Review Article

Anticancer Properties of Curcumin and Interactions With the Circadian Timing System

Integrative Cancer Therapies
Volume 18: 1–10

DOI: 10.1177/1534735419889154
journals.sagepub.com/home/ict
SAGE

Arpan De, PhD[1], Dilshan H. Beligala, PhD[1], Tyler M. Birkholz, MS[1], and Michael E. Geusz, PhD[1]

Abstract

The phytochemical curcumin is a major component of turmeric. It has recognized activity against cancer cells and affects several intracellular signaling pathways. Many molecules targeted by curcumin also regulate the circadian timing system that has effects on carcinogenesis, tumor growth, and metastasis. Although the circadian clock within cells may be suppressed in tumors, cancer cells are subjected to daily hormonal and neural activity that should be considered when timing optimal curcumin treatments. Rapid curcumin degradation in blood and tissues provides a challenge to maintaining sustained levels suitable for inducing cancer cell death, increasing the need to identify when during the circadian cycle rhythmically expressed molecular targets are present. Curcumin is well tolerated by individuals ingesting it for possible cancer prevention or in combination with conventional cancer therapies, and it shows low toxicity toward noncancerous cells at low dosages. In contrast, curcumin is particularly effective against cancer stem cells, which are treatment-resistant, aggressive, and tumor-initiating. Although curcumin has poor bioavailability, more stable curcumin analogs retain the anti-inflammatory, antioxidant, antimitotic, and pro-apoptotic benefits of curcumin. Anticancer properties are also present in congeners of curcumin in turmeric and after curcumin reduction by intestinal microbes. Various commercial curcuminoid products are highly popular dietary supplements, but caution is warranted. Although antioxidant properties of curcumin may prevent carcinogenesis, studies suggest curcumin interferes with certain chemotherapeutic agents. This review delves into the complex network of curcuminoid effects to identify potential anticancer strategies that may work in concert with daily physiological cycles controlled by the circadian timing system.

Keywords

circadian, curcumin, cancer stem cell, epithelial-mesenchymal transition, melatonin, unfolded protein response, neurogenesis

Submitted May 11, 2019; revised September 26, 2019; accepted October 22, 2019

The Many Cancer Cell Targets of Curcumin

Ideally, medically effective phytochemicals act primarily on a single cellular pathway, thereby minimizing detrimental off-target effects that could negate derived benefits. Any discussion of the highly promising anticancer properties of curcumin, derived from the *Curcuma longa* rhizome, and similar congeners present in turmeric[1] needs to be balanced with a consideration of their multiple molecular targets and low bioavailability.[2] Descriptions of the many signal transduction pathways, transcription factors, and cellular events suppressed by curcumin appear to have added to its appeal and much attention by researchers. It is conceivable that the ability of curcumin to act on multiple targets provides combined, if not synergistic, actions that may be behind its attractive anticancer properties.[3] Several studies describe its suppression of STAT3 and NF-κB pathways that promote cancer cell proliferation and cell survival.[4] Curcuminoids also act on pathways used in cancer cell autophagy, proliferation, invasion, and apoptosis that rely on PI3k/Akt-1/mTOR,[5-9] Ras/Raf/MEK/ERK,[10] GSK-3beta,[11] and p53.[12,13]

[1]Bowling Green State University, Bowling Green, OH, USA

Corresponding Author:
Michael E. Geusz, Department of Biological Sciences, Bowling Green State University, 217 Life Science Bldg, Bowling Green, OH 43403, USA.
Email: mgeusz@bgsu.edu

Along with these actions, curcumin causes mitotic arrest of many types of cancer cells, often at G1 or G2/M.

Curcumin crosses the blood-brain barrier and has potentially therapeutic effects on amyloid plaque formation and other chronic processes in Alzheimer's disease.[14] Studies report differential molecular effects between curcumin delivered to healthy subjects at low dosages, for example, 80 mg/day, and higher dosages, 500 mg/day or more, which are often tested after a disease state or tissue damage has begun.[15] High curcumin levels may present a risk to healthy cells with both carcinogenic and pro-oxidant effects reported in vitro and in animal studies.[16-18] Rhythmic rather than sustained curcumin delivery may be important to avoid suppressing beneficial acute inflammatory and immune responses needed for healing and tissue maintenance while also minimizing exposure to continuous high dosages.

Cell signaling targets of curcumin that are also important for circadian rhythm generation and expression will be discussed in this article. These molecular pathways include components of epithelial-mesenchymal transition (EMT), endoplasmic reticulum (ER) stress, and inflammation. Molecules of particular interest are peroxisome proliferator-activated receptor-γ (PPAR-γ), sirtuin (SIRT) proteins, and components of the circadian clock timing mechanism, including PER2, BMAL1, and CLOCK. The impact of curcumin on circadian timing will also be considered through its effects on pluripotency genes and neurogenesis, which requires examination because of the stem-like state of neurons in the master circadian clock located in the hypothalamic suprachiasmatic nucleus (SCN).[19] The SCN receives retinal light signals through the retinohypothalamic tract that allow the circadian clock to entrain to daily cycles while synchronizing itself and regulating the phase of circadian clocks throughout the body through neural and endocrine routes.[20]

Interestingly, studies have shown that in most tissues and organ systems single cells have independently running circadian clocks that are synchronized to each other.[21,22] The molecular timing mechanism of these clocks regulates numerous cellular processes including cell division, differentiation, and cell death.[4,23-28] Neurogenesis in the dentate gyrus is under circadian control, and loss of core circadian clock gene BMAL1 directs differentiation into astrocytes rather than neurons.[28] Molecular targets of curcumin rhythmically vary due to control by the circadian timing system, and curcumin can in turn alter this temporal organization by affecting circadian timing within the SCN or in tissues bearing tumors.

Curcumin Effects on EMT and Cancer Stem Cells

EMT precedes metastasis as cancer cells become more motile and aggressive and express genes typical of stem cells.[29,30] These cancer stem cells (CSCs) are important in tumor growth because of their resistance to anticancer chemotherapy and radiation treatments and because they differentiate and proliferate to form recurrent tumors. During metastasis, cancer cells that are dynamically transitioning to enhanced aggressive and migratory states through EMT also dedifferentiate to acquire stem cell properties and become CSCs.[31] Conventional anticancer therapies often fail to eradicate such cancer cells that have undergone EMT and acquired a CSC state. The mechanistic and functional links through which the EMT program triggers cancer cells to become stem-like are implicated in drug resistance.[32] CSCs are thus clinically important because of their resistance to treatments and their potential to form tumors.

