

Circadian disruption in respiratory diseases

2025-06-28

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Contents

(1) Overview of circadian rhythm

(2) Association with respiratory diseases

- Sepsis
- Asthma
- COPD

Contents

(1) Overview of circadian rhythm

(2) Association with respiratory diseases

- Sepsis
- Asthma
- COPD

Neurophysiology of the circadian rhythm

Circadian rhythm is a result of an autonomous, intrinsic timekeeping system called the “**circadian clock**”

- Genetically controlled
- Temporally orchestrates physiological processes to adapt the internal environment with the external cues
- The circadian machinery comprises a hierarchical network of oscillators that work in synchrony with one another at the cellular, tissue, and organ system level

Neurophysiology of the circadian rhythm

Endogenous “circadian clock”

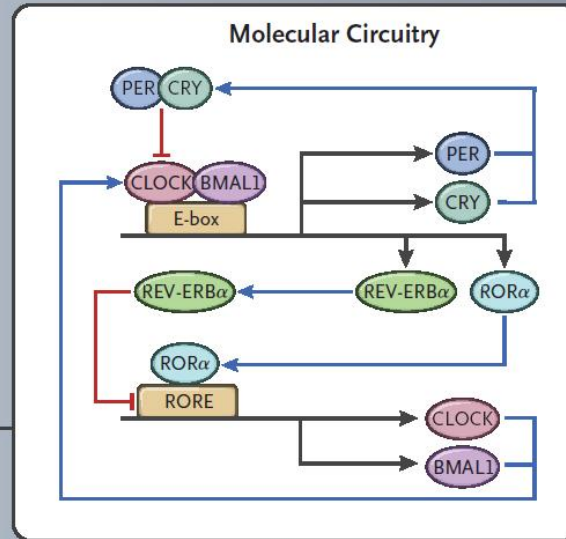
(1) Central clock (master clock)

- Suprachiasmatic nucleus (SCN) in hypothalamus
- Receives input from the external environment to synchronize with the external environment
- Regulates the peripheral clocks either through the neuronal (sympathetic or parasympathetic) or hormonal signals (e.g., melatonin, glucocorticoids, or catecholamines)

(2) Peripheral clocks

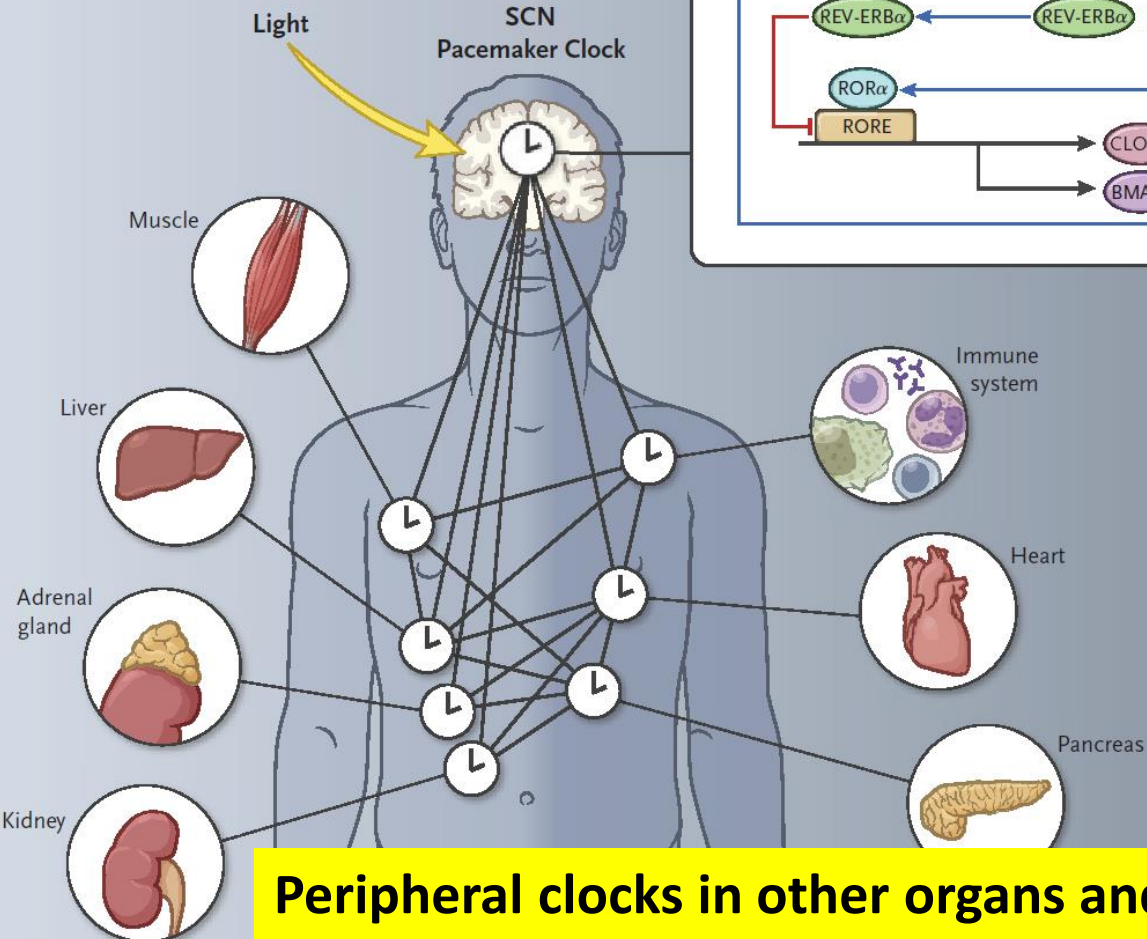
- Independent clock residing in almost every cell of the peripheral organs (heart, liver, stomach, lungs, intestine, and kidneys)

Light-dark cycle

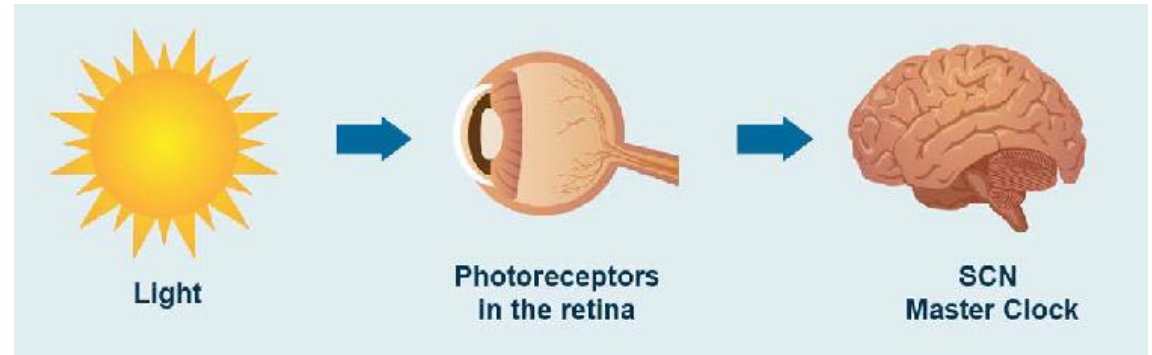


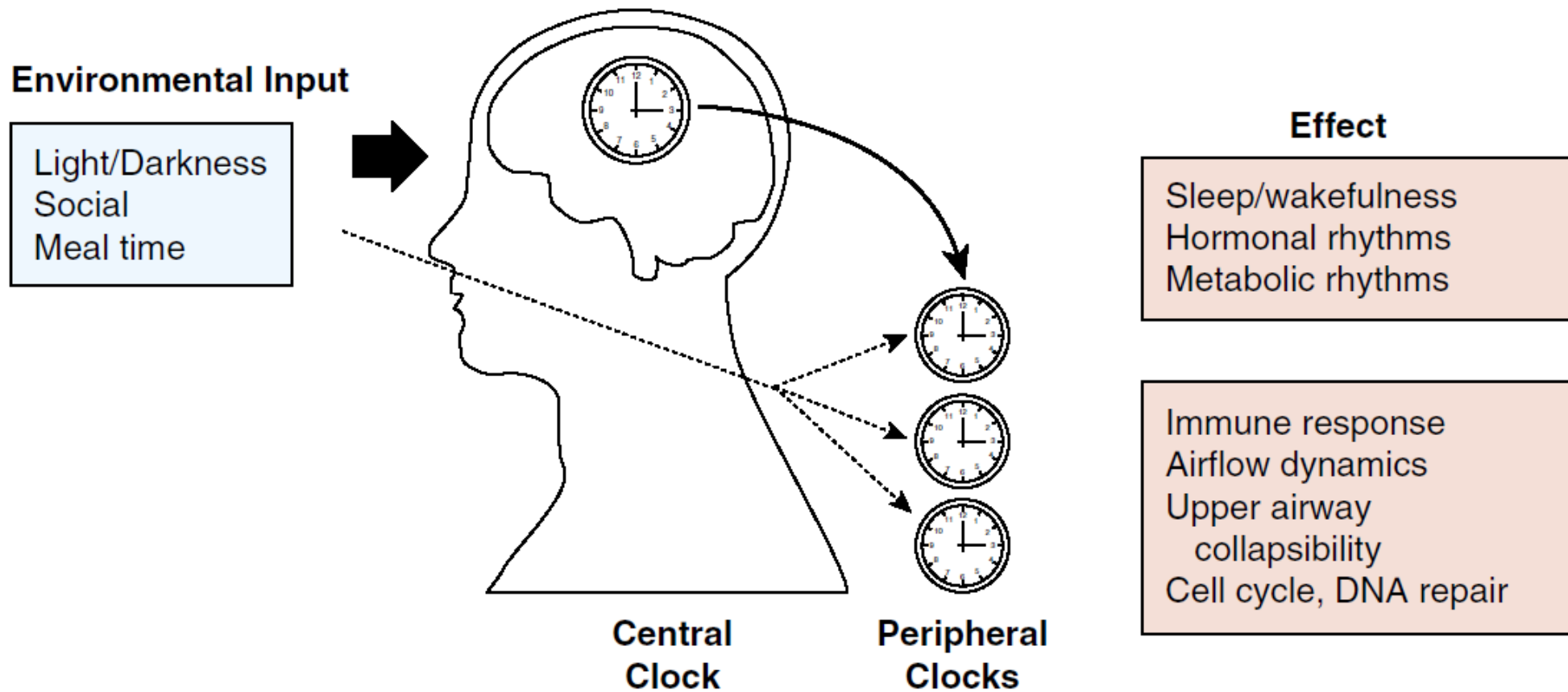
Photoreceptors are special intrinsically photosensitive retinal ganglion cells (ipRGCs) containing **melanopsin**

- **Suprachiasmatic nucleus (SCN) in hypothalamus** → **Central pacemaker**
- Acts as the master clock
 - transmits light information by activating the master clock
- Regulates multiple physiological processes (including sleep, arousal, autonomic nervous system, feeding cycles, mood, and movement)
- Keeps the peripheral clocks in other tissues synchronized with the external environment



Peripheral clocks in other organs and tissues





External time cues (**Zeitgeber**)

- **Light**
- Temperature
- Food availability

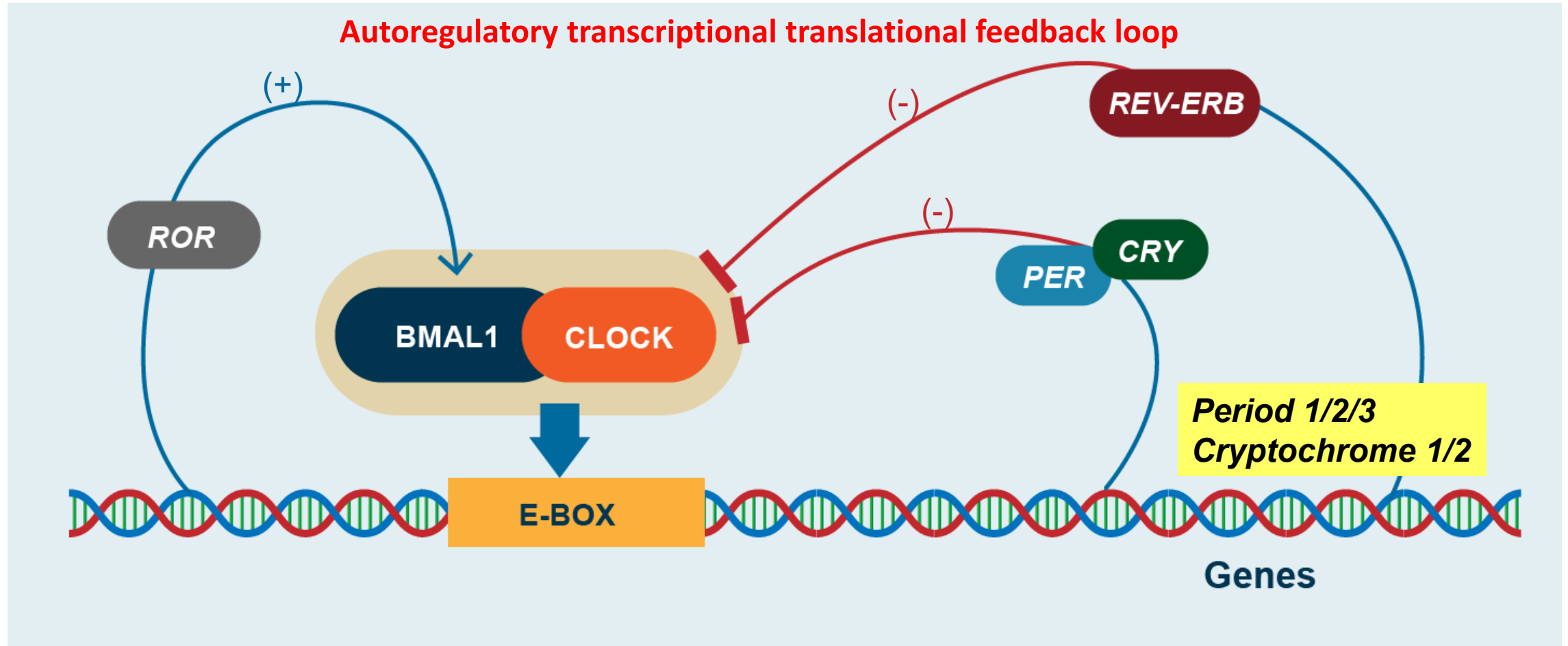
The phase of circadian clock is determined by environmental cues “entrainment”

Neurophysiology of the circadian rhythm

Complexity of the system

- Ablation of the SCN
 - does not abolish the circadian rhythms in the peripheral clock completely, highlighting the endogenous, self-sustaining nature of the peripheral clocks
- Role of other zeitgebers, such as food intake time, exercise, or stress
 - modulate the peripheral clock independently

Molecular biology of the circadian rhythm



At a cellular level, circadian rhythms are generated by autoregulatory negative feedback loop of transcription factors, collectively referred to as the clock genes

Circadian rhythm in clinical context

Diurnal variability in many diseases

- Myocardial infarction
- Ischemic stroke
- Sudden cardiac death
- Asthma
- Hypertension
- Seizures

