Chapter 2
Pulmonary Diseases, a Matter of Time

Cecilia G. Sanchez

Abstract Age-related progressive loss of lung function contributes to disability and premature death. How the circadian clock regulates the development and progression of age-related lung diseases, and the underlying molecular mechanisms, are still largely unknown. The chronobiology of the lung and the role of the circadian clock in the pathophysiology of age-related lung disease will be discussed in this chapter. We describe the molecular links between the circadian clock and the specific hallmarks of aging to provide a better understanding of healthy lung aging and age-related lung disease. Furthermore, the impact of external factors in the intrinsic circadian regulation will be integrated into the complex profiling of age-related lung diseases as well as chrono-therapeutic approaches. Finally, gaps in our knowledge and future directions will be discussed.

Keywords Circadian clock · Lung · Sleep · COPD · Emphysema · Pulmonary fibrosis · Aging

2.1 Introduction

The mammalian circadian system is organized in a hierarchical manner. A central pacemaker located in the suprachiasmatic nucleus of the brain's hypothalamus is responsible for the synchronization of cellular circadian oscillators in most peripheral body cells, including the cells in the lung. Furthermore, cell-autonomous oscillators control cellular functions in response to specific stimuli (Albrecht 2012; Bando et al. 2007; Reilly et al. 2007).

Circadian rhythms are generated at the cellular level by an autoregulatory feedback loop of interconnected transcription factors referred to collectively as clock genes (Hirota and Fukada 2004; Mohawk et al. 2012). In mammals, the

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S.M. Jazwinski et al. (eds.), *Circadian Rhythms and Their Impact on Aging*, Healthy Ageing and Longevity 7, DOI 10.1007/978-3-319-64543-8_2

BMAL1:CLOCK activator complex regulates expression of period (PER1–3) and cryptochrome (CRY1–2) genes. The heterodimers PER and CRY, are phosphorylated. Upon translocation to the nucleus, PER and CRY proteins associate with the BMAL1:CLOCK complex and suppress their own transcription by blocking the activity of the BMAL1:CLOCK complex (Grimaldi et al. 2009). Nuclear receptors REV-ERBα (NR1D1; nuclear receptor subfamily 1, group D, member 1) and retinoic acid-related orphan receptor-α (RORα) regulate the timing and amplitude of BMAL1 expression. Circadian disruption, defined as changes in amplitude or timing of clock gene expression, can alter clock-controlled output genes and, consequently, mechanical and physiological processes in the lung (Sundar et al. 2014; Dong et al. 2016b; Hadden et al. 2012). Much of the current evidence demonstrating adverse health outcomes from circadian rhythm disruption comes from studies with shift workers. Circadian rhythms synchronize the sleep-wake cycle and also play a major role in the onset and severity of diseases. A lack of synchrony between central and peripheral oscillators increases the risk of metabolic, endocrine, and cardiovascular disease. In murine studies, a single 6-h advance repeated over 8 weeks can increase mortality in older mice (Davidson et al. 2006). A daily 4-h advance for 10 weeks leads to metabolic, endocrine, and neurophysiological disease (Karatsoreos et al. 2011). Moreover, in humans, prolonged sleep restriction was shown to alter lipid and carbohydrate metabolism, insulin resistance, growth hormone and corticosteroid secretion. In consequence, it may increase the risk of obesity, diabetes, and cancer (Buxton et al. 2012; Karlsson et al. 2001; Van Cauter et al. 1997; Hennig et al. 1998; Grundy et al. 2013). Similar to shift workers, patients in the intensive care unit experience circadian rhythm disruption due to noise, interaction with caregivers, mechanical ventilation, pain, medications, artificial light, and the illness itself, accompanied by sleep fragmentation and delirium (Madrid-Navarro et al. 2015; Figueroa-Ramos et al. 2009). Internal desynchronization may also arise in response to other environmental perturbations, including feeding time, viral infection, and cigarette exposure (Evans and Davidson 2013; Hirota and Fukada 2004; Wolff et al. 2013). Nevertheless, a temporary misalignment, like jet lag, doesn't have significant consequences.

Posttranslational modifications can also affect the molecular clock regulators (Hirayama et al. 2007; Nakahata et al. 2008). Nevertheless, the changes in those modifications and their effect on clock-dependent cellular functions in the lung are largely unknown. Recent studies revealed that TGFβ1, a pro-fibrotic mediator, increases the amplitude of Bmal expression and the rhythmicity of other circadian clock regulators. Those studies also showed that TGFβ1 regulates the post-translational changes in BMAL1 and that BMAL1 promotes the effects of TGFβ1 in epithelial cells and during myofibroblast differentiation (Dong et al. 2016a). Nevertheless, there is a need to identify the impact of circadian disruption at the tissue level and the associated relevant posttranslational modifications in specific pathophysiological conditions. It is also important to determine the use of clock regulators as biomarkers of pulmonary dysfunction in specific lung pathologies, as well as the potential for novel Chrono- pharmacology agents and strategies to improve vaccine efficacy and to treat and/or prevent the progression of age-related lung disease.

2.2 Chronobiology of the Lung

The human organism shows an intricate temporal structure consisting of rhythmic variations, at multiple frequencies, of most biologic variables such as development and aging. Rhythms are also externally synchronized by environmental factors such as light-darkness, social routine, work schedule, and food intake (Smolensky et al. 1999; Haus et al. 1993). The clock modulates stress responses and physiological processes unique to each organ (Ko and Takahashi 2006; Panda et al. 2002; Stangherlin and Reddy 2013; Gossan et al. 2013; Patel et al. 2014). In consequence, circadian variations are found in respiratory volume (RV), respiratory minute volume (RMV), vital capacity (VC) and forced expiratory value per sec (FEV1) (Zaslavskaia et al. 2004). Airway caliber and inflammation also follow circadian patterns. Airway resistance peaks in the morning, reaches its lowest point at noon, and increases in the afternoon (Hruby and Butler 1975). The circadian clock also modulates the intrinsic properties of each cell at the levels of mRNA and protein expression, metabolism, and responsiveness to extracellular stimuli (Fig. 2.1). In addition, the direct exposure to high concentrations of oxygen, pollutants, particulates, smoke, and pathogens, as well as the cumulative effects of sleep disruption,

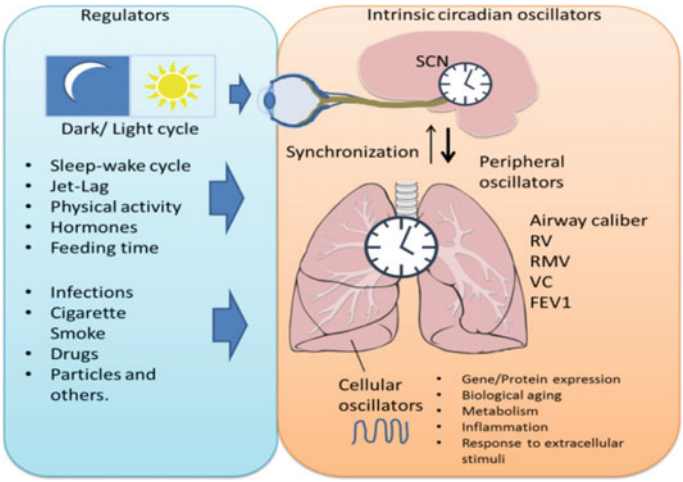

Fig. 2.1 The dark-light cycle is the most important synchronizer of the circadian rhythms. Other environmental factors include sleep–wake and activity cycles, meal timing as well as direct lung exposure to infections, drugs, cigarette smoke and particles. Intrinsic circadian oscillations in the brain (SCN) and the periphery organs. In this case, the lung is synchronized via humoral signals and the autonomic nervous system. The circadian system actively synchronizes the temporal sequence of biological functions with the environment. Airway caliber, RV, RMV, VC and FEV1 are circadian regulated. Cellular oscillators regulate mRNA/protein expression, hallmarks of biological aging, metabolism, inflammation and response to stimuli. *SCN* suprachiasmatic nuclei. Respiratory volume (*RV*), respiratory minute volume (*RMV*), vital capacity (*VC*), forced expiratory value per sec (*FEV1*)

alters the circadian clock in the lung (Gebel et al. 2006; Hwang et al. 2014; Hu et al. 2011; Sundar et al. 2014; Vasu et al. 2009; Pilorz et al. 2014) (Fig. 2.1).

