Investigating the Role of Non-Coding RNAs in the Regulation of Circadian Clock Genes and Their Disruption in Metabolic Disorders and Neurodegenerative Diseases

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Abstract

The circadian clock is an internal timekeeping mechanism that coordinates physiological and behavioral rhythms within a roughly 24-hour cycle, overseeing functions like metabolism, hormone release, and sleep-wake patterns. Disruption of these circadian rhythms has been closely associated with metabolic issues such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD), as well as neurodegenerative conditions like Alzheimer's and Parkinson's disease. Recent progress has underscored the significant influence of non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), in the precise regulation of circadian clock gene expression. These ncRNAs can serve as post-transcriptional regulators, epigenetic modifiers, and molecular sponges, directly affecting key clock genes like CLOCK, BMAL1, PER, and CRY. This review compiles current insights into the interaction between ncRNAs and circadian clock regulation, highlighting how their dysregulation is linked to metabolic and neurodegenerative diseases. Additionally, we examine experimental methods for uncovering ncRNA-driven clock mechanisms and consider potential therapeutic approaches targeting ncRNAs to restore circadian balance.

Keywords

Circadian clock genes, MicroRNAs (miRNAs), Long non-coding RNAs (lncRNAs), Circular RNAs (circRNAs), Non-coding RNAs (ncRNAs), Neurodegenerative diseases, Metabolic disorders, Chronobiology, Epigenetic regulation

Introduction

Biological rhythms are essential for life, allowing organisms to adjust to regular environmental shifts, particularly the cycle of day and night. These rhythms are governed by the circadian clock, a conserved molecular system that controls the expression of many genes and synchronizes physiological activities such as energy metabolism, hormone secretion, and neuronal functions (Takahashi, 2017).

The central molecular clock is composed of transcriptional-translational feedback loops that include CLOCK, BMAL1, PER, and CRY proteins. These proteins' oscillatory behavior influences gene expression in peripheral tissues like the liver, pancreas, and brain (Partch et al., 2014). Disruptions in these loops, whether due to genetic mutations, environmental factors like light exposure, or epigenetic changes, can result in arrhythmicity, which is linked to metabolic and neurodegenerative diseases (Bass & Takahashi, 2010).

Non-coding RNAs (ncRNAs), such as miRNAs, lncRNAs, and circRNAs, are crucial in post-transcriptional regulation, RNA stability, chromatin remodeling, and transcriptional feedback loops (Ransohoff et al., 2018). The dysregulation of these ncRNAs is associated with imbalances in metabolic homeostasis and neurodegenerative conditions (Shen et al., 2020).

Metabolic disorders like obesity, type 2 diabetes mellitus (T2DM), and NAFLD often show circadian disruptions. ncRNAs influence this disruption by altering the rhythmic expression of genes involved in insulin signaling, lipid metabolism, and energy use (Gatfield & Schibler, 2007). Likewise, neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) exhibit circadian irregularities, including fragmented sleep-wake cycles and disrupted neuronal clock gene expression.

Grasping how ncRNAs regulate circadian clocks holds significant translational potential. By pinpointing ncRNAs that affect core clock genes, scientists can devise new therapeutic approaches to restore circadian rhythms and alleviate related metabolic and neurodegenerative disorders.

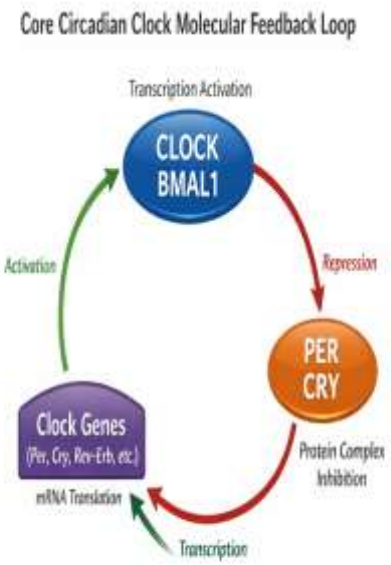


Figure 1: Core circadian clock molecular feedback loop (CLOCK/BMAL1 → PER/CRY → CLOCK/BMAL1).

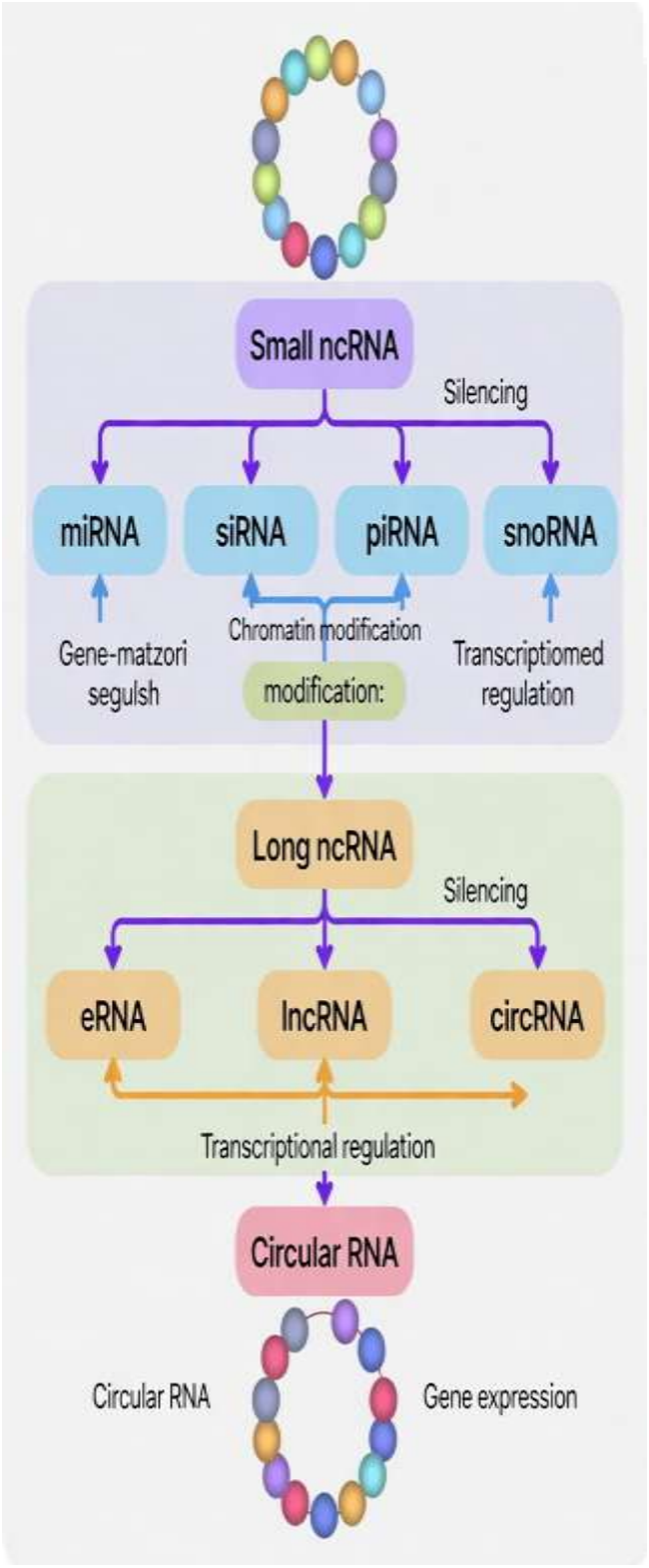


Figure 2: Overview of ncRNA classes and their mechanisms of action.

