Most living organisms show circadian (≈24 h) rhythms in physiology and behavior. These oscillations are generated by endogenous circadian clocks, present in virtually all cells where they control key biological processes. Although circadian gating of mitosis has been reported for many years in some peripheral tissues, the underlying molecular mechanisms have remained poorly understood. Here we show that the cell cycle inhibitor p21\textsuperscript{WAF1/CIP1} is rhythmically expressed in mouse peripheral organs. This rhythmic pattern of mRNA and protein expression was recapitulated in vitro in serum-shocked differentiated skeletal muscle cells. p21\textsuperscript{WAF1/CIP1} circadian expression is dramatically increased and no longer rhythmic in clock-deficient Bmal1\textsuperscript{−/−} knock-out mice. Biochemical and genetic data show that oscillation of p21\textsuperscript{WAF1/CIP1} gene transcription is regulated by the antagonistic activities of the orphan nuclear receptors REV-ERB\textbeta/β and ROR\textgamma/γ, which are core clock regulators. Importantly, p21\textsuperscript{WAF1/CIP1} overexpressing Bmal1\textsuperscript{−/−} primary hepatocytes exhibit a decreased proliferation rate. This phenotype could be reversed using small interfering RNA-mediated knockdown of p21\textsuperscript{WAF1/CIP1}. These data establish a novel molecular link between clock and cell cycle genes and suggest that the G\textsubscript{1} progression phase is a target of the circadian clock during liver cell proliferation.

Many physiological and behavioral processes display day-night oscillations in most organisms including mammals. These biological rhythms are controlled by endogenous self-sustained circadian (≈24 h) oscillators that operate not only in the central clock located in the suprachiasmatic nuclei of the hypothalamus but also in virtually all peripheral cells. Light is the main synchronizer of the central clock, which in turn coordinates the phases of peripheral oscillators regulating specific physiological outputs. Forward genetics and biochemical approaches have established the molecular basis underlying circadian oscillations in mammalian tissues (1–4). This mechanism involves complex interlocked positive and negative transcriptional/posttranslational feedback loops between the clock genes Clock, Bmal1, Per1, Per2, Cry1, and Cry2 and their protein products. The robustness of the oscillations is ensured by additional regulators such as the REV-ERB\textalpha/α (NR1D1) and ROR\textalpha/α (NR1F1) orphan nuclear receptors (5, 6). Furthermore, extensive multilevel posttranslational regulation of various clock components has also been shown to play an important role in the molecular clock mechanism (7).

There are substantial evidences that progression through the cell cycle occurs at specific times of the day/night cycle, suggesting that a function of the circadian clock system is to control this fundamental process. Notably, after the initial observation almost 40 years ago that cell division of the unicellular algae Euglena was controlled by an endogenous clock (8), numerous studies have shown a circadian variation of the proliferative activity in mammalian tissues such as the epithelia of tongue, skin, oral mucosa, intestine, esophagus, stomach, duodenum, jejunum, and rectum as well as in bone marrow and pancreas (9–15). Although several cell cycle regulators have been reported to be expressed rhythmically, the mechanism and the physiological relevance of this regulation remain poorly understood (16–20). However, Matsuo et al. (16) have recently demonstrated that mitosis is gated by the circadian clock in regenerating liver through the control of Weel kinase, a regulator of the G\textsubscript{2}/M transition.

p21\textsuperscript{WAF1/CIP1} (hereafter referred as p21) is a member of the Cip/Kip family of cyclin-dependent kinase inhibitors, which negatively regulates cell cycle progression by inhibiting the activity of cyclin E-cdk2 complexes during G\textsubscript{2} phase progression and blocking DNA replication through binding to proliferating cell nuclear antigen. p21 is also a major target of p53 activated after DNA damage and plays an important role during epidermis differentiation (21–24). Here we investigate the molecular mechanism that links clock genes to p21 and show that genetic disruption of the circadian clock system results in aberrant p21 expression and altered cellular proliferation.

