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An integrated multi-omics analysis identifies novel regulators of circadian rhythm and sleep disruptions under unique light environment in Antarctica

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Light is the dominant zeitgeber for biological clocks, and its regulatory mechanism for sleep–wake activity has been extensively studied. However, the molecular pathways through which the unique Antarctic light environment, with polar days in summer and polar nights in winter, affects human sleep and circadian rhythm remain largely unidentified, although previous studies have observed delayed circadian rhythm and sleep disruptions among expeditioners during polar nights. In this study, we conducted comprehensive dynamic research on the expeditioners residing in Antarctica for over one year. By integrating the phenotypic changes with multi-omics data, we tried to identify the novel candidate regulators and their correlation networks involved in circadian and sleep disorders under abnormal light exposure. We found that during the austral winter, expeditioners exhibited delayed bedtime and getting up time, reduced sleep efficiency, and increased sleep fragmentation. Meanwhile, serum dopamine metabolite levels significantly increased, while serotonin metabolites and antioxidants decreased. These changes were accompanied by altered expression of genes and proteins associated with neural functions, cellular activities, transcriptional regulation, and so on. Through the correlation and causal mediation analysis, we identified several potential pathways modulating human sleep–wake activity, involving genes and proteins related to neural function, glucose metabolism, extracellular matrix homeostasis, and some uncharacterized lncRNAs. Based on the identified causal mediators, LASSO regression analysis further revealed a novel candidate gene, Shisa Family Member 8 (*SHISA8*), as a potential key regulatory hub in this process. These findings shed light on the probable molecular mechanisms of sleep disorders in Antarctica and suggest *SHISA8* as a novel candidate target for medical intervention in sleep disorders under unique light environments.

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INTRODUCTION

Light is the primary zeitgeber synchronizing human circadian rhythms to the solar day. Previous evidence suggested that light modulates the human circadian system by inhibiting the secretion of melatonin [1], as well as affecting the suprachiasmatic nucleus (SCN) through activating intrinsically photosensitive retinal ganglion cells (ipRGCs) [2]. Additionally, light indirectly stimulates the ascending arousal system to enhance alertness, through as yet unidentified pathways [3]. However, some of the key molecules involved in these pathways and how they interact with each other to influence human sleep–wake activity are still unclear.

Antarctica is the farthest, most inaccessible, and coldest continent on Earth [4], with 98% of the continent covered by a huge ice sheet averaging 2,500 meters in thickness [4]. The light–dark cycle changes dramatically in the Antarctic Circle, which is more intense as the latitude increases. This results in polar days in summer, during which the sun never sets, and on the contrary, polar nights in winter. This unique light environment serves as an excellent natural laboratory to investigate the impact of light on human circadian rhythms and sleep homeostasis. Due to the absence of a local population, studies can only be conducted among expeditioners to obtain human physiopsychological changes under this extreme environment.

The Chinese Zhongshan Station (69° 22′ 24″ S, 76° 22′ 40″ E) is located in the Antarctic Circle. On average, there are approximately 50 polar days from November to the following January in summer [5]. Conversely, during the winter months from May to July, expeditioners have to endure about 60 days of polar nights, relying solely on artificial light instead of natural sunlight [5].

Under the unique light environment, sleep problem is the most common and disturbing disorder among winter-over expeditioners. An early study conducted at McMurdo Station found that 63% of expeditioners reported difficulty falling asleep and feeling sleepy during the daytime [6]. Recent studies involving expeditioners from diverse socio-cultural backgrounds have also shown delayed sleep onset and offset time, reduced sleep duration, decreased sleep efficiency, aggravated sleep fragmentation, and altered sleep architecture during overwintering, which could be

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alleviated through light therapy [7–19]. Consistent with these findings, we previously reported that the secretion acrophase of urine 6-sulphatoxymelatonin (aMT6s), a melatonin metabolite, delayed by 2.52 h during the austral winter at the Zhongshan Station, accompanied by a shift in chronotype towards eveningness preference [5]. However, previous research predominantly focused on elucidating phenotypic changes, rather than exploring the underlying molecular mechanism. With the advancement of multi-omics technologies, we now have the opportunity to identify novel regulators that contribute to circadian and sleep alteration under the Antarctic abnormal light environment, leading to a deeper understanding of these phenotypic changes.

In this study, we aim to reveal the underlying mechanisms of biological rhythms and sleep changes in Antarctic winter-over expeditioners. Through constructing advanced analytical models, we will integrate the phenotypic changes with multi-omics sequencing data, encompassing transcriptomics, metabolomics, and proteomics, to obtain the signaling network and critical regulators modulating sleep–wake activity. Hopefully, this study may identify potential targets for medical prevention and treatment of sleep disorders under abnormal light environments.

MATERIALS AND METHODS

Subjects and study protocol

This project has been approved by the ethics committee of Peking Union Medical College (ethics number: 2018004). The winter-over expedition team comprised nineteen men. Twelve of them, aged 26–53 years old (average age was 39.58 ± 9.17 years old), participated in the entire study procedure and acquired available data and samples. Before departing to Antarctica, all the volunteers underwent a comprehensive physical examination and signed informed consent.

The expedition team boarded the Xuelong icebreaker ship and departed from Shanghai (China) on October 31, 2018. After a one-month voyage, they arrived at Zhongshan Station on December 4, 2018. Later on, they resided at Zhongshan Station for about 12 months before leaving Antarctica on December 7, 2019. The subjective and objective sleep status of expeditioners were evaluated during four representative periods: pre-Antarctica (October 2018), Antarctica-1 (pre-winter, March 2019), Antarctica-2 (winter, July 2019), and Antarctica-3 (summer, November 2019). The fasting venous blood samples, 10 mL for each participant, were collected during pre-Antarctica and Antarctica-2 for multi-omics sequencing. All the samples were stored in a freezer at −80 °C at Zhongshan Station and transported back to China at −40 °C via the Xuelong icebreaker ship. The detailed itinerary and study design are shown in Fig. 1A. The anthropometric characteristics and tests included for each participant are detailed in Supplementary Table 1.

Environment of Zhongshan Station and lifestyle

The Chinese Zhongshan station (69° 22′ 24″ S, 76° 22′ 40″ E) is situated in the Larsemann Hills of Southeast Antarctica [20], with an average altitude of 11 meters [21] and an annual average temperature of -10 °C [22]. The station consists of 15 multifunctional buildings covering an area of 2700 m^2, including office buildings, dormitory buildings, research buildings, entertainment buildings, garages, and so on. It typically accommodates about 17–19 expeditioners during the austral winter. Equipped with automatic central heating systems, the indoor temperature of Zhongshan Station is 16–20 °C throughout the year, offering expeditioners a comfortable thermal environment comparable to the ambient temperature before they depart from Shanghai in October 2018. According to the global meteorological data supplied by Meteomanz.com (http://www.meteomanz.com/index?l=1), the daily average outdoor temperature at Zhongshan Station in March (Antarctica-1), July (Antarctica-2), and November (Antarctica-3) of 2019 was −15 to −2.5 °C, −31.5 to −3.7 °C, and −9.4 to 1.2 °C, respectively. For detailed meteorological data during the study periods, please refer to Supplementary Table 2.