In an elegant work, Haspel et al.(2014) determined that approximately 1067 genes exhibit reproducible rhythmic expression in healthy lung and that 321 of these are uniquely rhythmic in mouse lung (Haspel et al. 2014). An important observation of the authors was that immune processes are heavily represented in the circadian transcriptome of the healthy mouse lung, a finding not emphasized in published meta-analyses of other mouse solid organs (Yan et al. 2008). As a result, they concluded that the mouse lung might be a valuable tool in examining how inflammation affects organ-wide circadian regulation.

Sex-based disparities occur in sleep disorders and chronic lung diseases. Therefore, it becomes critical to determine sex-based differences in circadian regulation of the lung transcriptome in a healthy lung. It is known that gonadal steroids in both male and female rodents modify the amplitude, movement, and phase of daily rhythms (Fitzgerald and Zucker 1976; Morin et al. 1977; Albers 1981; Davis et al. 1983; Iwahana et al. 2008). Recent studies in rats revealed a direct effect of progesterone on pineal melatonin release and strongly suggest a temporal effect of this ovarian hormone on pineal function (San Martin and Touitou 2000). Therefore, we can expect that significant changes occur in the central and peripheral clocks during the menstrual cycle. In fact, Forced vital capacity (FVC) and Forced expiratory volume (FEV1) were found to change during the menstrual cycle in studies of cystic fibrosis patients; the same study found significantly higher FVC and FEV1 during the luteal phase than during ovulation and menstruation, probably due to changes in progesterone level (Johannesson et al. 2000). Besides, exposure to constant light was shown to upregulate follicle-stimulating hormone and estradiol levels and downregulate progesterone level in both the maternal and fetal circulation (Gao et al. 2016). Expression of clock genes was also studied in female, and male mice maintained on a 12 h light/12 h dark cycle (control) or exposed for four weeks to a regimen of shifting light mimicking chronic jet lag (CJL). Interestingly, among CJL females, expression of clock genes Bmal1 and Rev-erbα decreased and expression of their repressors, Per2 and Cry2, increased. In contrast, among CJL males, expression of Clock was decreased, whereas Per2 and Rev-erbα expression increased. Those changes correlated with alterations in lung mechanics, leading to the conclusion that circadian disruption alters lung mechanics and clock gene expression in a sexually dimorphic manner (Hadden et al. 2012). Future understanding of the role of neuroendocrine mediators, sex differences, and environmental factors in biological rhythms is central to advancing our understanding of age-related lung disorders.

There are rhythms of about seven days duration (circaseptan rhythms), known as the rhythmic response to an environmental load, antigen, or therapeutic agents, and poorly studied in the context of lung therapies. A study in 26 elderly patients with chronic obstructive pulmonary disease (COPD) analyzed the circadian, circaseptan, and circasemiseptan (3.5-day) rhythms of external respiratory function (ERF) before and after routine treatment (RT). In this study, Circasemiseptan variations were found in respiratory volume (RV), vital capacity (VC), and FEV1

before RT. After RT, these were detected in respiration rate (RR), RMV, and VC (Zaslavskaia et al. 2004). Circaseptan rhythms were also studied in an animal model of urethane-induced lung cancer. In this model, powerful high-amplitude of circaseptan oscillations arose after injection of the carcinogen in the targeted lungs (Riabykh et al. 1994).

Rhythms of approximate 1-year duration are called circannual rhythms, this type of rhythm is observed experimentally in animals kept under experimental laboratory conditions and never exposed to variations in day length or temperature. Seasonal variation observed in the immune response may be due to environmental factors including differences in day length or in the function of the pineal gland (light/dark-related) or the thyroid gland (temperature-related) and the prolactin levels. Also, differences in exposure to drugs and a variety of antigens, including microorganisms can induce seasonal variation. Various biological processes with immunological roles show seasonal variation in humans. Nevertheless, how seasons might broadly impact human pathophysiology is still unknown (Dopico et al. 2015).

Importantly, seasonal variations were found in 9 of the 16 clock genes, BMAL1, CLOCK, CRY1, CSNK1D, CSNK1E, NR1D2, RORA, TIMELESS30, and NFIL3. BMAL1 was found to be a common seasonal gene with increased summer expression in each peripheral blood mononuclear cell (PBMC) data set. Interestingly, the glucocorticoid receptor (NR3C1), which has anti-inflammatory properties, showed a strong positive correlation with BMAL1 expression, with lowest expression level in winter. By contrast, receptors for the prostaglandins (PTGDR, PTGIR, and PTGER4), leukotrienes (CYSLTR1), and oxoeicosanoids (OXER1) were expressed at a higher level in the winter. Receptors for adiponectin (ADIPOR1), estradiol (ESR2), and antidiuretic hormone (CUL5) were expressed at a higher level in the summer (Dopico et al. 2015). This study also revealed that 5136 unique genes out of 22,822 genes tested showed significant seasonal differences in expression (Dopico et al. 2015). Therefore, seasonal changes in expression of circadian genes might impact the immune responses. In fact, the circadian rhythms influence the immune functions of natural killer cell activity, lymphocyte proliferation, monocyte and macrophage gene expression, as well as the levels of inflammatory mediators, IL-6, tumor necrosis factor and IFN-γ (Boivin et al. 2003; Thompson et al. 2014; Hwang et al. 2014; Martin 1999).

2.3 A Time for Pulmonary Diseases

The lung is constantly responding to insults during chronological aging. Consequently, older individuals have an increased risk of developing respiratory impairment. Dysfunction in the molecular clock mediates changes in the immune, inflammatory, and DNA-damage responses that correlate with exacerbation of some

pathological respiratory conditions, such as pulmonary edema, asthma, and allergic attacks (Froy 2010). Nevertheless, the effects of environmental exposures on circadian-clock regulation and the impact of circadian disruption on various pathophysiological lung conditions are not completely understood. Here, we will review some of the literature concerning abnormalities in the circadian clock and their association with lung disease. We expect that research in the next decade will determine the concurrence of rhythm-related risk factors leading to pathologic events and the development of chronic lung diseases. We also hope that the study of the circadian regulation will provide a better understanding of the onset and progression of those diseases and identify effective treatments. Furthermore, we expect that future research will also result in the use of clock molecules as biomarkers of pulmonary dysfunction.

2.3.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is characterized by the loss of lung elasticity due to emphysema and airway obstruction as a result of inflammatory narrowing and fibrosis. At the cellular level, COPD represents a complex interplay between lung epithelial cells, endothelial cells, neutrophils, macrophages, and multiple subpopulations of both $CD8^+$ and $CD4^+$ T cells (Bosken et al. 1992; Lams et al. 1998; Saetta et al. 1999; Amin et al. 2003; Lee et al. 2011). In spite of recent advances, there is still a fundamental lack of knowledge about the cellular, molecular, epigenetic, and genetic causes of COPD (Sanchez 2016a). Considering that smoking tobacco alters major components of the circadian clock and constitutes a major risk factor for COPD, an understanding of the role of the circadian clock in the pathogenesis of COPD is a critical need (Vestbo et al. 2013; Mannino 2003). Cigarette smoke (CS) can affect circadian secretion of corticosterone (CORT), an adrenal steroid and a major component of the stress response, and serotonin (5-hydroxytryptamine; 5-HT), leading to sleep and mood disorders in smokers and patients with COPD (Sundar et al. 2014).