Curcumin appears capable of killing CSCs while promoting differentiation of metastatic cells.[33] For example, Wnt/β-catenin signaling, which elevates the stem cell protein OCT-4,[34] is inhibited by curcumin in colon[35] and gastric cancer cells.[36] Curcumin also suppresses human cancer cell growth by binding to SIRT1, thereby facilitating its degradation.[37] Rather than suppressing tumor growth by causing apoptosis, curcumin suppresses cell proliferation of human colon cancer cells in a mouse xenograft model.[35] Curcumin appears to induce G1 cell-cycle arrest of colon cancer cells by interfering with CDK2 kinase activity.[38] Curcumin also suppresses human colon cancer cell migration by inhibiting NF-κB activation of plasminogen activator and matrix metalloproteinase-9 (MMP-9) genes that are needed in cell invasion.[39]

Curcumin effectively suppresses invasive properties of breast cancer cells. Specifically, it interrupts the EMT program by downregulating expression of several EMT-related proteins including Slug, AXL, Twist1, N-cadherin, β-catenin, vimentin, and fibronectin.[40] An in vitro study has revealed the anti-metastatic properties of curcumin where it perturbed MEKK3 and p-ERK signaling pathways and inhibited VEGF, MMP-2, and MMP-9 resulting in the suppression of invasion and migration of human non-small lung cancer cells.[41]

Curcumin downregulates CXCR4, a protein serving in cell adhesion and migration, and upregulates one of the core clock proteins PER2 in human follicular lymphoma cells, which is otherwise downregulated in lymphoma cell lines and primary acute myeloid leukemia-derived cells.[42] PER2 has possible tumor suppressor functions and its downregulation is associated with poor prognosis in breast cancer patients.[43] The same study also showed that PER2 functions as a transcriptional corepressor and epigenetically represses expression of EMT-related genes Twist1, Slug, and Snail in metastatic breast cancer cells. PER2 degradation induced by hypoxia promotes EMT in these cancer cells.

Curcumin might target CSCs through direct or indirect effects on CSC self-renewal pathways.[44] Wnt/β-catenin,

sonic hedgehog, and Notch are 3 major pathways considered to play pivotal roles in CSC self-renewal mechanisms in various cancers. Curcumin reduced the β-catenin/TCF transcriptional activity in intestinal and stomach cancer cell lines.[45] Attenuation of Wnt receptor Frizzled-1 and induction of enhanced activity of the proapoptotic activating transcription factor 3 by curcumin resulted in increased apoptosis in metastasizing, poorly and moderately differentiated head and neck squamous carcinoma cells.[46] Curcumin-induced cell death was observed in esophageal squamous carcinoma cells resulting in fewer CSCs in the surviving cell line after curcumin treatment.[47] Interestingly, curcumin also induced apoptosis and decreased proliferation through reduced Notch-1 activation by downregulation of γ-secretase complex components in human and mouse esophageal adenocarcinoma cells. In the same study, curcumin targeted and decreased Notch-1 specific microRNAs miR-21 and miR-34a and upregulated tumor suppressor let-7a miRNA.[48] A novel curcumin analogue diflourinated curcumin reduced expression of histone methyltransferase EZH2 (a major epigenetic regulator of CSC state) and enhanced concomitant expression of several tumor-suppressive miRNAs including let-7a in human pancreatic cancer cells.[49] Surprisingly, curcumin was reported to cause one subtype of colon CSCs to proliferate while other CSCs were suppressed.[50]

EMT in noncancerous cells is initiated by inflammation,[30] suggesting a connection with cancer cells that tend to develop and reside in a pro-inflammatory microenvironment.[51] Curcumin also suppresses EMT in noncancerous cells[7] and during peritoneal fibrosis.[52] It also acts on noncancerous tumor stromal cells to repress pancreatic cancer cell EMT.[53] CSC sensitivity to curcumin encourages caution because curcumin might accelerate differentiation of normal mesenchymal stem cells found in organs and tissues. Curcumin increases adult neurogenesis in the dentate gyrus of the hippocampus.[54-56] The hippocampus also expresses daily rhythms in cell proliferation and neural synapse strength,[57,58] suggesting that the phase of the cycle most sensitive to curcumin could be identified for use in minimizing potential disruption. Neurons may be particularly sensitive to curcumin. High curcumin concentrations have toxic effects on neural stem cells in vitro,[59] and a mouse lupus model shows greater brain atrophy in the presence of curcumin.[60]

Possible Curcumin Effects on Stem-Like Cells of the SCN

Like curcumin, anticancer agents developed to exploit the stem-like properties of CSCs may also affect important mesenchymal stem cells within multiple organs that have potential for tissue regeneration and repair. There are proteomic and transcriptomic similarities between CSCs and mesenchymal stem cells of adult animals. The SCN clock might be particularly sensitive to curcuminoids because many SCN neurons have an immature phenotype, expressing stem cell-associated proteins.[19] In particular, RORα and Six3 genes are expressed distinctly in early SCN development, which persists into adult ages.[61] The stem-like state of mature neurons in the master circadian clock includes expression of Sox2, a transcription factor with an established function in neural development.[62,63] In addition to Sox2, a fraction of adult human SCN cells express nestin, vimentin, and glutamate-aspartate transporter that are considered as neural stem and progenitor cell markers.[64] The adult SCN also contains cells expressing doublecortin and doublecortin-like proteins that are usually found in neuroblasts undergoing a final differentiation into neurons.[65,66] Interestingly, SCN cells express high levels of at least 3 genes prominent in cancer cells (Blcap, Msi2, and Zfhx3), suggesting that curcumin may alter circadian clock properties of these cells.[19]

Curcumin uses a comprehensive and a diverse range of mechanisms to exert its anticancer effects. One such mechanism is by suppressing oncogenic pluripotency genes such as Oct4, Sox2, and NANOG.[67] Oct4 and Sox2 are expressed in adult SCN neurons,[68] and because curcumin crosses the blood-brain barrier it might alter these stem-like cells. Curcumin has been shown to induce apoptotic cell death by Oct-4 inhibition in NCCIT human embryonic carcinoma cells.[11] To inhibit these pluripotency genes, curcumin upregulates tumor-suppressive microRNAs such as the let-7 family, miR-26a, miR-101, miR-146a, and miR-200b as shown in pancreatic cancer.[69] CSC targeting was also observed in studies using curcumin-loaded nanoparticles.[70] As mentioned above, curcumin is also known to inhibit EMT in breast cancer cell lines by suppressing multiple EMT- and CSC-related genes, thereby preventing cancer cell invasion.[40] Additionally, curcumin was shown to induce the differentiation of glioma-initiating cells evident by a reduction in nestin expression.[71]

Integration of circadian clock theory into cancer prevention and therapy remains a novel approach.[72-75] Cancer growth was shown to be inhibited by circadian reprogramming of the tumor transcriptome with meal timing[76] or with agents that synchronize circadian clocks directly including dexamethasone.[77] There are few reports describing effects of curcumin on the SCN or circadian clocks. One study claims that dietary curcumin lowers SCN serotonin levels in rats after ethanol exposure.[78] Serotonin modulates the phase-shifting effects of retinal light exposure on the SCN circadian clock,[79,80] suggesting an additional possible influence of curcumin on circadian timing mechanisms. Reviews by Kuol et al[81,82] provide a compelling argument that the nervous system can alter carcinogenesis and cancer progression, particularly through its interaction with the immune system. These key influences include growth factor

release, control of cancer cell EMT, metastasis regulated by vagal nerve activity, and neurogenesis induced by intestinal resident stem cells.

