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Invited Review Article

Chronopharmacology of immune-related diseases

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ABSTRACT

Clock genes, circadian pacemaker resides in the paired suprachiasmatic nuclei (SCN), control various circadian rhythms in many biological processes such as physiology and behavior. Clock gene regulates many diseases such as cancer, immunological dysfunction, metabolic syndrome and sleep disorders etc. Chronotherapy is especially relevant, when the risk and/or intensity of the symptoms of disease vary predicably over time as exemplified by allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke, and peptic ulcer disease. Dosing time influences the effectiveness and toxicity of many drugs. The pharmacodynamics of medications as well as pharmacokinetics influences chronopharmacological phenomena. To escape from host immunity in the tumor microenvironment, cancer cells have acquired several pathways. Immune checkpoint therapy targeting programmed death 1 (PD-1) and its ligand (PD-L1) interaction had been approved for the treatment of patients with several types of cancers. Circadian expression of PD-1 is identified on tumor associated macrophages (TAMs), which is rationale for selecting the most appropriate time of day for administration of PD-1/PD-L1 inhibitors. The therapies for chronic kidney disease (CKD) are urgently needed because of a global health problem. The mechanism of the cardiac complications in mice with CKD had been related the GRP68 in circulating monocytes and serum accumulation of retinol. Development of a strategy to suppress retinol accumulation will be useful to prevent the cardiac complications of CKD. Therefore, we introduce an overview of the dosing time-dependent changes in therapeutic outcome and safety of drug for immune-related diseases.

Introduction

One of the most indispensable biological functions is the circadian clock (suprachiasmatic nuclei; SCN) and acts like a multifunction timer to regulate homeostatic systems such as sleep and activity, hormone levels, appetite, and other bodily functions with 24 h cycles.[1–6] The function of physiology as well as the pathophysiology of diseases is influenced by biological rhythms. Chronopharmacology is the science elucidating the biological rhythm dependencies of medications. 24 h rhythms of biochemical, physiological and behavioral processes under the control of circadian clock induce the dosing-time-dependence in the effectiveness and toxicity of many drugs. The pharmacodynamics of medications as well as pharmacokinetics cause chronopharmacological phenomena. Chronotherapy is especially relevant in the following cases.[7–13] The risk and/or intensity of the symptoms of disease vary predicably over time as exemplified by allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke, and peptic ulcer disease. Circadian clock genes are identified as molecules that ultimately control a vast array of circadian rhythms in physiology and behavior under healthy condition,[14–19] but they also regulates the state of several diseases such as cancer, metabolic syndrome and sleep disorder etc.[20–23]

The circadian rhythms have been demonstrated in pathogens, vectors, infectious diseases and immune system.[24] This approach leads to a new field of time-based personalized treatment of infected patients. The host defense against pathogens are different among individuals. Among the factors influencing host immune response, those associated with circadian disruptions are emerging. The circadian clock controls the two partners of host defense: microbes and immune system. The infections are closely associated with circadian rhythms from viewpoints of susceptibility, clinical presentation, and severity. The experimental and clinical evidences

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highlight the importance of the interplay between the circadian clock and viral infections.[25] The circadian rhythms driven by the master clock in the brain synchronizes with clocks in peripherals, involving our immune system that regulates the severity of infections. These rhythms also affect the efficacy of therapeutic agents and vaccines. Recent knowledge of the interplay between the circadian clock and viral infections are summarized to inform therapeutic strategies against SARS-CoV-2 and COVID-19.[26] Many studies supports the role of the circadian clock in regulating various aspects of viral replication, host responses, and associated pathogenesis.

The host immune system recognizes cancer cells as foreign and works to eliminate them through the action of tumor-antigen-specific T cells, lymphocytes, and macrophages. In a physiological context, the binding of programmed death 1 (PD-1) to its ligand (PD-L1) functions to prevent excessive immune responses and autoimmunity.[27] However, the interaction between PD-1 and PD-L1 suppresses the host antitumor immune response. Immune checkpoint inhibitors have been developed as aiming to prevent the binding of immune checkpoint protein to the ligand, and they enables to release the brake on the host antitumor immune response and enhance the killing of tumor cells. Although the blockade of PD-1/PD-L1 interactions promotes T cell-mediated antitumor effects, antitumor activity of tumor associated macrophages (TAMs) is also suppressed by the PD-1/PD-L1 pathway. In recent findings, the circadian expression of PD-1 is identified on TAMs, which is rationale for selecting the most appropriate time of day for administration of PD-1/PD-L1 inhibitors.[27] The antitumor efficacy of PD-1/PD-L1 inhibitor varies according to its administration time. Selecting the most appropriate dosing time of PD-1/PD-L1 inhibitors may aid in developing cancer immunotherapy with higher efficacy.

The novel therapies to CKD are urgently needed because of a global health problem.[28–30] The mechanism of cardiac complications in mice with CKD have been investigated. The CLOCK/BMAL1-mediated transactivation of G protein-coupled receptor 68 (GPR68) in circulating monocytes is induced by serum accumulation of retinol, and their migration into the heart ventricle exacerbates inflammation and fibrosis. Increased serum retinol levels in CKD patients are also sufficient for inducing the expression of GPR68 and inflammatory cytokines in human monocytes. As lipophilic non-dialyzable compounds, including retinol, often accumulate in CKD patients due to a lack of elimination through renal metabolism and dialysis, development of a strategy to suppress retinol accumulation will be useful to prevent the cardiac complications of CKD. The aim of this review is to provide an overview of the dosing time-dependent changes in therapeutic outcome and safety of drug for immune-related diseases.

Biological time and molecular clock

Biological time structure describes the sum of non-random and thus predictable time-dependent biologic changes, including, with growth, development and aging, a spectrum of rhythm with different frequencies.[7,12] The site of the circadian pacemaker in mammals is SCN of the anterior hypothalamus (Fig. 1).[1,2,9,10,14,15] Like any timing system, the circadian clock is composed of three parts: an input pathway adjusting the time, a central oscillator generating the circadian signal, and an output pathway manifesting itself in circadian physiology and behavior. The diurnal differences in light intensities are considered to be the major environmental cue involved in circadian entrainment.