**EXPERIMENTAL PROCEDURES**

**Animals**—All animal experiments were conducted in compliance with the CNRS regulation on animal ethics. Bmal1\textsuperscript{−/−} mice in the C57Bl/6j background (kindly provided by C. A. Bradfield, University of Wisconsin, Madison, WI) were used at 8–12 weeks of age, before they develop arthropathy (25).
Heterozygous animals were crossed to generate knock-out mice and wild type littermates. Animals were housed in a 12-h light/12-h dark cycle (light/dark 12:12) in a temperature- and humidity-controlled environment and fed ad libitum. Zeitgeber time 0 (ZT0)5 referred to lights on. For the constant darkness experiment, light was kept off at constant darkness 0 for 24 h.

Cell Culture—NIH 3T3 cells were from ATCC and grown under standard conditions. C2C12 cells were maintained in growth medium consisting of Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum. Undifferentiated C2C12 were grown to confluence and then transferred to differentiation medium consisting of Dulbecco’s modified Eagle’s medium plus 2% horse serum. Differentiation medium was changed every 48 h. After 10 days, cells were stimulated with 50% fetal bovine serum for 2 h, and then the medium was replaced with Dulbecco’s modified Eagle’s medium plus 2% horse serum. 

5 The abbreviations used are: ZT, Zeitgeber time; siRNA, small interfering RNA; WT, wild type.
horse serum. Cells were collected every 4 h, and extracts were prepared for mRNA and protein analysis. Primary hepatocytes were isolated by in situ perfusion procedure using purified Liberase (Roche Diagnostics). Cells were plated at 2.5 × 10⁴ cells/cm² in collagen-coated 35-mm culture dishes in William’s E medium supplemented with 10% fetal calf serum (v/v), 100 IU penicillin, 100 mg/ml streptomycin, and 5 μg of bovine insulin at 37 °C in 5% CO₂. After cell attachment, medium was renewed without fetal calf serum and supplemented with 1 μM dexamethasone.

**Plasmid Construction and Cotransfection Assays**—A 2240-bp fragment upstream of the first exon from the p21 gene has been amplified from mouse genomic DNA by PCR with the following primers: p21prom, forward, 5’-GCTCGAGGGGCGCGCGGATCCTTAAGGATGAACTTTAAAGGC-3’; and reverse, 5’-GATCCCTTGTGCCGCGCCACAGTACTCTTTTGGCGGCGACAG-3’. The resulting fragments were digested by NotI or BamHI, respectively, and ligated into pcDNA3.1. All the constructs were verified by sequencing. CLOCK and BMAL1 expression vector was obtained by annealing phosphorylated oligonucleotides containing wild type or mutated RORE elements and surrounding sequences from pBKS to generate the p21Prom::Luc construct. The resulting double strand fragment into a TATA box containing 4x-TATA::Luc, forward, 5’-GATCTAGGAGGCGCGCGGATCCTTAAGGATGAACTTTAAAGGC-3’; and reverse, 5’-GATCTGAGAGGGCAGGCATC-3’. RORE wild type and consensus RORE (26). The following vectors for ROR were made by annealing phosphorylated oligonucleotides: (proRORE)4x-TATA::Luc, forward, 5’-GATCTGAGAGGGCAGGCATC-3’; and reverse, 5’-GATCTGACTGATCCATAAGTACTCTATTTGGCGGCGACAG-3’. RORE mutant by using Promega reagents and a Berthold Centro LB960 luminometer. Luciferase activities were normalized to total protein concentrations.