During the expedition, there were 64 days of continuous daylight (polar days, the sun did not set from 20 November 2018 to 22 January 2019), and 45 days of continuous darkness (polar nights, the sun did not rise from 30 May 2019 to 13 July 2019). The duration of sunshine in 2019 is shown in Supplementary Fig. 1. During the austral winter, outdoor activities were discouraged except for necessary maintenance work. Due to the lack of natural sunlight, during polar nights, expeditioners relied solely on artificial lighting within the station. We used the digital luminometer (Smart Sensor AS803, China) to measure the light intensity of the dining room (6 measuring points) and four living quarters (2 measuring points for each quarter) in Zhongshan Station in March, July, and November 2019. Supplementary Table 3 shows that lighting conditions inside the station were limited, particularly during the polar night period. Without the interference of natural sunlight (July 10, 2019), the average light intensity ranged from approximately 18–25 lux in the living quarters and 30–40 lux in the dining room.

Measurement and statistics of sleep status, activity and white light exposure

Participants wore the PHILIPS Actiwatch Spectrum PRO (Philips Respironics, Inc.; Murrysville, PA, USA) research-grade wrist actigraphy device for at least fourteen days to obtain objective data on sleep, activity, and white light exposure in 1-minute epochs during each study period. They were instructed to press the event marker button before going to bed and after waking up each day. Following data collection, the actigraphy was connected to a computer via a USB link, and the data were downloaded and analyzed using Philips Actiware 6 software (version 6.3.0). The bedtime and getting up time were manually reviewed and revised based on the event markers entered by the participants. The time in bed (hours), total sleep time (hours), onset latency (minutes), sleep efficiency (%), wake after sleep onset (WASO, minutes), awakenings (times), and white light exposure during awakening (lux) of each day were then calculated automatically by the Philips Actiware 6 software [23]. The averages of the parameters for each participant during the data collection period were then computed to represent their overall sleep status and light exposure level. We used the Chronos-Fit software (V1.05) to calculate the acrophase of activity based on the activity data from the actogram.

The Pittsburgh Sleep Quality Index (PSQI) [24], consisting of 18 items, was used to evaluate the subjective sleep status of expeditioners. According to the internationally acknowledged scoring method, scores of seven subscales were calculated, including sleep duration, sleep latency, sleep disturbances, sleep quality, sleep efficiency, daytime dysfunction, and use of sleeping medication. The total PSQI score is derived by adding up these subscale scores.

All data were represented as mean ± SD and analyzed using IBM SPSS Statistics 25 software (IBM Inc., Chicago, USA). Data were tested for normality using the Shapiro–Wilk tests. Since tests were conducted for each participant at each time point repeatedly, data with normal distribution and homogeneous variance was analyzed using variance (ANOVA) for repeated measures followed by the Bonferroni method, including bedtime, getting up time, onset latency, and awakenings. Data with non-normal distribution or non-homogeneous variance was examined using the Friedman rank-sum test for dependent variables, including time in bed, total sleep time, WASO, sleep efficiency, acrophase of activity, average daily white light exposure during awakening, and scores of PSQI. The statistical tests were justified as appropriate and data met the assumptions of the tests used. Two-tailed $P < 0.05$ was considered statistically significant.

Blood sample collection and multi-omics analysis

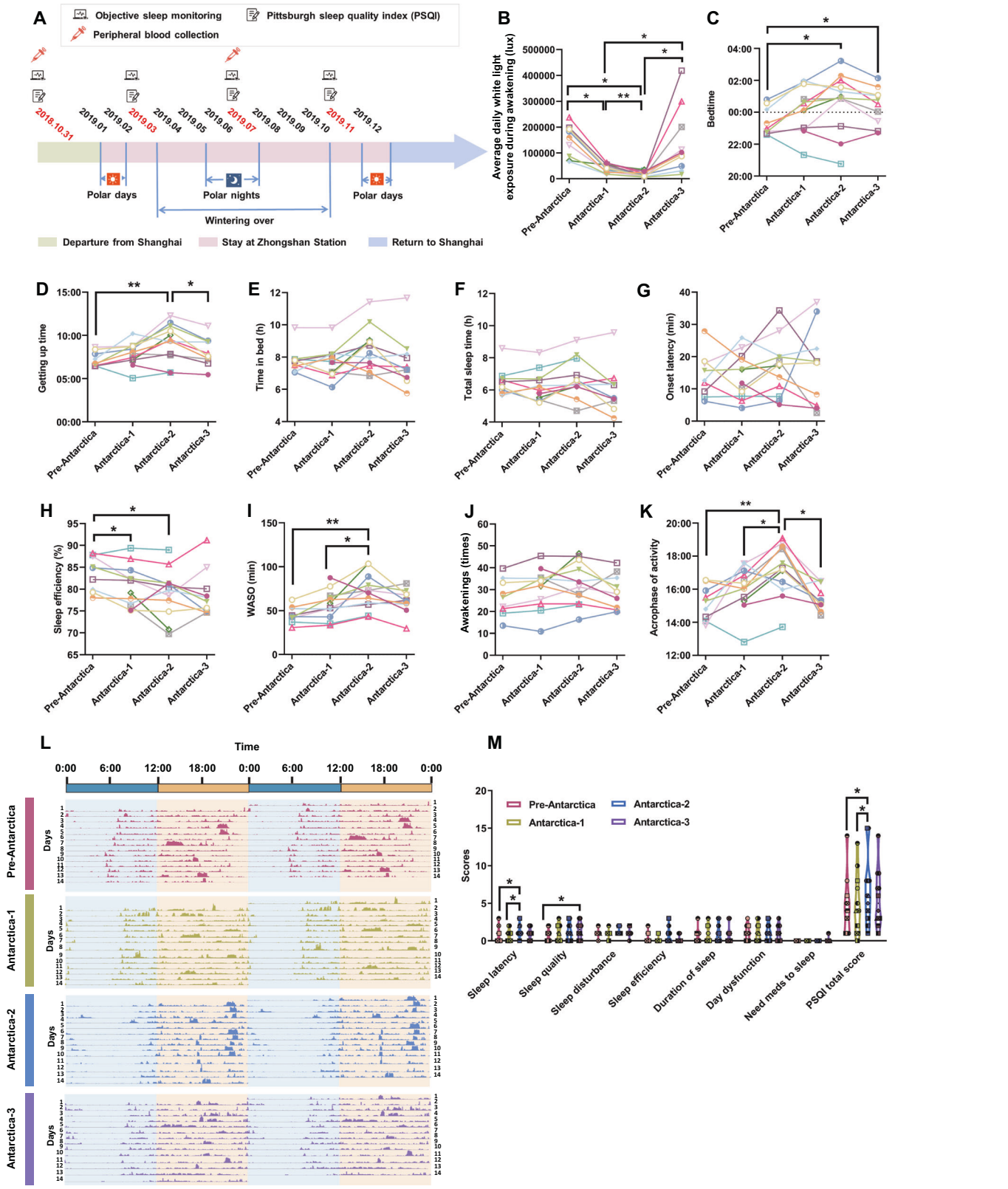
The fasting venous blood samples were collected between 7:00~8:00 a.m. and stored at −80 °C for preservation. Five milliliters of whole blood for each participant was used for genome-wide transcriptome sequencing. Serum samples were used for neurotransmitter-targeting metabolomics (100 μL serum) and untargeted proteomics (20 μL serum) sequencing. Detailed information for blood collection and multi-omics analysis is provided in Supplementary File 1.

Correlation analysis

The repeated measures correlations between sleep parameters, differential genes, proteins, and neurotransmitters were analyzed by Repeated measures correlation (rmcorr) to determine the common within-individual association for paired measures assessed on two occasions for multiple individuals. The "rmcorr" package of R software (V2021.09.1) was used to obtain correlation coefficients (r) and P values. The code used for repeated measures correlations analysis is provided in Supplementary File 2. $P < 0.05$ was considered as statistically significance.