Disturbance in the circadian rhythm

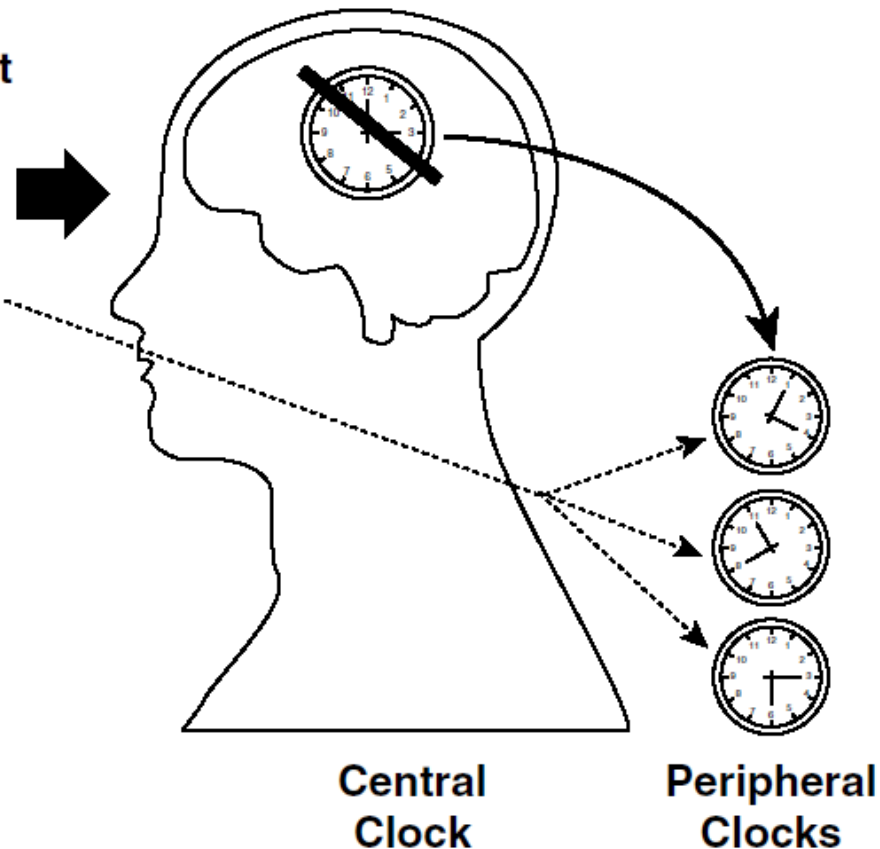
Negative health outcomes from circadian rhythm disruption

- Studies of shift workers

Environmental Input

Shift work
Hospital setting
Cigarette smoke
Genetic
Behavioral

Pathogens
(bacteria/virus)

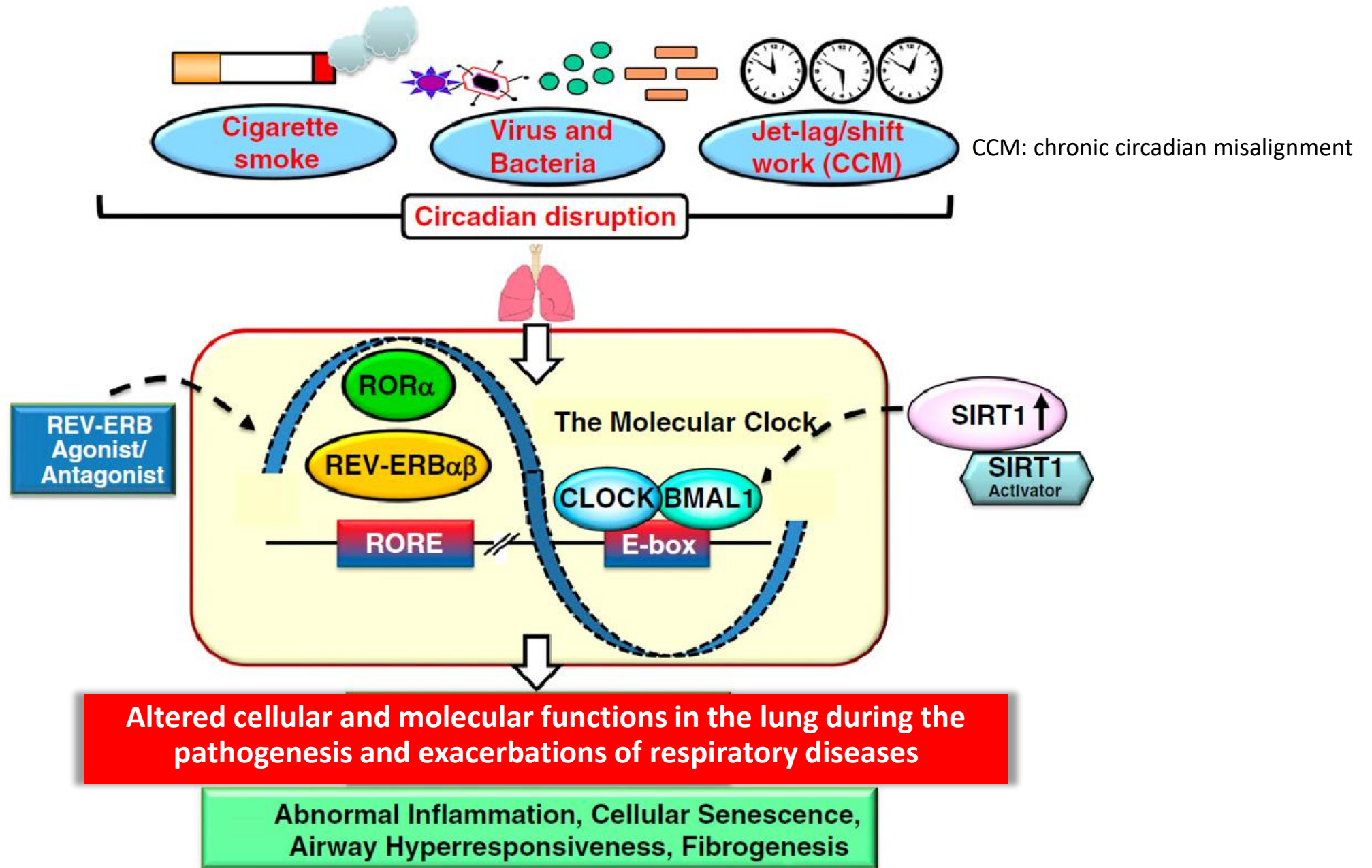


↑ Cardiometabolic risk
↑ Some cancer risk

Effect

Sleep disorders
Inflammation
Metabolic abnormalities
Mood disorders

Increased sepsis risk
Increased asthma/COPD
exacerbation risk
Increased cancer risk



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Circadian effect on sepsis

Immune cells have an endogenous circadian clock

Light-dark cycles influence

- Natural killer cell activity
- lymphocyte proliferation
- monocyte proliferation

Levels of inflammatory mediators (IL-6, TNF, and IFN-gamma) have a diurnal variation

CIRCADIAN RHYTHM

Inflammation

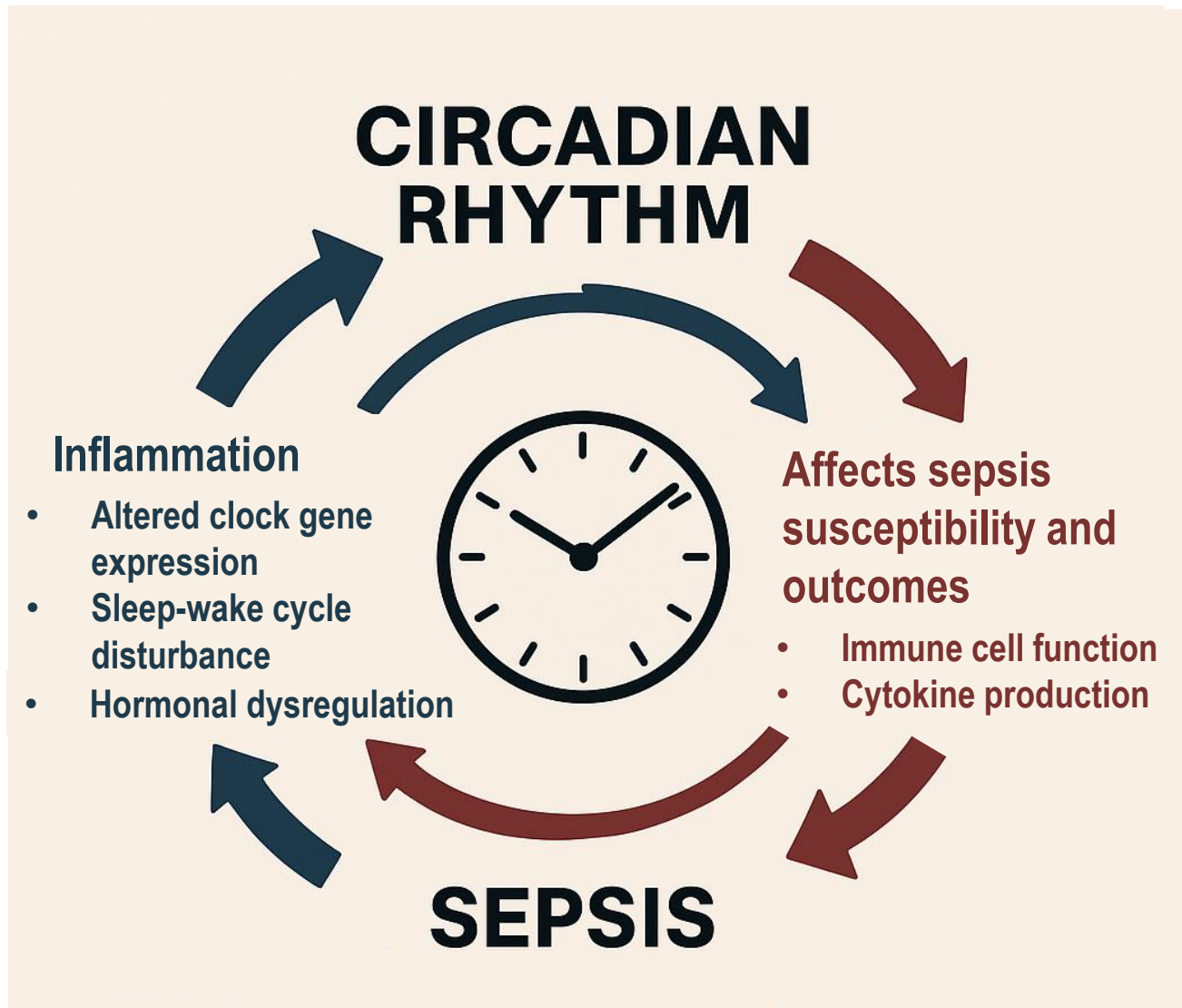
- Altered clock gene expression
- Sleep-wake cycle disturbance
- Hormonal dysregulation



Affects sepsis susceptibility and outcomes

- Immune cell function
- Cytokine production

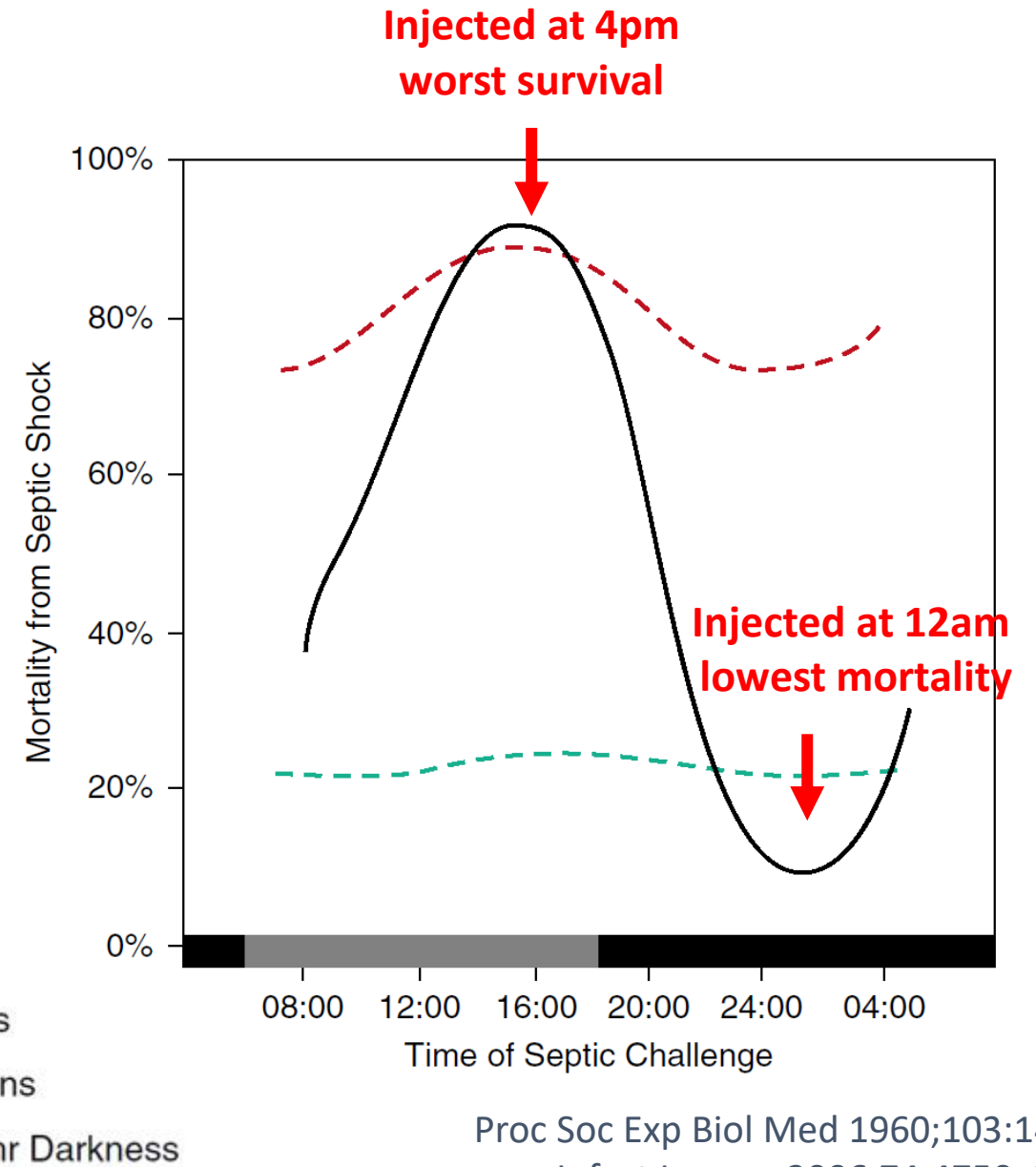
SEPSIS



Circadian effect on sepsis

Documented in controlled animal experiments

- Endotoxin injection in mice at different times of the day (under 12-h light & 12-h dark environment)
- *Period 2* genetic disruption (*period2^{-/-}*)
→ abolished diurnal effect of endotoxin on survival

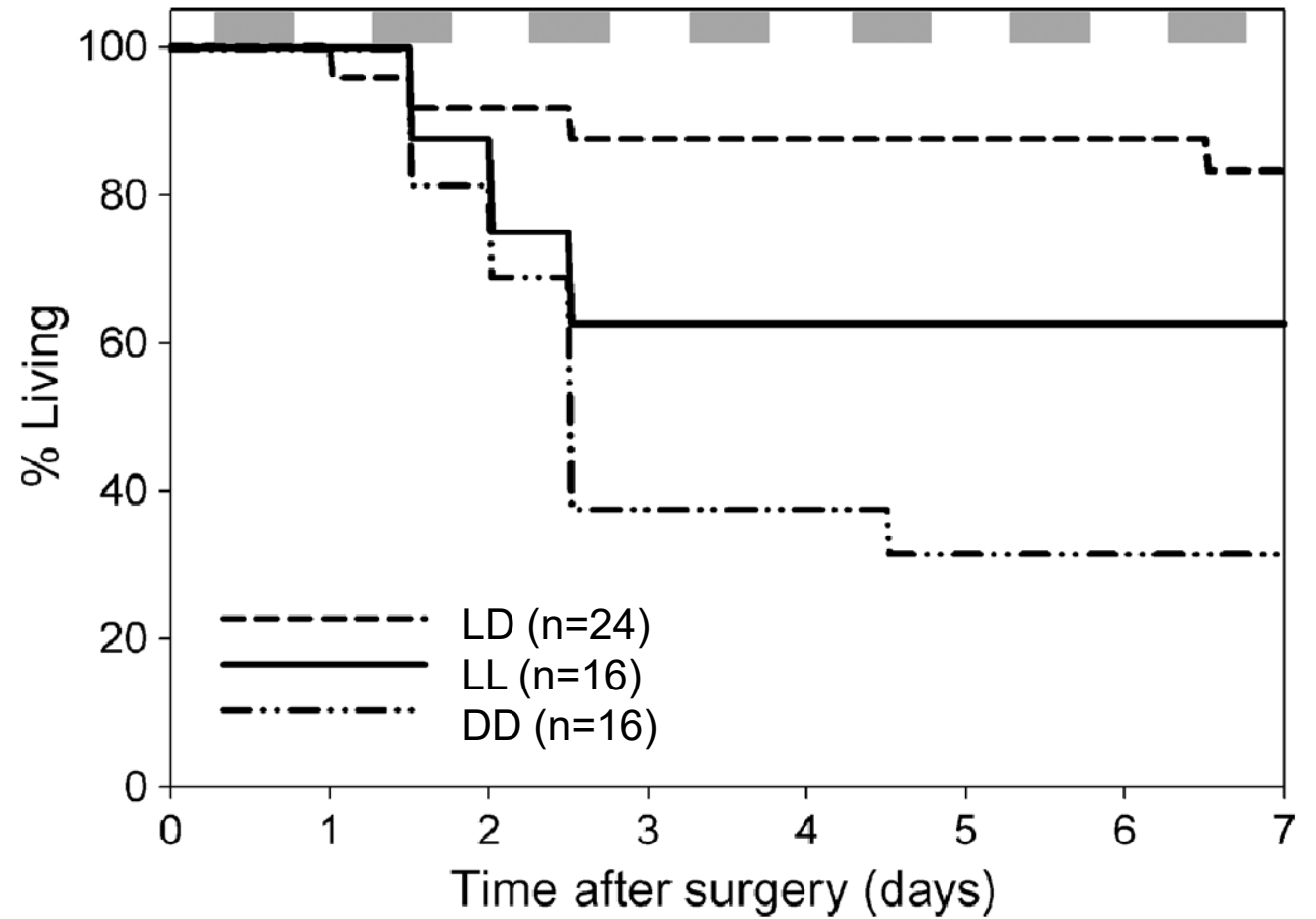


Circadian effect on sepsis

Absence of circadian cues

→ less likely to recover from sepsis

- 1-week survival
- Light/dark cycle (83.33%)
- Constant light (62.5%)
- Constant dark (31.25%)



