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Hidden Role of Sleep Disorders in Tumor Biology

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BMC Cancer

RESEARCH Open Access

Sleep disturbances and the risk of lung cancer: a meta-epidemiological study

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Abstract

Background The relationship between sleep disturbances and lung cancer is complex and bidirectional. This meta-epidemiological study aimed to explore the potential association between sleep disruption and the risk of pulmonary cancer.

Methods We conducted a comprehensive literature search of the PubMed, Embase, Cochrane Library, and Web of Science databases to retrieve relevant studies. We employed the Newcastle–Ottawa Scale to assess the quality of the observational studies. Stata 17.0 was used to synthesize and conduct a meta-analysis of odds ratios (ORs) and corresponding 95% confidence intervals (CIs). We used funnel plot analysis and Egger's regression test to evaluate potential publication bias.

Results A total of 11 studies were included with 469,691 participants. The methodological quality of the included studies ranged from moderate to high. Compared with 7–8 h of sleep time, short sleep duration was associated with a 13% higher lung cancer risk [OR, 1.13; 95%CI: 1.02–1.25; $I^2=67.6\%$; $P=0.018$] and long sleep duration with a 22% higher risk [OR, 1.22; 95%CI: 1.12–1.33; $I^2=6.9\%$; $P<0.001$]. Insomnia symptoms [OR, 1.11; 95%CI: 1.07–1.16; $I^2=0\%$; $P<0.001$] and evening chronotype [OR, 1.15; 95%CI: 1.05–1.26; $P=0.002$] were all related to a higher risk of lung cancer. Egger's test revealed no publication bias for sleep duration ($P=0.13$).

Discussion This systematic review is the first one which observes positive correction between sleep disturbances and the incidence of lung cancer. While the plausible mechanism is not clear, it is hypothesized that the association of short sleep duration and lung cancer mainly mediated by melatonin secretion and the immune-inflammatory balance. Further studies are needed to examine whether other risk factors, such as age, occupation, cumulative effect of sleep disturbances might mediate the relationship between sleep disturbances and lung cancer risk.

Conclusion The present study revealed that insufficient and excessive sleep duration, insomnia symptoms, and evening chronotype were significantly predictive of an increased risk of lung cancer. This finding underscores the need to account for sleep disturbances as an independent risk factor for evaluating susceptibility to lung cancer.

Trial registration CRD42023405351.

Keywords Sleep disturbances, Lung neoplasm, Epidemiological study, Meta

Sleep disturbances and the risk of lung cancer: a meta-epidemiological study

- Methods
  - Total 11 studies
    - 469,491 patients

    - Most studies were conducted in Europe and America
    - Two in Canada
    - One in China

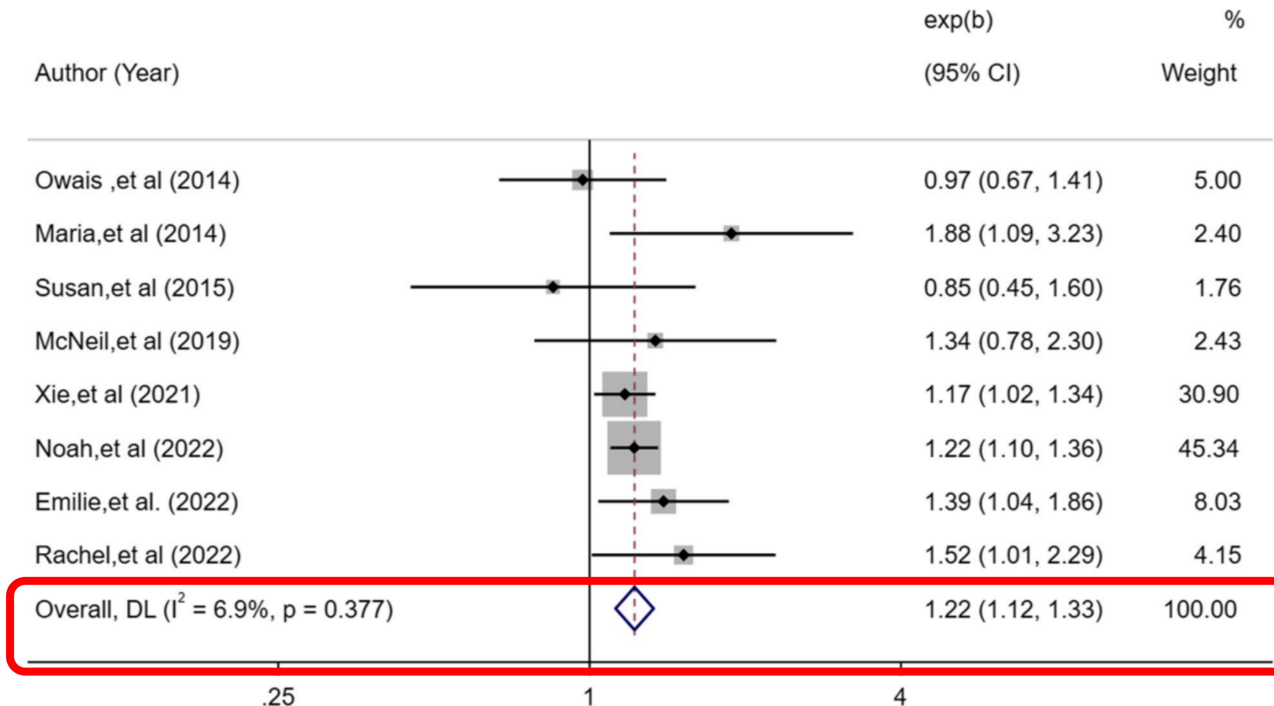
Short sleep duration & cancer risk

Author (Year)	exp(b) (95% CI)	% Weight
Owais ,et al (2014)	1.18 (0.77, 1.81)	4.37
Maria,et al (2014)	2.12 (1.17, 3.85)	2.50
Susan,et al (2015)	1.03 (0.88, 1.20)	14.99
McNeil,et al (2019)	1.04 (0.70, 1.55)	4.96
Xie,et al (2021)	1.18 (1.07, 1.30)	19.22
Cao,et al (2022)	1.17 (1.09, 1.26)	21.03
Noah,et al (2022)	0.96 (0.89, 1.04)	20.58
Emilie,et al. (2022)	1.16 (0.86, 1.56)	7.59
Rachel,et al (2022)	1.52 (1.01, 2.29)	4.74
Overall, DL (I^2 = 67.6%, p = 0.002)	1.13 (1.02, 1.25)	100.00

.25 1 4

Fig. 2 Forest plot of association between short sleep duration and cancer risk

Long sleep duration & caner risk



Author (Year)	exp(b) (95% CI)	% Weight
Owais ,et al (2014)	0.97 (0.67, 1.41)	5.00
Maria,et al (2014)	1.88 (1.09, 3.23)	2.40
Susan,et al (2015)	0.85 (0.45, 1.60)	1.76
McNeil,et al (2019)	1.34 (0.78, 2.30)	2.43
Xie,et al (2021)	1.17 (1.02, 1.34)	30.90
Noah,et al (2022)	1.22 (1.10, 1.36)	45.34
Emilie,et al. (2022)	1.39 (1.04, 1.86)	8.03
Rachel,et al (2022)	1.52 (1.01, 2.29)	4.15
Overall, DL (I^2 = 6.9%, p = 0.377)	1.22 (1.12, 1.33)	100.00

