Why do cancer cells break from host circadian rhythm? Insights from unicellular organisms

Aliaa A. Alamoudi1,2

1 Clinical Biochemistry Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
2 Stem Cell Unit, King Fahad Medical Research Center, Jeddah, Saudi Arabia

Correspondence
Aliaa A. Alamoudi, Clinical Biochemistry Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. Email: aaalamoudi2@kau.edu.sa

Abstract
It is not clear why cancer cells choose to disrupt their circadian clock rhythms, and whether such disruption governs a selective fitness and a survival advantage. In this review, I focus on understanding the impacts of clock gene disruption on a simpler model, such as the unicellular cyanobacterium, in order to explain how cancer cells may alter the circadian rhythm to reprogram their metabolism based on their needs and status. It appears to be that the activation of the oxidative pentose phosphate pathway (OPPP) and production of NADPH, the preferred molecule for detoxification of reactive oxygen species, is a critical process for night survival in unicellular organisms. The circadian clock acts as a gatekeeper that controls how the organism will utilize its sugar, shifting sugar influx between glycolysis and OPPP. The circadian clock can thus act as a gatekeeper between an anabolic, proliferative mode and a homeostatic, survival mode.

KEYWORDS
cancer, circadian clock, cyanobacteria, NADPH, oxidative pentose phosphate shunt

INTRODUCTION

A strong relationship has been suggested between circadian clock disruption and cancer.1-3 Indeed, mutations of clock genes and disruption of the circadian clock have been associated with increased risk of cancer and cancer progression.4,5 However, the exact mechanisms by which a disrupted clock can favor tumorigenesis and tumor progression are not yet fully understood. It is also not clear whether—and if so, how—a disrupted clock governs a selective fitness advantage for cancer cells. One way to look at this is through cancer evolution. Cancer cells need to evolve to compete for limited resources and space.6 In order to do so a cancer cell would need to become independent from the host, and break loose from any tissue control that regulates its proliferation6; and one could speculate that this might include developing metabolic cycles reminiscent of those in unicellular organisms, that are at odds with circadian control of metabolism.7 Given the circadian clock’s tight control over cell metabolism, a disrupted clock can play an essential role in reprogramming cancer metabolism, which is an essential hallmark of cancer development and progression. Around 50% of mouse liver metabolites show circadian variation, and 28% of all metabolites in U2OS cells were found to be clock-controlled and produced in a rhythmic fashion.8 Furthermore, clock genes control the expression of key metabolic enzymes, in addition to mitochondria morphology (fusion and fission) and function, as reflected by changes in the cyclooxygen-consumption rate.9 However, questions concerning the evolutionary function of circadian rhythms and their role as tight metabolic regulators in normal cells, and how cancer cells might manipulate this control, remain unanswered.

Circadian oscillators are believed to have evolved in all organisms to anticipate an organism’s metabolic needs in association with the day-and-night cycle. In addition, circadian control over reproduction and cell division is believed to have evolved to avoid the effect of harmful radiation of the sun, or, according to a second hypothesis, to temporarily separate DNA replication, protecting it thus from reactive oxygen species (ROS) associated with oxidative metabolism.10 This is seen in yeast cells, which show various metabolic cycles yet strictly limit DNA replication to the reductive cycle while stopping it during oxidative cycles.11 In that sense, the temporal partitioning of various metabolic
Circadian clock governs reproducible fitness in cyanobacterium

The clock system has been conserved in all organisms, from prokaryotes to mammals. Cyanobacteria retain one of the simplest forms of the circadian clock, and they have been extensively studied to understand how these circadian rhythms are generated and how they are influenced by environmental stimuli. The circadian clock system governs reproducible fitness in cyanobacteria. When grown separately in pure cultures, arrhythmic and dampened-rhythm strains of cyanobacteria do not differ in their rate of growth compared to wild-type (WT) strains, whether in rhythmic light/dark conditions (LD) or constant light (LL). However, when cultures compete together in a mixed environment, WT strains outcompete mutated strains in LD 12:12 cycles. Interestingly, however, mutated strains compete effectively or even outgrow WT strains in constant light, indicating that a functioning clock could be a disadvantage in constant arrhythmic environments—in this case, of course, the zeitgeber was the external light. Given the photosynthetic nature of cyanobacteria, a non-functioning clock may allow for continued photosynthesis, and thus unchecked growth. In addition, reports have shown that cyanobacterial strains with a free-running period (FRP) that runs closely to the LD cycle also tend to outcompete other strains in LD cycles, but not in constant arrhythmic cycles. Such observations indicate that the reproducible fitness of an organism—in this case, cyanobacteria—relies on the interaction between its molecular circadian clock and its environmental cycles, rather than just an inherent function of the molecular clock’s transcription factors that might induce growth disturbances when mutated.