Three mammalian Period genes (Per1, Per2, and Per3) are rhythmically expressed in the SCN. Per1 and Per2 are induced in response to light.[19] Particularly, Per1 induction is thought to be an initial event in light-induced resetting and entrainment of the circadian biological clock.[18] The transcriptional machinery of the core clockwork controls a clock-controlled rhythm as shown in Figure 1.[1,2,9,10,14,15] Namely, CLOCK (circadian locomotor output cycle kaput)-BMAL1 (brain and muscle ARNT-like protein 1) heterodimers act through an E box enhancer to activate the transcription of Pers, vasopressin and Dbp mRNA showing a specific output function.[15,17] This activation can be inhibited by the PER and CRY proteins.[16] A circadian rhythm of Pers mRNA expression is discovered in other tissues as well as SCN.[31] The circadian rhythm in the SCN controls that in the peripherals, since the circadian rhythm in physiological function and Pers mRNA expression are abolished in SCN-lesioned rats.[31] Such hierarchical construction of circadian clock system may play a key role in organizing biological rhythms in the whole body. However, the mechanisms controlling circadian output pathways are poorly understood but seem to involve both nervous and humoral signals.[4,5] Plasma glucocorticoid concentrations indicate a circadian rhythm via the HPA axis under the

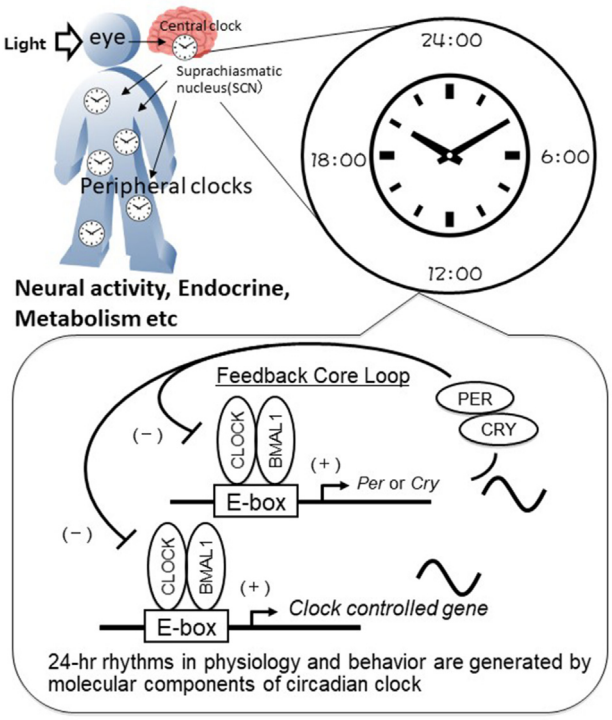

Fig. 1. Shematic diagram of the circadian system under control of the SCN of the anterior hypothalamus, the site of the circadian pacemaker in mammals.[1,2,9,10,14,15] The circadian clock is composed of three components: an input pathway adjusting the time, a central oscillator generating the circadian signal, and an output pathway manifesting itself in circadian physiology and behavior. The various environmental factors such as lighting condition, feeding schedules, social interactions and several drugs regulate the circadian rhythms of physiology and behavior. The daily changes in light intensities are thought to be the major environmental cue involved in circadian entrainment. Light-signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retinohypothalamic tract. Clock genes were identified as the genes that ultimately control a vast array of circadian rhythms in physiology and behavior. The clock genes are expressed not only in the SCN, but also in other brain regions and various peripheral tissues. Such a cascade of clock genes may contribute to the organization of biological rhythms in the whole body. The mechanisms employed by circadian output pathways are likely to involve both nervous and humoral signals. CLOCK and BMAL1 heterodimers activate clock genes and clock-controlled genes transcription in simplified model of the dual regulation of a core feedback loop. The PER and CRY proteins shut down CLOCK-BMAL1 upregulation in the nucleus, forming a negative feedback loop. The phosphorylation of PER1 (period) and PER2 by CKIε (casein kinase I epsilon) may regulate their cellular location and stability. Clock-controlled genes products including DBP (D-element binding protein) and AVP (arginine vasopressin) transduce the core oscillation to downstream output systems.

regulation of the SCN. Glucocorticoids control various physiological responses and developmental processes by binding to and modulating the transcriptional activity of their cognate nuclear receptor.[32,33] A single administration of dexamethasone induces a transit induction of Per1 and Dbp mRNA levels.[33] Glucocorticoid hormones are particularly attractive candidates as humoral circadian signal, since they are endogenous substances and play a critical role in the entrainment of peripheral oscillators but not SCN.[33]

Chronobiology of disease occurrence and molecular clock

Chronotherapy is based on the circadian rhythms in physiological functions and diseases. Previous report shows the approximate peak time of 24 h rhythms relative to the diurnally active human beings (Fig. 2).[8] 24 h rhythms in the processes related to the pathophysiology of diseases cause significant day–night patterns in the manifestation and severity of many medical conditions as described previously (Fig. 3).[8]

BMAL1 contributes to the regulation of cell differentiation and general physical functions. BMAL1-deficient mice exhibit significant reduced number of B cells in the peripheral blood, spleen and bone marrow.[34] The number of pre-B cells in bone marrow of BMAL1-deficient mice is similar to that in control mice. Normal T and B cell development is observed by adoptive transfer of BMAL1-deficient bone marrow cells to lethally irradiated BALB/c Rag2−/− recipients, whereas significant impairment of B-cell development is detected by adoptive transfer of BALB/c bone marrow cells to lethally irradiated BMAL1-deficient recipients. Consequently, BMAL1 plays an important role in the development of B cells, but not other immune cells.

Neutrophils eliminate pathogens efficiently but can cause severe damage to the host if they over-activate within blood vessels. Therefore, neutrophil-intrinsic circadian clock coordinates immune defense and vascular protection.[35] BMAL1 regulates the expression of the chemokine CXCL2 to induce chemokine receptor CXCR2-dependent circadian variations in the transcription and migratory properties of circulating neutrophils. BMAL1 also plays an important role in controlling the circadian rhythms in Ly6C-expressing (Ly6Chigh) monocyte numbers. Circadian rhythm in Ly6Chigh inflammatory monocytes induce the time of day-dependent changes in their trafficking to inflammation sites.[36] This cyclic pattern of trafficking confers protection against listeria monocytogenes. Myeloid cell-specific deletion of BMAL1 induces expression of monocyte-attracting chemokines and disrupts circadian variation of Ly6Chigh monocytes, predisposing mice to development of pathologies related to acute and chronic inflammation. The disruption of circadian rhythm of cytokine and cytolytic factors are observed in Per1-mutated splenic natural killer (NK) cells.[37] The alteration of circadian rhythm of NK cell immune factors is accompanied by changing the circadian rhythm of Bmal1 and Per2.

The Bmal1 defective macrophages confer protection against pneumococcal pneumonia.[38] Infected Bmal1 knockout mice show both reduced weight loss and lower bacterial burden in circulating blood. Bmal1 defective macrophages reveal increased phagocytic ingestion of bacterial. The analysis of the Bmal1 defective macrophages identify altered cell morphology and increased motility. Bmal1 defective cells are also more susceptible to infection by two major respiratory viruses of the Paramyxoviridae family, namely RSV and PIV3.[39] Embryonic fibroblasts prepared from Bmal1 knockout mice produce nearly 10-fold more progeny virus than their wild-type controls. Bmal1 can control cellular innate immunity against specific RNA viruses. The time of day of host infection also affects virus progression in mice and cells.[40] Furthermore, herpes and influenza virus infections are enhanced when host circadian rhythms are altered by deficient in Bmal1. Intracellular trafficking, biosynthetic processes, protein synthesis, and chromatin assembly all play a critical role in controlling the circadian rhythm of virus infection.