**Real-time PCR**—Measurements were performed with a Light Cycler 1.5 (Roche Applied Science, Meylan, France) using SYBR green 1 dye detection according to the manufacturer’s recommendations. cDNA was added to a reaction mixture (Faststart DNA SYBR Green I; Roche Diagnostics) with appropriate primers at 0.5 μM each and amplified using the following PCR conditions: 10 min at 95 °C, 30 s at 95 °C, 10 s at 65 °C, and 10 s at 72 °C for 45 cycles and then melting curve analysis. Relative mRNA abundance was calculated using a standard curve method. Expression levels were normalized to the levels of 36B4. The following primers were used: p21 forward, 5’-GCAGACCCACGCTGACAGTTT-3’; and reverse, 5’-GAGAGGGCGGCGGAAGCTATATATAGGATGACAG-3’. The resulting fragments were digested by EcoRI and ligated into pcDNA3.1. To construct expression vectors for REVERBα (NM_145434) and REVERBβ (NM_011582), the respective open reading frames were amplified by PCR from mouse liver cDNA using the following primers: REVERBα forward, 5’-GGTGAAGACATGACGACCC-3’; and reverse, 5’-GGGTCCTGAGGTCGTC-3’. REVERBβ forward, 5’-CCGCCGACACAGTACTCTTTTGGCGGCGACAG-3’; and reverse, 5’-GATCTGACTGATCCATAAGTACTCTATTTGGCGGCGACAG-3’. The resulting fragments were digested by NotI and BamHI, respectively, and ligated into pcDNA3.1. All the constructs were verified by sequencing. CLOCK and BMAL1 expression vector have described previously (27). NIH3T3 cells were cotransfected for 7 h with reporter (100 ng) and expression (300 ng) vectors using Lipofectamine (Invitrogen). Cells were incubated for 48 h in fresh medium, and luciferase activity was determined using Promega reagents and a Berthold Centro LB960 luminometer. Luciferase activities were normalized to total protein concentrations.

**Circadian Clock Regulation of p21Waf/CIP1**

**FIGURE 2. Circadian expression of p21 in differentiated C2C12 myoblasts.** Cells were serum-shocked for 2 h and collected at the indicated times for 52 h. A, p21 mRNA expression. Data were expressed relative to the time 0 value, which was given the arbitrary value of 1 and as the mean ± S.D. B, p21 protein expression, EF-1α was used as a control for loading.
Circadian Clock Regulation of p21^Waf/CIP1

**A**

**B**

**C**

**D**

**E**

**F**

(consRORE)3x-TATA::Luc
(consROREmut)3x-TATA::Luc
pcDNA
RORγ
REV-ERBα
REV-ERBβ
The effects of different siRNA oligonucleotides on gene expression were assessed by a luciferase reporter system. The luciferase reporter is driven by a minimal promoter containing ROR-α and REV-ERB-α binding sites. Transfection of siRNA (100 nM) was performed into AG654 hepatocytes for 16–24 h. Radiolabeled cells were collected 24 h later and assayed for DNA synthesis and protein expression.

**RESULTS AND DISCUSSION**

*p21* is a Clock-controlled Gene—We and others previously identified through genome-wide analysis of rhythmic gene expression in peripheral tissues or cells several cell cycle genes including *p21*, a well known cell cycle inhibitor (18, 27). Real-time PCR analysis of *p21* mRNA levels in the liver from mice kept in constant darkness confirmed that *p21* expression is controlled by an endogenous oscillator, with peak and trough values at constant darkness 0 and constant darkness 8, respectively (Fig. 1A). Genomic analyses of circadian gene expression in peripheral tissues have shown that very few (10%) clock-controlled genes oscillate in more than one tissue (28). Profiling different peripheral organs for *p21* expression revealed that its rhythmic gene expression pattern was not restricted to the liver as the heart and skeletal muscle displayed a similar gene expression pattern (supplemental information, Fig. S1). These observations show that the high tissue specificity of clock-controlled gene expression does not apply to *p21*, possibly because its main function is related to an essential and ubiquitous cellular process.