It is what happens at night: carbon flux to the oxidative pentose phosphate pathway is essential for ROS detoxification

The importance of an FRP matching the lengths of day and night has also been associated with plant growth. Interestingly, however, a functioning clock that matches the lengths of day and night may not only be important for the photosynthesis machinery in plants but also, perhaps more importantly, for controlling starch degradation at night to avoid sugar deprivation. Indeed, the rate of starch degradation abruptly adjusts to the onset of darkness, to avoid starch exhaustion, which can ultimately affect maintenance and growth at night. Metabolic regulation to ensure homeostasis during the dark phase is a common theme among photosynthetic organisms. Cyanobacteria maintain a temporally partitioned metabolism in which anabolism occurs mainly during the day and catabolic activities at night. One major metabolic activity that occurs during the day in cyanobacteria is...
FIGURE 1 Circadian clock controls sugar flux during the day and night in cyanobacteria to ensure homeostasis. During the day, the circadian clock redirects carbon flux (glucose) to the OPPP to produce NADPH for ROS detoxification to ensure homeostasis and survival during the night time. During hours of light, glucose is utilized mainly for glycolysis for synthesis of intermediate building blocks that can be used for proliferation and ensuring reproducible fitness. This dynamic is controlled via and interplay between both the circadian transcription machinery and cellular redox, represented by the NADPH/NADP ratio.

The accumulation of excess photosynthate as energy stores, via the synthesis of glucose polymers, or glycogen.[30,31] Similar to starch degradation in plants, mutations in glycogen biosynthesis can hinder the cell growth of cyanobacteria in LD cycles.[32] Interestingly, apart from its role in energy storage for the night, glycogen degradation plays a role as an “electron sink” that can neutralize excess ROS under high light intensity.[25,33,34]

This happens because the majority of carbon flux produced from glycogen degradation is redirected to the oxidative pentose phosphate pathway (OPPP) rather than to glycolysis, to produce NADPH, the preferred molecule for ROS detox when photosynthesis is inactive.[25,35]

The activation of the OPPP appears to be a critical process for night survival, as the inactivation of OPPP genes appears to affect cell growth in LD cycles.[36] These results are consistent with data showing the importance of NADPH balance for regulating diurnal metabolism in Synechocystis PCC 6803, in addition to other findings describing that the fitness advantage of the circadian rhythm in S. elongatus is due to its ability to anticipate the approach of dark, rather than to anticipate the morning period.[37] In continuous light cycles, however, Cyanobacteria can depend on photosynthesis for NADPH production.[25,35]

Therefore, the homeostasis of metabolic changes during the day and night is clearly essential for the survival and reproducible fitness of such organisms. The day induces daytime metabolic programs for anabolism, while night stimulates cellular redox maintenance to detoxify ROS that have accumulated during the day (Figure 1). The shift and transition from the photosynthetic pathway to oxidative metabolism in OPPP are not only controlled by circadian transcription regulation, but also by cellular redox, represented by the NADPH/NADP ratio.[25] (Figure 2). Darkness was also found to induce redox regulation in Arabidop-

FIGURE 2 The link between circadian clock and NADPH. The transcriptional circadian clock regulates the OPPP, which in turn produces NADPH, which can regulate the expression of circadian clock genes. NADPH can also activate Prx required for ROS detoxification.

The crosstalk between circadian regulation and cellular redox is critical for cyanobacterium survival

The link between circadian regulation and redox control has been further shown in cyanobacteria with mutant Rpa A,[35] a conserved circadian transcriptional regulator that normally peaks close to dusk to activate nighttime metabolic processes. Strains with mutant Rpa A were found to accumulate high levels of ROS and were unable to detoxify those levels at night, leading to cell death.[35] Interestingly, Rpa A was essential for activating OPPP genes, which in turn were essential for NADPH production.[35] The close link between the OPPP and circadian clock was further demonstrated with a study showing that pharmacological and genetic methods of inhibiting OPPP resulted in a disturbed circadian clock in human U2OS cells, in addition to mouse tissue and Drosophila.[38] The inhibition of PPP appeared to alter the period and phase of the circadian transcripts in a NADPH-dependent manner (Figure 2).

The shifting between the photosynthetic and anabolic status, and the homeostatic status during night regulates the survival and reproducible fitness of photosynthetic organisms. Circadian regulation is a key regulator for this shift. Indeed, cyanobacteria with clocks locked in the day mode (disrupted KaiA expression) showed increased oxidative stress and metabolic imbalance, resulting in decreased viability in LD cycles.[39] while those with a clock locked in night mode (disrupted KaiC) showed a survival mode that perhaps allows growth but at the expense of competitive fitness.[24,25]

We can conclude that maintaining cellular redox is undoubtedly critical for the survival of organisms such as cyanobacteria. Ensuring that the sugar sources are utilized for redox homeostasis, through the efficient production of NADPH when photosynthesis and thus the alternative NADH production stop, is essential for an organism’s viability.
Circadian output is a key player that orchestrates this metabolic change between day and night by regulating rate-limiting steps in metabolism. In a sense, the circadian clock can act as a gatekeeper that controls how energy will be utilized in an organism and redirects it based on internal and external stimuli.

Do cancer cells “want” to behave similarly to unicellular organisms with respect to circadian metabolic effects?