Fig. 3 Forest plot of association between long sleep duration and cancer risk

Insomnia & caner risk

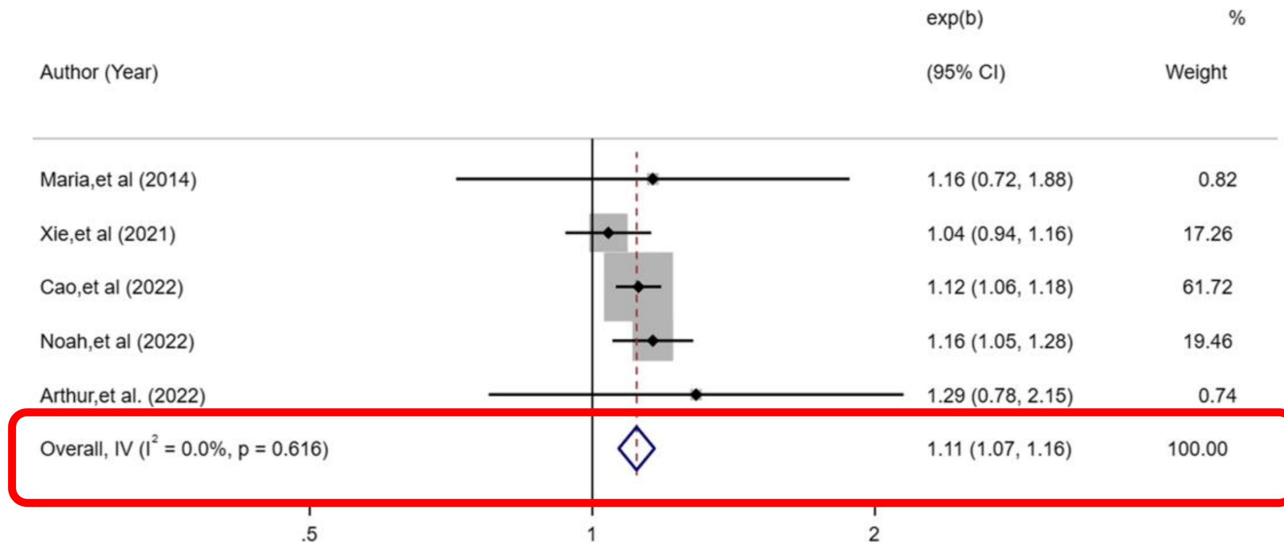


Fig. 4 Forest plot of association between insomnia symptoms and cancer risk

Chronotype and cancer risk

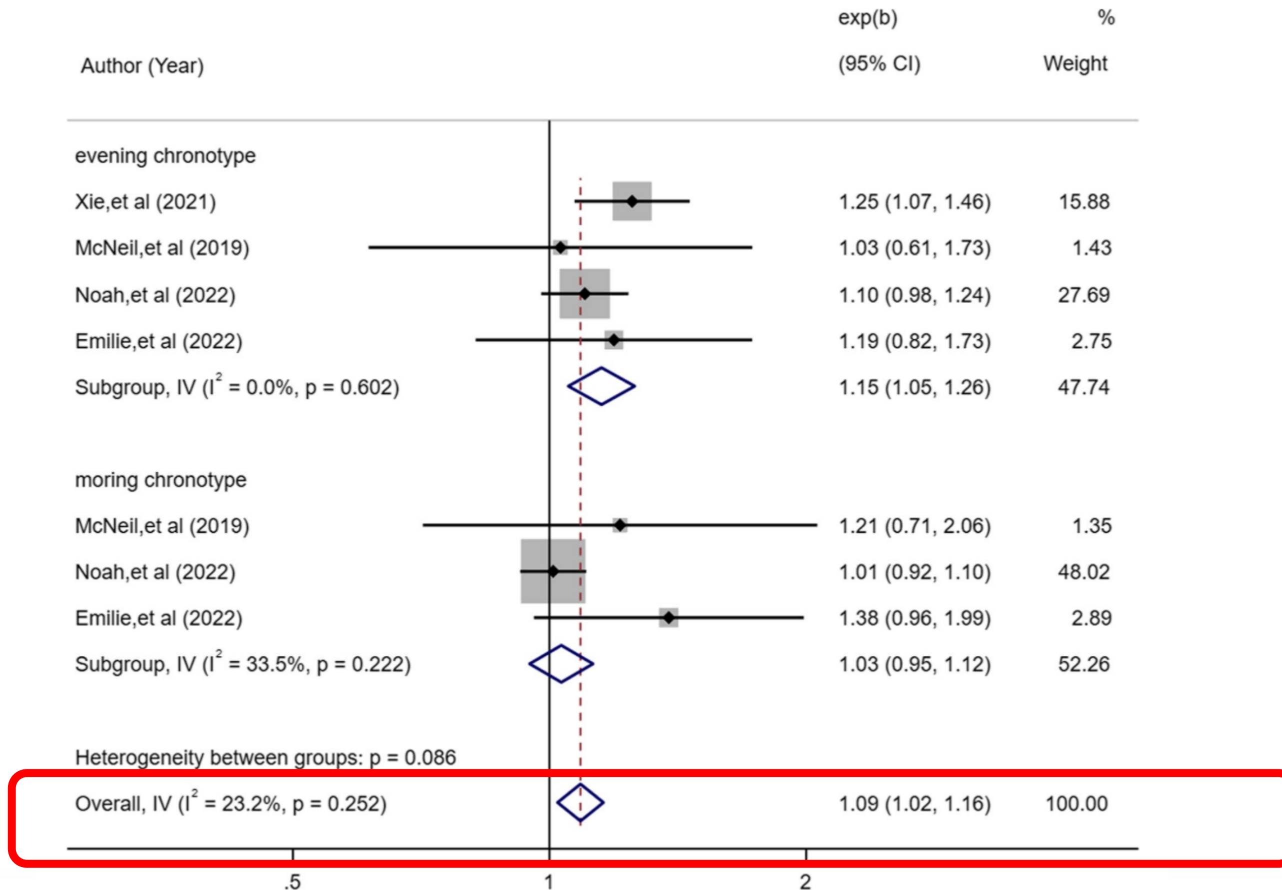


Fig. 5 Forest plot of association between chronotype and cancer risk

Sleep disturbances and the risk of lung cancer: a meta-epidemiological study

- Conclusion
  - Insufficient & excessive sleep duration
  - Insomnia symptoms
  - Evening chronotype

→ Increased risk of lung cancer

Contents

- **Sleep in Cancer Pathogenesis & Treatment**
  - Circadian Rhythm
  - Melatonin
  - Immune-Inflammatory balance

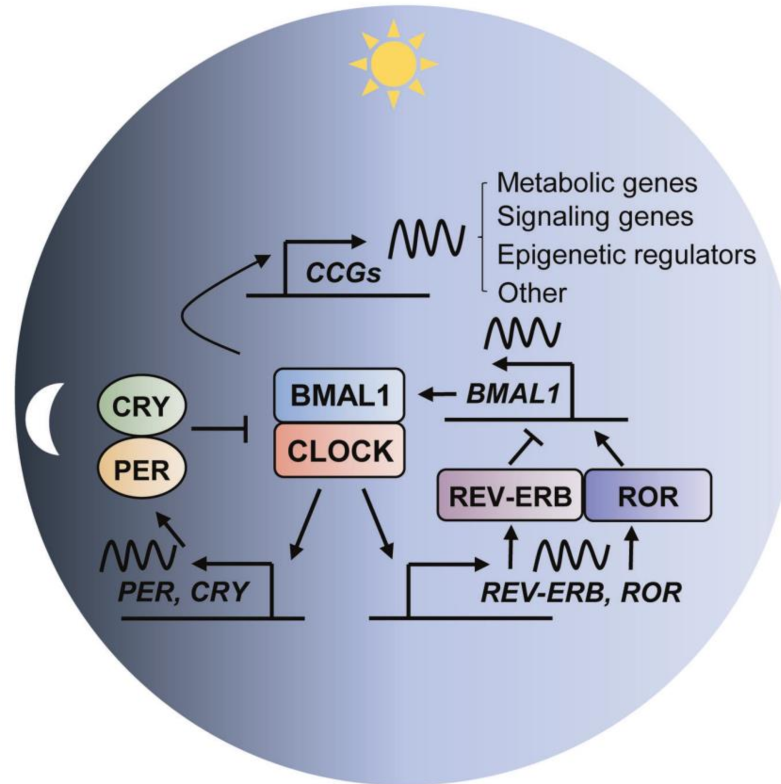
Complex interactions between sleep & cancer

M.P. Mogavero, L.M. DelRosso, F. Fanfulla et al. Sleep Medicine Reviews 56 (2021) 101409

Fig. 1. Schematic representation of the complex interactions between sleep and cancer. The symbol "+" indicates stimulation while up and down arrows indicate increase and decrease, respectively. HPA = hypothalamic-pituitary-adrenal; IL = interleukin; ROS = reactive oxygen species; TNF-α = tumor necrosis factor α; VEGF = vascular-endothelial growth factor serum levels.

