Introduction
Plants rely on an endogenous timekeeper to optimally prepare for the recurrent cycles of day and night, light and darkness, energy production and energy consumption, activity of pollinators, as well as seasonal changes that tell them when to flower or shed their leaves [1,2]. The ‘circadian’ clockwork (from Latin circa diem, about one day) is entrained to the periodic light regime of the environment: plants use this information to control internal processes so that they take place at the most appropriate time of day for maximal output and performance. This global system works at various genomic levels.

The core clockwork consists of negative feedback loops through which clock proteins sustain their own 24-h rhythm [3-6]. In the model plant Arabidopsis thaliana, the Myb-type transcription factors LATE ELONGATED HYPOCOTYL (LHY) and CIRCADIAN CLOCK ASSOCIATED 1 (CCA1) oscillate with a peak around dawn (Figure 1a). LHY and CCA1 activate the expression of four PSEUDO-RESPONSE REGULATORS (PRRs) that are sequentially expressed, starting with PRR9 in the morning, followed by PRR7, PRR5 and TOC1/PRR1. This activation occurs indirectly via inhibition of the evening complex (EC), which is a repressor of the PRRs (Figure 1b); three proteins, LUX ARRHYTHMO (LUX)/PHYTOCLOCK1 (PCL1) and the plant-specific proteins EARLY FLOWERING 3 (ELF3) and ELF4, interact to form the EC. The PRRs induce the EC in the late evening, whereas CCA1 and LHY repress EC expression. The EC, in turn, indirectly activates CCA1 and LHY by directly inhibiting the repressive PRRs. These and other clock proteins regulate rhythmic molecular and biochemical processes in the cell (Figure 1c) (see section ‘From a single oscillating mRNA to the rhythmic transcriptome’). These molecular-genetic events have been integrated into quite sophisticated systems models (reviewed at a systems level in Bujdoso and Davis [7]).

Overall, the principles of rhythm generation in plants are the same as in mammals or Drosophila, but the components involved are largely different, pointing to independent origins of the timekeeping mechanisms. In mammals, the core loop comprises the transcription factors CLOCK and BMAL1, which activate the expression of Cryptochrome and Period genes. The PERIOD/CRYPTOCHROME complex, in turn, represses BMAL1/CLOCK-mediated transcription of their own genes. Additional feedback loops consisting of transcriptional activators and repressors interlock with this central loop to regulate the expression of the core clock genes (for a detailed description, see Zhang and Kay [8], Staiger and Köster [9], and Dibner et al. [10]).

In this review, we summarize recent insights into the blueprint of the circadian clock and the function of clock proteins based on genomic studies in Arabidopsis and other plant species (Figure 2). Furthermore, we describe how large-scale biology has greatly advanced our understanding of how timing information is translated into rhythmic processes in the plant cell.

Abstract
Large-scale biology among plant species, as well as comparative genomics of circadian clock architecture and clock-regulated output processes, have greatly advanced our understanding of the endogenous timing system in plants.
opportunely performed just after the compilation of the Arabidopsis genome [12,13]. Cycling gene clusters could thus be linked to nearby non-coding DNA, and conserved elements in the upstream regions revealed phase-specific promoter elements [12,14-16]. These studies provided valuable insights into the genome-wide mechanism of clock outputs for the first time. Groups of genes that are co-ordinately directed to certain times of the day pointed to entire pathways that were not previously known to be clock-regulated, such as the phenylpropanoid pathway [12].

Subsequently, many homologous genes were found to be clock-regulated and phased to similar times of day in poplar and rice, as they are in Arabidopsis [17]. Furthermore, the same three major classes of cis-regulatory modules of Arabidopsis were found in poplar and rice. The morning module consists of the morning element (CCACAC), which confers expression at the beginning of the day, and a ubiquitous G-box (CACGTG) regulatory element associated with regulation by light and by the phytohormone abscisic acid. The evening module consists of the evening element (AAAAATATCT), which confers expression at the end of the day, and the GATA motif, which is associated with light-regulated genes. The midnight modules come in three variants, ATGGCC (PBX), AAACCTCT (TBX) and AAGCC (SBX). This points to a strong conservation of clock-regulated transcriptional networks between mono- and dicotyledonous species [17]. As shown in Figure 1c, oscillations of the output genes can be accomplished through direct binding of rhythmically expressed clock proteins to phase modules in the promoters of output genes, or via intermediate transcription factors.

