Chapter 2
Circadian Rhythms in Health and Disease

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Keywords Circadian clock · Health · Circadian disruption · Metabolism · Immune system · Cancer · Jetlag · Shift work · Inflammation · Metabolic syndrome · Microbiota

2.1 The Mammalian Circadian System

2.1.1 The Circadian Clock

The regular changes between day and night caused by the Earth's rotation around its axis influences all life on this planet, from single cells to higher life forms, including humans [1–3]. To anticipate these recurring environmental changes organisms have developed the so called circadian (lat. *Circa* and *dies*, approximately one day) timing system. Results obtained from cyanobacteria with genetically altered circadian clocks have demonstrated the evolutionary advantage of having a circadian clock [4]. Lesion experiments in rodents located the mammalian circadian clock to the ventrolateral hypothalamus, right above the optic chiasma, the suprachiasmatic nuclei (SCN) [5, 6]. The SCN drives the animal's rhythmic behavior and physiology including the sleep-wake cycle, food intake behavior, body temperature, hormonal secretion, cardiovascular activity, acuity of the sensory system, renal plasma flow, intestinal peristaltic and detoxification [7–12] (Fig. 2.1A). In addition to the circadian clock in the central nervous system, so called "peripheral circadian clocks" have been discovered in almost all tissues, organs and even in single cells throughout the body [13, 14]. Importantly, circadian rhythms in tissue culture from peripheral clocks and the SCN persist for days, weeks and even years, demonstrating that non-SCN cells, such as the liver, the adrenal gland and even single cells contain their own endogenous circadian oscillators [15–18].

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R. Teperino (ed.), *Beyond Our Genes*,
https://doi.org/10.1007/978-3-030-35213-4_2