Circadian effect on sepsis

Circadian rhythm affects sepsis susceptibility and outcomes

- Immune cell trafficking
- Cytokine production
- Hormonal signals (cortisol, melatonin)

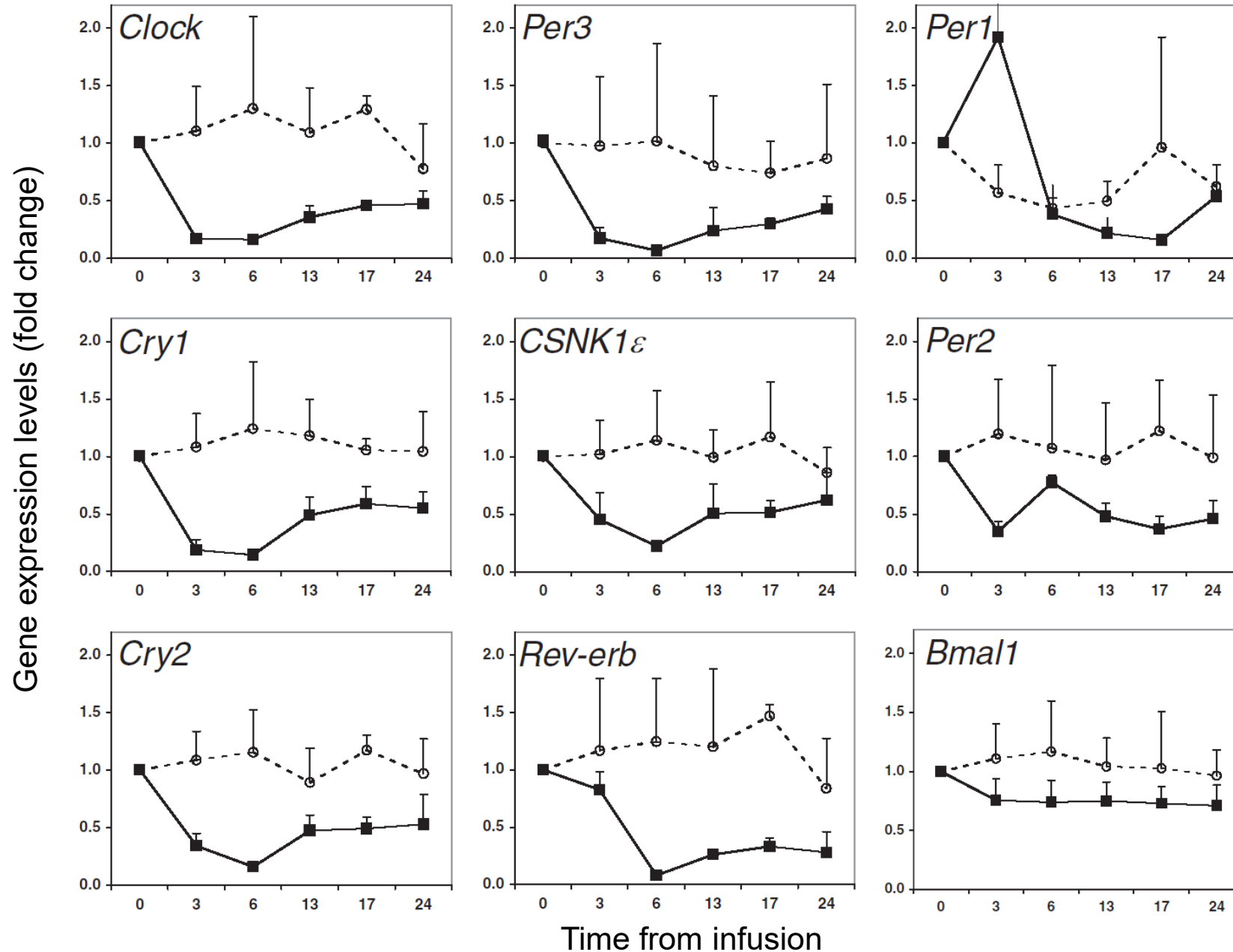
Impact of sepsis on circadian rhythm

More research needed

Circadian rhythm may be suppressed during acute inflammatory illness

- Systemic inflammation affects the brain (including the SCN — the master clock)
- Dysregulation of core clock genes (↓ *BMAL1*, *PER2*, etc.) in central and peripheral tissues
- Altered melatonin secretion, leading to sleep-wake disturbances
- Blunting of hormonal rhythms (e.g., cortisol, body temperature), which correlates with poor prognosis

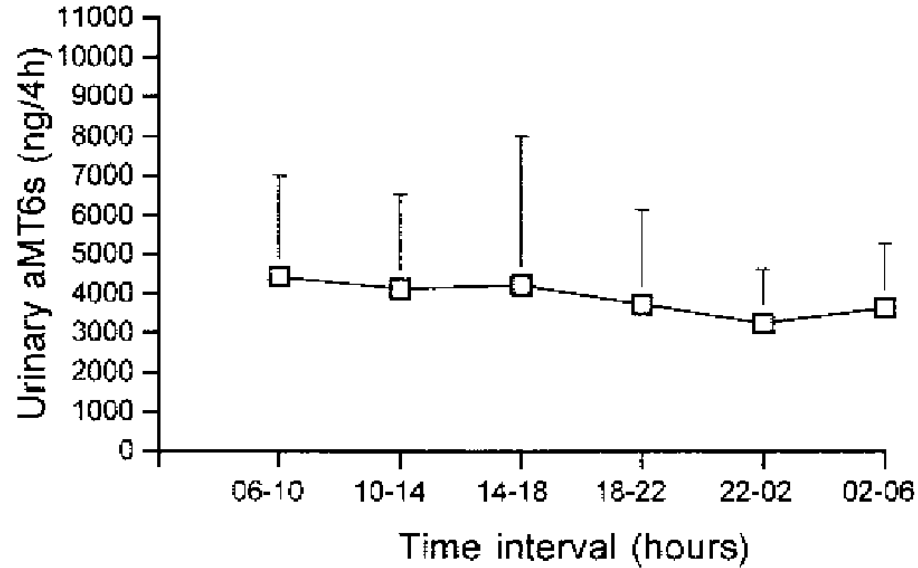
Impact of sepsis on circadian molecular clocks



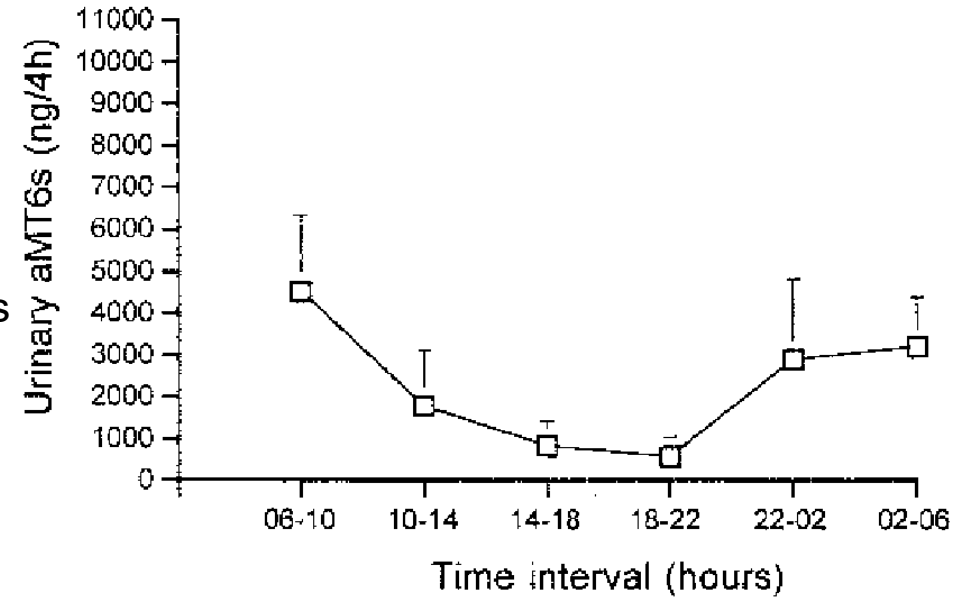
- Healthy volunteers
- Gene expressions in peripheral blood leukocytes after endotoxin infusion
- Significant decrease in *Clock*, *Per3*, *Cry1*, *SNK1*, and *Rev-erb*
- Reaching the nadir within 3-6 hours
- Lasting for at least 17 hours

Impact of sepsis on melatonin secretion

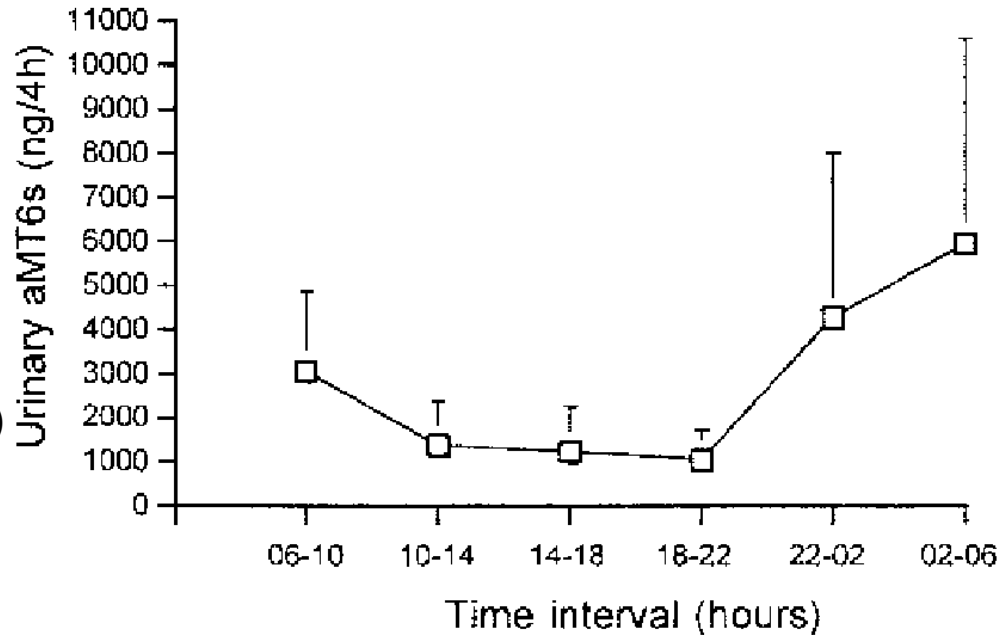
a)
ICU patients
with sepsis



b)
ICU patients
without sepsis



c)
Non ICU
patients
(control group)



- **Melatonin secretion**
- Starting 9-11 pm
- Peak 1-3 am
- Falling 7-9 am

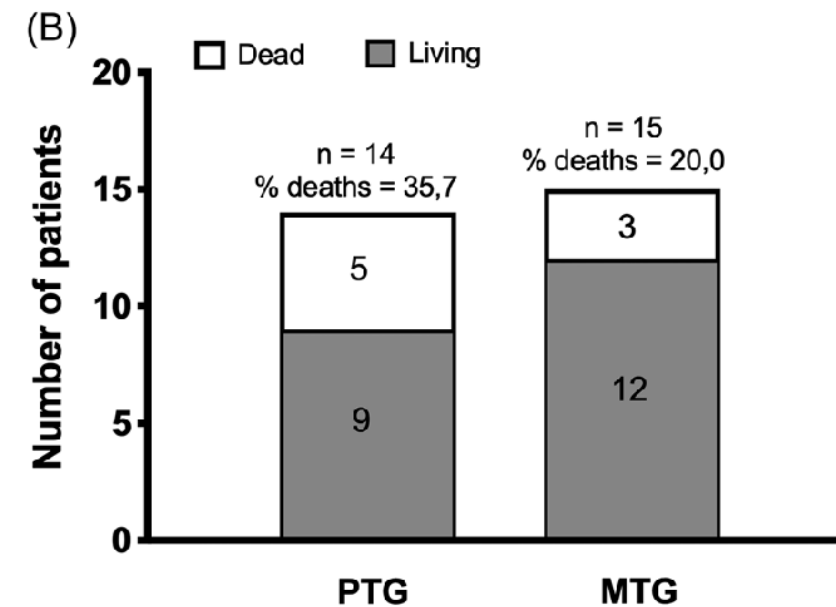
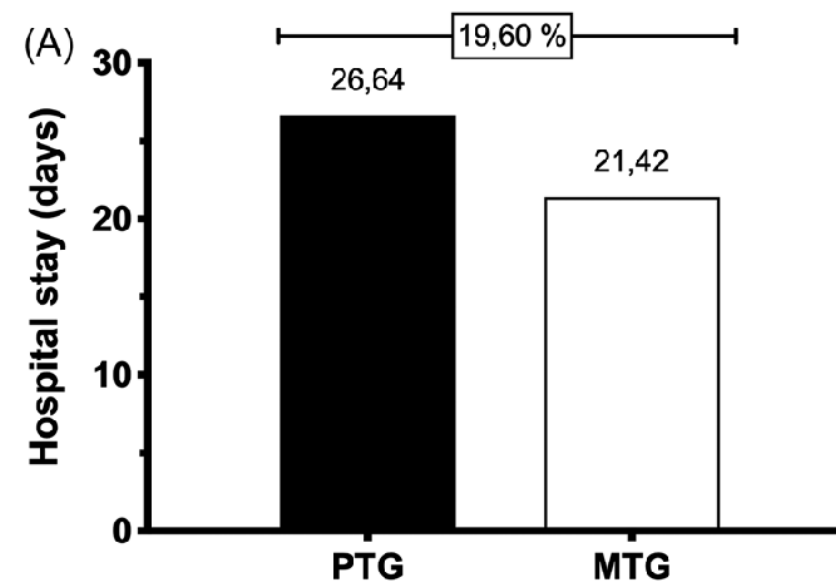
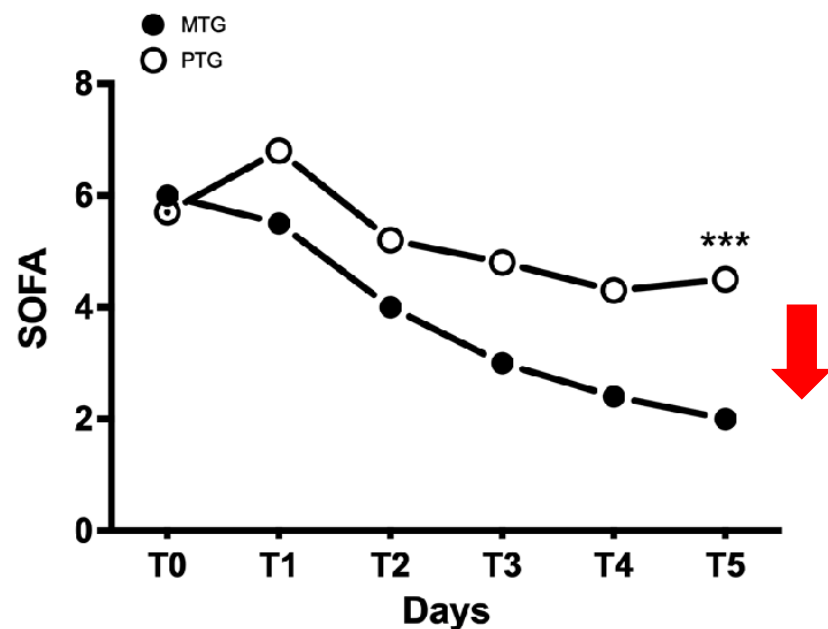
"6-Sulfatoxymelatonin" (aMT6s) as a metabolite excreted by the kidneys