Causal mediation analysis

The causal mediating effect was tested using the "PROCESS ()" function in the "bruceR" package of R software (V2021.09.1). We analyzed whether the



independent variable X (differential genes, proteins, or serum neurotransmitter metabolites) would affect the dependent variable Y (sleep indicator) through the mediating factor M (differential genes, proteins, or serum neurotransmitter metabolites), with examination time as the covariate and ID of expeditioners as the multilevel model (HLM) cluster. A mixed linear model was constructed, and the standard error (SE) and 95% confidence interval (CI) of the model were calculated using the Markov Chain Monte Carlo (Quasi Bayesian) method with 10,000 simulations (nsim = 10000). In this model, the regression coefficient of X to M was denoted as "a", and the regression coefficient of M to Y was denoted as "b". The significance of a×b

Fig. 1 Winter-over expeditioners experienced sleep disorders during the austral winter. A The itinerary of the winter-over expeditioners of the 35th Chinese Antarctic expedition. The expedition team left Shanghai on Oct. 31, 2018. After 34 days of voyage, they arrived at Zhongshan Station and stayed for 12 months before they returned to China. During the expedition, there were 65 polar days and 45 polar nights. Subjective and objective sleep examinations were conducted during four representative periods, i.e. pre-Antarctica (October 2018), Antarctica-1 (pre-winter, March 2019), Antarctica-2 (winter, July 2019), and Antarctica-3 (summer, November 2019). The fasting venous blood samples were collected during pre-Antarctica and Antarctica-2. **B** The average daily white light exposure of expeditioners during awakening. **C**–**J** Changes in objective sleep parameters during each time period. During the austral winter, expeditioners showed significantly delayed sleep–wake rhythm (**C**, **D**), decreased sleep efficiency (**H**), and increased sleep fragmentation (**I**). **K** The acrophase of activity was delayed during the austral winter. **L** The actogram of one representative expeditioner exhibited a delay in the sleep-wake cycle during the austral winter. **M** Subscale scores of the Pittsburgh Sleep Quality Index (PSQI). Sleep latency and PSQI total score increased during the austral winter, indicating difficulty falling asleep and decreased sleep quality. Pre-Antarctica, October 2018; Antarctica-1, March 2019, before austral winter; Antarctica-2, July 2019, austral winter; Antarctica-3, November 2019, austral summer. *$P < 0.05$ versus pre-Antarctica, **$P < 0.01$ versus pre-Antarctica (mean ± SD, n = 9–12).

was tested and pathways with $P < 0.05$ were considered to have casual mediating effects. The code used for causal mediation analysis is provided in Supplementary File 3.

Least absolute shrinkage and selection operator (LASSO) regressive analysis

LASSO regression is a regression analysis method introduced by Robert Tibshirani in 1996. It penalizes the model parameters by adding L1 regularization terms to the loss function, causing some coefficients to approach zero and eventually eliminate from the model, and therefore aids variable selection and construction of models with fewer coefficients[25]. We employed the "glmnet" package of R software (V2021.09.1) to perform LASSO regression analysis. Genes and proteins in causal mediating pathways were further screened to identify key regulators closely related to sleep changes. The code used for LASSO regressive analysis is provided in Supplementary File 4.

RESULTS

Winter-over expeditioners displayed delayed circadian rhythm and sleep disorders during the austral winter

Compared with departure, the daily exposure to white light of expeditioners during awakening reduced significantly before winter and during the austral winter ($\chi^2 = 20.850$, $P < 0.001$, $P^{\text{Antrctica-1}} = 0.023$, $P^{\text{Antrctica-2}} = 0.023$) (Fig. 1B). Objective sleep monitoring revealed that the average bedtime and getting up time of expeditioners were delayed by 1.25 h and 1.98 h, respectively, during the austral winter (bedtime: $F = 15.316$, $P < 0.001$, $P^{\text{Antrctica-2}} = 0.019$; getting up time: $F = 17.688$, $P < 0.001$, $P^{\text{Antrctica-2}} = 0.008$) (Fig. 1C, D). Meanwhile, sleep efficiency significantly decreased ($\chi^2 = 13.050$, $P = 0.005$, $P^{\text{Antrctica-2}} = 0.020$) (Fig. 1H), while wake after sleep onset (WASO) increased ($\chi^2 = 15.900$, $P = 0.001$, $P^{\text{Antrctica-2}} = 0.004$) (Fig. 1I). There were no significant changes in time in bed, total sleep time, sleep latency, or number of awakenings (Fig. 1E, F, G, J). Consistent with delayed sleep–wake rhythm, we also observed postponement of the peak activity timing of expeditioners by 1.95 h on average ($\chi^2 = 12.300$, $P = 0.006$, $P^{\text{Antrctica-2}} = 0.008$) (Fig. 1K). For example, Fig. 1L displayed the actogram of one representative expeditioner, demonstrating the delay in the sleep–wake cycle during the austral winter. Additionally, expeditioners experienced decreased sleep efficiency before winter ($\chi^2 = 13.050$, $P = 0.005$, $P^{\text{Antrctica-1}} = 0.039$) (Fig. 1H). During the austral summer, expeditioners displayed a delay in bedtime ($F = 15.316$, $P < 0.001$, $P^{\text{Antrctica-3}} = 0.018$) (Fig. 1C).

In support of objective sleep changes, the subjective sleep latency and PSQI total score significantly increased during the austral winter, indicating a reduction of overall sleep quality among expeditioners (sleep latency score: $\chi^2 = 9$, $P = 0.029$, $P^{\text{Antrctica-2}} = 0.025$; PSQI total score: $\chi^2 = 10.25$, $P = 0.017$, $P^{\text{Antrctica-2}} = 0.025$) (Fig. 1M).

Taken together, winter-over expeditioners at Zhongshan Station experienced circadian rhythm and sleep disorders primarily during the austral winter, characterized by delayed sleep–wake rhythm, decreased sleep efficiency, and aggravated sleep fragmentation.

Sleep disorders are associated with serum neurotransmitter metabolite levels

Human sleep–wake activity is synergistically coordinated by a variety of neurotransmitters, such as melatonin, adenosine, dopamine, and γ-aminobutyric acid (GABA) [26]. Therefore, we detected the serum levels of 42 neurotransmitter metabolites pre-Antarctica and during the austral winter. OPLSDA analysis revealed significant variations in the profile of serum neurotransmitter metabolites during the austral winter compared to baseline levels (Fig. 2A). The differential neurotransmitter metabolites were clustered into three metabolic pathways, namely antioxidant, dopamine, and serotonin metabolism. Specifically, the levels of antioxidant metabolites, cysteine (Cys) and glutathione (GSH), significantly decreased (Cys: $t = 6.162$, $P < 0.001$; GSH: $V = 40$, $P = 0.044$) (Fig. 2B). We also observed increases in dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), while the level of 5-hydroxyindole-3-acetic acid (5HIAA), a metabolite of serotonin, decreased (DOPAC: $t = 4.307$, $P = 0.001$; HVA: $V = 10$, $P = 0.021$; 5HIAA: $t = 2.535$, $P = 0.028$) (Fig. 2B). Correlation analysis showed that DOPAC was positively correlated with bedtime, getting up time, WASO, peak activity time, and PSQI total score, while negatively correlated with sleep efficiency (Fig. 2C). Another dopamine metabolite, HVA, was positively correlated with sleep onset and offset time (Fig. 2C). Antioxidant Cys was negatively correlated with getting up time, WASO, and peak activity time, and positively correlated with sleep efficiency (Fig. 2C). 5HIAA presented negative correlations with sleep latency score and PSQI total score (Fig. 2C). In summary, expeditioners exhibited increased dopamine metabolism and oxidative stress, while repressed serotonin metabolism during the austral winter. These neurohormonal alterations may contribute to the development of sleep disorders.

