Journal of
APPLIED
BIOMEDICINE

J Appl Biomed
7: 15–33, 2009
ISSN 1214-0287

REVIEW

Clock genes in health and diseases

Valérie Mongrain[1, 2, 3], **Nicolas Cermakian**[1, 2]

[1]Laboratory of Molecular Chronobiology, Douglas Mental Health University Institute, Montréal, Canada
[2]Department of Psychiatry, McGill University, Montréal, Canada
[3]Present address: Center for Integrative Genomics, University of Lausanne, Switzerland

Received 29th January 2009.
Published online 11th March 2009.

Summary
Circadian rhythms, rhythms of about 24 h in various physiological functions, are getting extensively characterized at the molecular level. The generation of circadian rhythms is acknowledged to originate from oscillations in the expression of several clock genes as well as in the regulation of their protein products. While the general entrainment of organisms to the light-dark cycle of the environment is mainly achieved through the master clock of the suprachiasmatic nucleus in mammals, the molecular clockwork is functional in various organs and tissues. The molecular components of the circadian system have been found to be essential for a diversity of basic and homeostatic systems ranging from the control of cell cycle, the regulation of cardiac and metabolic function, to the fine-tuning of sleep and mental health. The present review will focus on the involvement of clock genes in human health and diseases.

Key words: clock genes; peripheral clocks; circadian rhythms; human; sleep disorders; psychiatric disorders; cancer; metabolism

INTRODUCTION

Biological rhythms evolved to adapt to the rotation of the Earth. Rhythms with a period of about 24 hours – termed circadian rhythms – are everywhere in biology from single-cell organisms to more complex organisms such as mammals (Dunlap et al. 2004). Besides their period, a second property of circadian rhythms resides in their endogenous origin; these rhythms are sustained even in the absence of time cue. Thirdly, circadian rhythms have the capacity to synchronize with the environment (via synchronisers or "Zeitgebers"). In the present review, we will describe the links between elements of the molecular machinery governing circadian rhythms and various physiological functions in mammals. We will put emphasis on the involvement of the "clock genes" in health and evidence of their dysfunction in various diseases (Table 1).

✉ Nicolas Cermakian, Douglas Mental Health University Institute, 6875 LaSalle blvd., Montreal, QC, H4H 1R3, Canada
💻 nicolas.cermakian@mcgill.ca
☎ 1-514-761-6131 ext 4936

Table 1. **Selected literature linking clock genes to human health or diseases**

Health dimension	Genes	Involved in	References
Sleep timing	*Clock*	Diurnal preference and DSPD	Katzenberg et al. 1998, Iwase et al. 2002, Robilliard et al. 2002,
	Per1	Extreme diurnal preference	Carpen et al. 2006,
	Per2	ASPD	Toh et al. 2001, Vanselow et al. 2006, Xu et al. 2007,
	Per3	Diurnal preference and DSPD	Archer et al. 2003, Pereira et al. 2005, Jones et al. 2007,
	CKIδ	ASPD	Xu et al. 2005,
	CKIε	DSPD	Takano et al. 2004.
Sleep homeostasis	*Clock*	Sleep duration, REM rebound	Naylor et al. 2000,
	Npas2	Sleep amount, activity rhythms Sleep EEG regulation	Dudley et al. 2003, Franken et al. 2006,
	Cry1/2	Sleep duration, delta regulation	Wisor et al. 2002,
	Per1/2,Dbp	Recovery sleep regulation	Franken et al. 2007, Wisor et al. 2002, 2008,
	Per3	Sensitivity to sleep pressure	Viola et al. 2007.
Sleep apnea	*Per1*	Changed in PBMCs of patients	Burioka et al. 2008.
Psychiatric diseases	*Clock*	Modulation of DA regulation Response to cocaine in brain	McClung et al. 2005, Uz et al. 2005, Lynch et al. 2008,
	Npas2	Regulation of MAOA	Hampp et al. 2008,
	Bmal1	Response to cocaine in striatum Changed in bipolar disorder Regulation of MAOA	Lynch et al. 2008, Yang et al. 2009, Hampp et al. 2008,
	Per1	Reward pathway	Angeles-Castellanos et al. 2008,
	Per2	Response to cocaine in brain Striatum neuronal activity	Uz et al. 2005, Lynch et al. 2008, Hampp et al. 2008,
	Cry1	Response to cocaine in striatum	Lynch et al. 2008,
	Rev-Erbα	Changed in bipolar disorder	Yang et al. 2009,
	Dbp	Changed in bipolar disorder	Yang et al. 2009.
Metabolism	*Clock*	Lipid and glucose metabolism Regulation of PPARα and lipid metabolism	Turek et al. 2005, Kennaway et al. 2007, Oishi et al. 2005, Inoue et al. 2005,
	Bmal1	Adipogenesis Changed with high cholesterol Glucose metabolism Type 2 Diabetes	Shimba et al. 2005, Gomez-Abellan et al. 2008, Gatfield and Schibler 2008, Woon et al. 2007,
	Per2	Changed with high cholesterol	Gomez-Abellan et al. 2008,
	Cry1	Changed with high cholesterol	Gomez-Abellan et al. 2008,
	Rev-Erbα	Bile acid production Triglyceride and lipid metabolism	Duez et al. 2008, Fontaine and Staels 2007,
	Rev-Erbβ	Lipid Metabolism in muscle	Ramakrishnan et al. 2005,
	Rorα	Lipid Metabolism in muscle Metabolism of steroids, xenobiotics and bile acids	Lau et al. 2004, Kang et al. 2007,
	Rorγ	Metabolism of steroids, xenobiotics and bile acids	Kang et al. 2007.
Cardiac Function	*Clock*	Platelet rhythmic activity Response of cardiomyocytes to fatty acids	Ohkura et al. 2008, Durgan et al. 2006,
	Bmal1	Susceptibility for hypertension	Woon et al. 2007,
	Per2	Aortic endothelial function	Viswambharan et al. 2007,