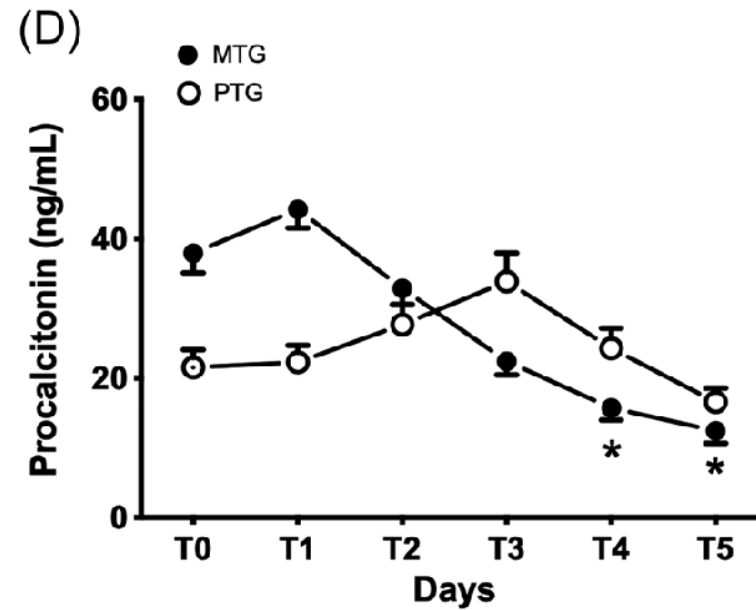
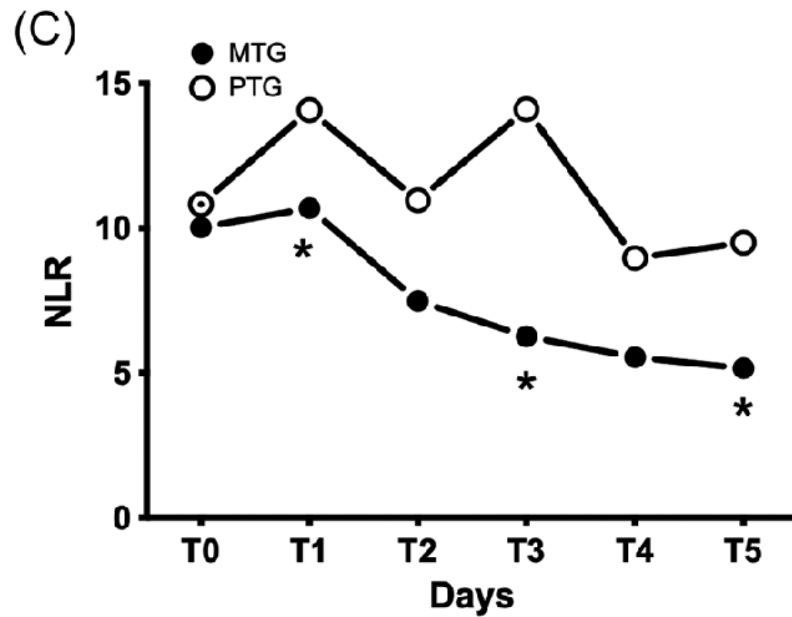
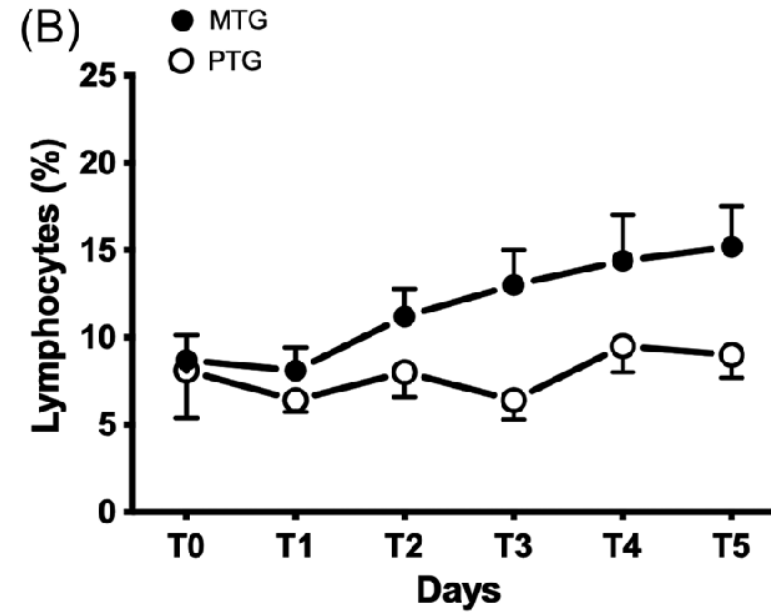
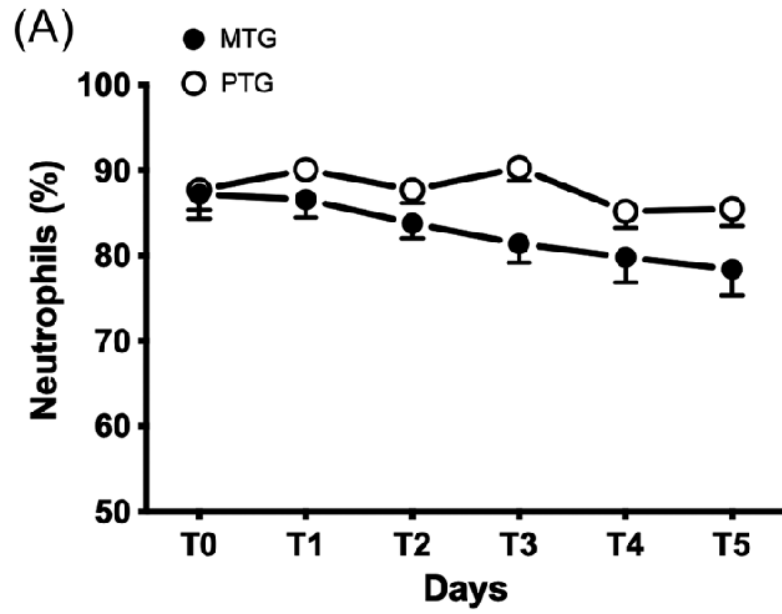
Clinical implications on sepsis treatment

- **“Chronotherapy”** modifying circadian rhythms with therapeutic intent
- Melatonin
 - One of the main endogenous mediators of the circadian rhythm
 - Anti-oxidative and anti-inflammatory effects
- Light therapy

A phase II, single-center, double-blind, randomized placebo-controlled trial to explore the efficacy and safety of intravenous melatonin in surgical patients with severe sepsis admitted to the intensive care unit

- Patients with severe sepsis
- IV melatonin 60mg per day for 5 days (n=15) vs. placebo (n=14)
- Primary outcome: SOFA score
- All-cause mortality, hospital stays, inflammatory response





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- COPD

Circadian effect on asthma

Diurnal variation of asthma symptoms: nocturnal worsening

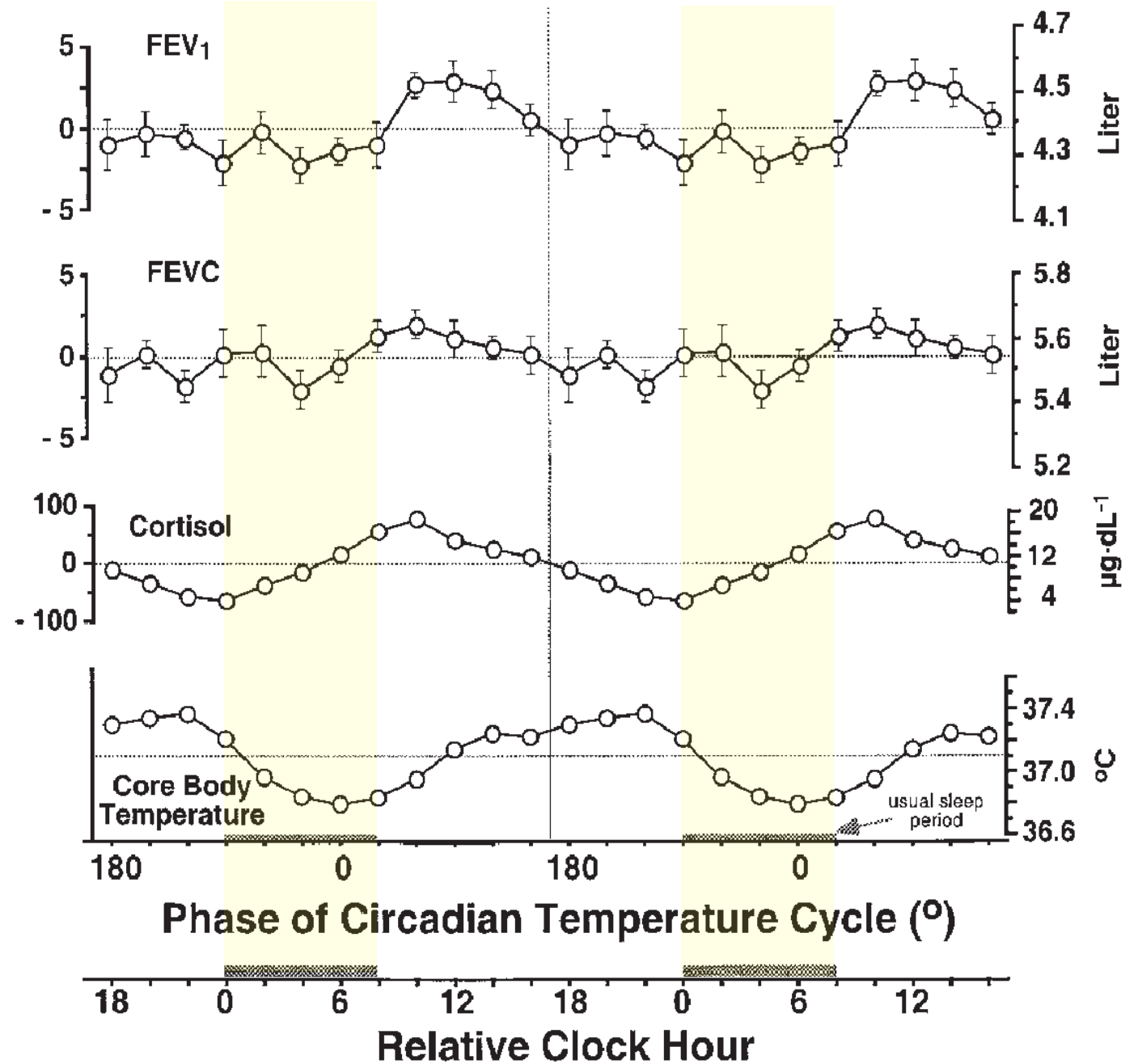
Frequent exacerbations and deaths in the early morning (around 4 am)

The circadian timing system drives diurnal changes in

- (1) Lung function
- (2) Airway inflammation

Endogenous circadian rhythm of lung function

- Healthy volunteers (n=10)
- “Constant routine” protocol
- Maintaining constant behavior (relaxed wakefulness)
 - Constant posture (semi-recumbent)
 - Regular small meals every 2 hour
 - Constant room temperature
 - Very low light (10 lux)



Circadian influence on airway inflammation – BAL

- 12 patients with mild asthma and nocturnal worsening of symptoms
- Two separate admissions with BFS (4am, 4pm)
BAL cell count

Table 2. Total cell counts and differential*

	Percentage		Total cell numbers ($\times 10^4$)	
	16:00 hours	04:00 hours	16:00 hours	04:00 hours
BAL				
Macrophages	87.7 \pm 2.1	83.0 \pm 2.2 [†]	1517 \pm 133	1730 \pm 188
Lymphocytes	9.9 \pm 2.0	12.6 \pm 1.6	169 \pm 32	254 \pm 40 [†]
Neutrophils	0.8 \pm 0.2	3.0 \pm 1.7 [†]	13 \pm 3	40 \pm 14 [†]
Eosinophils	1.5 \pm 0.6	1.3 \pm 0.4	27 \pm 13	24 \pm 6
Blood				
White blood cells ($\times 10^6$ /mL)			5.9 \pm 1.2	6.1 \pm 1.6
Eosinophils/mm ³			332 \pm 167	417 \pm 193 [†]

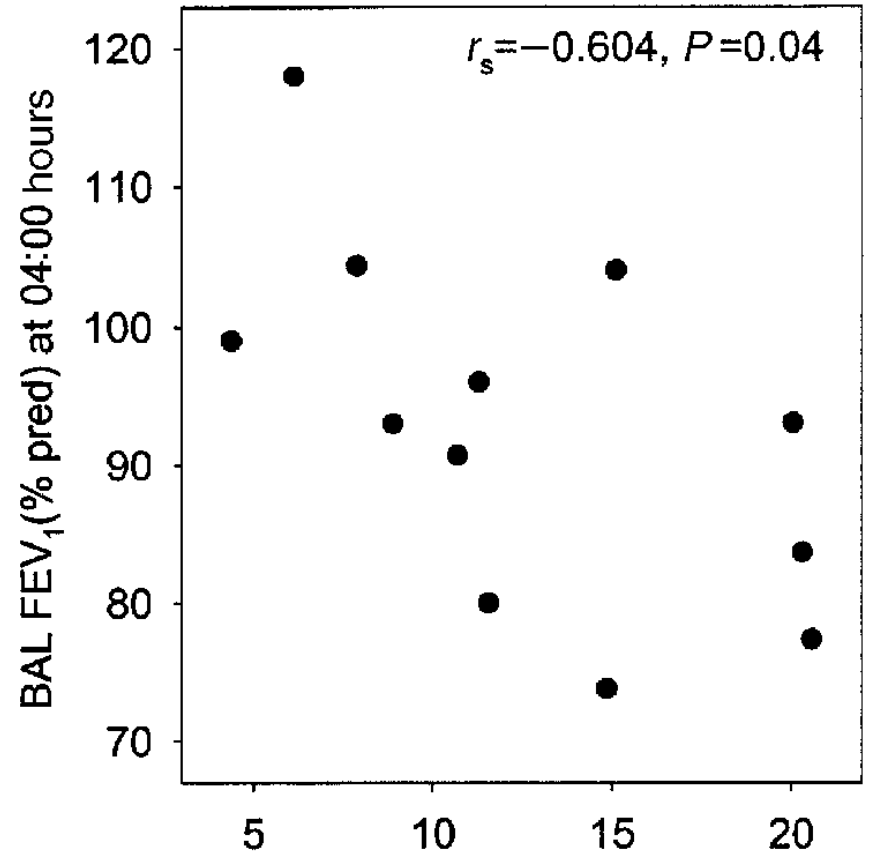
BAL, bronchoalveolar lavage.

*Mean \pm standard error of means. [†] $P < 0.05$, 04:00 vs. 16:00 hours.

