiquitination and subsequent degradation by the proteasome. While phosphorylation events that occur inside the drawn circle are important to determine the circadian period, additional events depicted outside of the circle do not play such a crucial role in determining period, although they naturally occur as a consequence of previous events. Model adapted from Larrondo et al., 2015.

nature makes them predictable, and as a consequence, molecular devices (circadian clocks) have appeared throughout evolution allowing organisms to track time, even in the absence of celestial cues, allowing anticipation to some of these challenges [1]. Most importantly, as we will discuss herein, now we understand that these clocks can also help anticipating rhythms in some biotic variables associated with organismal interactions.

Circadian clocks (from the latin *circa diem,* or approximately a day) are endogenous cellular molecular machineries that confer 24 h rhythms to biological processes including, but not limited to, gene expression, physiology and behavior [1]. For almost all eukaryotic organisms where clocks have been described – insects, mammals, birds, plants and fungi – a common molecular blueprint is displayed: the core clock has an internal autonomous oscillator based on a transcription-translation negative feedback loop (TTFL) [2–4], with the presence of additional loops in plants [5]. While in bacteria most studies have only concentrated in the cyanobacteria *Synechococcus elongatus* [6], no clock components have been described in Archaea. Nevertheless circadian oscillations of peroxiredoxins oxidation have been also observed in the latter, which suggests that the three domain of life share a common evolutionary ancestor in the origin of circadian rhythms [7].