	Per3	Sympathovagual balance	Viola et al. 2008,
	Rev-Erbα	Circadian activity of PAI-1	Wang et al. 2006.
Cancer and cell cycle	*Clock*	Cell growth and proliferation	Miller et al. 2007,
	Npas2	DNA damage	Hoffman et al. 2008,
	Bmal1	Hepatocytes proliferation	Gréchez-Cassiau et al. 2008,
	Per1	Altered in tumor cells and during chemotherapy	Chen et al. 2005, Terazono et al. 2008,
		Suppression of cancer cells growth via effects on TNFα	Suzuki et al. 2008,
		Control of DNA damage and cell growth	Gery et al. 2006,
	Per2	Cell cycle and survival in tumor	Yang and Stockwell 2008,
		Tumor progression	Yang et. 2008,
		Altered in tumor cells and during chemotherapy	Chen et al. 2005, Terazono et al. 2008,
		Response to DNA damage	Fu et al. 2002,
	Per3	Breast cancer marker	Zhu et al. 2005,
		Altered in tumor cells	Chen et al. 2005,
	Rorγ	Thymocytes differenciation	Kurebayashi et al. 2000, Sun et al. 2000,
	CKIε	Cell cycle and survival in tumor	Yang and Stockwell 2008.
Immune function	*Bmal1*	Development of B cells and functioning of macrophages	Sun et al. 2006, Hayashi et al. 2007,
	Per1	Changed in response to LPS	Okada et al. 2008,
		Changed in response to IL-6	Motzkus et al. 2002,
	Per2	IFNγ production	Arjona and Sarkar 2006, Liu et al. 2006,
		Changed in response to LPS	Okada et al. 2008.
Ageing	*Clock*	Age-related changes following exposure to radiations	Antoch et al. 2008,
	Bmal1	General ageing and lifespan	Kondratov et al. 2006,
	Per2	Changed expression in pineal	Sitzmann et al. 2008,
		Cognitive decrement	Pallier et al. 2007.
Reproduction	*Clock*	Spermatogonia and spermatocytes functioning	Morse et al. 2003,
		Male fertility	Dolatchad et al. 2006,
		Release of LH and pregnancy	Miller et al. 2004, 2006,
	Bmal1	Leydig cells functioning	Alvarez et al. 2008,
	Per1	Spermatids physiology	Morse et al. 2003,
	Per1/2	Efficiency of reproduction	Pilorz and Steinlechner 2008.

Abbreviation: ASPD, advance sleep phase disorder; DA, dopamine; DSPD, delayed sleep phase disorder; IFNγ, interferon gamma ; IL-6, interleukin 6; LH, luteinizing hormone; LPS, lipopolysaccharides; MAOA, monoamine oxidase A; PAI-1, plasminogen activator inhibitor-1; PBMC, peripheral blood mononuclear cells; PPAR, peroxisome proliferator-activated receptor; REM, rapid eye movement; TNFα, tumor necrosis factor alpha.

CORE-CLOCK MECHANISMS

Circadian rhythms originate from molecular regulatory loops of transcription, post-transcriptional modifications, translation and post-translational modifications (Dardente and Cermakian 2007). These feedback loops generate 24 h rhythms in the levels of messenger RNAs (mRNA) from clock genes and their protein products, as well as in the activity of these clock proteins. In mammals, the core-clock proteins CLOCK and BMAL1 associate and activate the transcription of many other clock genes (*Crys, Pers, Rev-Erbs, Rors*) and clock-controlled genes via E-box elements in their promoters (Gekakis et al. 1998, Ueda et al. 2005). The products of these genes then feed back on CLOCK/BMAL1 activity or *Clock/Bmal1* gene transcription (see Fig. 1 for a summary). For example, CRYs and PERs form complexes repressing the activity of the CLOCK-BMAL1 heterodimer and therefore repress their own