In patients with COPD, airway obstruction progresses with time and exacerbations of the disease tend to arise about once per year (Tashkin 2013). Patients with COPD experience sleep abnormalities, including symptoms of insomnia, daytime sleepiness, and nocturnal oxygen desaturation due to hypoventilation. These defects were determined in early studies on sleep quality using overnight polysomnography (Fleetham et al. 1982; Cormick et al. 1986). The studies with morning-symptom diaries confirm that morning is the most difficult time of day for many patients with COPD (Globe et al. 2016). Sleep disruption also causes significant neuropsychological changes, and its impact is perceived in the quality of life of the patients with diverse chronic lung diseases (Lewis 2001). The severity of the symptoms during COPD exacerbations varies diurnally and shows elevated risk for intubation during early morning hours (Tsai et al. 2007; Truong et al. 2016).

Smoking is the greatest risk factor for COPD (Vestbo et al. 2013; Mannino 2003). Exciting research is emerging showing the effects of tobacco smoking on the components of the circadian clock. Gene expression analysis of the lung from rats exposed to CS revealed a CS–exposure-dependent shift in the cyclical expression of genes involved in the inflammatory response and those controlling the circadian rhythm. (Gebel et al. 2006). Another study using whole CS (WS) and filtered CS (FS) revealed a differential CS-mediated modulation of genes related to circadian pathways in the lung. For example, Rev-Erb alpha expression is downregulated by WS and FS compared to controls. Interestingly, WS was more efficient than FS in decreasing Rev-Erb alpha expression (Vasu et al. 2009).

At the posttranslational level, it was found that Bmal1 is preferentially acetylated and degraded in the lungs of mice exposed to CS and in patients with COPD, compared with lungs of the nonsmoking controls, linking it mechanistically to CS-induced reduction in Sirt1. In fact, the targeted deletion of Bmal1 in lung epithelium confirmed an increase in CS-mediated inflammation (Hwang et al. 2014).

Lung function in COPD patients is also altered following viral infection, including infection with influenza A. Chronic CS exposure combined with infections with influenza A, changed the timing of clock gene expression in parallel with increased lung inflammation (Sundar et al. 2015). As future studies elucidate the interrelationship between circadian rhythm and COPD, new therapeutic targets and approaches will likely emerge.

2.3.2 Idiopathic Pulmonary Fibrosis (IPF)

IPF is a chronic, progressive, and irreversible idiopathic interstitial pneumonia of unknown origin. The mean survival is approximately 3–5 years from the time of diagnosis with a rate of progression that is highly variable and heterogeneous (Raghu et al. 2011; Bjoraker et al. 1998; Flaherty et al. 2002; Nicholson et al. 2000). IPF is an interstitial lung disease that is primarily associated with advanced age (Thannickal 2013). The disease is characterized by temporal heterogeneity of fibrosis characterized by clusters of actively proliferating fibroblasts/myofibroblasts, fibroblastic foci", and honeycomb structures (Raghu et al. 2011). TGF-β1 is a key regulator of myofibroblast differentiation and collagen deposition. Studies using animal models of pulmonary fibrosis, as well as in vitro studies using human epithelial cells and normal lung fibroblasts, revealed that TGF-β1 alters circadian rhythmicity and promotes Bmal expression while reducing Bmal1 acetylation (Dong et al. 2016a). Importantly, Bmal1 acetylation occurs in vivo and is regulated in a circadian manner. Bmal1 acetylation facilitates Cry1 interaction with the Clock–Bmal1 complex (Hirayama et al. 2007). The studies suggest that fibrogenesis occurs concomitant with significant changes in Bmal1, leading to dysfunctional clock regulation (Dong et al. 2016a). Furthermore, reduction of Bmal1 damped the effects of TGF-β1 on epithelial-mesenchymal transition and cell migration (Dong

et al. 2016a). The results support the role of the circadian clock in the expression of profibrotic genes involved in mesenchymal transition and invasion, relevant for lung cancer and pulmonary fibrosis.

2.3.3 Obstructive Sleep Apnea (OSA)

Ten percent of the U.S. population is affected by Obstructive Sleep Apnea (OSA), defined by repetitive episodes of obstruction in the upper airway during sleep, leading to chronic intermittent hypoxemia, sleep fragmentation, and chronic fatigue. Remarkably, OSA patients experience few or no problems with their breathing or airway patency while awake (Dempsey et al. 2010). Enlargement of soft-tissue structures both within and surrounding the airway contributes significantly to pharyngeal airway narrowing in most cases of OSA. Accumulation of even relatively small amounts of edematous fluid enlarges upper-airway soft-tissue structures in OSA patients and snorers, especially in the soft palate, which may be tugged caudally and constricted during apnea. Obesity also contributes indirectly to upper airway narrowing, and a broad range of candidate genes that might link genetic mechanisms of obesity with OSA are under investigation (Patel 2005; Young et al. 2002; Dempsey et al. 2010). Recent studies in mice revealed that obesity does not predispose mice to increased occurrence of central or obstructive apnea during sleep, but does lead to more pronounced circadian variability in respiration (Davis et al. 2013). Importantly, sleep-disordered breathing is recognized as a risk factor for the development of hypertension and other cardiovascular diseases. Sleep disruption per se increases sympathetic nerve activity and blood pressure (Morgan et al. 1996). Cardiovascular structure and function also change via neurohumoral activation, oxidative stress, and inflammation in OSA-induced cardiovascular morbidity and mortality (Dempsey et al. 2010). COPD and OSA have detrimental effects that are synergistic. Their comorbid association leads to compromised gas exchange (hypoxia and hypercapnia) and higher rates of morbidity and death (Khatri and Ioachimescu 2016). In animal models, OSA has been linked to metabolic syndrome, inflammation, hypertension, stroke, and cancer (Truong et al. 2016; Arias et al. 2006; Arble 2015, #6506). The prevalence of OSA is increasing, especially in the middle-aged population.

Sleep loss induces tissue-specific epigenetic and transcriptional alterations to circadian clock genes (Cedernaes et al. 2015). Therefore, it is expected that sleep disruption in patients with OSA leads to further changes in the circadian clock genes and their target genes. Recent population studies reveal that advancing age uniquely and robustly predicts OSA in females and reinforces the understanding that age-related changes in sex hormones play a role in the development and/or manifestation of sleep-disordered breathing (Cairns et al. 2016). There is a need for future studies to determine the circadian rhythms and sex differences in co-morbidity incidence in patients with OSA.

2.3.4 Infectious Disease and Vaccine Efficacy in the Elderly

It is possible that infectious agents exploit the circadian clock machinery. Circadian regulation has been shown to be altered in patients with pulmonary tuberculosis, as indicated by circadian deregulation of plasma hormones, including adrenocorticotropic hormone, which regulates the levels of cortisol; follicle-stimulating hormone; luteinizing hormone; hydrocortisone; testosterone; progesterone; and estradiol. The results of a study of 12 healthy subjects and 32 patients with infiltrative lung tuberculosis indicate that healthy subjects show fluctuations in the hormones that come to an acrophase in the morning hours, with stable time and amplitude structure. In contrast, tuberculosis patients exhibited impaired circadian cycling of the hormones, with acrophase in day and evening hours, reduced mean levels and amplitude in fluctuation, and non-coincidence in time (Karimdzhanov et al. 1993; Singh et al. 1991). Plasma melatonin levels are also lower in patients with pulmonary tuberculosis (Ozkan et al. 2012).