Differential gene expression profiles related to sleep disorders

To further investigate the underlying mechanism of sleep disturbances in winter-over expeditioners, we compared the genome-wide transcriptome profile of peripheral blood leukocytes between pre-Antarctica and the austral winter. PCA analysis suggested significant changes in gene expression patterns in Antarctica (Fig. 3A). Among the 38,809 genes identified through RNA-seq, there were 1,096 differentially expressed genes (DEGs), with 667 downregulated and 429 upregulated during the austral winter (Fig. 3B). The heat map of DEGs is shown in Supplementary Fig. 2. Intriguingly, consistent with the phenotypic changes, the expression of the *NFIL3* gene, which facilitates circadian rhythm regulation, was downregulated ($t = 3.004$, $P = 0.012$) (Fig. 3C). In contrast, the *NR1D1* gene, which inhibits the crucial transcriptor BMAL1 for circadian rhythm regulation, was upregulated ($t = 3.329$, $P = 0.007$) (Fig. 3D). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed and found that downregulated DEGs were associated with innate immune function, cellular autophagy, and so on, while upregulated DEGs were mostly linked to immune functions, including

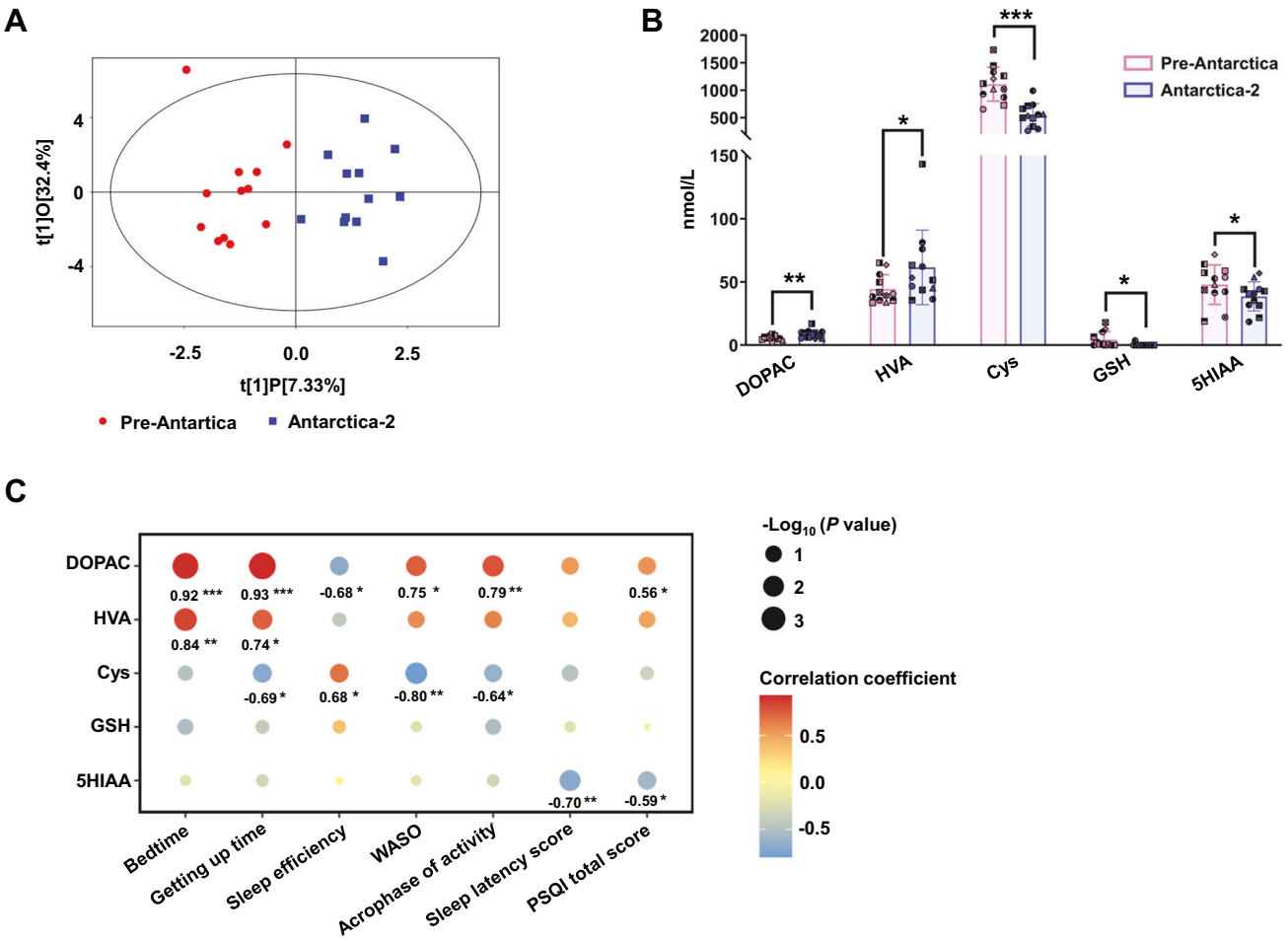


Fig. 2 Serum dopamine, serotonin, and redox metabolites are associated with sleep disorders. A Orthogonal partial least squares discriminant analysis (OPLSDA) showed a different profile of serum neurotransmitter metabolites between the austral winter and baseline. **B** During the austral winter, serum levels of DOPAC and HVA significantly increased, meanwhile, Cys, GSH, and 5HIAA decreased, indicating the activation of dopamine metabolism accompanied by the repression of antioxidant and serotonin metabolism. **C** Associations of sleep parameters and serum neurotransmitter metabolites. Only correlation coefficients with significance were presented ($P < 0.05$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, n = 12. Pre-Antarctica, October 2018; Antarctica-2, July 2019, austral winter. DOPAC 3,4-dihydroxyphenylacetic acid, HVA homovanillic acid, Cys cysteine, GSH glutathione, 5HIAA 5-hydroxyindole-3-acetic acid.

innate immune dysfunction and B cell immune function (Fig. 3E). Furthermore, we screened out 61 DEGs based on their fold changes (|Log2 (Fold change) |>0.5) and explored their potential correlations with sleep parameters. According to Fig. 3F and Supplementary Table 4, 27 genes, predominantly involved in nervous system function and transcriptional regulation, may be implicated in sleep disturbance. We also identified 18 additional genes that could potentially contribute to improved sleep quality, many of which are cell cycle regulators.

Changes in serum protein profiles are relevant to sleep disorders

The OPLSDA analysis revealed distinct serum protein profiles between pre-Antarctica and during the austral winter (Fig. 4A). A total of 753 serum proteins were identified, of which 24 significantly decreased and 33 significantly increased in Antarctica (Fig. 4B). Gene Ontology (GO) functional clustering analysis suggested that downregulated proteins were primarily enriched in biological processes such as erythrocyte function, glial cell differentiation, and metabolic reprogramming (Fig. 4C), and upregulated proteins were mainly associated with processes such as transmembrane transportation and negative regulation of peptidase activity (Fig. 4D). Correlation analysis between differential proteins and sleep indicators revealed that 22 proteins, involved in regulating cell activity, neural function, and so on, were positively correlated with bedtime, getting up time, WASO, acrophase of activity, sleep latency score and/or PSQI total score, while negatively correlated with sleep efficiency (Fig. 4E, Supplementary Table 5). Conversely, other proteins participating in immune, metabolic, and transport processes may be associated with improved sleep quality (Fig. 4E, Supplementary Table 5).