transcription (Kume et al. 1999, Sato et al. 2006), whereas nuclear receptors of the REV-ERB and ROR families respectively repress or activate the transcription of *Bmal1* gene (Preitner et al. 2002, Sato et al. 2004, Akashi and Takumi 2005, Guillaumond et al. 2005, Mongrain et al. 2008). Also, the system is regulated by the activity of protein kinases, notably CKIδ/ε and GSK-3, and phosphatases, which controls the association, nuclear translocation and degradation of clock proteins via modulation of their phosphorylation levels (Lowrey and Takahashi 2000, Gallego et al. 2006, Meng et al. 2008). Adding to the complexity of the molecular circadian machinery is the partial and sometimes tissue-specific redundancy of these clock genes (i.e. *Npas2/Clock; Per1/2; Cry1/2;* and possibly *Bmal1/2*; Reick et al. 2001, Dardente et al. 2007, DeBruyne et al. 2006, 2007) and the presence of other feedback elements such as DEC1-2, which appear to form an additional negative feedback loop with CLOCK/BMAL1 (Gréchez-Cassiau et al. 2004, Hamaguchi et al. 2004, Sato et al. 2004, Nakashima et al. 2008).

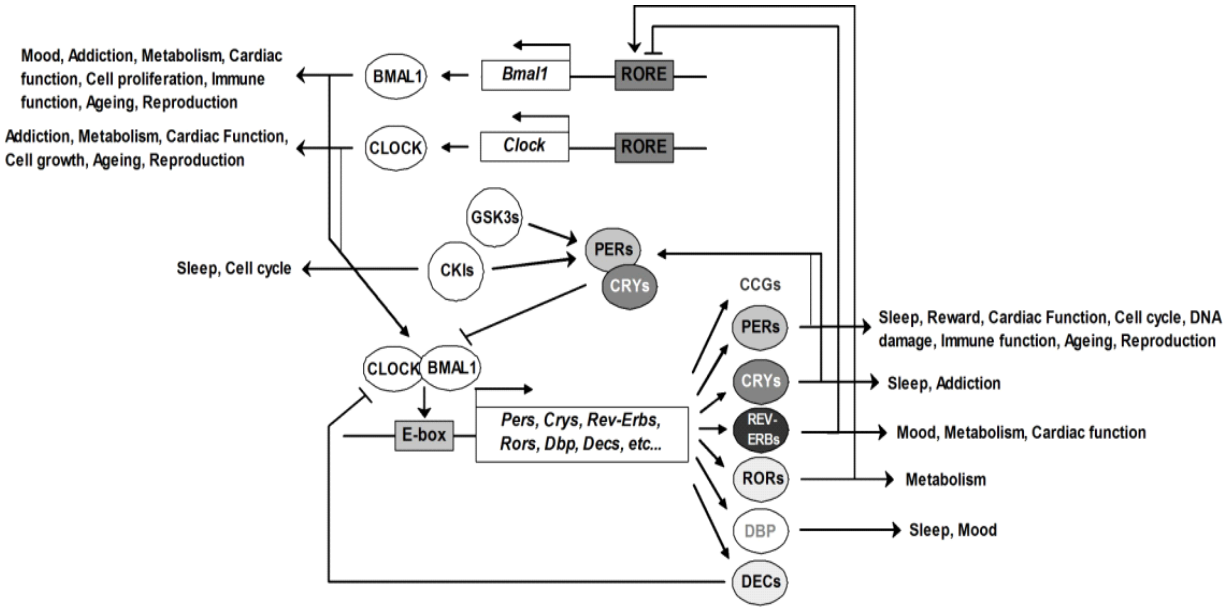

Fig. 1. **Schematic view of the circadian clock mechanisms and their association with physiology.** The CLOCK/BMAL1 heterodimer activates the expression of a number of clock genes. Among these, *Pers* and *Crys* give rise to protein products that inhibit their own expression, while *Rev-Erbs* and *Rors* genes products repress or activate the transcription of *Clock* and *Bmal1* respectively. Evidence showed that these clock components are associated with the normal regulation of sleep, reproduction, psychiatric diseases and mood, cardiac and metabolic function, immune system, cell cycle and proliferation and the ageing process.

The central circadian clock has been localized to the suprachiasmatic nuclei (SCN) of the hypothalamus (Ralph et al. 1990, Silver and Schwartz 2005) and is reset daily by photic inputs from the retina (Hastings and Herzog 2004, Silver and Schwartz 2005). Many other brains regions and peripheral organs have been shown to also express clock genes in a circadian manner (Yamazaki et al. 2000, Reick et al. 2001, Abe et al. 2002, Cermakian and Sassone-Corsi 2002, Schibler et al. 2003, Granados-Fuentes et al. 2004, Yoo et al. 2004, Lamont et al. 2005). Nevertheless, the properties of the different circadian oscillators within an organism appear to differ. The molecular oscillations of individual cells within peripheral tissues desynchronize such that overall tissue rhythm becomes flattened earlier than in the SCN, most likely due to the lack of electrical and/or chemical coupling between cells (Yamazaki et al. 2000, Welsh et al. 2004, Liu et al. 2007a). Also, the synchronization of non-SCN oscillators seems to occur via a wide range of endogenous rhythmic signals (e.g. glucocorticoid, neuronal activity, temperature rhythms) that are mainly dependent on the SCN (Damiola et al. 2000, Reppert and Weaver 2002, Stratmann and Schibler

