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REVIEW

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# Targeting cell cycle regulators: A new paradigm in cancer therapeutics

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**Key words:** Cyclins, Cyclin-dependent kinases, Taxanes, Cell cycle inhibitors, Targeted therapy

**Abstract:** Dysregulation of the cell cycle is a molecular hallmark of cancer, which leads to uncontrolled proliferation and self-renewal of neoplastic cells. To maintain this phenotype, cells acquire multiple molecular alterations and bypass several cellular checkpoints that are involved in the prevention of genomic instability and uncontrolled cell proliferation. Therefore, targeting cell cycle regulators could prove to be a promising anti-cancer approach. Recent advancements in the understanding of cancer cell susceptibilities have revealed a therapeutic opportunity to selectively target the cell cycle in malignant cells. This review highlights major cell cycle dysregulation in cancerous cells and the latest developments on anti-cancer agents that target cell cycle factors which are either in clinical practice or in clinical trials at present. In light of increasing drug resistance in cancer patients, the article also discusses mechanistic insights for the exploration of probable therapies that could be used to target these cell cycle factors. Additionally, it outlines the future research necessary to develop new therapies and optimize existing ones to achieve maximum efficacy. Thus, this article aims to provide a comprehensive understanding of the advancements in cancer therapies targeting dysregulated cell cycle factors.

| **Abbreviation** | |
|---|---|
| **Ack1** | Activated Cdc42-associated kinase 1 |
| **AKT** | Ak strain transforming |
| **ALL** | Acute lymphoblastic leukemia |
| **AML** | Acute myeloid leukemia |
| **APC** | Anaphase promoting complex |
| **AR** | Androgen receptor |
| **AS1** | Antisense RNA 1 |
| **ATM** | Ataxia Telangiectasia Mutated |
| **ATR** | Ataxia telangiectasia and Rad3-related protein |
| **BCL-2** | B-cell lymphoma 2 |
| **BCR** | BTB-Cul-3-Rbx1 |
| **BCR-ABL** | Breakpoint cluster-Abelson tyrosine kinase |
| **BRCA** | Breast cancer gene |
| **BUB1B/BUBR1** | Budding inhibited by benzimidazole-related 1 |
| **CAMTA1** | Calmodulin binding transcription activator 1 |
| **CBX4** | Chromobox protein homolog 4 |
| **CCAT1** | Colon cancer-associated transcript 1 |
| **CCNA** | Cyclin A gene |
| **CD133** | Prominin-1 |
| **CD44** | Phagocytic-glycoprotein 1 |
| **CDC** | Cell division cycle |
| **CDH1** | Cdc20 homolog 1 |
| **CDKi** | CDK inhibitors |
| **CDKs** | Cyclin dependent kinases |
| **Cdt1** | Cdc 10 dependent transcript 1 |
| **CENP-A** | Centromere protein A |
| **CeRNAs** | Competing endogenous RNAs |
| **CHK** | Checkpoint kinase |
| **CHL-1** | Cell adhesion molecule L1 |
| **CIP** | CDK interacting protein |
| **circRNAs** | Circular RNAs |
| **CKI** | Cyclin-dependent kinase inhibitors |
| **c-Myc** | cellular-Myelocytomatosis gene |
| **COX-2** | Cyclooxygenase-2 |
| **CRC** | Colorectal cancer |
| **CRL4** | Cullin-RING ubiquitin ligase complex 4 |

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|---|---|
| **CRPC** | Castration-resistant prostate cancer |
| **CUX1** | Cut like homeobox 1 |
| **DBC1** | Deleted in breast cancer 1 |
| **DBF4** | Dumbbell former 4 |
| **DDR** | DNA Damage Repair |
| **DNA** | Deoxy ribonucleic acid |
| **DNMT3A** | DNA methyltransferase-3-alpha |
| **DSB** | Double Strand Break |
| **DTL** | Denticleless E3 ubiquitin protein ligase homolog |
| **DUB** | Deubiquitinase |
| **DUPA** | 2-[3-(1,3-dicarboxy propyl) ureido] pentanedioic acid |
| **E2F** | Eukaryotic transcription factor |
| **EF3** | Elongation factor 3 |
| **EMI1** | Early mitotic inhibitor 1 |
| **EMS** | E2F1 mRNA-stabilizing factor |
| **ER** | Estrogen receptor |
| **ERBB2** | v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 |
| **ERK** | Extracellular signal-regulated kinase |
| **ETS1** | ETS proto-oncogene 1, transcription factor |
| **EZH2** | Enhancer of Zeste Homolog 2 |
| **FBW7** | F-box and WD repeat domain-containing 7 |
| **FDA** | Food and Drug Administration |
| **FOXC1** | Forkhead box protein C1 |
| **G1** | Gap 1 |
| **G2** | Gap 2 |
| **GAS5** | Growth arrest-specific 5 |
| **GINS** | Go, Ichi, Nii, and San; five, one, two, and three in Japanese |
| **GSK3β** | Glycogen synthase kinase 3β |
| **Gαi1** | Guanine nucleotide-binding protein G(i), alpha-1 subunit |
| **HDAC** | Histone deacetylase complex |
| **HER2** | Human epidermal growth factor receptor 2 |
| **HGSOC** | High grade serous ovarian cancer |
| **HL** | Hodgkin's lymphoma |
| **HMGA2** | High mobility group AT-hook 2 |
| **HMGB1** | High mobility group box 1 |
| **Hog1** | High-osmolarity glycerol 1 |
| **HPV** | Human papilloma virus |
| **HR** | Hormone receptor |
| **HSP90** | Heat shock protein 90 |
| **INK4** | Inhibitor of CDK4/6 |
| **KIP** | Kinase inhibitory protein |
| **KRAS** | Kirsten rat sarcoma viral oncogene homolog |
| **LATS2** | Large tumor suppressor kinase 2 |
| **LKB1** | Liver kinase B1 |
| **LncRNA** | Long non-coding RNA |
| **LSCC** | Laryngeal squamous cell carcinoma |
| **LUCAT1** | Lung cancer-related transcript 1 |
| **MAD** | Mitotic arrest-deficient |
| **MAPK** | Mitogen activated protein kinases |
| **MCC** | Mitotic checkpoint complex |
| **MCL-1** | Myeloid cell leukemia-1 |
| **MCM** | Minichromosome maintenance complex |
| **MDM2** | Mouse double minute 2 homolog |
| **MET** | Mesenchymal Epithelial Transition |
| **MGMT** | O6-methylguanine-DNA methyltransferase |
| **miRNA/miR** | MicroRNA |
| **MM** | Multiple myeloma |
| **MMP9** | Matrix metalloproteinase-9 |
| **M-phase** | Mitotic phase |
| **MPS1** | Monopolar spindle 1 |
| **MRE** | miRNA response element |
| **MRN** | Mre11, Rad50 and Nbs1 complex |
| **mRNA** | Messenger RNA |
| **MSP1** | Myeloma-derived stromal cell line |
| **MTA2** | Nucleosome remodeling and histone deacetylase (NuRD) |
| **mTOR** | Mammalian target of rapamycin |
| **MYT1** | Membrane-associated tyrosine- and threonine-specific cdc2-inhibitory kinase |
| **NBS1** | Nijmegen breakage syndrome protein 1, Nibrin |
| **ncRNAs** | non-coding RNAs |
| **NEDD8** | Neural precursor cell expressed, developmentally down regulated 8 |
| **NF-kB** | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| **NPC** | Nasopharyngeal carcinoma |
| **NSCLC** | Non-small cell lung cancer |
| **NTRK2** | Neurotrophic tyrosine receptor kinase 2 |
| **ORIs** | Origin of replication |
| **OTUB1** | OTU deubiquitinase, ubiquitin aldehyde binding 1 |
| **OXA** | Oxaliplatin |
| **PAF** | Platelet-activating factor |
| **PARP** | Poly-ADP ribose polymerase |
| **PCAT1** | Prostate cancer-associated transcript 1 |
| **PCNA** | Proliferating cell nuclear antigen |
| **PDK1** | Phosphoinositide-dependent kinase-1 |
| **PDX** | Patient-derived xenograft |
| **PI3K** | Phosphatidylinositol 3-kinase |
| **PLKs** | Polo-Like Kinases |
| **Pre-IC** | Pre-initiation complex |
| **PROTACs** | Proteolysis targeting chimeras |
| **PTBP1** | Polypyrimidine tract binding protein 1 |
| **PTEN** | Phosphatase and tensin homolog |
| **RAD50** | RAD50 Double Strand Break Repair Protein |
| **RAS** | Rat sarcoma |
| **Rb** | Retinoblastoma |
| **RNA** | Ribo nucleic acid |
| **RNATx** | RNA therapeutics |
| **RPS9** | Ribosomal protein S9 |
| **RRM2** | Ribonucleotide reductase subunit M2 |