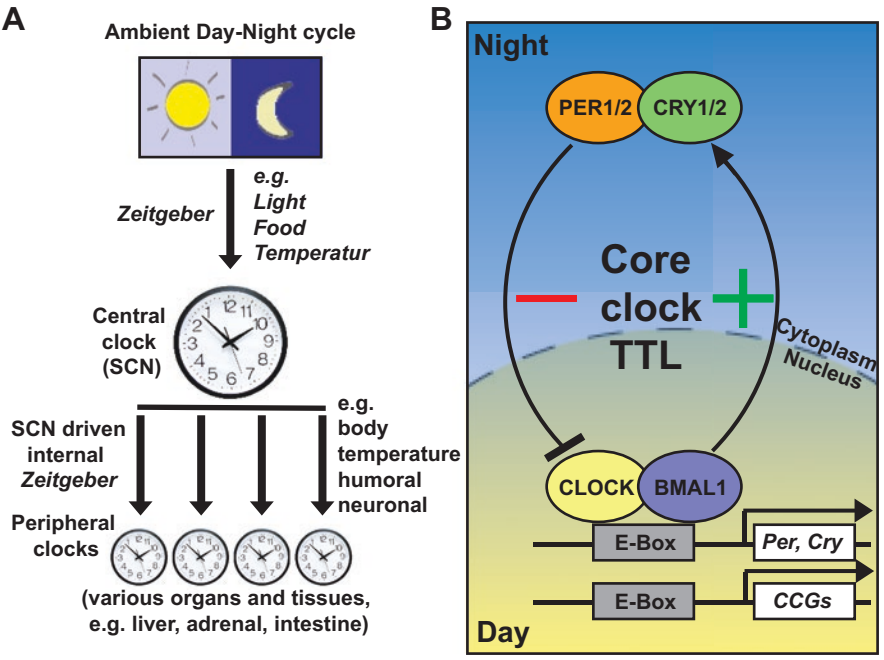

Fig. 2.1 The mammalian circadian clock. (**A**) Hierarchy of the circadian system: the central circadian clock located in the suprachiasmatic nucleus (SCN) is entrained to the environmental day by external *Zeitgeber*. The SCN orchestrates subordinated peripheral circadian clocks in various organs and tissues by internal signals. (**B**) Simplified molecular mechanism of the mammalian circadian clock: the core circadian clock is composed of a positive - negative feedback loop involving the genes Clock, Bmal1, Period and Cryptochrome. During the day BMAL1 and CLOCK proteins are expressed at high levels. The CLOCK::BMAL1 heterodimer is part of the positive arm of the transcription-translational feedback loop (TTL). The heterodimer binds to the E-Box in the promotor of clock genes, such as *Per1*, *Per2*, *Cry1*, *Cry2* and clock controlled genes (CCGs) and induces the transcription of these genes. The negative arm of the TTL is represented by the proteins from PER and CRY. During the night PER and CRY form dimers in the cytoplasm and translocate back to the nucleus where they block their own transcription

2.1.2 The Mammalian Molecular Clock Machinery

On the molecular level the mammalian circadian clock consists of a subset of clock genes, which form a cell-autonomous transcription-translational autoregulatory feedback loop [19]. Components of the positive limb are the two transcription factors: Circadian locomotor output cycles kaput (Clock) and Brain and muscle ARNT-like factor 1 (Bmal1). BMAL1 heterodimerizes with CLOCK by interaction of their basic helix-loop-helix (bHLH) domain [20] and binds to an E-Box enhancer element in the promotor of the Period (Per1/Per2/Per3) and Cryptochrome (Cry1/Cry2) genes. As part of the negative limb PER and CRY form a complex and after translocation to

the nucleus the PER:CRY heterodimer represses their own transcription by inhibiting the enhancer activity of CLOCK:BMAL1 [14] (Fig. 2.1B).

In addition to the core loop, multiple accessory feedback loops have been discovered. The nuclear receptors (NRs) Rev-erb (Rev-erbα, Rev-erbβ) and retinoic acid receptor-like orphan receptor (RORα, RORβ, and RORγ), both activated through E-Box elements, rhythmically repress or activate the transcription of Bmal1 by binding to the RRE-element in the promotor of Bmal1 [21]. Another CLOCK:BMAL1-driven transcriptional loop involves the PAR-bZip (proline and acidic amino acid-rich basic leucine zipper) D-box-binding transcription factors (DBP), Thyrotroph embryonic factor (TEF), Hepatic leukemia factor (HLF) and E4 promoter–binding protein 4 (E4BP4), which feed back to the core loop e.g. by binding to a D-Box in the promotor of Cry1 [22]. Together, these accessory feedback loops are believed to stabilize the rhythm of the core loop [23]. In the past years a variety of posttranslational events acting on the (pre-) mRNA or proteins, including phosphorylation, sumoylation, ubiquitylation, intracellular transport, degradation or micro RNAs have been identified to be involved in the delay of several hours between mRNA and protein peaks and are thus critical for the fine-tuning of the 24-h oscillations (reviewed by [24]).

2.1.3 The Circadian Clock Regulates Overall Physiology

The basis for the circadian control of major physiological processes, including metabolism, immune functions and cell proliferation is that apart from clock genes, many non-clock genes contain E-boxes, D-boxes and RRE elements. Thereby, circadian clock components, such as CLOCK:BMAL1, DBP or REV-ERBα can rhythmically regulate the transcriptional activity of these so called clock-controlled genes (CCGs) [25] (Fig. 2.1B). Comparison of transcriptome profiling between various peripheral organs and the SCN has demonstrated that in any given tissue or organ thousands of genes are oscillating with a frequency of 24 hours and thus are controlled by circadian clocks [9, 26, 27]. Altogether, the results from these studies lead to the estimation that 50% of the whole transcriptome oscillates in at least one organ [26]. However, while the rhythmic core components of the circadian clock are conserved among tissues, the CCGs rarely overlap between tissues, and thus reflect the physiological function of each organ [28]. For example, in case of the liver, genes relevant for oxidative metabolism, mitochondrial functions, and amino acid turnover show circadian rhythms [29]. Experiments on mice with tissue-specific clock disruption in various peripheral clocks, such as the liver, the adrenal gland, the pancreas, the retina etc. further indicate that tissue-specific peripheral circadian clocks are the major circadian driver of their own specific functions [30–33]. For example, in rodents it has been demonstrated that the adrenal circadian clock regulates the rhythmic secretion of glucocorticoids [31, 34]. Similarly, mice with a liver-specific

disruption of the circadian clock show abnormal glucose homeostasis, leading to defects in metabolic responses [30]. Even functions of single cells are controlled by their own clocks. For example the autonomous circadian clock in macrophages and T cells, two different immune cell subtypes, regulate the rhythmic expression of inflammatory markers, cytokine release or rhythmic response to antigen presentation [18, 35, 36].