Sleep disorders and cancer: State of the art and future perspectives, Sleep Medicine Reviews, Volume 56, 2021.

Circadian molecular clock mechanism



This autoregulatory feedback loop cycles between the CLOCK/BMAL1 transcriptional activator complex and its repressors (PER/CRY, REV-ERBα) or activators (RORα/β) to constitute the molecular clock oscillator that drives the expression of multiple **clock-controlled genes (CCGs)**, such as metabolic genes, signaling genes, and epigenetic regulators.

Roles of circadian clocks in cancer pathogenesis and treatment.
Exp Mol Med **53**, 1529–1538 (2021).

Circadian molecular clock mechanism

- Epigenetic or genetic inactivation of Bmal1 and/or Clock
  - increase tumor proliferation or growth rates in several types of cancer
    - hematologic cancer, colon cancer, pancreatic cancer, tongue squamous cell carcinoma, breast cancer, lung adenocarcinoma, hepatocellular carcinoma, nasopharyngeal carcinoma, and glioblastoma

Roles of circadian clocks in cancer pathogenesis and treatment.
Exp Mol Med **53**, 1529–1538 (2021).

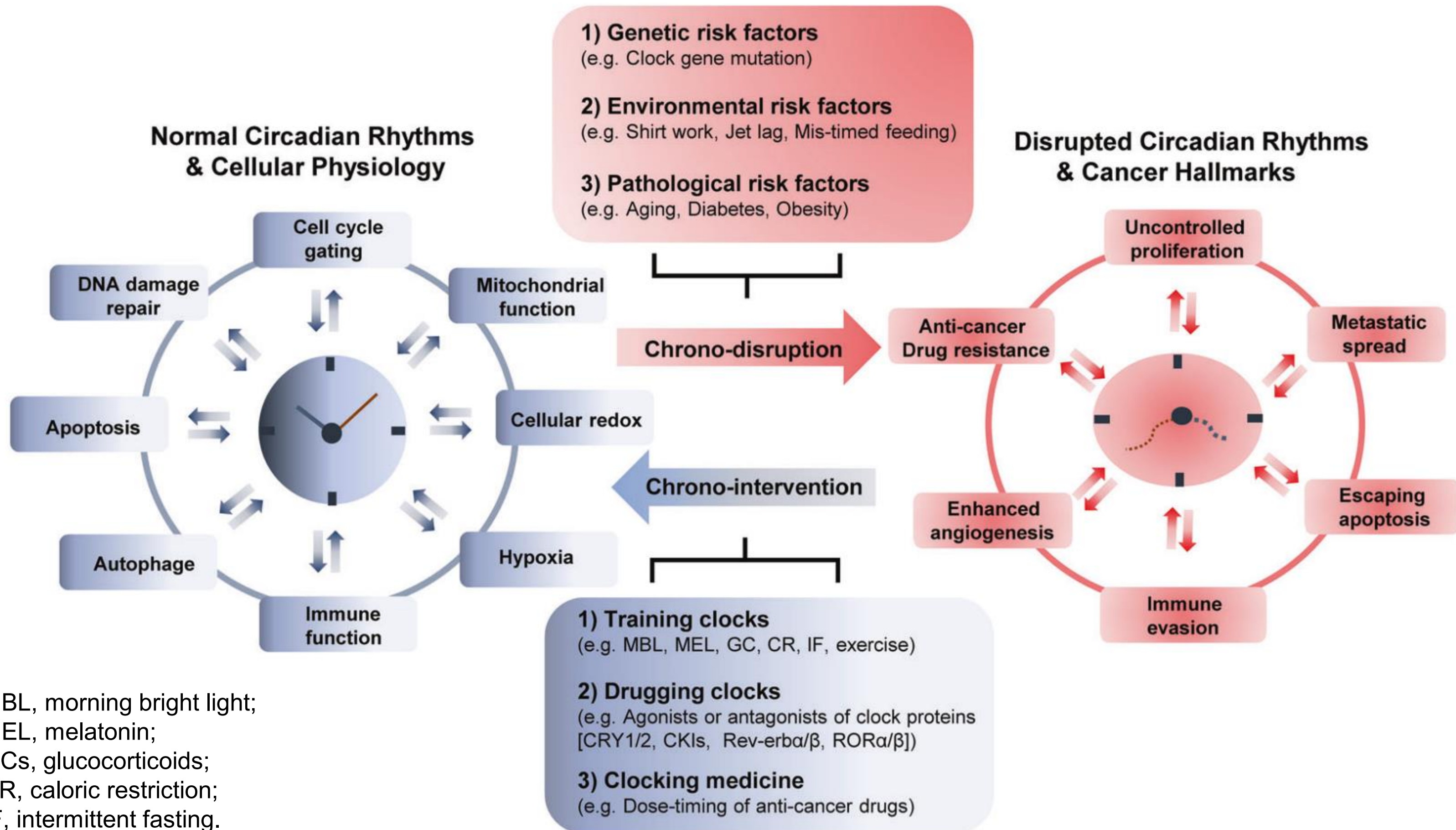
Circadian disruption

- night shift work
- chronic jet lag

→ increases the risk of the incidence and development of the most common cancer types (i.e., breast, lung, prostate, colorectal, and skin cancers)

Cancer in the fourth dimension: what is the impact of circadian disruption?
Cancer Discov. 10, 1455–1464 (2020).

Chrono-disruptive factors and chrono-therapeutic interventions in cancer pathogenesis and treatment



MBL, morning bright light;
MEL, melatonin;
GCs, glucocorticoids;
CR, caloric restriction;
IF, intermittent fasting.

Roles of circadian clocks in cancer pathogenesis and treatment.
Exp Mol Med **53**, 1529–1538 (2021).

Chrono-intervention

- Targeting circadian rhythms in cancer treatment
  - Training circadian clocks
  - Drugging clocks
  - Clocking medicine

Roles of circadian clocks in cancer pathogenesis and treatment.
Exp Mol Med **53**, 1529–1538 (2021).

Training circadian clocks

- Morning bright light
  - daytime blue light enhances night-time circadian melatonin inhibition of tumor growth in prostate, liver, and breast cancers

Circadian gating of epithelial-to-mesenchymal transition in breast cancer cells via melatonin-regulation of GSK3beta. Mol. Endocrinol. 26, 1808–1820 (2012).

