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Could ROS signals drive tissue-specific clocks?

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Circadian clocks have emerged to fine-tune the physiology of organisms to periodic changes in the environment in a dynamic fashion. Negative implications of circadian disruptions in humans, animals and plants have encouraged extensive studies of clock-controlled biological processes in various model species. Recently, it has been shown that the transcription-dependent and -independent biological oscillators are largely driven by cellular oxidative cycles that are intrinsically linked with metabolism. Essentially, the clock is viewed as an integrated network that encompasses cytosolic, genetic and metabolic dimensions. Furthermore, in multicellular organisms, the clock network is organized in a tissue-specific manner. Here we discuss questions that remain unanswered: How do these dimensions communicate with each other and how do tissue-specific clocks exchange temporal information within multicellular organisms?

To ensure accurate timing, circadian clocks must be synchronized by exogenous cues known as zeitgebers. Although light is the most common cue that tunes the clock, other non-photic zeitgebers exist such as temperature,[1,2] sugars,[3,4] and energy status.[5] Upon synchronization, the circadian clock conveys temporal information to numerous output pathways. Specifically, metabolic regulation by the circadian clock has received significant interest due to the vast implications in human diseases.[6,7] In plants, the clock regulates metabolic processes such as photosynthesis, isoprenoid biosynthesis, and starch, nitrogen and sulfur metabolism.[8,9] The tight interplay between the circadian clock and metabolism is associated with extensive cross-talk, such that a metabolic process acting downstream of the clock can convey its status through signaling molecules that feedback to the core clock circuitry and thus act as input signals for fine-tuning the clock.[10,11]

Further understanding of the role of the plants' biological clock in metabolism was revealed by Lai et al.,[11] showing that reactive oxygen species (ROS) can act as input signals to the clock, hence providing evidence of direct cross-talk between the circadian clock and metabolism.[10] In contrast to light and temperature, ROS represent endogenous clock input signals that are the inevitable byproducts of aerobic metabolism.[12] Both mammals and plants not only scavenge ROS, but can also actively produce them, suggesting that ROS homeostasis is under strict cellular control.[12,13] Furthermore, it was demonstrated that exogenous application of ROS-generating agents affected the transcription of several clock output genes. ROS homeostasis is influenced by other zeitgebers such as light and temperature in various organisms and might therefore have a more essential role in clock regulation.[14-16] For example, in dormant seeds the clock is not running, but starts upon imbibition.[17] As early as two days following seed imbibition, circadian gene expression is manifested without any entraining cycles or prolonged light exposures.[18] Although light and temperature cycles accelerate the appearance of rhythmicity, the authors suggested that during imbibition a synchronization signal is released. The nature of this signal has, however, remained elusive. Here we propose that ROS is a good candidate for

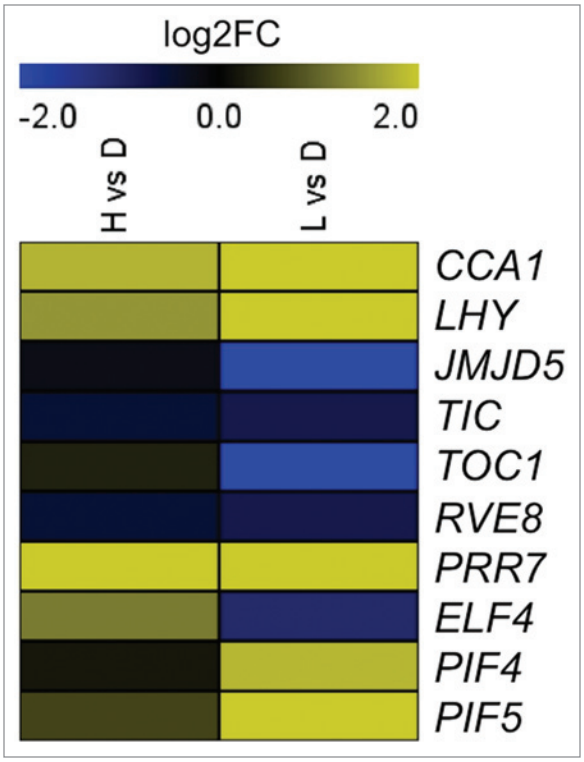

Figure 1. H_2O_2 might synchronize the Arabidopsis clock in the dark. The gene expression data shown were extracted from microarray experiments performed on seedlings grown for 7 d in the light or grown on 5 mM H_2O_2 in the dark as compared with dark grown seedlings.[19] Among the core clock genes, *CCA1* and *LHY* are modulated in a similar level by H_2O_2 as by light, while *TOC1* is only modulated by light. H vs D: H_2O_2 treatment vs. dark grown seedlings. L vs D: Light vs. dark grown seedlings. AGI codes: *CCA1* (At2g46830); *LHY* (At1g01060); *JMJD5* (At3g20810); *TIC* (At3g222380); *TOC1* (At5g61380); *RVE8* (At3g09600); *PRR7* (At5g02810); *ELF4* (At2g40080); *PIF4* (At2g43010); *PIF5* (At3g59060).