The inflammatory lung diseases in human being frequently show circadian rhythm in symptom severity and pulmonary function. The pulmonary antibacterial responses are modulated by a circadian clock within epithelial club (Clara) cells.[41] These drive

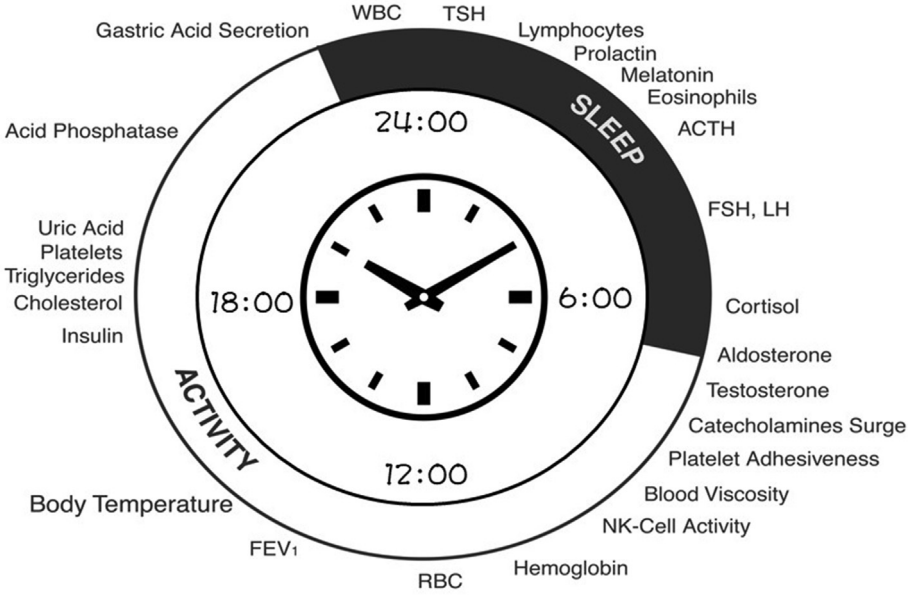

Fig. 2. Demonstration of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep, when physiological or biochemical function indicates a peak.[8] The findings demonstrate the approximate peak time of 24 h rhythms relative to the diurnally active human beings. The peak in serum cortisol, aldosterone, testosterone, platelet adhesiveness, blood viscosity and NK-cell activity is observed during the initial hours of daytime. Hematocrit is greatest and airway caliber (FEV1) best around the middle and afternoon hours, respectively. Insulin, cholesterol, triglycerides, platelet numbers, and uric acid peak later during the day and evening. The rhythms of basal gastric acid secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) indicates a peak at specific times during the nighttime.

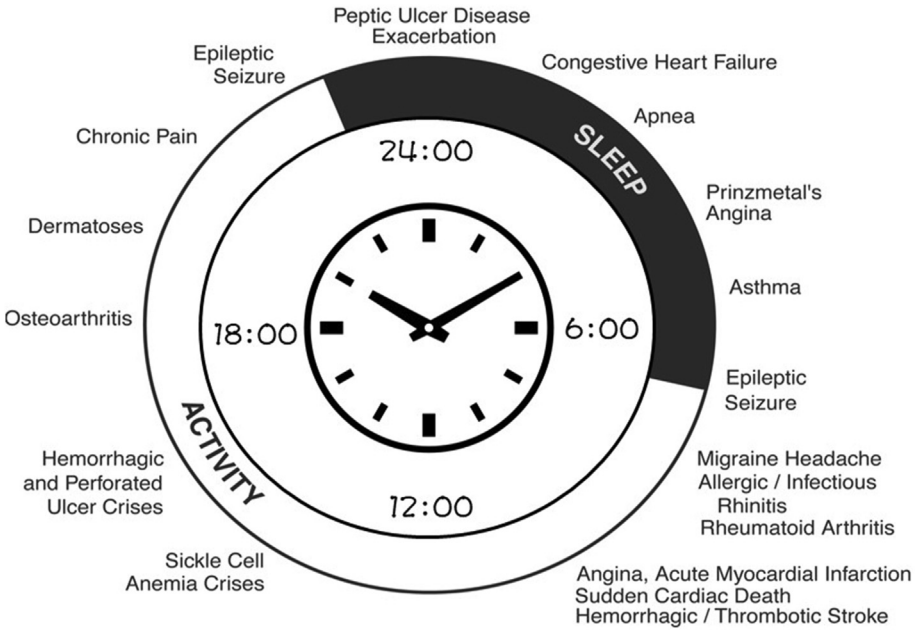

Fig. 3. Demonstration of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events of diseases are worst or most frequent.[8] The onset of migraine headache is most frequent in the morning around the time of awakening from nighttime. The sneezing, runny nose, and stuffy nose in allergic and infectious rhinitis are worst in the morning upon arising from nighttime. The symptoms of rheumatoid arthritis are worst when awaking from nighttime, while those of osteoarthritis are worst later in the day. The morbid and mortal events of myocardial infarction are greatest during the initial hours of daytime. The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. The ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to five hours of daytime. The pain and gastric distress at the onset and acute exacerbation of peptic ulcer disease are most likely in the late evening and early morning. The seizures of epilepsy are common around sleep onset at night and offset in the morning. The symptoms of congestive heart failure are worse nocturnally. The manifestation of ST-segment elevation in Prinzmetal's angina is most frequent during the middle to later half of the nighttime. The risk of asthma attack is greatest during nighttime.

circadian neutrophil recruitment to the lung via the chemokine CXCL5 whose expression is regulated by Bmal1. Adrenalectomy blocks the circadian responses of inflammation and the circadian expression of CXCL5, suggesting a critical role for the adrenal axis in driving CXCL5-mediated immune function and pulmonary neutrophil recruitment. Although the occupancy of glucocorticoid receptor at the Cxcl5 locus shows circadian rhythms, this is disrupted in mice with bronchiole-specific ablation of Bmal1.

Influenza is a leading cause of respiratory mortality and morbidity. The inflammation response is modulated by circadian clock machinery and is essential for fighting infection, a balance of antiviral defense and host tolerance. The survival in influenza infection is influenced by circadian rhythm.[42] Circadian regulation of influenza infection is mediated by enhanced inflammation as proven by increased cellularity in bronchoalveolar lavage, pulmonary transcriptomic profile and histology, but it is not attributable to viral burden. Better survival is related to a time-dependent preponderance of NK and NKT cells and lower proportion of inflammatory monocytes in the lung. The mechanism regulating circadian gating of influenza infection have been clarified by means of using a series of genetic mouse mutants.