Because of its antioxidant effects curcumin at high levels might also unfavorably alter the redox balance of cells. The binding of transcription factors BMAL1 and CLOCK as a dimer to promoter elements of clock-controlled genes is sensitive to cellular redox state as shown by circadian clock responses to cellular metabolism.[83] Consequently, these potential curcumin effects on the SCN or other circadian timing structures could have an indirect impact on cancer.

Coupling Between the Circadian Timing and Immune Systems

Circadian clocks within immune cells and cytokine oscillations in the circadian timing system produce rhythmic immune activity[84,85] in part by regulating the NF-κB transcription factor pathway, which has been reviewed elsewhere.[86] Curcumin is an effective anti-inflammatory agent and blocks signaling through the canonical NF-κB pathway by acting on I-κB. Curcumin increases PPAR-γ activity in reactive astrocytes, thereby inhibiting inflammation through NF-κB.[87] NF-κB activity is commonly elevated in cancer cells, providing them an anti-apoptotic benefit, which is then lost following curcumin exposure.

The circadian timing system and immune system are tightly intermeshed, feeding back on each other.[86] SIRT1 is a histone deacetylase that controls the circadian clock by downregulating NF-κB and modifying 2 critical circadian clock proteins, BMAL1 and PER2.[37,88-90] Therefore, curcumin has converging effects on genes controlled by NF-κB—directly and indirectly through SIRT1 and PPAR-γ and through genes serving in the internal timing mechanism of the clock. Although SIRT1 alters acetylation and stability of BMAL1 and PER2, computer modeling suggests PER2 is the major target.[91] This complexity affects any scheme for optimal timing of curcumin dosing but could be simplified by limiting consideration to only the target organ's internal timing or any circadian rhythms within the tumor.

Curcumin Effects on ER Stress and the Unfolded Protein Response

Cancer cells respond to chemotherapy and resulting ER stress with an unfolded protein response (UPR) that promotes survival by minimizing harm to the cell. Nevertheless, cancer cells do succumb to overwhelming ER stress. For example, curcumin induces apoptosis of prostate cancer cells through an ER stress response that produces sufficiently disrupted protein folding, as indicated by increased expression of the Ca^{2+}-binding protein calreticulin and additional markers of ER stress.[92] Similarly, curcumin causes apoptosis of lung, gastric, colon, thyroid, and cervical cancer through ER stress.[93-96] Curcumin has also been shown to inhibit the proliferation of hepatocellular carcinoma cells through ER stress caused by the UPR, which upregulates calreticulin expression and downregulates the expression of calnexin and other proteins.[97]

Calreticulin is a calcium-binding ER chaperone protein assisting in protein folding that is upregulated during periods of ER stress.[92] It is also expressed on the cell surface as the dominant pro-phagocytic signal in a variety of human cancers.[98-100] Calreticulin expression is also increased in tumors compared with normal tissue,[101,102] and it has been shown that calreticulin expression can be a biomarker for bladder urothelial cancer.[103] Calreticulin may be an effective target for immune-based drug development to treat a variety of cancers,[98,99] and it can be used as a marker for the prognosis of various cancers, which can provide a new clinical tool for physicians.[102]

Modified curcuminoids with improved bioavailability may also be a useful target for immune-based drug development. One curcumin derivative shows promising effects on mouse colon cancer cells by inducing cell death through ER stress.[104] Another curcumin analog, C-150, was shown to be more potent than curcumin and increased the survival rate in treated rats with glioblastoma compared with controls, while also decreasing tumorigenesis in the eyes of a Drosophila cancer model.[105] In addition, novel delivery systems increase curcumin bioavailability, and many curcumin analogs have been studied to determine their potency against a number specific cancers.[106] Thus, curcumin and various analogs have much potential for treating various types of cancer by increasing UPR. Furthermore, because calreticulin is upregulated by UPR and its cell-surface expression is increased in numerous cancers, it may also be a therapeutic target or a biomarker to study the efficacy of curcumin in cancer treatment.

Opportunities for Timed Optimal Curcuminoid Delivery

Interactions between curcuminoids and their circadian and noncircadian targets are complex, but it may be possible to identify an optimal phase for curcumin delivery that maximizes efficacy while minimizing potentially negative effects. Twice-daily curcumin dosing would be expected to maintain more sustained tissue levels, which is particularly important to offset the fast degradation of curcumin. However, greater efficacy may result from a single high dose that targets molecules or cellular processes that are available within a limited phase of the circadian cycle, as shown with 5-fluorouracil,[107] roscovitine,[108] temozolomide,[109] and interferon treatments.[110] Melatonin is one of the most important hormones released in a daily rhythm that should be considered in relationship to timing of curcumin.[111] This pineal gland hormone is released in darkness and under circadian clock control. Curcumin delivery at night would be expected to augment the ability of melatonin to prevent EMT and cancer cell migration, as has been

described in bladder cancer cells in culture and in mouse xenograft studies.[112] Because curcumin typically targets CSCs, nighttime curcuminoid delivery should be considered when designing medical treatments for cancer patients at risk of metastasis or cancer cell infiltration. On the other hand, morning curcumin delivery might complement melatonin effects by suppressing CSCs after melatonin levels have declined.

For individuals taking turmeric or curcumin as a cancer preventative, the challenge is to find a phase that maximizes circadian system effects on curcumin pharmacokinetics while maintaining curcumin benefits to functioning of the circadian system. Few studies suggest how circadian clocks in intestinal epithelia might modulate curcumin absorption. Optimal bioavailability may result from taking curcumin with meals, in line with its consumption in traditional cuisines where dietary fats help solubilize curcumin and may protect it from degradation.[23] Curcuminoids do not appear to act directly on products of the core circadian clock genes. Indirect effects have been described that may weaken or strengthen clock stability, amplitude, period, or phase relationships between circadian clocks of neighboring cells. Because curcumin alters SIRT1 and PPAR-γ levels, which in turn modify circadian clock proteins,[37,87-90] oral curcumin delivery may affect circadian timing, particular by acting on clocks of the gastrointestinal tract. Nevertheless, additional studies are needed to determine when during daily cycles curcumin and other phytochemicals are beneficial or detrimental.