To test genetically that *p21* is controlled by clock genes, we next analyzed its expression in *Bmal1*-null mice, a clock-deficient model that exhibits a profound alteration of the circadian system (25, 29, 30). A dramatic increase of *p21* mRNA levels from ZT4 to ZT16 with 8–12-fold overexpression at ZT8 was observed in the liver of *Bmal1*−/− mice as compared with wild type animals (Fig. 1B). Although this observation suggests that BMAL1 represses *p21* transcription, the lack of cognate E-box element in the *p21* promoter and first intron makes unlikely a direct inhibitory mechanism. *p53*, a well known regulator of *p21* that has also been reported to oscillate in the human oral mucosa (17, 31), is expressed identically in *Bmal1*−/− and wild type livers in which no significant rhythmicity can be detected (Fig. 1C). *p53* is therefore not a putative circadian regulator of *p21*. Consistently, recent data showed that *p53* expression is neither rhythmic in wild type mouse liver nor altered in *Per2*-null mice and that *Per1* overexpression in colon cancer cells leads to the inhibition of *p21* in response to ionizing radiation independently of *p53* (19, 32). These and our observations strongly suggest that clock genes regulate *p21* through a p53-independent pathway.

To extend our analyses of the interactions between clock and cell cycle genes in the liver, we also investigated the effect of the *Bmal1* mutation on three additional genes, *Wee1*, *Cd6*, and *Ccn2*. *Wee1* is a known clock target regulating the G2/M transition (16) that is expressed at intermediate and constant levels in *Bmal1*−/− animals (Fig. 1D). *Cd6* and *Ccn2*, which encode cell cycle protein involved in the G1 phase and G1/S transition, are also regulated by the clock, and their expression is coordinated with *p21*. The coordinated expression of *Wee1*, *Cd6*, and *Ccn2* with *p21* suggests that they are target genes of the clock.

**FIGURE 3.** ROR and REV-ERB nuclear receptors regulate *p21* transcription. A, a scheme of the *p21* gene region containing two conserved RORE. B and C, cotransfection of NIH3T3 cells with a luciferase reporter construct driven by a 5′-2240-bp *p21* fragment and CLOCK, BMAL1 expression vectors (B) or RORα, RORγ, REV-ERBα, or REV-ERBβ expression vectors as indicated (C). D–F, as in C, cells were cotransfected with luciferase reporter constructs containing a minimal promoter and driven by either wild type or mutated multimerized versions of the promoter RORE ((proRORE)4x-TATA:Luc and ((proROREmut)4x-TATA:Luc)) (C) or intronic RORE ((intRORE)4x-TATA:Luc and (intROREmut)4x-TATA:Luc)) (D) together with RORα, RORγ, REV-ERBα, or REV-ERBβ expression vectors as indicated. Reporter constructs driven by a wild type or mutated consensus RORE element ((consRORE)3x-TATA:Luc and ((consROREmut)3x-TATA:Luc) were used as controls (F). Normalized values are shown as mean ± S.D. from at least three independent experiments.
Circadian Clock Regulation of p21\textsuperscript{Waf/Clp}

respectively, showed neither a significant oscillation in wild type liver nor an alteration of their expression in the mutant liver (Fig. 1, E and F).

The p21 protein is a short-lived molecule that undergoes proteasomal degradation and that is consequently nearly undetectable in adult mouse tissues unless cell cycle arrest is stimulated (33, 34). As the p21 mRNA was also found to oscillate in the cardiac and skeletal muscles, we analyzed p21 protein expression in C2C12 cells, a well established cellular model of skeletal muscle terminal differentiation during which the p21 protein is induced (35). Differentiated C2C12 myotubes were subjected to a serum shock to synchronize the cellular circadian clocks, and p21 mRNA and protein level were monitored for 52 h (36). Results show that the p21 gene is clock-controlled in differentiated myotubes and that the p21 protein display a rhythmic expression pattern that mirrors that of the mRNA (Fig. 2, A and B).

Altogether, these results demonstrate that the cell cycle inhibitor p21 gene is a circadian clock output in addition to Wee1 and that these two genes are differentially affected by the Bmal1 mutation. They further suggest a regulatory mechanism that does not directly involve the core clock component BMAL1.