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|---|---|
| **RS** | Replication stress |
| **RSC** | Chromatin structure remodelling complex |
| **RUNX1** | Runt related transcription factor 1 |
| ***S. pombe*** | *Schizosaccharomyces pombe* |
| **SAC** | Spindle Assembly checkpoint Spindle assembly checkpoint |
| **SCF** | Skp-Cullin-F box |
| **SCLC** | Small cell lung cancer |
| **Ser** | Serine |
| **shRNA** | Small hairpin RNA |
| **siRNAs** | Small interfering RNAs |
| **SIRT1** | Sirtuin 1 |
| **SKP1** | S phase kinase-associated protein 1 |
| **SLC31A1** | Solute carrier family 31 member 1 |
| **SMAC** | Second mitochondrial activator of caspase |
| **SNHG4** | Small Nucleolar RNA Host Gene 4 |
| **SOX17** | SRY-box transcription factor 17 |
| **S-phase** | Synthesis phase |
| **SphK2** | Sphingosine kinase 2 |
| **STAT3** | Signal transducer and activator of transcription 3 |
| **T-ALL** | T-cell acute lymphoblastic leukemia |
| **TCGA** | The Cancer Genome Atlas |
| **TEAD** | Transcriptional enhanced associate domain |
| **TGF-** | Transforming growth factor beta |
| **Thr** | Threonine |
| **TME** | Tumor microenvironment |
| **TNBC** | Triple-negative breast cancer |
| **TP53** | Tumor protein P53 |
| **TTK** | Threonine tyrosine kinase |
| **Tyr** | Tyrosine |
| **UBE2N** | Ubiquitin conjugating enzyme E2 N |
| **USP** | Ubiquitin-specific peptidase |
| **VEGF** | Vascular endothelial growth factor |
| **WAF1** | Wildtype p53-activated fragment 1 |
| **XRCC5** | X-ray repair cross complementing 5 |
| **YAP** | Yes-associated protein 1 |
| **ZEB1** | Zinc finger E-box binding homeobox factor 1 |
| **ZH2** | Zeste homolog 2 |

## Introduction

Cancer is an unregulated condition that is caused by alterations in the genes responsible for the regulation of cell function, leading to continuous and excessive cell division [1,2]. One of the primary factors contributing to this phenomenon is modifications in cell cycle regulators, which compromises their surveillance ability responsible for maintaining the normal functioning of the cell cycle [3]. This continuous division and growth of cancerous cells lead to the invasion of normal tissues and organs. Ultimately, resulting in the spread of cancerous cells (metastasis) (Fig. 1) [4]. The cell cycle is a highly controlled system of functionally linked proteins that carry out accurate and timely duplication of genomic DNA followed by segregation of daughter cells. It is defined by two distinct stages, interphase (consisting of the G1 phase, S-phase, and G2 phase) and M phase [5]. The timely transition of cells from one phase to another phase is guided by the accumulation and degradation of cyclins along with their catalytic partners; cyclin-dependent kinases (CDKs) under the close surveillance of several checkpoints like DNA damage checkpoint, replication stress checkpoint, and mitotic checkpoint [6–8]. Defects in these checkpoints lead to the aforementioned behavior of the cell cycle transforming them into cancerous cells. Abrupt DNA damage checkpoint is one of the most commonly reported defects leading to the accumulation of errors causing mutations [9–11].

This review comprehensively discusses the regulators of the cell cycle and their contribution to the oncogenic transformation of normal cells. It also focuses on the cyclins, CDKs, CDK inhibitors (CKIs), major checkpoint regulators, and E3 ubiquitin ligases as therapeutic targets. The probable therapies which could be used to target cell cycle factors, allow the cells to exit the cell cycle and terminate the hyperproliferative nature of the same. Despite the extensive research, there are still some emerging issues like cancer drug resistance, drug non-specificity, immune evasion, and tumor microenvironment (TME) which could be addressed by using novel therapeutics like combination drug therapy, gene therapy, targeting ubiquitin ligase system, etc.

## Cell Cycle Factors and Cancer Progression

The well-coordinated regulation of the cell cycle is pivotal to the normal growth and survival of the organism. Furthermore, the research of many diseases, including cancer, revolves around comprehending the mechanistic regulation of the cell cycle. Mutation in genes involved in cell cycle regulation is one of the critical factors responsible for oncogenesis, proliferation, and progression [7,12,13]. The cell cycle regulation involves two important mechanisms. First is the phosphorylation of target proteins by kinases [5] And the second component is checkpoint/s that scrutinize the appropriate progression of each phase and delay the progression, upon encountering any trouble [11,14,15]. The processes are interlinked; phosphorylation-based activation of kinases such as ATM and ATR activates the checkpoint system in the cell cycle which in turn activates the downstream kinases for licensing the cell cycle [13].