Recent work with influenza virus suggests that the virus directly exploits the deregulation of the clockwork (Edgar et al. 2016). Influenza virus infection is a public health problem that is generally more severe in individuals greater than 65 years of age. Respiratory infections can constitute major triggers of exacerbations of asthma and COPD through a robust host inflammatory response and an increase in bronchial hyper-responsiveness (Murray et al. 2004; Traves and Proud 2007). A recent study indicates that influenza virus infection promotes chronic CS-mediated inflammation and fibrosis (Sundar et al. 2015). Innate immune pathogen recognition mechanisms are under circadian control, as demonstrated by TLR9 expression and function (Silver et al. 2012). Conversely, viral and bacterial infection can alter the timing and amplitude of clock gene expression in the lungs. Viral respiratory infection mediated by influenza A causes molecular clock dysfunction in the lungs and increases mortality in Bmal1 knockout mice, suggesting a deficiency in the immune response to respiratory infection (Sundar et al. 2015). Mice with deficits in growth hormone releasing hormone signaling respond to influenza virus challenge with a progressive decrease in sleep and lower survival rates. The sleep response to influenza infection is mediated, in part, by regulation of hypothalamic sleep-related transcripts and enhanced corticosterone secretion (Alt et al. 2007).

Circadian clock regulation is critical for bronchial immune responses and the function of bronchial glucocorticoid receptors. The targeting of *Bmal1* in bronchiolar exocrine cells (Clara cells), leads to an exaggerated but apparently ineffective neutrophilic inflammatory response to bacterial infection, including to *Streptococcus pneumoniae* (Gibbs et al. 2014; Nouailles et al. 2014). At the molecular level, deficiency in Bmal 1 contributes to altered glucocorticoid receptor occupancy at the Cxcl5 locus and leads to enhanced Cxcl5 expression, implicated in tissue remodeling and polymorphonucleocyte-driven destructive inflammation in pulmonary tuberculosis (Gibbs et al. 2014; Nouailles et al. 2014).

A recent work revealed that Bmal1 selectively contributes to granulocyte circadian regulation in the endotoxemic lung (Haspel et al. 2014). Endotoxemia can also disrupt the circadian expression and periodicity of core molecular clock genes in murine lung, with some becoming arrhythmic and others showing a distorted but rhythmic pattern compared with baseline (Haspel et al. 2014). In consequence, endotoxins reprogram the circadian lung metabolome. The authors demonstrated in the lungs, a rhythmic accumulation of urate, a terminal product of purine metabolism, which was found to correlate with rhythmic infiltration of granulocytes producing myeloperoxidase, a catalytic enzyme responsible for the conversion of urate to allantoin.

Taking into account that light and daily rhythms are thought to have a strong influence on immune function (Roberts 2000) and that events affecting the immune system can alter the response to vaccination, it is plausible that vaccination administered in the morning or in the evening might influence the immune response to the vaccine. Few published human studies have addressed this question. Studies concerning flu shot efficacy do not show an association between vaccination time and subject response, similar to the results of studies with hepatitis B vaccine (Langlois et al. 1995; Karabay et al. 2008). However, it was demonstrated that the feelings of stress and loss of sleep become locked into a feed-forward circuit that ultimately diminishes the immune response against influenza virus after vaccination (Pedersen et al. 2009; Miller et al. 2004).

2.3.5 Lung Cancer

Dysfunction of the circadian clock is involved in tumorigenesis, and altered expression of some clock genes has been found in cancer patients and may be related to the process of tumorigenesis (Mazzoccoli et al. 2011).

Prolonged subjection to unstable work or lighting schedules, particularly in rotating–shift-workers, is associated with an increased risk of immune-related diseases, including several cancers. In 2007, The International Agency for Research on Cancer (IARC) concluded, “Shiftwork that involves circadian disruption is probably carcinogenic to humans” (Group 2A classification) (Straif et al. 2007). Lung cancer is one of the most deadly cancers, contributing to over a quarter of all cancer deaths in the United States. Lung cancer is considered an age-associated disease, whose progression is in part due to the accumulation of genomic instability and the age-related decline in system integrity and function (Levine et al. 2015). Association of clock genes with lung cancer was determined in 78 Brazilian patients with non-small cell lung cancer (NSCLC) (Couto et al. 2014). Those studies revealed that polymorphisms in the clock control gene nocturnin (*CCRN4L/NOC*) and *PER3* may represent a risk factor in the occurrence and development of NSCLC in Brazilian patients (Couto et al. 2014).

Chronic shift-lag can alter the circadian expression of clock genes *Per2* and *Bmal1*, and the cytolytic factors perforin and granzyme B, as well as the cytokine

IFN-γ. These alterations correlate with suppressed circadian expression of natural killer cell cytolytic activity and promotion of lung tumor growth (Logan et al. 2012). There is also evidence that a severe alteration in growth hormone-insulin-like growth factor axis function in patients with lung cancer is concomitant with loss of circadian rhythmicity of hormone secretion (Mazzoccoli et al. 2012).

Finally, it seems that adenocarcinoma of the lung functions as a potent endogenous circadian organizer in other tissues, rewiring the pathophysiological dimension of a distal tissue such as the liver. This was recently demonstrated by high-throughput transcriptomic and metabolomics studies, revealing a unique signature of transcripts and metabolites cycling exclusively in livers of tumor-bearing mice (Masri et al. 2016).

For this reason, it has been proposed that behavioral, hormonal, and/or light-based strategies to improve circadian organization may help patients suffering from advanced lung cancer to increase the quality of life, as a consequence of profound circadian disruption. (Grutsch et al. 2011). Future investigations will be important to strengthen current knowledge and shed light on the pathophysiology of circadian disruption on cancer risk in humans.

2.3.6 Asthma

The prevalence of asthma in the elderly affects more than 10% of patients of 60 years of age or older, while the estimated prevalence for COPD represents a 20–30% in patients older than 70 years of age (Hardie et al. 2005; Murtagh et al. 2005). Approximately 70% of adult asthma-related deaths occurred between 12:00 A.M and 6:00 A.M (Litinski et al. 2009).

Lung function varies in a circadian rhythm in healthy individuals. An episode of nocturnal asthma exacerbates the normal variation in lung function from daytime to night-time (Calhoun 2003). At night, a significant change in β-adrenergic receptor density and function occurs in patients with nocturnal asthma (Szefler et al. 1991). Decreased serum epinephrine levels, increased vagal nerve tone and cholinergic activity, esophageal reflux, and increased circulating eosinophils are known as contributors of the late-night/early-morning deterioration of lung function in asthma patients (Martin et al. 1990; Bates et al. 1994). The airflow obstruction correlates with an increase in inflammatory cells specifically associated with an increase in the number of airway $CD4^+$ lymphocytes and their capacity to generate IL-5 (Kelly et al. 2004).

Bonnet and colleagues identified the circadian rhythms of airway responsiveness to histamine and methacholine and correlation with airway tone in patients with mild asthma (Bonnet et al. 1991). Asthma patients also have disordered circadian rhythms of salivary melatonin and cortisol (Fei et al. 2004). Other factors, such as late-phase response to allergen exposure, sleep apnea, and lung volume changes during sleep, may also play a role in nocturnal asthma symptoms. Some early studies underscore the effects of sleep per se in worsening asthma and increased

airway resistance in asthmatic shift workers. Those studies observed that a decline in the peak expiratory flow rate was related to the change in sleep schedule, as opposed to the time of day (Clark and Hetzel 1977). Taking in account that the peripheral clocks of the lung and the immune system seems to be strongly interrelated, it is expected that the timing of an attack on the lung immune system by an allergen, virus or a therapeutic intervention might eventually affect the asthma symptoms, by altering the immune response. Future research is needed to elucidate the role of the circadian clock in asthma.