Unicellular organisms that are locked in the day or night mode might show an imbalance between their proliferation rate and reproducible fitness, and their cellular homeostasis and cell survival. Thus, a regular shift between metabolic pathways is needed. These cells would need to ensure that ROS detoxification is maintained regularly. However, a different story could be speculated for cancer cells. Despite the metabolic plasticity seen in cancer cells, a constant switching between metabolic pathways might not be favorable for a cancer cell. In one way such switching could act as a checkpoint halting cell cycle and cell division. In addition a regular phase of ROS detoxification might not be essential or even beneficial for a cancer cells. ROS can strongly mediate tumorigenesis and tumor progression, an observation that has been widely studied.\[40–42\] Such an effect is not only due to hypermutations arising from ROS-mediated genomic instability, but also by oxidation-mediated regulation of important oncogenic and tumor suppressor proteins such as inactivation of the tumor suppressor PTEN.\[43,44\] However, despite the importance of ROS for tumor development, cancer cells need also to regulate ROS detoxification, as excessive ROS can induce apoptosis and cell death. This would be specifically true at times in which cancer cells might be undergoing stress such as during metastasis and anti-cancer therapy.\[45\] Simply put, cancer cells need to regulate ROS generation and detoxification but at different times than their normal counterparts. Controlling their own metabolism and breaking loose from tissue signals that regulate it would therefore provide cancer cells with reproducible and survival fitness. To elaborate more on this speculation, it would be important to discuss more extensively what is currently know about cancer metabolism, and the role of circadian clock machinery therein. That is the aim of the following sections.

Cancer cells reprogram their energy metabolism

Cancer cells adjust and reprogram their energy metabolism to maintain cell division and proliferation, which is considered one of their essential hallmarks.\[46,47\] One of the main outcomes of the reprogramming is a rapid production of metabolic intermediates necessary for cell growth. To achieve this, cancer cells “prefer” glycolysis to oxidative phosphorylation (OXPHOS), despite the presence of oxygen and functional mitochondria—a phenomenon known as the “Warburg effect.” However, this appears to be true in a cell-type-specific manner, because many cancer cells also rely on OXPHOS.\[48–50\] Despite the low ATP yield, glycolysis ensures a rapid and constant supply of intermediates, which can serve as a supply of building blocks, such as nucleotides.

In recent years, great interest has also been directed towards tumors’ ability to modulate the PPP (pentose phosphate pathway), both directly and indirectly.\[51,52\] The PPP—which branches from glycolysis after the first committed step of glucose metabolism and the synthesis of glucose-6-phosphate—can be divided into two phases: the oxidative branch, which generates NADPH and ribonucleotides, and the non-oxidative branch, which comprises a series of reversible reactions that interconvert glycolytic intermediates and pentose phosphates. The different phases and the reversible nature of this pathway make it essential for the cell, allowing the cell to adapt to its metabolic needs. For example, if cells are under stress, the pathway is directed toward increasing the oxidative phase, synthesizing NADPH, and directing the non-oxidative phase toward replenishing glucose-6-phosphate to restart the cycle. On the other hand, rapidly dividing cells direct the non-oxidative phase toward utilizing the glycolytic intermediates to synthesize pentose phosphates, which are used for DNA synthesis.\[52\] This has been nicely shown with oncogenic kRAS in pancreatic ductal adenocarcinoma (PDCA). The oncogenic pathway appears to direct glucose carbons to the non-oxidative pathway of PPP without altering the oxidative pathway.\[53\] However, when comparing metastatic sub-clones of PDAC with primary tumors or locally infiltrating clones, metastatic clones seem to rely on the oxidative pathway of PPP.\[54\]

Various onco-proteins and tumor suppressors have been found to modulate both phases of the PPP by regulating various mechanisms, such as the expression and activity level of PPP enzymes.\[52,55,56\] Overall, the PPP mainly depends on the availability of sugar, and several of the regulatory mechanisms introduced so far for the oncogenic regulation of the PPP rely on controlling the glucose flux. Despite the importance of aerobic glycolysis in some tumors, it is also becoming apparent that cancer cells are characterized by metabolic plasticity, which allows them to switch between glycolysis and OXPHOS, to adjust their metabolism according to their needs and microenvironment.\[57\] The plasticity of cancer cells’ metabolism can be demonstrated, for example, with matrix-detached cancer cells. Unlike blood cells, epithelial cells and cancer cells of epithelial origin similarly need to be attached to the extracellular matrix. Matrix detachment was found to induce metabolic stress and the loss of glucose transport, leading to ATP deficiency.\[58\] In addition, matrix detachment induced ROS production in detached cells. Interestingly, ATP deficiency can be rescued in mammary epithelial cells through the overexpression of ErBb2, which is dependent on glucose flux to the PPP.\[58\] Treatment with an antioxidant could also rescue ATP deficiency without enhancing glucose uptake;\[58\] thus, showing the importance of the PPP in scavenging the ROS to ensure the survival of metabolically stressed cells during matrix detachment. However, cancer cells must detach and extravasate to metastasize. Cancer cells require sufficient ATP to endure the metabolic stress associated with this process. This can be obtained from catabolic processes, through increasing fatty acid oxidation and/or enhancing OXPHOS, which both require NADH and NADPH in return, as a reducing power against oxidative stress.\[59\]
Overall, it appears that, similarly to unicellular organisms, the homeostasis and balance between utilizing sugars for anabolic processes, and utilizing it for scavenging ROS, is essential for the reproductive fitness (cell division) and survival of cancer cells. However, despite the importance of glucose in cancer metabolism it is important to acknowledge that given the metabolic plasticity of cancer cells these cells can heavily rely on various nutrients other than glucose for ATP and NADPH production.[60–63] Fatty acids (FA) have been extensively described as a major fuel that cancer cells utilize either through de novo synthesis or exogenous uptake.[64] Accumulated FA in cancer cells not only plays a role in lipid metabolism, which is essential for cancer proliferation, but is also an essential source of ATP and NADPH during metabolic stress.[64,65] Beta-oxidation of stored lipid results in the oxidative degradation of FA to generate acetyl-CoA, which can subsequently enter the TCA cycle for the generation of NADH and FADH2 required for electron transport chain. Indeed FA oxidation can lead to a much higher yield of ATP than glucose oxidation. In addition, it is known that TCA intermediates can be a source of NADPH, for example through the decarboxylation of isocitrate to alpha ketoglutarate by isocitrate dehydrogenase 2 and 3, or the conversion of malate to pyruvate in the cytosol. Moreover, studies have shown that FA oxidation can supply ATP and NADPH to protect against ROS toxicity in tumor cells.[64,65]