### *Cyclins and cyclin-dependent kinases (CDKs)*

Cyclins were discovered by Tim Hunt in Sea Urchins as an essential protein that is degraded after each cycle of the cell division [16,17]. Cyclins A and B were identified through further studies in other organisms such as *Schizosacchromyces pombe*, *Drosophila melanogaster*, and *Xenopus*, that were shown to be required for cell cycle entry [17,18]. Later, Sir Paul Nurse and Lee Hartwell discovered the existence of kinase proteins that in coordination with cyclins phosphorylate the target proteins and aid in cell cycle entry and progression [18,19]. As the cells proceed

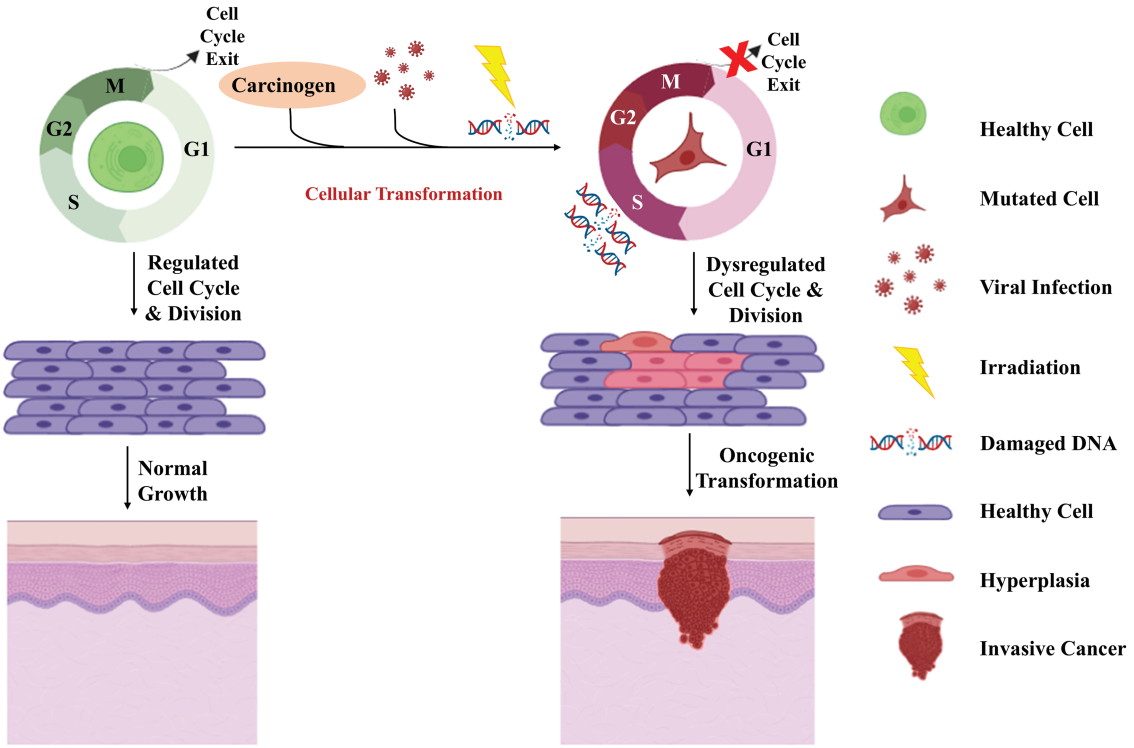


**FIGURE 1.** Oncogenic transformation of the normal cells. Exposure to carcinogens, radiations, or onco-viral infections may lead to a dysregulated cell cycle, resulting in the accumulation of mutations, and eventually genomic instability. The dysregulated cell cycle and genomic instability cause the oncogenic transformation of normal cells into neoplastic cells. These neoplastic cells with persistent mutations end up causing hyperplasia followed by an invasive cancerous stage (Created using BioRender graphics).

through the cell cycle, sequentially four major cyclins are involved namely, cyclin D, E, A, and B which regulate the activities of their respective cyclin-dependent kinases (CDKs). For normal functioning of cells, these factors are strictly regulated by various mechanisms including cell cycle-specific transcription and degradation of the gain-of-function/loss-of-function mutations in the viral genes, such as p27, p53, Rb, CCNE1/2, and various others, results in aberrant expression of the cell cycle factors, contributing to tumor development and progression. Consequently, targeting these factors may serve as an effective strategy for developing therapeutics for tumor management and inhibition [20].

*Cyclin D and CDK4/6*

The cell cycle is regulated and driven by a set of cyclin proteins and their catalytic partner CDKs [21]. Cyclin D activates and forms a complex with CDK4/6, which phosphorylates proteins like pRb. Upon hyperphosphorylation, pRb gets inactivated leading to the release of transcription factor E2Fs. This process subsequently leads to the activation of E2Fs, which facilitates the transcription of downstream genes including cyclin E, CDKs, and CDCs [22–24]. Cyclin-CDK complexes are inhibited by cyclin-dependent kinase inhibitors (CKIs) [25]. The CKIs involved in the regulation of cyclin-CDKs can be categorized into inhibitors of CDK4/6 (INK4) and kinase inhibitory protein/CDK interacting protein (KIP/CIP). The INK4 inhibitors (p16, p15, p18, p19) inhibit cyclin D-CDK4/6 by inactivating CDK4/6 whereas KIP/CIP inhibitors (p27, p57, p21) promote cyclin D-CDK4/6 complex by inhibiting CDK2, thus promoting the proliferative activity of cells (Fig. 2) [20,26]. During the late G1 phase, cyclin D-CDK4/6 activates cyclin E-CDK2, which phosphorylates pRb and facilitates the G1-S transition (Fig. 2) [20]. The dysregulated activity of CDK4/6 kinases in association with cyclin D [27], results in hyperphosphorylation of pRb that leads to loss of cell cycle regulation thereby, uncontrolled cell proliferation [28,29]. Hyperactivity of cyclin D has been reported in various cancers such as endometrial carcinoma [30], non-small cell lung cancer (NSCLC) [31], head and neck carcinoma [32], pancreatic cancer [33], and colorectal cancer [34]. Overexpression of CDK4 has been reported in uterine cancer [35], colorectal cancer [34], cervical cancer [36], melanoma [37] as well as NSCLC [31]. The CDK4 gene amplification has been found in glioblastomas [38], uterine cervix cancer [39], osteosarcomas [40], rhabdomyosarcomas [41], and liposarcomas [42]. Overexpression and gene amplification of CDK6 have been reported in leukemia [43], gliomas [44], and lymphomas [43]. Targeting CDK4/6 has been a breakthrough in the treatment of breast cancer and can be effective in the treatment of other cancers as well [20].