ncRNA Type	ncRNA Name	Target Clock Gene	Mechanism of Action	Tissue	Functional Outcome
miRNA	miR-219	CLOCK	Binds 3′UTR → inhibits translation	SCN (brain)	Modulates behavioral rhythmicity, sleep-wake cycle
miRNA	miR-132	BMAL1	Binds 3′UTR → suppresses expression	SCN (brain)	Adjusts photic entrainment of the clock
miRNA	miR-142-3p	BMAL1	Post-transcriptional repression	Liver	Alters glucose metabolism and circadian rhythm
miRNA	miR-34a	PER2	mRNA degradation	Liver	Disrupts PER2 rhythmicity, affecting metabolic pathways
lncRNA	Per2AS	PER2	Antisense transcript → transcriptional repression	Liver	Stabilizes negative arm of the circadian loop

ncRNA Type	ncRNA Name	Target Clock Gene	Mechanism of Action	Tissue	Functional Outcome
lncRNA	TUG1	BMAL1	Transcriptional modulation	Neurons	Regulates mitochondrial metabolism rhythm
lncRNA	NEAT1	SCN neuronal activity	Acts as scaffold → modulates transcription	SCN (brain)	Influences circadian amplitude; linked to neurodegeneration
circRNA	Cdr1as	CLOCK (via miR-7 sponge)	miRNA sponge → indirect regulation	SCN (brain)	Maintains neuronal clock stability
circRNA	CircBmal1	BMAL1	Transcriptional regulator	Liver	Modulates rhythmic lipid metabolism

Table 1: Examples of ncRNAs regulating core circadian genes.

Review of Literature

Molecular Basis of Circadian Clock Regulation

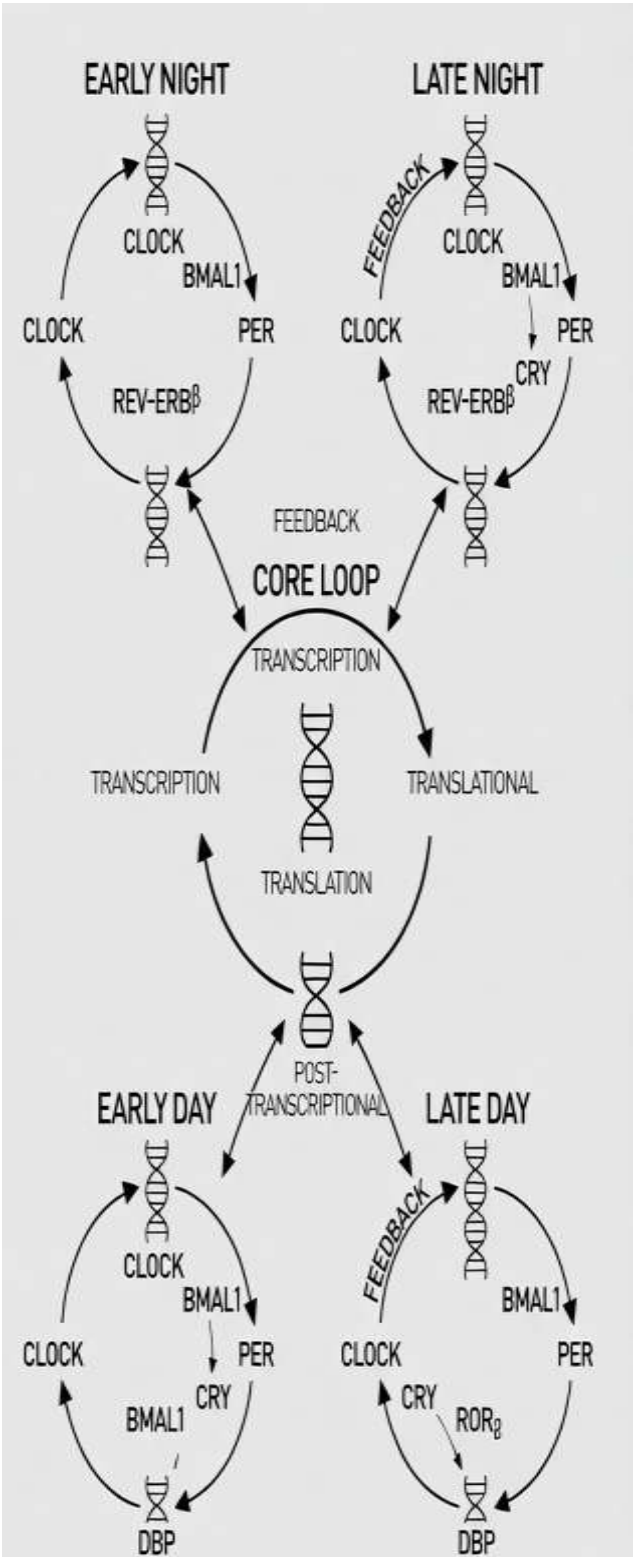
Circadian rhythms are regulated by transcriptional-translational feedback loops (TTFLs).

In the positive loop, the heterodimer formed by CLOCK and BMAL1 initiates the transcription of the PER and CRY genes.

Conversely, in the negative loop, the proteins PER and CRY suppress the activity of CLOCK/BMAL1, thus completing the cycle.

Additional loops involving REV-ERBα/β and RORα/β adjust the expression of BMAL1 (Takeda & Maemura, 2011). Environmental or genetic disruptions can cause circadian arrhythmicity, potentially leading to disease (Bass

& Takahashi, 2010).



