A Profound Relationship between Circadian Rhythm Dysfunction and Cancer Progression: An Approach to Exploration

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ABSTRACT: Circadian (~ 24-hour) rhythm has been observed in all living organisms. In humans, the circadian system governs different physiological functions such as metabolism, sleep-wake cycle, body temperature, hormone secretion, and cellular proliferation. The suprachiasmatic nucleus (SCN) of the anterior hypothalamus is the principal circadian pacemaker. The SCN receives input signals primarily from the retinohypothalamic tract (RHT), sends output signals to different parts of the hypothalamus, pineal gland, and the peripheral clocks through the neural or humoral network. The functions of the circadian clock are mediated by the rhythmic expression of the core clock genes through a complex feedback loop. Disruption of clock functions influences the development of several pathologic conditions, including cancer, shift work, chronic or acute jet lag, and light-at-night affect the circadian activity, leading to development of several physiological disorders, more specifically cancer. Circadian dysfunction alters the expression of core clock genes that promote the deregulation of the cell cycle, increase cell proliferation and survival, decrease apoptotic activity, alter metabolic functions, increase metastatic property, collectively induces cancer progression.

KEY WORDS: circadian rhythm, SCN, circadian rhythm dysfunction, clock genes, melatonin

ABBREVIATIONS: 5-HT, hydroxytryptamine/serotonin; **AMPAR**, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **AMPK**, adenosine 5′-monophosphate-activated protein kinase; **Bcl-2**, B-cell lymphoma-2; **BMAL1**, Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1; **cAMP**, cyclic adenine monophosphate; **CAT**, catalase; **CDK**, cyclin-dependent kinase; **cGMP**, cyclic guanosine monophosphate; **CK**, Casein kinase; **CLOCK**, circadian locomotor output cycles kaput; **CREBP**, cAMP response element binding protein; **CRY**, cryptochrome; **FBXL3**, F-box/LRR repeat protein 3; **GABA**, gamma-aminobutyric acid; **GPx**, glutathione peroxidise; **GSK3β**, glycogen synthase kinase-3β; **HIF**, hypoxia inducible factor; **HPA**, hypothalamic pituitary axis; **IL**, interleukin; **JNK**, c-Jun N-terminal kinase; **MAPK**, mitogen-activated protein kinase; **MMP**, matrix metalloproteinases; **NF-κB**, nuclear factor-kappaB; **NMDAR**, N-methyl-D-aspartate receptor; **NPAS2**, neuronal period-aryl hydrocarbon receptor nuclear translocator single-minded protein 2; **Nrf2**, nuclear factor erythroid 2-related factor; **PER**, period; **PI3K**, phosphatidylinositol-3-kinase; **PPAR**, peroxisome proliferator activated receptor; **Rev-Erbα**, nuclear receptor subfamily 1 group D member 1; **RHT**, retino-hypothalamic tract; **ROR**, retinoid-related orphan receptor; **SCN**, suprachiasmatic nucleus; **SNP**, single nucleotide polymorphism; **SOD**, superoxide dismutase; **TGF**, transforming growth factor; **TNF**, tumor necrosis factor; **VEGF**, vascular endothelial growth factor

I. INTRODUCTION

The term "circadian" was coined by Franz Halberg.[1] It is developed from the Latin words *circa* meaning "around" and *dies* meaning "day." The biological rhythms are ubiquitously present in organisms ranging from cyanobacteria to mammals, including humans.[2–4] Many physiological functions like the sleep-wake cycle, core body temperature, heart rate, blood pressure, hormone secretion, feeding behavior, and the number of immune cells in the blood have rhythmically oscillated in a circadian fashion.[3–7] The circadian events in the mammalian system are regulated by an endogenous clock or circadian clock. The daily rhythms are associated with the expression of several genes (clock genes) related to cellular activities and metabolic controls in different tissues.[8] Several time-cues (zeitgebers) like environmental temperature, light-dark cycle, physical activity, feeding pattern, and social factor are associated with the circadian system.[9–11]

The suprachiasmatic nucleus (SCN) acts as the circadian clock in the mammalian brain and synchronizes with circadian rhythms of central and peripheral tissues.[4,12] The SCN is a small, paired structure bilaterally positioned at the anterior part of

the hypothalamus just above the optic chiasma. The SCN receives signals from the retina on exposure to light through the retinohypothalamic pathway.[13,14] The non-visual photosensitive ganglionic cells of the retina regulate the activities of the circadian clock.[15] The activity of SCN depends on the expression of the clock genes [*Period* (*Per*), *Cryptochromes* (*Cry*), and others], which is typically controlled by the transcription-translation feedback loop (TTFL).

Disruption in circadian rhythms causes various physiological disorders and initiate the consequences of pathologies that promote the development of several cancers, including breast, prostate, endometrial, colon, lung, and ovarian cancers, and hepatocellular carcinoma.[16–18] Transient disruption of the circadian system occurs during chronic and acute jet lag, shift work, night work, and insomnia. Circadian misalignment in shift work, night work, and the modern lifestyle may associate with sleep disorders, metabolic dysfunctions, cardiovascular and inflammatory diseases, neuropsychiatric illness, and cancer.[19,20] Several studies have established the link between shift work and a higher risk of cancer.[21–27] Shift work changes the normal physiological activities like feeding pattern, sleep-wake cycle, and circadian clock functions, melatonin secretion that advance the development of cancer. Acute jet lag is a common problem during traveling through multiple time zones. Frequent crossing of alternative time zone causes circadian dysfunction. However, it becomes chronic for airline pilots and flight attendants. The increased rates of cancer incidences have been observed in airline pilots and flight attendants. The predominant type is skin cancer, followed by prostate and breast. Exposure to cosmic ionizing radiation may be associated with a higher incidence of skin cancer.[4,28,29] The present review has focused on the influence of circadian rhythm dysfunction in the progression of cancer in the sight of molecular aspects.

II. STRUCTURAL ORGANIZATION AND NEURAL CONNECTIONS OF THE SUPRACHIASMATIC NUCLEUS

The suprachiasmatic nucleus (SCN) is the site of the master clock in the mammalian brain.[30,31] SCN drives daily variation in many physiological processes such as the sleep-wake cycle and core body temperature regulation, hormone secretion, heart rate, blood pressure, glucose homeostasis.[32] The SCN is a pair of ovoid bodies containing about ~ 10,000 (total ~ 20,000) neurons and supporting cells.[31,33] It is located bilaterally on either side of the third ventricle in the area of the anteroventral hypothalamus, just above the optic chiasm.[13] The neurons of the SCN are the smallest in size (~ 10 μm) and closely packed. It has two parts: core and shell. Shell lies at the dorsal side of the core; the core is the part of the ventral or ventrolateral portion of the SCN.[34] The ventral core region receives input from the retina and transmits signals to the dorsal shell region. The neurons of the core are more active than the neurons of the shell.

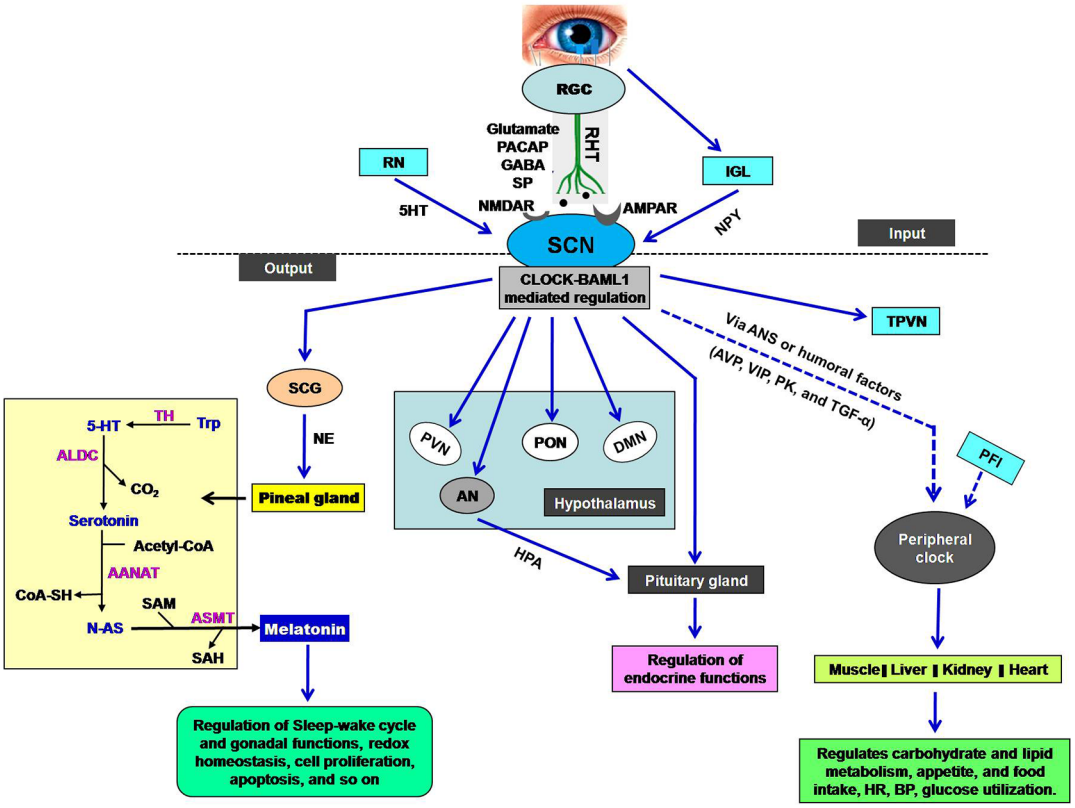
The neurons of the SCN secretes a variety of neurotransmitter, including acetylcholine (Ach), glutamate, neuropeptide Y (NPY), serotonin (5HT), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), arginine vasopressin (AVP), γ-aminobutyric acid (GABA), gastrin-releasing peptide (GRP), and somatostatin.[12] Most of the GRPergic and VIPergic neurons are present in the ventrolateral SCN (core region); they primarily receive retinothalamic input; while AVPergic neurons delineate in the shell region.[34] GABAergic receptors of the SCN also exhibit inhibitory effects.[35]

Retinohypothalamic tract (RHT) primarily arises from retinal ganglionic cells (RGCs). RGCs contain melanopsin,[36] which is very sensitive to blue light (464–484 nm wavelength) and transmits the photic signal to SCN. Only a small fraction of RGCs express melanopsin (Opn4). The principal excitatory neurotransmitters of RHT are glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP). Another neurotransmitter substance P (SP) also might be present in RHT.[12] Conversely, GABAergic inhibitory neurons are co-localized with glutamatergic neurons.[37] Moreover, SCN also indirectly receives light signals from the intergeniculate leaflet of the thalamic lateral geniculate nucleus. The efferent connections from SCN terminate at the preoptic, paraventricular, and dorsomedial nucleus of the

hypothalamus.[38,39] The afferent and efferent pathways of SCN are illustrated in Fig. 1.