The information from numerous microarray experiments conducted under different light and temperature regimes by the community were assembled into the easy-to-use DIURNAL database [18]. This site is widely consulted to check for rhythmic transcript patterns, reflecting the growing awareness of the importance of temporal programs in gene expression [18].

Rhythmically expressed genes in Arabidopsis were found to be over-represented among phytohormone- and stress-responsive pathways. This revealed that endogenous or environmental cues elicit reactions of different intensities depending on the time-of-day [15,19]. This so-called ‘gating’ is thought to optimize the response to a plethora of stimuli impinging on the plant, and may be of particular relevance for sessile organisms [2]. An example of this is how the PRR5, PRR7 and PRR9 proteins contribute to the cold stress response [20]. These PRRs also contribute to coordinating the timing of the tricarboxylic acid cycle [21]. In this way, one set of regulators directly link global gene expression patterns to rhythmic primary metabolism and stress signaling.

A similar systems-based approach identified the circadian clock as a key player in other facets of metabolism, since CCA1 regulates a network of nitrogen-responsive genes throughout the plant [22]. CCA1 also
has a role in coordination of the reactive oxygen species response that occurs each day as part of light harvesting for photosynthesis and the reaction to abiotic stress, such as the response to high salt [23]. Another clock-optimized process is the regulation of plant immunity. The defense of Arabidopsis against Pseudomonas syringae or insects depends on the time-of-day of pathogen attack [24-26]. Furthermore, genes that are induced upon infection with the oomycete Hyaloperonospora arabidopsidis, which causes downy mildew disease, have more CCA1 binding sites in their promoters than expected [27]. cca1 mutants show reduced resistance when infected at dawn. Since lhy mutants are not impaired in disease resistance, this points to a specific effect of the CCA1 clock protein rather than a general effect of the clock [27]. Similarly, the RNA-binding protein AtGRP7 (Arabidopsis thaliana glycine-rich RNA binding protein 7), which is part of a negative feedback loop downstream of the core oscillator, plays a role in immunity [28-30].

Microarray analysis has also contributed to the question of whether there is one clock for all parts of the plant. Plants, unlike animals, do not have their circadian system organized into a master clock situated in the brain and ‘slave’ clocks in peripheral organs [31]. However, the differential oscillatory patterns of core clock genes in Arabidopsis shoots and roots point to a distinct clock in roots that runs only on the morning loop [32].

**Post-transcriptional control contributes to rhythms of the transcriptome**

Soon after discovering the effect of the clock on transcription, it became apparent that clock-controlled promoter activity does not always lead to detectable oscillations in mRNA steady-state abundance. This was attributable to a long half-life of the transcripts [33]. In Arabidopsis, a global search for short-lived transcripts identified a suite of clock-controlled transcripts. For some of these, the mRNA stability changes over the circadian cycle [34]. Corresponding factors that may coordinate the half-life of sets of transcripts are yet to be identified, although candidates include RNA-binding proteins that themselves undergo circadian oscillations [35].

A prominent role for post-transcriptional control in circadian timekeeping was suggested by the long period phenotype of the prmt5 mutant defective in PROTEIN ARGinine METHYltransferase 5 [36-38]. Among the protein substrates of PRMT5 are splicing factors, and
thus PRMT5 has a global impact on splicing. Alternative splicing of the clock gene PRR9 is affected by loss of PRMT5 and the transcript isoform encoding functional PRR9 is barely detectable in prmt5 mutants, suggesting that the circadian defect may partly be caused by changes in PRR9 splicing [36]. Additional splicing factors that affect circadian rhythms are SPLICEOSOMAL TIMEKEEPER LOCUS1, the SNW/Ski-interacting protein (SKIP) domain protein SKIP, and the paralogous RNA-binding proteins AtGRP7 and AtGRP8 [39-41]. Notably, AtGRP7 and AtGRP8 form a feedback loop through unproductive alternative splicing and decay of transcript isoforms with a premature termination codon, associating for the first time nonsense-mediated decay with the circadian system [42,43].