Similar to FA, glutamine is considered a major nutrient for tumors. Not only does it act as a major source of macromolecules, but it can also be a substrate for oxidative metabolism.[60,62] Indeed many tumor cells display an oncogenic dependency or “addiction” to glutamine in cell culture,[66,67]; in addition, glutaminolysis is considered a tumor hallmark. Overall glutaminolysis supplies glutamate for the TCA cycle while glutamine derived malate can be metabolized in to pyruvate via maleic enzyme resulting in the release of NADPH. Interestingly, a few studies have confirmed that sustained NADPH generated from this pathway can play a role in redox homeostasis as seen in pancreatic cancer cells for example.[68]

However, despite the reliance on various nutrients it is worth mentioning that this appears to be dependent on tissue context, and the mechanisms remain to be elucidated. For example, despite the reliance on glutamine metabolism for proliferation in vitro, when grown in vivo lung tumors are dispensable of glutamine and rely on glucose as a major carbon source for TCA.[69] Furthermore, lipid metabolism dysregulation appears to vary across various tumors and various molecular subtypes.[61]

Cancer cells might choose to disrupt circadian machinery to stop the switching between metabolic pathways at different stages of tumorigenesis

As discussed above, the transcriptional circadian clock, together with the cell’s reducing power (NADPH), can act as a gatekeeper that control how an organism will utilize energy. Such gatekeepers can redirect energy based on the organism’s demand and internal and external stimuli.

FIGURE 3 The Proliferative versus survival mode of a cancer cell.
An early-stage tumor is in a highly proliferative state. High glucose availability allows high glycolytic rate to supply intermediate building blocks of metabolism, while limiting oxidative phosphorylation. Glucose diverted to the PPP would mainly be utilized in the non-oxidative pathway to ensure nucleotide synthesis. Cells show less oxidative stress and thus less demand for NADPH. Cells that need to metastasize show less glucose uptake, are metabolically stressed, and require energy from OXPHOS, and therefore may require a higher supply of NADPH in order to maintain their redox status and ensure their survival. A disrupted clock ensures that one mode dominates over the other, according to the cell’s needs.

Similarly to unicellular organisms, cancer cells may alter their status depending on the context and cell demand (Figure 3). This metabolic plasticity allows cells to tailor their metabolic needs and energy demands throughout the various stages of tumor progression, allowing cancer cells to face challenges of oxygen and nutrient scarcity and therapeutic interventions.[70,71] Some studies have shown metabolic heterogeneity related to tissue of origin, for example, liver colorectal and lung cancer showing a glycolytic preference.[72,73] However, of even more interest is the importance of metabolic plasticity and adaptability to metastatic phenotypes, an area where ever more studies show that switching between glycolysis and OXPHOS might be an essential mechanism to help cells adapt in hostile conditions, specifically those associated with metastasis.[57,75]