III. SIGNALING EVENTS IN THE SCN ON EXPOSURE TO LIGHT

RHT sends the photic signal into the SCN on exposure to light on RGCs. The neurons of the RHT secrete glutamate that binds AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) receptors to depolarize the membrane. Activation of glutamatergic receptors regulates the rhythmic expression of clock genes in SCN (Fig. 2). Glutamate-mediated AMPA or NMDA activation increases intracellular calcium through ryanodine receptors or via the cAMP-mediated system.[31,40] High levels of cytosolic calcium activate intracellular protein kinases. Calcium binds with calmodulin for the activation of calcium-calmodulin-dependent protein kinase (CaMK); it also activates mitogen-activated protein kinase (MAPK) and protein kinase A (PKA). PKA promotes the phosphorylation of cAMP response element-binding protein (CREB) that can translocate to the nucleus to exert ultimate effects (Fig. 2).[41] MAP kinase and phosphorylated CREB, induce the expression of numerous clock-related genes in SCN.[42–44] Activated CREB binds to cAMP response elements (CREs) on



SCN: Suprachiasmatic nucleus, RN: Raphe nuclei, IGL: Intergeniculate leaflet, TPVN: Thalamic paraventricular nucleus, SCG: Superior cervical ganglion, MT: Melatonin, PVN: Paraventricular nucleus, PON: Preoptic nucleus , DMN: Dorsomedial nucleus, AN: Arcuate nucleus, PFI: Periodic food intake, PACAP : Pituitary adenylate cyclase-activating polypeptide, NPY: Neuropeptide Y, 5HT: 5-hydroxy tryptamine/Serotonin, GABA: Gamma amino butyric acid AVP: Arginine vasopressin , VIP: Vasoactive intestinal polypeptide, SP: Substance P, **PK: Prokineticin, and TGF-α: NE: Norepinephrine Transforming growth factor α, RHT: Retino-hypothalamic tract , HPA: Hypothalamic pituitary axis, ANS: Autonomic nervous system; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR: N-methyl-D-aspartate receptor; HR: Heart rate; BP: Blood pressure; Trp: Tryptophan; TH: Tryptophan hydroxylase; 5HT: 5-hydroxy tryptophan; ALDC: Aromatic L- amino acid decarboxylase; AANAT: arylalkylamine N-acetyl transferase; N-AS: N-acetyl serotonin; ASMT: acetylserotonin O-methyl transferase; SAM: S-adenosyl methionine: SAH: S-adenosyl homocysteine**

FIG. 1: Outline presentation of input connections from retina and other areas to the SCN and output signaling to the hypothalamus pituitary, pineal gland, and peripheral tissues for regulation of circadian rhythm

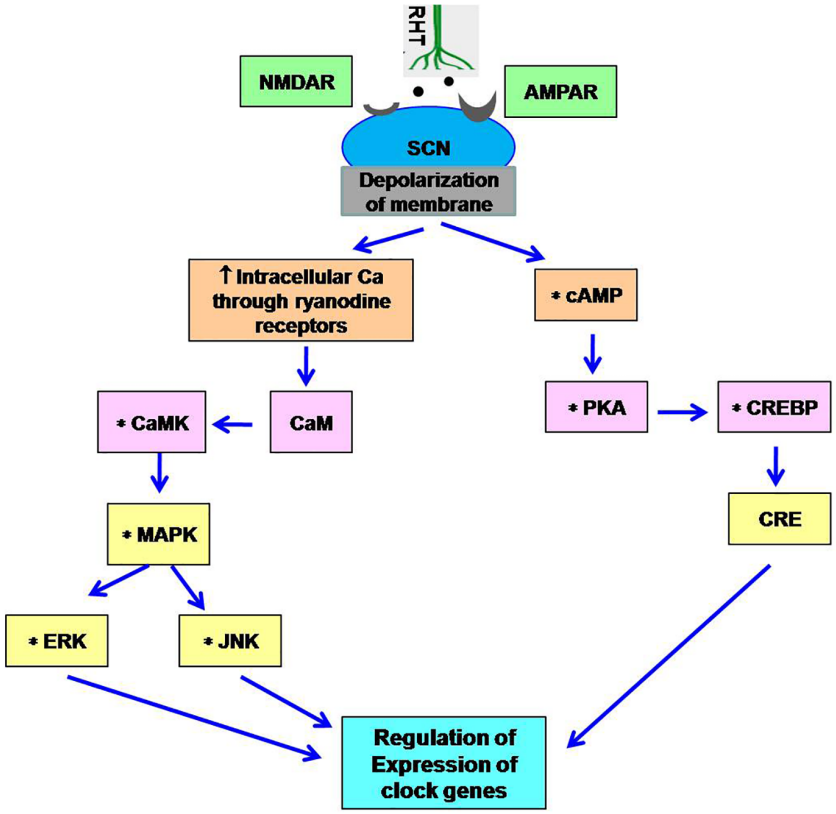


FIG. 2: Events of signal transduction in SCN on exposure to light

DNA in association with co-activator, such as CREB binding protein (CBP). CRE is mostly present at the upstream of the promoter region of the clock genes (Fig. 2).[44,45] The 5′-flanking region of *Per1* and *Per2* genes carries CRE that interacts with CREB for the induction of the expression of *Per* genes.[46] The mutational study had revealed that CRE has a functional role in the expression of *Per* genes.[30] Light exposure is the key signal for the activation of CREB. Application of light impulse in early subjective night activates NMDA receptors and starts phosphorylation at Ser133 and Ser142 of CREB within few minutes. The result is the phase delay of the clock.[47,48] Another study had indicated that the mutant S142A mice are not able to phosphorylate Ser142 and incapable to show the phase shift.[48]

The mammalian circadian clock is also linked with the MAP kinase pathways. There are four different types of MAP kinases in the mammalian system. These are (1) extracellular signal-regulated kinases (ERKs), (2) ERK/big MAP kinase 1 (BMK1), (3) c-Jun N-terminal kinase (JNKs), and (4) the p38 family of MAPKs. The latter two are known as stress-activated MAPKs (SAPKs).[5] The rhythmic appearance of phosphorylated ERK, phospho-p38, and JNK was observed in mammalian SCN.[49] Obrietan et al.[43] reported that activation of p44/42 mitogen-activated protein kinase (MAPK) signaling cascade in the SCN starts after brief exposure to light during the subjective night.

In addition to glutamate, other neurotransmitters are also involved in the signal transduction process

in SCN. VIP secreting neurons are responsible for intra-SCN communication.[50] VIP binds with VPAC2 receptors, causes the closing of potassium channels to depolarize the SCN neurons.[51] The ultimate result is PKA-dependent phosphorylation of CREB that induces *Per1* and *Per2* expression.[52] The deficiency of VIP or its receptor in SCN cells showed low levels of *Per1* and *Per2* expression.[53] GRP secreting cells were found in the SCN core part. It acts through BB2 receptors to induce *Per1*, *Per2*, and c-*fos* expression.[54] Most of the GABAergic neurons are co-localized with neuropeptides secreting cells in SCN. GABA signaling stimulates inhibitory G (Gi) protein.[31] Thus, GABA balances the response of excitatory activity.

Light exposure also stimulates the activity of CREB protein-regulated transcription co-activator 1 (CRTC1). CRTC translocates to the nucleus for its activity. This protein co-activates CREB for expression of both Per1 and salt inducible kinase 1 (SIK1) within the SCN as the gene of SIK1 is clustered with Per1. SIK1 is a Ser/Thr protein kinase (AMP-dependent protein kinases family). SIK1 inhibits further expression of Per1 with an appropriate time delay through phosphorylation and deactivation of CRTC1. Thus, SIK1 exerts negative feedback on exposure to light in clock mechanisms and potentially involves in the regulation of circadian rhythms. This pathway may also be a target for the treatment of circadian dysfunctions including jet lag, and shift work problems.[55]

IV. SCN-PINEAL LOOP FOR MELATONIN SYNTHESIS AND ITS REGULATION

SCN regulates the synthesis and secretion of melatonin. SCN sends the signal to the pineal gland via the superior cervical ganglion (SCG) of sympathetic system. The efferent nerves move downward as the medial forebrain bundle and terminated at the upper part of the spinal cord. The preganglionic nerves converge on the SCG of the sympathetic system. The noradrenergic postganglionic neurons ascend toward the direction of the pineal gland, where they innervate the pineal parenchymal cells.[56–58] The stimulation of sympathetic nerves of the pineal gland starts during the night (dark period). Dark-mediated stimulation induces the release of noradrenaline (NA) from the postganglionic end that triggers melatonin synthesis. Thus, the sympathetic neurotransmitter (noradrenaline) regulates melatonin secretion from the pineal gland. Blood melatonin concentration is high during the night. Brainard et al.[59] reported that melatonin level decreases in human volunteers with dilated pupils who were exposed to monochromatic blue light (464 nm) during the night for 90 minutes (2:00 to 3:30 AM). Despite the pineal gland, extrapineal tissues, including skin, lens, ciliary body, gastrointestinal tract, testis, ovary, uterus, bone marrow, placenta, oocytes, red blood cells, plantlets, lymphocytes, astrocytes, glia cells, mast cells, and neurons can produce melatonin.[60]

Tryptophan is the precursor molecule for melatonin synthesis. At the initial step, tryptophan hydroxylase produces 5-hydroxytryptophan through hydroxylation. After decarboxylation, 5-hydroxytryptophan is converted to serotonin. Arylalkylamine N-acetyl transferase (AANAT) and acetylserotonin O-methyltransferase (ASMT) convert serotonin to melatonin (Fig. 1).[61] Both AANAT and ASMT are primarily present in the pinealocytes. The expression of these enzymes is NA-dependent.[59,61] Melatonin is synthesized in the pineal mitochondrial matrix.[62] Mitochondrial fission and fusion are the main regulatory mechanism.[63] Mitochondrial fusion enhances melatonin production at dark and mitochondrial fission-induced reduction of melatonin synthesis occurs in the daytime.[64] Mitochondrial fusion proteins mitofusin 1 (Mfn1) and Opa1 control fusion,[65] while dynamin-related protein 1 (DrP1) regulates fission.[66,67]

V. MELATONIN RECEPTORS

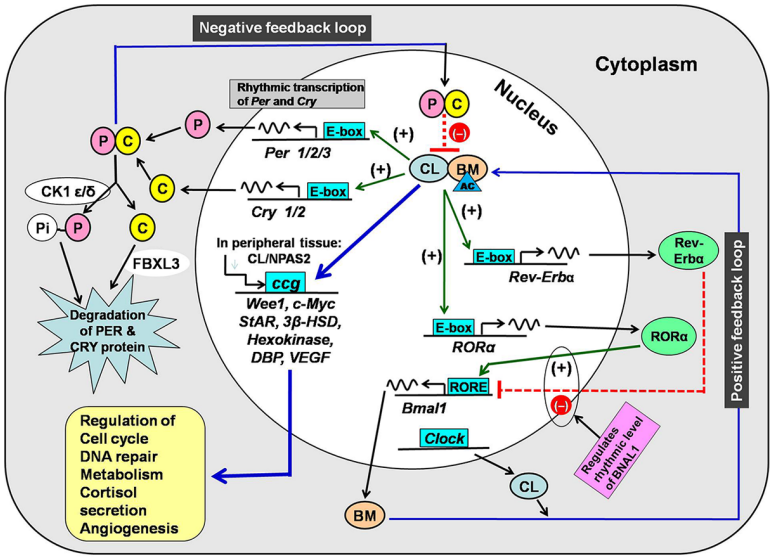
Melatonin acts through three receptors: MT1, MT2, and MT3.[61,68,69] MT1 and MT2 are the G-protein coupled cell surface receptors. MT1 receptor decreases cAMP levels by stimulating inhibitory alpha subunit (Giα) of heterotrimeric G-protein; this activity diminishes PKA activation. MT2 receptor activates Gq-coupled phospholipase C (PLC) for the production of inositol 1,4,5-trisphosphate (IP_3). IP_3 increases intracellular Ca^{2+} levels followed by activation protein kinase C (PKC). PKC can activate MAP

kinase and PI3 kinase/Akt pathways.[70] MT3 receptor is an intracellular cytosolic receptor that is an enzyme quinone reductase 2 (QR2, E.C. 1.10.99.2).[71] MT3-mediated action shows antioxidant activities. Melatonin is an amphipathic molecule, can cross the cell membrane. Intercellular melatonin interacts with ROR (retinoid-related orphan receptor) and RZR (isoforms as nuclear receptors of retinoic acid receptor superfamily), calmodulin (CaM), and calreticulin (calcium-binding protein), tubulin. RZR/ROR regulates the metabolic activity, expression of clock genes, lymphocyte maturation, pro-inflammatory cytokine synthesis.

VI. MOLECULAR EVENTS IN CLOCK FUNCTIONS

Different clock genes are expressed in the SCN and other peripheral tissues. Human expresses approximately 12–14 core clock genes and other 37 circadian associated genes.[6,72,73] The operation of mammalian circadian rhythm is mediated by a complex network of positive and negative feedback loops (Fig. 3).[74] There are multiple sets of clock genes like 3 *Period* (*Per* 1-3), 2 *Cryptochrome* (*Cry* 1-2), *Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1* (BMAL1), *Circadian locomotor output cycles kaput* (CLOCK), 3 *Retinoid-related orphan receptor* (*Ror* α, β and γ), 2 *Reverse-erythroblastosis (Rev-Erb* α and β) and casein kinases 1 (CK1δ and ε) in the mammalian circadian system. Furthermore, some other genes [*Neuronal period-aryl hydrocarbon receptor nuclear translocator single-minded 2* (*Npas2/Mop4*), *Aryl hydrocarbon receptor nuclear translocator like 2* (*Arntl2/Mop9*), and *F-box/LRR-repeat 3 (Fbxl3*)] are also involved in clock functions.[30,75] The functional aspects of these genes are given in Table 1.

Cryptochromes (CRYs) are petrin/flavin-containing protein; it is related to DNA repairing enzymes DNA photolyases but it does not show DNA-repairing activity.[76] Association of CRY with



P: PER, C: CRY, BM: BMAL1, CL: CLOCK, , AC: Acetyl group, CK1: Casein kinase1, ccg: Clock controlled genes , 3β-HSD: 3-Beta-hydroxysteroid dehydrogenase, Pi: Phosphate, ROR: Retinoid-related Orphan Receptor, FBXL3: F-box/LRR repeat protein 3, NPAS2: Neuronal period-aryl hydrocarbon receptor nuclear translocator single-minded protein 2, Rev-Erbα: Nuclear receptor subfamily 1 group D member 1, DBP: Albumin D-site-binding protein, VEGF: Vascular endothelial growth factor, StAR: Steroidogenic acute regulatory protein, E-box: Promoter sequence for binding of clock-Bmal1 complex (CACGTG), (+) Induction, (—) Repression.