Relevance of chronobiology and chronopharmacologic concepts to drug effectiveness and side effect

Chronopharmacology indicates the findings of a chronobiological study to pharmacological phenomena.[8] Chronobiological approach involves less risk of error and/or false information than the conventional homeostatic approach. Chronopharmacology includes the chronotoxicology describing undesired or harmful effects from chemical, physical or other agents including poisons, pollutants and overdoses of drugs upon biologic temporal characteristics and as a function of biologic timing and the chronotherapy endeavoring to cure or prevent disease, with proper regard to temporal characteristics, for example corticosteroid therapy timed to simulate the adrenocortical cycle in Addison's disease.

Glucocorticoids are often used for the therapy of systemic inflammatory diseases such as rheumatoid arthritis (RA), although their beneficial effects have to be balanced with potential complications arising from high doses, prolonged use or dose splitting.[43] A modified-release prednisone (a kind of glucocorticoid formulation) has been developed to be taken in accordance with biological rhythms. Morning symptoms of RA are caused by nocuturnal elevation of IL-6 levels. The early-morning rise in cortisol can be supplemented with exogenous glucocorticoid replacement therapy if this is given as the recently developed chronotherapy formulation.

The circadian rhythm of serum cortisol in day-active humans peaks in the morning, generally around 08:00. Time-dependent effects of corticosteroid medications have been studied on adrenal suppression after a single infusion of methylprednisolone (MP) at different clock times to diurnally active healthy subjects.[44,45] When MP is infused between 08:00 and 16:00, cortisol secretion remains normal. Moderate suppression of cortisol secretion is detected when MP is infused during the late afternoon and early evening. By contrast, cortisol secretion is markedly suppressed when MP is infused between 00:00 and 04:00. The dosing time-dependent inhibitory effect of MP on cortisol secretion is due to the circadian rhythm in drug-induced inhibition of hypothalamic-pituitary-adrenal (HPA) axis. Inhibition of ACTH secretion is more likely caused when MP is infused late in the day and at night rather than during the morning and early afternoon hours. Once-daily administration of corticosteroid tablet at morning has negligible effect on HPA axis.[46,47] On the other hand, the same daily dose split into four equal administrations to coincide with daily meals and bedtime results in causing significant HPA axis suppression.

A sustained-release theophylline, a once-daily dosing of armophylline (600–900 mg/24 h), is administered into eight patients suffering from nocturnal asthma either at 08: 00 or 20: 00 for 8 day durations in cross-over randomized, double-blind, study.[48] The monitoring parameters are self-measured peak expiratory flow (PEF), heart rate, oral temperature, and self-rated fatigue checked every 2 h during the waking span as well as upon spontaneous nocturnal awakenings, and subjects are also measured duration and characteristics of sleep rated every morning. Additionally, the parameters described above as well as serum theophylline concentration are measured every 2 h during the 24 h of the eighth day of each timed treatment span. Dosing at 08:00 fails to prevent a nocturnal dip in PEF, which is lower about 20% from the level achieved at the time of the diurnal crest. In contrast, dosing at 20:00 moderates the nocturnal fall in PEF. It is lower only about 10% from the level of diurnal peak and within the physiologic limits of non-asthmatic persons. The theophylline concentration peak height (Cmax) is greater and time-to-peak (Tmax) shorter with dosing at 08:00 than at 20:00. Dosing of theophylline at 20:00 indicates its serum concentration plateau of about 12 h. A statistical significant correlation between PEF and the corresponding-in-time serum theophylline concentration is observed with dosing at 20:00 but not with dosing at 08:00. A small, but statistically significant, higher heart rate results from 20:00 dosing in five out of eight subjects relative to the 08:00 dosing.

Chronopharmacodynamics

Biological rhythms influence the pharmacokinetics and pharmacodynamics of medications as well as the pathophysiology of diseases. Chronopharmacology is the science investigating the biological rhythm dependencies of medications. The biological rhythms at the cellular and subcellular level cause the dosing-time dependence in the pharmacodynamics of medications that are unrelated to their pharmacokinetics.[49–52] This phenomenon is termed chronesthesy, which is composed of rhythms in receptor number or conformation, second messengers, metabolic pathways, and/or free-to-bound fraction of medications.

Tumor tissue is composed of not only cancer cells, but also numerous noncancer cells such as fibroblasts, epithelial cells, lymphocytes, macrophages, and myeloid-derived suppressor cells. The tumor microenvironment is also related to the extracellular matrix, growth factors, and cytokines, and supports tumor growth and resistance to chemotherapy.[27] Although immune cells infiltrate tumor tissue to eliminate cancer cells, there are several pathways through the tumor microenvironment to escape host immunity. One of important pathways is an immune checkpoint mediated by PD-1 receptor and its ligand PD-L1. PD-L1 binds to PD-1 receptor expressed on T cells and TAMs, preventing their antitumor activities through the induction of exhaustion and apoptosis. Immune checkpoint inhibitors targeting the PD-1/PD-L1 interaction are used in immunotherapy such as advanced cancers such as melanoma, renal cancer, and lung cancer. Although they have long-term, potentially clinical benefits, only a few patients (20%–30%) are estimated to have a positive response to PD-1/PD-L1 blockade therapy, and primary or acquired resistance may lead to tumor progression in patients with a clinical response. The circadian expression of PD-1 is observed in TAMs obtained from B16 melanoma-bearing mice (Fig. 4).[27] DEC2, a component of circadian clock, rhythmically suppresses NF-kB-mediated transactivation of Pdcd1 gene, encoding PD-1, thereby governing its diurnal expression in TAMs. The antitumor efficacy of BMS-1, a small molecule inhibitor of PD-1/PD-L1, is enhanced by administering the drug at the time of day when PD-1 expression increased on TAMs. Identification of the diurnal expression of PD-1 on TAMs may be useful for selecting the most appropriate time of day to administer PD-1/PD-L1 inhibitors.

Chronopharmacokinetics

Chronopharmacokinetics shows biologic time-related changes in the pharmacokinetics of an agent quantified by parameters of one or several curve patterns (models). Chronopharmacokinetic studies have been reported for many drugs in an attempt to explain chronopharmacological phenomena and demonstrate that the time of administration is a possible factor of variation in the pharmacokinetics of a drug. Time-dependent differences in