*Cyclin E, A, and CDK2*

CDK2 is involved in G1/S transition [13]. It becomes active when it binds to one of its two regulatory partners, cyclins A or E, to form a functional, heterodimeric complex [2]. Cyclin D-CDK4/6 mediated sequestration of p27/p21, and transcription of cyclin E activates and increases the activity of CDK2 in the late G1 phase [45]. Interestingly, WEE1-mediated phosphorylation of CDK2 at Tyr-15 inhibits its

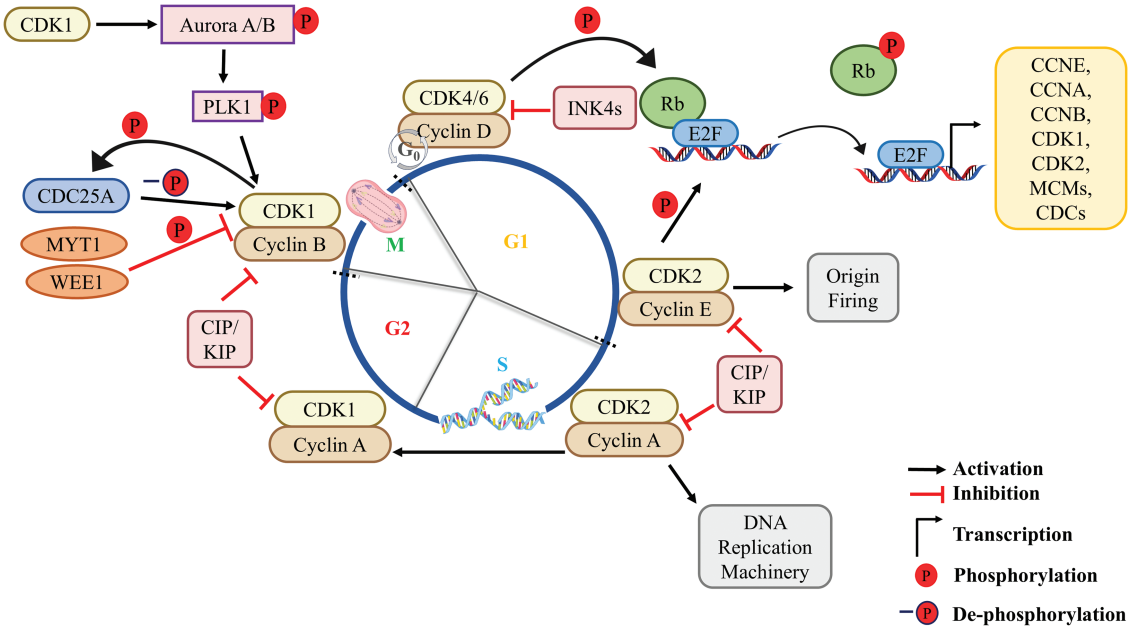


**FIGURE 2.** Overview of the molecular mechanism of the cell cycle. In a quiescent cell, the mitogenic signal triggers the activation of cyclin D-CDK4/6 complex resulting in E2F-mediated transcription of downstream genes (CCNE, CCNA, CCNB, CDKs, CDC6, Cdt1, MCMs, etc.). During the late G1 phase, the activated cyclin E-CDK2 complex initiates the loading of replication-related proteins resulting in the onset of origin firing which transits the cell into the S-phase. In the S-phase, cyclin A-CDK2 initiates DNA replication and progresses to the G2 phase. In the G2 phase, accumulated cyclin B in the cytoplasm gets translocated into the nucleus upon being phosphorylated by PLK1. CDC25A removes the inhibitory phosphorylation from CDK1, caused by WEE1 and MYT1. Activated cyclin B-CDK1 complex activates mitotic machinery followed by mitotic exit. P, phosphorylation; -P, dephosphorylation.

activity. This inhibitory phosphorylation is removed by CDC25A/B phosphatases (Fig. 2). Cyclin E-CDK2 complex phosphorylates and activates various proteins including cyclin A which are needed for DNA replication and cell cycle progression [46]. An E3 ubiquitin ligase system, $SCF^{FBXW7}$, rapidly breaks down cyclin E during S-phase (Fig. 3) [47]. Active cyclin E-CDK2 complex induces the expression of various factors responsible for DNA replication such as cell division cycle 6 (CDC6), chromatin licensing and DNA replication factor 1 (Cdt1/CDC10 dependent transcript 1), minichromosome maintenance complex (MCM2-7), cyclin A, EMI1 (APC/C inhibitor), etc. which helps in origin recognition, origin firing, DNA unwinding, thereby ensuring single replication per cell cycle [48]. To ensure a single round of replication per cell cycle, two essential steps before DNA synthesis must be carried out: origin licensing and origin firing. Origin licensing involves the assembly of the pre-replication complex (pre-RC) onto the origin of replication (ORIs) and occurs during late mitosis and early G1 phase when cells have low levels of CDK activity [49]. Origin activation occurs during the G1/S transition and generates a pre-initiation complex (pre-IC) [50,51]. Pre-IC formation, in contrast to origin licensing, necessitates high kinase activity; that is achieved through the combined action of two S-phase kinases, CDK2 and CDC7, which bind to the regulatory proteins; cyclin E/A and DBF4, respectively [52–54]. The above kinases work together to phosphorylate several replication factors (CDC45, GINS, replicative MCMs, etc.) and promote replicative protein recruitment to ORIs. DNA polymerases and additional proteins are recruited following helicase activation and subsequent DNA unwinding, ultimately resulting in origin firing [55]. The above events make the entry into the S-phase of the cell cycle.

At the onset of the S-phase, CDK2 binds to cyclin A2 to form an active cyclin A-CDK2 complex for the progression of DNA replication or S-phase [5,52,56] (Fig. 2). Both E2F-dependent transcription, as well as inactivation of APC/$C^{CDH1}$ (which degrades cyclin A, Fig. 3), are crucial for cyclin A-CDK2 activity. This inactivation of APC/$C^{CDH1}$ is a result of cyclin E-CDK2 mediated transcription of EMI1 [57,58]. E2F-mediated transcription results in the accumulation of cyclin A-CDK2 activity, which triggers the cell to initiate DNA replication [13]. Cyclin A-CDK2, later in S-phase also controls the timing of cyclin B-CDK1 activation and mitotic entry of cells by regulating CDH1 levels (Fig. 3) [59].