FIG. 3: Mechanism of performance of positive and negative feedback loop for the regulation of expression of core clock genes of the mammalian circadian system. CLOCK/NPAS2–BMAL1 regulates the expression of tissue-specific clock-controlled genes.

TABLE 1: List of human circadian clock genes, their chromosomal loci, functions, and SNP–mediated diseases[6,32,97]

Genes	Locus	Protein	Functions	SNP–associated diseases
Per1	17p13.1	PER 1/2/3 (PER – Period)	PER protein exerts a repressive effect on the CLOCK–BMAL complex to regulate its transcription. PER1 and PER2 have a tumor–suppressive effect	Glioma and prostate cancer
Per2	2q37.3			Diabetes, breast cancer, prostate cancer, and advanced sleep phase disorder
Per3	1p36.2			Diabetes, bipolar disease, breast cancer, prostate cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, and delayed sleep phase disorder
Cry1	12q23.3	CRY 1/2 (CRY – Cryptochrome)	CRY forms heterodimers with PER represses its transcription by inhibiting CLOCK–BMAL1 mediated transactivation	Diabetes, depression disease, glioma, breast cancer, prostate cancer, and hepatocellular carcinoma
Cry2	11p11.2			Diabetes, depression disease, breast cancer, prostate cancer, and non–Hodgkin's lymphoma
Clock	4q12	CLOCK (Circadian locomotor output cycles kaput)	CLOCK heterodimerizes with BMAL1 to enhance target gene (*Per* and *Cry*) expression CLOCK has several important functions in cellular micro–environment. It has the capacity of chromatin remodeling due to its histone acetyltransferase activity The UV radiation mediated genotoxic stress is protected by CLOCK as it involves growth arrest, DNA repair, and apoptosis. The result is the stoppage of cell cycle and proliferation at the time of DNA damage	A variant in the Clock gene is associated with dyslipidemia, diabetes, infertility, colorectal cancer, breast cancer, glioma, bipolar disease and evening preference in sleep–wake behavior
Npas2	2q11.2	NPAS2 (Neuronal period–aryl hydrocarbon receptor nuclear translocator single–minded protein 2)	*NPAS2* has expressed in vascularized tissue. NPAS2 protein is a member of the basic helix–loop–helix PAS class of transcription factors. It dimerized with BMAL1 and then binds to E–box to regulate the expression of clock–controlled genes. Moreover, it has tumor suppressor activity	SNP (intronic A > G) of NPAS2 is associated with breast cancer
Bmal1	11p15.2	BAMAL1 (Brain and muscle aryl hydrocarbon receptor nuclear translocator–like 1)	BMAL1 is the transcription inducer of various clock components. Its activity depends upon heteromeric dimerization with CLOCK. PER–CRY conjugates repress the inductive effect of the CLOCK–BMAL1 complex	SNP of BMAL1 promotes Infertility, bipolar disease, and breast cancer

TABLE 1: (*continued*)

Genes	Locus	Protein	Functions	SNP–associated diseases
Arntl2	12p11.23	ARNTL2 (Aryl hydrocarbon receptor nuclear translocator like)	Its activity is similar to BMAL1	
CK1ε	22q13.1	CK1ε (Casein kinase 1 epsilon)	CK1ε/δ phosphorylates PER protein to regulate its cytoplasmic accumulation	Delayed sleep phase disorder
CK1δ	17q25.3	CK1δ (Casein kinase 1 delta)		Advanced sleep phase disorder
Rev–Erbα	17q21.1	Reverse–erythroblastosis α [Nuclear receptor subfamily 1 group D member 1 (NR1D1)]	REV–ERBα exerts antagonistic effects against RORα mediated activity, inhibits the expression of *Bmal1*	Mutation in Rev–Erbα is associated with leukemia
Rev–Erbβ	3p24.2	Reverse–erythroblastosis β [Nuclear receptor subfamily 1 group D member 2 (NR1D2)]	Act as a transcription repressor to regulate energy utilization and metabolism	
Rorα	15q22.2	Retinoid–related orphan receptors alpha	ROR proteins belong to the nuclear receptor family RORs regulate the rhythmic expression of clock components. CLOCK/NPAS2–BMAL1 complex induces the transcription of *Rorα*, *Rorβ*, and *Rorγ*. RORα mostly increases the transcription of BMAL1 at the positive feedback loop The tissue–specific different isoforms of RORs are due to the use of alternative promoter and exon splicing activity. These isoforms regulate physiological functions	It has potent tumor–suppressive activity. Mutation in *Rorα* increases the risk of breast cancer
Rorβ	9q21.13	Retinoid–related orphan receptors beta		SNP induces breast cancer
Rorγ	1q21.3	Retinoid–related orphan receptors gamma		
Fbxl3	13q22.3	F–box/LRR–repeat protein 3	It regulates the rate of degradation of CRY protein, maintains its cytoplasmic concentration	

the electron transferring flavin alters the redox state of the protein and DNA binding property. The PAS [PER (period)-ARNT (aryl hydrocarbon nuclear receptor translocator)-SIM (single-minded)] domain of PER protein promotes dimerization during their functional state. The *Per* and *Cry* genes are rhythmically transcribed which is modulated by CLOCK and BMAL1 complex. CLOCK belongs to bHLH-PAS [basic helix-loop-helix (bHLH)–PER-aryl hydrocarbon receptor nuclear translocator (ARNT)-single minded (SIM)] protein.[77] The function of the positive feedback loop arises when the PAS-PAS heterodimeric form of CLOCK and BMAL1 induces the expression of many genes (*Per*, *Cry*, *Rev-Erb*) related to circadian rhythm. CLOCK-BMAL1 complex recognizes the specific nucleotide sequence CACGTG, termed as E-box, which is present at the upstream of the *Per*, *Cry*, and 2 orphan nuclear receptors, *Ror* and *Rev-Erb*.[78–80] Mutation of *the Clock* genes (dominant-negative *Clock* allele, CLOCK-Δ19) produces mutant CLOCK, which cannot regulate the transcriptional activity after binding with BMAL1. The CLOCK mutation significantly reduces PER (1-3), CRY (1-2) levels in SCN, shows abnormally long circadian periods.[78,81] Despite CLOCK, NPAS2 (MOP4) in SCN is also involved in circadian activity. The NPAS2 is a paralog of CLOCK; it may heterodimerize with BMAL1 in the SCN to regulate the transcriptional control of clock genes. However, CLOCK:BMAL1 and NPAS2:BMAL1 act differently at the promoter level.[82] The peripheral vascularized tissues contain neuronal period-aryl hydrocarbon receptors for NPAS2 instead of CLOCK protein. Its function is very similar to CLOCK protein. The peripheral cells are not arrhythmic in absence of CLOCK, while CLOCK deficient *Npas2* knockout cells show arrhythmic behavior.[83]

CLOCK-BMAL1 complex transiently regulates the transcription-translation process of the clock components like PER, CRY, RORα, REV-ERBα (Fig. 3). Accumulation of PER and CRY in the cytoplasm promotes the formation of the heterodimer. The heterodimeric PER-CRY complex then translocates to the nucleus, where PER-CRY heterodimer inhibits the transactivating effects of CLOCK-BMAL1, resulting in termination of transcription of *Per*, *Cry*, *Ror*, and *Rev-Erb* genes. This inhibition completes the PER-CRY-mediated negative feedback loop (Fig. 3).[84,85] Reppert and Weaver[30] had suggested two mechanisms for the negative feedback effect. It is assumed that CRY protein may either directly pull the CLOCK-BMAL1 heterodimer from E-Box or CRY protein disrupts the CLOCK-BMAL1 heterodimer.

Another regulatory step is the acetylation of BMAL1. The CLOCK protein shows intrinsic acetyltransferase activity. CLOCK-mediated acetylation occurs at the specific lysine residue (K538) of BMAL1 that induces the formation of heterodimeric BMAL1-CLOCK complex. Initially, acetylated BMAL1 indirectly helps in RNA polymerase II (Pol II) pause release to continue the elongation of mRNA. The TIP60 (60 kD Tat-interactive protein) acetylates Lys538 of BMAL1, leading to recruitment of the co-activator BRD4 (bromodomain-containing protein 4) and the pause release factor P-TEFb (positive transcription elongation factor b).[86–88]

BRD4 belongs to the bromodomain and extra terminal domain (BET) protein family. The bromodomain can bind with acetylated lysines of histones, as well as transcription factors.[89] The cellular pause release factor P-TEFb is composed of T-type cyclins and CDK9 (cyclin-dependent kinase 9).[90] BRD4 activates P-TEFb and forms transcriptional activators BRD4-PTEFb (super elongation complex), which starts phosphorylation of Ser2 at the carboxy-terminal domain (CTD) of Pol II, resulting in the release of active Pol II followed by elongation of *E-box*-containing circadian genes.[91] In association with phosphorylation of Pol II, P-TEFb phosphorylates the other two factors: i) the pausing factors NELF (negative elongation factor) ii) and DSIF (DRB sensitivity inducing factor). Phosphorylation of NELF releases active Pol II. On the other hand, phosphorylated-DSIF acts as a positive elongation factor.[90,92,93] Petkau et al.[91] also reported that the acetylation of Lys538 of BMAL1 is low in TIP60-deficient cells, leading to a reduction of BRD4-P-TEFb recruitment along with the expression of *Dbp*, *Per1*, and *Nr1d1* genes. The substitutional mutation of Lys538 to Arg showed the interaction of TIP60 with BMAL1, but BRD4-P-TEFb complex formation and pause release of Pol II were diminished. Acetylation is also useful for the binding of CRY with chromatin-bound

CLOCK-BMAL1 complex. This binding starts repressive activity by imposing the transcriptionally silent RNA Pol II; therefore, acetylation of BMAL1 also involves in repressive activity.[94] Thus, the pause release and pausing of RNAPol II serve as a checkpoint for the expression of core clock genes in the regulatory step of the mammalian circadian clock functions.

CRY and PER levels tend to decrease at night. Low levels of CRY and PER no longer continue their repressive activity. This initiates a new cycle of the transcription activation by the CLOCK-BMAL1 complex.[6,95] Degradation of Cry protein promotes the recruitment of co-activators such as CBP/p300 followed by *Per* and *Cry* transcription. Newly synthesized Cry and Per protein again stop their transcription after interaction with the CLOCK-BMAL1 complex at the repression phase of the circadian cycle.[96]

The orphan nuclear receptors RORα and REV-ERBα (transcriptional regulator) have a separate feedback loop in the regulation of BMAL1 mediated expression. They bind a particular target sequence, called RORE sequence (AAAGTAGGTCA), which is present at the upstream of the *Bmal1* promoter. After translocation of RORα and REV-ERBα to the nucleus from the cytoplasm, they compete with each other for binding to the ROR responsive element (RORE). They exert an antagonistic effect at the functional level. RORα activates *Bmal1* transcription, while REV-ERBα inhibits transcriptional activity. This antagonistic effect maintains the rhythmic level of BMAL1 protein as well as CLOCK-BMAL1 complex formation.[11,32,80,84,97]

The degradation of PER and CRY are mediated by cytoplasmic casein kinases CK1δ and CK1ε, and FbxL3, respectively. CK1δ and CK1ε can phosphorylate the PER proteins for their degradation.[98,99] The importance of phosphorylation was studied by *tau* (τ) mutation in the Syrian hamster, which shows a short-period phenotype.[100] Actually, the *tau* locus encodes casein kinase 1 (CK1). Replacement of a conserved arginine178 by cysteine during mutation decreases V_{max} of the enzyme as well as autophosphorylation capacity.[101] Mutant casein kinase has more affinity to bind with PER but shows low phosphorylation capacity. Alternatively, Gallego et al.[3] proposed that the kinase mutant $CK1\varepsilon^{tau}$ increases kinase activity to enhance the rate of phosphorylation of specific residues for degradation of PER, resulting in a change in period length of circadian functions. Toh et al.[102] reported that familial advanced sleep phase syndrome (FASPS) was associated with mutation of CK1δ and CK1ε, which phosphorylates the PER2 protein. The degradation of PER depends on the ubiquitination of the protein. In this process, phosphorylation of PER is a prerequisite step to recruit the ubiquitin ligase. The stability of PER1 and PER2 are very less when CK1δ and CK1ε are overexpressed.[98] Phosphorylation of PERs induces the formation of binding sites for β-transducin repeat-containing protein (βTrCP) that is the part of F-box containing E3 ubiquitin ligase.[103,104] The degradation of CRYs is done by another ubiquitin E3 ligase (F-box protein), known as FbxL3.[105] Mutation of FbxL3 lowers the degradation of CRYs, resulting in prolonged stability of CRYs and extended period length.[80] Despite the degradation of PERs and CRYs, Phosphorylation of BMAL1 is done by casein kinase 2 alpha (CK2α), which is also associated with control of circadian clock functions.[106] BMAL1 is also rhythmically SUMOylated in *in vivo* conditions. Proper SUMOylation is essential for the interaction with CLOCK.[107] Lee et al.[108] had shown a close relationship between BMAL1 SUMOylation and turnover of BMAL1. The SUMOylation effect is also associated with promyelocytic leukemia (PML).