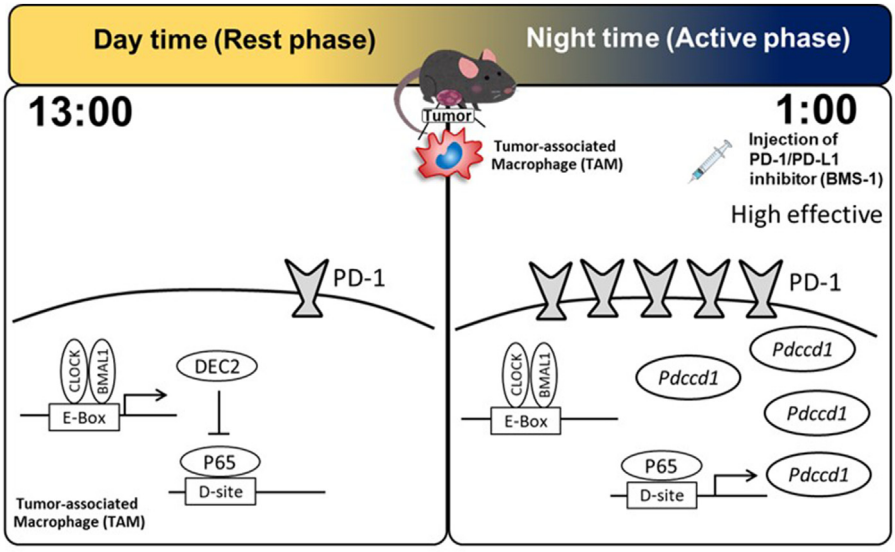

Fig. 4. Circadian expression of PD-1 in tumor associated macrophages (TAMs) underlies the dosing time-dependent difference in antitumor effect of immune checkpoint inhibitor BMS-1, a small molecule inhibitor of PD-1/PD-L1.[27] A component of NF-kB, p65, enhances the transactivation of Pdcd1 gene encoding PD-1, but the NF-kB-mediated transactivation of Pdcd1 is periodically repressed by DEC2. The time-dependent repressesion of NF-kB-mediated transactivation by DEC2 governs diurnal expression of PD-1 in TAMs. The antitumor efficacy of BMS-1 is enhanced by administering at the time of day when PD-1 expression is increased on TAMs.

pharmacokinetics are caused by 24 h rhythms at each process such as absorption, distribution, metabolism, and elimination. Those rhythms are associated with 24 h variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, drug protein binding, liver enzyme activity and/or hepatic blood flow, glomerular filtration, renal blood flow, urinary pH, and tubular resorption.[8] Chronopharmacokinetics can, but not always, be responsible for daily variation in drug effects and/or adverse effects.

The microarray analysis detect many genes showing circadian expression in the liver.[53] The liver is a biological clock capable of generating its own circadian rhythms.[54] Analysis of relative levels of gene expression in the liver of rats is studied as a function of time of day.[53] A circadian rhythm is demonstrated for six genes composed of regulation of gene transcription of drug metabolism enzymes and transporters.[53] The retinoic acid receptor-alpha and the retinoid X receptors (RXR), nuclear receptor, play a critical role in control of gene expression by forming transcriptionally active complexes on DNA. Aryl hydrocarbon receptor nuclear translocator (Arnt) also works as a transcription factor in diverse signaling events including response to xenobiotics.

A PAR bZip transcriptional fector DBP also plays a key role in central clock oscillation. DBP participates in the control of several clock outputs such as locomotor activity, sleep distribution, and liver gene expression. Also, DBP is a main factor regulating circadian expression of the steroid 15 α-hydroxylase (Cyp2a4) and coumarin 7-hydroxylase (Cyp2a5) genes in mouse liver.[55] In addition to DBP, other PAR bZip transcriptional fectors HLF, and TEF are also involved in circadian output pathway. DBP, HLF, and TEF triple mutant mice are born at expected Mendelian ratios, but are epilepsy prone, age at an accelerated rate, and die prematurely.[56] DBP, TEF, and HLF accumulate in a strong circadian fashion in many peripheral tissues, including liver and kidney. The disruption of these three genes in mice causes gene expression alterations of many proteins involved in drug metabolism and xenobiotic transporters. The triple mutant mice also exhibit altered responses to xenobiotic agents (Fig. 5).[56]

Chrono-drug delivery system (DDS)

The rationale behind chronotherapy has been reported.[57–60] Chronopharmaceutics describe contemporary challenges to the development of DDS. The traditional goal of pharmaceutics such as a constant drug release rate is becoming obsolete due to advances in chronobiology, chronopharmacology, and global market constraints. However, the major bottleneck in the development of chrono-DDS matching the circadian rhythm may be the availability of appropriate technology. The technologies in chronopharmaceutics are composed of CONTIN®, physicochemical modification of the active pharmaceutical ingredient, OROS®, CODAS®, CEFORM®, DIFFUCAPS®, chronomodulating infusion pumps, TIMERx®, three-dimensional printing, controlled-release erodible polymer and controlled-release microchip strategies.[13] As examples of Chrono-DDS on the market, these are compounds such as theophylline (Uniphyl®), famotidine (Pepcid®), simvastatin (Zocor®), COER-verapamil (Covera-HS®, Verelan® PM), diltiazem (Cardizem® LA) and propranolol (InnoPran® XL). Most data have been compiled from FDA electronic orange book,[60] specific product package inserts and United States patents and specific pharmaceutical company websites. Future development in chronopharmaceutics may be made at the interface of other emerging disciplines such as system biology and nanomedicine. Such novel and more biological approaches to drug delivery may lead to safer and more efficient disease therapy in the future. Chronotherapy is known especially for antitumor agents. Chronomodulated infusion of oxaliplatin (peak at 16:00), 5-FU (peak at 04:00), and folinic acid (peak at 04:00) is compared with a constant-rate infusion method.[61,62] The circadian stage at which anticancer drugs are given to patients should be carefully considered. One approach to increasing the efficiency of pharmacotherapy is administering drugs at times during which they are best tolerated.

Monitoring of rhythm, overcome of rhythm disruption and manipulation of rhythm

The monitoring of rhythm, overcome of rhythm disruption and manipulation of rhythm from viewpoints of molecular clock are essential to improved progress and diffusion of chronopharmacotherapy.[9,10]

Rhythm monitoring

The qualitative evaluation of circadian clock gene expression is essential for a thorough understanding of the circadian clock. The technique using biopsy samples of hair follicle cells from the head or chin has been developed as a convenient, reliable, and less invasive method for detecting human clock gene expression.[63] The circadian phase of clock gene expression in hair follicle cells accurately reflects that of individual behavioral rhythms. This method is appropriate for evaluating the circadian clock expression in human periphery, even if rotating shift workers suffer from a serious time lag between circadian gene expression rhythms and lifestyle. Determination of internal body time (BT) via a few-time-point assay has been a longstanding challenge in medicine because the metabolomics-based detection of BT (“metabolite-timetable

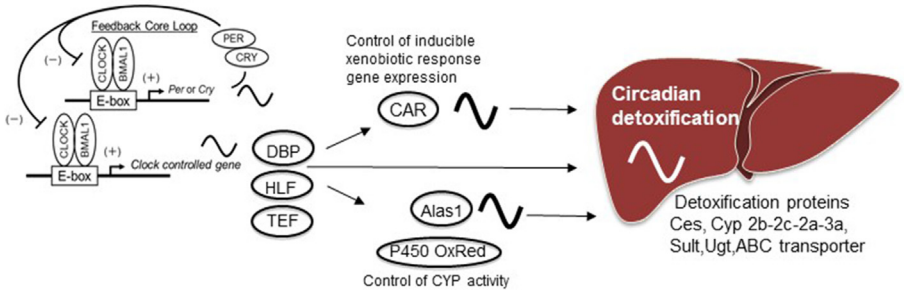

Fig. 5. Regulation of circadian clock in the xenobiotic detoxification and transporter system.[56] The model indicates the different level of control of circadian detoxification by PAR-domain basic leucine zipper (PAR bZip) transcription factors such as DBP, HLF, and TEF under the control of circadian clock. The PAR bZip proteins regulate the expression of many enzymes and regulators involved in drug metabolism and transport in intestine and liver. PAR bZip directly regulates some genes encoding detoxification enzymes and transporter. CAR mostly regulates the expression of other detoxification enzymes and transporter. Other enzymes and transporter seem to be under the control of both CAR and PAR bZip proteins.