REV-ERB and ROR Nuclear Receptors Regulate p21 Expression—A close analysis of the phase relationship between the profiles of p21 and other known clock components suggested the orphan nuclear receptors Rev-erba and Rev-erb\textbeta{} (NRIID2) as two putative direct negative regulators because they are Bmal1 targets, and both peak when p21 is low. Consistently, Rev-erba is a known target of the CLOCK:BMAL1 heterodimer (5, 37). These two repressors bind to the same DNA response elements as ROR orphan nuclear receptors (termed RORE; consensus sequence: WAWNTRGGTCA), which in contrast, activates transcription. Although Rev-erba and Rev-erb\textbeta{} are ubiquitously expressed, ROR receptors display more complex expression patterns, with ROR\textalpha{}4 and ROR\textgamma{} (NRI1F3) being the only isoforms detected in liver. Interestingly, two evolutionary conserved RORE are present in the promoter and first intron regions of the p21 gene (Fig. 3A). This suggested that p21 oscillation could directly result from an alternative activation and repression mediated by ROR and REV-ERB proteins, respectively. However, because we could not exclude a direct negative regulation of the p21 gene by the CLOCK:BMAL1 heterodimer as shown previously for c-myc (19), we tested the response of a 2240-bp 5’ fragment of the p21 promoter fused to a luciferase reporter gene (p21Prom::Luc construct) in a cotransfection assay. No significant increase over basal activity could be observed in contrast to the reporter gene driven by Per1 consensus E-box elements (Fig. 3B). In contrast, ROR\textgamma{} transactivated the same p21Prom::Luc reporter construct, which contained the proRORE, by ∼2.5-fold, whereas ROR\textalpha{}4 did not (Fig. 3C). A deletion mutant lacking the proRORE site (p21Prom\textalpha{}1663::Luc construct) abolished the ROR\textgamma{}-dependent activation (Fig. 3C). Both REV-ERB\textalpha{}o and REV-ERB\textbeta{} could antagonize the ROR\textgamma{}-dependent transactivation of the p21 promoter (Fig. 3C). A reporter construct containing a multimerized proRORE ((proRORE)4x::TATA::Luc) was activated 2.2- and 1.6-fold in the presence of ROR\textgamma{} and ROR\textalpha{}4, respectively, consistently with the results obtained using the full promoter sequence (Fig. 3D). Similarly, ROR\textgamma{} activity was antagonized by coexpressing REV-ERB\textalpha{}o or REV-ERB\textbeta{}. The relatively modest induction mediated by the proRORE suggested that part if not most of the p21 circadian regulation may involve additional response element(s). To address this issue, the identified intronic RORE (intrRORE), which virtually matches the previously defined consensus RORE sequence, was tested. Cotransfection of the ((intrRORE)4x-TATA::Luc) reporter construct together with ROR\textgamma{} and ROR\textalpha{}4 resulted in a 2- and 9-fold activation, respectively (Fig. 3E), that is similar to that obtained with the consensus element (Fig. 3F). REV-ERB\textalpha{}o and REV-ERB\textbeta{} significantly repressed the ROR-dependent activation (Fig. 3, E and F). Corresponding mutated elements showed no response (Fig. 3, D and E). Altogether, these data demonstrate that the p21 locus contains functional elements that specify the responsiveness to the ROR and REV-ERB clock components.