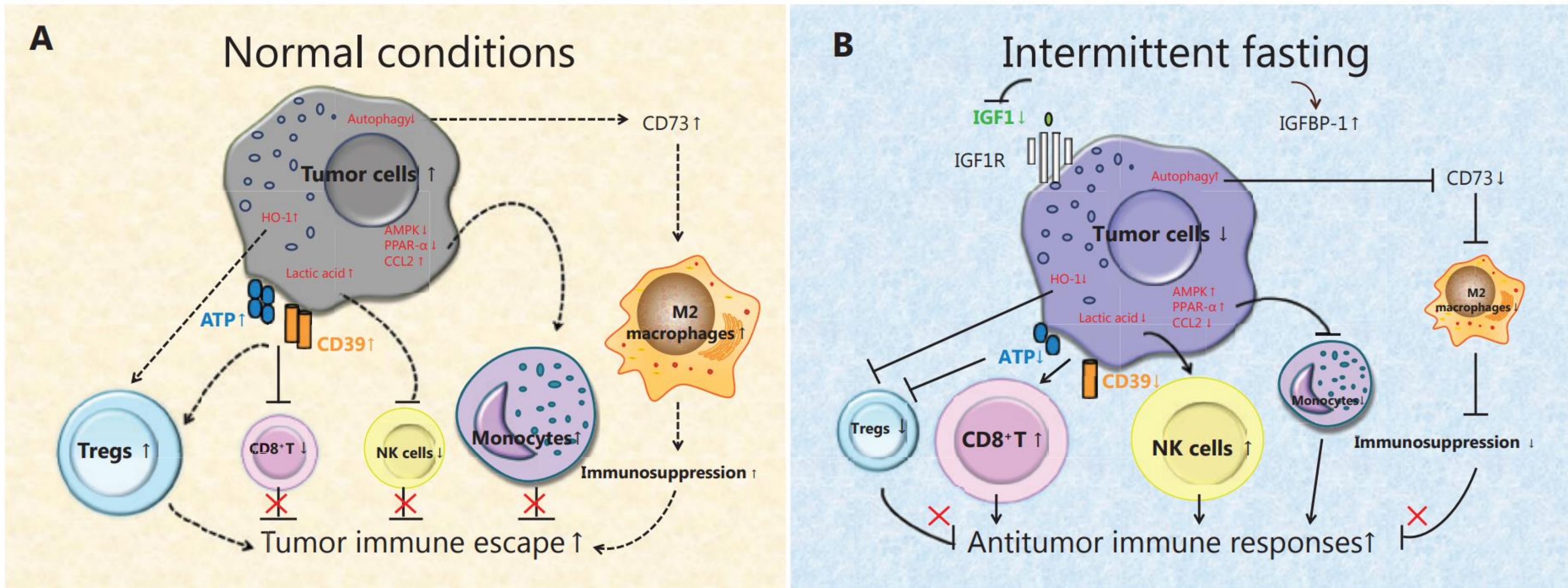
Effect of daytime blue-enriched LED light on the nighttime circadian melatonin inhibition of hepatoma 7288CTC Warburg effect and progression. Comp. Med. 68, 269–279 (2018).

Training circadian clocks

- Intermittent fasting
  - diet-based therapy that alternates between fasting and free feeding/eating for a period of time
  - Inhibit tumor growth and improve anti-tumor immune responses
  - Increase cancer sensitivity to chemotherapy and radiotherapy
  - Reduce the side effects of traditional anticancer treatments

The role and its mechanism of intermittent fasting in tumors: friend or foe? Cancer Biol. Med. 18, 63–73 (2021).

The effect of intermittent fasting (IF) on tumor immune responses



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Sleep disorders and cancer: State of the art and future perspectives, Sleep Medicine Reviews, Volume 56, 2021.

Training circadian clocks

- Melatonin
  - Regulate the sleep-wake rhythm
  - Anti-tumor effect
    - Anti-oxidant effect
      - Protect against DNA damage
      - Act as a scavenger of ROS (Reactive Oxygen Species)
      - Stimulate DNA repair mechanism
      - Improve functioning of the mitochondrial respiratory chain
    - Increase expression of the p53 protein
      - Inhibit cell proliferation, promote apoptosis, reduce VEGF and endothelin-1
    - Inhibit hypoxia by acting on the ERK/Rac1 pathway

Sleep disorders and cancer: State of the art and future perspectives,
Sleep Medicine Reviews, Volume 56, 2021.

Training circadian clocks

- Melatonin
  - Act on the metabolism of estrogen
  - Reduced melatonin level
    - Increase risk of hormone-related cancers like breast & prostate cancer

Training circadian clocks

- Melatonin
  - Used as an adjuvant in radiotherapy
  - Enhance the therapeutic outcome of chemotherapy

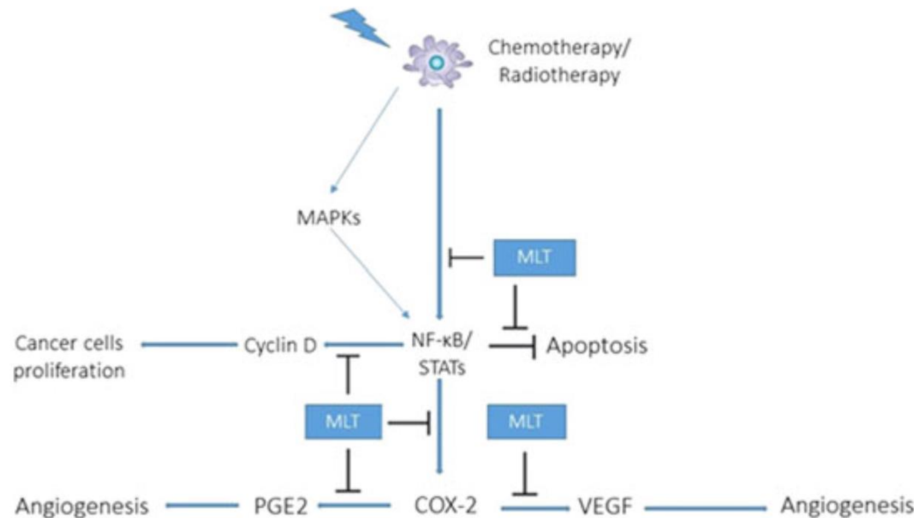

FIGURE 2 Mechanisms of antitumor activity of melatonin in radiotherapy and chemotherapy. Melatonin through suppression of angiogenesis and proliferation, as well as via stimulation of apoptosis help to better outcome of therapy. COX: cyclooxygenase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; STAT: signal transducer and activator of transcription; VEGF: vascular endothelial growth factor [Color figure can be viewed at wileyonlinelibrary.com]

Melatonin and cancer: from the promotion of genomic stability to use in cancer treatment. J Cell Physiol 2019;234:5613e27.

Training circadian clocks

- Melatonin
  - Implications for tumor prevention
    - Breast, ovarian, prostate, colorectal and gastric cancers

Melatonin for the prevention and treatment of cancer.
Oncotarget. 2017 Jun 13;8(24):39896-39921.

Contents

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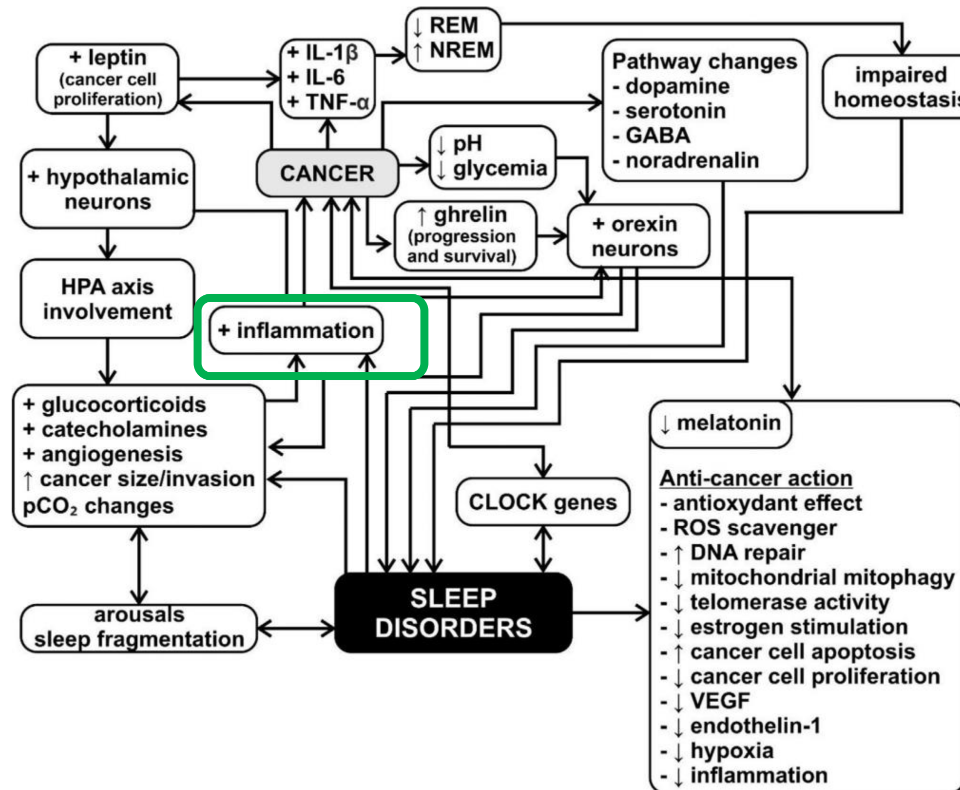
Complex interactions between sleep & cancer



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Sleep disorders and cancer: State of the art and future perspectives, Sleep Medicine Reviews, Volume 56, 2021.