2006, Kornmann et al. 2007). Additionally, and consistent with the specific functions of the different organs, tissue-specificity in the expression of clock-controlled genes has been reported (Panda et al. 2002, Storch et al. 2002, Duffield 2003). A requirement for proper organism functioning and health seems to reside in the synchronisation of the different clocks within the organism, such that internal desynchrony appears to lead to disease. Examples of such health problems due to deregulated rhythms will be highlighted in the present review.

In addition to adjusting the organism to the external time, clock genes are found to be required for homeostatic systems in mammals. For example, mutations of some clock genes (*Clock*, *Npas2*, *Cry1*/*Cry2*) were found to modify parameters of the homeostatic regulation of sleep in mice (Naylor et al. 2000, Wisor et al. 2002, Dudley et al. 2003, Franken et al. 2006) and changes in clock gene expression in the forebrain are linked with the homeostatic response of slow-wave activity during sleep in the mouse (Franken et al. 2007, Wisor et al. 2008). A role for clock genes in the reproductive system was also underlined by recent studies. Notably, intact clock genes appear important for normal fertility, successful pregnancy, delivery and weaning (Miller et al. 2004, 2006, Dolatshad et al. 2006, Alvarez et al. 2008, Pilorz and Steinlechner 2008). Whether the clock genes govern these functions independently of their role in circadian timekeeping is unclear given the difficulty to distinguish clock-related from clock-unrelated roles.

CLOCKS GENES AND CIRCADIAN OR SLEEP DISORDERS

Intact clock machinery has been reported to be essential for maintenance and stability of circadian rhythms in rodents (see Cermakian and Boivin 2003 for a review). In humans, some pathological conditions are characterized by the misalignment of the sleep episode relatively to the light-dark cycle. Studies of the biology of clock genes in circadian rhythm disorders (mainly delayed sleep phase disorder and advance sleep phase disorder, DSPD, ASPD) have contributed to understanding their etiology as well as to underline their complexity. Additionally, other sleep disorders have been reported to involve changes in clock genes expression.

More than a decade ago, a single nucleotide polymorphism in the human *CLOCK* gene was linked to sleep timing preference (Katzenberg et al. 1998). Thereafter, the *T* allele of this T3111C polymorphism was observed to be weakly associated to late sleep timing or DSPD (Iwase et al. 2002, Robilliard et al. 2002) but not in all populations studied (Pedrazzoli et al. 2007). Similarly, a silent polymorphism in human *PER1* gene seems to be related to extreme diurnal preference (Carpen et al. 2006). Regarding the *PER2* gene, studies have demonstrated that some polymorphisms have no effect on sleep timing (Johansson et al. 2003, Carpen et al. 2005), while one (A2106G) leading to decreased PER2 protein amounts is of great interest in the pathophysiology of ASPD and was shown to be the cause of a familial case of this disorder (Toh et al. 2001, Vanselow et al. 2006, Xu et al. 2007). The involvement of *PER2* polymorphisms in circadian disorders seems to involve changes in PER2 protein phosphorylation levels (Gallego and Virshup 2007). Accordingly, in another family with ASPD, the disorder is caused by a nucleotide change in the *CKI*δ gene (Xu et al. 2005), while a polymorphism in *CKI*ε was found to associate with DSPD (Takano et al. 2004). Many studies reported data about a variable number tandem repeat polymorphism in the human *PER3* gene in relation to diurnal preference or circadian disorders. Overall, the allele with 5 repeats appears to be linked to morningness while the allele with 4 repeats associates with delayed sleep schedule and DSPD (Archer et al. 2003), although this appears to depend on age and latitude (Pereira et al. 2005, Jones et al. 2007). However, subjects specifically selected for their genotype (5/5 and 4/4 individuals) were shown to have similar sleep schedule but to differ in markers of sleep pressure: individuals with the 5/5 genotype show indications of greater sensitivity to sleep deprivation than 4/4 individuals (Viola et al. 2007). Overall, studies in humans and rodents show their importance of functional clock machinery for appropriate sleep timing and sleep homeostasis.