The neurons of the SCN are the principal regulator of circadian oscillations; however, the astrocytes of the SCN have an unexpected role in circadian rhythm. It has also suggested that modification of astrocyte functions can modulate complex neural activities like cognition, fear, sleep, and behavioral performances. Generally, the neurons of the SCN are metabolically active during circadian daytime, whereas SCN astrocytes are active during circadian nighttime. These astrocytes suppress the activity of SCN neurons by modulating the activity of glutamatergic gliotransmission of NMDA receptors. The study also revealed that in the presence of Cry1/2-null SCN neurons, astrocytes can drive molecular activities as well as circadian rhythm in mice. However, astrocytically dependent rhythms were significantly shorter than the SCN neuronal rhythms. Astrocytic clocks operate this activity by

modulating the core clock gene expression via glutamatergic signals. Thus, not only SCN neurons but also astrocytes can autonomously regulate the expression of clock genes in the SCN.[109,110]

VII. RELATIONSHIP TO THE PERIPHERAL CLOCKS

The circadian oscillators are not typically present in the SCN. They also exist in peripheral organs, particularly in the cells. The SCN acts as a synchronizer for the peripheral oscillators. The process of synchronization is mediated by the autonomic nervous system and hormones.[31] However, peripheral tissues can maintain their oscillation in the circadian fashion in the absence of SCN. Ablation of SCN in mice showed the rhythmic expression of mRNA in the peripheral tissues (adrenal gland, liver, kidney, and heart), which is synchronized with the light-dark cycle.[111] The circadian clock governs the physiological functions through transcriptional and translational regulation. Tissue-specific peripheral clocks involve in this regulatory mechanism.[85] Several types of post-transcriptional modifications of mRNA such as splicing, polyadenylation, and decay function are essential to make mature mRNA of clock proteins.[112,113] However, post-translational modifications like acetylation, O-GlcNAcylation, poly-ADP ribosylation, phosphorylation, SUMOylation, and ubiquitination effectively construct the mature protein.[85,94,114,115]

VIII. IMPACT OF CIRCADIAN DYSFUNCTION IN PROGRESSION OF CANCER

SCN is the central circadian pacemaker. Any impairment in the SCN-mediated clock system advances cancerous growth in the different tissues. At the experimental level, bilateral electrolytic lesions of the SCN increase tumorigenesis after implantation of Glasgow osteosarcoma and pancreatic ductal adenocarcinoma cells in the mice model system.[116] It has assumed that disruption of the circadian clock advances cancer initiation or progression through four ways: i) Circadian clock components regulate the expression of numerous genes that are involved in a daily rhythm, regulation of cell cycle, DNA repair, metabolism, and so on. Circadian dysfunction disrupts most of the cellular functions, leading to cancer development (Fig. 4). ii) Circadian clock protein may interact with oncogenic protein that initiates cancer. iii) The activity of clock proteins alter with the variation of different cellular environments like redox state, expression of co-factors, covalent modification (acetylation, phosphorylation) of the clock protein. These modifications influence oncogenic programs. iv) Circadian disruption alters the secretion of cytokines, hormones, neurotransmitters, and tumor-specific metabolites, resulting in the advancement of malignancy. Cancer cells impose the circadian clock disruption that governs metabolic reprogramming and survival advantages. The circadian clock acts as a gatekeeper that regulates the cell cycle, DNA repair, sugar utilization, metabolism, detoxification, autophagy, and so on. Disruption of the circadian clock is crucial for proliferation, survival, and metabolism.[117]

The importance of several circadian core genes, their functions, and the effect of polymorphism has reported to establishing their role in disease progression.[6,11,32,33] The dysfunction of clock genes activity may increase cancer susceptibility as they contribute to the regulation of DNA damage and repair, carcinogen metabolism and/or detoxification process, regulation of cell cycle, and apoptosis; these activities are driven by clock gene-mediated regulation of expression of *p16*, *p21*, *Cyclin D1*, *Wee1*, and *p53* (Fig. 4).[118–121] Variants of the clock genes like *Arntl*, *Clock*, *Bmal1*, *Ck1ε*, *Cry*1-2, *Npas2*, and *Per*1-3 are associated with human breast carcinoma, colorectal carcinoma, prostate carcinoma, Non-Hodgkin lymphoma, and pancreatic carcinoma.[6,11,118]

In modern society, humans have extended their work schedule that changes their lifestyle. Many works such as medical services, supply of electricity, operation of nuclear power plants, transport services, monitoring of satellite movements and the space shuttle, and continuous operation of industrial work are going on round the clock. In these sectors, people are working round the clock in different shifts, including night-shift work. A survey report indicated that 15–30% of adults of Americans, Europeans, and Australians were involved in shift work.[122] Shift work, night work, inappropriate lifestyle, and light-at-night disrupt

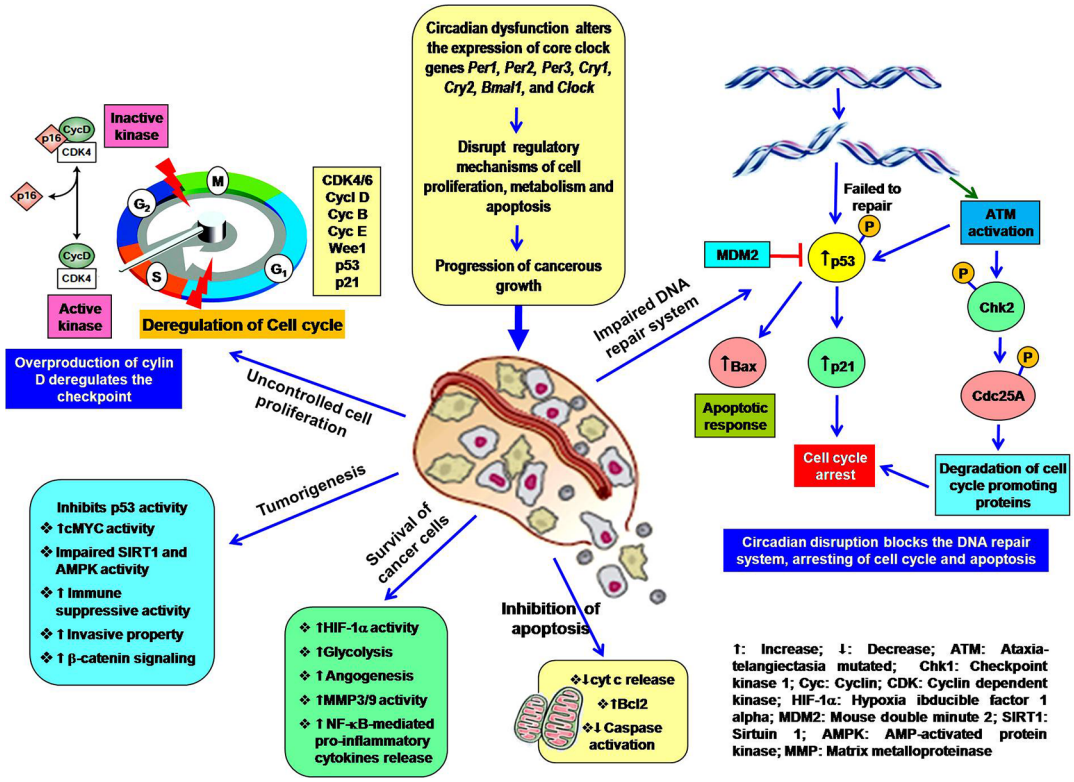


FIG. 4: Circadian clock dysfunction influences cancer development

the internal circadian clock machinery that leads to impaired sleep-wake cycle, metabolic disorder, and cancer progression. Disruption of circadian clock function by anthropogenic factors like shift work and light exposure at night advances hormone-dependent cancers.[123,124] Based on epidemiological and experimental studies, International Agency for Research on Cancer (IARC) has categorized the shift work as "carcinogenic to humans (Group 2A)."[125] There are several impact of night-shift work on cancer progression; these include i) desynchronization of clock functions, ii) night time light-induced melatonin suppression, iii) impaired physiological activities and sleep, iv) improper lifestyle management, and v) inappropriate vitamin D metabolism.[4,126] Concerning night-shift work and cancer risk, contradictory analyses are also present. Dun et al.[127] had made a meta-analysis based on 57 eligible studies. They observed that fixed or rotating night-shift work does not influence cancer in all aspects. The intensity, duration, and pattern of nightshift work may be associated with cancer, but night-shift work has little association with cancer risk. Moreover, night-shift work may reduce the cancer risk in Asians compared to Americans and Europeans. The Asian people have distinct food habits, lifestyles, and gene pools than others. Thus, a negative finding is also available.

Chronic jet lag is also related to circadian dysfunction. The experimental study had revealed that impose of jet lag in mice suppresses the expression of *Per2* and *Rev-Erbα*, leading to the development of Glasgow osteosarcoma, lymphoma, and hepatocellular carcinoma (HCC).[10] Mutation of clock genes, particularly *Cry1/2*$^{-/-}$, *Per2*$^{-/-}$, or *Per1*$^{-/-}$, *Per2*$^{m/m}$ in mice are susceptible to malignancies on exposure to chronic jet lag.[128]

A. Circadian Dysfunction and Expression of Clock Gene

Impaired expression of core clock genes is associated with cancer cells. Dysfunction of circadian

rhythm creates an imbalance in the expression of oncogenes and tumor suppressor genes. This effect advances the metabolic alteration, cell proliferation, chemoresistance, apoptosis inhibition, invasiveness, and migration of the cancer cells.[129] The pattern of clock gene expression is not similar in different cancer cells. Inappropriate expression of core clock genes *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Bmal1*, and *Clock* is positively associated with carcinogenesis in humans.[118] Several experimental studies indicated the role of core clock genes in cancer development. *Per2* (*Per2*$^{m/m}$) mutation in mice showed circadian dysfunction,[130] the animals were susceptible to tumor growth in different experimental conditions (exposure of gamma rays, treatment with diethylnitrosamine).[128,131–133] Li et al.[134] reported that PER1 also had anti-tumor activity. Alteration in *Per* genes in mice exhibits salivary, liver, ovarian cancers, and lymphoma.[132,133] Lee et al.[128] reported that both Per2 and p53 are most important in tumorigenesis; lacking both genes aggressively advances tumor formation. Clock mutation (Clock$^{\Delta 19/+}$) is also associated with cancer as the mutation decreases PER expression. Mutation of Bmal1, Cry1, and Cry2 in mice shows lymphoma, liver, and ovarian cancer.[128] Contradictory results are also available. Some reports indicated that mutation of Per has no effects on tumorigenesis.[135] Puram et al.[136] reported that CLOCK and BMAL1 complex induces the proliferation of cells in acute myeloid leukemia (AML) and deletion of BMAL1 restricts the progression of leukemia. Another report indicated that deletion of CRY and mutation in p53 make the mice less sensitive to tumor growth.[137] Thus clock genes exhibit bifunctional activities. The mutation of clock genes acts as a tumor-inducing factor in some tissue, while tumor-suppressive action is also possible. The database of The Cancer Genome Atlas (TCGA) and the NCBI Gene Expression Omnibus (GEO) supports the differential expression pattern of clock gene in tumor samples and non-tumor samples.[72,138] Chuffa et al.[139] indicated the impaired expression of various clock genes in different cancer cells. Low levels of *Per1*, *Per2*, *Cry1*, *Cry2*, and *Bmal1* expression were observed in leukemia, melanoma, breast, liver, colon, and prostate cancer. Alternatively, breast and liver cancer cells express an increased level of *Clock* genes. The expression of *Rev-Erbα* was also high in breast and colon cancer. SCN-melatonin axis operates the anti-cancer property. SCN promotes melatonin synthesis that has tried to preserve the normal levels of Per, Cry, Bmal1, and RORα in cancer cells. Per2 and Cry2 exhibit tumor-suppressive activity.