Another relevant question of concern is how to identify an optimal phase that minimizes possible off-target curcumin effects on neurogenesis in young and older cancer patients. Because curcumin induces differentiation of CSCs it may also affect immature cells such as neuroblasts more effectively than differentiated ones. In cancer patients there is the additional concern of compatibility of curcumin with chemotherapeutic agents. Interaction of curcumin with treatments in some cases augments the anticancer agent's effects such as with 5-fluorouracil and esophageal squamous cell carcinoma[113] and colon cancer cells.[33,114] There are also reports of curcumin interfering with cancer treatments[115] and concerns that curcumin can cause oxidative damage at high concentrations.[116]

As cancer progresses to late stages, the circadian timing system can be highly disturbed,[117,118] perhaps by altered sleep patterns, pain, cachexia, and possibly cytokine release initiated by tumors acting on the circadian timing mechanism. The SCN circadian clock, for example, is altered by cytokines,[119] but circadian clocks in cells near the tumor might be more profoundly influenced. Studies indicate that circadian timing disruption, such as from light exposure at night during late work schedules, significantly increases risk of breast, prostate, non-Hodgkin lymphoma, and other cancers.[120-123] Loss of circadian rhythms within cells is also considered a causal factor in carcinogenesis and aggressive tumor growth.[124-126] Therefore, the ability of curcumin to act on circadian clock proteins could provide a way to reestablish proper circadian timing before cancer initiation and in late stage cancer patients, possibly suppressing cancer cells while improving sleep cycles, mood, and quality of life. Curcumin may in this way prove beneficial during advanced cancer stages, along with its more direct anticancer properties.

Although little is known about circadian cycles within cancer cells of tumors, in vitro studies have characterized circadian rhythms in cell lines derived from cancers of brain, breast, colon, and lung.[127-133] Furthermore, circadian timing within acute myeloid leukemia cells promotes rather than impedes their proliferation.[134] The presence of circadian rhythms in some cancer cells and tumors[135,136] raises the possibility that there are rhythmic targets within tumors that could be exploited by strategically timed delivery of curcumin. The ability of a noncancer cell to use its internal circadian clock to predict when nutrients will be available from a meal, or after daily awakening from sleep, appears to be synchronized with cell cycle growth and mitotic phases. In cancer cells that have their own circadian timing these potentially selective advantages could be extended to an ability to predict when cancer cell DNA replication occurs or daily immune surveillance is maximal.[84] In fact, evidence from animal models does challenge the generally held view that disrupted circadian timing enhances cancer cell survival and proliferation, particularly during chemotherapy.[75]

Whether cancer cells of a specific tumor are intrinsically rhythmic or not, they are exposed to the usual daily rhythms of numerous hormones including melatonin at night and corticosteroids that reach a peak during the morning[137] and persist in cancer patients.[138,139] Daily serum corticosteroid rhythms likely induce the core clock gene Per1.[140] Dexamethasone is in fact often used to synchronize circadian clocks in tumor-derived and non-cancer cell cultures.[77]

Cortisol has immune suppressive effects[141] and, in the absence of unusual stressors, is minimal at night when adaptive immune functions show greatest activity.[142] Like cortisol,[143] curcumin inhibits pathways dependent on NF-κB, indicating it too should be delivered when possible during the morning if the goal is to avoid immune system suppression. On the other hand, it may be desirable to use curcumin to suppress excessive inflammation at night. It is recommended that glucocorticoid treatments when used to treat rheumatoid arthritis by restoring temporal order in the circadian system are best applied near the normal time of morning elevated cortisol.[141] Because it has similar effects on the immune system, curcumin should therefore be applied in the morning to have the least disruptive effect on the circadian system. Like cortisol treatments, curcumin delivered at this phase might also be beneficial in maintaining proper phase relationships between the circadian clocks of the body.

Along with circadian clocks in normal tissue, circadian behavior of cancer cells should be considered in any optimal dosing strategy for curcumin. Evidence described above that EMT and metastasis are timed by the circadian system indicates that cancer patients with undisturbed circadian rhythms should take curcumin when these events are most likely to occur. Research is beginning to characterize when EMT is most likely in cancers of specific tissues, which have circadian rhythms that vary in phase with the SCN and with each other. Circadian rhythms in tissues and organs also vary between cancer patients and between healthy individuals. This additional complexity is being addressed by customizing cancer therapies to better match the circadian timing systems of individuals as a type of personalized medicine.[144]

Finally, some individuals who have survived cancer or are maintaining cancer remission, such as some leukemia patients, may consume curcumin near maximum tolerable limits. One caution that should be considered is the potential disruptive effects on the circadian system. Limiting the highest dosing to only part of the day may be more beneficial, although additional research is needed to identify when particular cancer cell types are most easily suppressed.

Conclusions

Considering the multiple cellular actions of curcumin, it is not surprising that optimal dosing strategies relative to the circadian system are also complex. Along with the many potential benefits of curcumin, potential harm should be addressed, particularly at high dosages, as shown by effects on normal stem cells, neurogenesis, and immune functions. Timing of curcumin delivery for cancer prevention or in combination with cancer therapies to target CSCs is likely to be most favorable when it is taken in the morning to minimize suppression of immune functions and possible disruption of the circadian timing system. Curcumin delivery in the morning might prolong the cancer cell EMT inhibition provided by melatonin at night, thereby enabling more sustained control throughout the day. Alternatively, when higher dosages are needed for immune suppression, anti-inflammation or aggressive cancer treatment, including enhanced CSC inhibition, multiple curcumin doses throughput the day can be warranted because of rapid curcumin clearance from the blood. Clearly, additional translational and clinical studies are needed to understand interactions between circadian clocks and curcuminoids.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Michael E. Geusz https://orcid.org/0000-0001-5193-4485

References

1. Yodkeeree S, Chaiwangyen W, Garbisa S, Limtrakul P. Curcumin, demethoxycurcumin and bisdemethoxycurcumin differentially inhibit cancer cell invasion through the down-regulation of MMPs and uPA. *J Nutr Biochem*. 2009;20:87-95.
2. Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol*. 2017;174:1325-1348.
3. Block KI, Gyllenhaal C, Lowe L, et al. Designing a broad-spectrum integrative approach for cancer prevention and treatment. *Semin Cancer Biol*. 2015;35(suppl):S276-S304.
4. Lee JH, Sancar A. Regulation of apoptosis by the circadian clock through NF-κB signaling. *Proc Natl Acad Sci U S A*. 2011;108:12036-12041.
5. Sokolosky ML, Stadelman KM, Chappell WH, et al. Involvement of Akt-1 and mTOR in sensitivity of breast cancer to targeted therapy. *Oncotarget*. 2011;2:538-550.
6. Liu LD, Pang YX, Zhao XR, et al. Curcumin induces apoptotic cell death and protective autophagy by inhibiting AKT/mTOR/p70S6K pathway in human ovarian cancer cells. *Arch Gynecol Obstet*. 2019;299:1627-1639.
7. Zhu FQ, Chen MJ, Zhu M, et al. Curcumin suppresses epithelial-mesenchymal transition of renal tubular epithelial cells through the inhibition of Akt/mTOR pathway. *Biol Pharm Bull*. 2017;40:17-24.
8. Zhao G, Han X, Zheng S, et al. Curcumin induces autophagy, inhibits proliferation and invasion by downregulating AKT/mTOR signaling pathway in human melanoma cells. *Oncol Rep*. 2016;35:1065-1074.
9. Shakeri A, Cicero AFG, Panahi Y, Mohajeri M, Sahebkar A. Curcumin: a naturally occurring autophagy modulator. *J Cell Physiol*. 2019;234:5643-5654.
10. Guo Y, Shan QQ, Gong PY, Wang SC. The autophagy induced by curcumin via MEK/ERK pathway plays an early anti-leukemia role in human Philadelphia chromosome-positive acute lymphoblastic leukemia SUP-B15 cells. *J Cancer Res Ther*. 2018;14(suppl):S125-S131.
11. Yun JH, Park YG, Lee KM, Kim J, Nho CW. Curcumin induces apoptotic cell death via Oct4 inhibition and GSK-3β activation in NCCIT cells. *Mol Nutr Food Res*. 2015;59:1053-1062.
12. McCubrey JA, Lertpiriyapong K, Steelman LS, et al. Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. *Aging (Albany NY)*. 2017;9:1477-1536.
13. Sidhar H, Giri RK. Induction of Bex genes by curcumin is associated with apoptosis and activation of p53 in N2a neuroblastoma cells. *Sci Rep*. 2017;7:41420.