Genes–proteins interaction may contribute to the alteration of sleep status

To elucidate the potential pathways underlying the development of sleep disorders of winter-over expeditioners, we first carried out the correlation analysis between sleep parameters and differential neurotransmitter metabolites, genes, and proteins. Significant correlations with strong coefficients ($r > 0.7$, $P < 0.05$) were presented in the network diagram (Fig. 5A). We found that objective sleep indicators and neurotransmitter metabolites (DOPAC, GSH, and Cys) displayed complicated relationships with other factors (Fig. 5A).

Based on the correlation analysis, we further explored potential signaling pathways regulating sleep through causal mediation models and discovered that the interaction between particular proteins and genes might affect the circadian rhythm and sleep status of winter-over expeditioners. Shisa Family Member 8

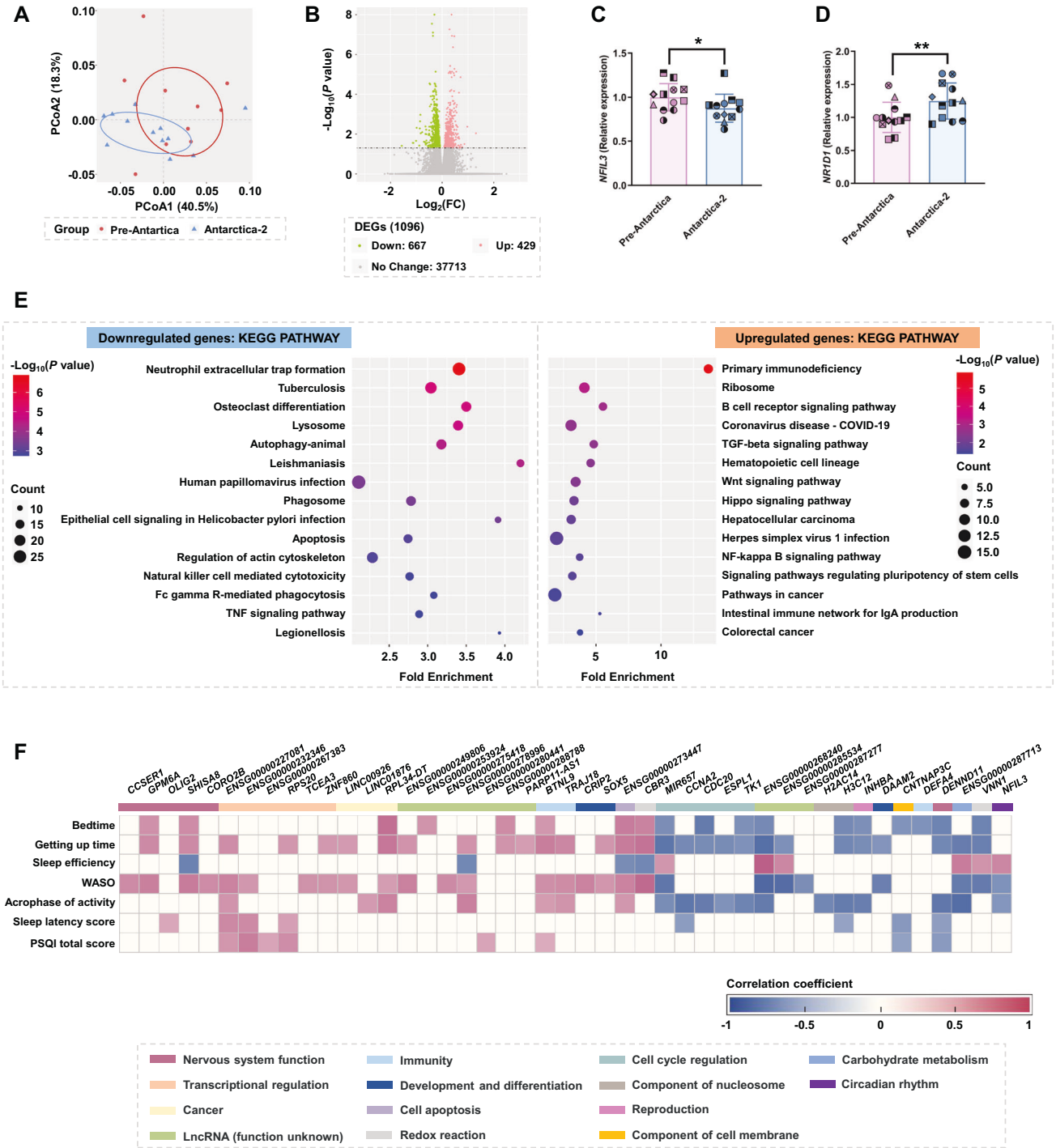


Fig. 3 Differential gene expression profiles related to sleep disorders. A Principal component analysis (PCA) showed different gene expression profiles of winter-over expeditioners after exposed to the Antarctic extreme environment. **B** Volcano plot of the differential genes ($P < 0.05$). **C**–**D** The expression of two clock genes, *NFIL3* (**C**) and *NR1D1* (**D**), changed significantly. **E** Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of differential genes. The bubble plot displayed different genes mapping to the corresponding functional pathways. The size of the bubble indicates the count of altered genes included in each KEGG pathway. **F** Associations of sleep parameters and differential genes. Only significant associations are shown with the correlation coefficient ($P < 0.05$). Pre-Antarctica, October 2018; Antarctica-2, July 2019, austral winter. *$P < 0.05$ versus pre-Antarctica, **$P < 0.01$ versus pre-Antarctica (mean ± SD, n = 12).

(SHISA8) plays a role in regulating the activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), a synaptic glutamatergic receptor, which may affect learning and memory activities [27]. As shown in Fig. 5B and Supplementary Table 6, the glucose transporter solute carrier family 2 member 1 (SLC2A1) may induce WASO by upregulating *SHISA8* expression. Dopamine receptor transporter EH domain containing 3 (EHD3) may promote the expression of lncRNA *ENSG00000273447*, leading to delayed getting up time (Fig. 5B, Supplementary Table 6). Phosphogluconate dehydrogenase (PGD) participates in the regulation of glucose metabolism by catalyzing the pentose phosphate pathway [28]. Our results showed that PGD may