Masri et al.[140] indicated a link between circadian clock disorder and epigenetics-induced cancer. Several studies suggested that shift work can induce epigenetic changes that alter circadian gene expression and carcinogenesis.[141–143] Hypermethylation at the promoter site of the core clock genes may induce epigenetic changes that can influence carcinogenesis.[144] Hypermethylation of the promoter differentially regulates the oncogenic process. Hormone-sensitive and insensitive breast cancer cells respond differentially to hypermethylation of the CRY2 promoter; the methylation effects are relatively less sensitive in estrogen receptor and progesterone (ER/PR)-negative cancer cells but reverse effects appear in ER/PR-positive tumor cells.[145] Alternatively, hypermethylation at the CLOCK promoter increases the expression of *CLOCK* and decreases the risk of breast cancer compared to normal individual.[146]

Different factors modulate the properties of DNA during carcinogenesis. Histone deacetylation is one of the important processes for this purpose. SIRT1 is a class of histone deacetylase that regulates the expression of clock genes in cancer cells. A high level of SIRT1 promotes cell proliferation due to its deacetylation activity. The deacetylation activity of SIRT1 antagonizes the effects of acetylation of BMAL. SIRT1 modulates the *Clock* and *Bmal1* transcription by regulating the activity of the RORα response element. The Clock:Bmal1 complex acts on the E-box promoter for the expression of SIRT1. Moreover, BMAL1 regulates the activity of NAMPT (NAD synthesizing enzyme) that controls the functions of SIRT1. Although, BMAL1 shows anti-cancer property by activating the p53;[147] results are also available in favor of BMAL1-induced cancer progression. Deletion of *Bmal1* decreases the number of leukemia stem cells.[136] BMAL1 increases the expression of MMP9 to influence the invasiveness and metastasis of breast cancer cells.[148] Thus, BMAL1 differentially regulates cellular

activity. Melatonin interferes with the expression of CLOCK, BMAL1, and SIRT1 that is the vital step for anticancer effects.[139,149,150] Thus, melatonin effectively modulates the expression of clock genes and SIRT1 activity in cancer cells.

B. Regulation of Cell Cycle by Clock Genes

DNA replication and cell cycle normally happen at night to avoid the effects of UV radiation.[33] The regulation of the cell cycle occurs at the different checkpoints (G_1/S, G_2/M). Cyclin-dependent kinases (CDK1, CDK2, CDK4, CDK6, different cyclins (cyclinD, cyclinA, cyclinB, cyclinE) and CDK inhibitors p21, p57, p27 essentially help to cross the checkpoint; these proteins are expressed in a circadian fashion.[151,152] Uncontrolled cell proliferation is the primary feature of cancerous growth. Deregulation of the cell cycle at the checkpoint starts excessive cell proliferation. During the cell cycle, cyclin B and cyclin-dependent kinase 1 (CDK1) form the active complex that is essential to cross the G2/M checkpoint. CLOCK-BMAL1 complex and ROR/REV-ERB can regulate the cell cycle.[132,153] However, Chk1, Wee-1, and Mik-1 proteins arrest the cell cycle when DNA damage is detected.[32] Per and Cry regulate the activity of ATM (ataxia-telangiectasia mutated), Chk1 (checkpoint kinase 1), Chk2, ATR (ATM and RAD3-related), TIM (Timeless), and MCM 2 (minichromosome maintenance protein 2).[33] The activity of *Bmal1*, *Clock*, *Per*, and *Cry* genes regulate DNA replication by modulating the activity of Wee-1 and p53 proteins, as well as thymidylate synthase.[128,154] PER proteins inhibit cyclin D, cyclin B, CDK4/6 MDM2 (mouse double minute 2)-induced p53 degradation, while CRY proteins block the functions of MYC.[4] P16-Ink4A inhibits CDK4 and CDK6-dependent phosphorylation of pRB and arrests the cell cycle at the G1/S checkpoint. Circadian disruption is unable to maintain the expression of PER2-NONO (RNA binding protein)- dependent expression of P16-Ink4A; thus, inhibition of phosphorylation of pRB no longer be maintained. Phosphorylation of pRB induces the expression of cyclin D and MYC for cell proliferation.[155,156]

CLOCK, BMAL1, and MYC are the transcription factors having a basic helix-loop-helix (bHLH) domain. They act through the E-box promoter.[157] A balance is necessary for the functions of CLOCK, BMAL1, and MYC to maintain normal cell growth, and to prevent tumorigenesis. Circadian dysfunction-mediated imbalance in CLOCK-BMAL1 activity makes the space for the functions of oncogenic MYC protein. MYC and MIZ1 cooperatively downregulate the expression of core clock genes.[158] A high level of MYC protein promotes cellular proliferative activity. MYC protein induces the expression of genes related to cell proliferation and survival.[120] MYC inhibits the clock gene expression through REV-ERBα, which has a negative effect on BMAL1 expression. Alternatively, MYC activates metabolic sensor protein AMPK to alter the glucose and amino acid metabolism.[159] AMPK is one of the vital metabolic regulators. This kinase enzyme regulates fatty acid metabolism, insulin sensitivity, glycolytic activity; alternatively, increases gluconeogenesis by decreasing PKA activity. Thus, metabolic reprogramming by oncoprotein increases the stability of tumor cells.

The proteins of core clock genes regulate the cell cycle and prevent cancer development. PER1 and PER2 have the ability to suppress breast cancer by inducing apoptosis. In breast tumors, the expression of both Per1 and Per2 becomes low. PER proteins suppress the expression of *c-Myc*. Per2 mutants show the deregulation of c-Myc expression followed by the disturbance in the expression of cyclin D1 and Gadd45. Per2 also maintains the activity of p53. p53 is a tumor suppressor protein, regulates DNA repair, genetic stability, cell cycle, cellular stress, and apoptosis. PER2 protects the p53 by inhibiting MDM2-mediated ubiquitination.[160,161] However, p53 and MDM2 maintain the intracellular PER2 levels that establish a feedback loop to regulate the concentration of PER2.[162,163] Overexpression of Per2 in colon cancer arrests cell cycle and starts apoptosis. CRY2 also controls the activity of MYC in two ways. It interferes with the post-translational modification of MYC and also increases the degradation of this protein through the FBXL3-containing E3 ligase. Deletion of MMYC in mice model induces MYC-mediated

lymphoma.[164] However, the expression of other checkpoint proteins like ATM and Chk2 is regulated by PER1. Another cell cycle suppressor protein is WEE-1. PER and CRY regulate the induction of WEE-1. Any defect in *Cry* expression alters the level of Wee-1 and Cyclin D1; the result is deregulation of the cell cycle. Therefore, disruption of PER and CRY causes impaired cell proliferation and tumor growth (Fig. 4).[132,165,166]

Replication of telomeres are the vital step for the cell cycle. A specific enzyme known as telomerase is responsible for this activity. Cancer cells also maintain the activity of telomerase to avoid telomere shortening. CLOCK-BMAL complex binds with the E-boxes present in the telomerase reverse transcriptase (TERT) gene promoter to regulate the expression of telomerase. Disruption of circadian rhythm deregulates the expression of telomerase and promotes undesirable cell growth.[167]

C. Influence of Light at Night on Cancer Development

Melatonin shows potent anti-cancer effects, and its synthesis is directly associated with environmental light. High-intensity of artificial light and insufficient day-light in the office environment suppress melatonin synthesis in the pineal gland and influences the incidence of tumor growth.[168] Several authors suggested that light-at-night is detrimental to health in all aspects, including cancer progression.[169–171] Melatonin acts as a potent oncostatic agent; it blocks carcinogenesis in different tissues, including the breast, prostate, ovaries, liver, kidney, lung, pancreas, colorectal, skin, and the gastrointestinal system.[172,173] Light-induced suppression of melatonin is a crucial factor in cancer progression.[174] Exposure to bright light at night suppresses melatonin secretion in shift workers and night workers. Song et al.[171] reported that light-induced suppression of melatonin increased the rate of development of breast, ovarian, and prostate cancer. Impaired melatonin secretion occurs in human volunteers after exposure to monochromatic blue light (464 nm) at night for 90 minutes (2:00 to 3:30 AM).[59] The epidemiological study had revealed that long-term night-shift work is associated with a high risk of cancer development in various tissues, like the breast and prostate.[174,175] Pauley[176] reported that the risk of breast cancer increased 36% to 60% in the females working in the night shift. Light-at-night shows the carcinogenic property. Shift work or exposure to bright light at night alters the circadian rhythm and melatonin secretion, which has a significant impact on the occurrence of breast cancer in females.[175,177–181] Papantoniou et al.[182] indicated that the prevalence of prostate cancer was high in males who were facing bright light at night. The people of urban and industrial areas are involved in night work and shift work. They are exposed to bright artificial light during subjective nighttime that hampers the blood melatonin levels. These people are vulnerable to the progression of cancer development due to hormonal imbalance, metabolic disorder, and inflammatory response. Therefore, inappropriate use of light-at-night may be associated with today's high rates of breast, prostate, colorectal and other cancers in the industrialized world.

D. Effect of SCN-Melatonin-Mediated Regulation of Clock Components

There is a close relationship between melatonin and SCN functions. SCN regulates the synthesis of melatonin from the pineal gland. Melatonin releases into the cerebrospinal fluid (CSF), circulated to the SCN and pars tuberalis (PT) of the pituitary gland. Agez et al.[183] reported that melatonin controlled the expression of core clock genes. The SCN displays the melatonin receptors (MT1 and MT2) on its surfaces. Both MT1 and MT2 receptors are G-protein-coupled. MT1 acts through the inhibitory G-alpha subunit (Gαi) of the trimeric G-protein. The binding of melatonin with MT1 decreases the intracellular cAMP levels. This effect critically regulates the expression of clock genes through a complex mechanism. The expression of *Cry1*, *Bmal1*, and *Clock* genes decreases after the deletion of MT1 receptor-gene without affecting MT2 expression.[184] Moreover, Hablitz et al.[185] reported another view; they proposed that the functions of melatonin receptors in SCN were mediated by G-protein-coupled inwardly rectifying potassium (GIRK) channels.

This activity regulates the depolarization membrane and signal transduction.

The SCN-melatonin feedback loop maintains the expression of clock genes, where BMAL1 plays a vital role. Night-time melatonin inhibits the activity of the ubiquitin-proteosome system that leads to interfering in proteasomal cleavage of BMAL1. The persistence of BMAL1 increases its availability and then enhances the levels of CRY, PER, REV-Erbα.[186] Exogenous supplementation of melatonin in rats before the onset of the dark phase, significantly improved the transcription rate of *Per1*, *Per2*, *Cry1*, *Cry2*, and *Bmal1* genes.[187] Chuffa et al.[139] reported that the SCN-melatonin loop is associated with the regulation of core clock gene expression, functions of the cell cycle, cell survival, and cell repair mechanisms. Melatonin shows pleiotropic effects. It efficiently regulates the clock gene activity in normal cells but differently regulates the gene expression in cancer cells.

E. Effect of Circadian Rhythm–Mediated Neuroimmune-Endocrine Regulation and Its Impact on Cancer Progression

The clock mechanism is very complex in the physiological system. SCN synchronizes the overall clock functions in the body but the cells and tissues have their clock mechanism. SCN is linked with the different areas of the hypothalamus (Fig. 1). There is an emerging relationship between SCN and hypothalamus-pituitary functions. The hypothalamus-pituitary-adrenal axis (HPAA) impacts the immune system. Secretion of adrenocorticotrophic hormone (ACTH) occurs in a circadian fashion. ACTH is the prime factor for stimulating the synthesis of glucocorticoids. This hormone is a potent anti-inflammatory agent, regulates the functions of immune cells, as well as inflammatory response. It is well known that chronic inflammation is a crucial factor in the development of cancer. The indigenous clock-mediated neuro-endocrine function helps to disseminate cancerous growth. Secretion of IL-6 is also circadian rhythm dependent.[188] This cytokine involves in numerous immune functions. Lee et al.[156] reported that IL-6 promotes the formation of a pro-metastatic niche in the liver. Foggo and Cavenagh[189] observed the nocturnal release of cytokines by malignant leukocytes that alter physiological activities and induce fever.