14. Tang M, Taghibiglou C. The mechanisms of action of curcumin in Alzheimer's disease. *J Alzheimers Dis*. 2017;58:1003-1016.
15. DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr J*. 2012;11:79.
16. Lopez-Lazaro M. Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. *Mol Nutr Food Res*. 2008;52(suppl 1):S103-S127.
17. Azmi AS, Sarkar FH, Hadi SM. Pro-oxidant activity of dietary chemopreventive agents: an under-appreciated anticancer property. *F1000Res*. 2013;2:135.
18. National Toxicology Program. NTP toxicology and carcinogenesis studies of turmeric oleoresin (CAS No. 8024-37-1) (major component 79%-85% curcumin, CAS No. 458-37-7) in F344/N rats and B6C3F1 mice (feed studies). *Natl Toxicol Program Tech Rep Ser*. 1993;427:1-275.
19. Beligala DH, De A, Geusz ME. A meta-analysis characterizing stem-like gene expression in the suprachiasmatic nucleus and its circadian clock. *Biomed Res Int*. 2018;2018:3610603.
20. Takahashi JS. Molecular architecture of the circadian clock in mammals. In: P Sassone-Corsi & Y Christen, eds. *A Time for Metabolism and Hormones*. Cham, Switzerland: Springer; 2016:13-24.
21. Liu AC, Welsh DK, Ko CH, et al. Intercellular coupling confers robustness against mutations in the SCN circadian clock network. *Cell*. 2007;129:605-616.
22. Kornmann B, Schaad O, Bujard H, Takahashi JS, Schibler U. System-driven and oscillator-dependent circadian transcription in mice with a conditionally active liver clock. *PLoS Biol*. 2007;5:e34.
23. Sarma A, Sharma VP, Sarkar AB, Sekar MC, Samuel K, Geusz ME. The circadian clock modulates anti-cancer properties of curcumin. *BMC Cancer*. 2016;16:759.
24. Bieler J, Cannavo R, Gustafson K, Gobet C, Gatfield D, Naef F. Robust synchronization of coupled circadian and cell cycle oscillators in single mammalian cells. *Mol Syst Biol*. 2014;10:739.
25. Lakatua DJ, White M, Sackett-Lundeen LL, Haus E. Change in phase relations of circadian rhythms in cell proliferation induced by time-limited feeding in BALB/c X DBA/2F1 mice bearing a transplantable Harding-Passey tumor. *Cancer Res*. 1983;43:4068-4072.
26. Granda TG, Liu XH, Smaaland R, et al. Circadian regulation of cell cycle and apoptosis proteins in mouse bone marrow and tumor. *Faseb J*. 2005;19:304-306.
27. Potten CS, Al-Barwari SE, Hume WJ, Searle J. Circadian rhythms of presumptive stem cells in three different epithelia of the mouse. *Cell Tissue Kinet*. 1977;10:557-568.
28. Malik A, Kondratov RV, Jamasbi RJ, Geusz ME. Circadian clock genes are essential for normal adult neurogenesis, differentiation, and fate determination. *PLoS One*. 2015;10:e0139655.
29. Das V, Bhattacharya S, Chikkaputtaiah C, Hazra S, Pal M. The basics of epithelial-mesenchymal transition (EMT): a study from a structure, dynamics, and functional perspective [published online February 5, 2019]. *J Cell Physiol*. doi:10.1002/jcp.28160
30. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest*. 2009;119:1420-1428.
31. Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene*. 2010;29:4741-4751.
32. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. *Nat Rev Clin Oncol*. 2017;14:611-629.
33. Buhrmann C, Kraehe P, Lueders C, Shayan P, Goel A, Shakibaei M. Curcumin suppresses crosstalk between colon cancer stem cells and stromal fibroblasts in the tumor microenvironment: potential role of EMT. *PLoS One*. 2014;9:e107514.
34. Teng Y, Wang X, Wang Y, Ma D. Wnt/beta-catenin signaling regulates cancer stem cells in lung cancer A549 cells. *Biochem Biophys Res Commun*. 2010;392:373-379.
35. Dou H, Shen R, Tao J, et al. Curcumin suppresses the colon cancer proliferation by inhibiting Wnt/β-catenin pathways via miR-130a. *Front Pharmacol*. 2017;8:877.
36. Zheng R, Deng Q, Liu Y, Zhao P. Curcumin inhibits gastric carcinoma cell growth and induces apoptosis by suppressing the Wnt/β-catenin signaling pathway. *Med Sci Monit*. 2017;23:163-171.
37. Lee YH, Song NY, Suh J, et al. Curcumin suppresses oncogenicity of human colon cancer cells by covalently modifying the cysteine 67 residue of SIRT1. *Cancer Lett*. 2018;431:219-229.
38. Lim TG, Lee SY, Huang Z, et al. Curcumin suppresses proliferation of colon cancer cells by targeting CDK2. *Cancer Prev Res (Phila)*. 2014;7:466-474.
39. Tong W, Wang Q, Sun D, Suo J. Curcumin suppresses colon cancer cell invasion via AMPK-induced inhibition of NF-kappaB, uPA activator and MMP9. *Oncol Lett*. 2016;12:4139-4146.
40. Gallardo M, Calaf GM. Curcumin inhibits invasive capabilities through epithelial mesenchymal transition in breast cancer cell lines. *Int J Oncol*. 2016;49:1019-1027.
41. Lin SS, Lai KC, Hsu SC, et al. Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and -9 and vascular endothelial growth factor (VEGF). *Cancer Lett*. 2009;285:127-133.
42. Skommer J, Wlodkowic D, Pelkonen J. Gene-expression profiling during curcumin-induced apoptosis reveals down-regulation of CXCR4. *Exp Hematol*. 2007;35:84-95.
43. Hwang-Verslues WW, Chang PH, Jeng YM, et al. Loss of corepressor PER2 under hypoxia up-regulates OCT1-mediated EMT gene expression and enhances tumor malignancy. *Proc Natl Acad Sci U S A*. 2013;110:12331-12336.
44. Li Y, Zhang T. Targeting cancer stem cells by curcumin and clinical applications. *Cancer Lett*. 2014;346:197-205.
45. Park CH, Hahm ER, Park S, Kim HK, Yang CH. The inhibitory mechanism of curcumin and its derivative against β-catenin/Tcf signaling. *FEBS Lett*. 2005;579:2965-2971.
46. Yan C, Jamaluddin MS, Aggarwal B, Myers J, Boyd DD. Gene expression profiling identifies activating transcription factor 3 as a novel contributor to the proapoptotic effect of curcumin. *Mol Cancer Ther*. 2005;4:233-241.