2.2 The Circadian Clock in Relation to the Environment

2.2.1 The Circadian System Is in Synchrony with the Environment

Although circadian rhythms are generated intrinsically, organisms are influenced by environmental changes e.g. light, temperature, food availability, humidity, social cues or sound, which act on the circadian system as environmental timing cues, so called "*Zeitgeber*" (Fig. 2.1A). As a rule of thumb, in nocturnal animals (such as mice) endogenous clocks runs a little faster than 24 hours, while in diurnal animals (such as humans) clocks "tick" slightly slower than 24 hours [37]. Consequently, to maintain periodicity, the circadian clock needs to reach a stable phase relationship, not just between organ clocks, but also with the environmental time. The synchronization of the internal circadian clock time to these external *Zeitgebers* is referred to as entrainment and the process to adjust as resetting [38].

Light is the dominant *Zeitgeber* for all organisms, but how does the circadian system sense the day and night information? The location of the SCN above the optic nerve is ideal to directly receive the light information from the environment through the retino-hypothalamic tract [39]. Briefly, neurotransmitter release from retinal fibers induces a calcium dependent signaling cascade in SCN neurons (activation of calmodulin, MAP kinases and PKA) and the phosphorylation of the transcription factor CREB (cAMP response element binding protein) [40–42]. Activation of the cAMP response element in the promotor of clock genes, e.g. *Per* genes, induces their expression. Thereby, the SCN processes information about significant variations in the availability of light. To further adjust the body time with the environmental daytime, the circadian system is organized in a hierarchical manner. The light-entrainable central clock in the brain orchestrates subordinated peripheral clocks by neuronal, humoral and systemic cues (i.e. body temperature) [43] (Fig. 2.1A). For example, neural output from the SCN to other brain regions is responsible for autonomic and neuroendocrine regulation [44]. These pathways allow the SCN to coordinate daily variations in physiology and behavior in accordance with the environment.

Abolished rhythms in behavior and physiology have been demonstrated in rodents with SCN lesion and in transplantation studies [5, 6, 8]. Consequently the SCN was described as the "master clock" controlling circadian rhythms throughout

the body. However, recent research on mice with a genetic disruption of the central clock indicated that peripheral clocks continue ticking, even in the absence of the SCN, although individual organ clocks gradually desynchronize from each other [45]. Accordingly, rather than a master clock, the SCN keeps peripheral circadian clocks in synchrony and thereby substantially enhances the physiology's efficiency. However, the molecular mechanisms underlying the SCN's controls over organ clocks are still not completely understood.

For a long time, it was believed that the SCN is the only clock capable of detecting environmental light information. However, these results were obtained from SCN lesion studies [46, 47]. Lesioning the SCN can damage the surrounding tissues including the retino-hypothalamic tract. Consequently the light input pathway to other peripheral tissues may have become defective. Later it was demonstrated in mice that the adrenal circadian clock can be activated by light via the autonomic nervous system [48] even at times when the SCN is irresponsive, indicating that a non-SCN pathway is involved [49]. Glucocorticoids, which are rhythmically produced in the adrenal gland, are potent synchronizing cues for other peripheral clocks [50, 51]. Therefore the adrenal gland may function as an internal synchronizer or 'body clock' acting to support the resetting role of the clock in the central nervous system [34].