Sleep in Immunity

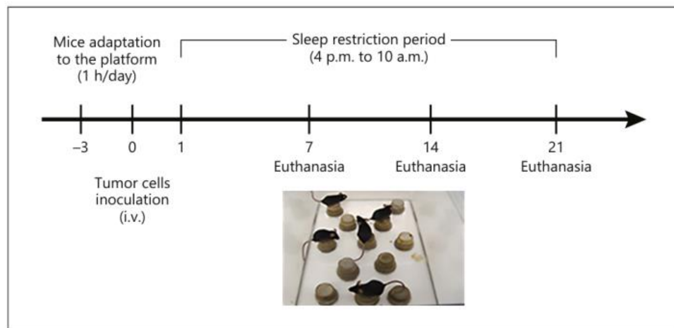
- Sleep
  - essential for optimal functioning of the immune system
    - activity of cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells that target and destroy cancer cells
  - Lower cortisol levels during sleep
    - allow the immune system to function more efficiently and reduce the risk of inflammatory diseases

The Triad of Sleep, Immunity, and Cancer: A Mediating Perspective.
Cells. 2024 Jul 24;13(15):1246.

Short sleep duration & cancer risk

- Sleep deprivation
  - detrimentally affects the number of cytotoxic cells, thereby decreasing the ability of the immune system to respond to tumor growth

Chronic Sleep Restriction Impairs the Antitumor Immune Response in Mice. Neuroimmunomodulation. 2018;25(2):59-67.



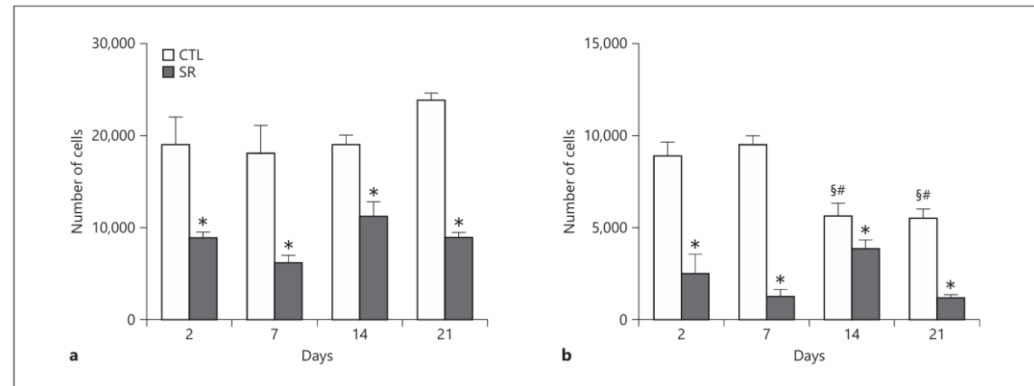


Fig. 3. Evaluation of CD8+ T cells and NK cells in the tumor microenvironment of sleep-restricted and control mice. The lungs of control (CTL; empty bars) and sleep-restricted mice (SR; filled bars) were processed, and the infiltrating CD3+CD8+ T cells (**a**) and CD3−NK1.1+ NK cells (**b**) were phenotypically analyzed by flow cytometry after 2, 7, 14, and 21 days of SR. Both the SR and CTL groups were intravenously inoculated with 3.5×10^5 B16F10 tumor cells. The numbers of both CD8+ T cells and NK cells were reduced in the SR mice. Two-way ANOVA with Newman-Keuls post hoc test showed that * $p < 0.05$ compared to the respective control groups, $^{\S} p < 0.05$ compared to the 2-day group, and $^{\#} p < 0.05$ compared to the 7-day group. $n = 5$ per group. All data are represented as mean ± SEM.

Sleep in Immunity

- chronic sleep disturbances
  - result in a persistent inflammatory state
  - elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α

→ contribute an environment conducive to cancer development

The Triad of Sleep, Immunity, and Cancer: A Mediating Perspective.
Cells. 2024 Jul 24;13(15):1246.

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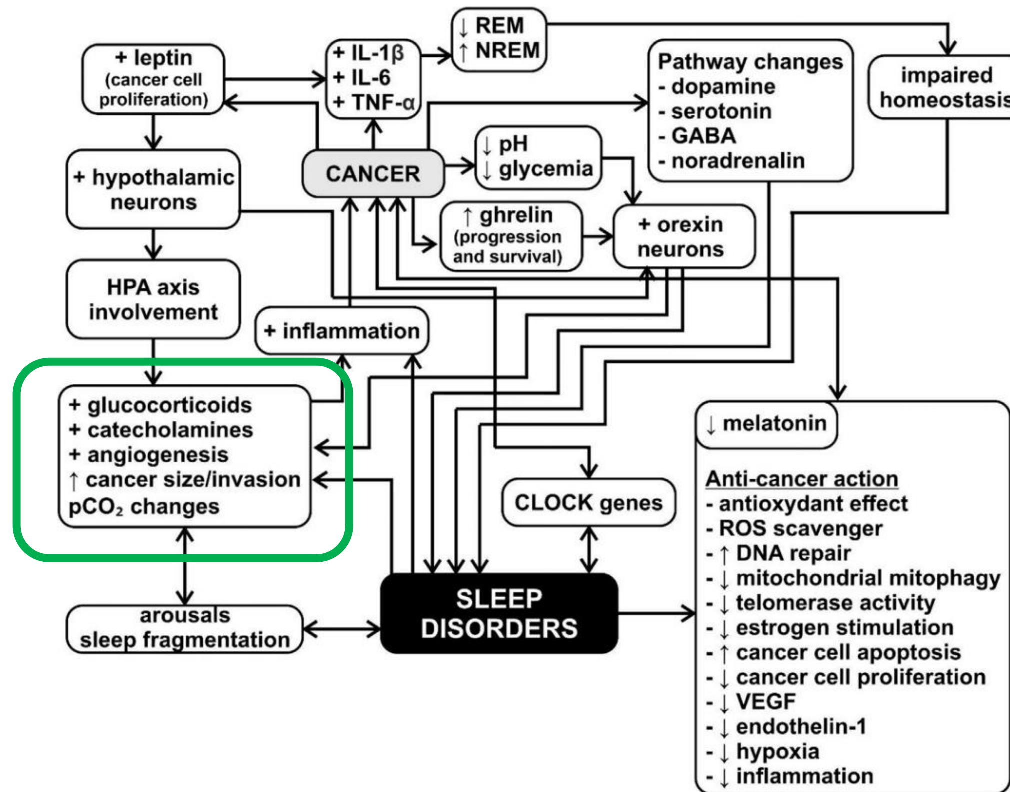
Complex interactions between sleep & cancer



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Sleep disorders and cancer: State of the art and future perspectives, Sleep Medicine Reviews, Volume 56, 2021.