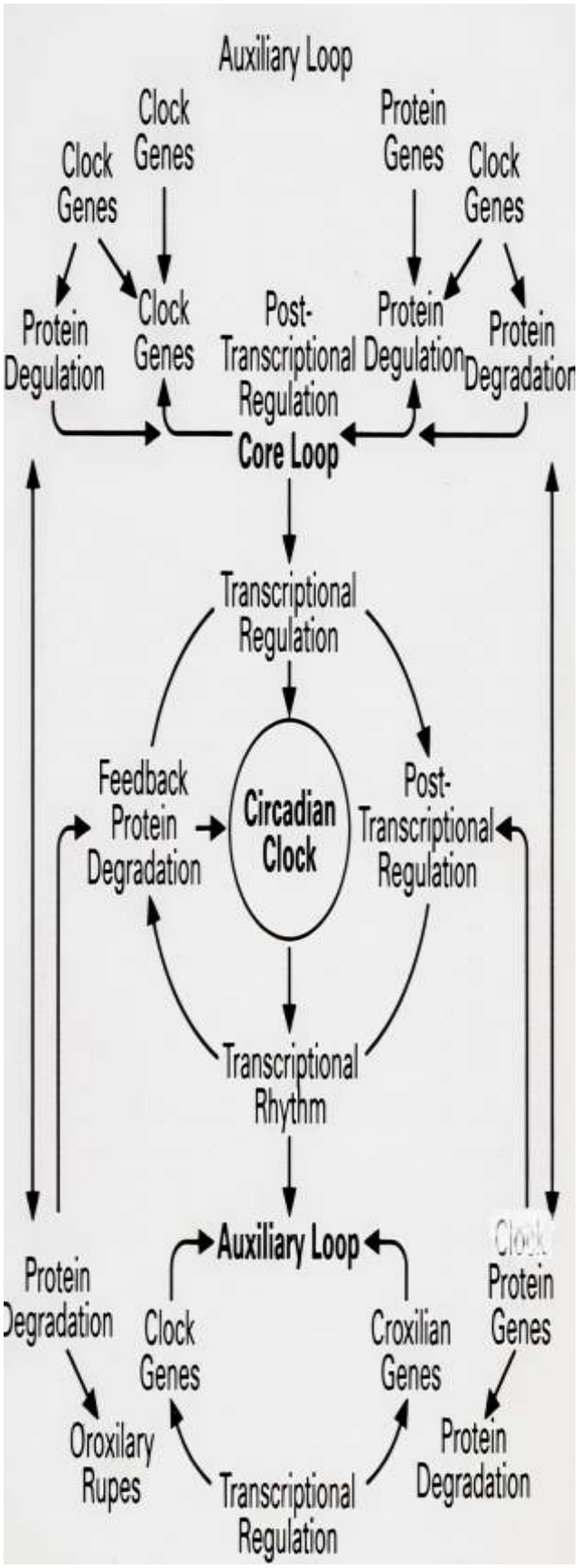


Figure 3: Core and auxiliary circadian loops with transcriptional/post-transcriptional regulation.

Non-Coding RNAs in Circadian Regulation

MicroRNAs (miRNAs)

- miRNAs, approximately 22 nucleotides in length, exert post-transcriptional control over clock genes:
- miR-219 and miR-132: Influence CLOCK and BMAL1 within the SCN (Cheng et al., 2007).
- miR-142-3p: Reduces BMAL1 expression in peripheral tissues, impacting glucose and lipid metabolism (Shende et al., 2011).
- miR-155: Affects CLOCK mRNA and circadian disruption associated with inflammation (Curtis et al., 2015).

Table 2: Key miRNAs regulating circadian clock genes.

miRNA	Target	Tissue	Disease Link
miR-219	CLOCK	SCN	Sleep disorders
miR-142-3p	BMAL1	Liver	T2DM
miR-155	CLOCK	Brain	Neuroinflammation

Long Non-Coding RNAs (lncRNAs)

- Long non-coding RNAs (lncRNAs) exceeding 200 nucleotides influence transcription and function as miRNA sponges:
- Per2AS: Influences the oscillations of PER2 (Koike et al., 2012).
- TUG1: Influences BMAL1 within neurons (Zhang et al., 2019).
- NEAT1: Impacts neuronal activity in the SCN and is linked to neurodegenerative conditions (Yamazaki et al., 2018).

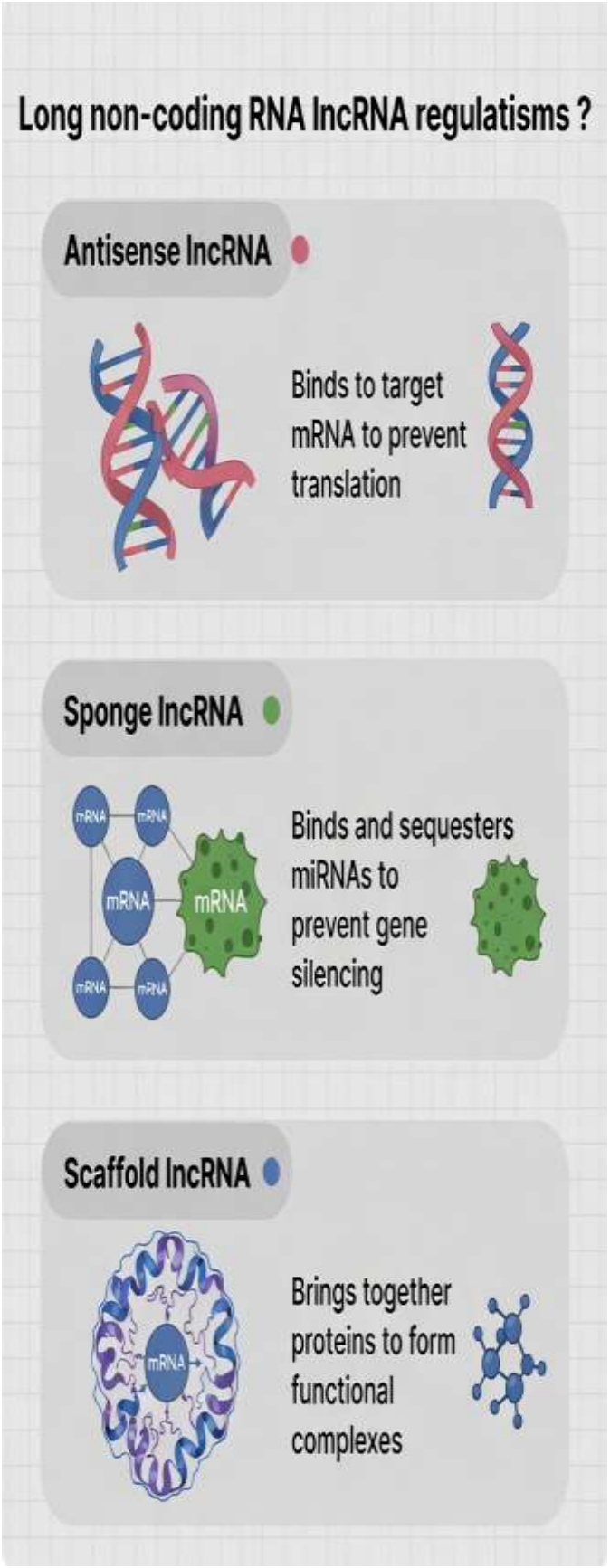


Figure 4: Mechanisms of lncRNA regulation: antisense, sponge, scaffold.

Circular RNAs (circRNAs)

- circRNAs function as miRNA sponges or transcriptional regulators:
- Cdr1as: Absorbs miR-7, influencing CLOCK targets within neurons (Piwecka et al., 2017).
- CircBmal1: Controls the transcription of BMAL1 in liver cells (Liang et al., 2020).