this signal as a ROS burst is commonly observed upon imbibition in many plants species.[19] Supporting our notion, many clock components are at the expressional level responsive to ROS. In dark-grown *Arabidopsis thaliana* seedlings, clock core genes are lower expressed as compared with light-grown seedlings.[20] However, when plants are grown in the presence of H_2O_2 in the dark, the expression level of several of these genes, including *CCA1*, *LHY1* and *PRR7,* resembles those of light-grown plants (**Fig. 1**). Nevertheless, the light-dependent clock output genes *PIF4* and *PIF5* are not affected by H_2O_2 in the dark.

In plants, ROS themselves represent a clock-controlled output whose levels exhibit daily oscillations and more than a third of the ROS-responsive transcriptome is circadian regulated.[11,21] Moreover, in other organisms, it is becoming increasingly evident that ROS homeostasis is circadian controlled. In mice, disruption of the core clock gene *Aryl hydrocarbon receptor nuclear translocator-like protein 1* (*BMAL1*) causes increased ROS levels and decreased expression of the master antioxidant regulatory factor *Nuclear factor erythroid 2-Related Factor 2* (*Nrf2*) and its targets.[22] Furthermore, in *Drosophila melanogaster*, the response to acute oxidative stress depends on the time at which exposure occurs and the loss of the core clock gene *PERIOD* results in increased oxidative stress sensitivity.[23] Glutathione levels in Drosophila also follow a diurnal rhythm.[24] Additionally, ROS regulate light-inducible gene expression through the core clock protein WHITE COLLAR (WC) in *Neurospora crassa*. ROS can directly affect the *N. crassa* clock as H_2O_2 promotes the dimerization of WC-1 and WC-2 in the absence of light and thereby stimulates a circadian rhythm and cellular redox homeostasis.[25] We showed in Arabidopsis that exogenous applications of ROS-promoting or -inhibiting compounds have profound effects on altering the phase of the circadian clock output gene *FLAVIN BINDING, KELCH REPEAT, F-BOX1* (*FKF1*).[11] These examples suggest conserved functions of ROS in the circadian network, whereby ROS can act as both zeitgebers as well as outputs of the clock.

As ROS are not evenly distributed throughout an organism, they may have local effects on tissue-specific oscillators. In plants, ROS accumulate to high levels in the vascular tissues, trichomes and to some extent guard cells.[11] ROS are rapidly generated and propagated over long distances and act as a systemic warning signal to enable quick responses to external stresses.[26] Therefore, it is possible for ROS to be a potential synchronizer of tissue-specific clocks as they can move rapidly through the vascular bundles in plants and from cell to cell.[26] Indeed, such 'inter-tissue' communication exists. In Arabidopsis, synchronization of the clocks between shoots and roots occurs.[27] Synchronicity in mammalian clocks is maintained by signals that travel across nerves where the brain's central pacemaker synchronizes daily signals between the different cells through neuropeptides.[28] In addition, energy signals that are released rhythmically in peripheral organs, including insulin, could also feedback to control suprachiasmatic nucleus rhythms.[29] Interestingly, hypothalamic energy sensing is closely linked to ROS generation where the elevation of ROS levels affect the responses in energy sensing neurons of the arcuate nucleus.[30,31]

Our perspective of the clock network continues to evolve; from metabolic oscillations being a circadian output to being an autonomous pacemaker itself. The autonomous pacemaker consists of a biochemical oscillator driven by oxidation cycles of peroxiredoxins that act independent of the transcription/translation feedback loops.[32] Furthermore, it was shown that peroxiredoxin rhythms are conserved across the eukaryotic, bacterial and archaeal domains, probably as they reflect endogenous rhythms of ROS.[33] Interestingly, the hyperthermophilic archaea Methanopyri that grow in anoxic environments lack ROS detoxification systems and circadian time-keeping.[33] From a physiological point of view, redox oscillations may have caused the emergence of multiple clocks to allow temporal separation of incompatible processes. This is, for instance, to restrict the expression of certain proteins to suitable redox environments.[34] The acquisition of aerobic metabolism and evolution of circadian systems seem to have co-occurred. Future studies should perhaps focus on understanding clocks as interdependent timers that couple both metabolism and transcriptional processes in different cell and tissue types.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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