Training circadian clocks

- Glucocorticoids
  - steroid hormones that are rhythmically secreted from the adrenal gland via suprachiasmatic nucleus (SCN) modulation of the hypothalamic–pituitary–adrenal (HPA) stress response axis
  - Dexamethasone
    - used as a supportive care comedication for cancer patients undergoing standard care pemetrexed/platinum doublet chemotherapy
    - very effective in the treatment of lymphoid malignancies, including leukemia, lymphomas, and multiple myeloma, with much work being done to enhance their effects and overcome resistance

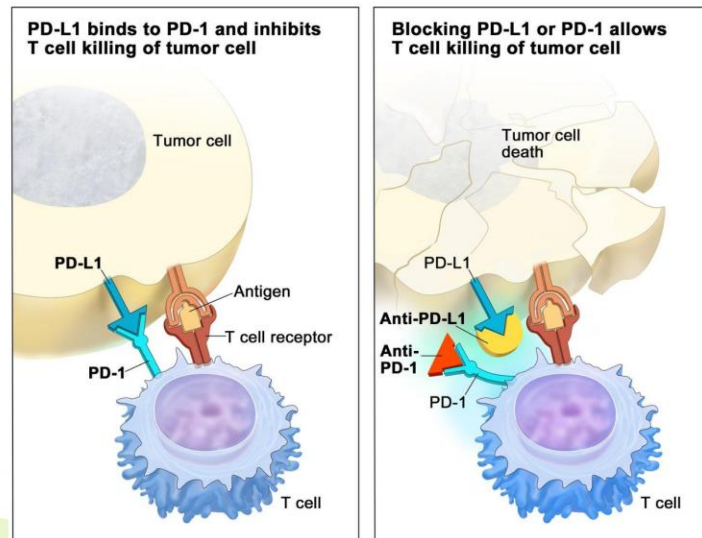
Training circadian clocks

- Glucocorticoids
  - may also be implicated in poorer responses to cancer therapies with immune checkpoint inhibitors, such as anti-PD-(L)1, due to their immunosuppressive functions

The role of the circadian clock in cancer hallmark acquisition and immune-based cancer therapeutics.
J. Exp. Clin. Cancer Res. 40, 119 (2021).

Immunotherapy

- Immunotherapy
  - Immune checkpoint inhibitors (ICIs)
    - blocking interactions between T cells and antigen presenting cells (APCs) or tumor cells that lead to T-cell inactivation
    - By inhibiting this interaction, the immune system is effectively upregulated and T cells become activated against tumor cells



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Harrison's Principles of Internal Medicine, 21e

Immunotherapy

- PD-1 (programmed cell death protein-1) inhibitor
  - Pembrolizumab
  - Nivolumab

- PD-L1 (programmed cell death-ligand 1) inhibitor
  - Atezolizumab
  - Durvalumab

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National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 5.2025 — June 20, 2025

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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TESTING RESULTS[mm,nn]

***EGFR* exon 19 deletion or exon 21 L858R mutation positive**	NSCL-21
***EGFR* S768I, L861Q, and/or G719X mutation positive**	NSCL-24
***EGFR* exon 20 insertion mutation positive**	NSCL-25
***KRAS* G12C mutation positive**	NSCL-26
***ALK* rearrangement positive**	NSCL-27
***ROS1* rearrangement positive**	NSCL-30
***BRAF* V600E mutation positive**	NSCL-32
***NTRK1/2/3* gene fusion positive**	NSCL-33
***METex14* skipping mutation positive**	NSCL-34
***RET* rearrangement positive**	NSCL-35
***ERBB2 (HER2)* mutation positive**	NSCL-36
***NRG1* gene fusion positive**	NSCL-37
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-38
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-39

Palliative chemotherapy

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c,d]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	
NO contraindications to PD-1 or PD-L1 inhibitors[d] AND NO *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements	**Contraindications to PD-1 or PD-L1 inhibitors[d] OR *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements**
Preferred • Pembrolizumab/carboplatin/pemetrexed[e] (category 1)[1,2] • Pembrolizumab/cisplatin/pemetrexed[e] (category 1)[2] • Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[3] Other Recommended • Atezolizumab[f]/carboplatin/paclitaxel/bevacizumab[e,g,h,i,j] (category 1)[4] • Atezolizumab[f]/carboplatin/albumin-bound paclitaxel[e,5] • Nivolumab/ipilimumab[e,6] • Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[7] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)[e] (category 1)[3] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[e] (category 1)[8] • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[e] (category 1)[8]	Useful in Certain Circumstances • Bevacizumab[g]/carboplatin/paclitaxel[h,i,j] (category 1)[9] • Bevacizumab[g]/carboplatin/pemetrexed[h,i,j,9,10] • Bevacizumab[g]/cisplatin/pemetrexed[h,i,j,11] • Carboplatin-combination therapy (category 1) ‣ Combination options include: albumin-bound paclitaxel,[12] docetaxel,[13] etoposide,[14,15] gemcitabine,[16] paclitaxel,[17] or pemetrexed[18] • Cisplatin-combination therapy (category 1) ‣ Combinations options include: docetaxel,[13] etoposide,[19] gemcitabine,[17,20] paclitaxel,[21] or pemetrexed[20] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Albumin-bound paclitaxel[24,25] • Docetaxel[26,27] • Gemcitabine[28-30] • Paclitaxel[31-33] • Pemetrexed[34]
ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 3–4)[f,k]	
Best supportive care (NCCN Guidelines for Palliative Care)	

Palliative chemotherapy

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c,d]

SQUAMOUS CELL CARCINOMA (PS 0–2)	
NO contraindications to PD-1 or PD-L1 inhibitors[d] **AND NO *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements**	**Contraindications to PD-1 or PD-L1 inhibitors[d]** **OR *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements**
Preferred • Pembrolizumab/carboplatin/paclitaxel[e] (category 1)[35] • Pembrolizumab/carboplatin/albumin-bound paclitaxel[e] (category 1)[35] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)[e] (category 1)[3] Other Recommended • Nivolumab/ipilimumab[e,7] • Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[e,7] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[e,8] (category 1) • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[e,8] (category 1)	Useful in Certain Circumstances • Carboplatin/albumin-bound paclitaxel (category 1)[12] • Carboplatin/docetaxel (category 1)[13] • Carboplatin/gemcitabine (category 1)[16] • Carboplatin/paclitaxel (category 1)[17] • Carboplatin/etoposide[14,15] • Cisplatin/docetaxel (category 1)[13] • Cisplatin/etoposide (category 1)[19] • Cisplatin/gemcitabine (category 1)[19,20] • Cisplatin/paclitaxel (category 1)[21] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Albumin-bound paclitaxel[24,25] • Docetaxel[26,27] • Gemcitabine[28-30] • Paclitaxel[31-33]
SQUAMOUS CELL CARCINOMA (PS 3–4)[f,k]	
Best supportive care (NCCN Guidelines for Palliative Care)	

Concurrent chemoradiation (CCRT)

CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[a]

Preferred (nonsquamous)

- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,b,c,d,e]
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,b,c,d,e,f]
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[4,b,c,d,e,g]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,b,c,d,e]

Preferred (squamous)

- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[6,b,c,d,e,g]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,b,c,d,e]

Consolidation Therapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After Definitive Concurrent Chemoradiation

- Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8,h,i] (category 1 for stage III; category 2A for stage II) (except tumors that are positive for *EGFR* exon 19 deletion or exon 21 L858R mutations)
- Osimertinib 80 mg once daily until disease progression (category 1 for stage III; category 2A for stage II) if *EGFR* exon 19 deletion or L858R[9,i]