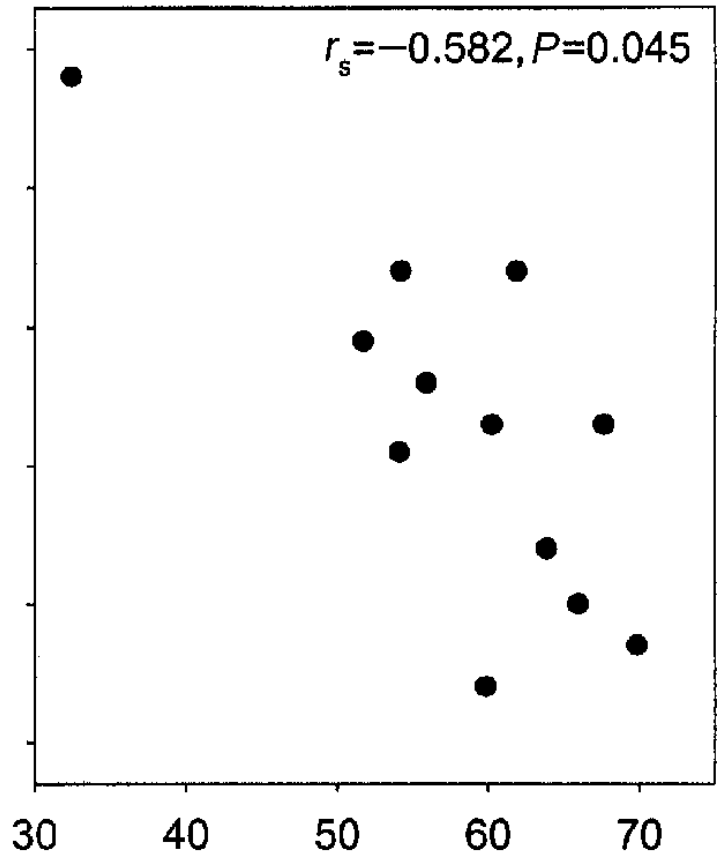
Table 3. BAL lymphocyte and eosinophil subpopulations*

	16:00 hours	04:00 hours
CD3 (% of CD45 ⁺ leucocytes within the lymphocyte gate)	92.8 ± 1.1	94.4 ± 0.9
CD4 (% of CD45 ⁺ leucocytes within the lymphocyte gate)	52.5 ± 4.4	58.1 ± 2.9 [†]
CD8 (% of CD45 ⁺ leucocytes within the lymphocyte gate)	36.5 ± 2.4	35.5 ± 3.4
CD19 (% of CD45 ⁺ leucocytes within the lymphocyte gate)	2.1 ± 0.6	1.8 ± 0.2
NK (% of CD45 ⁺ leucocytes within the lymphocyte gate)	5.1 ± 1.2	4.2 ± 0.8
CD4/CD25 (% of CD4 ⁺ lymphocytes)	18.7 ± 2.8	23.6 ± 3.0 [†]
CD4/CD69 (% of CD4 ⁺ lymphocytes)	66.4 ± 3.2	62.7 ± 3.5
CD4/HLA-DR (% of CD4 ⁺ lymphocytes)	64.5 ± 4.7	66.7 ± 4.7
EOS/CD69 (% of eosinophils)	68.3 ± 7.6	69.6 ± 5.6
EOS/HLA-DR (% of eosinophils)	50.4 ± 6.0	37.4 ± 5.6

Significant inverse relationship with FEV₁



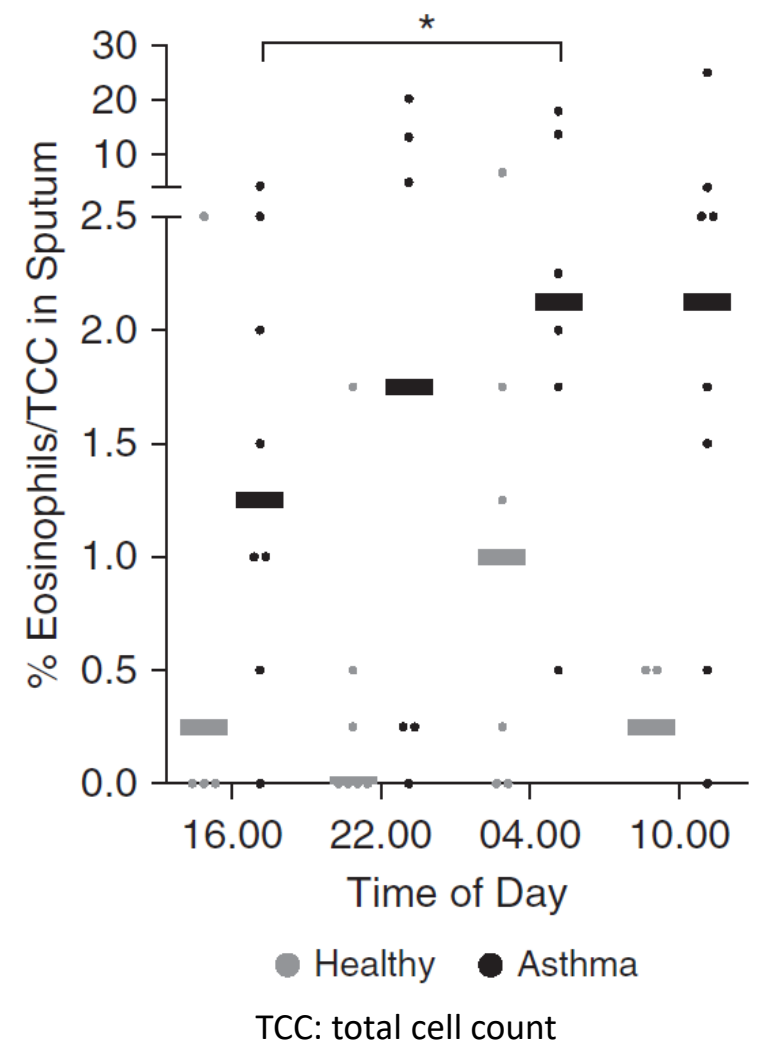
(a) BAL lymphocytes (%) at 04:00 hours



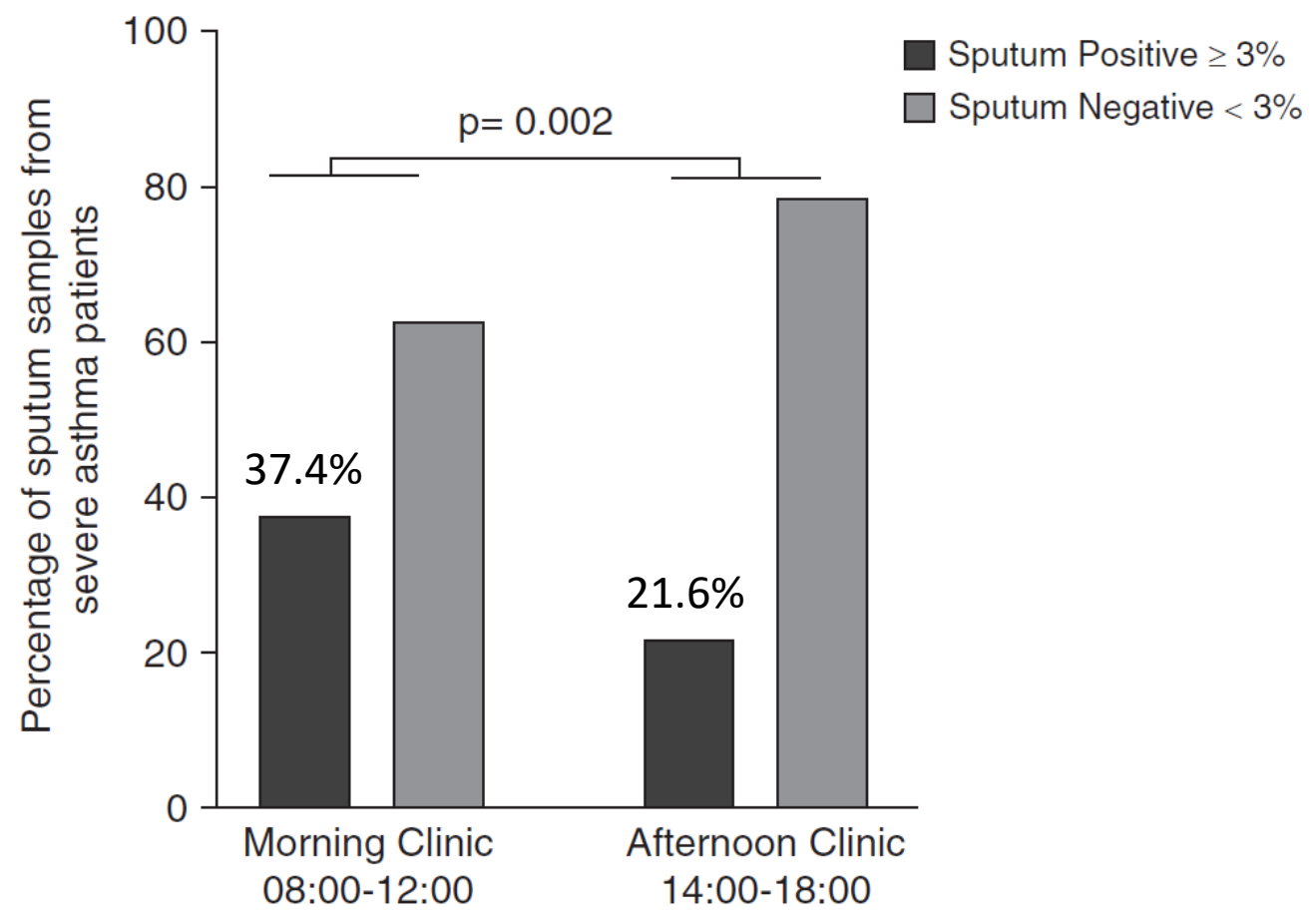
(b) CD4⁺ cells (as % CD45⁺) at 04:00 hours

Circadian influence on airway inflammation – Sputum biomarker

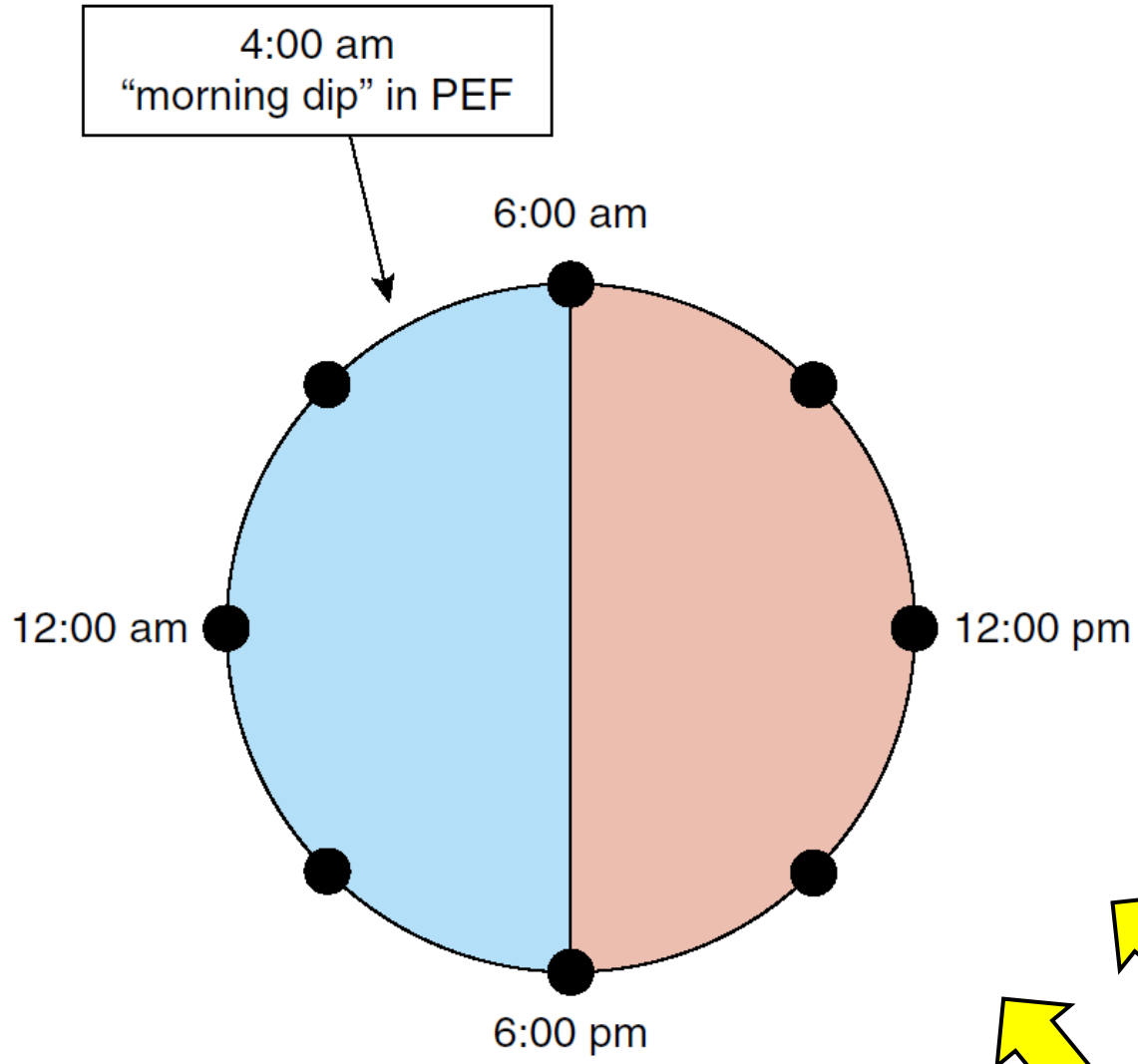
- 10 healthy volunteers and 10 adults with mild/moderate atopic asthma



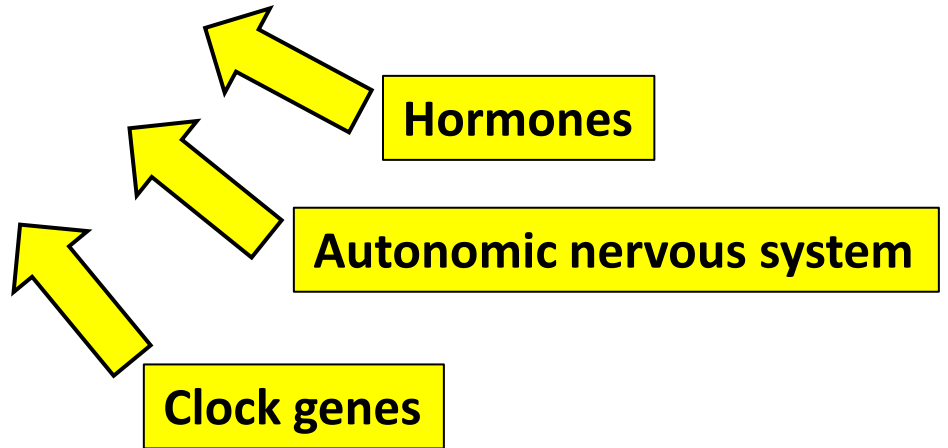
- Patients with severe asthma
- Morning clinic (n=131)
- Afternoon clinic (n=193)



- Nighttime**
- ↓ Cortisol
 - ↓ Epinephrine
 - ↓ β_2 Receptor
 - ↑ Vagal activity
 - ↓ Body temp
- ↓ FEV₁
 - ↓ FVC
 - ↓ PEF
- ↑ Nocturnal symptoms



- Daytime**
- ↑ Cortisol
 - ↑ Epinephrine
 - ↑ β_2 Receptor
 - ↓ Vagal activity
 - ↑ Body temp
- ↑ FEV₁
 - ↑ FVC
 - ↑ PEF