An early-stage tumor contains cells that are undergoing high proliferation and thus depend on glycolysis intermediates. These cells would therefore need a high supply of glucose, a high rate of glycolysis, and a constant supply of NAD to maintain glycolysis, which can be gained by the interconversion of lactate–pyruvate. In addition, any glucose diverted to the PPP would mainly be utilized in the non-oxidative pathway to ensure nucleotide synthesis. These cells may also show less oxidative stress and thus less demand for NADPH. In that sense, the cells need a steady phase of glycolysis without much switching toward OXPHOS or diverting of the sugar toward the OPPP at this phase. The cells, thus, maintain a constant environment in which cellular redox is maintained, represented by the NADH/NAD ratio. Given the limited OXPHOS, the cells do not sense the urge to divert their sugar toward the OPPP for NADPH production. A functional clock, which could
switch their metabolism toward the oxidative pathways, would slow their glycolytic machinery and thus slow their growth, thereby being disadvantageous for their reproductive fitness. However, OXPHOS is not necessarily defective in cancer cells, merely uncoupled from glucose uptake; that is, OXPHOS does not increase at the same rate it would be expected to give the increased glucose uptake. If so, the cell would still need to maintain OXPHOS to ensure the proper scavenging of ROS. In that case, the cancer cell may compromise its cellular redox homeostasis for the sake of fast proliferation. Cells at this stage may also make use of the tumor-promoting features of ROS, such as direct DNA damage, hence enhancing carcinogenic transformation. On the other hand, cancer cells that metastasize and detach from the matrix show less glucose uptake, are metabolically stressed, might demand a larger supply of ATP energy from OXPHOS, and therefore may require a higher supply of NADPH in order to maintain their redox status and ensure their survival. In essence, these cells might maintain their survival mode and ensure homeostasis over fast proliferation. In that case, such cells clearly need a diurnal shift in their metabolism. They need to start with glycolysis but ensure a functioning clock that can allow them to shift their carbon toward oxidative pathways. This is supported with evidence showing that OXPHOS activity in breast cancer cell lines increase with metastatic potential. In addition, in an orthotopic xenograft model, circulating cancer cells appeared to rely on OXPHOS more that primary tumor or metastatic cells, indicating that invasive cells might favor OXPHOS and ATP production because their survival depends on mastering the upcoming hostile and stressful challenges.

Circadian clock machinery regulates key metabolic enzymes and proteins

The circadian clock plays a role in cancer development and progression by regulating several tumor hallmarks such as cell cycle and cell proliferation, DNA damage repair, and apoptosis. Given the wide array of metabolic elements regulated by the circadian clock, it would be expected to play a role in cancer through altering tumor metabolism. However, very few studies have started to establish this link, and such links remain supported through indirect evidence.

The circadian rhythm is believed to control and regulate daily metabolism, mainly by regulating key metabolic enzymes. When using a mass-spectrometry-based proteomic analysis on mice mitochondria, approximately 38% of the total mitochondrial proteins, including key enzymes such as pyruvate dehydrogenase (PDH) (its major components), showed a diurnal oscillation, with a peak during the early light phase. PDH is a key enzyme that acts as a gatekeeper for the entry of pyruvate—the end product of glycolysis—into the mitochondria and the TCA cycle; thus, directing pyruvate toward OXPHOS. Other enzymes that exhibit a circadian rhythm include glucose-6-phosphatase (gluconeogenesis), pyruvate kinase (glycolysis) and glucokinase (glycogen synthesis).

Interestingly, mitochondrial respiration also shows diurnal oscillation, the peak of which changes in response to different nutrients. These diurnal regulations clearly depend on clock proteins, because the effect was attenuated in mice that lacked PER 1 and PER 2 proteins. Therefore, the diurnal function of mitochondria might be established by the cyclic levels of key enzymes, which in turn are triggered by substrate availability.

Clock genes are regulated by epigenetic mechanisms that follow circadian rhythms but the products of those genes themselves can interact with proteins to induce chromatin remodeling, leading to various metabolic changes. A known example is the interaction between CLOCK and sirtuin 1 (SIRT1), a NAD+-dependent protein that can regulate various tumor metabolic proteins. Through its deacetylation capacity SIRT1 can have tumor-promoting functions, such as deacetylating and thus inactivating P53. On the other hand it can also have tumor-suppressing functions through its role in repairing DNA and limiting genomic instability. The tight regulation of SIRT1 by the NAD+/NADH ratio, which represents the cell’s energy status, evidences the close links between the circadian clock, the cellular energy status, and the deacetylation of cellular proteins, which can regulate the entire dynamics of tumor progression.

Oncogenic signals and circadian clock machinery can interact to alter tumor metabolism

The exact mechanism that governs metabolic plasticity is not fully understood; however, it is clear that it relies on intrinsic oncogenic signals in addition to external stimuli from the tumor microenvironment. Currently there is a lack of studies linking the molecular clock to metabolic plasticity in cancer. However, one can speculate on the existence of such a link for various reasons: (1) The strong cross talk between the molecular clock and oncogenes and tumor suppressors which play a crucial role in cancer metabolism. Of major importance for example is the ability of c-MYC, a strong regulator of tumor metabolism, to disrupt molecular clock and alter glucose and glutamine metabolism, linking oncogenic signaling with circadian and metabolic disturbance. (2) The strong connection between the light-sensing pathway and oxygen sensing pathway in the form of hypoxia and hypoxia-inducible factor 1 (HIF-1) signaling pathway. Indeed, HIF-1α can bind to the BMAL1 promoter; thus, directly regulating the molecular clock; in contrast, HIF-1α promoter can be bound and controlled by CLOCK/BMAL1, thereby regulating hypoxia-driven genes. (3) The molecular clock not only has a strong influence on metabolic processes but it can act as a strong nutrient sensor; this was clearly seen when a high fat diet in mice was able to alter circadian rhythm and molecular clock gene expression.