method") will lead to the development and dissemination of chronotherapy and precision medicine.[64] Based on circadian blood metabolomics, individual BT can be detected under various conditions, showing its robustness against genetic background, sex, age, and feeding differences. The power of this approach is also shown by the sensitive and accurate detection of circadian rhythm disorder in jet-lagged animal model. A molecular timetable method, which is based on circadian-oscillating substances in multiple mouse organs or blood, has been conducted to estimate internal body time from samples taken at only a few time points. This molecular-timetable concept is also applied to estimate and evaluate internal body time in humans.[65] A 1.5 day reference timetable of oscillating metabolites in human blood samples with 2 h sampling frequency while simultaneously controlling for the confounding effects of activity level, light, temperature, sleep, and food intake has been established. The internal body time within 3 h from just two anti-phase blood samples is accurately detected by using this metabolite timetable as a reference. Therefore, molecular-timetable method with human blood may enable optimized and precision medicine.

The disruption and maintenance of biological rhythms

The altered circadian rhythm is sometimes related to therapeutic effects, or may lead to illness and altered homeostatic regulation. The relationships between the rest-activity circadian rhythm (CircAct) parameters, HRQoL, several health-related quality of life (HRQoL) scales and survival are demonstrated in an independent cohort of chemotherapy-naive metastatic colorectal cancer patients participating in an international randomized phase III trial (Fig. 6).[66] The circadian timing system constitutes a novel therapeutic target. Interventions that normalize circadian timing system dysfunction may affect quality of life and survival in cancer patients. The relationships between CircAct parameters, HRQoL, and survival, which were demonstrated for the international study involving previously untreated metastatic colorectal cancer patients, confirm prior single-institution findings in mostly pretreated metastatic colorectal cancer patients. On the other hand, several drugs cause alterations in the 24 h rhythms of biochemical, physiological and behavioral processes.[67,68]

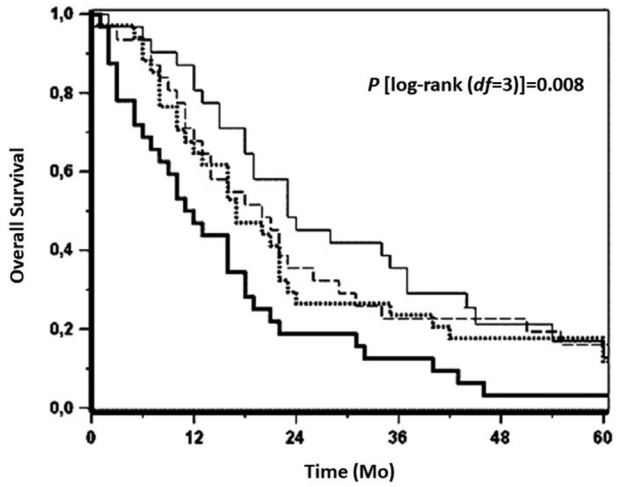

Fig. 6. Kaplan–Meier survival curves according to the dichotomy index (I < O) split by the quartiles of their distribution.[66] The rest-activity circadian rhythm (CircAct) parameters correlated with several health-related quality of life (HRQoL) scales. The circadian timing system constitutes a novel therapeutic target. The manipulation that normalize the alteration of circadian timing system may improve quality of life and survival in cancer patients. The dichotomy index (I < O) integrates the circadian control of sleep and takes into account the relative difference in activity between the rest and wakeful spans. Thick solid line, first quartile; thin dashed line, second quartile; thick dotted line, third quartile; thin solid line, fourth quartile. Log-rank test (df = 3): P = 0.008 for I < O. Reproduced with permission from the Ref. 66.

Interferons (IFNs) have been widely used as antiviral and antitumor agents, but cause adverse neuropsychiatric effects such as depression and neurosis and they sometimes lead to suicide.[69,70] Administration of IFNs during the early active phase in diurnally active humans are suggested to cause alterations of the 24 h rhythms in the lymphocyte counts and cortisol levels (Fig. 7).[9,71] There are significant and highly reproducible diurnal rhythm of several lymphocyte subsets with the lowest levels at 08:00–10:00 and the highest levels at 22:00 to 24:00.[72–75] Levels of circulating monocytes are also low at 08:00 and high at 20:00–24:00.[74] Plasma cortisol levels remains at a low level during the night, increases in the early morning and reaches a maximum at about 08:00 just at the time of the lowest levels of peripheral blood mononuclear cells (PBM),[74–76] indicating an inverse relationship between plasma cortisol concentration and numbers of PBM. The administration of IFN at night has a negligible effect on the function of HPA axis and thus minimizes disturbance of circadian rhythm of cortisol secretion. Moreover, the highest IFN plasma levels should parallel the highest PBM levels. Lymphopenia will occur the next morning, but to a lesser degree. Lymphopenia may be alleviated if IFN is administered on less than a daily schedule. Therefore a shift of about 12 h in IFN administration, from the morning to the late evening, can, in theory, render the drug more effective and also result in less side effects to the patient.

The disruptive effect of interferon-α (IFN-α) on the mRNA expression of Clock and Bmal1, important factors in activating the transcription of Pers, vasopressin and the Dbp gene indicating specific output function, is demonstrated in mice.[11] Furthermore, the rhythm of locomotor activity and body temperature are severely blunted by the repetitive administration of IFN-α. Interestingly, an inhibition of mRNA expression of each clock gene in the SCN is observed by the repetitive administration of IFN-α during the early active phase, but not the early rest phase.[11] Similar dosing schedule-dependent inhibition of Per1 mRNA expression is also shown during the repetitive administration of IFN-γ, which can be induced by IFN-α or IFN-β in combination with other cytokines.[76] The expression of IFN-γ receptor in SCN follows a 24 h rhythm with a peak at the early active phase.[77] This may account for the administration of IFN-α during the early rest phase decreases its side effect on circadian clock. The observations in humans described above nicely correspond to the results showing that alteration of the clock genes is induced by IFN-α administration during the early active phase in nocturnally active rodents. Furthermore, the dosing-time dependent disruptive effect of IFN-α on clock genes in SCN may be applicable to other drugs as shown in the case of IFN-γ. Thus, alteration of the clock function, a new concept of adverse effects, can be overcome by devising a dosing regimen that minimizes adverse drug effects on clock function. Also, the influence of 5-fluorouracil (5-FU) on the expression of clock genes is studied to explore the mechanism underlying chemotherapeutic agent-induced disturbance of circadian rhythms.[68] Continuous administration of 5-FU to mice suppresses the oscillation in the expressions of Per1 and Per2 mRNA in the liver and SCN. These results indicate a possible pharmacological action of 5-FU on the circadian clock mechanism, which is the cause underlying its adverse effects on circadian rhythms of physiology and behavior.