Circadian effect on asthma

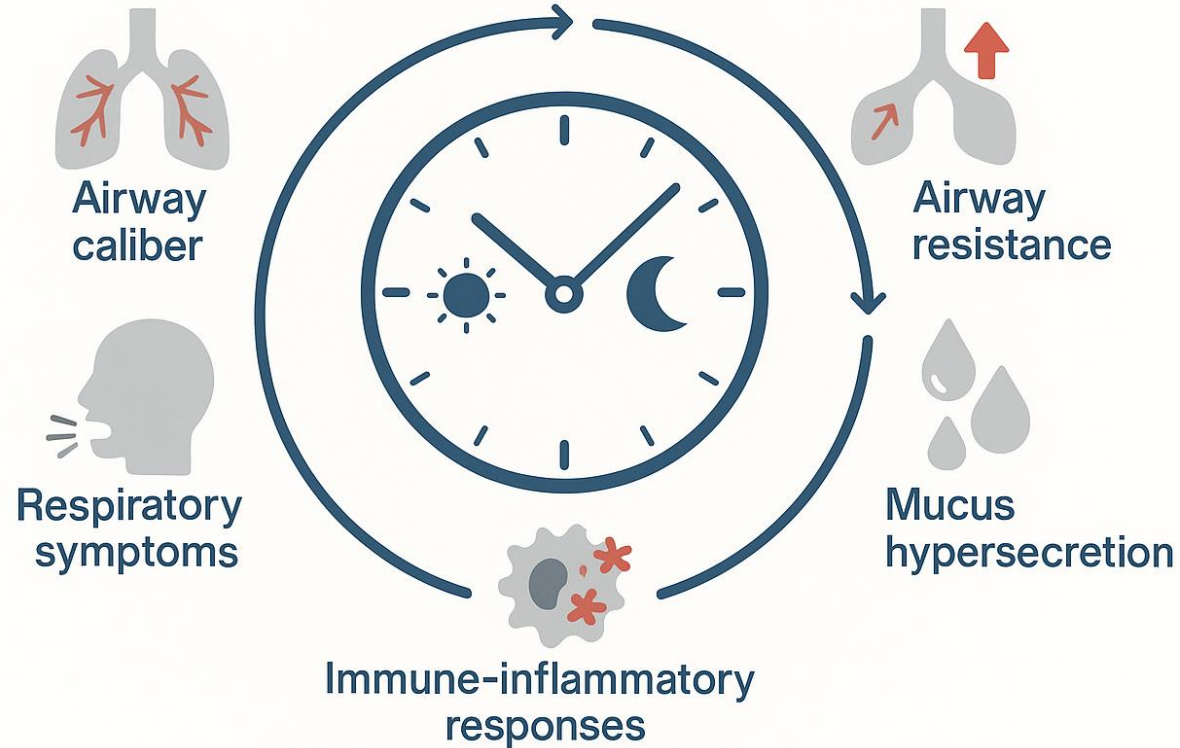
Circadian clock genes regulate oxidative stress and inflammation

Clock genes and molecules study results

- | | |
|-----------------------------------|---|
| <i>BMAL1</i> | <ul style="list-style-type: none">• <i>BMAL1</i>^{-/-} mice show signs of advanced aging and underlying pathologies, correlated with increased levels of reactive oxygen species and inflammation• <i>BMAL1</i>^{-/-} mice have increased level of lipid peroxidation markers• <i>BMAL1</i>^{-/-} mice show upregulation of prostaglandin synthase gene, TNF- α, and IL-6 |
| <i>REV-ERBα</i> | <ul style="list-style-type: none">• <i>Rev-erba</i>^{-/-} mice show loss of circadian gating of endotoxin response (no attenuation of IL-6)• <i>Rev-erba</i> is highly expressed in oxidative skeletal muscle and plays a role in mitochondrial biogenesis and oxidative function• <i>Rev-erba</i> deficiency in skeletal muscle leads to reduced mitochondrial content and oxidative function |
| <i>CLOCK</i> | <ul style="list-style-type: none">• <i>CLOCK</i>^{-/-} mice show significantly reduced NF-κB response |

- Hormones
- Autonomic nervous system
- Clock gene expressions

Circadian Timing System



Lung function variability
Airway inflammation

Clinical implication in asthma

- “Chronotherapy” to synchronize the **drug concentrations** to rhythms in disease activity, increasing efficacy as well as reducing adverse effects
 - Drug effects on the morning dip in PEF and FEV₁
 - Systemic corticosteroids
 - Inhaled corticosteroids
 - Long-acting beta-2 agonists, long-acting anti-cholinergics
 - Leukotriene antagonist

Contents

(1) Overview of circadian rhythm

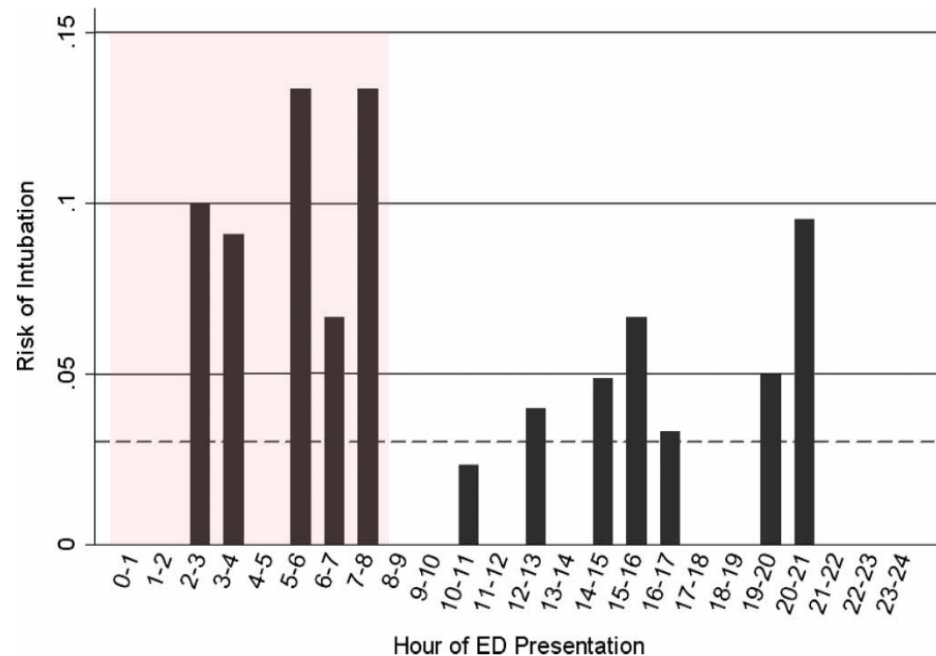
(2) Association with respiratory diseases

- Sepsis
- Asthma
- **COPD**

Circadian effect on COPD

Less established due to the heterogeneous nature of COPD

- Variable symptom severity through out the day
 - Some report worsening of their symptoms in the early morning upon awakening while others complain of nocturnal symptoms resulting in sleep disruption
- Elevated risk for severe exacerbation during early morning in the emergency department

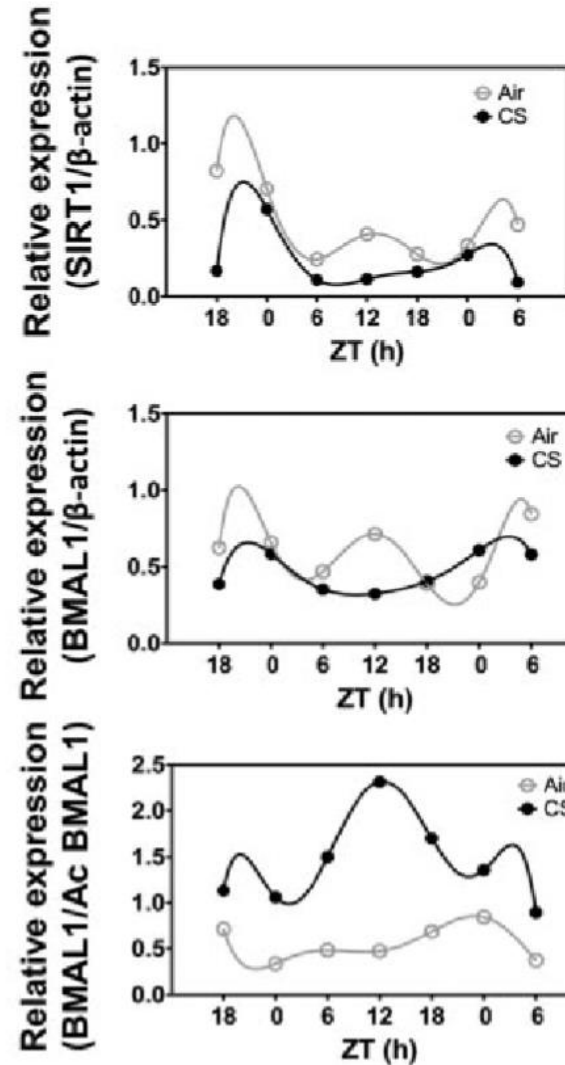
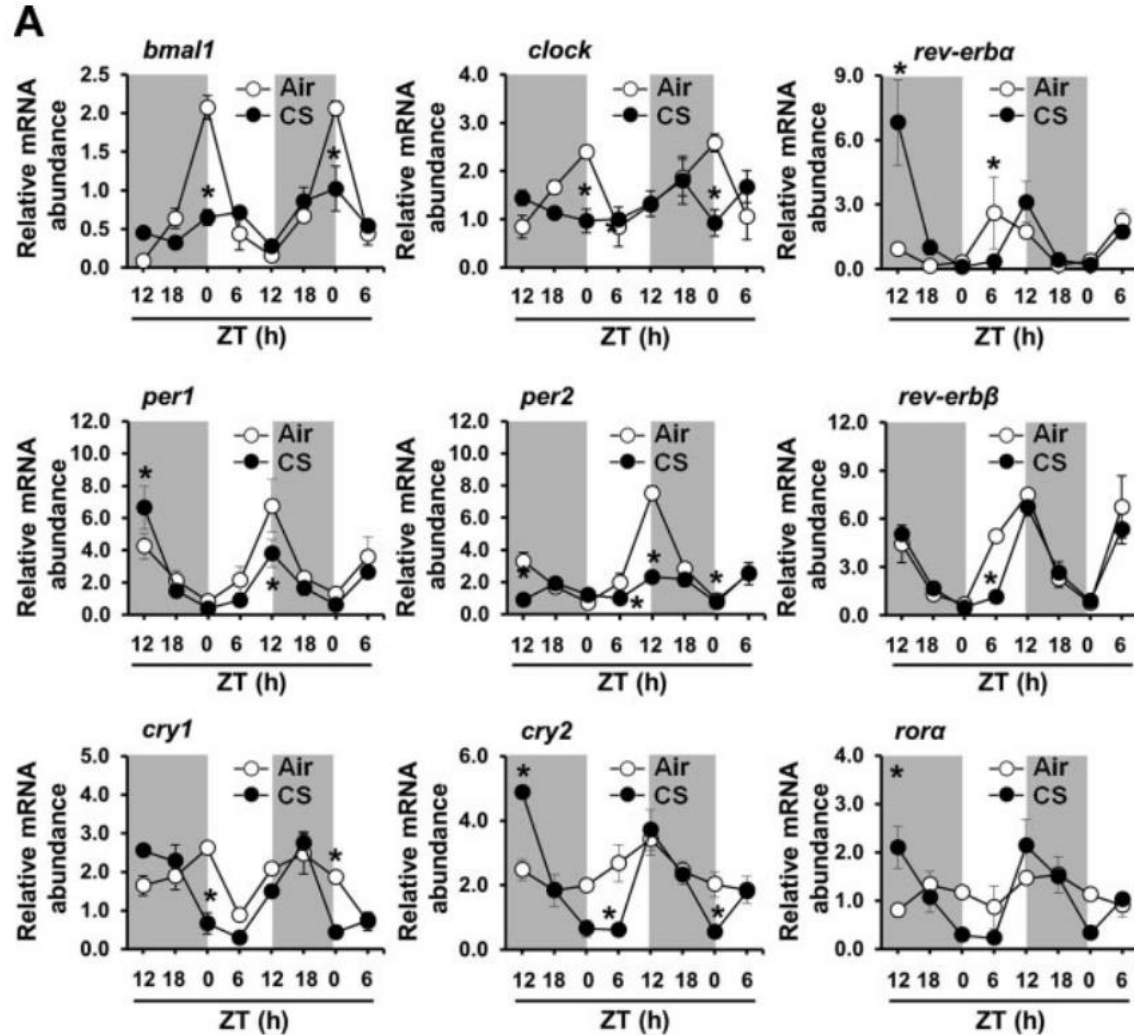


- 29 emergency department in the US and Canada
- Patients with COPD acute exacerbation
- Presentation during the night (00:00~07:59 h) (NT) vs. other time of the day

NT patients → 3x more likely to be intubated (OR 3.46; 95%CI 1.10–10.9)

Influence of cigarette smoke exposure on circadian clock genes – Mouse model

Acute cigarette smoke exposure differentially affects clock and *SIRT1* gene expression in mouse lungs

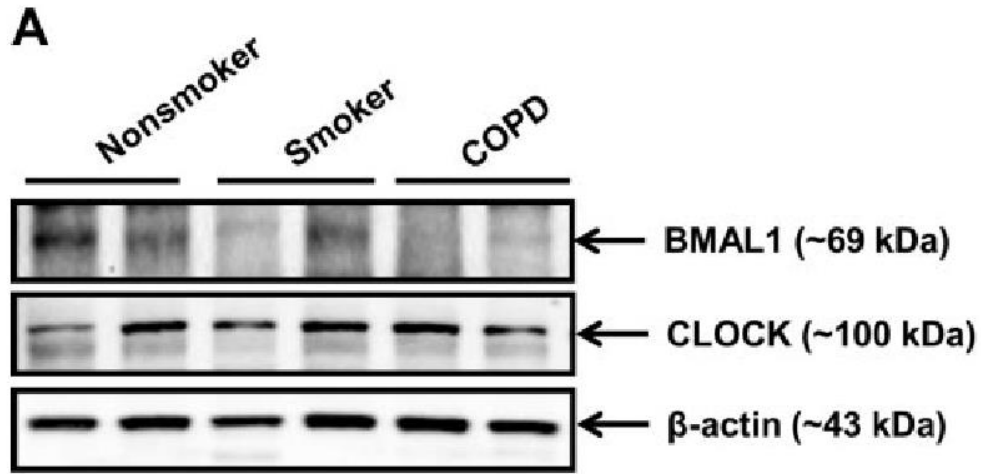


Reduced SIRT1 expression

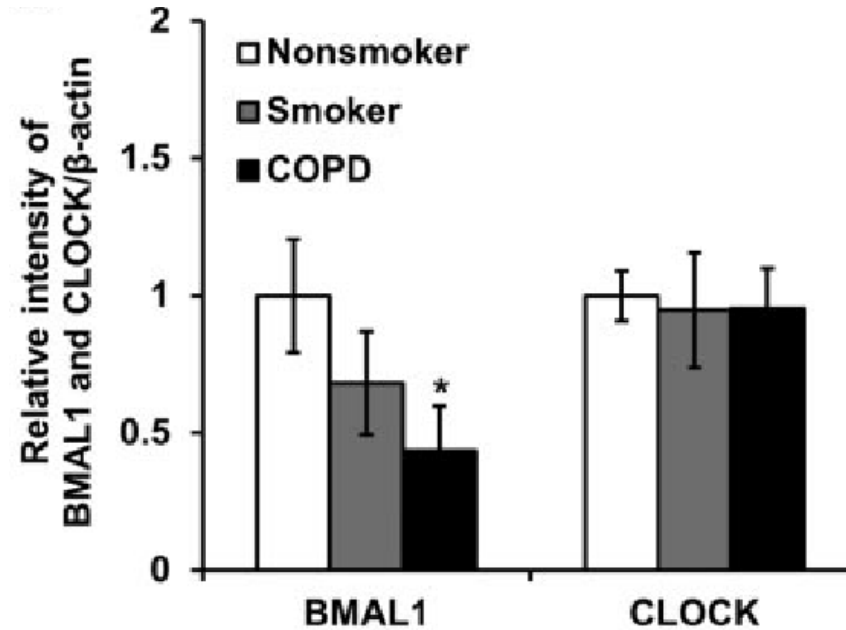


Elevated level of acetylated BMAL1

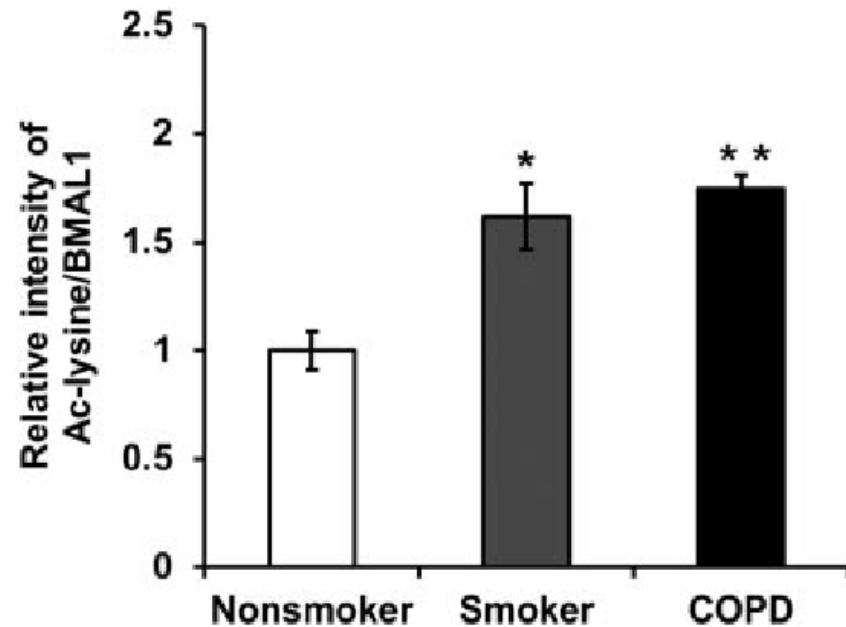
Influence of cigarette smoke exposure on circadian clock genes – Human samples