Peroxiredoxins display a non-transcriptional circadian rhythm with a role in cancer

When discussing circadian rhythm in cancer metabolism, it is essential to account for the non-transcriptional dependent circadian rhythm of peroxiredoxins (Prxs), which are antioxidant proteins. These very
Breaking loose from a circadian rhythm can help cancer cells evolve

The somatic cell evolution model (or somatic mutation theory) in cancer is a widely accepted model that describes how cancer tends to develop as an evolutionary process that mirrors species evolution. A normal cell in a tissue is part of a whole and is functioning part of a multicellular society. However, it has been suggested that for carcinogenesis to happen cancer cells need to evolve and acquire self-defined fitness. Cancer cells start acting as single cells breaking loose from tissue-level control. Proliferating cells are also thought to be in competition with each other for nutrients, space and various growth factors and they start evolving phenotypes that enhance their individual fitness and survival.

Somatic mutations accumulate in cancer cells resulting in genetic variations that are selected for by natural selection if advantageous for the cell. Thus, the survival fitness of a clone of cells determines whether an acquired oncogenic mutation is selected for or not. While a functional clock bestows reproducible fitness on unicellular organism in a rhythmic environment, such functioning clock was found to be a disadvantage in constant arrhythmic environments, slowing the growth of these organisms. It appears to be the case that cancer cells “choose” to disrupt their clock to control their own metabolism. This allows them to maintain a constant rhythm that supports proliferation over homeostasis, or perhaps the opposite during stressful times.

The need to disrupt the clock is also supported with the proposition that the circadian clock could be thought of as one of the checkpoints for cell division, allowing it to occur in specific time windows. Despite the parallels that can be drawn between cyanobacterium and cancer cells regarding circadian metabolic effects, there would be many questions to address, given the differences between the respective models. For example, other than light—the main zeitgeber for cyanobacteria—what are the main zeitgebers in the environment of a proliferating cells that might alter circadian rhythms in cancer.

CONCLUSIONS AND OUTLOOK

In conclusion, it is plausible to think of the circadian clock as a gatekeeper that controls how the organism will utilize energy (sugar and other energy-rich carbon sources) to either proliferate or induce homeostasis and ROS detoxification. Unicellular organisms that are locked in the day or night mode might show an imbalance between their proliferation rate and reproducible fitness, and their cellular homeostasis and cell survival. Similarly, cancer cells have an altered circadian rhythm to reprogram their metabolism based on their needs and status. An early-stage tumor contains cells that are undergoing high proliferation and thus depend on glycolysis intermediates to maintain cell division. These cells also make use of the generated ROS (to generate mutation diversity). On the other hand metastatic cells might require a cell-survival mode, and a homeostatic profile that maintains ROS detoxification. More studies would be needed to determine the epigenetic regulation of the circadian clock and whether it plays a role in cancer metabolic plasticity. Given the circadian clock’s strong orchestration of the cell cycle, it would also be important to study the effects of the metabolic cue in this regulation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Aliaa A. Alamoudi https://orcid.org/0000-0001-5428-8853
REFERENCES

1. Blakeman, V., Williams, J. L., Meng, Q.-J., & Streuli, C. H. (2016). Circadian clocks and breast cancer. Breast Cancer Res., 18(1), 89.

2. Kelleher, F. C., Rao, A., & Maguire, A. (2014). Circadian molecular clocks and cancer. Cancer Lett., 342(1), 9–18.

3. Masri, S., & Sassone-Corsi, P. (2018). The emerging link between cancer, metabolism, and circadian rhythms. Nat. Med., 24(12), 1795–1803.

4. Shafi, A. A., & Knudsen, K. E. (2019). Cancer and the circadian clock. Cancer Res., 79(15), 3806–3814.

5. Sulli, G., Lam, M. T. Y., & Panda, S. (2019). Interplay between circadian clock and cancer: new frontiers for cancer treatment. Trends Cancer, 5(8), 475–494.

6. Gatesby, R. A., & Brown, J. (2017). Mutations, evolution and the central role of a self-defined fitness function in the initiation and progression of cancer. Biochim Biophys Acta Rev Cancer, 1867(2), 162–166.

7. Moore, A. (2020). Metabolic Cycles in Cancer Cells? BioEssays, 42(4), 200048.

8. Krishnalah, S. Y., Wu, G., Altman, B. J., Gower, J., Rhodes, S. D., Coldren, F., ... Weljie, A. M. (2017). Circadian molecular clocks in prostate cancer. J. Urol., 197(2), 266–273.

9. Kohsaka, A., Das, P., Hashimoto, I., Nakao, T., Deguchi, Y., Gouraud, S. ... Maeda, M. (2014). The circadian clock protein BMAL1 controls coupling between transcription and metabolism. Genes Dev., 28(4), 428–440.

10. Shostak, A., (2017). Circadian clock, cell division, and cancer: from the post-transcriptional level. Biochim Biophys Acta Rev Cancer, 1867(2), 162–166.

11. Graf, A., Schlereth, A., Stitt, M., & Smith, A. M. (2010). Circadian control of carbohydrate availability for growth in Arabidopsis plants at night. Proc. Natl. Acad. Sci. USA, 107(20), 9458–9463.

12. Inoue, K., Araki, T., & Endo, M. (2018). Circadian clock during plant development. J. Plant Res., 131(1), 59–66.

13. Fu, L., Pelicano, H., Liu, J., Huang, P., & Lee, C. C. (2002). The circadian clock regulates the p53 pathway in prostate cancer cells. Cancer Res., 62(2), 162–166.