The Cyclin E1 gene, *CCNE1* is highly amplified in many cancers such as ovarian cancers [60], endometrial cancer [61], hepatocellular carcinoma [62], etc. CDK2 is also reported to be overexpressed in prostate cancer [63] and B cell lymphoma [64]. Since FBXW7/FBW7 is directly involved in the degradation of cyclin E [58,65] (Fig. 3), loss of FBXW7 is associated with colon [66,67] and breast cancer [68,69] where cyclin E is not timely degraded resulting in hyperproliferation. Thus, targeting CDK2 could be a better target for cancer therapeutics.

### *Cyclin A, B and CDK1*

The mitotic cyclins, cyclin A and B (which accumulate in the S-phase) bind to, and activate CDK1 during the G2 phase; cyclin A-CDK1 then propels G2 cells into mitosis [52]. CDK1 accumulates in an inactive form as a result of phosphorylation (inhibitory) at Thr-14 and Tyr-15 by kinases MYT1 and WEE1, respectively. At the end of G2,

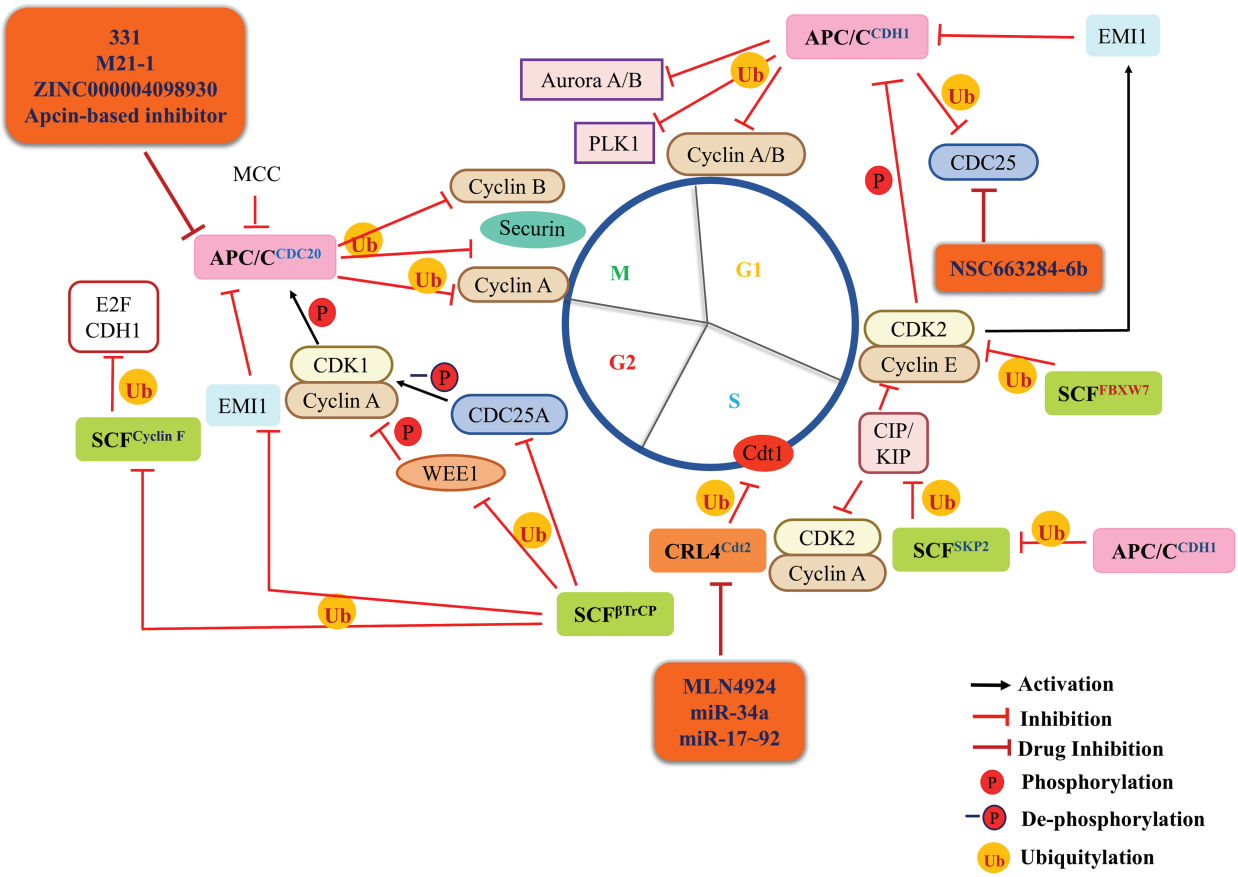


**FIGURE 3.** Targeting E3 ubiquitin ligase system as a novel approach for cancer therapeutics. The three major E3 Ubiquitin Ligase complexes that regulate the normal cell cycle progression are Anaphase Promoting Complex or Cyclosome (APC/C, pink round square), Skp-Cullin-F box (SCF, green round square) and Cullin Ring Ubiquitin Ligase 4 (CRL4, peach round square) with their respective adapter proteins. APC/$C^{CDH1}$ becomes active in anaphase where it modulates the mitotic regulators like Aurora A and PLK1, etc. At the end of the M phase, APC/$C^{CDH1}$ maintains a low level of mitotic and S-phase cyclins thus stabilizing the G1 phase and preventing premature S-phase occurrence. At the end of the G1 phase, cyclin E-CDK2 complex inactivates APC/$C^{CDH1}$ and mediates E2F-dependent transcription of EMI1 which further inactivates APC/$C^{CDH1}$. Degradation of cyclin E by $SCF^{FBXW7}$ and BTB-Cul-3-Rbx1 (BCR) complex marks the entry of the cell in the S-phase. During S-phase, $CRL4^{Cdt2}$ degrades Cdt1 and p21 to ensure a single round of DNA replication per cell cycle. During the G2 phase, $SCF^{\beta TrCP}$ regulates the activity of CDK1 by degrading WEE1 (activation) and CDC25A (inactivation). $SCF^{\beta TrCP}$ also degrades EMI1 which inhibits the activity of APC/$C^{CDC20}$. Also, during the G2 phase, $SCF^{cyclin\ F}$ ensures the degradation of E2F and CDH1. In the early M-phase, APC/$C^{CDC20}$ mediates the degradation of cyclin A and pushes the cell into metaphase. In metaphase, APC/$C^{CDC20}$ degrades cyclin B and securin to ensure anaphase onset. During the anaphase, APC/$C^{CDH1}$ mediates the degradation of cyclin B to exit the cell cycle. In addition, APC/C and SCF E3 ligase control each other to regulate their expression. In cancerous cells, the dysregulated expression of this ubiquitin ligase system leads to prolonged degradation of tumor suppressor proteins like KIP/CIP and constant expression of oncogenic proteins, which could be targeted for cancer therapeutics using several drugs mentioned in orange round boxes (and are under clinical trials). P, Phosphorylation; -P, dephosphorylation; Ub, ubiquitination; black arrow, activation; red hammerhead arrow, inhibition; maroon hammerhead arrow, inhibition by drugs.