Immunoblot analysis of **BMAL1** and **CLOCK** in whole-tissue lysates extracted from **lung tissue** shows **down-regulated BAML1 in smoker and COPD**



Relative level of **BMAL1** was significantly **decreased** in lung tissue from smokers and patients with COPD compared to nonsmokers



Increased **acetylation of BMAL1** in lungs of smokers and patients with COPD

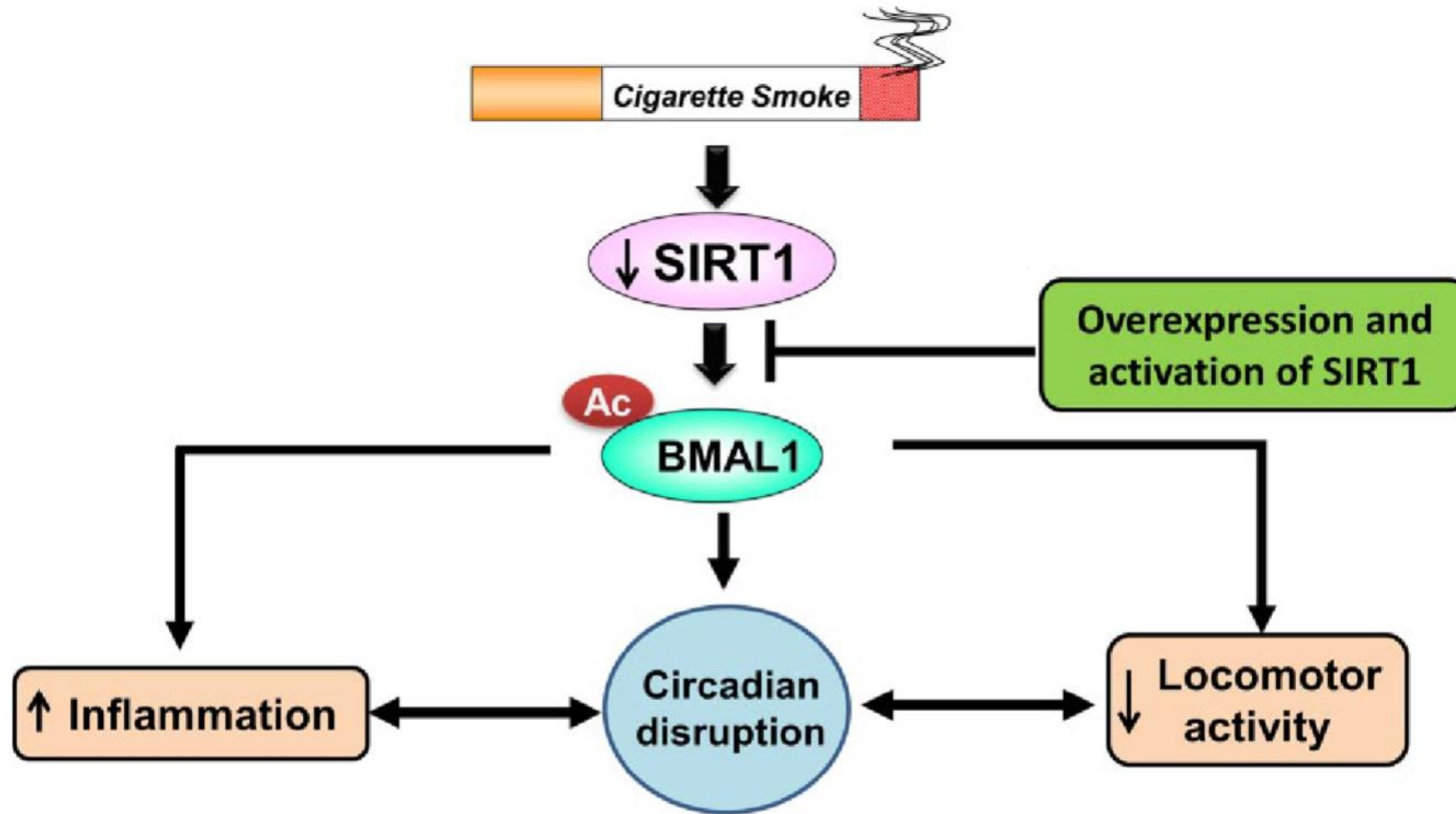
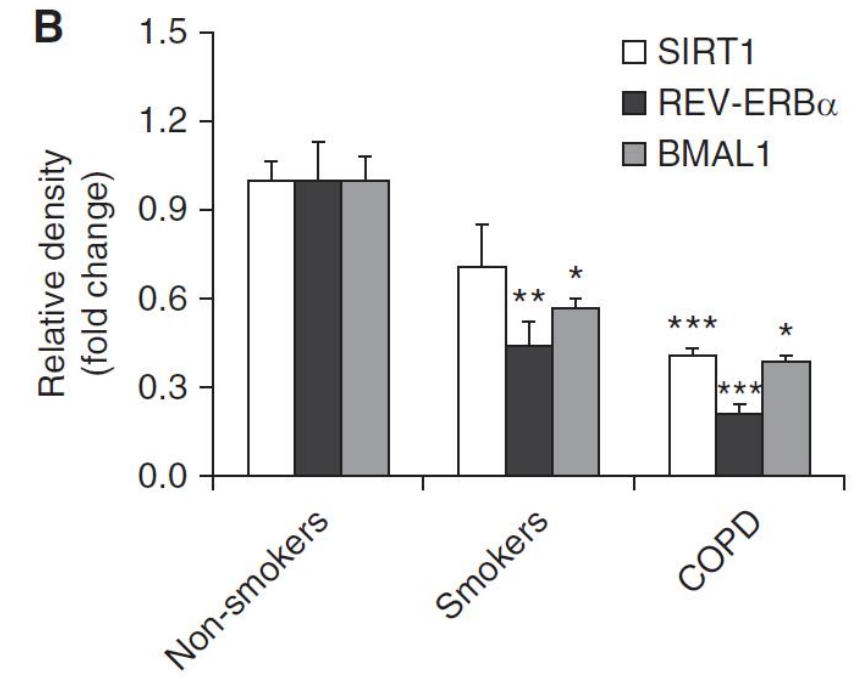
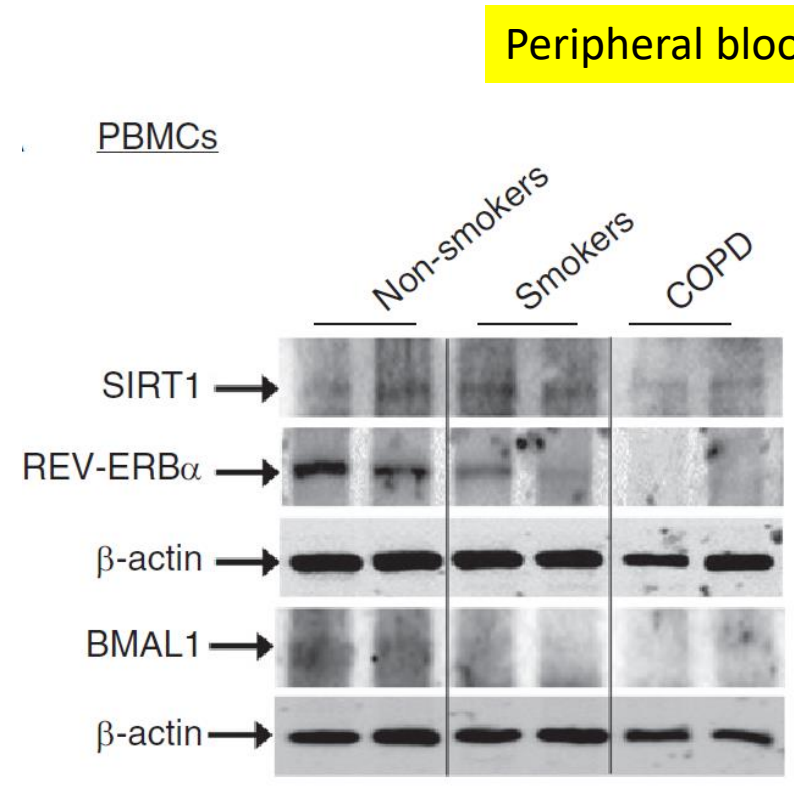
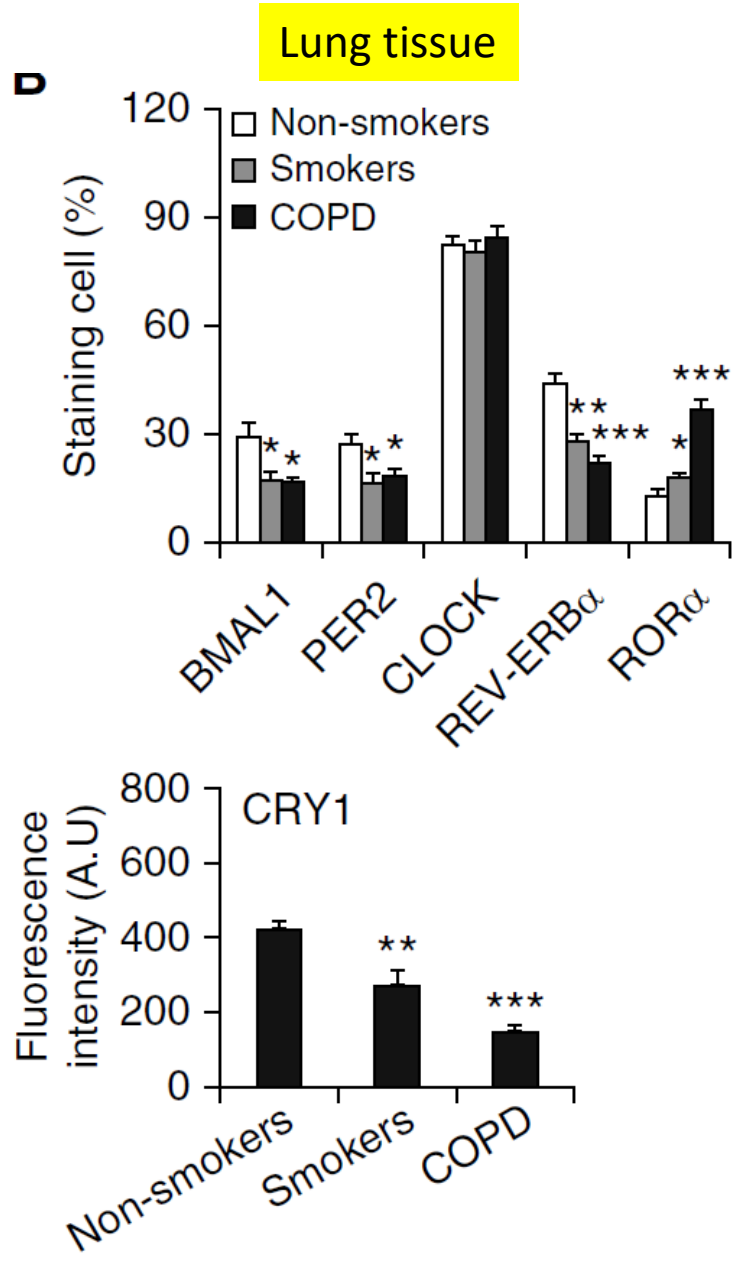


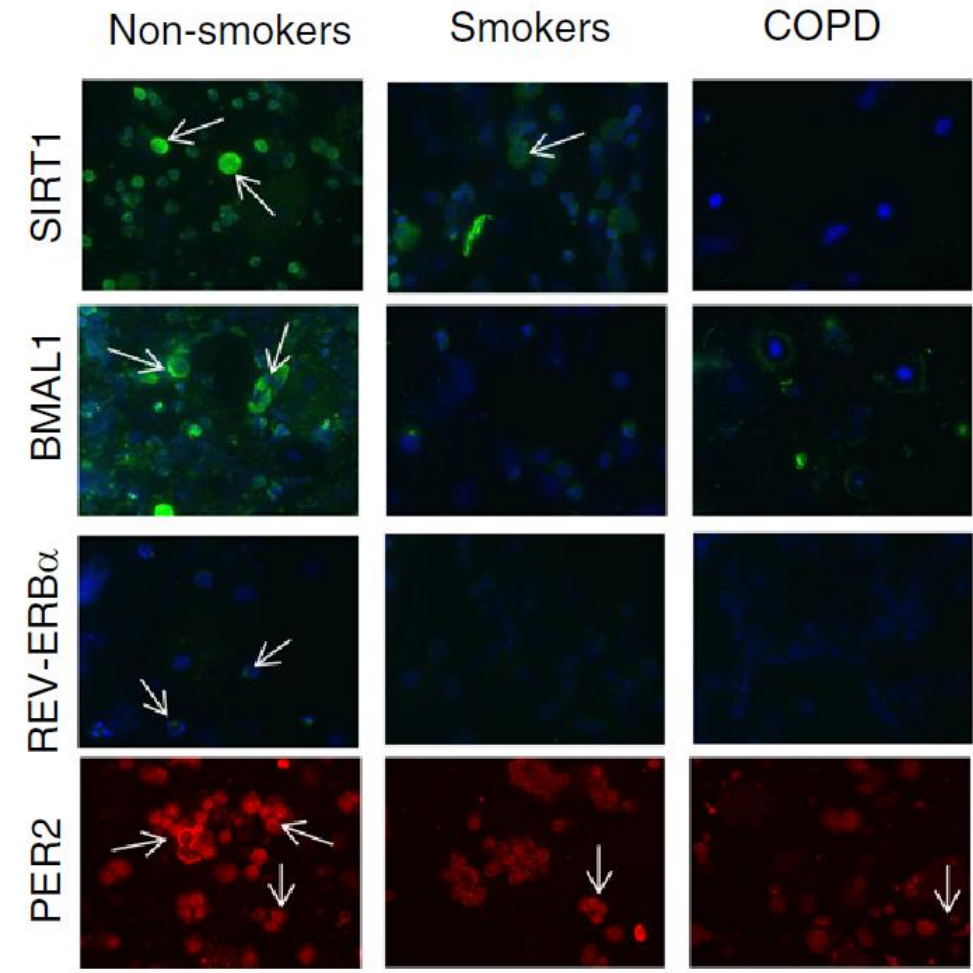
Figure 13. Environmental circadian disruption after CS exposure is SIRT1-BMAL1 dependent, and is associated with increased inflammation and reduced locomotor activity. CS exposure affects SIRT1 levels in the lung, which leads to BMAL1 acetylation/degradation, culminating in increased inflammation, circadian disruption (altered gene expression of clock and clock-controlled genes), and reduced locomotor activity. Overexpression or pharmacologic activation of SIRT1 in cell-specific BMAL1-knockout mice does not attenuate lung inflammation, suggesting that the effects of CS on circadian clock function and inflammatory responses are mediated almost entirely by SIRT1-BMAL1-dependent mechanism.