The adjustment and manipulation of biological rhythms

The 24 h rhythms of physiology and behavior are influenced by various environmental factors such as lighting condition, feeding

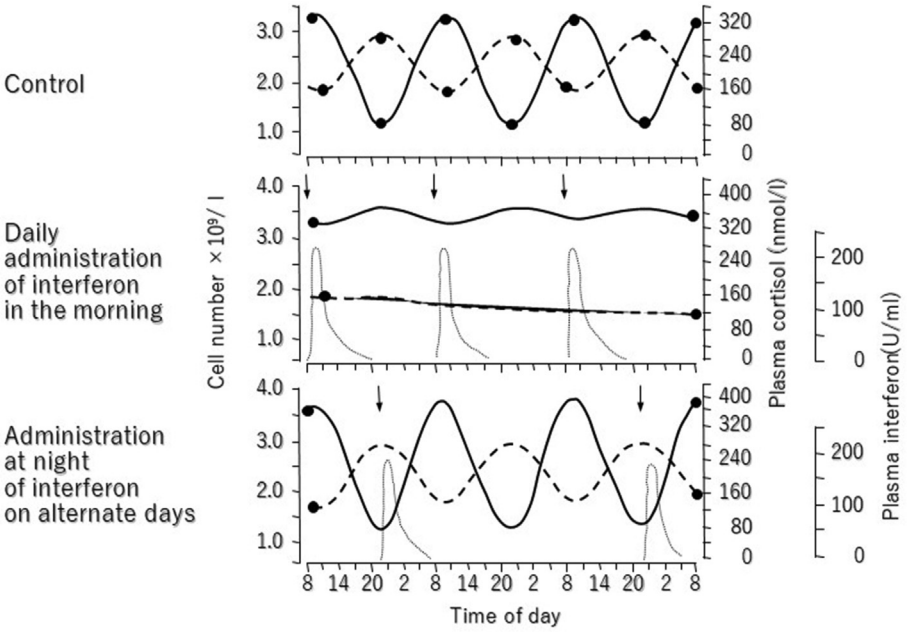

Fig. 7. The influence of interferons (IFNs) administration on circadian rhythm of total lymphocytes (o—o) and plasma cortisol concentration (•—•) in patients.[9,71] IFNs administration is shown by the arrows. IFN plasma concentration is shown by dotted lines. In top: normal variations; in middle: variations modified by daily administration of interferon in the morning; in bottom: variations amplified by administration at night of IFNs on alternate days. Several drugs cause disruption in the circadian rhythms of biochemical, physiological and behavioral processes. The disruption of rhythmicity is sometimes related to therapeutic effects, or may lead to illness and altered homeostatic regulation. IFNs have been widely used as antiviral and antitumor agents. However, IFNs induce adverse neuropsychiatric effects such as depression and neurosis. Furthermore, they sometimes lead to suicide. When IFNs are administered during the early active phase in diurnally active humans, disruption in the circadian rhythm are demonstrated by the changes in the lymphocyte counts and cortisol levels. Reproduced with permission from the Ref. [9].

schedules, genetic factors and social communications as well as administration of several drugs.[78–81] Since the period of the central circadian pacemaker of humans is slightly longer than 24 h, the daily phase-advances of the circadian clock is entrained with 24 h period by the light–dark cycle. The time-of-day dependent phase-shifting effects of light are summarized in a phase–response curve (PRC) in humans.[6] Morning light stimuli advances phase of the central circadian pacemaker, exposure of light from the late afternoon to evening delays the pacemaker, whereas light stimuli during the midday has no significant phase-shifting effects. On the other hand, the PRCs demonstrated by phase-shifting agents such as melatonin and 5-hydroxytryptamine (5-HT, serotonin) are distinct from light. The phase advances induced by administration of those agents occur between midday and early evening, whereas phase delays is observed between late night and midday. The phase shifts caused by nonphotic zeitgebers are similar to phase shifts produced by dark pulses presented to animals housed in constant light. Photic and nonphotic effects on circadian pacemaker may be critical factors of disrupted timekeeping function in depressive illness.

SCN neurons receive environmental light via direct synaptic connections with the retina, which entrains the phase of SCN oscillator to the external photoperiod. The SCN clock then synchronizes overt rhythms in physiology and behavior. Light stimuli rapidly induce the expression of Per1 and Per2 in a time-of-day-dependent manner.[18] The responsiveness of Per1 gene to light is closely related to the phase shift of behavioral rhythm. The light stimuli-induced phase delays in locomotor activity rhythm during subjective night are significantly inhibited when mice are pretreated with Per1 antisense oligodeoxynucleotide (ODN).[78] Therefore, the gated expression of Per1 in the SCN is an important process of photic entrainment. Either photic or nonphotic stimuli can entrain the SCN clock. Several drugs have also been investigated to modulate the circadian rhythm by causing a phase shift in the oscillation of central or peripheral clock.[6,79]

A variety of physiological rhythmic variables are influenced by the cyclic variation of environmental cues.[80] One of those factors is feeding schedule.[81] The pattern of diet intake substantially modifies plasma cortisol levels and body temperature rhythm.[82,83] Namely, the 24 h rhythm of the plasma cortisol levels can be kept normal only when the feeding pattern is diurnal, but the rhythmicity is reversed or disturbed under a nocturnal or continuous feeding pattern. In patients with diurnal TEN, there is a clear cortisol rhythm with a peak of 08:00, whose pattern was quite similar to the well-established cortisol rhythm in normal subjects. Patients with nocturnal TEN also show a cortisol rhythm, but the peak appears at 16:00. There is no appreciable difference in the amplitude of the rhythm between the two groups. Patients with continuous TEN does not show any consistent circadian cortisol rhythms. In the diurnal TEN group, there is a clear body temperature rhythm with a peak at 20:00, whose pattern is similar to the well-established body temperature rhythm in normal subjects. The nocturnal TEN group also shows a temperature rhythm, but the peak appeared at 04:00. The continuous TEN group does not show any consistent body temperature rhythms. These results suggest that the timing of diet intake may have a synchronizing effect on the circadian cortisol rhythm in man.

