



# Circadian Rhythm Dysregulation and Leukemia Development: The Role of Clock Genes as Promising Biomarkers

Anubha Bajaj\*

Department of Health and Clinical Research, India

\*Corresponding Author's E-mail: [anubhabajaj23@gmail.com](mailto:anubhabajaj23@gmail.com)

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## Abstract

The circadian clock (CC) is a day by day gadget that regulates the oscillations of physiological methods and may reply to the outside surroundings so one can maintain inner homeostasis. For the functioning of the CC, the clock genes (CG) act in distinct metabolic pathways via the clock-managed genes (CCG),

Presenting cell regulation. The CC's interruption can bring about the improvement of various diseases, together with neurodegenerative and metabolic disorders, in addition to cancer. Leukemia's correspond to a set of malignancies of the blood and bone marrow that arise whilst changes in ordinary cell regulatory methods purpose the out of control proliferation of hematopoietic stem cells. This overview aimed to partner a deregulated CC with the manifestation of leukemia, searching out viable pathways concerning CG and their viable role as leukemic biomarkers.

**Keywords:** circadian rhythm, leukemia, clock genes, mobileular cycle, biomarkers

## INTRODUCTION

The circadian rhythm, or circadian clock (CC), is a hierarchically cyclic device that regulates the day with the aid of using day oscillations of physiological techniques and can respond to outdoor surroundings changes to preserve internal homeostasis. Because some of the ones outside shifts are due to the 24-h rotation of the Earth, and so are expected to arise approximately at the same time every day, the circadian regulation permits the human organism to count on the ones changes and synchronize them with inner physiology [1].

Starting with within the 1980s, research that culminated with within the characterization of the number one clock gene (CG) in *Drosophila melanogaster* paved the way for the characterization of extra genes and proteins, predominant to what we now understand due to the fact the circadian clock.

For the control, the activation and repression of CC genes

may additionally need environmental stimuli—known as zeitgebers (ZTGBs)—which can be a photic or a non-photic stimulus, wherein the maximum studied are the photic stimuli, or the moderate/dark cycle. They are chargeable for sending signs to the suprachiasmatic nucleus (SCN) with within the vital frightened device, stimulating CG transcription located in peripheral tissues, and promoting cell metabolic functions [2].

The CC response to ZTGBs is based upon at the electricity of the stimulus and the circadian phase during which its miles applied. In addition to being able to synchronize the circadian rhythm beneathneath. Ordinary conditions, the ones standards form an adaptive benefit that the CC transmits to the body. However, faulty exposure to ZTGBs can disturb circadian homeostasis and characteristic risky consequences on human health [3].

Furthermore, the disruption of the CC in mammals can result in the development of numerous diseases, collectively with neurodegenerative and metabolic disorders, further to

cancer. There is Proof that artificial moderate, shift work, and jet excursion can make a contribution to circadian rhythm misalignment [4].

### Circadian Clock Genes

The CC can be divided into operation stages: systemic and mobileular. The vital clock at a systemic scale, known as the “master” clock, is regulated through manner of approach of the SCN with within the anterior hypothalamus and is chargeable for coordinating the cell-self-sustaining clocks in peripheral tissues, further to extraordinary thoughts regions, immediately via neural and humoral signs, even as it's miles given a stimulus from an outdoor surroundings, collectively with moderate change, temperature, sleep deprivation, and feeding. At the mobileular level, the CC is regulated through manner of approach of excessive first-class and awful transcription-translation remarks loops (TTFL), which control the rhythmicity of mobileular, metabolic, and physiologic sports The clock is driven absolutely through manner of approach of the transcription of the easy helix-loop-helix (bHLH) genes CLOCK (circadian clock regulator) and BMAL1/ARNTL (thoughts and muscle Arnt-like protein-1, moreover known as aryl hydrocarbon nuclear receptor translocator-like), and the Per-Arnt-Sim (PAS) gene NPAS2 (neuronal PAS vicinity protein 2) CLOCK/BMAL1 and NPAS2/BMAL1 form a heterodimer that, even as occupying the Enhancer field (E-field) regions on their promoting goal, will stimulate the expression of the middle clock genes, collectively with PER1/2/3 (period circadian clocks 1, 2, and 3, respectively), CRY1/2 (cryptochrome circadian clocks 1 and 2, respectively), and TIM (timeless) The higher expression of PER, CRY, and TIM permits them to bind to the CLOCK-BMAL1 and NPAS2-BMAL1 complexes and inhibit their expression, constituting the awful control [5].