2.4 The Circadian Clock Regulates the Markers of Aging. Implications for the Pathophysiology of Age-Related Lung Disease

The effects of chronology on molecular rhythms in the human lung are not well understood. Early studies using rat tissue explants demonstrated that, whereas no significant change occurred in some tissues, 50% of explants from the lung and the retrochiasmatic area of the suprachiasmatic nucleus showed major circadian deregulation with age. Nevertheless, circadian rhythms were initiated in these arrhythmic tissues by forskolin stimulation, indicating that the aged tissues retained the capacity to oscillate (Yamazaki et al. 2002). Human studies revealed that the elderly population shows various circadian disturbances, including dampened amplitude of rhythmicity and decreased responsiveness to light (Mitteldorf 2013). On the other hand, changes in the expression of circadian clock genes alter biological aging. Evidence shows that disruption of the circadian system is associated with premature aging in mice, but the molecular basis of this phenomenon is still unclear (Grosbellet et al. 2015). In this section, we will explore the current understanding of the relationship between chronological aging, circadian clock, and biologic lung aging, taking into consideration that the lung is a vital organ constantly responding to insults.

The idea that circadian clock regulation can modulate the rate of aging is supported by earlier studies in which transplantation of pineal gland from young to old mice prolonged life span (Lesnikov and Pierpaoli 1994). Between 10 and 20% of the genes in any given cell are regulated by the circadian machinery, so it is expected that the hallmarks of aging can be regulated by circadian rhythms.

The term “hallmarks of aging” was first coined by Lopez-Otin et al. (2013) to describe cellular and molecular factors that contribute to the aging process. Those hallmarks are manifested during normal aging. Experimental aggravation accelerates aging; and conversely, its experimental amelioration can retard the aging process and increase life span (Lopez-Otin et al. 2013). The hallmarks include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin et al. 2013).

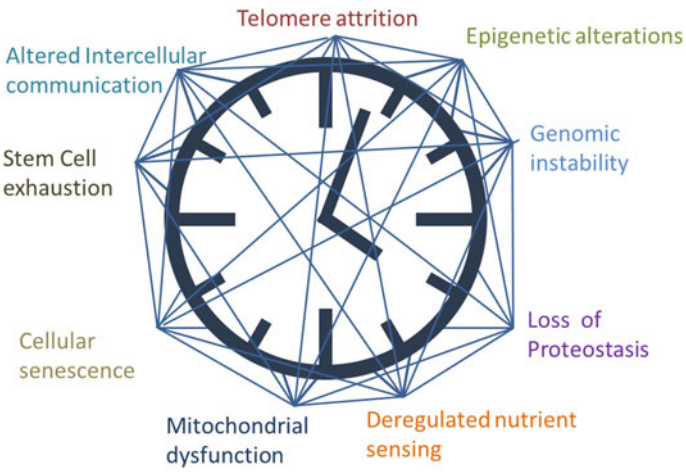

Fig. 2.2 Representation of the circadian clock regulation of biological aging

We now recognize that those hallmarks are tightly interconnected and act as mediators of the development and progression of age-related diseases. A major question remaining is how circadian systems regulate the hallmarks of biological aging, and how they influence "healthy aging" or age-related lung diseases (Fig. 2.2).

2.4.1 Telomere Attrition

Recent studies in humans and mice revealed that telomerase activity exhibits endogenous circadian rhythmicity. Specifically, those studies revealed that expression of telomerase reverse transcriptase (TERT) mRNA is under the control of CLOCK-BMAL1 heterodimers and that a loss of rhythmic telomerase activity leads to shortened telomere length. Furthermore, the authors described an increase in phosphorylation of histone H2A variant H2AX, a marker of DNA damage, in Clock-deficient mouse embryo fibroblasts (MEFs) after stimulation with staurosporine (Chen et al. 2014).

Several studies indicate that disease severity and smoking status in COPD, including perpetuation of lung inflammation, correlate directly with reduced telomere length in alveolar, endothelial, and smooth muscle cells, as well as in circulating lymphocytes (Amsellem et al. 2011; Tsuji et al. 2004; Albrecht et al. 2014). Concerning IPF, telomere attrition is a known driving factor in lung fibrosis. Mutations in telomerase genes have been found in 8–15% of familial and in 1–3% of sporadic cases of pulmonary fibrosis (Armanios 2013; Satoh 2016; Meiners et al. 2015). A negative slope in a plot of telomere length against age was found to be steeper in IPF patients than in controls, suggesting an accelerated rate of telomere

erosion in IPF patients. Furthermore, telomere length was found to be an independent predictor of survival in IPF (Dai and Gao 2016).

In asthma, telomere shortening was recently found to correlate with bronchial cell senescence. Those studies provide evidence that fibroblasts of adult asthmatic patients show significantly accelerated aging, which suggests a potential role of the continuous production of inflammatory mediators (Hadj Salem et al. 2015). With OSA, shorter telomere length was found in circulating leukocytes in patients compared to subjects without OSA (Barcelo et al. 2010). In patients with lung cancer, reduced telomere length is associated with poor prognosis (Frias et al. 2008). Specific studies are needed to understand the role of clock and telomere attrition in the development and progression of age-related lung diseases.

2.4.2 Genomic Instability

The clock gene machinery controls DNA-damage recognition and repair (Manzella et al. 2015; Kang et al. 2010). The circadian clock protein cryptochrome 2 interacts with TIMELESS, a primary regulator of the DNA replication machinery (Benna et al. 2010), and partner of the cell-cycle checkpoint protein Chk1 playing a major role in the DNA-damage checkpoint response (McFarlane et al. 2010). TIMELESS is critical for lung morphogenesis and correlates with poor survival of patients with lung cancer (Xiao et al. 2003; Yoshida et al. 2013).

Smoking is one of the most important environmental factors known to cause DNA damage and change the expression of circadian clock genes (Wistuba et al. 2002; Hwang et al. 2014). Nevertheless, alveolar epithelial cells and endothelial cells in patients with COPD and IPF have higher levels of DNA damage and damage response than those in asymptomatic smokers and nonsmokers (Aoshiba et al. 2012; Korfei et al. 2011; Kuwano et al. 1996), suggesting progression of DNA damage during disease progression. Dust mite-induced asthma causes oxidative damage and DNA double-strand breaks in the lungs (Chan et al. 2016). Thus, DNA damage can have a potential role in the pathogenesis of asthma (Chan et al. 2016). Unfortunately, little is known about the possible role of allergen-induced DNA damage and DNA repair as modulators of asthma-associated pathology.

2.4.3 Epigenetic Alterations

Whole-blood DNA methylation patterns change with chronological age, and multiple CpG sites with replicable associations with age have been identified (Florath et al. 2014). Epigenetic regulation is also regulated by the circadian clock, as indicated by recent observations that histone and DNA methylation are highly dynamic processes with more than 100 DNA methylation sites that oscillate in synchrony with the cell cycle (Brown et al. 2007), a cycle that is gated by the

circadian clock (Merrow and Roenneberg 2004; Nagoshi et al. 2004). The results of recent studies suggest that epigenetic age acceleration, based on DNA methylation age at 351 loci in 1820 subjects, is correlated with frailty, a clinically relevant aging-related phenotype, through pathways unrelated to cellular senescence as assessed by telomere length (Breitling et al. 2016). Several studies link epigenetic alterations with chronic lung disease. Using data on 2029 females from the Women's Health Initiative, a national survey that began in 1993 and enrolled postmenopausal women between the ages of 50 and 79 years (1998), one study identified DNA methylation age of blood as a predictor for future onset of lung cancer, and this association was even stronger in older individuals. The results indicated that epigenetic marks can be used as biomarkers for lung cancer susceptibility (Levine et al. 2015). Nevertheless, the value of the epigenetic clock in age-related lung diseases is currently unknown.

2.4.4 Loss of Proteostasis

The autophagy-lysosomal system and the ubiquitin-proteasomal system are regulators of protein quality control. Basal autophagy and other metabolic pathways are also rhythmically activated in a clock-dependent manner (Ma and Lin 2012). Recent studies indicate that proteolytic systems contribute to chronic lung diseases. Specifically, aberrant proteostasis contributes to COPD, severe emphysema, and pulmonary fibrosis (Bouchecareilh and Balch 2011; Sosulski 2015).