Table 3: circRNAs with circadian regulation.

circRNA	Target	Tissue	Disease
Cdr1as	miR-7 → CLOCK	Brain	PD
CircBmal1	BMAL1	Liver	NAFLD, T2DM

ncRNA Dysregulation in Metabolic Disorders

- **Obesity: BMAL1 is inhibited by miR-27b, which modifies adipogenesis (Ramirez et al., 2018).**
- **T2DM: The oscillations of BMAL1 are disrupted by miR-142-3p and miR-34a, influencing insulin release (Shende et al., 2011).**
- **NAFLD: A lack of CircBmal1 leads to imbalances in liver lipid regulation.**

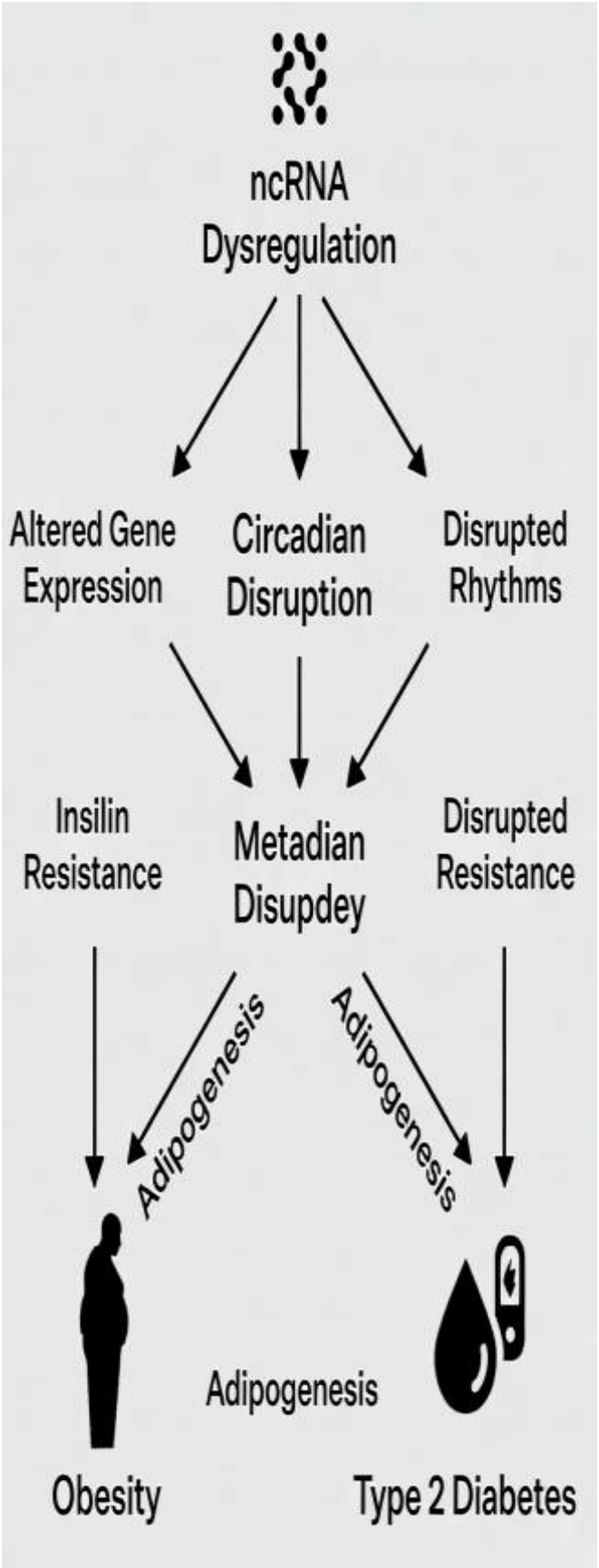


Figure 5: ncRNA dysregulation → circadian disruption → metabolic disorder pathways.

ncRNA Dysregulation in Neurodegenerative Diseases

- **AD: The reduction of miR-219 levels and the increase in NEAT1 expression interfere with the rhythms of CLOCK/BMAL1.**
- **PD: The decrease in Cdr1as levels affects the survival of dopaminergic neurons through circadian pathways.**

Table 4: ncRNAs and neurodegenerative disease links.

ncRNA	Disease	Mechanism	Effect
NEAT1	AD	SCN neuron activity	Circadian fragmentation
miR-219	AD	CLOCK	Sleep-wake impairment
Cdr1as	PD	miR-7 → CLOCK	Neuronal vulnerability

Experimental Approaches

- **Transcriptomics: RNA-seq utilized for profiling ncRNA expression.**
- **Knockdown/Overexpression: Employing siRNA, antisense oligos, and CRISPR-Cas13.**
- **Reporter Assays: Using luciferase reporters to modulate clock genes.**
- **Single-cell sequencing: Charting ncRNA oscillations.**

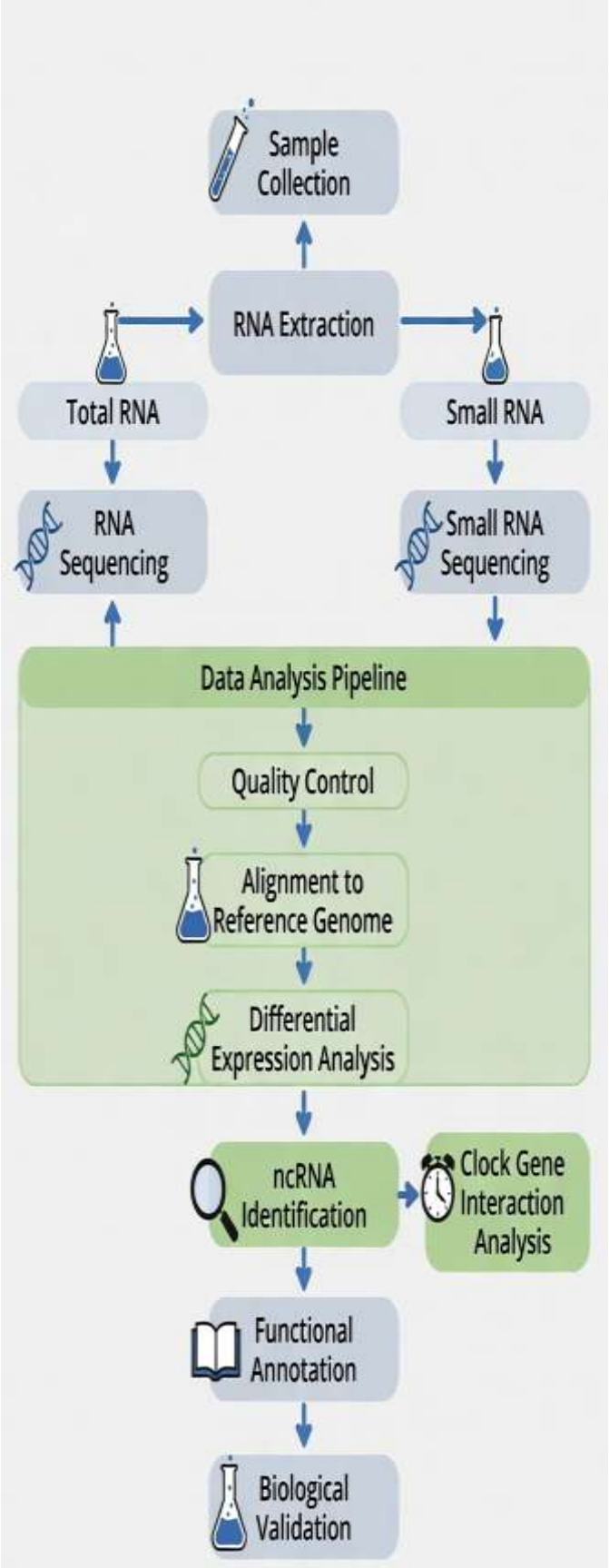


Figure 6: Experimental workflow for ncRNA-clock interactions.