In the early hours of dawn, even with the binding of the CLOCK-BMAL1 complex in its purpose E-area sequence, the immoderate levels of CRY and PER bind to this complex and inhibit their transcription, growing the repressive law. Consequently, CRY and PER repress their non-public expression, and thru manner of method of the sunrise, the dearth of producing of CRY and PER proteins motives reduced levels with withinside the cellular nucleus and, with withinside the absence of binding to CLOCK-BMAL1, permits the ones complexes to start their transcription, growing the active law [6]. In the early evening, due to the immoderate expression of CG at a few degree withinside the day, the levels of CRY and PER rise again; in this manner, they manipulate to enter the nucleus thru manner of method of binding with casein kinase 1 epsilon (CK1ε), constituting the PER-CRY-CK1ε complex, and they suppress the excessive excellent transcription of CLOCK-BMAL1, therefore restarting another cycle.

### Clock Gene Dysregulation and Disease Development

The CC controlled thru manner of method of CGs has

advanced over hundreds of tens of lots and lots of years thru manner of method of effectively orchestrating the metabolism, isolating and dividing metabolic techniques like anabolism and catabolism, and optimizing the metabolic overall performance of intervals of feeding and fasting [7].

Thus, the CC contains a vital pacemaker in severe tissues and modulates a large range of metabolic targets, which encompass insulin sensitivity, LDL cholesterol synthesis, fat oxidation, and power expenditure. Furthermore, there may also be evidence to suggest that the disruption of the CC will growth the danger of metabolic diseases, proving all another time that it is a critical physiological regulator [8].

The CC can also motive the misalignment of nutrient flows and make a contribution to the pathophysiology of type 2 diabetes mellitus at the tissue level. Insulin resistance is also a essential determinant of the disease. CLOCK and BMAL1 adjust the muscle's sensitivity to insulin via changes in protein stages and membrane translocation of the insulin-sensitive glucose transporter (GLUT4). There is also a energy of the CC on the interruption of the pancreatic clock, causing an ailment in insulin secretion.

Studies have confirmed that the interaction of CGs and neoplasms—together with many mobileular capabilities, which encompass the cell cycle and cell division—are controlled in detail with the useful resource of the use of components of the molecular clock In the cell cycle, CGs act as crucial regulators in particular degrees, wherein they might each stimulate or save you cell proliferation. The cell cycle consists of four critical degrees—G1 (pre-replicative), S (synthesis), G2 (post-replicative), and M (mitosis and cell division)—specifically controlled with the useful resource of the use of the interest of cyclins, cyclin-set up kinases (CDKs), and CDK inhibitors (CDIs). In among each of these degrees there are checkpoints that have a look at whether or not or now no longer the DNA replication modified into a success and decide whether or not or now no longer the cell will maintain to the subsequent section or if the cycle can be interrupted. These cell cycle manage mechanisms have been confirmed to have genes that can be regulated with the useful resource of the use of CGs, called clock-controlled genes (CCGs).The CCGs, particularly Myc, Wee1, p21, p53, and cyclins genes, have already been reported in special forms of maximum cancers, in which their expression or suppression can make contributions to pathology development and development Thus, out of manage cell proliferation is a hallmark of maximum cancers, and the price of proliferation is predicated upon on the cell cycle Clock Genes' Role with in the Leukemia Pathway [9].