2.2.2 Environmental Factors Can Disturb the Circadian Organization

Body clocks adjust the organism's behavior and physiology to recurring environmental changes related to day and night (such as food availability or the presence of predators). Consequently, virtually all aspects of behavior (e.g. sleep/wake cycle, fasting/feeding cycle), physiology (e.g. hormone secretion, immune response) and metabolism (e.g. glycolysis or fat-metabolism) show circadian rhythms [52]. However, in our modern society, frequent flyer, aircrew members and shift workers are exposed to artificial changes in environmental conditions.

What happens with the circadian system in people that no longer live in accordance with their inner clock time? In experiments on rodents exposed to an abrupt change in the light-dark cycle (so called Jetlag), it was found that (i) clock genes within the molecular clock as well as (ii) different tissue clocks adjust with different speed to the new light-dark conditions [34, 53]. For example, in mice the clock resides in the SCN and the adrenal reset within a few days to the new day-night conditions. This is not surprising, since both clocks are light responsive (see 3.2.1). In contrast, light-insensitive organs, e.g. the liver and the pancreas entrain weeks later [34]. As a consequence of the different resetting speeds of the circadian clocks throughout the body, even a single shift in the light-dark cycle globally disrupts the circadian system [34]. Although the disruption is temporary, it can affect the organism's behavior and physiology, e.g. hormone secretion, even for a few weeks.

In humans, shift work, in particular the night shift, is one of the most frequent reasons for the disruption of the circadian system. According to worldwide epidemiological data, up to 30% of the working population are employed in non-standard work hours e.g. evening or rotating shifts [54]. Similar to results obtained from rodents, modern life style disrupts circadian rhythms in humans [55]. Working in non-regular shifts causes significant alterations of sleep and biological functions, which, in turn can affect people's physical and psychological wellbeing. There is accumulating evidence that living in mismatch between your inner clock time and the external daytime time in the long-term provokes a wide range of pathologies including gastrointestinal diseases, metabolic syndrome, cardiovascular diseases, inflammation, mood disorders and even cancer [56–59]. The impact of the circadian clock on the development and progression of diseases, in particular during changing environmental conditions, will be introduced in the next section.

2.3 The Circadian Clock and Diseases

2.3.1 Circadian Regulation of Metabolic Functions

Emerging evidence closely links circadian clock function to metabolic homeostasis. Major regulators of energy homeostasis, such as glucose transporter Sglt1, Glut2 and Glut5, peptide transporter Pept1 or lipid regulator such as Pparγ, fluctuate between day and night in various organs e.g. liver, intestine, muscle and adipocytes [30]. Accordingly, disruption of circadian clock function may contribute to the development of metabolic diseases. Indeed, metabolic syndrome has frequently been found in people living in mismatch with their environment. A higher body mass index (BMI), increased blood pressure and enhanced triglycerides correlate with the time nurses spend working on rotating shifts and sets them at higher risk of developing Type-2-diabetes [60]. In accordance to symptoms found in shift workers, mice with tissue-wide genetic disruption of the circadian clock, e.g. by loss or mutation of the core clock genes Bmal1 and Clock, reveal disturbed energy homeostasis [61]. The diurnal variation in glucose and triglycerides as well as the rhythms in gluconeogenesis is blunted. In addition, overall glucose and triglycerides in the blood are enhanced. The mice become less tolerant for glucose and more sensitive for insulin and show increased fat mass [30, 61, 62]. Interestingly, similar results were obtained in mice with tissue-specific circadian clock dysfunction, e.g. in adipocytes or hepatocytes [30, 63], indicating that organ-specific peripheral circadian oscillators play a prominent role in energy regulation. Of note, not all metabolic alterations were found in all different genetic mouse models for clock disruption, in particular weight gain was not consistently observed. Nevertheless, wildtype mice with a generally functional circadian clock develop metabolic syndrome when kept under simulated shift work conditions [64, 65].