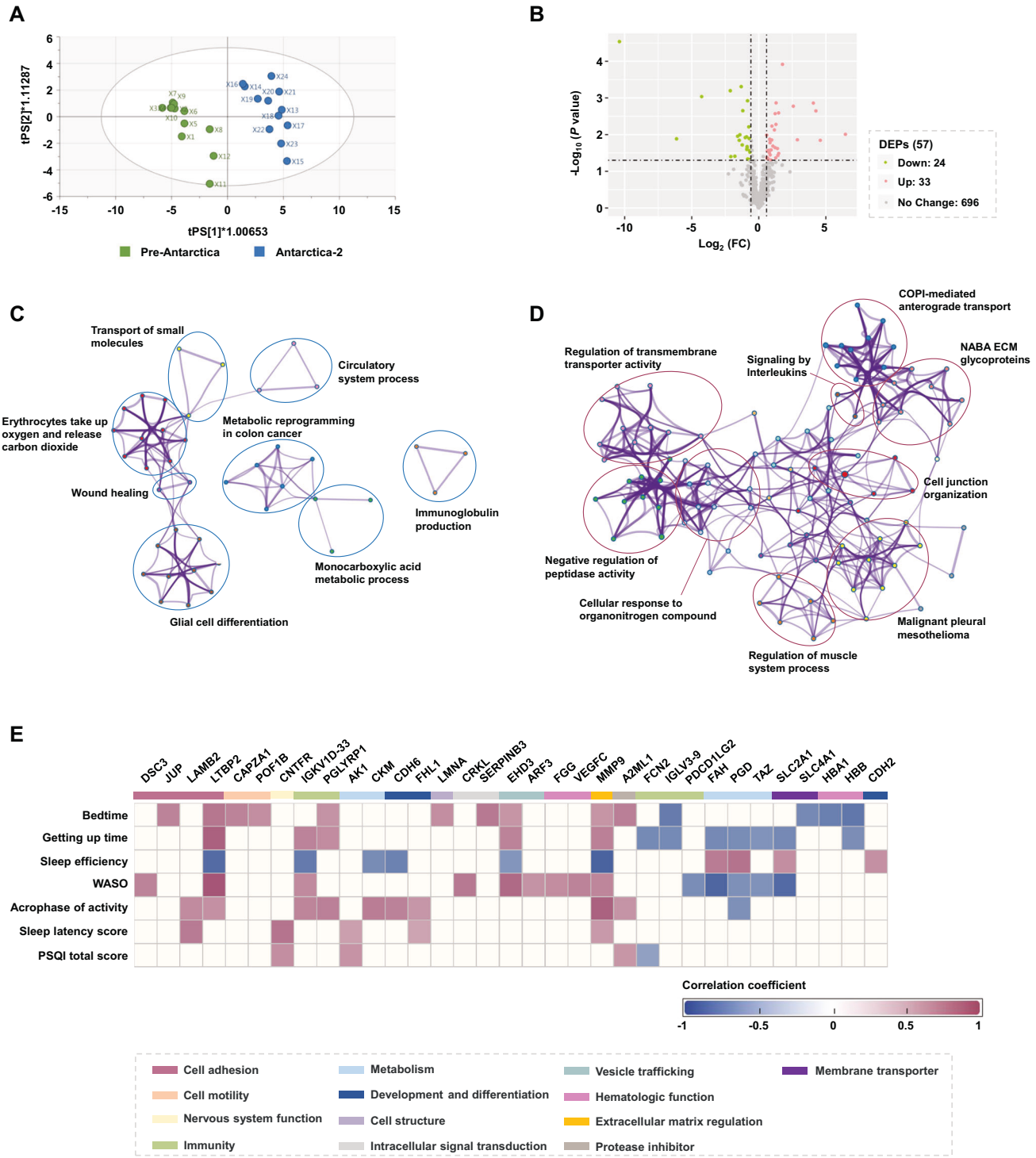


Fig. 4 Changes in serum protein profiles are associated with sleep disorders. A OPLSDA showed an obvious difference in serum protein profiles between pre-Antarctica and Antarctica-2. **B** Volcano plot of the differential proteins in serum ($P < 0.05$, Fold change > 1.5). **C** Gene Ontology (GO) term enrichment analysis showed that downregulated proteins were mainly involved in erythrocyte function, glial cell differentiation, and metabolic reprogramming. **D** GO term of upregulated proteins was enriched in biological processes such as transmembrane transportation and negative regulation of peptidase activity. **E** Associations of sleep parameters and differential proteins. Only significant associations are shown with the correlation coefficient ($P < 0.05$). n = 12. Pre-Antarctica, October 2018; Antarctica-2, July 2019, austral winter.

improve sleep efficiency by enhancing the expression of lncRNA *ENSG00000268240* (Fig. 5B, Supplementary Table 6).

In addition, particular genes may also affect sleep status by modulating protein expression. SOX5 is one of the members of the SRY-related HMG-box (SOX) family of transcription factors, involved in controlling the pace of neurogenesis [29]. Our results suggested that *SOX5* may increase WASO and postpone getting up time through enhancing the expression of latent transforming growth factor beta binding protein 2 (LTBP2), an extracellular matrix protein (Fig. 5C, Supplementary Table 6). Matrix

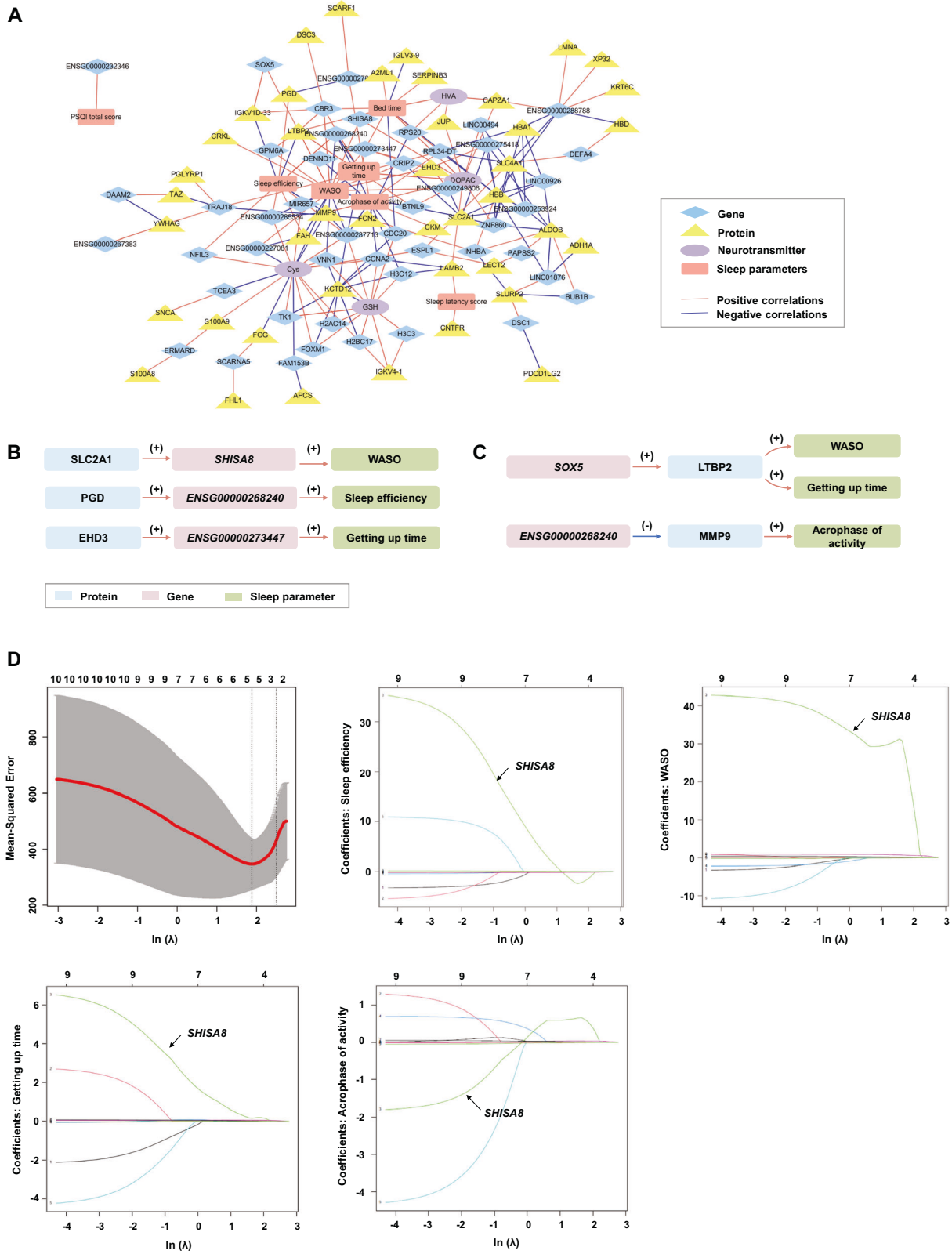


Fig. 5 Interplay between specific genes and proteins may modulate human sleep–wake activity. A The network diagram showed strong correlations ($P < 0.05$, $r > 0.7$) between sleep parameters and differential neurotransmitter metabolites, genes, and proteins. Red lines, positive correlations; blue lines, negative correlations. **B** Differential genes mediated the regulatory effects of specific proteins on human sleep. Red arrows, positive coefficient. The arrows drawn from proteins to genes and sleep parameters imply the conception that those indicators affect one another in the direction depicted. **C** Specific genes affect human sleep through differential proteins. Red arrows, positive coefficient; blue arrows, negative coefficient. **D** Based on the causal mediation results, the least absolute shrinkage and selection operator (LASSO) regressive analysis identified the *SHISA* gene as a key factor in sleep modulation. n = 12.