Disruption of circadian molecular clock mediated by Sirtuin 1 in COPD

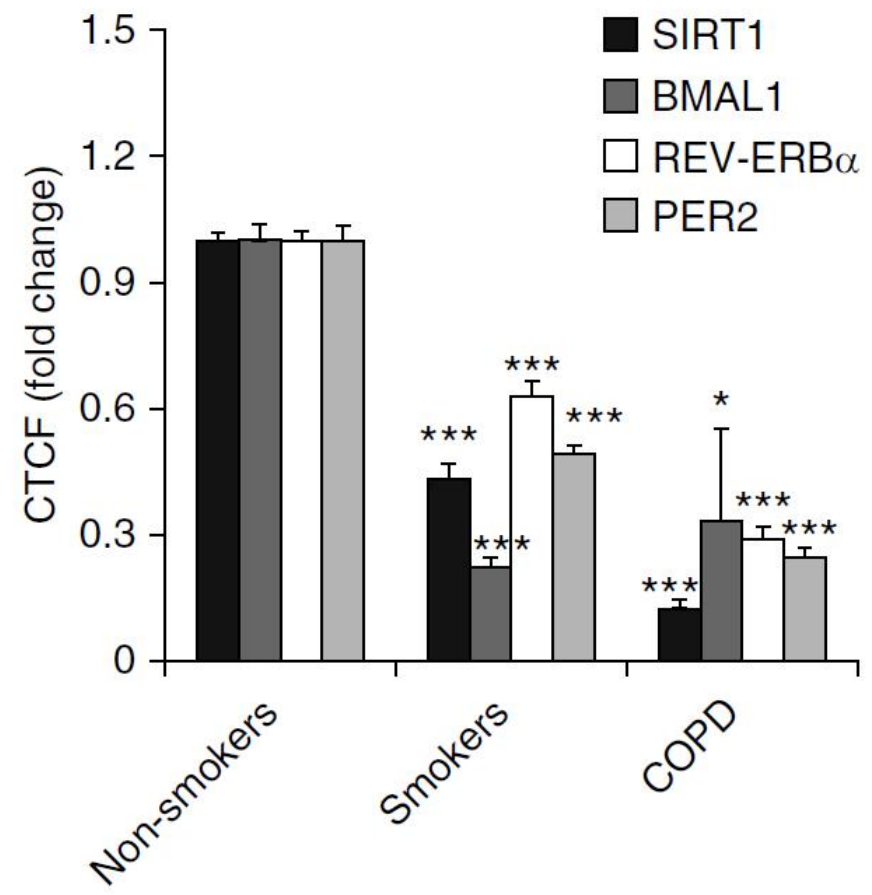


Disruption of circadian molecular clock mediated by Sirtuin 1 in COPD

A Sputum cells

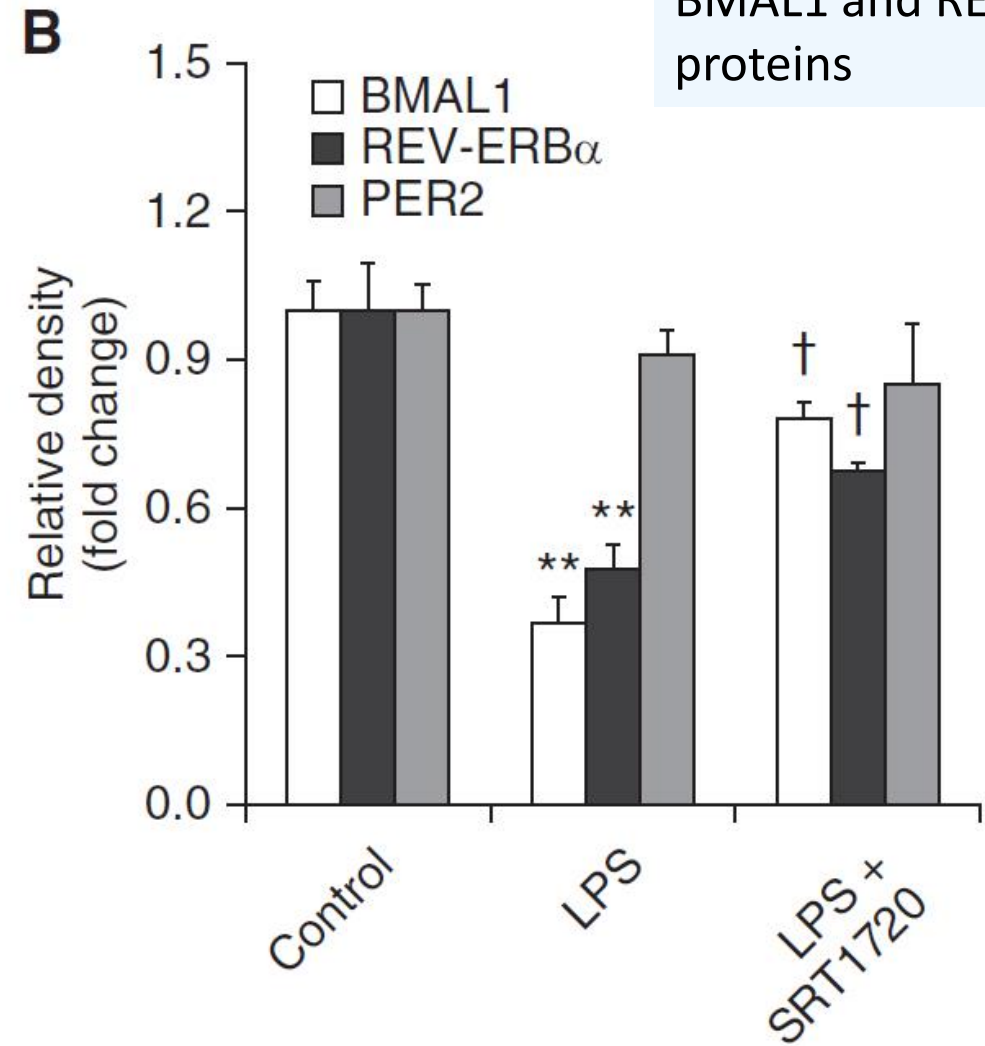
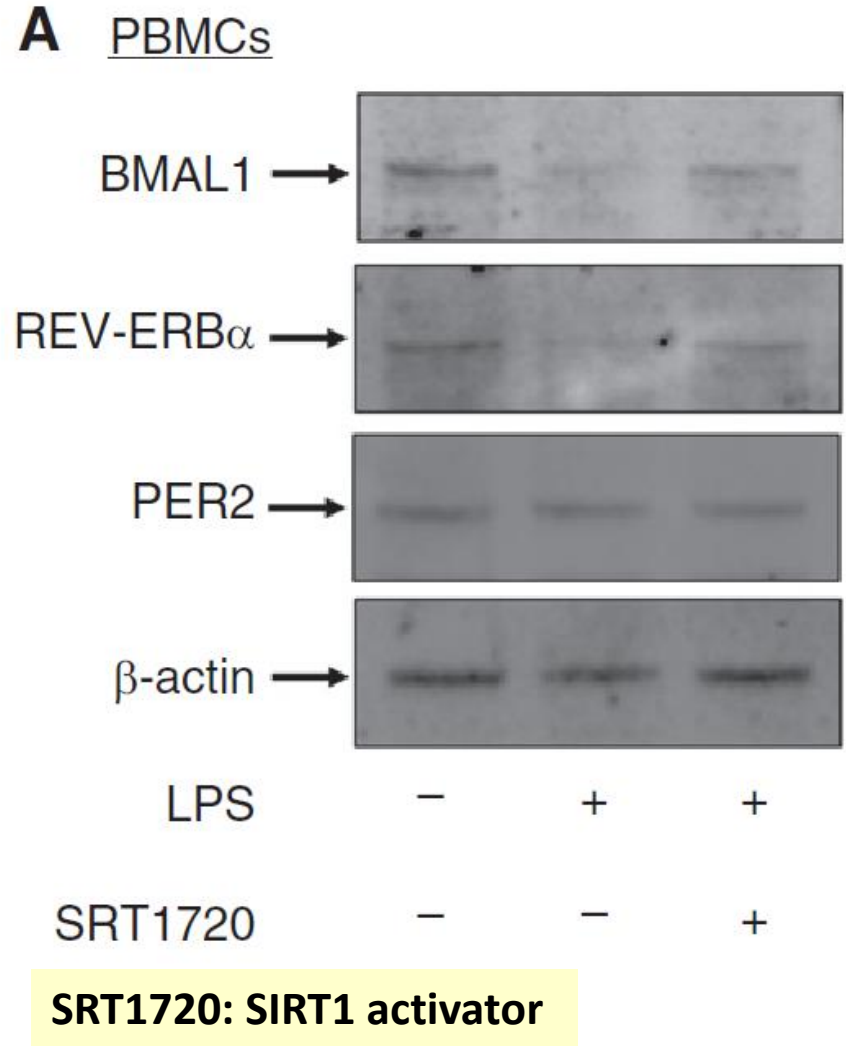


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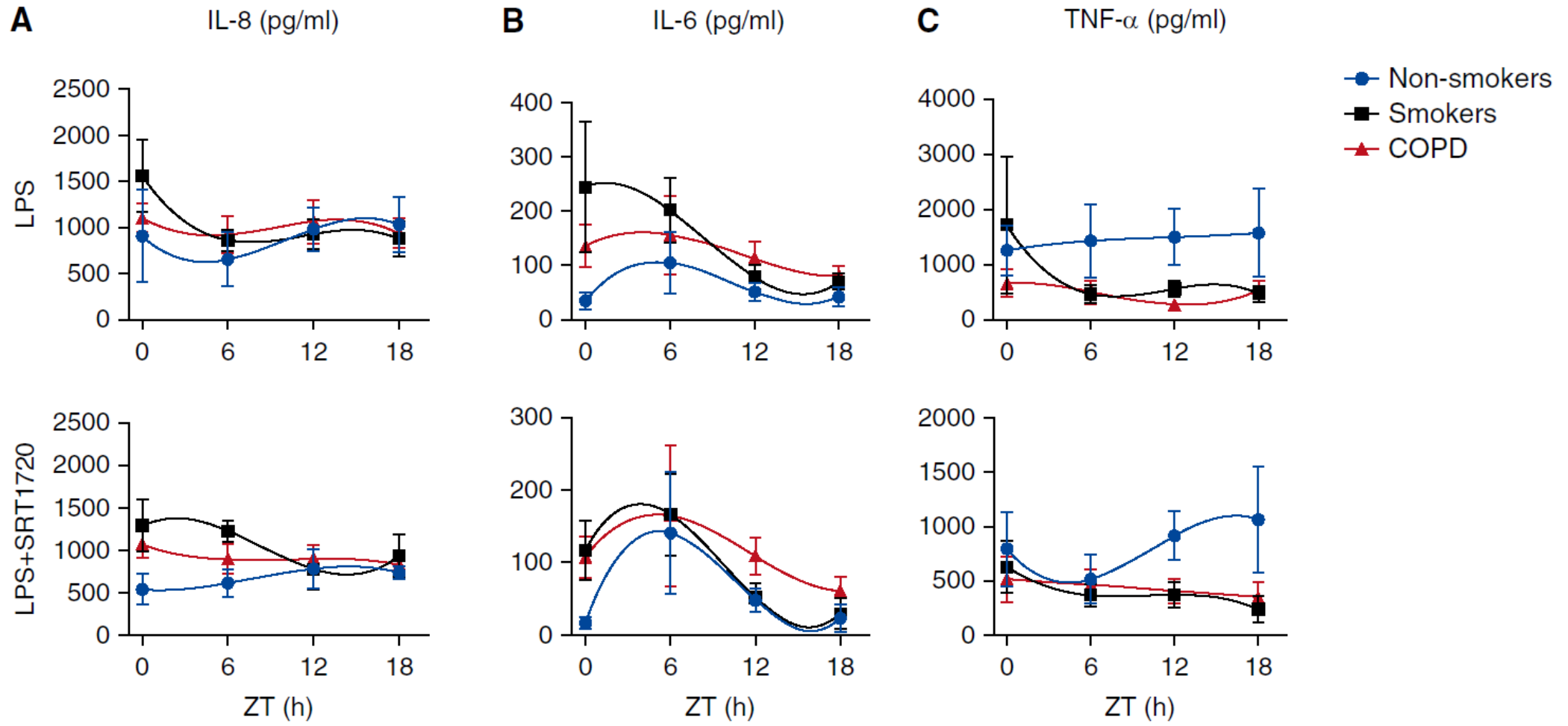


Disruption of circadian molecular clock mediated by Sirtuin 1 in COPD

SRT1720 **inhibit** LPS-induced reduction of BMAL1 and REV-ERB α proteins



Disruption of circadian molecular clock mediated by Sirtuin 1 in COPD

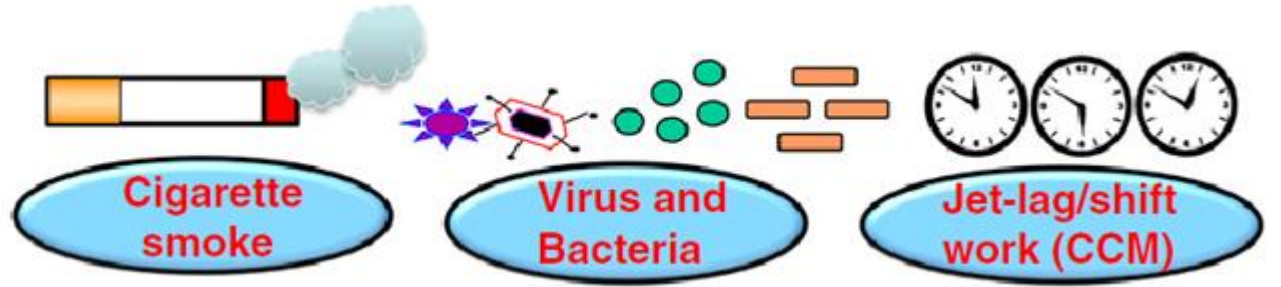


SIRT1 activator SRT1720 is able to inhibit LPS-induced cytokine release in PBMCs
More effectively in non-smokers than in smokers and patients with COPD

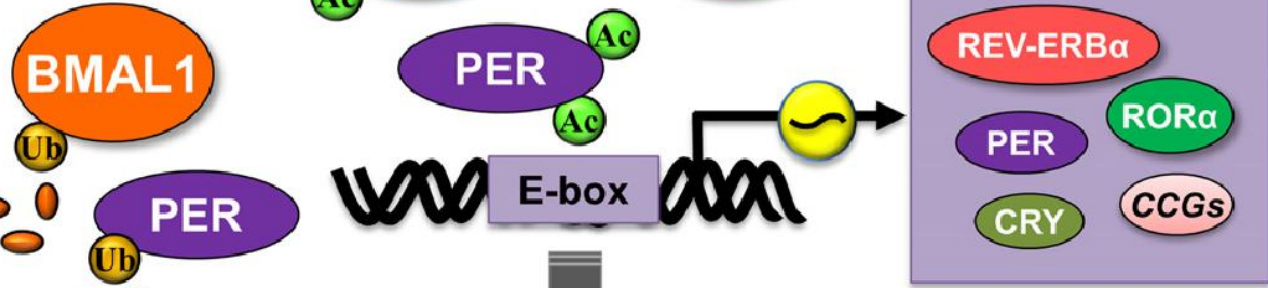
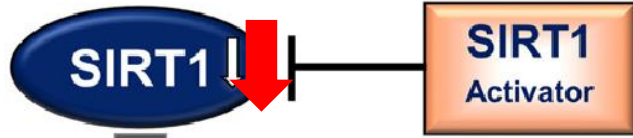
Oxidative/Carbonyl Stress (Environmental Tobacco Smoke)



Macrophages and Epithelial cells



CCM: chronic circadian misalignment



Affects the rhythmic expression of clock genes



Summary

Circadian rhythm is an autonomous intrinsic time keeping system

Circadian disruption is associated with respiratory diseases

- Circadian effects on the susceptibility to sepsis and its prognosis
- Circadian effects on asthma in terms of lung function and airway inflammation
- Reduced SIRT1 by cigarette smoking and disturbed clock molecular expressions