People who work unusual hours expose their circadian system to light during the night and in addition tend to consume fat-rich food at odd hours. In natural

conditions, the daily fasting-feeding cycle is set by the central clock [66]. Although the dominant *Zeitgeber* for the central clock is light, peripheral circadian clocks, including the liver and the digestive tract, respond mostly to the timing of food intake [67]. However, when food is presented to rodents during rest hours, food-born signals can override the coordinated signals from the central clock and peripheral circadian clocks uncouple from the SCN [68]. Consequently, shift workers eating at unusual hours uncouple their peripheral circadian clocks, including those relevant for metabolism, from the SCN. In addition, artificial exposure to light at night in rodents can desynchronize all body clocks from each other [34] and has been shown to increase body mass by shifting the time of food intake [69]. Thus, shift work conditions and irregular feeding cycles cause circadian disturbance within and between the clocks in various organs, including the ones relevant for energy homeostasis, which is sufficient to induce metabolic malfunction. Moreover, shift workers eat at odd hours and at the same time, they tend to consume food with higher fat content. Metabolic processes can feed back to the circadian clock. A high fat diet (HFD) alters clock gene expression in the central clock, which in turn influences the response of the central clock to light [70] and disrupts behavioral rhythms in mice [71]. Mice under *ad libitum* HFD become more active during their usual resting time and show increased food uptake during the wrong time of the day [70]. Consequently, these mice exhibit circadian disruption similar to mice exposed to daytime-restricted food access (see section above). Taken together, light exposure at night, changes in food timing and diet may explain why metabolic disorders have frequently been linked to shift work.

2.3.2 Circadian Control of the Immune Response

A wide range of immunological functions, ranging from numbers of peripheral blood mononuclear cells as well as the level of cytokines, undergo daily fluctuations in humans and rodents [72, 73]. Interestingly, the highest number of immune cells (i.e. leukocytes, phagocytes) was detected in the circulation during the resting phase, namely during the night for humans and during the day in rodents [74–76]. Consequently, the susceptibility to infection likely underlies circadian variation. Indeed, experiments on mice demonstrated a higher inflammatory response to infection with *Salmonella typhimurium*, *Leishmania major* parasites and a higher pathogenicity of *Listeria monocytogenes* during their active phase [74, 76, 77]. A similar modulation of inflammatory response across the day has been observed in humans. For example, during the early morning the inflammatory response was strongest in people's reaction to allergic asthma [78] and in people suffering from sepsis an enhanced mortality was observed during the night [79].

Recent research indicated the existence of circadian clocks even in single cells of the immune system. For example, autonomous oscillations of clock gene expression has been found in T cells from mice and humans [36] and in macrophages [18]. Similar to the functionality of organs regulated by their intrinsic clocks, these single

cell oscillators have been shown to mediate cell-type specific functions. For example the T cell clock was reported to control rhythmic cytokine release after stimulation of toll-like receptors (TLR) and gates a time of day-dependent immune response to immunization with antigen-loaded dendritic cells [35]. The macrophage clock continues ticking in culture and the clocks of macrophages obtained from mice sacrificed during the night induce an elevated cytokine release after LPS stimulation compared to macrophages harvested from animals euthanized during the day [18]. The physiological relevance of the circadian clock in immune cells, specifically in phagocytes, has been assessed in mice in the context of an infection with *Leishmania major* parasites [76]. The daytime-dependent differences in an inflammatory response to parasites were absent when experiments where performed in mice lacking the circadian clock in hematopoietic cells, indicating that the circadian clock in these immune cells is mediating the observed effect [76].

Other peripheral clocks may be involved in mediating an inflammatory response. For example lung epithelial cells can drive immune cell recruitment to an infection site by controlling the daytime-dependency of cytokine release after *Streptococcus pneumoniae* infection [80]. Consequently, besides circadian clocks residing in immune cells, an inflammatory response following pathogen stimulation seems to be driven by multiple body clocks. Accordingly, disruption of the circadian organization, as experienced during jetlag and shift work [34], was shown to relate to immune deficits. Severely reduced survival has been observed in mice undergoing simulated shift work conditions and subjected to endotoxic shock following LPS injection [81]. Similar to rodents, simulated night shift disrupts circadian rhythms of immune functions in humans [82] and thereby may enhance the susceptibility to infection and inflammation. Indeed, Boscolo and colleagues reviewed literature indicating an increased risk of night shift workers to develop autoimmune diseases [83]. Accordingly, results obtained by the research group of Kumar indicate that jetlag may enhance the susceptibility to infection with malaria due to disturbed circadian regulation of itching behavior [84].