In another approach, a high-resolution RT-PCR panel based on fluorescently labeled amplicons was used to systematically monitor alternative splicing of the core oscillator genes [44]. Alternative splicing events were observed 63 times, and of these, at least 13 were affected by low temperature. This suggested that alternative splicing might serve to adjust clock function to temperature changes. More recently, RNA-Seq analyses identified alternative splicing of many clock genes, and an event leading to the retention of an intron in CCA1 was conserved across different plant species [45]. In the future, a systematic comparison of alternative splicing networks (both for core clock genes and clock output genes) to the corresponding transcriptional programs will unravel the contribution of alternative splicing to the rhythms in transcript and protein abundance.

To date, the extent to which proteins undergo circadian oscillations in the plant cell has not been systematically studied. An initial proteomic study in rice revealed a difference in expression phases between mRNAs and proteins, suggesting regulation at the post-transcriptional levels [46]. Uncoupling of protein rhythms from mRNA rhythms has also been observed in mouse liver, where 20% of soluble proteins show a rhythm in protein abundance but only half of them originate from rhythmic transcripts [47].

**Noncoding RNAs and the plant clock - a not-so-well defined connection**

A prominent class of small noncoding RNAs are micro-RNAs (miRNAs), which are 19 to 22 nucleotide long single-stranded RNAs that base-pair with mRNA targets and thereby control the level of target transcripts or the level of translation of these mRNAs [48]. miRNAs that oscillate across the circadian cycle have been widely described in mammals and Drosophila. In these organisms, miRNAs target clock components and play a role in entrainment or regulation of clock output [49,50].

In Arabidopsis, a suite of miRNAs was interrogated for rhythmic expression. Using tiling arrays, miR157A, miR158A, miR160B and miR167D were found to be clock-controlled [51]. On the other hand, miR171, miR398, miR168 and miR167 oscillate diurnally but are not controlled by the clock [52]. The functional implications of these mRNA oscillations are not yet clear. Based on the prominent role miRNAs play in modulating the circadian clock in Drosophila or mammals, such a function is to be expected in plants, where miRNAs so far have demonstrated roles only in clock output, such as seasonal timing of flowering [53].

Another class of noncoding RNAs is naturally occurring antisense transcripts (NATs). In Arabidopsis, rhythmic NATs were detected for 7% of the protein coding genes using tiling arrays [51]. Among these were the clock proteins LHY and CCA1, TOC1, PRR3, PRR5, PRR7 and PRR9. In the bread mold Neurospora crassa, NATs have been implicated in clock regulation. Suites of large antisense transcripts overlap the clock gene frequency in opposite phase to sense frq. These NATs are also induced by light and thus appear to play a role in entrainment by light signals [54]. A causal role for noncoding RNAs in the plant circadian system has yet to be established.

**Forward and reverse genetics to define the core oscillator mechanism**

Forward genetic screens of mutagenized plants carrying clock-controlled promoters fused to the LUCIFERASE reporter for aberrant timing of bioluminescence were instrumental to uncover the first clock genes, TOC1, ZEITLUPE and LUX/PCL1 [55-58]. Likely because of extensive redundancy in plant genomes, most other clock genes were identified by reverse genetic approaches and genome-wide studies. In fact, up to 5% of transcription factors have the capacity to contribute to proper rhythm generation [59]. A yeast one hybrid screen of a collection of transcription factors for their binding to the CCA1/LHY regulatory regions revealed CIRCADIAN HIKING EXPEDITION (CHE) as a modulator of the clock [60].