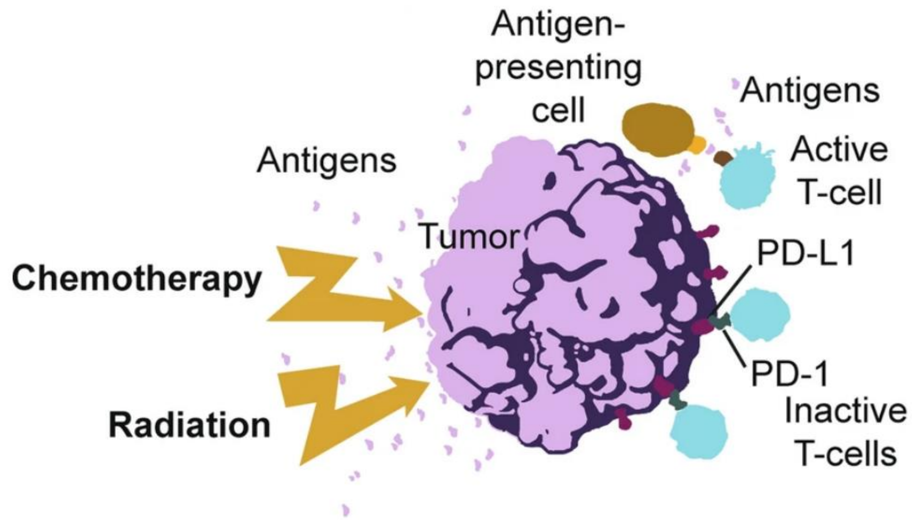
Chemoradiation

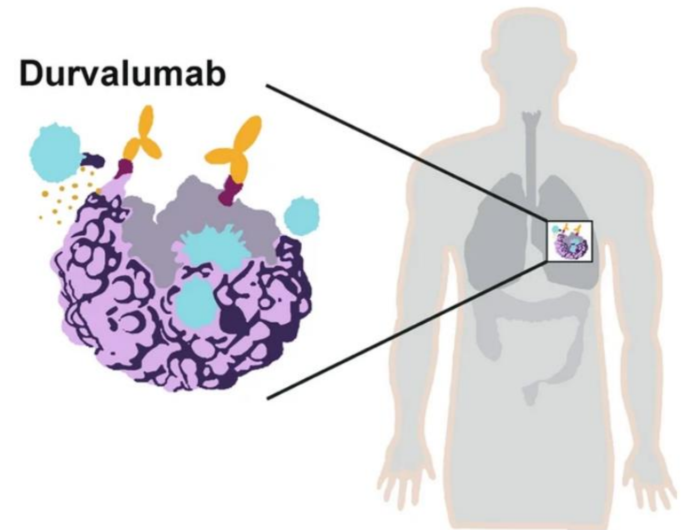
Chemoradiation induces tumor antigen release and an adaptive immune response

PD-L1 overexpression leads to immune cell evasion

Durvalumab

Durvalumab reverses immune suppression and leads to a systemic antitumor response





Perioperative chemotherapy

PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors[a]

- **Nivolumab 360 mg and platinum-based doublet chemotherapy every 3 weeks for up to 4 cycles[1,2] with the option of continuing single-agent nivolumab as adjuvant treatment after surgery (for patients with no known *EGFR* mutations or *ALK* rearrangements) (category 1);[2]**
  Systemic Therapy Following Surgical Resection
- **Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.**
  - **Platinum-doublet chemotherapy options include:**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m^2 or 200 mg/m^2 day 1 (any histology)**
    - ◊ **Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 (nonsquamous histology)**
    - ◊ **Cisplatin 75 mg/m^2 day 1, gemcitabine 1000 mg/m^2 or 1250 mg/m^2 days 1 and 8 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m^2 day 1, paclitaxel 175 mg/m^2 or 200 mg/m^2 day 1 (any histology)**
  - **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m^2 day 1 (nonsquamous histology)**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m^2 or 1250 mg/m^2 days 1 and 8 (squamous histology)**
- **Pembrolizumab 200 mg and cisplatin-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1);[3]** Systemic Therapy Following Surgical Resection
  - **Cisplatin 75 mg/m^2 day 1, gemcitabine 1000 mg/m^2 days 1 and 8 (squamous histology)**
  - **Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 (nonsquamous histology)**
- **Durvalumab 1500 mg and platinum-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent durvalumab as adjuvant treatment after surgery (for patients with no known *EGFR* mutations or *ALK* rearrangements) (category 1);[4]**
  Systemic Therapy Following Surgical Resection
  - **Platinum-doublet chemotherapy options include:**
    - ◊ **Carboplatin AUC 6 day 1, paclitaxel 200 mg/m^2 day 1 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 (nonsquamous histology)**
    - ◊ **Carboplatin AUC 5 day 1, pemetrexed 500 mg/m^2 day 1 (nonsquamous histology)**
  - **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
    - ◊ **Carboplatin AUC 5 day 1, gemcitabine 1250 mg/m^2 days 1 and 8 (squamous histology)**

Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors

Adjuvant Chemotherapy

Systemic Therapy Following Surgical Resection

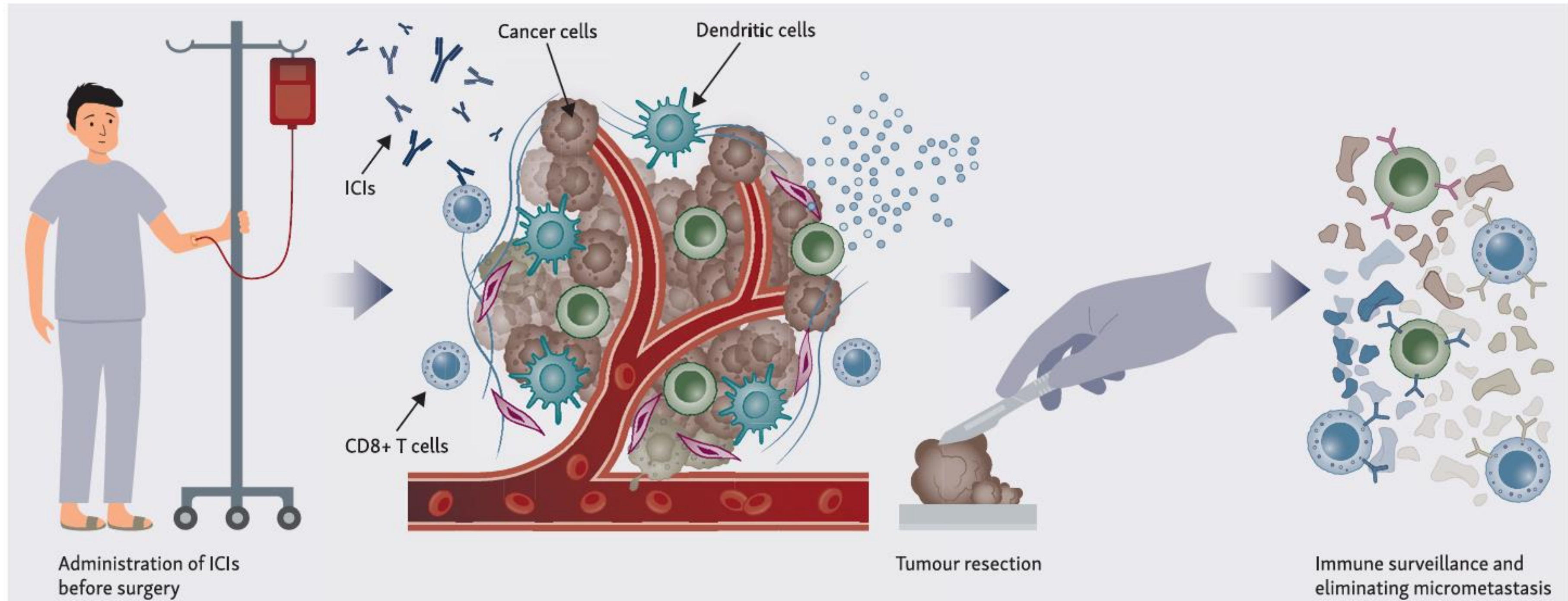


Figure 1. The rationale of neoadjuvant immunotherapy. Neoadjuvant immunotherapy induces a broader and stronger T-cell response by targeting the entire tumour. Intact lymph nodes may further enhance antitumour immunity. By contrast, upfront resection reduces tumour volume, limiting the neoantigen burden and potentially impairing T-cell activation and expansion by immune checkpoint inhibitors (ICIs). Following tumour resection, activated and more diverse T cells continue surveillance and eliminate micrometastases.