the accumulated inactive cyclin B-CDK1 complexes are activated by phosphatase CDC25, which removes the inhibitory phosphorylation of CDK1. CDC25 works in a positive feedback loop with active cyclin B-CDK1. As cyclin B-CDK1 activates additional CDC25, which subsequently removes inhibitory phosphorylation from cyclin B-CDK1, resulting in complete activation of the complex (Fig. 2) [20,70]. CDK1 can also be activated by cyclin H-CDK7 mediated phosphorylation at Thr-161 [71]. CDK1 activity is necessary for mitotic entry and multiple mitotic events. Widespread phosphorylation of over a thousand CDK1 substrates, including B-Raf (BRAF, a proto-oncogene), p53, checkpoint kinases (CHK1/2), etc., initiate entry into mitosis once CDK1 activity thresholds are reached [72]. Simultaneously, CDK1 stimulates PLK1, Aurora A/B, the mitotic kinases that phosphorylate other mitotic proteins (Fig. 2). Every cell organelle undergoes structural alterations as a preparatory measure for cytokinesis (completion of cell division). Increased cytoplasmic CDK1 activity during prophase causes centrosome separation and cell rounding. Additionally, the fast nuclear import of activated cyclin B-CDK1 causes chromosomal condensation, APC/C activation, nucleolar disassembly, and nuclear envelope permeabilization [13,20]. The anaphase-promoting complexes ($APC^{CDC20}$ and $APC^{CDH1}$) degrade cyclin B during the late mitosis (Fig. 3), resulting in chromosomal separation, completion of mitosis, cytokinesis, and attenuation of CDK1 activity [46].

Amplification of the cyclin B gene *(CCNB1)* has been closely associated with neuroendocrine prostate cancer [73],

lung cancer [74], breast cancer [75], etc. According to The Cancer Genome Atlas (TCGA) database, CDK1 was found to be significantly abundant in 17 out of 24 cancers including cervical cancer, cholangiocarcinoma, urothelial carcinoma, glioblastoma, etc. [76–78]. The deregulation of upstream or downstream mediators of CDK1 is linked with various cancers. Ribosomal protein S9 (RPS9) is an upstream activator of CDK1 and knockdown of RPS9 in colon cancer inhibits the growth of cancerous cells by downregulating CDK1 at the G2/M phase resulting in checkpoint activation which in turn induces apoptosis [79]. Mutations in DNA methyltransferase-3-alpha (DNMT3A), a positive activator of CDK1, increases the expression of CDK1 which induces leukemia [72]. Considering the fact that CDK1 is highly abundant in human cancer, it could act as a potential target for developing novel cancer therapies (Fig. 3).

*Cell cycle checkpoints*

The cell cycle is a highly orchestrated biological phenomenon that results in DNA replication and cell division. The cell cycle regulatory Checkpoint factors determine whether a cell should continue to the next phase of the cell cycle or abort the process [57,58,80]. They monitor DNA damage, loss of replication fork integrity, and inadequate spindle assembly during different phases of the cycle (Fig. 4) [13].

*DNA damage checkpoint*

During interphase, the presence of DNA double-strand breaks (DSBs) activates checkpoint protein kinase Ataxia Telangiectasia Mutated (ATM) signaling cascade.

Upon the initial response, DNA damage sensor complex MRN (MRE1, RAD50, and NBS1) assembles at the double-strand break (DSB) sites, activating ATM which in turn