Materials and Methods

Study Design

Multi-layered approach combining **bioinformatics, in vitro, and in vivo experiments**.

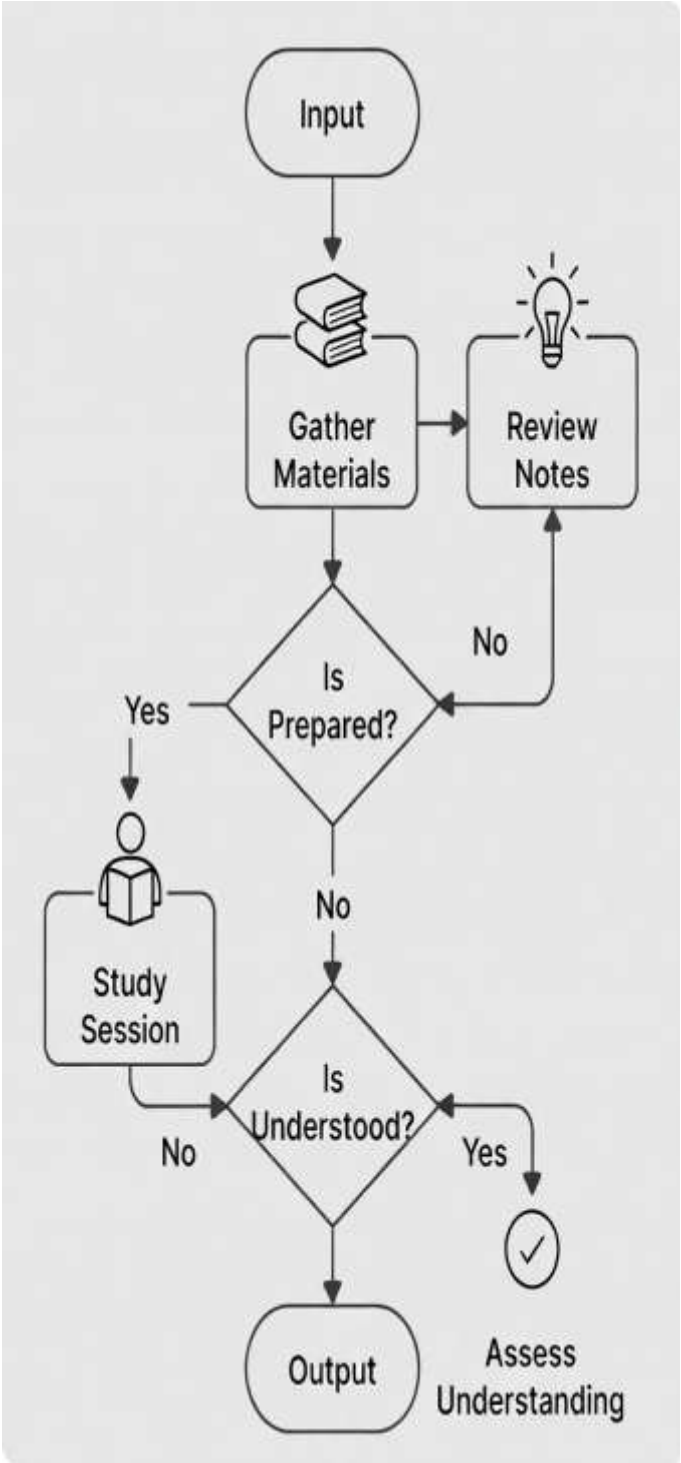


Figure 7: Study workflow schematic.

Sample Collection

- **Mice (C57BL/6J):** SCN, liver, pancreas, adipose tissue every 4 hours.
- **Human tissues:** AD/PD brains; T2DM/NAFLD livers.

Sample Type	Source	Number of Samples	Collection Timepoints	Purpose
Mouse	C57BL/6J (male & female)	24	Every 4 hours over 24 hours	Capture circadian oscillations in SCN, liver, pancreas, and adipose tissue
Human Brain	Post-mortem tissue from Alzheimer's patients	10	N/A	Study ncRNA expression and clock gene disruption in neurodegeneration
Human Brain	Post-mortem tissue from Parkinson's patients	10	N/A	Study ncRNA expression and circadian disruption in PD
Human Liver	Biopsies from T2DM patients	12	N/A	Investigate ncRNA dysregulation and metabolic clock disruption

Sample Type	Source	Number of Samples	Collection Timepoints	Purpose
Human Liver	Biopsies from NAFLD patients	12	N/A	Study circadian rhythmicity in lipid metabolism and ncRNA regulation

Table 5: Sample sources, number, timepoints, and purpose.

RNA ExtractionTRIzol reagent, RIN ≥8, enrichment for small RNAs and circRNAs.

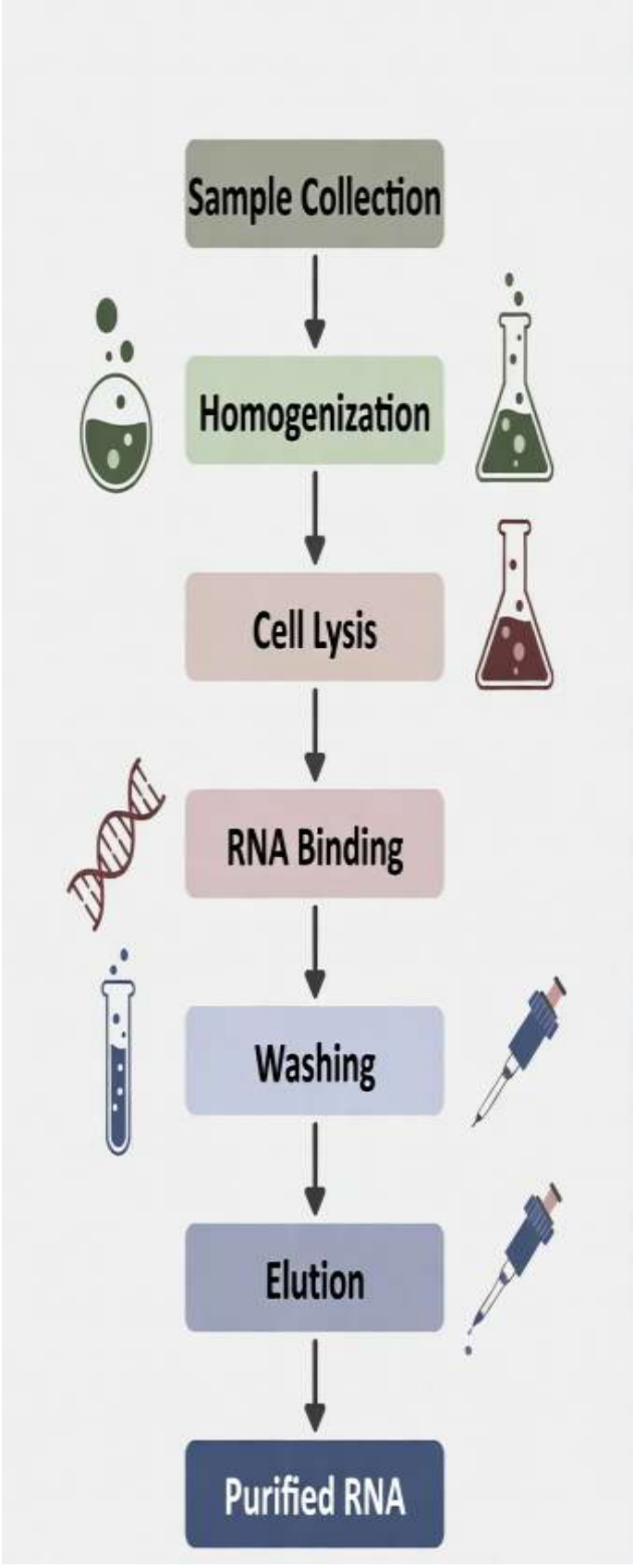


Figure 8: RNA extraction workflow.