Shift-work sleep disorder (SWSD) has been classified as a circadian and sleep disorder (AASM, 2005) and is most likely the result of misalignment between clocks of different tissues, as well as between circadian clocks and the light/dark cycle. Sleep complaints including excessive daytime sleepiness, poor sleep quality or insomnia are hallmarks of SWSD (Sudo and Ohtsuka 2002, Portela et al. 2004, Paim et al. 2008). But these are only a part of the problems experienced by individuals suffering from SWSD – see Costa (1996) and Schwartz and Roth (2006) for reviews. Other dysfunctions affecting shift-workers will be treated in the next sections where they serve to reinforce the associations between clock genes and specific health issues. Another example of sleep pathology changing the normal sleep/wake

pattern is sleep apnea, where hypoxic episode and awakenings during sleep generate very shallow sleep and drastic sleepiness during wakefulness. Recently, *PER1* rhythmic expression in peripheral blood cells has been shown to be affected in sleep apnea patients (Burioka et al. 2008). Changes in clock gene expression in sleep apnea might underlie alterations of circadian rhythms in vigilance, sympathetic activity, cortisol metabolism and inflammatory mediators in these patients (Andreas and Eichele 2008). Moreover, the susceptibility of these patients to cardiovascular disease may result, at least in part, from such changes in central or peripheral clock mechanisms, as discussed in a subsequent section.

CLOCK GENES AND OTHER PSYCHIATRIC DISORDERS

Links have been reported between the molecular components of the circadian system and psychiatric disorders such as schizophrenia, Alzheimer's disease, major depressive disorder, bipolar disorder, anxiety disorder, drug addiction and alcoholism. Evidence for such links resides in the observations of changes in circadian functions or sleep as well as modifications of clock gene sequence and expression. Since these evidence were recently reviewed in details (Lamont et al. 2007, McClung 2007a, Turek 2007, Barnard and Nolan 2008), only an overview of the latest findings will be provided here.

Interestingly, bipolar disorder has been associated with a reduced circadian amplitude in clock genes expression (e.g. *BMAL1*, *REV-ERBα*, *DBP*) and reduced phosphorylated levels of GSK3β in fibroblasts from patients (Yang et al. 2009). Also, a possible mechanism for normal circadian changes in mood as well as for the link between clock genes and mood disorders was revealed in recent work showing that the regulation of monoamine oxidase A (a key enzyme in dopamine metabolism) was under the control of the clock proteins BMAL1, NPAS2 and PER2 (Hampp et al. 2008). This study also reported that mutation of *Per2* in animals leads to reduced neuronal activity in the striatum and to reduced monoamine oxidase A activity in the mesolimbic dopaminergic system, which is particularly relevant to mood regulation but also to the reward/addiction system.

Robust associations between drug addiction and molecular circadian clocks were also highlighted. First, self-administration of drug of abuse shows circadian variations in rats with a peak of cocaine administration during the active period (Lynch et al. 2008). Of note, the sensitization to cocaine administration also shows a time of day-dependent effect in rodents (Akhisaroglu et al. 2004). Second, repeated administration of cocaine alters the expression of many clock genes in rat and mouse brains. For example, a single or a repeated exposure to cocaine differentially increases the expression of different clock genes (*Per1*, *Per2*, *Per3*, *Clock*) in the hippocampus and the striatum (Uz et al. 2005). Also, self-administration of cocaine up-regulates the expression of *Bmal1*, *Clock*, *Cry1* and *Per2* in the rat striatum (Lynch et al. 2008), indicating that the chronic effects of cocaine consumption could be mediated by changes in clock components in various brain regions. Related observations were also made with other responses of the reward pathway, such as for food or chocolate (Angeles-Castellanos et al. 2008). Third, an intact CLOCK protein appears also important for proper dopamine biosynthesis since increased expression and phosphorylation of tyrosine hydroxylase have been observed in the *Clock* mutant mouse and this in combination with an increase in cocaine reward and excitability of dopamine neurons of the midbrain ventral tegmental area (McClung et al. 2005). Fourth, exposure to drug of abuse appears to entrain circadian oscillators in the body independently of the signals from the master SCN clock (Kosobud et al. 2007). Evidence regarding the involvement of circadian genes in drug sensitivity and sensitization especially by way of the mesolimbic dopaminergic system have been reviewed recently (McClung 2007b) as well as the effects of drug of abuse on the expression of clock genes (Perreau-Lenz and Spanagel 2008).

CLOCKS GENES AND METABOLISM

Considerable evidence points towards the involvement of molecular clock components in the regulation of metabolism, as well as the responsiveness of the clock to metabolic challenges. Increased metabolic dysfunctions are associated with circadian disorganization, for example in shiftworkers or in animals with a deficient circadian clock. Indeed, lipid metabolism seems to be impaired when eating is redistributed during night shifts, as higher LDL cholesterol and higher triacylglycerol have been reported with night food intake in humans (Lennernäs et al. 1994, Holmbäck et al. 2002). These are the main characteristics of the so-called metabolic syndrome experienced by night workers along with a higher body mass index than day workers (Biggi et al. 2008,

Copertaro et al. 2008). Also, hallmarks of metabolic syndrome, such as high LDL and total cholesterol levels, are associated with decreased expression of *BMAL1, PER2* and *CRY1* in human adipose tissue (Gomez-Abellan et al. 2008). Finally, a *BMAL1* haplotype associates with type 2 diabetes in human (Woon et al. 2007).