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Small Cell Lung Cancer

Version 4.2025 — January 13, 2025

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PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]

- Consolidation Therapy
  - Durvalumab 1500 mg day 1 every 28 days (category 1)[a,4]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[b,5]

PRIMARY THERAPY FOR EXTENSIVE STAGE SCLC[c]:

Four cycles of cytotoxic chemotherapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles

Preferred Regimens
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,k,6]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[d,e,k]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]

Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[9]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[10]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[11]

Useful in Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[12]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[13]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[14]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

Training circadian clocks

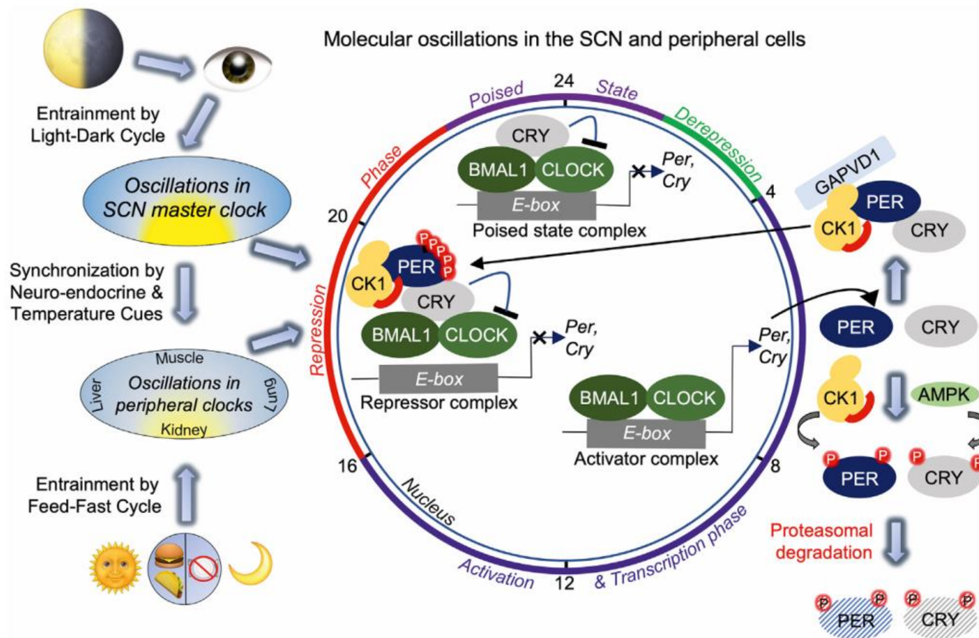
- Glucocorticoids
  - may also be implicated in poorer responses to cancer therapies with immune checkpoint inhibitors, such as anti-PD-(L)1, due to their immunosuppressive functions

The role of the circadian clock in cancer hallmark acquisition and immune-based cancer therapeutics. J. Exp. Clin. Cancer Res. 40, 119 (2021).

- Targeting circadian rhythms in cancer treatment
  - Training circadian clocks
  - Drugging clocks
    - Agonists or antagonists of clock proteins
  - Clocking medicine

Drugging clocks

- Casein kinases 1δ and 1ε (CK1δ/ε)
  - critical components of the circadian clockwork that determine the circadian period and re-entrainment kinetics via phosphorylation of PERs to regulate their timed nuclear entry and activity



THE CATHOLIC UNIVERSITY OF KOREA
CATHOLIC MEDICAL CENTER

SCIENCE ADVANCES | RESEARCH ARTICLE

BIOCHEMISTRY

Cell-based screen identifies a new potent and highly selective CK2 inhibitor for modulation of circadian rhythms and cancer cell growth

Tsuyoshi Oshima[1,2]*, Yoshimi Niwa[1]*, Keiko Kuwata[1], Ashutosh Srivastava[1], Tomoko Hyoda[3], Yoshiki Tsuchiya[4], Megumi Kumagai[5], Masato Tsuyuguchi[6], Teruya Tamaru[7], Akiko Sugiyama[1], Natsuko Ono[1], Norjin Zolboot[1], Yoshiki Aikawa[1], Shunsuke Oishi[1], Atsushi Nonami[8], Fumio Arai[9], Shinya Hagihara[1,2,10], Junichiro Yamaguchi[11], Florence Tama[1,12], Yuya Kunisaki[9], Kazuhiro Yagita[4], Masaaki Ikeda[5], Takayoshi Kinoshita[6], Steve A. Kay[1,13], Kenichiro Itami[1,2,14†], Tsuyoshi Hirota[1,10†]

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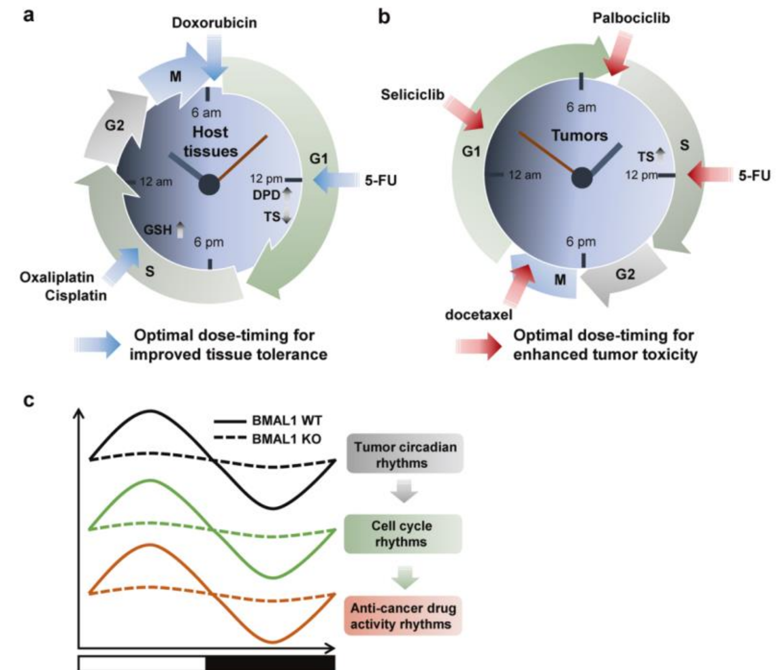
Compounds targeting the circadian clock have been identified as potential treatments for clock-related diseases, including cancer. Our cell-based phenotypic screen revealed uncharacterized clock-modulating compounds. Through affinity-based target deconvolution, we identified GO289, which strongly lengthened circadian period, as a potent and selective inhibitor of CK2. Phosphoproteomics identified multiple phosphorylation sites inhibited by GO289 on clock proteins, including PER2 S693. Furthermore, GO289 exhibited cell type–dependent inhibition of cancer cell growth that correlated with cellular clock function. The x-ray crystal structure of the CK2α-GO289 complex revealed critical interactions between GO289 and CK2-specific residues and no direct interaction of GO289 with the hinge region that is highly conserved among kinases. The discovery of GO289 provides a direct link between the circadian clock and cancer regulation and reveals unique design principles underlying kinase selectivity.

Sci. Adv. 5, eaau9060 (2019).

- Targeting circadian rhythms in cancer treatment
  - Training circadian clocks
  - Drugging clocks
  - Clocking medicine

Clocking medicine

- Circadian clocks
  - regulate absorption, distribution, metabolism, and elimination of drugs
  - Circadian timing of cancer medicine



Roles of circadian clocks in cancer pathogenesis and treatment. *Exp Mol Med* **53**, 1529–1538 (2021).

Summary

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  - complex and bidirectional

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Summary

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  - complex and bidirectional
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  - through the disruption of circadian rhythms, reduction of melatonin secretion, and inflammatory responses, leading to unregulated cell proliferation
- insufficient and excessive sleep duration, insomnia symptoms, and evening chronotype
  - significantly predictive of an increased risk of lung cancer
- early detection and management of sleep disturbances
  - could be a promising means of mitigating the burden of lung cancer

바쁘신 시간에도 경청해주셔서 감사합니다.