Chronopharmacological strategy of kidney-liver-heart axis via retinol and monocytes

CKD affects the functions of other organs,[84,85] which causes complications such as cardiovascular disease and cranial nerve disorder.[86,87] Heart failure is the leading cardiovascular complication in CKD patients.[88–90] These clinical observations suggest a significant pathophysiological link between the heart and kidneys.[91–93] Although CKD-induced hypertension is closely associated with increased risks of cardiovascular morbidity and

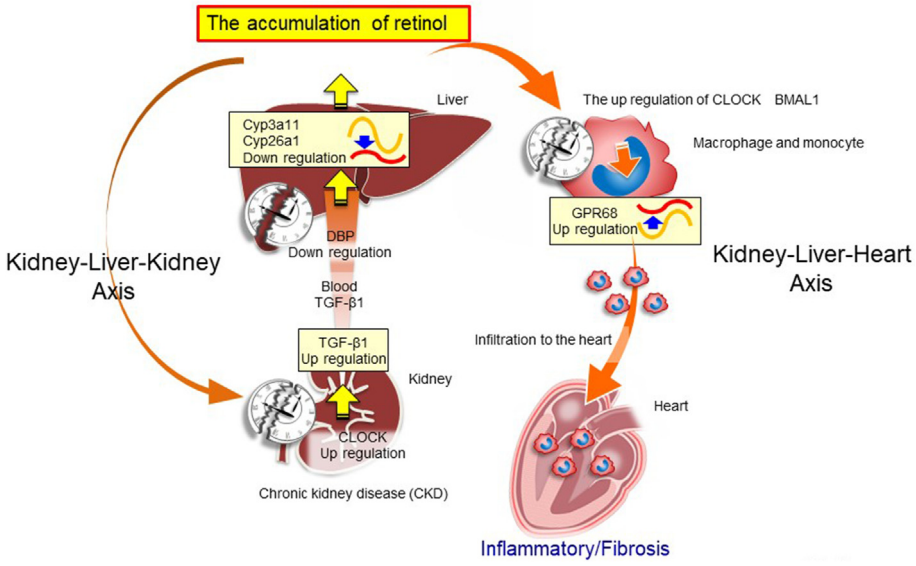

Fig. 8. Malfunction of the circadian clock show abnormal rhythms in various series of physiological processes such as pathogenesis of cardiovascular disease.[28–30] CKD-induced cardiac inflammation and fibrosis are attenuated in a mutated Clock gene (Clk/Clk), even though they have high blood pressure and increased serum angiotensin II levels. A study for the mechanism underlying the attenuation of heart disorder in Clk/Clk mice with 5/6Nx led to identification of the monocytic expression of G protein-coupled receptor 68 (GPR68) as a risk factor of CKD-induced inflammation and fibrosis of heart. 5/6Nx causes the expression of GPR68 in circulating monocytes via altered CLOCK activation by increasing serum levels of retinol and its binding protein (RBP4). The high-GPR68-expressing monocytes have increased potential for producing inflammatory cytokines, and their cardiac infiltration under CKD conditions exacerbates inflammation and fibrosis of heart. Serum retinol and RBP4 levels in CKD patients are also sufficient to cause the expression of GPR68 in human monocytes. The dysfunction of hepatic metabolism causes the accumulation of serum retinol in 5/6Nx mice. Cyp3a11 and Cyp26a1 expression, encoding key proteins in retinol metabolism, decrease in 5/6Nx mice. The dysfunction of Cyp is induced by the decreased expression of D-box-binding protein (DBP). Furthermore, the decreased expression of the Dbp gene is induced by a raise of plasma transforming growth factor-β1 (TGF-β1) in 5/6Nx mice.

mortality, several humoral and cellular immune responses are also involved in the cardiovascular complications in CKD patients.

Abnormal increase in serum retinol levels is detected in mice with 5/6 nephrectomy (5/6Nx), an experimental model of CKD, which is caused by the down-regulation of hepatic expression of Cyp3a11, Cyp26a1, and Dbp through increasing of serum TGF-β1. The elevated retinol levels also induce the activation of caspase and apoptotic cell death in the kidney, further exacerbating the pathologies of CKD (Fig. 8).[28–30] In contrast, 5/6Nx-induced renal inflammation and apoptotic cell death are attenuated in Clock mutant (Clk/Clk) mice even though they exhibit high serum levels of retinol and its binding protein (RBP4). Serum accumulation of retinol induces the CLOCK/BMAL1-mediated transactivation of GPR68 in circulating monocytes, and migration of GPR68-expressing monocytes into the heart ventricle exacerbates inflammation and fibrosis.[94] Although mice with a mutated Clock gene exhibit heart failure due to alteration of circulatory functions,[95] the continuous increase in the expression levels of Clock and Bmal1 in circulating monocytes is also involved in the cause of heart failure in 5/6Nx mice. GPR68 is activated by an acidic extracellular pH and shear stress. The activation of this proton receptor induce the production of inflammatory cytokines.[96–102] Consequently, the cardiac migration of GPR68-expressing monocytes play a critical role in the pathophysiology of CKD-induced heart failure. In 5/6Nx mice, retinol-induced expression and transcriptional activity of CLOCK and BMAL1 is mediated via STRA6. During the progression of CKD in patients, the serum retinol levels are also increased due to alteration of the hepatic metabolism pathway.[29,103] There is a correlation between retinol, RBP4 levels, GPR68, and cytokines expressions in the serum of CDK patients. Similar pathology may be revealed in human.

In regard to novel treatment of CKD, inhibition of G0/G1 switche 2 (G0s2) ameliorates nephritic inflammation in 5/6Nx mice.[30] The expression of chemokine (C–C motif) ligand 2 (Ccl2) is increased in kidney of 5/6Nx mice in response to G0s2 activation, but pathologies of CKD are ameliorated by down regulation of G0s2 expression. A high-throughput chemical screen of 9600 synthetic small molecules from a chemical library identify transcriptional inhibitors of G0s2.[104] NS-3-008 is a novel G0s2 inhibitor and administration of this inhibitor ameliorate renal dysfunction in 5/6Nx mice, indicating that inhibition of G0s2 function have therapeutic benefits for treatment of CKD.

Conclusions

The master clock in the brain regulates peripheral clock in the other organs, and controls the circadian rhythms of immune system and the severity of infections. These rhythms also control the effect and pharmacokinetics of therapeutic drugs and vaccines. Since circadian systems control the immune system by various molecular and physiological pathways, the alteration of circadian rhythm is related to the onset of disease and its progression. Clock genes have been demonstrated to control pathways involved in cellular proliferation, apoptosis, and DNA damage response, as the altered rhythms of clock genes are related to various diseases. However, Clock genes differentially control functional pathways of immunocompetent cells. To establish the chrono-drug discovery and development, the essential criteria for new drug discovery and development are to increase the probability of success in clinical trials for proof of concept, which involves the development of a promising strategy for drug target identification and validation to decrease the gap between non-clinical and clinical trials. The collaboration among the academia, the basic research institutes, the hospital institutions, the government, and the industry such as pharmaceutical companies, is essential to achieve the purpose described above. Additionally, to promote the method and development of new modality drug discovery demonstrated by

antibodies, nucleic acids, and clock genes is critical for academic research, along with a combination of chemical and biological information is essential. Overall, clock genes are critical candidates for therapy associated with immune system and the severity of infections, as shown by the accumulated data.

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Conflict of interest

The authors have no conflict of interest to declare.

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