Work on animals with mutation in clock genes has led to similar observations. Notably, obesity and metabolic syndrome have been reported in *Clock* mutant animals (Turek et al. 2005). According to theses observations, *Clock* would be an important regulator for lipids but also for glucose metabolism as hyperglycemia and hypoinsulinemia are associated with the metabolic syndrome of *Clock* mutant mice (Turek et al. 2005), although less drastic effects were found on a different genetic background (Oishi et al. 2006). Also, mutations of *Clock* or *Bmal1* has been linked to defect in glucose metabolism (Rudic et al. 2004) even when these mutations are restricted to specific peripheral tissues (Kennaway et al. 2007, Gatfield and Schibler 2008, Lamia et al. 2008).

In the liver, the effects of the circadian molecular machinery on lipid metabolism was shown to result from the circadian regulation of key lipid-metabolism players such as low-density lipoprotein receptor and polypeptide-1 (Kudo et al. 2008). Also, data support a role for nuclear receptors in linking circadian clocks and metabolism (Bookout et al. 2006, Yang et al. 2006). An example is the control of bile acid production by REV-ERBα (Duez et al. 2008). In fact, REV-ERBα is an essential regulator of metabolic reactions as it is involved in lipid metabolism, adipogenesis and energy balance – see Duez and Staels (2008) for a review. Nuclear receptors of the ROR family, particularly RORα and RORγ, were also found to be involved in numerous metabolic pathways as those of steroids, xenobiotics and bile acids production (Kang et al. 2007). Moreover, RORα and REV-ERBα are transcriptional regulators of factors involved in triglyceride and lipoprotein metabolisms (i.e. ApoC-III and ApoA1, Fontaine and Staels 2007) while RORα and REV-ERBβ have a similar role for lipid metabolism components in skeletal muscle (Lau et al. 2004, Ramakrishnan et al. 2005).

Other important nuclear receptors are those of the Peroxisome proliferator-activated receptor (PPAR) family, which regulate lipid and glucose metabolisms as well as inflammatory processes. Indeed, data showed that the expression of PPARα is regulated by CLOCK-BMAL1 (Oishi et al. 2005) and that this regulation is directly involved in lipid metabolism (Inoue et al. 2005). Data suggest that significant crosstalk with PPAR nuclear receptors are mediated by REV-ERBα, placing it at a strategic position for circadian regulation of energy homeostasis (Duez and Staels 2008). Lastly, the link between the circadian system and lipid regulation by way of PPAR also appears to be bidirectional as the molecular clock machinery is shown to be affected by mediators of lipid homeostasis and the PPAR pathway (Nakahata et al. 2006, Shirai et al. 2006, 2007, Nakamura et al. 2008).

Additional support to the involvement of nuclear receptors in bridging circadian rhythms and metabolism come from studies in which the disruption of the function of coactivators – e.g. PGC-1α or PGC-1β (Liu et al. 2007b, Sonoda et al. 2007) – or co-repressors – e.g. NCoR/HDAC3 (Alenghat et al. 2008) – of nuclear receptors was shown to alter behavioural circadian rhythms and metabolic processes.

CLOCKS GENES AND CARDIAC FUNCTION

Clock components have been linked to the proper functioning of the cardiovascular system either directly or via their effects on metabolism. Initial evidence were provided by the observations of an increased risk of cardiovascular events (e.g. stroke, sudden cardiac death, myocardial infarction, ventricular arrythmias) at specific clock times, notably between 6 AM and noon (Muller et al. 1987, Siegel et al. 1992, Eksik et al. 2007, Shea et al. 2007, Kawakami et al. 2008). Moreover, individuals submitted to circadian misalignment are more at risk of developing cardiovascular problems. Accordingly, shift work has recently been observed to increase the probability of developing atherosclerosis and myocardial infarction at a younger age (Haupt et al. 2008) and to exacerbate the negative effects of high blood pressure on coronary heart diseases (Virkkunen et al. 2007). Other studies revealed that shift workers present more risk than daytime workers of undergoing coronary heart diseases, hypertension, and cerebrovascular incidents (Boggild and Knutsson 1999, Ellingsen et al. 2007). Even a single night shift was recently shown to increase blood pressure and heart rate as well as to reduce heart rate variability in shift workers (Su et al. 2008). Circadian disorganization has also been associated with increased cardiovascular diseases in rodents (Martino et al. 2008), and altered clock gene expression in cardiovascular organs (Martino et al. 2007). On the whole, these data show that appropriate circadian alignment is necessary to maximize cardiovascular health.