Autophagy has significant physiological significance for the lung, and alterations in autophagy have been implicated in the pathogenesis of various pathological lung conditions, including COPD and IPF (Sanchez 2016b). Autophagy has been shown to be reduced in IPF. Deficient autophagy induces acceleration of epithelial cell senescence and myofibroblast differentiation of lung fibroblasts and the progression of IPF (Patel et al. 2012; Araya et al. 2013; Ricci et al. 2013). The role of autophagy in the pathogenesis of COPD/emphysema appears to be complex and cell–type-specific. Mitophagy in alveolar epithelial cells contributes to the pathogenesis of COPD (Mizumura et al. 2014) and autophagy-deficient mice are protected from CS-associated ciliary dysfunction (Cloonan et al. 2014). Nevertheless, recent studies indicate that impairment of CS-induced autophagy accelerates lung aging, COPD-emphysema exacerbations, and pathogenesis (Vij et al. 2016).

Rhythmic autophagic induction may be essential for temporal remodeling of proteomes and organelles. Periodic removal of mitochondria and other organelles may facilitate the adjustment of the bioenergetic properties throughout different circadian phases (Ma et al. 2012). Circadian regulation of several transcriptional regulators of autophagy genes is mediated by transcription factor CEBPB, linking the circadian clock to autophagy and maintenance of nutrient homeostasis in mice (Ma et al. 2011). In addition to the role of transcription factors, studies in zebrafish indicate that the circadian clock directly regulates autophagy genes, specifically Nr1d1 and Per1b, which are critical for maintaining autophagic rhythms in

zebrafish (Huang et al. 2016). Furthermore, pathways involved in autophagic regulation, such as the mTOR and AMPK pathways, appear to undergo circadian regulation; however, their roles in driving rhythmic autophagy activation in lung tissue remains to be explored. Interestingly, studies in MEFs revealed that treatment with lysosomal inhibitors significantly enriches the protein Bmal1 to a degree comparable to that achieved with MG132 treatment, indicating that autophagy and the proteasome plays a major role in Bmal1 degradation (Jeong et al. 2015).

Another mechanism of proteostasis is the proteasome, which regulates Bmal1/Clock function but also exhibits circadian rhythmicity in expression level and activity (Stratmann et al. 2012; Desvergne et al. 2016). The healthy aging of the lung does not involve impairment of proteasome function (Caniard et al. 2015). By contrast, COPD and direct exposure to cigarette smoke alter pulmonary proteasome expression and activity which inversely correlate with lung function (van Rijt et al. 2012).

The rhythms match the circadian oscillations in oxidative protein damage (Desvergne et al. 2014). Using synchronized human embryonic kidney (HEK) 293 cells and primary dermal fibroblasts, it was shown that the levels of carbonylated protein and proteasome activity vary rhythmically following a 24-h period, in part due to the circadian expression of a nuclear factor, erythroid 2 like 2 (NRF2) and the proteasome activator PA28α/β. Interestingly, no circadian modulation of proteasome activity or carbonylated protein level was observed in senescent fibroblasts compared to control fibroblasts (Desvergne et al. 2016). Therefore, it is plausible that age-associated alterations in the circadian systems may contribute to altered proteasome activity and accumulation of oxidized proteins in age-related lung diseases.

Stress signals lead to selective activation of downstream signaling cascades, including activation of PERK, a type I membrane protein located in the endoplasmic reticulum, which phosphorylates the translation initiation factor eIF2α, leading to attenuation of global protein synthesis (Harding et al. 2000). Inhibition of eIF2α allows selective expression of ATF4, a regulator of genes involved in protein folding, antioxidant responses, autophagy, amino acid metabolism, and apoptosis (Harding et al. 2003). Active PERK phosphorylates and activates NRF2, a master regulator that promotes cell survival by counteracting oxidative stress and modulating redox signaling (Niture et al. 2010; Hybertson et al. 2011). Altered NRF2 expression has been associated with the pathogenesis of chronic lung diseases, such as asthma, COPD, and IPF, contributing to excessive oxidative stress in the lung (Cho and Kleeberger 2007; Cho et al. 2006). Importantly, NRF2 is known to be regulated in a circadian manner (Pekovic-Vaughan et al. 2014). Therefore, circadian control of the NRF2/glutathione pathway plays a significant role in combating oxidative/fibrotic lung damage, which might prompt new chronotherapeutic strategies for the treatment of human lung diseases, including IPF (Pekovic-Vaughan et al. 2014; Malhotra et al. 2011; Kumar et al. 2011).

2.4.5 Deregulated Nutrient Sensing

NAD+ is a promising candidate to be an integrator of circadian-rhythm and nutrient-sensing pathways. Several studies have demonstrated that the circadian clock regulates the synthesis of the essential metabolic cofactor nicotinamide adenine dinucleotide (NAD+), which plays a central role in redox reactions and is an important cofactor of the class III histones and protein deacetylases (sirtuin family of NAD+-dependent deacetylases). CLOCK:BMAL1 directly regulates nicotinamide phosphoribosyltransferase (NAMPT) transcripts and NAD+ levels (Peek et al. 2012; Ramsey et al. 2009; Nakahata et al. 2009). In circadian mutant mice, NAD+ supplementation restores protein deacetylation and enhances oxygen consumption (Peek et al. 2013).

Class III deacetylases participate in both protein deacetylation and ADP-ribosylation and constitute a rapid means of upregulating mitochondrial energy production during nutrient deprivation. SIRT1 and SIRT3 are members of the sirtuin family that regulates a range of metabolic processes, senescence, and life span (Saunders and Verdin 2007; Donmez and Guarente 2010; Haigis and Sinclair 2010; Peek et al. 2012). Sirt1 and Sirt3 have been implicated in the pathogenesis of age-related lung diseases, such as COPD and IPF. Sirt1 is decreased in macrophages and lungs of smokers and COPD patients, leading to an increase in NF-κB–dependent proinflammatory mediators in lung and markers of oxidative and nitrosative stress (Rajendrasozhan et al. 2008). Others showed that the progressive decline in Sirt1 is accompanied by increasing levels of IL-8 and MMP9 with increasing disease severity, whereas induction of SIRT1 protects against COPD/emphysema in animal models and contributes to correcting the imbalance in the TIMP-1/MMP-9 ratio (Yao et al. 2013). Bmal1 is acetylated and degraded in the lungs of mice exposed to CS and in patients with COPD, compared with lungs of nonsmoking controls, linking it mechanistically to CS-induced reduction in SIRT1 (Hwang et al. 2014).

Circadian control of the activity of SIRT3 generates rhythms in the acetylation and activity of oxidative enzymes and respiration in isolated mitochondria. In liver of *Bmal1*$^{-/-}$ mice, acetylation is increased at specific lysine residues of the antioxidants MnSOD (Lys^{122}) (Tao et al. 2010) and IDH2 (Lys^{413}) (Yu et al. 2012), known targets of Sirt3. Thus, it was demonstrated that Sirt3 activity is under the control of the circadian clock (Peek et al. 2013). Aging and TGF-β treatment lead to Sirt3 deficiency, acetylation of MnSOD and IDH2, and promotion of pulmonary fibrosis (Sosulski et al. 2016).

2.4.6 Mitochondrial Dysfunction and Oxidative Stress

In mitochondria, both metabolic and cellular defense mechanisms are carefully regulated. Mitochondrial instability has been reported in lung cancer, suggesting

that mitochondrial dysfunction contributes to the progression of lung cancer and multidrug resistance (Mambo et al. 2005; Kamp et al. 2011; Lee et al. 2015; Ma et al. 2015).