14. Yang, X., Wood, P. A., Oh, E.-Y., Du-Quiton, J., Ansell, C. M., & Hrushesky, W. J. M. (2009). Down-regulation of circadian clock gene Period 2 accelerates breast cancer growth by altering its daily growth rhythm. Breast Cancer Res. Treat., 117(2), 433–441.

15. Cao, Q., Gery, S., Jun, D., Rubin, B. E., & Golden, S. S. (2015). The circadian clock in a broader network context. Trends in Immunol., 36(10), 541–552.

16. Gery, S., Jun, D., Rubin, B. E., & Golden, S. S. (2018). The circadian clock and cancer: new frontiers for cancer treatment. Proc. Natl. Acad. Sci. USA, 115(15), E580–E589.

17. Welkie, D. G., Rubin, B. E., Chang, Y.-G., Diamond, S., Rifa, A. L., Liwag, A., & Golden, S. S. (2018). Genome-wide fitness assessment during diurnal growth reveals an expanded role of the circadian clock in breast cancer. Mol. Cancer Ther., 17(11), 2667–2679.

18. Kuwahara, S., Kawaoka, S., & Golden, S. S. (2019). A hard day’s night: cyanobacterium cyanobacteria. Proc. Natl. Acad. Sci. USA, 116(1), 505–507.

19. Li, X., Shen, C. R., & Liao, J. C. (2014). Diurnal rhythm of a unicellular diazotrophic cyanobacterium under mixotrophic conditions and elevated carbon dioxide. Photosynth. Res., 118(1-2), 51–57.

20. Shinde, S., Zhang, X., Singapuri, S. P., Kalra, I., Liu, X., Morgan-Kiss, R. M., & Wang, X. (2020). Glycogen metabolism supports photosynthesis start through the oxidative pentose phosphate pathway in cyanobacteria. Plant Physiol., 182(1), 507–517.

21. Latifi, A., Ruiz, M., & Zhang, C.-C. (2009). Oxidative stress in cyanobacteria. FEMS Microbiol. Rev., 33(2), 258–278.

22. Repoussou, A., & Prombona, A. (2016). c-MYC targets the central oscillator gene Per1 and is regulated by the circadian clock at the post-transcriptional level. Biochim. Biophys. Acta, 1859(4), 541–552.

23. Hojo, H., Enya, S., Arai, M., Suzuki, Y., Nojiri, T., Kangawa, K., ... Kawakita, S. (2017). Remote reprogramming of hepatic circadian transcription by breast cancer. Oncotarget, 8(21), 34128–34140.
40. Aggarwal, V., Tuli, H., Varol, A., Thakral, F., Yerer, M., Sak, K., ... Sethi, G. (2019). Role of reactive oxygen species in cancer progression: molecular mechanisms and recent advancements. Biomolecules, 9(11), 735. LID: https://doi.org/10.3390/biom9110735 (doj LID -> 735, 2218-273X (Electronic)).

41. Perillo, B., Di Donato, M., Pezone, A., Di Zazzo, E., Giovannelli, P., Galasso, G., ... Migliaccio, A. (2020). ROS in cancer therapy: The bright side of the moon. Exp. Mol. Med., 52(2), 192–203 (2092-6413 (Electronic)).

42. Sabharwal, S. S., & Schumacker, P. T. (2014). Mitochondrial ROS in cancer: Initiators, amplifiers or an Achilles’ heel? (1474-1768 (Electronic)).

43. Kim, J. H. et al., Mitochondrial ROS-derived PTEN oxidation activates PI3K pathway for mTOR-induced myogenic autophagy. (1476-5403 (Electronic)).

44. Leslie, N. R. et al., Redox regulation of PI3-kinase signalling via inactivation of PTEN. (0261-4189 (Print)).

45. Moloney, J. N., & Cotter, T. G. (2018). ROS signalling in the biology of cancer. (1096-3634 (Electronic)).

46. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. Cell, 144(5), 646–674.

47. Lu, J., Tan, M., & Cai, Q. (2015). The Warburg effect in tumor progression: Mitochondrial oxidative metabolism as an anti-metastasis mechanism. Cancer Lett., 356(2 Pt A), 156–164.

48. Ashton, T. M., Mckenna, W. G., Frederick, D. T., Kunz-Schughart, L. A., & Higgins, G. S. (2018). Oxidative phosphorylation as an emerging target in cancer therapy. Clin. Cancer Res., 24(11), 2482–2490.

49. Janiszewska, M., Suva, M. L., Riggi, N., Houtkooper, R. H., Auwerx, J., Clement-Schatlo, V., ... Stamenkovic, I. (2012). Imp2 controls oxidative phosphorylation and is crucial for preserving glioblastoma cancer stem cells. Genes Dev., 26(17), 1926–1944.

50. Gopal, Y. N. V., Rizos, H., Chen, G., Deng, W., Frederick, D. T., Cooper, Z. A., ... Davies, M. A. (2014). Inhibition of mTORC1/2 overcomes resistance to MAPK pathway inhibitors mediated by PGC1α and oxidative phosphorylation in melanoma. Cancer Res., 74(23), 7037–7047.