How the molecular components of the circadian clocks and particularly how the precise synchronization or desynchronisation between peripheral oscillators could contribute to cardiovascular health or dysfunction, respectively, was the topic of a detailed recent review (Young and Bray 2007). The link between circadian clock and cardiac health seems to be multifactorial. Among the factors, many cardiovascular components and mediators have been found to be clock-regulated. Notably, the circadian rhythm in platelet activity has been reported to depend on the core-clock component CLOCK (Ohkura et al. 2008), whereas the expression of plasminogen activator inhibitor-1, a major contributor to fibrinolysis, also seems to be clock-regulated (Naito et al. 2003, Wang et al. 2006). Orphan nuclear receptors also seems to be involved in coupling cardiac physiology to circadian rhythms since PPARγ was recently shown to control circadian variations in blood pressure and heart rate via the control of the *Bmal1* gene (Wang et al. 2008). Finally, genetic variations in clock genes were linked to specific cardiovascular phenotype. Particularly, haplotypes for the core-clock gene *Bmal1* have recently been associated with hypertension in both human and rodents (Woon et al. 2007). Moreover, the cardiac autonomic response, more precisely the sympathovagal balance during sleep, depends on the variable number tandem repeats polymorphism in the *PER3* gene (Viola et al. 2008). Therefore, the molecular clock appears highly relevant to cardiovascular physiology.

CLOCKS GENES AND CANCER

One of the most striking associations between circadian rhythms and health relates to cancer. Epidemiological studies have showed an increased incidence of cancer in shift-workers or individuals chronically submitted to jet lag (Hansen 2001, Rafnsson et al. 2001, Buja et al. 2006, Viswanathan et al. 2007). Moreover, increased light levels at night have been observed to co-distribute with breast cancer in women (Davis et al. 2001, Reiter et al. 2007, Kloog et al. 2008). The expression of clock genes in cancer patients undergoing surgery have been reported to be changed (Azama et al. 2007). Also, the expression of clock genes is changed in tumor cells (Filipski et al. 2005, You et al. 2005) and, more precisely, some tumor show altered *PER* gene expression likely due to changes in promoter sequence (Chen et al. 2005). Furthermore, the association between clock genes and cancer resides not only in the fact that a good circadian synchronization and intact circadian machinery are important for cancer prevention but also in the observation that the occurrence of cancer generates a circadian dysfunction, which itself can exacerbate cancer state. Accordingly, circadian rhythms disruption was shown to increase tumor growth (Filipski et al. 2002, 2003, 2004, Otálora et al. 2008). On the other hand, greater amplitude of circadian rhythms in human, as indexed by rest/activity or cortisol rhythms, was associated with increased survival to cancer (Mormont et al. 2000, Sephton et al. 2000), and the response to chemotherapy have been shown to depend on the phase of the circadian cycle with better tumor regression, higher survival rate and less side effects when the therapeutic agents are given at specific circadian time (Gorbacheva et al. 2005, Iurisci et al. 2006, Wood et al. 2006, Lévi et al. 2008). Nevertheless, side effects of chemotherapy are observed on the clock machinery, notably in reducing the amplitude of *Per* gene expression (Terazono et al. 2008), which might in turn contribute negatively to the association between circadian disruption and tumor progression.

What mechanisms are behind this control of tumors by the circadian system? The circadian control of the cell cycle is a likely route for this control (Chen and McKnight 2007, Lévi et al. 2007). Indeed, the cycle of cell division of normal and cancer cells has been reported to be under circadian control as clock-controlled genes are involved in the cell cycle and in cell proliferation, including Wee1, c-Myc and p21 (Matsuo et al. 2003, Fu et al. 2002, 2005, Granda et al. 2005, Wood et al. 2006, Gréchez-Cassiau et al. 2008, Dagenais-Bellefeuille et al. 2008). Of note, CKIε and PER2 appear to be particularly important for cell cycle and cell survival in tumor cells (Yang and Stockwell 2008). Also, mutation of *Clock* decrease cell growth and proliferation in fibroblasts (Miller et al. 2007), while the proliferation of hepatocytes from *Bmal1* KO mice is slowed down compared to wild-type counterparts (Gréchez-Cassiau et al. 2008).

Among clock components, *Per* genes appear central for their involvement in cancer mechanisms. First, a genetic variation in the *PER3* gene was proposed as a marker of breast cancer in young women (Zhu et al. 2005). Second, *PER* genes have been reported to act as tumor suppressors (Lee 2006), given that *Per1* and *Per2* are potential modulator of DNA damage (Fu et al. 2002, Gery et al. 2006). Third, recent studies showed that on one side *Per1* is

involved in the suppression of cancer cells proliferation via TNF-α (Suzuki et al. 2008) while on the other hand that *Per2* is crucial to prevent tumorigenesis (Yang and Stockwell 2008, Yang et al. 2008). Despite the evidence supporting an anti-tumoral role of clock components, disruption of the circadian timing system produced by mutation of *Cry1* and *Cry2* does not increase cancer predisposition or DNA damage by itself (Gauger and Sancar 2005). This suggests that not any disruption of clock function leads to tumorigenesis.