In studies on shift workers, a higher prevalence to develop chronic gastrointestinal inflammation was observed, including inflammatory bowel diseases (IBD), a group of chronic inflammatory disorders of the gastrointestinal tract manifesting as Crohn's disease (CD) or ulcerative colitis [85] (reviewed by Swanson et al. [86]). For example, nurses on rotating shifts discover a higher prevalence of irritable bowel syndrome [87]. Since major players of the immune system are under circadian regulation and about 70% of the immune system is located in the gastrointestinal system [88], it is not surprising, that strong associations have been found between working on rotating shifts and gastrointestinal diseases. This association was further supported by experiments on rodents exposed to simulated shift work conditions. Enhanced development and progression of chronic inflammation within the gastrointestinal tract was observed [89, 90]. Altogether, these studies indicate the importance of the circadian system for a functional immune defense. However, future studies are required to further examine the molecular link between circadian disruption and inflammatory diseases following shift work. Nevertheless, experiments

on rodents identified that a functional circadian clock maintains the intestinal barrier, a key function for gastrointestinal immune homeostasis [89], which protects against the invasion of foreign pathogens. Elevated translocation of pro-inflammatory bacterial products such as LPS from the intestinal lumen into systemic circulation elicits a strong pro-inflammatory response [89]. Since the barrier dysfunction is an underlying factor of IBD [88], circadian disruption may promote intestinal inflammation due to elevated intestinal permeability.

2.3.3 The Circadian Clock and Environmental Factors Control Microbiome Fluctuations

Amongst others, the microbiome forms an important aspect of nutrient supply and immune responses. Intestinal microbiota are strongly influenced by the host's immune system and in turn the immune system is constantly challenged to contain the microbes in the intestinal lumen. The first line of defense are intestinal epithelial cells (IECs), which form a biochemical and physical barrier that maintains segregation between luminal microbial communities and the mucosal immune system and thereby maintains immune homeostasis [88]. The second defense line is represented by the host's immune system. The presence of microbiota and pathogens in the gut is sensed in IECs e.g. by clock-controlled TLR [91]. Surface marker and metabolic end products from microbiota activate cytokine secretion to initiate an immune defense, which protects against potential pathogens [92]. Nevertheless, microbiota can become pathogenic and intensely attack the immune system, leading to inflammation and even carcinogenesis. Bacterial signaling in health and disease at the intestinal epithelial interface has been recently reviewed by Coleman & Haller [93].

Interestingly, the host's circadian clock controls the intestinal immune homeostasis by regulating the abundance of immune cells, such as lymphocytes and the barrier function of the intestine by controlling mucus and antimicrobial peptide secretion [91, 94–96]. In addition, major regulators of microbiota composition are under the control of the host's circadian clock (reviewed by [97]). Given the symbiotic relationship between humans and their resident gut bacteria, it is not surprising that daytime-dependent oscillations in microbiota composition and function have been reported in humans, and in mice [98]. Moreover, diurnal rhythms in microbiota have been demonstrated to rely on a functional circadian clock, since disruption of the circadian clock in mice either deficient for two major clock genes (Per1 and Per2), or kept under jetlag conditions, partly abolishes the oscillations in microbiota composition, e.g. in *Bacteroidales* and *Ruminococcaceae* respectively [98].

Environmental factors, such as changes in the light dark cycle, and irregular meal times, can strongly influence the diurnal fluctuations in the microbiome. Rotating light dark cycles in mice have been reported to cause a microbial imbalance, so called *dysbiosis* [98, 99]. Shift work conditions may likely cause dysbiosis through disturbance of the circadian system, since the circadian clock has been

reported to – at least partly – control microbiota fluctuations. For example, the abundance of various operational taxonomic units (OTUs) becomes arrhythmic in mice kept in simulated jetlag conditions [98]. In addition, circadian disruption has been reported to cause an imbalance in the intestinal barrier [89, 99]. Since, the clock controls the expression of barrier markers, such as cytosolic occluding (OCLN), claudin-1 (CLDN1) and E-cadherin (CDH1) [89, 100, 101], this may constitute a mechanism how circadian disruption affects intestinal permeability. Although mainly harmless, microbiota can induce an immune response and lead to chronic inflammation, such as IBD, when the intestinal barrier function is disturbed. Indeed, mice exposed to rotating light-dark cycles, show increased sensitivity to LPS [81], and are more susceptible to IBD [90, 102, 103].