The activity of the immune cells is related to the circadian rhythm. Maximum numbers of $CD8^+$ effector T lymphocytes have observed during the daytime. These cells express β-adrenergic and CX3CR1 receptors. SCN regulates the functions of the sympathetic nervous system (SNS). Epinephrine and norepinephrine is the primary neurotransmitter of the SNS. SNS is active in the daytime. High levels of circulatory adrenalin in the daytime increase circulatory T lymphocytes.[190] The number of naïve T lymphocytes and neutrophils are high at night. The redistribution of naïve T lymphocytes during the daytime is mediated by chemokine CXCL12 and the expression of chemokine CXCR4. The lymphocytes and neutrophils express CXCR4 on their surfaces. $CD8^+$ effector T cells involve in immediate effects and naïve T cells influence adaptive immunity against the cancer cell migration and survival. Thus, the circadian pattern of immune cell distribution restricts the activity of the circulatory tumor cells. Misalignment of circadian rhythm alters the distribution of immune cells and BMAL1 may also link with these circadian fluctuations. BMAL1 regulates the expression of programmed cell death ligand 1 (PD-L1) to limit the immune cell exclusion property of the cancer cells. The impaired immune cell distribution promotes the survival of circulatory tumor cells.[191]

F. Clock Components, Immune Functions, and Relation to Carcinogenesis

Chronic inflammation, suppression of immunocytotoxicity of the malignant cells, evasion of immune surveillance, angiogenesis, and tissue invasion induce cancerous growth. The immune system always tries to eliminate cancer-producing malignant cells, as well as stem cells. Maturation and functions of the immune cells, including NK cells, monocytes/macrophages, dendritic cells (DCs), B cells, and T cells follow the circadian rhythm.[192] The numbers of naïve $CD4^+$ and $CD8^+$ T cells reach the peak at the resting phase, while the effector T cells rise during the active phase. The cytokines are in an oscillating

manner and start secretion during the active phase. However, the levels of pro-inflammatory cytokines remain high at the resting phase. The cancer cells release tumor-specific antigens (TSA) that activate the wings of adaptive and innate immunity. These responses create the protective measure against the detrimental effects of cancer. Scheiermann et al.[193] indicated that clock gene components regulate immune functions. CLOCK, BMAL1, Cry, Per, and Rev-Erbα regulate the maturation and functions of immune cells. Rev-Erbα is essential for DC maturation and expression of co-stimulatory molecules. TSA induces the polarization of tumor-associated macrophages towards M1-like macrophages; they start phagocytosis and release pro-inflammatory cytokines. Per1 and Per2 control the maturation of M1 macrophages; disruption of Per1 and Per2 increases the numbers of M1 macrophages. BMAL1 regulates the time-dependent release of pro-inflammatory cytokines. Cry also involves in the regulation of inflammatory response through the adenylyl cyclase system. Rev-Erbα enhances the expression of CX3CR1 and MMP9. CLOCK and RORγt essentially regulate the maturation of Th17 cells, secretion of IL-17A, IL-17F, Il-22, and the chemokine CCL20.[73,194–198] Disruption of circadian rhythm alters the expression of core clock genes and weakens the surveillance of immune defense against malignancy, leading to increased risk of cancer progression.

Jet-lag mediated circadian disruption alters the cytokine profiles and natural killer (NK) cell activity in rats, leading to tumor growth.[199] Impaired activity of clock genes (Per2, Bmal, Cry, Rev-Erbs) alters the expression of cytokines (GM-CSF, IL-2, IL-10, IL-6, IL19, IL-1β, TNF-α, MCP-1, and IFN-γ), and chemokines (CCL2, CXCL6), as well as chemokine receptors (CCR2, CX3CR1).[33] High levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) had observed in the myeloid-specific knockout of Bmal condition that indicates the anti-inflammatory effects of clock components.[193,194] The progression of inflammatory response depends on the activation of NF-κB. BMAL1, CLOCK, and CRYs control the activity of NF-κB. Low levels of BMAL1 promote the activation of NF-κB through phosphorylation of the p65 subunit,[200] while CLOCK in association with p65 induces the expression of NF-κB-mediated inflammatory genes.[201] CRY activates the NF-κB through the cAMP-PKA-mediated system.[202] Secretion of pro-inflammatory cytokines is the crucial factor for cancer development. Inflammatory cytokines increase cell proliferation and survival, decrease apoptosis. These cytokines also induce oxidative stress that is associated with genetic instability, DNA damage, lipid peroxidation, impaired redox homeostasis, and metabolic impairment. The collective effects are the progression of cancer. Chen et al.[203] reported that clock gene components regulate the expression of transforming growth factor-beta (TGF-β) that balances immune functions polarizing the maturation of Th2 cells, development of T regulatory (Treg) cells, and inducing IL-10 secretion. Clock, Bmal, and Rev-Erb acts through RORγt and NFIL3, and regulate the differentiation of Th17 cells, which produce IL-17, an aggressive inflammatory cytokine.[197] BMAL1 is the most important component in immune functions. It regulates T cell proliferation, their movements, programmed cell death protein 1 (PD1) expression. Another important factor is CRY, which involves in B cell development.[33] Thus, the circadian clock components regulate immune functions in different ways. Circadian disruption alters the pattern of immune cell development, their activity, trafficking, and cytokine secretion; these effects indirectly or directly affect cancer progression.

G. Impact of Circadian Dysfunction on Metabolism and Cancer Progression

The circadian clock involves in regulation of the metabolism of carbohydrates, amino acids, and fatty acids.[204,205] Chronodisruption changes the metabolic profiles. Dysfunction of the circadian clock is the contributor to cancer, diabetes, obesity, and cardiovascular disorders.[206] Altered levels of plasma triglyceride, high-density lipoprotein, glucose, C-reactive protein, TNF-α, and IL-6 have found in metabolic diseases.[207] The circadian clock regulates the function of nuclear receptors like PPARα, PPARγ, REV-ERBα, RORα, HNF4α, TRα, and NURR1 to control metabolic activity. Polymorphism of clock genes influence the metabolic disorders.[32] Circadian misalignment and impaired cholesterol metabolism,

secretion of lipase enzyme and lipid metabolism, glycerol levels, free fatty acid concentration can create an alternative metabolic network towards the formation of dyslipidemia.[208]

Circadian activity and reprogramming of metabolism have a link with carcinogenesis. The tumor cells secrete tumor-specific metabolites (glycolytic byproducts, lipoprotein, chemokines, inflammatory cytokines, and other tumor-derived waste) that are circulated through blood. The tumor-specific metabolites alter the pattern of metabolism and also affect the clock function. Additionally, metabolic fluctuation may impact clock components.[10] A study on lung adenocarcinoma in mice (*Kras*$^{LSL–G12D/+}$; *p53*$^{fl/fl}$) had revealed that release of IL-6 from lung tissue is transported to the liver, where IL-6 hampers the insulin activity and glucose sensitivity. IL-6 also changes the pattern of lipid metabolism and influences inflammatory response in hepatic tissue.[209,210] Chronic circadian disruption promotes metastasis through immune-reactive pathways.[211] Hojo et al.[212] also reported the link between breast cancer and enhanced oxidative stress in the liver. The function of BMAL1 has already been discussed; however, BMAL2 can promote tumor metastasis. BMAL2 is expressed in primary metastatic tumors and acts through tomato receptors. BMAL2 regulates the expression of *Smoc2*, *Wnt5a*, and *Ccl7* genes. The secreted modular calcium-binding protein 2 (*Smoc2*) is the most important factor for the migration of cancer cells. Thus, circadian dysfunction and liberation of tumor-specific metabolites are crucial for cancerous growth in different tissues.

Cancer cells show high levels of lipid metabolism. Inhibition of acetyl-CoA carboxylase decreases fatty acid synthesis that effectively restricts the lung adenocarcinoma in mice.[213] Another important enzyme in tumor cells is acetate-dependent acetyl-CoA synthetase. This enzyme provides acetyl-CoA for fatty acid synthesis and also regulates histone acetylation. Acetylation of histone may induce epigenetic changes and also alters the expression pattern of genes. There is a complex relationship between clock function and the activity of acetyl-CoA synthetase. Activation of acetyl-CoA synthetase is regulated by sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase enzyme. The intracellular NAD^+/NADH ratio is the prime regulator of SIRT1 activity. Therefore, any defect in circadian clock functions modulates the SIRT1 activity and indirectly promotes the action of acetyl-CoA synthetase followed by the growth of the tumor cells.[214] Metformin is the inhibitor of complex I of the mitochondrial electron transport chain. This inhibition lowers the free intracellular NAD^+ by increasing reduced NAD (NADH) concentration. Blocking of conversion of pyruvate to lactate also gives the same effects. The downfall of the NAD^+/NADH ratio alters the metabolic scenario of the cells. The application of metformin indirectly affects the activation of SIRT1 and facilitates cancer prevention.[10] The circadian clock also regulates the activity of nicotinamide phosphoribosyltransferase (NAMPT) for the synthesis of NAD^+.[215] Thus, circadian disruption alters the intracellular NAD^+ levels and activates SIRT1, which increases the expression of oncoproteins. Exploration of clock dysfunction and alteration in tumor-specific metabolites will make a pavement for the improvement of cancer treatment.

Another important factor is AMPK (AMP-activated protein kinase), which is the metabolic regulator. The functions of AMPK are linked with the circadian clock. AMPK is activated through phosphorylation during a low ATP state. Phosphorylated AMPK regulates mitochondrial biogenesis, cell proliferation, and clock functions. AMPK inactivates Cry1 by phosphorylation and Per2 by inducing CK1. This impaired activity of clock components deregulates metabolic activity, cell cycle and cell proliferation, apoptotic activity, and tumor suppression. These effects adversely affect cancer progression.[216]

H. Circadian Clock Function and Oxygen Sensing in Cancer

The formation of solid tumors is the common feature in most cancer, where a hypoxic environment emerges at the initial stage of growth. The appearance of hypoxia in the tumor microenvironment advances the pathologies of cancer. Hypoxia induces the expression of a transcription factor, called hypoxia-inducible factor 1 (HIF-1) that regulates the expression of many genes for the reprogramming of

metabolism in an altered environment, cell survival, angiogenesis, and metastasis.[217] HIF-1 belongs to a family of basic helix-loop-helix–Per-ARNT-Sim (bHLH–PAS) protein. Functionally, HIF-1 is a heterodimer, comprises HIF-1α and HIF-1β subunits.[218,219] Hypoxia induces the expression of the HIF-1α subunit; whereas HIF-1β is constitutively expressed in the cell.[220] In normoxic conditions, HIF-1α is degraded in 26S proteosome through E3 ubiquitin ligase that indicates less function during normal physiological conditions. HIF-1 interacts with hypoxia response element (HRE), this promoter is present upstream of HIF-1 inducible genes. The hypoxia-response element contains the cis-acting 5′-RCGTG-3′ (R = purine; mostly adenine) sequence in the core of the promoter.[221] This region of the promoter resembles an E-Box-like sequence. Circadian clock and hypoxic response are persistently related. The oxygen concentration in the blood exhibits a circadian rhythm that maintains the stability of HIF-1α in normal cells. HIF-1α modulates the expression of core clock genes in peripheral tissues (kidney, brain, and hepatocytes).[222] However, the CLOCK–BMAL1 complex acts on the HIF-1α promoter to regulate the expression of genes related to hypoxic response.[223] The experimental result revealed that disruption of *Bmal1* alters the HIF-1α-dependent genes.[224] Thus, the reciprocal relationship between the circadian clock and hypoxia signaling maintains a balance in the normal cellular functions. Circadian disruption and excess production of HIF-1α during tumor growth deregulates the expression pattern of genes related to cancer progression.

IX. CIRCADIAN DYSFUNCTION AND CANCER DEVELOPMENT IN DIFFERENT TISSUES

A. Breast Cancer

Numerous epidemiological studies reported that the rates of breast cancer are higher (30% to 60%) in night-shift female workers.[225,226] The occurrence of breast cancer is three to five times lower in the female of the developing countries compared to the female of the industrialized world because high-intensity electric light adversely affects the life of the population of the modern industrialized sector.[227] Premenopausal women who are facing long-term rotating night-shift work in their adulthood are prone to breast cancer.[27,228] Light-at-night alters the circadian rhythm and melatonin secretion, which is strongly associated with the risk of breast cancer in females.[175,177–181] The results of meta-analysis strongly support the shift work and breast cancer.[229–232]

Breast tissue comprises a milk-producing gland, known as alveoli, which contains secretory epithelial cells. The alveoli are surrounded by a network of branched epithelial ducts. The basement membrane covers the outer part of the ducts. Outside the basement membrane, fibroblast and adipocyte-rich extracellular matrix encircle the tissue.[233] Breast cancers are classified into different groups based on tumor markers. Three markers estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR) are used for the categorization of breast cancer.[234] On the marker status, breast cancers are grouped as i) luminal A (ER^+, $PR^{+/-}$, $HER2^-$), ii) luminal B (ER^+, $PR^{+/-}$, $HER2^+$), iii) HER2 (ER^-, PR^-, $HER2^+$), and iv) Basal (ER^-, PR^-, $HER2^-$). The basal tumor is also called triple-negative.[18,235]