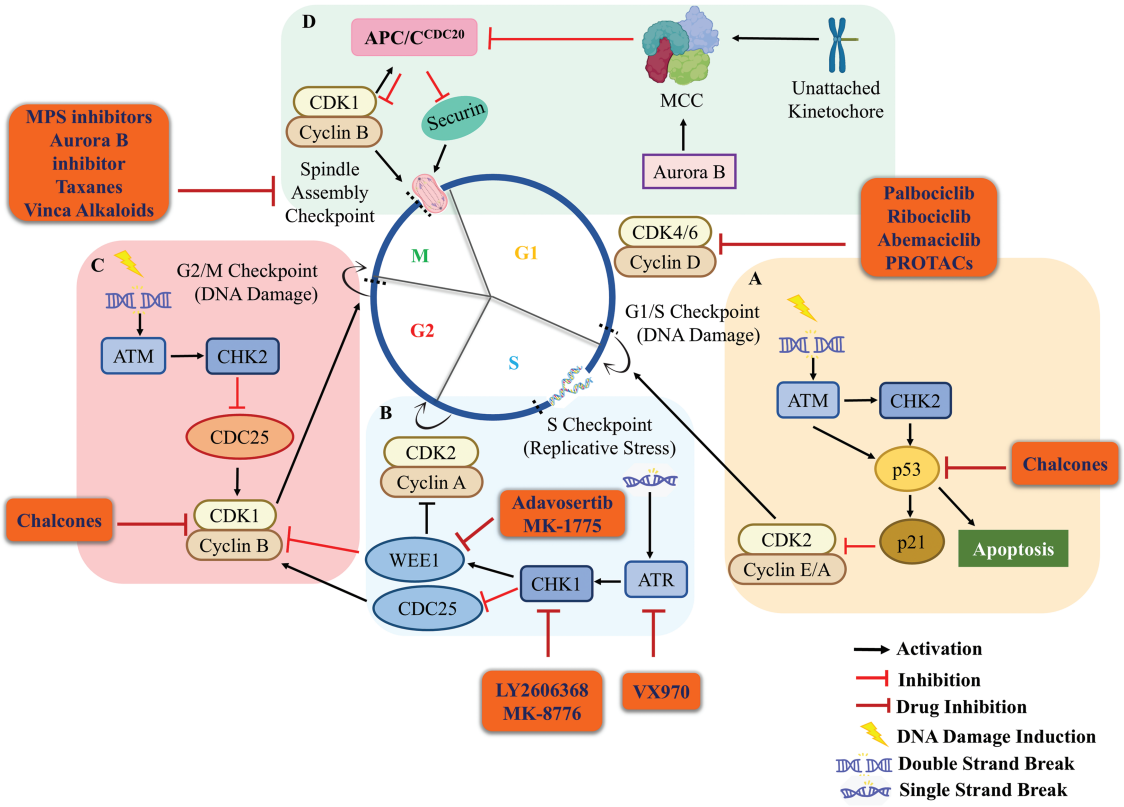


**FIGURE 4.** Cell cycle checkpoint regulation and inhibitory effect of drugs on it. (A) During the G1 phase, the DSBs trigger the G1/S checkpoint where ATM is recruited at DSBs by the MRN complex. ATM phosphorylates and activates CHK2 and p53 which in turn activates p21 which inhibits the activity of cyclin E/A-CDK2. This results in the halting of cells in the G1 phase and damage is repaired. If the damage is beyond repair p53 activates the apoptotic machinery of the cells. (B) Stress generated during the replication recruits ATR at the single-strand breaks (SSBs), ATR activates CHK1 which activates WEE1. WEE1 phosphorylates CDK2 thus inactivating cyclin A-CDK2. Thereby, inhibiting the transition of cells from the S to G2 phase to maintain the genomic integrity. (C) In the G2 phase, DNA damage is sensed and ATM-CHK2 signaling gets activated. CHK1/2 in turn inactivates the phosphatase CDC25 which cannot remove the inhibitory phosphorylation of CDK1 caused by WEE1. This aborts the activation of cyclin B-CDK1 and arrests the cells in the G2 phase, thus, limiting the cells from entering into the mitotic phase. (D) During the metaphase of M-phase, chromosomes align at the equator and spindle fibers attach to kinetochores for proper segregation of chromosomes in anaphase. Any unattached kinetochore generates a "wait anaphase" signal which activates the mitotic checkpoint complex (MCC). MCC inhibits the anaphase-promoting complex $APC^{CDC20}$ inhibiting the degradation of cyclin B-CDK1 and securin. This inhibits the progression of cells from metaphase to anaphase of the cell cycle. During cancer conditions, most of these proteins involved in cell surveillance are aberrantly expressed due to the accumulation of a series of mutations. Most of these mutations upregulate the expression of CDKs and disturb the normal physiology of the cell cycle checkpoints. These aberrations serve as potential targets for cancer therapeutics and small structural molecules/drugs (given in orange round box) have been designed to combat them. The orange round boxes show different drugs that target cell cycle and checkpoint factors to inhibit cancer progression and are under clinical trials. Black arrow, activation; red hammerhead arrow, inhibition; maroon hammerhead arrow, inhibition by drugs.

phosphorylates a wide range of substrates. Essential targets in DNA damage response include the protein checkpoint kinase 2 (CHK2; phosphorylation at Thr-68) and the transcription factor p53 (phosphorylation at Ser-15) [81]. Simultaneously, ATM also stabilizes p53 by phosphorylating a p53 degradation E3 ubiquitin ligase machinery, MDM2 [81]. CHK2 also activates p53 by phosphorylating it at Ser-20 [82]. Activated p53 in turn then transactivates p21, a CDK inhibitor, leading to the inactivation of cyclin-CDK complexes particularly in the G1 phase (cyclin E-CDK2), blocking the transition of cells from G1 to S-phase (Fig. 4A) [13]. Mutation or aberration of p53 and p21 thus, results in loss of G1/S checkpoint system [80]. Post DNA replication, ATMs are recruited at DSBs activating CHK2. CHK2 phosphorylates and inactivates CDC25A/C, therefore the latter is not available to dephosphorylate and activate CDK1, ensuring the inactivation of CDK1. This results in the halting of cells at the G2 phase by inhibiting the G2/M transition (Fig. 4C) [13,81].

Cells can exit the cell cycle in two ways: reversibly by undergoing quiescence or irreversibly by apoptosis or senescence [13]. In response to DNA damage, the DNA damage checkpoint can either induce quiescence, senescence, or apoptosis during the interphase of the cell, predominantly through p53-dependent pathways [83]. The most prevalent mutation in cancer is p53 alterations [84]. ATM is a tumor suppressor that induces cell cycle arrest or apoptosis by activating CHK2, p53, DBC1, and other downstream proteins [85]. In contrast, ATM activity and signaling are reported to be elevated in certain cancers such as melanoma, prostate cancer, pancreatic cancer, etc., [13,86]. It is possible that those cancer cells have gained resistance against ATM-induced apoptosis and cell cycle arrest. Further work needs to be done to elucidate this mechanism. In prostate cancer cells, Ack1 kinase phosphorylates androgen receptor (AR) at Thr-267 which mediates the recruitment of phosphorylated AR to the enhancer region of ATM genes resulting in the increased expression of ATM [87]. In pancreatic cancer, overexpression of transcription factor CUX1 serves as the activator for DNA Damage Repair (DDR) genes and upregulates the expression of ATM [88]. Hence, ATM-based anti-cancer therapy should be carefully studied and designed, based on the characteristics of the tumor.

*Replication stress checkpoint*

DNA replication stress checkpoint gets activated only during S-phase of the cell cycle. Delay or stalling of DNA replication forks, falling off polymerases from the fork, collision with transcription machinery, DNA damage, etc., eventually exposes single-stranded DNA for too long resulting in replication-induced stress. During the S-phase response to DSBs, DNA resection engages homologous recombination repair leading to the generation of single-stranded DNA. Accumulation of single-stranded DNA activates the replicative stress kinases; ataxia telangiectasia mutated and Rad3-related protein (ATR) and CHK1 [13]. CHK1 phosphorylates the WEE1 and CDC25A/C resulting in their activation and degradation, respectively [20]. WEE1-dependent inhibitory phosphorylation of CDKs, particularly CDK2 and CDK1 results in the inactivation of cyclin-CDK complex, halting the cells in the S-phase. This provides a greater window of time to resolve the replicative stress (RS) and ensures complete duplication of the genome [89]. Simultaneously, the inhibition of CDC25 results in the accumulation of inactivated CDK1 ensuring no premature onset of the mitotic events (Fig. 4B) [13].