Abnormal clock function with aging might influence mitochondrial function. Mutations in mtDNA and oxidative DNA damage have been observed to accumulate in the lung and other tissues during human aging. Several studies suggest that the increase in mtDNA content of aging tissues may be effected through a feedback mechanism to compensate for the functional decline of mitochondria in human aging, and that smoking may modulate the mechanism (Lee et al. 1998, 1999). It is also possible that aging is concomitant with deficient autophagic degradation of mitochondria, a mechanism that can itself be circadian regulated, leading to accumulation of dysfunctional mitochondria (Sosulski et al. 2015; Jacobi et al. 2015). Similarly, exposure to CS impairs mitophagy (Ahmad et al. 2015). There are few studies connecting asthma with mitochondrial dysfunction; however, a recent study demonstrates a significant reduction in mitochondrial glucocorticoid and estrogen receptors in human bronchial epithelial cells from fatal asthma cases (Simoes et al. 2012).

During aging, autophagic clearance of mitochondria declines and dysfunctional mitochondria provoke chronic oxidative stress, which disturbs the cellular redox balance (Salminen et al. 2012b). Reduced mitochondrial oxidative capacity and abnormal coupling are also evident as a consequence of perinatal nicotine exposure, but the mechanisms need to be elucidated (Cannon et al. 2016). Exposure to airborne particulate matter, as well as to profibrotic factor TGF-β, leads to a decrease in mitochondrial respiratory function (Delgado-Buenrostro et al. 2013; Sosulski et al. 2015). It is possible that the environmental induced mitochondrial dysfunction can be associated to circadian changes. According to the circadian gene expression database (http://expression.gnf.org/circadian), several respiratory chain components, including subunits of complex I, appear to display a circadian expression pattern in mice, and a number of others that remain to be analyzed contain E-box motifs for clock transcription factor complexes in their promoters (Hogenesch et al. 1998). Deficiency in Sirt3 also alters antioxidant response and mitochondrial dynamics and function. Therefore, changes in the circadian regulation of Sirt3 might have significant consequences for mitochondrial function and response to injury.

It is also evident that mitochondrial proteins, such as prohibitins, can modulate the internal circadian clock. Prohibitins are versatile proteins located in the inner mitochondrial membrane and involved in mitochondrial function and morphology. Prohibitin 2 (PHB2) is a modulator of period length (Kategaya et al. 2012). Downregulation of PHB2 increases circadian-driven transcription, thus revealing that PHB2 acts as an inhibitor in the molecular clock. Even if no significant differences are found in PBH2 expression in COPD, prohibitin 1 (PHB1) was previously found to be significantly downregulated in bronchial epithelial cells of patients with COPD and likely contributes to oxidative stress in the COPD lung (Soulitzis et al. 2012).

Several defects in mitochondrial dynamics, including mitophagy, have been reported in chronic lung diseases (Sosulski et al. 2015). Reduced expression of PINK1 is observed in the lungs of aging mice and IPF patients and is associated with pulmonary fibrosis (Sosulski et al. 2015; Bueno et al. 2014). Changes in mitochondrial dynamics may also be relevant to the pathogenesis of COPD (Hara et al. 2013; Hoffmann et al. 2013; Aravamudan et al. 2014). It has been shown that mitochondria of primary bronchial epithelial cells from COPD patients show elongation and fragmentation, swelling, and depletion of cristae (Hoffmann et al. 2013). Mitochondrial dysfunction is also linked to inflammatory responses (Escames et al. 2013; Lopez-Armada et al. 2013). Thus, strategies aimed at controlling excessive oxidative stress within mitochondria might have a therapeutic purpose against inflammation (Lopez-Armada et al. 2013, Yue and Yao 2016).

Mitochondrial dysfunction in muscle cells may contribute to the loss of muscle strength, leading to a decline in physical function, which is a systemic manifestation of COPD (Lloreta et al. 1996; Mayer et al. 2013). Currently, mitochondria-targeted interventions are being developed in studies to elucidate the role of mitochondrial metabolism and recycling in lung aging, COPD, and pulmonary fibrosis.

2.4.7 Cellular Senescence

Cellular senescence and the inflammatory profile of senescent cells play significant roles in the pathogenesis of chronic lung diseases, including COPD and lung fibrosis (Tsuji et al. 2010; Aoshiba and Nagai 2009; Bartling 2013; Chilosi et al. 2013). Senescent cells recruit the immune system to facilitate their removal from tissues. Nevertheless, during ageing, their senescence-associated secretory phenotype (SASP) drives major pro-inflammatory consequences (Ovadya and Krizhanovsky 2014). On one hand, senescence decreases the ability of cells to transmit circadian signals to their clocks. Conversely, the introduction of telomerase completely prevents this reduction of clock gene expression associated with senescence (Kunieda et al. 2006). On the other hand, deficiency in circadian clock regulation can result in senescence. In fact, deficiency of Bmal1 results in the development of premature aging in mice, with an increase in the number of senescent cells in different tissues (lungs, liver, and spleen). However, it appears that Bmal1 doesn't play a significant role in replicative senescence, as demonstrated by similar rates of proliferation and senescence in primary fibroblasts isolated from wild-type and *Bmal1*$^{-/-}$ mice (Khapre et al. 2011).

2.4.8 Stem Cell Exhaustion

The influence of circadian rhythm on the regulation of stem cells has recently begun to be evaluated. Clocks have been suggested to underlie heterogeneity in stem cell

populations to optimize cycles of cell division during wound healing (Brown 2014). A link is also emerging between the circadian clock and metabolic transcriptional regulation by epigenetic mechanisms, implying a role of this interaction in stem-cell homeostasis (Avitabile et al. 2016). Nevertheless, little is known about the role of circadian rhythm in human mesenchymal bone marrow stem cell (BMSC) properties. Rev-erbα and the Wnt/β-catenin signaling pathway are known to play important roles in BMSC aging, and it has been suggested that Rev-erbα may promote BMSC aging and function as a negative regulator during late-stage osteogenesis (He et al. 2015). Recent data confirm that circadian rhythms also play a role in the regulation of mesenchymal stem cell differentiation and division, key factors in maintaining mesenchymal stem cell properties (Boucher et al. 2016). Stem cell-based therapy is being proposed for the treatment of chronic lung diseases (Gore et al. 2016; Lin et al. 2015; Zhang et al. 2014; Pierro and Thebaud 2010). In consequence, there is a need to determine the role of the circadian clock in the maintenance of lung progenitor cells, specifically, the role the circadian clock regulators play in stem cell maintenance to preserve lung integrity during aging and tissue repair. The identification of factors that potentiate the regenerative capacity of stem cells is crucial for the development of next-generation therapeutics for chronic lung diseases.

2.4.9 Intercellular Communication

A prominent aging-associated alteration in intercellular communication is the proinflammatory phenotype that accompanies aging in mammals (Salminen et al. 2012a, b). Circadian rhythms mediated by light/dark cycles influence the immune functions of natural killer cell activity, lymphocyte and monocyte proliferation and their secretome (Boivin et al. 2003). Eight percent of all mRNA transcripts in macrophages show oscillation of expression over a 24-h period. Bronchiolar epithelium is part of the cell-specific timing mechanism that regulates overall homeostasis of immunological responses (Gibbs et al. 2014). Conversely, cytokines in the lung can also reprogram the circadian rhythm (Haspel et al. 2014; Dong et al. 2016b).