A side effect of rotating light schedules is an altered timing of food uptake, which may be an additional factor causing the observed dysbiosis in shift workers. The feeding rhythm and the content of the diet has been described to orchestrate diurnal microbiota composition in mice [104]. Accordingly, HFD, but not regular chow diet, promoted microbiota dysbiosis in mice during simulated shift work conditions [99]. On one hand, the timing of feeding behavior sets the phase of specific microbiota oscillations, i.e. the peak in the abundance of *Bacteroides* shifted by ~12 hours when mice were exposed to daytime restricted feeding [98]. On the other hand, the microbiota can manipulate the host's feeding behavior. Potential mechanism have been reviewed by Alcock et al. [105]. By influencing the circadian clock, i.e. as observed in mice fed a HFD, the microbiota may affect the host's metabolism [106]. Taken together, the balance between the circadian system and microbes presents another risk factor for metabolic and inflammatory disorders.

2.3.4 Environmental Changes Promote Cancer Through Clock Dysfunction

Cancer is one of the most common causes of death. Interestingly, developed countries exhibit a ten-fold higher tumor incidence compared to developing nations. This difference can be attributed to risk factors including lifestyle, diet, obesity, physical inactivity, alcohol consumption and smoking. In 2007 the World Health Organization has classified shift work as "probably carcinogenic" based on results from various experimental and epidemiological studies [107]. For example, night shift work resulted in a higher incidence of endometrial and colorectal cancer in nurses [108] and increased the risk to develop non-Hodgkin lymphoma [109]. Studies in humans were supported by experiments in rodents, e.g., chronic jetlag condition promoted the incidence of lung cancer in rats following injection of tumor cells [110] and enhanced the progression of Glasgow osteosarcoma in mice [111]. Jetlag and shift work disturb the circadian system. Consequently, another so far completely underestimated risk factor for carcinogenesis has been identified: circadian clock disruption. The molecular clock has been shown to rhythmically regulate cellular functions,

including proliferation, DNA damage response, senescence, apoptosis, angiogenesis and metabolism. These functions can become hallmarks of cancer, when uncontrolled. Interestingly, disruption of the circadian clock is associated with a higher proliferation rate and enhanced tumor growth [112, 113]. This is not surprising, since several tumor-suppressor and key cell cycle genes, such as *Myc* and *Ccnd1* are directly controlled by the CLOCK-BMAL1 dimer [114].

Recently, alterations of circadian clock genes have been found in various cancer cell lines and tumor tissues from humans and mice (summarized by Kiessling et al. [115]). Suppression of the circadian clock in melanoma cells has been identified as causal for enhanced tumor growth in mice [116]. Thus, the circadian clock may become a target to develop novel strategies to treat cancer in people undergoing shift work or repeated jetlag. Indeed, resetting the clock in B16 melanoma cells inoculated in mice restored the rhythmic expression of clock and cell cycle genes, which in turn slowed down the speed of the cell cycle and dramatically reduced tumor growth [116].