47. Almanaa TN, Geusz ME, Jamasbi RJ. Effects of curcumin on stem-like cells in human esophageal squamous carcinoma cell lines. *BMC Complement Altern Med*. 2012;12:195.
48. Subramaniam D, Ponnurangam S, Ramamoorthy P, et al. Curcumin induces cell death in esophageal cancer cells through modulating Notch signaling. *PLoS One*. 2012;7:e30590.
49. Bao B, Ali S, Banerjee S, et al. Curcumin analogue CDF inhibits pancreatic tumor growth by switching on suppressor microRNAs and attenuating EZH2 expression. *Cancer Res*. 2012;72:335-345.
50. Kantara C, O'Connell M, Sarkar S, Moya S, Ullrich R, Singh P. Curcumin promotes autophagic survival of a subset of colon cancer stem cells, which are ablated by DCLK1-siRNA. *Cancer Res*. 2014;74:2487-2498.
51. Afify SM, Seno M. Conversion of stem cells to cancer stem cells: undercurrent of cancer initiation. *Cancers (Basel)*. 2019;11:E345.
52. Zhao JL, Guo MZ, Zhu JJ, Zhang T, Min DY. Curcumin suppresses epithelial-to-mesenchymal transition of peritoneal mesothelial cells (HMrSV5) through regulation of transforming growth factor-activated kinase 1 (TAK1). *Cell Mol Biol Lett*. 2019;24:32.
53. Wang Q, Qu C, Xie F, et al. Curcumin suppresses epithelial-to-mesenchymal transition and metastasis of pancreatic cancer cells by inhibiting cancer-associated fibroblasts. *Am J Cancer Res*. 2017;7:125-133.
54. Xu Y, Ku B, Cui L, et al. Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res*. 2007;1162:9-18.
55. Kim SJ, Son TG, Park HR, et al. Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J Biol Chem*. 2008;283:14497-14505.
56. Dong S, Zeng Q, Mitchell ES, et al. Curcumin enhances neurogenesis and cognition in aged rats: implications for transcriptional interactions related to growth and synaptic plasticity. *PLoS One*. 2012;7:e31211.
57. Gilhooley MJ, Pinnock SB, Herbert J. Rhythmic expression of per1 in the dentate gyrus is suppressed by corticosterone: implications for neurogenesis. *Neurosci Lett*. 2011;489:177-181.
58. Chaudhury D, Wang LM, Colwell CS. Circadian regulation of hippocampal long-term potentiation. *J Biol Rhythms*. 2005;20:225-236.
59. Attari F, Zahmatkesh M, Aligholi H, et al. Curcumin as a double-edged sword for stem cells: dose, time and cell type-specific responses to curcumin. *Daru*. 2015;23:33.
60. Foxley S, Zamora M, Hack B, et al. Curcumin aggravates CNS pathology in experimental systemic lupus erythematosus. *Brain Res*. 2013;1504:85-96.
61. VanDunk C, Hunter LA, Gray PA. Development, maturation, and necessity of transcription factors in the mouse suprachiasmatic nucleus. *J Neurosci*. 2011;31:6457-6467.
62. Hoefflin S, Carter DA. Neuronal expression of SOX2 is enriched in specific hypothalamic cell groups. *J Chem Neuroanat*. 2014;61-62:153-160.
63. Venere M, Han YG, Bell R, Song JS, Alvarez-Buylla A, Blelloch R. Sox1 marks an activated neural stem/progenitor cell in the hippocampus. *Development*. 2012;139:3938-3949.
64. Pellegrino G, Trubert C, Terrien J, et al. A comparative study of the neural stem cell niche in the adult hypothalamus of human, mouse, rat and gray mouse lemur (*Microcebus murinus*). *J Comp Neurol*. 2018;526:1419-1443.
65. Geoghegan D, Carter DA. A novel site of adult doublecortin expression: neuropeptide neurons within the suprachiasmatic nucleus circadian clock. *BMC Neurosci*. 2008;9:2.
66. Saaltink DJ, Havik B, Verissimo CS, Lucassen PJ, Vreugdenhil E. Doublecortin and doublecortin-like are expressed in overlapping and non-overlapping neuronal cell population: implications for neurogenesis. *J Comp Neurol*. 2012;520:2805-2823.
67. Mollaei H, Babaei E. Therapeutic potential of novel nano-based curcumin compounds in vitro and in vivo. *Asian Pac J Cancer Prev*. 2017;18:885-888.
68. Beligala DH, De A, Malik A, et al. Musashi-2 and related stem cell proteins in the mouse suprachiasmatic nucleus and their potential role in circadian rhythms. *Int J Dev Neurosci*. 2019;75:44-58.
69. Momtazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A. Curcumin as a microRNA regulator in cancer: a review. *Rev Physiol Biochem Pharmacol*. 2016;171:1-38.
70. Hong IS, Jang GB, Lee HY, Nam JS. Targeting cancer stem cells by using the nanoparticles. *Int J Nanomed*. 2015;10:251-260.
71. Zhuang W, Long L, Zheng B, et al. Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy. *Cancer Sci*. 2012;103:684-690.
72. Levi F. The circadian timing system, a coordinator of life processes. Implications for the rhythmic delivery of cancer therapeutics. *Conf Proc IEEE Eng Med Biol Soc*. 2006;(suppl):6736-6739.
73. Yu EA, Weaver DR. Disrupting the circadian clock: gene-specific effects on aging, cancer, and other phenotypes. *Aging (Albany NY)*. 2011;3:479-493.
74. Sotak M, Sumova A, Pacha J. Cross-talk between the circadian clock and the cell cycle in cancer. *Ann Med*. 2014;46:221-232.
75. Sancar A, Lindsey-Boltz LA, Gaddameedhi S, et al. Circadian clock, cancer, and chemotherapy. *Biochemistry*. 2015;54:110-123.
76. Li XM, Delaunay F, Dulong S, et al. Cancer inhibition through circadian reprogramming of tumor transcriptome with meal timing. *Cancer Res*. 2010;70:3351-3360.
77. Kiessling S, Beaulieu-Laroche L, Blum ID, et al. Enhancing circadian clock function in cancer cells inhibits tumor growth. *BMC Biol*. 2017;15:13.
78. Jagota A, Reddy MY. The effect of curcumin on ethanol induced changes in suprachiasmatic nucleus (SCN) and pineal. *Cell Mol Neurobiol*. 2007;27:997-1006.
79. Flett J, Colwell CS. Serotonin modulation of calcium transients in cells in the suprachiasmatic nucleus. *J Biol Rhythms*. 1999;14:354-363.
80. Ying SW, Rusak B. 5-HT7 receptors mediate serotonergic effects on light-sensitive suprachiasmatic nucleus neurons. *Brain Res*. 1997;755:246-254.