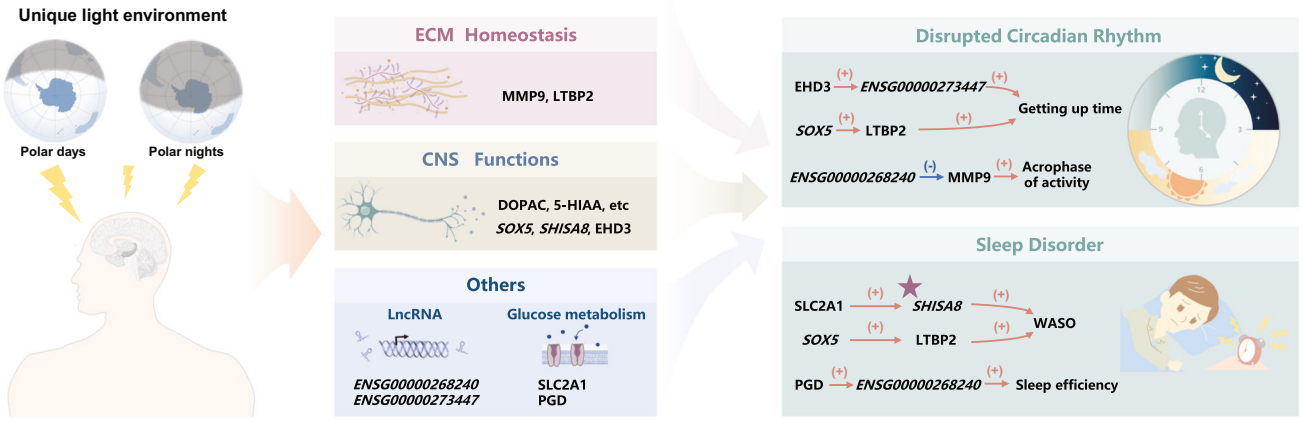


Fig. 6 The specific gene–protein interactions might disrupt circadian rhythms and sleep among winter-over expeditioners. Under the unique light environment during the polar night period, winter-over expeditioners at Zhongshan Station experienced delayed circadian rhythms, increased sleep fragmentation, and decreased sleep efficiency. These phenotypic changes may be associated with interactions between regulators of neural function (neurotransmitter metabolites, *SOX5*, *SHISA8*, EDH3), extracellular matrix homeostasis (MMP9, LTBP2), glucose metabolism (SLC2A1, PGD), and uncharacterized lncRNAs. Specifically, *SHISA8* may be a key factor for sleep regulation among winter-over expeditioners.

metallopeptidase 9 (MMP9) participates in maintaining extracellular matrix homeostasis, and its expression is regulated by circadian rhythm genes [30–32]. Interestingly, we found that a functionally unknown lncRNA *ENSG00000275418* may advance the circadian rhythm by suppressing MMP9 expression (Fig. 5C, Supplementary Table 6).

Lastly, we tried to screen out the most pivotal mediators influencing sleep–wake activity through Least absolute shrinkage and selection operator (LASSO) regressive analysis. Our results showed that the model error was minimized when $\lambda = 6.11$. Notably, the *SHISA8* gene may play a dominant role in sleep modulation (Fig. 5D).

In summary, our findings demonstrate that specific genes and/or proteins involved in regulating neural function, extracellular matrix homeostasis, glucose metabolism, and some uncharacterized lncRNAs may interplay with each other, and ultimately affect the sleep–wake activity. Specifically, the *SHISA8* may function as a pivotal regulatory hub in coordinating the human circadian rhythm and sleep.

DISCUSSION

As a crucial physiological process of the central nervous system, sleep plays a pivotal role in regulating metabolic homeostasis, immune function, memory consolidation, and so on. Disruption of circadian rhythm and sleep induced by abnormal light exposure, such as shift work and light pollution, has been linked to a variety of adverse outcomes [33–35]. Therefore, exploring the mechanism of sleep disorders under altered light conditions and identifying potential targets for clinical intervention are of great scientific importance and practical value. Our research took advantage of the natural unique light environment in Antarctica to investigate how changes in light exposure affect the molecular pathways regulating the circadian rhythm and sleep among expeditioners. In addition to supporting previous findings, we have, for the first time, discovered that abnormal light–dark cycle and weak light intensities induced alteration of factors regulating neural function, extracellular matrix (ECM) homeostasis, and glucose metabolism, which may contribute to delayed circadian rhythms and sleep disorders. Notably, we proposed a new candidate gene, *SHISA8*, as a key regulator of both sleep–wake rhythm and sleep quality (Fig. 6). Hopefully, this study may provide novel targets for the prevention and treatment of sleep disorders under Antarctic extreme environments. More importantly, our findings also shed light on developing strategies to improve the sleep quality of occupational groups in a wide range of fields working under abnormal light environments, such as shift workers, astronauts, submarine crew, and mine workers.

Winter-over expeditioners are exposed to various adverse environmental factors, including unique light environment, low temperatures, and confinement. In this study, however, we consider light as the dominant factor affecting circadian rhythm and sleep during the austral winter. The amount of light required for circadian rhythm entrainment depends on multiple factors. In a controlled environment without scheduled sleep and activity, a 12:12 light–dark cycle with light intensity between 200 and 1000 lux was found to be necessary to maintain circadian synchrony [36]. Nevertheless, during the austral winter, the artificial illumination at Zhongshan Station usually fell below 50 lux, which may in turn induce circadian misalignment and sleep problems. Evidence suggests that cold exposure increases wakefulness and decreases rapid eye movement (REM) sleep [37–39]. Despite outdoor temperatures at Zhongshan Station ranging from −31.5 to −3.7 °C during the austral winter, indoor temperatures remained steady at 16 to 20 °C. Since outdoor activities were strictly restricted during this period, the impact of cold on sleep was greatly minimized, if not eliminated. Long-term isolation-induced socio-psychological stress represents another potential contributor to sleep disturbances. Previous research reported elevated cortisol levels in volunteers associated with decreased sleep duration, increased arousal, and shortened REM latency during a 105-day confinement [40]. However, during the winter-over expedition, subjective negative moods, such as stress, anxiety, depression, fatigue, and so on, did not exhibit any significant changes in Antarctica compared to pre-departure, nor did the salivary cortisol levels (data not shown). Therefore, we suppose the detrimental effects of long-term isolation and confinement on expeditioners might be relatively moderate in this study.

During the austral winter, we observed a simultaneous delay in bedtime, getting up time, and acrophase of activity by 1.24, 1.98, and 1.95 h, respectively. Our previous study at the Zhongshan Station also reported a 2.52-h delay in the acrophase of urine 6-sulphatoxymelatonin rhythm during polar nights [5]. Meanwhile, compared with departure, the sleep onset and offset time were 1.46 h and 1.80 h later, respectively [5], which is consistent with our current study. Along with the delayed circadian phase, we also observed a decrease in sleep efficiency by 4.49% on average,

primarily due to an increase in awakening time after sleep onset. In a longitude study among winter-over expeditioners at German Stations Neumayer II and III from 2008 to 2014, the sleep efficiency of men dropped by 5.2%, similar to our findings [11]. Another research on the Indian expedition team at Maitri Station reported a greater decrease in sleep efficiency during the mid-winter compared to pre-departure, dropping from 97.7% to 88.0% [9]. Therefore, the lack of light exposure during the austral winter seems to impair the sleep quality of expeditioners regardless of the social-cultural background, albeit to different extents.