Leukemia's are a set of malignancies of the blood and bone marrow that arises at the same time as adjustments in everyday mobileular regulatory techniques motive the out of manage proliferation of hematopoietic stem cells. This employer of ailments is typically categorized into subtypes defined with the useful resource of the use of cell lineage that can be each lymphocytic and myeloid, and in line with

the kind and diploma of cell maturation, with the ones being acute or chronic [10].

Among the causes, leukemia's might be superior because of reciprocal chromosomal errors or chromosomal deletions, in addition to elemental mutations and epigenetic adjustments. It is frequently assumed that the ones errors in maximum cancers cells are as a consequence of out of manage cell cycle development, specifically because of the truth cell cycle checkpoints fail and lead the cell to end up cancerous.

We already realize that the CG and the cell cycle are robustly coupled, cooperating for correct cell functioning, and the dysregulation of the CC may have an impact on cell homeostasis and promote maximum cancers development. Therefore, regardless of the reality that the abilities of the CC in normal frame shape are clear, studies that portray its adjustments in maximum cancers, at the side of leukemia's, are lacking, and leaving a gap with within the clarity and description in their abilities in neoplastic cells. For this reason, the purpose of this take a look at is to research and grow to be aware about the feature of circadian rhythm clock genes in leukemia development, and the further implications.

## DISCUSSION

The Period genes, as described before, are important to manipulate the terrible expression of the circadian clock, and disruption in the ones genes' expression will bring about dysregulated clock-controlled gene expression. These adjustments can need cancerous cells' proliferation and life, at the same time as the defective cells will now not undergo apoptosis. For instance, PER1 and PER2 proteins have already been described as tumor suppressors in maximum cancers cell cultures, as nicely in animal experiments.

In the cell cycle, immoderate ranges of PERs inhibit c-Myc gene transcription with the useful resource of using binding to its E-box sequence, stopping cyclin D1 expression and cell proliferation and, at the same time as necessary, inducing apoptosis. On the contrary, at the same time as the ranges of PERs are low, the c-Myc/cyclin D1 mechanism may be over activated, so you can increase cell proliferation.

In the studies found, PERs have been demonstrated to be extensively down regulated in all four varieties of leukemia patients compared to healthy controls. Moreover related an up-regulation of Myc and cyclin D1 expression in CLL patients compared to the controls. These results be given as real with the pathophysiology of the PER genes already described in distinct varieties of maximum cancers, wherein decreased PER expression seems to be related to prolonged aggressiveness and a worse prognosis, indicating that the equal mechanism possibly moreover takes region in leukemia. Accordingly, Yang et al. installed that patients afflicted with each AML or ALL simplest had prolonged ranges of PER1 and PER3 at the give up of their treatment, respectively, indicating that this immoderate expression

of the Period genes might also play an lively feature in tumor suppression in leukemia, as described in distinct maximum cancers kinds. In this way, the PER genes can also additionally need to emerge as a possibly biomarker for the perception of the pathology development at the same time as the PER ranges are low, as nicely for an fantastic response in leukemia treatment at the same time as their ranges are prolonged.

## CONCLUSION

In this review, clock genes have been examined to have a vital effect on cellular cycle development, and consequent dysfunctions in CGs bring about changes within the normal cellular functioning, regularly inducing constant cellular proliferation and stopping apoptosis. PER1/2/3, BMAL1, CLOCK, REV-ERB $\alpha$ , and PPAR $\alpha$  have been down regulated in all sorts of leukemia, suggesting their cappable characteristic in leukemic improvement. Moreover, NPAS2, CK1 $\epsilon$ , and SHARP1 have been up regulated in leukemia; but their expression modified into limited to as a minimum one or subtypes of leukemia. In addition, CRY1/2 and TIM genes showed particular regulation ranges in leukemic cells; thus, more studies is essential to be able to display and affirm their function within the disease. In short, this newsletter pointed to the CGs as promising leukemia biomarkers; but, more in vitro and in vivo experiments, further to medical trials, are required for a better elucidation of CGs' involvement in leukemia biology, aiming to enhance the diagnosis, prognosis, and sufferers' medical follow-up.

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