51. Kowalik, M. A., Columbano, A., & Perrà, A. (2017). Emerging roles of the pentose phosphate pathway in hepatocellular carcinoma. Front. Oncol., 7, 87.

52. Patra, K. C., & Hay, N. (2014). The pentose phosphate pathway and cancer. Trends Biochem. Sci., 39(8), 347–354.

53. McDonald, O. G. et al., Epigenomic reprogramming during pancreatic cancer progression links anabolic glucose metabolism to distant metastasis. (1546-1718 (Electronic)).

54. Ying, H. et al., Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. (1097-4172 (Electronic)).

55. Düvel, K., Yecies, J. L., Monen, S., Raman, P., Lipovsky, A. I., Souza, A. L., ... Mannig, B. D. (2010). Activation of a metabolic gene regulatory network downstream of mTOR complex 1. Mol. Cell, 39(2), 171–183.

56. Ying, H., Kimmelman, A. C., Lyssiotis, C. A., Hua, S., Chu, G. C., Fletcher-Sananikone, E., ... Depinho, R. A. (2012). Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell, 149(3), 656–670.

57. Jia, D., Lu, M., Jung, K. H., Park, J. H., Yu, L., Onuchic, J. N., ... Levine, H. (2019). Elucidating cancer metabolic plasticity by coupling gene regulation with metabolic pathways. Proc. Natl. Acad. Sci. USA, 116(9), 3909–3918.

58. Schafer, Z. T., Grassian, A. R., Song, L., Jiang, Z., Gerhart-Hines, Z., Irie, H. Y., ... Brugge, J. S. (2009). Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment. Nature, 461(7260), 109–113.

59. Cha, Y. H., Yook, J. I., Kim, H. S., & Kim, N. H. (2015). Catabolic metabolism during cancer EMT. Arch. Pharm. Res., 38(3), 313–320.

60. Cassim, S., Vučetić, M., Ždralović, M., & Pouysségur, J. (2020). Warburg and beyond: The power of mitochondrial metabolism to collaborate or replace fermentative glycolysis in cancer. Cancers, 12(5), 1119.
80. Masri, S., Kinouchi, K., & Sassone-Corsi, P. (2015). Circadian clocks, epigenetics, and cancer. Curr. Opin. Oncol., 27(1), 50–56.
81. Chen, S.-T., Choo, K.-B., Hou, M.-F., Yeh, K.-T., Kuo, S.-J., & Chang, J.-G. (2005). Deregulated expression of the PER1, PER2 and PER3 genes in breast cancers. Carcinogenesis, 26(7), 1241–1246.
82. Nakahata, Y., Kaluzova, M., Grimaldi, B., Sahar, S., Hirayama, J., Chen, D., ... Sassone-Corsi, P. (2008). The NAD+ dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. Cell, 134(2), 329–340.
83. Solomon, J. M., Pasupuleti, R., Xu, L., Mcdonagh, T., Curtis, R., Disteфанo, P. S., & Huber, L. J. (2006). Inhibition of SIRT1 catalytic activity increases p53 acetylation but does not alter cell survival following DNA damage. Mol. Cell. Biol., 26(1), 28–38.
84. Ming, M., Shea, C. R., Guo, X., Li, X., Soltani, K., Han, W., & He, Y.-Y. (2010). Regulation of global genome nucleotide excision repair by SIRT1 through xeroderma pigmentosum C. Proc. Natl. Acad. Sci. U. S. A, 107(52), 22623–22628.
85. Verlande, A., & Masri, S. (2019). circadian clocks and cancer: time-keeping governs cellular metabolism. Trends Endocrinol. Metab., 30(7), 445–458.
86. Altman, B. J., Hsieh, A. L., Sengupta, A., Krishnanaiah, S. Y., Stine, Z. E., Walton, Z. E., ... Dang, C. V. (2015). MYC disrupts the circadian clock and metabolism in cancer cells. Cell Metab., 22(6), 1009–1019.
87. Bartman, C. M., & Eckle, T. (2019). Circadian-hypoxia link and its potential for treatment of cardiovascular disease. Curr. Pharm. Des., 25(10), 1075–1090.
88. Wu, Y., Tang, D., Liu, N., Xiong, W., Huang, H., Li, Y., ... Zhang, E. E. (2017). PRDX6 promotes lung tumor progression via its GPx and iPLA2 activities. Free Radical Biol. Med., 69, 367–376.
89. Kohsaka, A., Laposky, A. D., Ramsey, K. M., Estrada, C., Joshu, C., Kobayashi, Y., ... Bass, J. (2007). High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab., 6(5), 414–421.
90. Peek, C. B., Ramsey, K. M., Marcheva, B., & Bass, J. (2012). Nutrient sensing and the circadian clock. Trends Endocrinol. Metab., 23(7), 312–318.
91. Milev, N. B., Rhee, S.-G., & Reddy, A. B. (2018). Cellular timekeeping: it’s redox o’clock. Cold Spring Harb. Perspect. Biol., 10(5), a027698.