81. Kuol N, Stojanovska L, Apostolopoulos V, Nurgali K. Crosstalk between cancer and the neuro-immune system. *J Neuroimmunol*. 2018;315:15-23.
82. Kuol N, Stojanovska L, Apostolopoulos V, Nurgali K. Role of the nervous system in cancer metastasis. *J Exp Clin Cancer Res*. 2018;37:5.
83. Merrow M, Roenneberg T. Circadian clocks: running on redox. *Cell*. 2001;106:141-143.
84. Abrahamsen JF, Smaaland R, Sandberg S, Aakvaag A, Lote K. Circadian variation in serum cortisol and circulating neutrophils are markers for circadian variation of bone marrow proliferation in cancer patients. *Eur J Haematol*. 1993;50:206-212.
85. Sato S, Sakurai T, Ogasawara J, et al. A circadian clock gene, Rev-erbα, modulates the inflammatory function of macrophages through the negative regulation of Ccl2 expression. *J Immunol*. 2014;192:407-417.
86. Cermakian N, Lange T, Golombek D, et al. Crosstalk between the circadian clock circuitry and the immune system. *Chronobiol Int*. 2013;30:870-888.
87. Wang HM, Zhao YX, Zhang S, et al. PPARgamma agonist curcumin reduces the amyloid-beta-stimulated inflammatory responses in primary astrocytes. *J Alzheimers Dis*. 2010;20:1189-1199.
88. Chung S, Yao H, Caito S, Hwang JW, Arunachalam G, Rahman I. Regulation of SIRT1 in cellular functions: role of polyphenols. *Arch Biochem Biophys*. 2010;501:79-90.
89. Miki T, Xu Z, Chen-Goodspeed M, et al. PML regulates PER2 nuclear localization and circadian function. *EMBO J*. 2012;31:1427-1439.
90. Asher G, Gatfield D, Stratmann M, et al. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell*. 2008;134:317-328.
91. Foteinou PT, Venkataraman A, Francey LJ, Anafi RC, Hogenesch JB, Doyle FJ 3rd. Computational and experimental insights into the circadian effects of SIRT1. *Proc Natl Acad Sci U S A*. 2018;115:11643-11648.
92. Rivera M, Ramos Y, Rodriguez-Valentin M, et al. Targeting multiple pro-apoptotic signaling pathways with curcumin in prostate cancer cells. *PLoS One*. 2017;12:e0179587.
93. Wu SH, Hang LW, Yang JS, et al. Curcumin induces apoptosis in human non-small cell lung cancer NCI-H460 cells through ER stress and caspase cascade- and mitochondria-dependent pathways. *Anticancer Res*. 2010;30:2125-2133.
94. Cao A, Li Q, Yin P, et al. Curcumin induces apoptosis in human gastric carcinoma AGS cells and colon carcinoma HT-29 cells through mitochondrial dysfunction and endoplasmic reticulum stress. *Apoptosis*. 2013;18:1391-1402.
95. Zhang L, Cheng X, Xu S, Bao J, Yu H. Curcumin induces endoplasmic reticulum stress-associated apoptosis in human papillary thyroid carcinoma BCPAP cells via disruption of intracellular calcium homeostasis. *Medicine (Baltimore)*. 2018;97:e11095.
96. Kim B, Kim HS, Jung EJ, et al. Curcumin induces ER stress-mediated apoptosis through selective generation of reactive oxygen species in cervical cancer cells. *Mol Carcinog*. 2016;55:918-928.
97. Cheng CY, Lin YH, Su CC. Curcumin inhibits the proliferation of human hepatocellular carcinoma J5 cells by inducing endoplasmic reticulum stress and mitochondrial dysfunction. *Int J Mol Med*. 2010;26:673-678.
98. Sun J, Mu H, Dai K, Yi L. Calreticulin: a potential anti-cancer therapeutic target. *Pharmazie*. 2017;72:503-510.
99. Eggleton P, Bremer E, Dudek E, Michalak M. Calreticulin, a therapeutic target? *Expert Opin Ther Targets*. 2016;20:1137-1147.
100. Chao MP, Jaiswal S, Weissman-Tsukamoto R, et al. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. *Sci Transl Med*. 2010;2:63ra94.
101. Zamanian M, Veerakumarasivam A, Abdullah S, Rosli R. Calreticulin and cancer. *Pathol Oncol Res*. 2013;19:149-154.
102. Fucikova J, Kasikova L, Truxova I, et al. Relevance of the chaperone-like protein calreticulin for the biological behavior and clinical outcome of cancer. *Immunol Lett*. 2018;193:25-34.
103. Kageyama S, Isono T, Iwaki H, et al. Identification by proteomic analysis of calreticulin as a marker for bladder cancer and evaluation of the diagnostic accuracy of its detection in urine. *Clin Chem*. 2004;50:857-866.
104. Zhang J, Feng Z, Wang C, et al. Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. *Am J Cancer Res*. 2017;7:275-288.
105. Hackler L Jr, Ozsvari B, Gyuris M, et al. The curcumin analog C-150, influencing NF-κB, UPR and Akt/Notch pathways has potent anticancer activity in vitro and in vivo. *PLoS One*. 2016;11:e0149832.
106. Vyas A, Dandawate P, Padhye S, Ahmad A, Sarkar F. Perspectives on new synthetic curcumin analogs and their potential anticancer properties. *Curr Pharm Des*. 2013;19:2047-2069.
107. Wood PA, Du-Quiton J, You S, Hrushesky WJ. Circadian clock coordinates cancer cell cycle progression, thymidylate synthase, and 5-fluorouracil therapeutic index. *Mol Cancer Ther*. 2006;5:2023-2033.
108. Sallam H, El-Serafi AT, Filipski E, Terelius Y, Levi F, Hassan M. The effect of circadian rhythm on pharmacokinetics and metabolism of the Cdk inhibitor, roscovitine, in tumor mice model. *Chronobiol Int*. 2015;32:608-614.
109. Slat EA, Sponagel J, Marpegan L, et al. Cell-intrinsic, Bmal1-dependent circadian regulation of temozolomide sensitivity in glioblastoma. *J Biol Rhythms*. 2017;32:121-129.
110. Koren S, Whorton EB Jr, Fleischmann WR Jr. Circadian dependence of interferon antitumor activity in mice. *J Natl Cancer Inst*. 1993;85:1927-1932.
111. Blask DE, Dauchy RT, Brainard GC, Hanifin JP. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. *Integr Cancer Ther*. 2009;8:347-353.
112. Shrestha S, Zhu J, Wang Q, et al. Melatonin potentiates the antitumor effect of curcumin by inhibiting IKKβ/NF-κB/COX-2 signaling pathway. *Int J Oncol*. 2017;51:1249-1260.
113. Tian F, Fan T, Zhang Y, Jiang Y, Zhang X. Curcumin potentiates the antitumor effects of 5-FU in treatment of esophageal squamous carcinoma cells through downregulating the