The expression of clock genes occurs normally in breast tissue[236] and varies with physiological conditions. In the last trimester of pregnancy, Bmal1 and Per1 mRNA levels increase in the breast tissue while the expression of Per2 decreases.[237] The expression patterns of more than a thousand genes in the lactating breast are clustered in two groups; one group is highly expressed in the morning and another group in the evening.[238] Suppression of core clock genes is common during aging and cancer progression.[168] Polymorphisms of *Clock*, *Per2*, *Per3*, *Bmal1*, *Cry1*, *Cry2*, *TIM*, and *ROR-β* genes had shown the prevalence of breast cancer.[32] Mutation of *Per* genes increases the risk of breast cancer and also decreases the survival rate of the patients.[72] Recently, Yang et al.[239] reported that 8q21 carries a gene ZNF704 that is amplified in breast cancer tissue. ZNF704 and SIN3A (corepressor) make a complex, which represses the expression of PER2; thus, overexpression of ZNF704, causes circadian dysfunction. ZNF704 promotes the proliferation, invasion, and

metastasis of breast cancer cells. Another important factor is the estrogen receptor, which interacts with PER2 and BMAL1. This association is essential for the formation of mammary acini.[240] Estrogen regulates the expression of its own receptor, while PER controls the estrogen pathway. Disruption of Per2 alters the ERα signaling pathway.[240] Suppression of *Per2* increases ERα stabilization. The rhythmic appearance of PER. mRNA does not maintain in ERα-positive breast cancer cells. Overexpression of *Per2* inhibits the proliferation of cancer cells in the breast.[241] PER and breast cancer protein, BRCA1 regulates the transcription of the estrogen receptor. Impaired activity of the estrogen receptor influences the aggressive growth of tumors.[166,242] Thus, inappropriate expressions of clock genes are associated with the risk of breast cancer. BMAL1 shows tumor suppressor activity. Overexpression of BMAL1 inhibits cell proliferation, tumor growth, and invasion. The activity of BMAL1 is not p53 dependent but mediated through the activation of the phosphoinositide 3-kinase (PI3K)–Akt–MMP-2 signaling pathway.[243] CLOCK is the breast cancer-inducing factor. Healthy breast tissue shows low levels of CLOCK expression and *CLOCK* knockdown inhibits the growth of breast tumors by downregulating the expression of several cancer-associated genes like *CCL5*, *BDKRB2*, and *SP100*. Hypermethylation of CLOCK promoter exhibits tumor-suppressive effects in the breast.[146,244]

The impaired light-dark cycle decreases nocturnal plasma melatonin that influences breast cancer. A low level of melatonin increases estrogen levels that are positively correlated with breast cancer. Estrogen plays a vital role in the progression of breast cancer. Melatonin binds with estrogen receptor α (ERα), interferes in estrogen activity.[245] MT1-mediated melatonin activity suppresses the expression of ERα.[246] At the functional level, melatonin inhibits the activity of ERα by suppressing the phosphorylation of this receptor.[246,247] Melatonin hampers estrogen synthesis by inhibiting the activity of aromatase, sulfatase, and aldo-keto reductase (AKRs) during breast cancer progression.[248,249] Melatonin also downregulates COX expression and PGE2 synthesis; these effects inhibit PGE2 and aromatase release.[250] 13-hydroxyoctadecadienoic acid (13-HODE) is the metabolic by-product of linoleic acid, which shows mitogenic activity. Melatonin restricts the uptake of linoleic acid, followed by its conversion to 13-HODE.[251]

It has already been stated that shift work causes epigenetic changes. A prospective cohort study had conducted on female shift workers in Denmark. The alteration in DNA methylation had found in many genes, including estrogen receptor α (*ESR1*), *CLOCK*, and *CRY2*. The pattern of methylation is different in 5,409 CpG (cytosines followed by guanine residues) in the day and night shift workers.[143] The CpG methylation in the PER1, PER2, and PER3 promoters alter the expression of 50% protein in breast tumors compared to normal breast tissue.[141] However, PER1 hypomethylation was also observed in ER^+/PR^+ breast cancer tissues.[252]

B. Ovarian Cancer

The risk of ovarian cancer is high among nightshift female workers compared to other females. The female reproductive cycle and hormonal rhythm are highly tuned with the expression of circadian genes in ovaries. The development of ovarian cancer is coupled with the inappropriate expression of circadian genes.[24,253] Analysis of variants of gene indicated that *Arntl*, *Cry2*, *CK1ε*, *NpasS2*, *Per3*, and *Rev1* are associated with the development of ovarian cancer. Moreover, two other transcription factors *KLF10* and *SENP3* are also used as biomarkers of ovarian cancer; variants form of *KLF10* increase the risk. Excess expression of *C-MYC* lowers *BMAL1* expression, resulting in the advancement of ovarian cancer.[254] Yeh et al.[255] reported that ovarian cancer cells diminished *BMAL* expression to increase their survival. Administration of cisplatin induced *BMAL* overexpression, followed by apoptosis. Ovarian cancer cells express a high level of Cry1 that can be used as a prognostic factor.[256]

Nighttime melatonin is the regulator of ovarian steroidogenesis as regulates the activity of steroid hormone synthesizing enzymes, such as aromatase, steroid sulfatase (STS), and 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1). Melatonin also maintains estrogen levels by controlling the activity of estrogen sulfotransferase (EST).[250,257,258] Thus,

circadian dysfunction or Light-at-night suppresses the melatonin secretion. Inappropriate melatonin levels deregulate the synthesis and secretion of steroid hormones that impact ovarian cancer.

C. Prostate Cancer

The most common cancer prevalence in men is prostate cancer, which exhibits the highest rate of occurrence.[259] Flynn-Evans et al.[260] observed the link between shift work and prostate cancer. Garcia-Saenz et al.[261] reported that the risk of prostate cancer is influenced by shift work and exposure to bright light-at-night. Prolonged nighttime illumination increased the rate of prostate cancer in males.[182] Wendeu-Foyet and Menegaux[262] reported that the relation between night shift work and prostate cancer is not conclusive, although the meta-analysis data indicates the 24% higher risk of prostate cancer. Later, Wendeu-Foyet et al.[26] again reported that a long duration of permanent night work along with prolongs shift length or consecutive nigh-shift in a weak may promote aggressive prostate cancer. However, the non-associative results were also reported by Barul et al.[263] The plasma androgens levels are strongly correlated with the development of prostate cancer. Production of androgen depends on the activity of circadian clock genes.[264] The role of circadian genes on the progression of prostate cancer is established by polymorphisms study, which exhibits that *Clock*, *Per1*, *Per2*, *Per3*, *Bmal1*, *Cry1*, *Cry2*, *TIM*, *ROR-a*, *ROR-b*, *CSNK1e*, *NPAS2*, and *NR1D1* genes regulate the development of prostate cancer.[11,32] Among these genes, *Per3* is specifically important for the progression of prostate cancer.[265] *CRY2*-variant C allele increases the risk of prostate cancer.[265] The clinical sample had revealed that expression of PER3 is downregulated in human prostate cancer specimens. There is a negative correlation between PER3 and BMAL1 expression. Cell culture study had revealed that PER3 expression is significantly downregulated in prostate cancer cell. Overexpression of PER3 suppresses cell growth. Low levels of PER3 trigger the high expression of BMAL1, which activates the WNT/β-catenin pathway in the downstream level. Activation of β-catenin signaling increases cell proliferation, inflammatory response, DNA instability, and decreases apoptosis; collectively promotes cancer development.[266]

Melatonin has anti-gonadal activity, regulates androgen synthesis. MT-1 receptor-mediated melatonin activity decreases intracellular cAMP levels in Leydig cells that interferes LH (luteinizing hormone)-dependent testosterone biosynthesis.[267] This function restricts the activity of prostate cancer cells. Melatonin inhibits the activity of the steroidogenic acute regulatory protein (StAR), cholesterol side-chain cleavage enzyme (cytochrome P450SCC), and 3β-hydroxysteroid dehydrogenase (3β-HSD) for the reduction of testosterone synthesis.[267,268] The regulation of testosterone synthesis prevents the progression of prostate cancer cells.

D. Colorectal Cancer

Schernhammer et al.[269] reported that a higher incidence (35%) of colorectal cancer was profoundly found among shift workers who worked at least three night-shift duties per month for 15 or more years. Later, other reports establish the impact of shift work on colorectal cancer.[22,270,271] There is a strong correlation between clock genes and colorectal cancer development. The study of polymorphisms had revealed that the deregulation of *Clock* and *Per3* increases the incidence of colorectal cancer.[32,272]

E. Hematopoietic Carcinoma

Deregulation of *Per* genes (mostly *Per2*) are associated with various types of leukemias such as chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and diffuse large B cell lymphoma (DLBCL). PER proteins, particularly PER2 regulate the expression of cell cycle regulators (cyclin D1 and A, c-Myc, Mdm2, and Gadd45α); these components regulate cell proliferation, as well as tumor-suppressive effects. Mutation in the *Per2* gene or downregulation of Per2 activity in mice disrupts the control of the cell cycle, promotes cancer development.[132,273,274] Lahti et al.[275] reported that shift work increased the risk of Non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma had also been found in the individuals carrying variants of the clock genes, mostly *Cry2*.[276,277] A particular family

of transcription factors, CCAAT/enhancer-binding proteins (C/EBPs), critically regulates cell proliferation and differentiation. C/EBP targets the expression profile of *Per2*, *Rev-Erbα*, and *Dbp* (albumin site d-binding protein) genes. Circadian dysfunction and deregulation of C/EBPs start hematologic malignancies as C/EBPα exerts tumor-suppressive effects in leukemias.[278–280] CpG promoter methylation causes *Bmal1* gene silencing that increases the rate of different hematological malignancies (B cell lymphomas, acute lymphocytic leukemia, acute myeloid leukemia).[142]

F. Hepatic Carcinoma

The liver is associated with the metabolism of various substances, including glucose, cholesterol, and bile acids. Circadian rhythm dysfunction promotes metabolic disorders, obesity, non-alcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma (HCC).[118,204] Single nucleotide polymorphism (SNP) of *Per3* and *Cry1* genes increases the risk of HCC.[281] HCC is linked with changes in lifestyle, work pattern, and metabolism. The leading cause of this malignancy is NAFLD which is the predominant consequence of obesity.[282] Excessive fat accumulation starts an inflammatory response in hepatic tissue, which promotes non-alcoholic steatohepatitis (NASH); the result is hepatic fibrosis followed by cirrhosis and finally HCC.[283] However, HCC may occur directly due to NAFLD without initiation of NASH.[284] Kettner et al.[285] reported that circadian disruption is the cause of dyslipidemia as well as NAFLD in mice. Similar effects were also observed in night shift workers.[286] At the experimental level, chronodisruption not only alters the metabolic pattern in the mice liver but also promotes oxidative stress and the synthesis of cellular proliferative factors. All these effects accelerate the NAFLD and then NASH to hepatic fibrosis. These effects initiate a regenerative wound healing process that triggers tumorigenesis in the later stage. The pathophysiological changes are very similar to NAFLD-mediated hepatic carcinogenesis of humans. The human HCC markers like *Trp53*, *Myc*, and β-catenin were also detected in the mice model.[283,285]

Bile acid plays a key role in the progression of HCC. Bile acids are synthesized from cholesterol and circulated through enterohepatic circulation. The intrahepatic bile acid level is controlled by the activity of the farnesoid X receptor (FXR, NR1H4). The bile acid-FXR complex regulates the cytochrome p450-dependent bile acid synthesis from cholesterol.[287] FXR also regulates steatosis and inflammatory response in the liver.[288] Circadian disruption affects the bile acid metabolism that enhances the rate of HCC more than two folds.[285] The constitutive androstane receptor (CAR, NR1I3) is activated during hepatic cholestasis.[289,290] Activation of CAR and β-catenin advances tumor progression in the liver. The CAR promotes the overexpression of *Cyp2b10*, β-catenin, and *c-Myc*.[285,291] The overexpression of *Cyp2b10* increases hepatocellular damage. Circadian dysfunction promotes overexpression of CAR (constitutive androstane receptor). CAR is an oncogenic protein, induces metabolic carcinogenesis. Circadian dysfunction or chronic jet lag-mediated ultimate responses are metabolic reprogramming, elevated levels of hepatic cholesterol and bile acids, expression CAR, and activation of β-catenin. Collectively, these events promote NALFD and NASH-mediated non-genotoxic HCC.[285]

G. Other Cancers

Shift work-mediated circadian dysfunction is also associated with other cancers like endometrial cancer,[292] lung cancer,[293] and pancreatic cancer.[294] A genetically engineered mouse model (GEMM) study had revealed that *Per2* (*Per2*$^{m/m}$) mutant mice with a *Kras*$^{LSL–G12D/+}$; *p53*$^{fl/fl}$ are severely affected in lung adenocarcinoma, and their overall survival rate is poor.[131]

X. ONCOSTATIC EFFECTS OF MELATONIN

Light-at-night reduces melatonin secretion from the pineal gland.[295] Melatonin exerts multidimensional activity to resist cancer development. Melatonin exhibits potent anti-cancer effects. The oncostatic effects of melatonin have observed in different tissues, including the breast, prostate, ovaries, liver, kidney, lung, pancreas, colorectal, skin, and the

gastrointestinal system.[172,173] The oncostatic effects of melatonin are mediated in different ways. The antioxidant property of melatonin is an important factor. Melatonin protects DNA and protein from oxidative damage. Oxidative stress (OS) generates highly reactive molecules [reactive oxygen species (ROS): O_2^-, H_2O_2 and $^\bullet OH$, reactive nitrogen species (RNS): $ONOO^-$, $NO^\bullet$, $^\bullet NO_2$, and reactive sulfur species (RSS)] that damage the membrane lipids, proteins, and DNA. DNA methyltransferase (DNMT) can methylate the C-5 position of deoxycytidine (dC), which is one of the ways of epigenetic change. The epigenetic changes in tumor suppressor genes promote cancer progression.[296] OS induces lipid peroxidation, disrupts the membrane integrity and induces the generation of lipid hydroperoxide-derived molecules that facilitate DNA adduct formation. Any type of DNA damage can induce cancer development. ROS activates Myc and Ras signaling to alter the metabolic programming in the oncogenic environment.[297,298] Melatonin or its derivatives (5-methoxytryptamine, 3-hydroxymelatonin, 6-, 4-, 2-hydroxy melatonin) involve in antioxidant reaction. Melatonin scavenges $^\bullet OH$, $RO^\bullet$, $ROO^\bullet$, $NO^\bullet$, and singlet oxygen ($^1O_2$) to protect the cells from ROS mediated damages. Melatonin enhances the activity of glutathione, vitamin E, and ascorbic acid to maintain intracellular redox homeostasis. It also maintains the levels of intracellular antioxidant enzymes like catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) by activating the nuclear erythroid 2-related factor 2 (Nrf2).[299]

Melatonin uplifts the DNA repair system to blocks the OS-induced DNA damage.[300] This indolamine influences the expression of genes of the DNA repair system via DNA-damage-responsive pathways.[301,302] Melatonin preserves the activity of p53 to protect the DNA from damages. Melatonin induces the expression of genes of antioxidant enzymes (CAT, SOD, GPx).[303] Moreover, melatonin prevents OS-induced expression of pro-oxidative enzymes (xanthine oxidase), nitric oxide synthase (NOS), and cyclooxygenase-2 (COX-2).