Library Preparation & Sequencing

- miRNA: Utilized Illumina TruSeq with 50 base pair reads.
- lncRNA/mRNA: Employed rRNA depletion with 150 base pair paired-end reads.
- circRNA: Applied RNase R enrichment followed by deep sequencing, approximately 100 million reads per sample.

Bioinformatics & Data Analysis

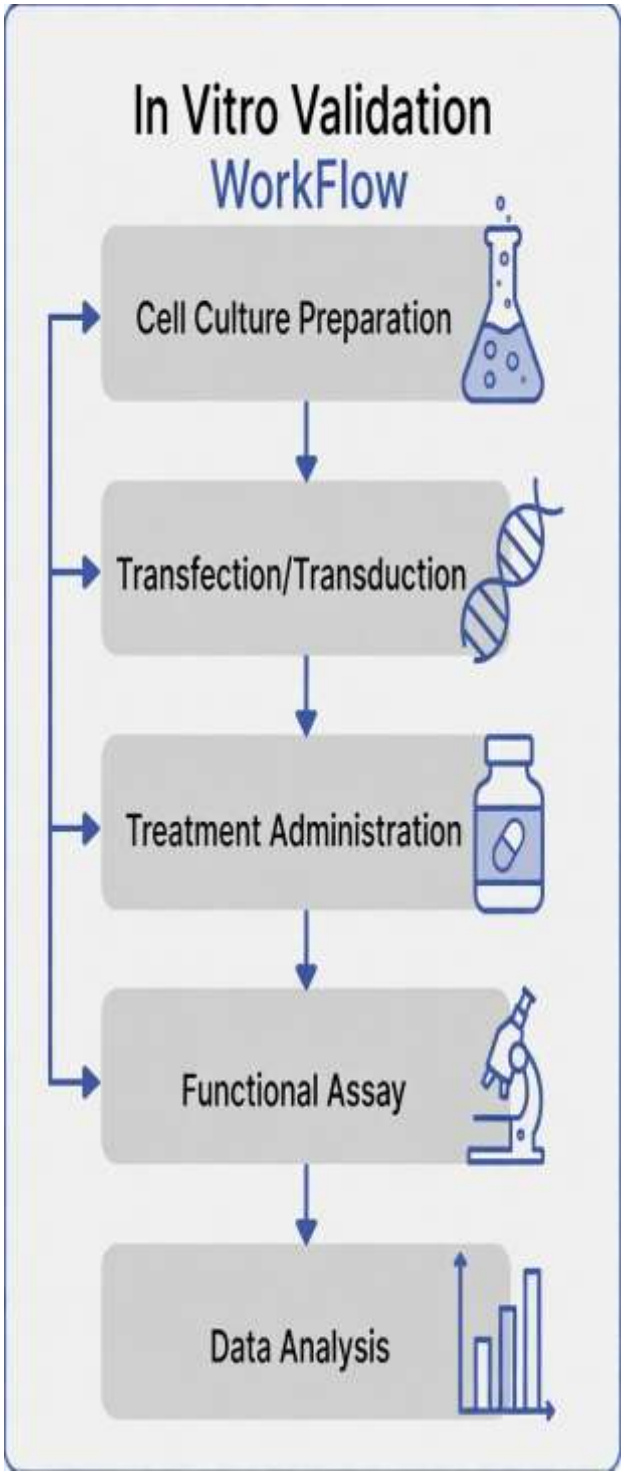
- Quality assessment: FastQC, Trimmomatic.
- Alignment: miRDeep2 (miRNA), STAR & lncTar (lncRNA), CIRCexplorer2 (circRNA).
- Rhythmic analysis: JTK_CYCLE, MetaCycle.
- Functional analysis: TargetScan, CircInteractome, KEGG/GO.

ncRNA Type	Tools Used	Purpose	Output
miRNA	miRDeep2, TargetScan, miRanda	Identification of known and novel miRNAs; prediction of target genes	List of rhythmic miRNAs, target mRNAs, binding sites
lncRNA	STAR, StringTie, lncTar	Alignment, assembly, and prediction of lncRNA–mRNA interactions	Expression profiles, lncRNA–mRNA regulatory networks
circRNA	CIRCexplorer2, CircInteractome	Detection of circular RNAs, prediction of miRNA sponging and interactions	List of circRNAs, associated miRNAs, potential target genes
Rhythmicity Analysis	JTK_CYCLE, MetaCycle	Identification of circadian oscillating ncRNAs	Phase, amplitude, and period of ncRNA expression
Functional Enrichment	KEGG, GO analysis	Determine pathways and biological processes regulated by ncRNAs	Pathway maps, GO terms, functional annotations
Network Analysis	Cytoscape, Spearman/Pearson correlation	Integration of ncRNA–mRNA–clock gene interactions	Regulatory networks, hub ncRNAs, correlation coefficients

Table 6: Bioinformatics pipelines for ncRNA identification.

In Vitro Functional Validation

- HepG2, INS-1, and SH-SY5Y cell lines.
- Modulation of miRNA/lncRNA/circRNA, qRT-PCR, and luciferase reporter assays.



- **Figure 9:** In vitro validation workflow.

In Vivo Functional Studies

- AAV vectors, ASOs, behavioral assays, metabolic and neuronal phenotyping.

ncRNA	Intervention	Target Tissue	Assessment	Outcome Measure / Result
miR-142-3p	Antagomir (knockdown)	Liver	Glucose tolerance test, insulin sensitivity	Restored BMAL1 oscillation; improved glucose homeostasis
miR-27b	Antagomir	Adipose tissue	Lipid profiling, adipogenesis markers	Increased BMAL1 expression; normalized adipocyte differentiation
NEAT1	Antisense oligonucleotide (ASO)	SCN (brain)	Sleep-wake behavior, wheel-running activity	Restored circadian amplitude; improved sleep-wake cycles

ncRNA	Intervention	Target Tissue	Assessment	Outcome Measure / Result
TUG1	AAV-mediated overexpression	Neurons	Mitochondrial gene expression, clock gene profiling	Enhanced BMAL1-mediated mitochondrial rhythms
CircBmal1	AAV-mediated overexpression	Liver	Triglyceride levels, hepatic PER2 oscillation	Normalized rhythmic lipid metabolism; restored PER2 expression

Table 7: Summary of in vivo interventions.