Intercellular communications are also highlighted by exosome secretion. Exosomes exhibit pleiotropic biological functions, including immune regulatory functions, antigen presentation, intracellular communication, and intercellular transfer of RNA and proteins. Exosomal protein and microRNA (miR) content reflects the physiological condition of the cells of origin, as presented in an interesting study with lung adenocarcinoma cells (Choi et al. 2014). Importantly, sleep fragmentation induces alterations in biosynthesis and cargo of plasma exosomes that affect tumor cell properties (Khalyfa et al. 2016). Exosomes can also enhance the transcriptional activity and abundance of β-catenin, a primary regulator of epithelial-mesenchymal transition (Choi et al. 2014). CS can modify the extra-vesicular components from bronchial epithelial cells, such as exosomes carry

miR-210 as paracrine mediators of myofibroblast differentiation (Fujita et al. 2015). To our knowledge, no studies have been done concerning the circadian regulation of exosome secretion and content in chronic lung diseases. Conversely, it appears that exosomes can regulate circadian gene expression, as shown in studies in *Neurospora* (Guo et al. 2009). It will be important to determine if exosomes have a circadian regulatory potential in the lung.

Intercellular communication can also lead to inter-tissue communication. This is highlighted by a recent study revealing that adenocarcinoma lung functions as a circadian organizer that rewires a distal tissue, such as the liver, through an altered proinflammatory response via the STAT3-Socs3 pathway. Future studies will need to address how aging regulates inter-tissue communication (Cairns and Mak 2016; Masri et al. 2016).

2.5 Chrono-Therapy for Age-Related Lung Diseases

Chrono-pharmacology, or circadian regulation of drug function, as well as chrono-tolerance and chrono- nutrition, are likely to become important research fields in chronobiological studies (Mitteldorf 2013; Tahara and Shibata 2014).

Melatonin. A crucial observation was the decline of the nocturnal melatonin peak in elderly persons and the capacity of melatonin to prolong life span. Different subtypes of melatonin receptors may address the issue of the various physiological actions of melatonin reported in individual tissues within the same species or similar tissues in different species. Beneficial effects of melatonin in attenuating aging-related deterioration have been demonstrated in several publications (Armstrong and Redman 1991; Jenwitheesuk et al. 2014). In fact, melatonin modulates the inflammatory and apoptosis status of the aging lungs, exerting a protective effect on age-induced damage (Puig et al. 2016). One study, aiming to determine whether melatonin administration can prevent the hyper-oxidative state that occurs in lung mitochondria with age, concluded that melatonin protects lung mitochondria from aging with similar benefits in male and female mice (Acuna-Castroviejo et al. 2012). Melatonin also reduces lung injury in bleomycin models of pulmonary fibrosis regarding mortality rate, the degree of inflammation, and fibrosis (Karimfar et al. 2015; Zhao et al. 2014; Yildirim et al. 2006; Genovese et al. 2005). Melatonin was found to be significantly reduced during the exacerbation period in patients with COPD (Gumral et al. 2009). In contrast, a daily dose of melatonin has been shown to protect lungs from histopathological changes in rabbits exposed to smoke (Unlu et al. 2006). A 4-week study revealed that melatonin could improve sleep in patients with asthma; however, long-term studies are needed to resolve conflicting data (Campos et al. 2004; Luo et al. 2004). Concerning cancer cells, melatonin has an inhibitory effect on the reduction in mitochondrial membrane potential that occurs upon doxorubicin treatment and the development of premature senescence at the cellular level and protects adenocarcinomic human alveolar basal epithelial cells (A549 cells), from

doxorubicin-induced senescence (Song et al. 2012). Melatonin orally administered to reset the circadian clock reduces the toxicity of various chemotherapeutic agents (Lewy et al. 1999; Lewy and Sack 1997; Lissoni et al. 1994; Lissoni 2000). Melatonin also enhanced the antitumor activity of berberine through activation of caspase/cyto C and inhibition of AP-2β/hTERT, NF-κB/COX-2, and Akt/ERK signaling pathways (Lu et al. 2016). Other positive results in animal studies suggest that melatonin prevents the increase in glucose levels that usually follows intermittent exposure to hypoxia seen in OSA (Kaminski et al. 2015). Exogenously administered melatonin can also protect lungs from reperfusion injury after prolonged ischemia in transplant models (Inci et al. 2002).

Chrono-toxicity has been evaluated for some therapies, particularly cancer therapies. One early study demonstrated that cisplatin-based chronotherapy has the advantage of relieving side effects of the chemotherapy in patients with advanced NSCLC and that the metabolism of cisplatin is circadian regulated (Li et al. 2015). Nevertheless, little is known about chrono- pharmacology and chrono- toxicity of most drugs currently used to treat chronic lung conditions.

Small molecules in chronotherapy. Approximately 200,000 compounds have already been screened and characterized as circadian regulators acting as modifiers of period length, phase delay, phase advance, phase attenuation, and amplitude (Tahara and Shibata 2014). Through chemical-screening approaches, a number of compounds that affect circadian rhythms have been discovered, including those presented in Table 2.1, such as casein kinase I inhibitors and synthetic ligands for the nuclear receptors REV-ERB and ROR (Sprouse et al. 2010; Badura et al. 2007; Gibbs et al. 2012; Cho et al. 2012; Solt et al. 2012). Some of those compounds had been proposed previously as therapeutic alternatives for diseases such as lung cancer (Hung et al. 2013; Tang et al. 2016; Parajuli et al. 1999; Schwandt et al. 2012; Ferguson et al. 2015; Hayashi et al. 2006) and exacerbated inflammation in models of acute lung inflammation and COPD (Ratcliffe and Dougall 2012; Brando

Table 2.1 Summary of small molecules as circadian regulators

Circadian effect	Molecules
Period-lengthening activity	Casein kinase 1 inhibitor (Sprouse et al. 2010; Badura et al. 2007); MAP kinase p38 inhibitor (Dusik et al. 2014; Pizzio et al. 2003; Hayashi et al. 2003); JNK inhibitor (Pizzio et al. 2003); PP2A inhibitor (Yang et al. 2004)
Period-shortening activity	DNA topoisomerase II inhibitor, PKC agonist, CDK inhibitor, and GSK3β inhibitor (Hirota et al. 2008)
Attenuation of phase shifts	Kinase inhibitors, including U0126 (ERK) (Coogan and Piggins 2003), KN-62 (CaMKII) (Golombek and Ralph 1994), KT5823 (PKG), and SB431542 (ALK) (Kon et al. 2008)
Phase delay and amplitude enhancement	Inducer of cellular cAMP, phosphodiesterase inhibitor (rolipram), and secondary inducer of cAMP (Chen et al. 2012; Hirota et al. 2012)
Amplitude reduction	Agonists of Rev-erbα or Rev-erbβ (Gibbs et al. 2012; Cho et al. 2012; Solt et al. 2012)

Lima et al. 2011; Arndt et al. 2005). It will be critical in the near future to determine whether strategies known to facilitate synchronization of the circadian clocks in younger individuals can do so in older individuals, and whether doing so allows patients with chronic lung disease to experience improved quality of life and/or live longer. Thus, it will be beneficial to determine whether the use of the small molecules capable of manipulating the clock leads to beneficial effects in chronic lung diseases.

2.6 Future Directions

The potential for novel chrono-pharmacological approaches for the treatment of lung disease needs to be determined in the near future in agreement with recent lines of evidence indicating that aging proceeds under control of a master clock or several redundant clocks (Mitteldorf 2016). It is plausible that resetting the clocks with biochemical interventions might regulate the hallmarks of aging and make an old lung behave like a young lung. Developing strategies to prevent circadian disruption effectively with aging to prevent the onset of age-related lung diseases and to provide effective strategies to diminish circadian disruption among patients with chronic lung diseases are worthwhile and accomplishable goals.

Acknowledgements I am grateful for the support of the Tulane Center for Aging and NIGMS-NIH Award Number P20GM103629, which made our studies of age-related lung diseases possible. I also apologize to investigators whose work may not have been cited due to space limitations.

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http://www.springer.com/978-3-319-64542-1

Circadian Rhythms and Their Impact on Aging
Jazwinski, S.M.; Belancio, V.P.; Hill, S.M. (Eds.)
2017, XIII, 361 p. 41 illus., 15 illus. in color., Hardcover
ISBN: 978-3-319-64542-1