The Bmal1 Mutation Disrupts the ROR/REV-ERB Balance—To genetically test in vivo the assumption that ROR\textalpha{}4, ROR\textgamma{}, Rev-erbo, and Rev-erb\textbeta{} are downstream of Bmal1 and upstream of p21, we analyzed their mRNA expression profiles throughout the 24-h cycle. ROR\textalpha{}4 was not rhythmic in wild type liver and not significantly affected by the loss of Bmal1 (Fig. 4A). In contrast, ROR\textgamma{} exhibited a robust rhythmic expression pattern in wild type liver with peak levels at ZT20, hence 4 h before that of p21, consistent with an activating role (Fig. 4B). Notably, ROR\textgamma{} was significantly overexpressed at all time points in Bmal1\textsuperscript{–/-} liver, a finding that, together with the functional RORE recently identified in the ROR\textgamma{} promoter (38), suggests a positive autoregulation antagonized by REV-ERB\textalpha{}o and/or REV-ERB\textbeta{}. The opposite situation was observed with Rev-erbo and Rev-erb\textbeta{}, which displayed a robust oscillation in WT animals but were nearly undetectable at all time points in Bmal1\textsuperscript{–/-} animals (Figs. 4, C and D). These genetic data together with biochemical data suggest that p21 up-regulation in Bmal1\textsuperscript{–/-} animals primarily results from the loss of Rev-erbo and Reverb\textbeta{} expression possibly combined with the increased expression of ROR\textgamma{}. In this context, the release of the REV-ERB-dependent inhibition of ROR\textalpha{}4 activity is also likely to play a role. Changes in additional unidentified positive and negative regulators of p21 expression may also play an additional role. From these data, we propose that in liver, the clock control of p21 high amplitude oscillation results from a ROR\textalpha{}4- and ROR\textgamma{}-dependent activation, which is rhythmically repressed by REV-ERB\textalpha{}o and REV-ERB\textbeta{}.

Impaired Proliferation in Bmal1\textsuperscript{–/-} Hepatocytes—Unlike a large number of cell types that undergo terminal differentiation associated with permanent withdrawal from the cell cycle, mature quiescent hepatocytes retain high proliferative potential. After partial hepatectomy or acute injury, growth-arrested hepatocytes can rapidly and synchronously enter the cell cycle (39). Although the p21 protein is undetectable in normal adult liver, it is strongly induced following partial hepatectomy, during which it regulates cell cycle progression (40). Overexpression of p21 in Bmal1\textsuperscript{–/-} mouse liver may thus compromise cell proliferation. Using a primary cell culture system, we observed that spontaneous proliferation of Bmal1\textsuperscript{–/-} hepatocytes was
significantly delayed by ~24 h, whereas p21 protein induction was higher in comparison with that of WT cells (Fig. 5A). If this phenotype was the result of p21 overexpression, then reducing p21 expression would rescue the WT phenotype. To test this hypothesis, Bmal1−/− cells were assayed for proliferation in the presence of either a specific or a control p21 siRNA. Results show that specific siRNA-mediated knockdown of p21 expression caused a significant increase of the proliferation of hepatocytes as compared with untreated or siRNA control Bmal1−/− cells.

In analogy to the work by Matsuo et al. (16), who showed that loss of clock activity in Cry1−/−/Cry2−/− double mutant animals resulted in a delayed liver regeneration, we show here that a mutation in another key core clock gene results in a very similar phenotype. The kinase Wee1, a critical regulator of the G2/M transition during cell division cycle, was proposed as a direct CLOCK:BMAL1 target mediating the circadian gating of mitosis in liver (16). Our data suggest that progression through G1 may also undergo a circadian control through the ROR/REV-ERB pathway targeting the cyclin-dependent kinase inhibitor p21. Along this line, the clock Δ19 mutation was also reported to reduce the proliferation of embryonic fibroblasts (41). Interestingly, it was also recently shown that the mamma-
Circadian Clock Regulation of p21Waf/CIP1

Cell cycle

Circadian clock

Weel

FIGURE 6. Molecular links between circadian clock and cell cycle genes. Shown are the pathways identified in the present work and in previous studies, suggesting that the cell division cycle is linked to circadian clock signaling at multiple levels via Weel, Per1, and p21 (see “Results and Discussion” for references).

lian PER1 protein interacts with the checkpoint kinase 2, an important link between DNA damage-activated kinases with checkpoint effectors and DNA repair (32). Collectively, these data suggest that the circadian clock can control cell proliferation at multiple levels including the G1 phase and G2/M transition as well as the DNA damage response pathway (Fig. 6). This raises the critical issue of how these actions are coordinated to provide an optimal circadian gating of the cell division cycle. These aspects are likely to become particularly relevant in the context of pathologies for which a strong circadian component is recognized including cancer as accumulating epidemiological, clinical, and experimental evidences indicate that disruption of the circadian system is linked to tumor cell growth (19, 42–44).

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