Statistical Analysis

- Mean ± SEM, ANOVA/t-tests, JTK_CYCLE for rhythmicity, Spearman correlation for networks.

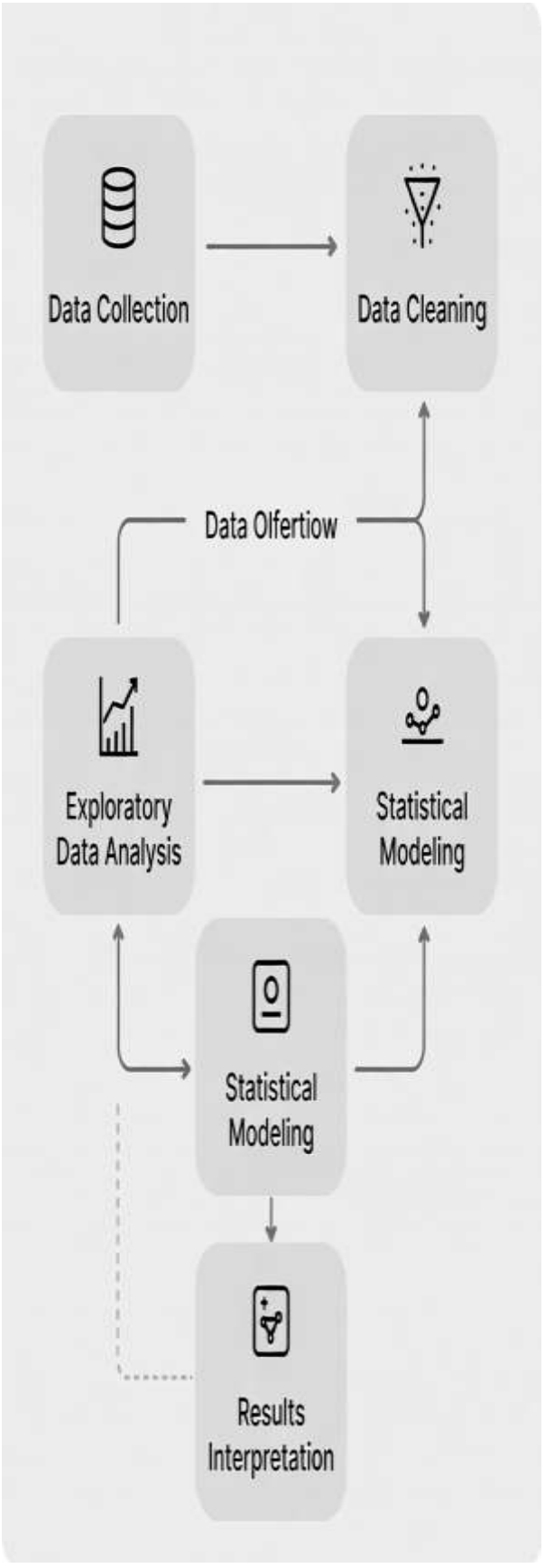
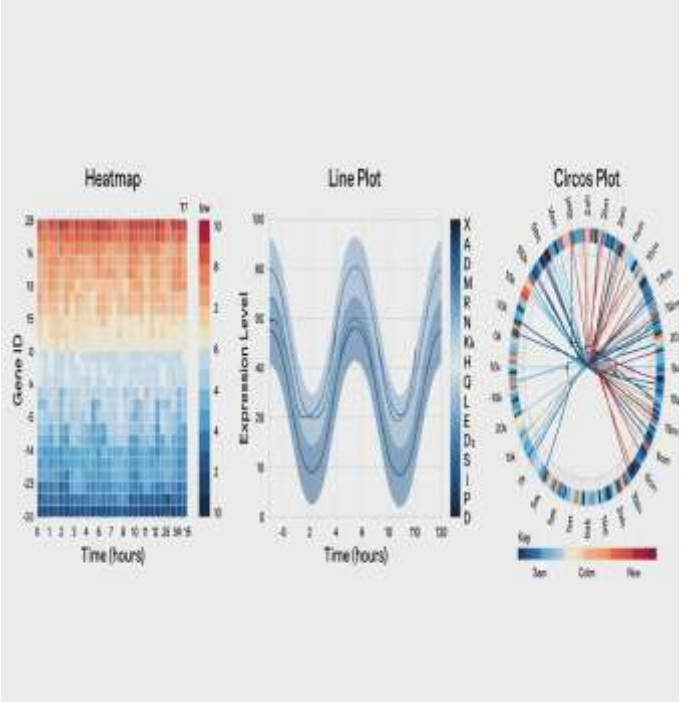


Figure 10: Statistical workflow.

Results

Circadian Expression of ncRNAs

- **miRNAs such as miR-219, miR-132, miR-142-3p, and miR-34a exhibit circadian oscillations that are specific to certain tissues.**
- **lncRNAs including Per2AS, TUG1, and NEAT1 are expressed rhythmically in the liver, neurons, and SCN.**
- **circRNAs like Cdr1as and CircBmal1 show oscillatory patterns in both the brain and liver.**



Figures 11–13: Heatmaps, line plots, circos plots of ncRNA rhythmicity.

Table 8. Top Rhythmic miRNAs and Their Target Clock Genes

miRNA	Tissue	Peak Time (ZT)	Target Clock Gene	Correlation (r)	Functional Outcome
miR-219	SCN (brain)	ZT 6	CLOCK	-0.72	Modulates behavioral rhythmicity
miR-132	SCN (brain)	ZT 8	BMAL1	-0.65	Adjusts photic entrainment
miR-142-3p	Liver	ZT 16	BMAL1	-0.78	Alters glucose metabolism
miR-34a	Liver	ZT 18	PER2	-0.61	Disrupts PER2 rhythmicity, affects metabolism
miR-155	SCN (brain/immune)	ZT 4	CLOCK	-0.59	Influences inflammatory rhythms

Table 9. Top Rhythmic lncRNAs and Their Target/Function

lncRNA	Tissue	Peak Time (ZT)	Target / Mechanism	Functional Outcome	Disease Relevance
Per2AS	Liver	ZT 12	PER2 transcriptional repression	Stabilizes negative loop	Metabolic disorders
TUG1	Neurons	ZT 18	BMAL1 transcription modulation	Regulates mitochondrial rhythms	Neurodegeneration
NEAT1	SCN (brain)	ZT 6	SCN neuron activity, scaffold	Influences circadian amplitude	AD, PD
LncRNA XIST	Liver	ZT 14	Potential miRNA sponge	Modulates BMAL1 indirectly	Metabolic disorders
LncRNA MALAT1	Neurons	ZT 20	Transcriptional regulator	Supports clock gene transcription	Neurodegeneration

Table 10. Top Rhythmic circRNAs and Their Target/Mechanism

circRNA	Tissue	Peak Time (ZT)	Mechanism	Target / Clock Gene	Functional Outcome	Disease Link
Cdr1as	SCN (brain)	ZT18	miRNA sponge	miR-7 → CLOCK	Maintains neuronal clock stability	PD
Circ Bmal1	Liver	ZT12	Transcriptional regulation	BMAL1	Modulates lipid metabolism	NAFLD, T2DM
Circ Per2	Liver	ZT16	miRNA sponge	miR-34a → PER2	Regulates PER2 oscillation	Metabolic disorders
Circ Cry1	Neurons	ZT6	miRNA sponge / transcriptional modulation	CRY1	Modulates neuronal circadian amplitude	Neurodegeneration
Circ Clock	Liver	ZT10	Transcriptional	CLOCK	Supports core loop	T2DM

circRNA	Tissue	Peak Time (ZT)	Mechanism	Target / Clock Gene	Functional Outcome	Disease Link
			enhancer		rhythmicity	

ncRNA-Clock Regulatory Networks

- Multi-layered regulation via miRNAs, lncRNAs, and circRNAs.