Multiple interacting neurotransmitters in the central nervous system (CNS) contribute to the transition between human wakefulness and sleep. Specifically, we found both the glutamatergic and dopaminergic systems with wake-promoting effects might be associated with the delayed circadian phase and impaired sleep observed in expeditioners.

Glutamate is one of the most important and abundant excitatory neurotransmitters in the mammalian CNS [41, 42]. Abnormal increase of the glutamate and glutamine levels in the thalamus may lead to shortened sleep duration and increased wakefulness [43], highlighting the crucial role of the glutamatergic system in regulating the sleep–wake cycle. In this study, *SHISA8*, a member of the Shisa family, has been identified as a novel key regulator inducing awakenings after sleep onset. According to previous reports, SHISAs modulate glutaminergic neurotransmission through regulating the surface trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), a synaptic glutamate receptor, as well as influence the AMPAR-mediated current amplitude [27]. This may partially explain the arousal effect of SHISA8. Our study suggested that SLC2A1 might function as an upstream regulator of *SHISA8*. SLC2A1 is a glucose transporter primarily located in the blood-brain barrier [44], whose nonsense or missense mutations induce daytime sleepiness and insomnia [45, 46]. Although a recent study in a small cohort suggested increased glutamine levels in cerebrospinal fluid of SLC2A1 deficiency patients [47], whether SLC2A1 affects sleep–wake activity through the glutaminergic system or SHISA8 remains largely unexplored.

Dopamine is another major neurotransmitter in the CNS with wake-promoting effects. Medications like amphetamines, which boost the dopaminergic system, have been widely used to treat narcolepsy [48]. In contrast, dopamine D2 receptor knockout resulted in reduced arousal levels in mice [49]. DOPAC, a neuronal metabolite of dopamine, showed significantly increased serum levels among winter-over expeditioners during the austral winter, which significantly correlated with sleep disorders. In support of our findings, early studies on patients with chronic insomnia found a positive correlation between urinary DOPAC levels and awakening time during sleep [50]. Additionally, sleep deprivation in rats was found to increase DOPAC levels in the basal forebrain and striatum, indicating the relevance between DOPAC levels and arousal [51, 52]. Furthermore, our research revealed that EHD3, a cell transporter mediating the recycling of D1-type dopamine receptors after endocytosis [53], may affect circadian rhythm by promoting the expression of the lncRNA *ENSG00000273447*. However, the specific regulatory mechanism of this pathway requires further exploration. In summary, the disturbance of the dopamine-dopamine receptor system may be involved in the development of sleep disorders in winter-over expeditioners.

Recent studies uncovered the functions of ECM in modulating circadian rhythm and sleep, through interactions with cell surface molecules or extracellular proteases [54]. According to our results, lncRNA *ENSG00000268240* may advance the circadian rhythm by inhibiting extracellular protease MMP9 expression. Recent evidence has highlighted the role of MMP9 in sleep–wake regulation. Hurtado Alvarado et al. [55] reported a significant increase in MMP9 levels in the hippocampus following sleep restriction. Breast cancer patients with circadian disruption were characterized by higher levels of serum MMP9 compared to controls with stable circadian rhythm [56]. Mechanism studies suggested that MMP9 cleaves pro-BDNF into activated mature BDNF, which in turn binds to and activates TrkB receptor and enhances the signal transduction activity of postsynaptic N-methyl-D-aspartate receptors (NMDAR), members of the glutamate receptor channel superfamily [57]. Therefore, the advancement of the circadian phase after MMP9 inhibition could be related to the repressed glutamate pathway activity in the CNS. However, the mechanism by which *ENSG00000268240* regulates MMP9 expression remains to be further elucidated. LTBP2 is another protein that binds to microfibers in ECM and interacts with transforming growth factor β (TGFβ) family members [58]. In this study, we proposed a novel potential function for LTBP2 in mediating the effects of the neurodevelopmental regulator SOX5 on sleep, potentially leading to increased WASO and delayed getting up time. Further investigations are necessary to validate our findings and elucidate their mechanisms.

It is well established that the circadian clocks, both central and peripheral, can affect glucose metabolism homeostasis through various pathways, such as regulating food intake, hormone secretion, insulin sensitivity, and energy metabolism [59]. Vice versa, glucose levels may also influence sleep–wake activity. Evidence from in vivo and in vitro research demonstrated that high glucose levels can repress the expression of arousal-regulating orexin and the electrical activity of orexin neurons [60, 61]. In support of this, we found both the glucose transporter SLC2A1 and the pentose phosphate pathway catalytic enzyme PGD may be involved in the development of sleep disorders. Fluctuations in glucose levels in the CNS could be partly responsible for these mechanisms.

As a natural laboratory for studying the impacts of light on sleep and circadian rhythms, Zhongshan Station provides us with a relatively controlled experimental condition. The participants in this project were all physically and mentally healthy adult males and resided in the same environment with similar lifestyles and diets, effectively minimizing the impact of various confounding factors. This helps us better interpret the long-term and relatively independent impact of changed light exposure on the human sleep–wake cycle and its underlying mechanisms. Yet, despite identifying several potential pathways and targets that may regulate sleep status, our findings remain speculative and require further functional experiments for validation and clarifying the specific molecular pathways.

To summarize, this study, for the first time, presented the neurotransmitter metabolites-genes-proteins interaction network which modulates circadian and sleep disorders in Antarctica and proposed several possible signaling pathways. Importantly, we have identified *SHISA8* as a key candidate gene in sleep regulation, which may provide new insights into the prevention and treatment of sleep disorders under abnormal light conditions.

DATA AVAILABILITY

All analyzed data is included in the article and its supplementary information files. Supplementary information (SI) is available at MP's website. According to the "Confidentiality" section in the informed consent approved by the ethics committee of Peking Union Medical College, the collected data will only be used in the research process of this study and shall not be used for other purposes or provided to third parties. If anyone needs to access the original data, please contact the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (sroffice@pumc.edu.cn).

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AUTHOR CONTRIBUTIONS

Chengli Xu conceived the project, raised funds, supervised the overall project and helped interpreting of data and drafting of manuscript; Shiying Liu, Yanlei Xiong, Xinyuan Liu, Yalei Xie and Xiaopei Wu prepared for the instruments, questionnaires, medical consumable material, and collected objective and subjective sleep data and blood samples of the winter-over expeditioners of the 35th Chinese Antarctic Research Expedition (CHINARE) before departure; Zhigang Zhang collected objective and subjective sleep data and blood samples of the winter-over expedition team in Antarctica; Shiying Liu, Jianan Wang, Xuan Tian, Liping Wang, Yanlei Xiong, Xinyuan Liu, Yalei Xie and Xiaopei Wu analyzed and verified the original objective and subjective sleep data; Shiying Liu, Jianan Wang and Xuan Tian analyzed and verified the data of genome-wide transcriptome, neurotransmitter-targeting metabolomics and untargeted proteomics sequencing; Shiying Liu and Jianan Wang constructed analytical models to perform integration analysis between phenotypic changes and multi-omics, and wrote the drafts of the manuscript; Chengli Xu, Shiying Liu, Jianan Wang, Xuan Tian and Liping Wang reviewed and edited the manuscript; all authors have read and approved the submitted version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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