Besides genetic alterations, the tumor microenvironment plays a determining role in tumorigenesis [117]. In this regard, inflammation and microbes were identified to be associated with tumorigenesis. For example, elevated intestinal permeability in a colorectal cancer mouse model resulted in increased infiltration of cytokines and chemokines, which induced an inflammatory response and thus may play a causative role in the development of several inflammatory and metabolic diseases, such as IBD and colitis-associated cancer [118]. In addition, increased intestinal permeability enhances the interaction between the intestinal microbiota and the host. It is already known that microorganism can trigger specific tumorigenic pathways to promote tumorigenesis by an increased frequency of gene mutations. For example, *Enterococcus faecalis* caused chromosomal instability in the host by extracellular superoxide production; *Escherichia coli* induced DNA double-strand breaks by their produced genotoxin or *Bacteroides fragilis* produces enterotoxin with an increased permeability, cellular proliferation and cytokine infiltration as consequence (reviewed by [119]). Frequent environmental changes, popular in people with a western lifestyle, likely promote cancer development or progression through disturbance of the circadian clock, induction of inflammation and microbiota dysbiosis. Taken together, environmental factors can severely influence the host's physiology, by acting on the circadian system, and thus promote the risk to develop various diseases, including chronic inflammation, metabolic disorders and even cancer (Fig. 2.2).

2.4 Chapter Conclusion

This chapter focuses on the basics of disturbances of the mammalian circadian system, such as during jetlag or shift work and related physiological changes affecting overall physiology and health. The described studies highlight the importance of

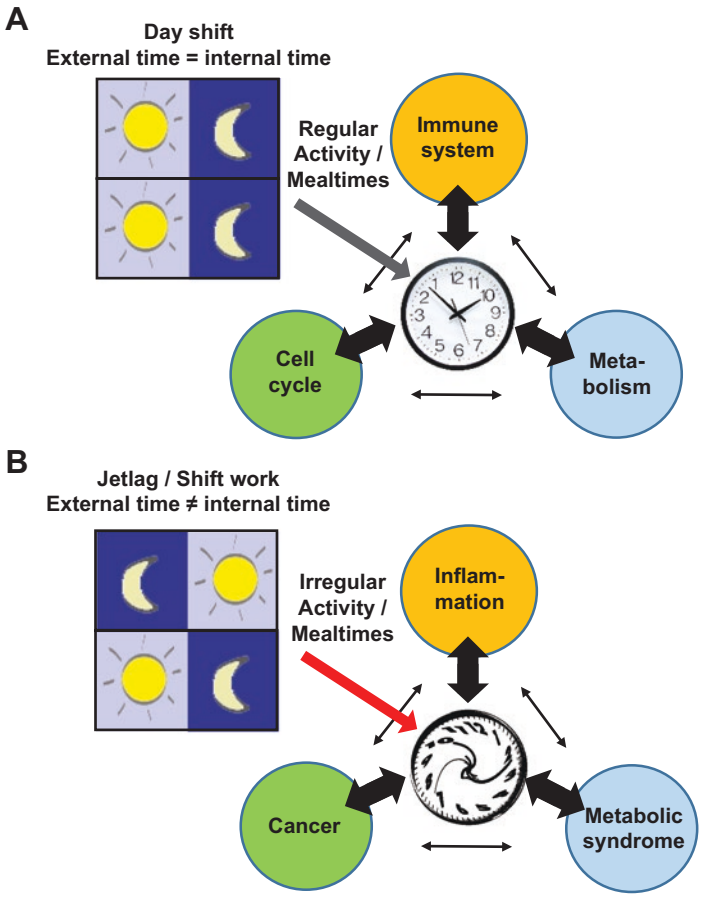

Fig. 2.2 Physiological consequences of circadian disruption. (**A**) Living in synchrony with the environmental day- night cycle results in regular light – dark exposure, mealtimes and rest-activity cycles and keeps the circadian system stably entrained with the environment. Several environmental factors can cause circadian disruption. (**B**) Changes in the environmental day-night cycle, such as occurs in shift workers or during jetlag, cause a disruption of the circadian system on multiple level. Dysfunction of circadian clocks can contribute to multifactorial diseases, such as inflammation, cancer and metabolic syndrome

the circadian system for a functional physiology and demonstrate its influence on metabolism, cell cycle and immune functions. Data obtained from mice exposed to circadian disruption illustrate the molecular and physiological consequences of environmental factors on the circadian system, which may lead to the development of physiological disorders. Consequently, the circadian clock may constitute a mechanisms by which the environment, diet, microbiota and the immune system affect multiple illnesses, and may represent a target for future therapies.

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