The links between the molecular biology of circadian rhythms and cancer could also be mediated, at least in part, by the circadian regulation of the immune system. The circulating levels of some immune cells (e.g. neutrophils, monocytes, lymphocytes) and cytokines (e.g. interleukin-2, 10, tumor necrosis factor-α) in the blood show circadian rhythmicity (Young et al. 1995, Born et al. 1997) as is the case for phagocytosis by neutrophils (Hriscu 2005). Also, data from mutant mice strongly support a role for *Bmal1* in B cell development and macrophage function (Sun et al. 2006, Hayashi et al. 2007) and for the implication of *Per2* in the circadian control of interferon-γ production (Arjona and Sarkar 2006, Liu et al. 2006). Additionally, mediators of the immune response have been shown to influence clock gene expression. Notably, inteleukin-6 was shown to induce *PER1* expression in human hepatoma cells (Motzkus et al. 2002), and tumor necrosis factor-α suppresses the expression of several clock genes in the liver and alters locomotor activity rhythms (Cavadini et al. 2007). Recently, lipopolysaccharide injection was found to blunt expression of *Per1* and *Per2* transcripts in both the SCN and the liver (Okada et al. 2008). Lastly, some studies showed that symptoms of inflammatory disease display circadian variations (Cutolo et al. 2003), while the hematopoietic lineage *per see* seems to be regulated in a circadian fashion (Berger 2008, Méndez-Ferrer et al. 2008).

CLOCK GENES AND AGEING

The molecular machinery of circadian clocks is also relevant to ageing and particularly to the age-related decrement in circadian amplitude, memory and cognitive function. It is well known that aged humans experience reduced amplitude in circadian rhythms of activity, core body temperature, melatonin secretion and EEG circadian hallmarks (Cajochen et al. 2006). Moreover, recent literatures supports the involvement of the central circadian clock in age-dependent changes in neuronal function. For example, data suggest that distinct neuronal populations of the SCN are implicated in different functional modifications in human dementia, as activity and temperature rhythms (Harper et al. 2008). In rats, the temporal relationship between the main circadian clock and peripheral oscillators appears modified with age (Yamazaki et al. 2002), and resetting of internal circadian clocks following phase shifts are modified in aged rats such that the synchrony between clocks is reduced (Davidson et al. 2008). In primates, age was shown to affect clock gene expression in pineal gland (Sitzmann et al. 2008). Mice mutant for the core clock component BMAL1 exhibit many signs of premature ageing in combination with a reduced lifespan (Kondratov et al. 2006). Similarly, recent data also showed that *Clock* mutant animals accelerate their ageing process following exposure to radiation as indexed by increased amount of hyperplastic lesions, higher mortality rate and stronger weight loss than wild-type littermates (Antoch et al. 2008). Overall, these results suggest that a proper functioning of the circadian system and its underlying molecular components is protective against age-related degeneration.

Animal studies lend support to the involvement of the circadian system in age-related changes in neurobehavioral functions. For example, circadian disruption impairs various aspects of cognition in rats (Fekete et al. 1985, Craig and McDonald 2008) and more particularly so in aged animals (Antoniadis et al. 2000). Also, treatment of a mouse model of Huntington's disease (a neurodegenerative disorder) improves the expression of *Per2* in combination with slowing cognitive decrement (Pallier et al. 2007). Notably, recent data suggest that the link between ageing and circadian rhythms could reside in the circadian regulation by nitric oxide, whose levels are greatly reduced with ageing (Kunieda et al. 2008). As well, inhibition of nitric oxide synthase activity leads to modifications in clock gene expression in aorta (Kunieda et al. 2008), this association could also explain the age-related susceptibility in cardiovascular disease since nitric oxide is a main regulator of the cardiovascular biology. Finally, the relationship between clock genes and neuronal or cellular health throughout ageing could be mediated by the control of the length of chromosome extremities (telomere), which could virtually indicate a role for circadian regulation of ageing in every cells of the organism, as suggested by a recent study (Qu et al. 2008).

CONCLUSION AND PERSPECTIVES

In conclusion, the molecular biology of circadian rhythms is involved in a wide variety of homeostatic functions in mammals and is of particular relevance to human health (Fig. 1). This molecular system does not only regulate various aspects of health but is also highly responsive to alterations in internal biology. It is increasingly obvious that elements identified as the molecular clock components – clock genes – do not only orchestrate animal physiology in relation to environmental light-dark cycle but also allow appropriate response to internal changes in physiology. Numerous example of such bidirectional regulation between the circadian clock and other physiological systems have been described in the present review. For instance, while the behavioral and biochemical effects of drug of abuse show a time-dependent response, the exposure to these substances modifies considerably the molecular regulation of clock genes. Another example is that normal molecular circadian organization seems required for appropriate anti-cancer protection but the occurrence of cancer generates considerable circadian disruption. In some cases, such bidirectional influences might exacerbate states of health that are already damaged. Accordingly, it might be of importance to consider clock genes as regulatory genes and/or early response genes and to assess their regulation on a routine basis in health research and treatment.

ACKNOWLEDGEMENTS

V. M. has been supported by fellowships from the Fonds de la Recherche en Santé du Québec (FRSQ) and Natural Science and Engineering Research Council (NSERC, Canada) and N. C. by an FRSQ salary award. Research in N. C.'s laboratory is supported by NSERC and the Canadian Institutes for Health Research.

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