activation of NF-κB signaling pathway in vitro and in vivo. *Acta Biochim Biophys Sin (Shanghai)*. 2012;44:847-855.
114. Shakibaei M, Buhrmann C, Kraehe P, Shayan P, Lueders C, Goel A. Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures. *PLoS One*. 2014;9:e85397.
115. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res*. 2002;62:3868-3875.
116. Burgos-Moron E, Calderon-Montano JM, Salvador J, Robles A, Lopez-Lazaro M. The dark side of curcumin. *Int J Cancer*. 2010;126:1771-1775.
117. Touitou Y, Bogdan A, Levi F, Benavides M, Auzeby A. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens. *Br J Cancer*. 1996;74:1248-1252.
118. Otalora BB, Madrid JA, Alvarez N, Vicente V, Rol MA. Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. *J Pineal Res*. 2008;44:307-315.
119. O'Callaghan EK, Anderson ST, Moynagh PN, Coogan AN. Long-lasting effects of sepsis on circadian rhythms in the mouse. *PLoS One*. 2012;7:e47087.
120. Blask DE, Dauchy RT, Dauchy EM, et al. Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention. *PLoS One*. 2014;9:e102776.
121. Filipski E, King VM, Li X, et al. Host circadian clock as a control point in tumor progression. *J Natl Cancer Inst*. 2002;94:690-697.
122. Lahti TA, Partonen T, Kyyronen P, Kauppinen T, Pukkala E. Night-time work predisposes to non-Hodgkin lymphoma. *Int J Cancer*. 2008;123:2148-2151.
123. Truong T, Liquet B, Menegaux F, et al. Breast cancer risk, nightwork, and circadian clock gene polymorphisms. *Endocr Relat Cancer*. 2014;21:629-638.
124. Levi F, Filipski E, Iurisci I, Li XM, Innominato P. Cross-talks between circadian timing system and cell division cycle determine cancer biology and therapeutics. *Cold Spring Harb Symp Quant Biol*. 2007;72:465-475.
125. Cadenas C, van de Sandt L, Edlund K, et al. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle*. 2014;13:3282-3291.
126. Fu L, Lee CC. The circadian clock: pacemaker and tumour suppressor. *Nat Rev Cancer*. 2003;3:350-361.
127. Sharma VP, Anderson NT, Geusz ME. Circadian properties of cancer stem cells in glioma cell cultures and tumorspheres. *Cancer Lett*. 2014;345:65-74.
128. Pendergast JS, Yeom M, Reyes BA, Ohmiya Y, Yamazaki S. Disconnected circadian and cell cycles in a tumor-driven cell line. *Commun Integr Biol*. 2010;3:536-539.
129. Fuhr L, El-Athman R, Scrima R, et al. The circadian clock regulates metabolic phenotype rewiring Via HKDC1 and modulates tumor progression and drug response in colorectal cancer. *EBioMedicine*. 2018;33:105-121.
130. Chakrabarti S, Paek AL, Reyes J, Lasick KA, Lahav G, Michor F. Hidden heterogeneity and circadian-controlled cell fate inferred from single cell lineages. *Nat Commun*. 2018;9:5372.
131. Fujioka A, Takashima N, Shigeyoshi Y. Circadian rhythm generation in a glioma cell line. *Biochem Biophys Res Commun*. 2006;346:169-174.
132. Zhang Y, Giacchetti S, Parouchev A, et al. Dosing time dependent in vitro pharmacodynamics of everolimus despite a defective circadian clock. *Cell Cycle*. 2018;17:33-42.
133. Chacolla-Huaringa R, Moreno-Cuevas J, Trevino V, Scott SP. Entrainment of breast cell lines results in rhythmic fluctuations of microRNAs. *Int J Mol Sci*. 2017;18:E1460.
134. Puram RV, Kowalczyk MS, de Boer CG, et al. Core circadian clock genes regulate leukemia stem cells in AML. *Cell*. 2016;165:303-316.
135. Mormont MC, Levi F. Circadian-system alterations during cancer processes: a review. *Int J Cancer*. 1997;70:241-247.
136. Xian LJ, Jian S, Cao QY, et al. Circadian rhythms of DNA synthesis in nasopharyngeal carcinoma cells. *Chronobiol Int*. 2002;19:69-76.
137. You S, Wood PA, Xiong Y, Kobayashi M, Du-Quiton J, Hrushesky WJ. Daily coordination of cancer growth and circadian clock gene expression. *Breast Cancer Res Treat*. 2005;91:47-60.
138. Haus E, Dumitriu L, Nicolau GY, Bologa S, Sackett-Lundeen L. Circadian rhythms of basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), cortisol, and melatonin in women with breast cancer. *Chronobiol Int*. 2001;18:709-727.
139. Zubelewicz-Szkodzinska B, Muc-Wierzgon M, Wierzgon J, Brodziak A. Dynamics of circadian fluctuations in serum concentration of cortisol and TNF-alpha soluble receptors in gastrointestinal cancer patients. *Oncol Rep*. 2001;8:207-212.
140. Fonken LK, Frank MG, Kitt MM, Barrientos RM, Watkins LR, Maier SF. Microglia inflammatory responses are controlled by an intrinsic circadian clock. *Brain Behav Immun*. 2015;45:171-179.
141. Spies CM, Straub RH, Cutolo M, Buttgereit F. Circadian rhythms in rheumatology—a glucocorticoid perspective. *Arthritis Res Ther*. 2014;16(suppl 2):S3.
142. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. *Blood*. 2009;113:5134-5143.
143. Bekhbat M, Rowson SA, Neigh GN. Checks and balances: the glucocorticoid receptor and NFκB in good times and bad. *Front Neuroendocrinol*. 2017;46:15-31.
144. Ballesta A, Innominato PF, Dallmann R, Rand DA, Levi FA. Systems chronotherapeutics. *Pharmacol Rev*. 2017;69:161-199.