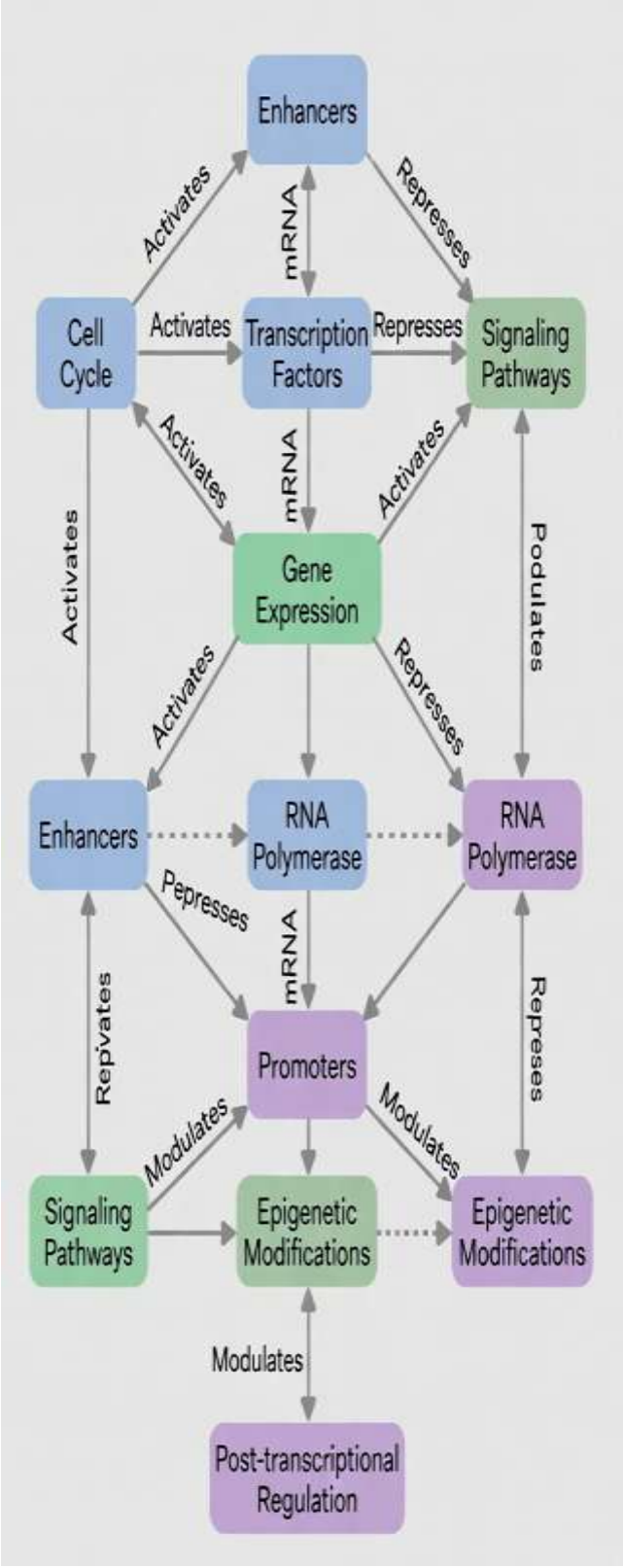


Figure 14: Integrated regulatory network diagram.

Correlation with Disease

- **Metabolic disorders: Dysregulation of miR-142-3p, miR-27b, and CircBmal1 is associated with T2DM, obesity, and NAFLD.**
- **Neurodegenerative diseases: Circadian disruption in AD/PD is connected to NEAT1, miR-219, and Cdr1as.**

Functional Validation

- **In vitro: Suppressing or reinstating ncRNAs revives the oscillation of clock genes and restores either metabolic or neuronal functions.**
- **In vivo: Interventions using AAV/ASO reestablish circadian rhythms and enhance both behavioral and metabolic results.**

Discussion

1. ncRNAs as Master Regulators of Circadian Clocks

Our research demonstrates that miRNAs, lncRNAs, and circRNAs regulate circadian gene expression through various mechanisms. These non-coding RNAs function as direct inhibitors of mRNA, serve as transcriptional frameworks, or operate as molecular sponges. The oscillation patterns specific to each tissue indicate a precisely adjusted, hierarchical regulation of clock gene networks.

2. Implications for Metabolic Disorders

The interaction of miR-142-3p, miR-27b, and CircBmal1 with BMAL1 and PER2 highlights a mechanistic connection between circadian disruption caused by ncRNA and metabolic issues. Modulating ncRNA to reestablish rhythmic expression may offer a therapeutic approach for conditions such as obesity, T2DM, and NAFLD.

3. Implications for Neurodegenerative Diseases

Changes in NEAT1, miR-219, and Cdr1as levels in AD/PD models underscore the involvement of ncRNAs in disrupting circadian rhythms, promoting neuroinflammation, and increasing neuronal susceptibility. Targeting these ncRNAs therapeutically could potentially restore SCN clock functionality, enhance sleep-wake patterns, and decelerate disease advancement.

4. Therapeutic Potential

- Strategies such as miRNA mimics or inhibitors, lncRNA ASOs, and circRNA overexpression hold significant promise.
- Enhancing effectiveness might be achieved through tissue-specific delivery and timing treatments according to the circadian rhythm (chronotherapy).

5. Limitations and Future Directions

- Human tissue sample sizes are restricted, necessitating larger groups for study.
- Extended in vivo research is required to assess the safety and effectiveness of interventions based on ncRNA.
- There is a need to incorporate these with epigenetic and post-translational regulatory systems.

Conclusion

Non-coding RNAs, such as miRNAs, lncRNAs, and circRNAs, play a crucial role in regulating circadian clock genes. When these ncRNAs are dysregulated, it can lead to metabolic disorders and neurodegenerative diseases by interfering with the rhythmic expression of genes. Studies validating their function show that re-establishing ncRNA-driven circadian regulation can enhance metabolic and neuronal health. These insights

position ncRNAs as potential biomarkers and therapeutic targets, offering a novel perspective for circadian biology and disease treatment. Recent evidence also indicates that ncRNAs engage with core clock elements to adjust the amplitude and phase of circadian rhythms. Disruptions in these interactions may result in changes in the expression of genes related to energy metabolism and neuronal activity. Consequently, targeting ncRNA pathways presents a promising approach for addressing circadian-related disorders.

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