Melatonin induces apoptosis in hematological, breast, prostate, hepatic, pancreatic, and colon cancer.[304] Melatonin can induce both intrinsic and extrinsic pathways of apoptosis. It increases cytosolic cytochrome c (cyt c) and pro-apoptotic protein Bid (BH3 interacting domain death agonist), activates caspase-3/8/9, while inhibits the expression of anti-apoptotic factor Bcl-2 (B cell lymphoma-2). Melatonin also activates Fas and Fas-ligand for the activation of the extrinsic pathway of apoptosis.[304] Melatonin increases endoplasmic reticulum stress for the induction of apoptosis; it elevates the levels of pro-apoptotic transcription factor CHOP [C/EBP (CCAAT-enhancer-binding protein) homologous protein].[305]

Sirtuin 1 (SIRT1) is an important regulator of many factors like p53, FoxO, PPARγ, NF-κB, p300 (co-activator). SIRT1 is a NAD-dependent deacetylase. High levels of cellular NAD^+ activate SIRT1, while an excess amount of NADH inactivates this enzyme. The NAD^+/NADH ratio is under the control of circadian rhythm, and cellular energy state. SIRT1 promotes cancer progression through deacetylation of p53. Inhibition of p53 activity decreases the rate of apoptosis of the malignant cells. Melatonin decreases SIRT1 and MDM2 (E3 ubiquitin-protein ligase) activity to restore the active p53. p53 triggers the intrinsic apoptotic pathway by elevating Bax and cytochrome c levels.[304,306]

Melatonin acts as an anti-proliferative agent and arrests the cell cycle. It decreases the expression of cyclin D1, B1, and CDK4, CDK1.[307] Melatonin lowers the quantity of beta-actin and alpha-tubulin, resulting in impaired cytoskeleton organization during cell division.[308] Melatonin also prevents thymidine incorporation during DNA replication that leads to the arrest the cell cycle.

Cancer cells can cross the basement membrane, enter the circulation, and finally form cancer in distant tissue.[309] Cancer cells reorganize the gene expression for their survival and metastasis. They modulate the expression of SUMO-specific protease 1, hypoxia-inducible factor 1α, and VEGF. The epithelial-to-mesenchymal transition (EMT) and expression of matrix metalloproteinases (MMP-2 and MMP-9) promote tumor metastasis.[310,311] Melatonin suppresses the expression of VEGF[312] and NF-κB-mediated MMP-9 expression[313] to block the metastasis. To prevent the EMT, melatonin inhibits the activity of Rho-associated protein kinase-1 (ROCK-1)[314] and myosin light-chain kinase

(MLCK)[315]; these enzymes effectively regulate cytoskeletal remodeling during EMT.

Hypoxia is very common in cancerous tissue. Hypoxia induces the expression of transcription factor hypoxia-inducible factor-1 alpha (HIF-1α), which induces the expression of hundreds of genes for the adaptation and survival of cancer cells in hypoxic conditions.[217] Melatonin inhibits the synthesis of HIF-1α, also decreases its stability.[316,317] This hormone blocks the translocation of HIF-1α into the nucleus.[318] Hypoxic condition induces ROS production. ROS increases the stability of HIF-1α. Melatonin scavenges ROS and decreases HIF-1α activity.[317]

Additionally, ROS induces an inflammatory response. Chronic inflammation is a crucial factor in the development of cancer. The inflammatory activity is positively modulated by pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-12, IL17, IL-18, TNF-α, and IFN-γ). Induction of NF-κB activity enhances the expression of these cytokines. There are five types of subunit [NFκB1 (p50), NFκB2 (p52), RelA (p65), RelB, and cRel] but at the functional level NF-κB forms either homodimer or heterodimer from these subunits. Melatonin blocks the activity of the p65 subunit of NF-κB that prevents heterodimer formation and nuclear translocation of NF-κB. Thus, melatonin indirectly controls the inflammatory response. Low levels of melatonin advance inflammatory cytokine secretions, mutagenesis, and oxidative damage that are strongly associated with the progression of various cancers.[319] Decreased melatonin secretion also imbalances the release of testosterone and estrogen which increases the risks of prostate, ovarian, and breast cancers.[320]

XI. CIRCADIAN DYSFUNCTION AND AN APPROACH TO CHRONOTHERAPY FOR CANCER PREVENTION

Approaches of chronotherapy are most important because the expression of the mammalian genes involved in physiological functions, DNA nucleotide excision repair and metabolic activities follows a circadian rhythm. Absorption, distribution, metabolism, and elimination of drugs are also mediated through a circadian manner.[321] Chronochemotherapy is an attractive step in the complex pattern of clock-cancer relationship as the mistiming of chemotherapeutic agents potentially increases the side effects. Chemotherapeutic agents have a specific action that can be heightened with the administration of the circadian system.[322] Chronotherapy indicates the intervening time of dosing to maximize the therapeutic efficacy and minimize the side effects.[20] Synergistic application of chemotherapy and chronotherapy is regarded as an alternative strategy of cancer treatment. Chemotherapeutic agents normally block uncontrolled cell proliferation. In the normal cell, there is a relationship between circadian clocks, cell cycle, and DNA repair process. Administration of chemotherapeutic agents at a specific time in relation to the circadian clock minimizes toxicities in normal cells without affecting the therapeutic efficacy in the cancer cells due to their inappropriate circadian clock functions.[33,323] A chronotherapy-mediated clinical trial of chemotherapeutic agents on breast cancer,[324] colorectal cancer,[325] and endometrial cancer[326] shows minimum level toxicity, including mucositis, stomatitis, and leucopenia. Agents of immunotherapy cause adverse effects on immune functions and inflammatory response. Subsequent release of cytokine, immune cell trafficking, and acute immune toxicity are linked with circadian clock time. Application of immunotherapeutic agents in specific daytime decreases the effects of cytokine release syndrome (CRS).[327–329]

Sustaining a proper circadian rhythm by maintaining the sleep pattern, eating behavior decreases the risk of cancer. Medication at the appropriate time in relation to the patient's lifestyle and circadian rhythm accelerates the overall effectiveness of the treatment.[330] The therapeutic agents that are targeting clock components are termed "clock-drugs." These drugs control the activity of clock components and give benefits for the treatment of cancer. Clock-drugs can directly modulate the expression of core clock genes. They also target the regulatory proteins of the circadian loop to maintain the activity and levels of core clock components.[20] They normalize the circadian rhythm by inhibiting the tumor-specific metabolites and prevent the progression of cancer in the other tissues. REV-ERBβ is highly expressed in breast cancer cells. A substance ARN5187 interacts with REV-ERBβ, inhibits autophagy, and induces

cytotoxicity in breast cancer cells.[331] Drugs targeting casein kinase 1δ, casein kinase 1ε, and Fbxw7 (a protein of F-box) control the phosphorylation and degradation of Per, Cry, and REV-ERBα, leading to modulation of CLOCK-BMAL1 activity and regulation of circadian functions.[332] Rosenberg et al.[333] reported that the expression level of both CK1δ/ε is very high in leukemia, breast, pancreas, and ovarian cancer. This finding indicates the importance of regulation casein kinases in circadian clock-mediated cancer treatment.

Oridonin is present in herbal extract, acts through Fbxw7 (E3 ubiquitin ligase) for the degradation of c-Myc.[334] RORγ induces the expression of androgen receptor (AR) in prostate cancer-specific animals. RORγ inhibition by ROR-γ-antagonists (SR2211, XY018, and XY011) restricts the prostate cancer progression by modulating the androgen signaling.[138] SR2211-mediated RORγ inhibition also improves pancreatic cancer. Nobiletin is present in the peels of citrus fruits inhibits RORs to exert anticancer effects.[335] SR9009, SR9011, and GSK4112, act as REV-ERBs agonists; they decrease autophagy and *de novo* lipogenesis, followed by suppression of tumor growth by inducing apoptosis.[336,337] Inhibition of CRY by KS15 reduces breast cancer cell proliferation.[338] LYC-53772 and LYC-54143 are the RORγt synthetic agonist, activate the differentiation o Th17 cells, resulting in upregulation of IL-17A, IL-17F, and GM-CSF, and IL-22 release for the destruction of cancer cells.[339] RORγ agonists also suppress the expression of PD-L1.[340] SR1078 is the RORα synthetic agonist which enhances the response of $CD8^+$ T cells for the cytotoxic effects against tumor cells.[341] The anti-cancer activity of clock-drugs alone does not reach the optimum level. Application of clock-drugs in combination with chemotherapeutic agents gives maximum efficacy. However, elaborative study and the effective clinical trials will increase the possibilities of the use of chrono-medicine in cancer therapy.

XII. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The circadian clock optimizes the different physiological activities round the clock. The suprachiasmatic nucleus (SCN) is the principal circadian pacemaker in the mammalian system, also synchronizes with peripheral clocks. The activity of SCN is mostly influenced by the photic signal. The expression of clock genes is regulated by a complex feedback system. Any alteration in the clock functions is detrimental to human health. Circadian dysfunction is associated with the development of different pathologies such as sleep disorders, diabetes, dyslipidemias, obesity, psychological illness, and cancer. These disorders are the major public health issue in modern society. People have subjected to circadian dysfunction due to extended shift work, rotating shift work, night work, exposure to bright light-at-night, chronic jet lag, and modern lifestyle. These factors increase the chance of cancer progression. Epidemiological evidence connects circadian disruption with cancer. Shift work is one of the prime factors of circadian dysfunction and is recognized as a carcinogen. Genetic components of the circadian system are the prime contributors to these disorders. SNP of circadian clock genes indicates the relationship between the expression of clock genes and carcinogenesis.

An approach to regulation of circadian functions could be the preventive measure against cancer development. Understanding the molecular mechanism of clock functions provides an opportunity to develop chrono-pharmacology for creating a new avenue of treatment of cancer. Malignancy can change the total scenario of the body ranging from tissue organization, physiological functions, and metabolic activities. Alteration of metabolism produces specific metabolites to advance cancerous growth. The tumor-selected metabolites in the blood can be used for the detection of cancer. For example, plasma branched-chain amino acid levels increase in pancreatic cancer. Several studies had already been conducted on the metabolomics of various cancers (colorectal, breast, and pancreas). The detailed study of cancer metabolites and their relationship with the circadian clock will be helpful for the detection of cancer in the early stage. Chronotherapy has already been established as an effective treatment for sleep disorders, jet lag problems, and shift work-related diseases. The study should also be required to explore the possibilities of applications of chemotherapeutic agents along with

chonotherapeutic strategies. This synergistic activity can improve the efficacy of the cancer treatment. Maintenance of time cues like the exposure of light, the spectral composition of light, timings of meals, adjustment of work patterns, will also be helpful to fight against cancer in our modern society. Thus, integrative research on circadian dysfunction, cancer progression, early detection, and possible approach to treatment will open a new arena of cancer study that will enlighten the way of protection of cancer development in the near future. Finally, it can say that increased public awareness about circadian dysfunction and its effects on the body will give a positive sense to the society to maintain the good health practices against circadian dysfunction.

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