These CHE studies attempted to bridge TOC1 with the regulation of CCA1/LHY, but failed to fully explain the effect of TOC1 on CCA1/LHY expression. Subsequently, chromatin immunoprecipitation (ChIP)-Seq showed that TOC1 directly associates with the CCA1 promoter, and this interaction is not dependent on CHE [61,62]. Thus, while CHE is not generally seen as a core clock component, its analysis revealed that genomic approaches can feasibly interrogate the capacity of a given transcription factor to modulate clock performance. Genome-wide analysis of cis-elements in clock-controlled promoters should identify the motifs that control rhythmic RNA expression of a clock-controlled gene, and this facilitates the identification of the trans factors that create such rhythms (Figure 1c).
correlates with promoter is rhythmically regulated, and this positively. It was shown that acetylation of H3 at the 

TOC1

acetyltransferase activity of CLOCK [65]. In contrast, REVEILLE8 (RVE8), a MYB-like transcription factor similar to CCA1 and LHY, promotes H3Ac at the TOC1 promoter, predominantly during the day [69]. However, it is unclear if CCA1 and RVE8 cause the histone modification at the TOC1 promoter, or if histone modification allows CCA1 or RVE8 to actively participate in regulation of TOC1 transcription, respectively. The underlying molecular mechanism of the temporal histone modification and components involved are currently elusive. Furthermore, it remains to be shown whether other histone modifications, such as phosphorylation, ubiquitination or sumoylation [70], also contribute to the clock gene expression and change across the day.

### Comparative genomics

The availability of an ever-increasing number of sequenced plant genomes has made it possible to track down the evolution of core clock genes. The Arabidopsis core oscillator comprises families of proteins that are assumed to have partially redundant functions [1,3]. The founding hypothesis was that the higher-land-plant clock derived from algae. The green alga Ostreococcus tauri, the smallest living eukaryote with its 12.5 Mb genome (10% of Arabidopsis) has only a CCA1 homolog, forming a simple two-component feedback-loop with a TOC1 homolog, the only PRR-like gene found in Ostreococcus [71]. This supported the hypothesis that the CCA1-TOC1 cycle is the ancestral oscillator (Figure 2).

Recent efforts to clone crop-domestication genes have revealed that ancient and modern breeding has selected variants in clock components. The most notable examples include the transitions of barley and wheat as cereals. The common spring varieties arose as late flowering cultivars, which profit from the extended light and warmth of European summers over that of the Middle East. That occurred from a single mutation in barley (Hordeum vulgare) in a PRR ortholog most similar to PRR7 termed Ppd-1 (Photoperiod-1) (Figure 2) [72]. In wheat (Triticum aestivum), since it is polyploid and recessive mutations rarely have any phenotypic impact, breeders selected promoter mutations at PPD that led to
dominant late-flowering [73]. Interestingly, in the beet *Beta vulgaris*, a PRR7-like gene named *BOLTING TIME CONTROL1* (*BvBTC1*) is involved in the regulation of bolting time, mediating responses to both long days and vernalization [74]. Evolution at PRR7 is thus a recurrent event in plant domestication.

As barley (*Hordeum vulgare*) moved north, early flowering was selected in a late-flowering context due to the presence of the spring allele at *ppdh1*. Mutations in the barley *ELF3* ortholog, termed *EAM8* (Figure 2), were selected [75]. Interestingly, the migration of bean and alfalfa to temperate Europe also coincided with *ELF3* mutations [76]. In Asia, rice varieties in domestication retained at a lower rate. Thus, as even the neighboring genes, as known by synteny, were genome [81]; this was not a linkage disequilibrium effect, the retention of clock genes has been more highly favored by keeping additional copies of clock genes [81]. By examining this is not always the case, as gene loss of these redundant copies has occurred at numerous loci [81].

In alloploids that arise from the intercrossing of species, the clock confronts allele choice issues between the potentially conflicting parental genomes. Alloploids are common in nature, are often easy to recreate in the lab, and are often more vigorous than the parents. Using a newly generated alloploid, the role of the clock in providing a genome-wide fitness was assessed [75,76]. Epigenetic modification at two morning clock loci [77]. It will be intriguing to assess the genome-wide population structure of clock gene variation as a possible driving force in species migration over latitude and altitude. Genome-wide efforts to explore this show that such studies have merit [78].

One identifying feature of plants within clades of multicellular organisms is the possibility of fertile polyploids. It is speculated that, over evolutionary time, all higher-land plants were at one time polyploid, and indeed, it has been estimated that up to 80% of extant higher-land plants were at one time polyploid, and multicellular organisms is the possibility of fertile poly-

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