Genetic instability, a characteristic of cancer, is a leading cause for intratumor heterogeneity posing a major challenge for therapy development. RS plays a significant role in promoting genomic instability in cancer [90]. Cyclin E is frequently overexpressed in triple-negative breast cancer and ovarian cancer [91,92], amplification of which is linked to induction of replicative stress, as a result of collision between replication and transcription machineries [93]. *CCNE1* and CDC25A amplification leads to aberrant origin firing which in turn produces immense replicative stress [94]. The hyperproliferative tendency of cancerous cells is a result of various overexpressing oncogenes which causes replicative stress [9,95]. Due to aforementioned reasons, cancer cell witnesses an increase in RS as they enter the S-phase, thereby increasing their dependency on ATR-mediated S and G2/M checkpoints for the resolution of the same. Thus, blocking ATR has great promise for developing treatment of various cancers [96]. The overexpression of cyclin E1 and CDC25A induces RS, which leads to lagging chromosomes and formation of chromatin bridges [93]. This replication stress is further intensified by inhibiting ATR or WEE1 kinases, ultimately resulting in death of tumor cells [93].

*Spindle assembly checkpoint*

Spindle assembly checkpoint (SAC) which gets activated in M-phase ensures that the duplicated DNA is equally distributed among the two daughter cells [97,98]. The multiprotein SAC machinery is activated if any kinetochore remains unattached to microtubules [13]. SAC allows unattached kinetochores to prevent aneuploidy by limiting premature chromosomal segregation [98]. The CDC20 (also known as CDC20A or p55CDC) stimulates the APC/C during mitosis, and ensures APC/$C^{CDC20}$ complex ubiquitinates the two anaphase inhibitors; cyclin B and securin to encourage sister chromatid separation and mitotic exit (Fig. 4D) [99]. Unattached kinetochores generate a diffusible signal of 'wait anaphase', activating a tetrameric complex; mitotic checkpoint complex (MCC consisting of Mad2, CDC20, BubR1, and Bub3) which turns-off the activity of APC/$C^{CDC20}$ (Fig. 4D) [97,100]. Once all the kinetochores are attached and bioriented to opposite spindle poles, the MCC disassembles. This frees up the CDC20, which acts as a co-activator, thus, turns on the APC/$C^{CDC20}$ [101,102]. The re-activated APC/C E3 ubiquitin ligase then marks the cyclin B and securin for degradation, allowing chromosomal segregation and anaphase to occur [13,97].

Cancerous cells are mostly aneuploid, having aberrant chromosomal configurations which are results of mitotic errors. Although, SAC gene mutations have been linked to cancer, they are uncommon [13]. Overexpression of SAC proteins (MPS1, MAD1, MAD2, BUBR1, and CDC20) may result in the delayed mitosis, cohesion fatigue, chromosomal

mis-segregation, eventually resulting in chromosomal-instability and aneuploidy. These genetic alterations can contribute to development of various malignancies including colon, pancreatic, oesophageal, oral, tonsillar, gastric, renal, cervical cancers, etc. [8,103,104]. BUB1B which is a downstream protein in SAC signaling pathway, is overexpressed in aggressive breast cancer and knockdown of *Bub1b* gene suppresses the tumorigenicity in breast cancer cells [105]. MPS1 (an upstream target of SAC) is overexpressed in triple-negative breast cancer, lung cancer, and neuroblastoma [106–108] making it a potential target for cancer therapeutics.

## Therapies Available for Targeting Cell Cycle Factors

Till date, indeed there are several therapies available such as gene therapy, stem cell therapy small-molecule inhibitors, etc., that target the growth of cancerous cells. Among them, targeting cell cycle proteins can be an effective strategy for cancer management [20,109,110]. The available drugs that target cell cycle factors like PLK4 inhibitors [111], Threonine Tyrosine Kinase (TTK) inhibitors [112–114], CDK4/6 inhibitors [115], are considered to be promising strategies for the treatment of cancer [116,117], yet very limited success has been achieved (Table 1). For that reason, more mechanistic work needs to be carried out to understand the process in detail which could lead to exploring and developing better and specific targeted therapies to supress and kill cancerous cells.

*CDK inhibitors*

CDK inhibitor class of drugs that have been proven to be effective treatments for cancer. Recently, INX-315; a potent CDK2 inhibitor; that effectively inhibits retinoblastoma protein (Rb) phosphorylation, leading to G1 phase cell cycle arrest [131], has been developed and is under preclinical study in CCNE1-amplified cancers [115]. Various other CDK2 inhibitors are under preclinical or clinical trials such as PE-07104091 (Tagtociclib), BLU-222, etc. [132,133]. To compensate for the overexpression of CDK1 in cancer, some CDK1 inhibitor drugs are already in preclinical testing like RO-3306 and CGP-74514A, which act by inducing G2 arrest, preventing cells with DNA damage from entering mitosis, thereby allowing the required time for DNA repair, and suppressing the tumorigenesis in both cancer cells and patient-derived xenograft (PDX) [134,135]. Another subcategory of CDK4/6 inhibitors; is Palbociclib, Ribociclib, and Abemaciclib, which have demonstrated effectiveness in treating hormone receptor-positive breast cancer. These inhibitors block the cyclin D-CDK4/6 pathway downstream by preventing pRb phosphorylation, causing senescence in cancer cells [117,136]. In patients with advanced-stage hormone receptor-positive, HER2 non-amplified (HR +HER2−) breast cancer, combinatorial therapy with CDK4/6 inhibitors and endocrine therapy is used as a

**TABLE 1**

**Current therapies available for targeting cell cycle factors to treat cancer progression**

| Drug | Target | Phase of clinical trials and type of cancer | References |
|---|---|---|---|
| AZD1152, AT9283 | Spindle assembly checkpoint | **II** → AML, multiple myeloma, SCLC, and prostate cancer | [13,118] |
| BAY 1161909, BAY 1217389, Mps-BAY2a | Spindle assembly checkpoint | **I** → Neuroblastoma, medulloblastoma, and breast cancer | [107,108,119] |
| Palbociclib, Ribociclib, Abemaciclib | CDK4/6 | ER-positive, HER2-negative metastatic breast cancer, and various solid tumors | [116,117,120,121] |
| ICEC0942 (CT7001) | CDK7 | **I/II** → ER+ Breast cancer | [122,123] |
| SKLB-M8 (Chalcone) | CDC2, p53, AKT, mTOR | Melanoma | [124] |
| Adavosertib (AZD1775) | WEE1 kinase | **II** → Small cell lung cancer (SCLC), ovarian cancer, non-small cell lung cancer (NSCLC), acute myeloid leukemia (AML), gastric adenocarcinoma, advanced solid tumors | [125,126] |
| VX970 | ATR | **II** → Recurrent ovarian, primary peritoneal, and metastatic urothelial carcinoma | [125,126] |
| LY2606368, MK-8776 | CHK1 | **II** → SCLC, breast, ovarian, TNBC, prostate cancer<br>**I** → Leukemia, lymphoma | [125,126] |
| Vinca alkaloids (Vinblastine and vincristine) | Mitotic spindle | Acute lymphoblastic leukemia, AML, Hodgkin's lymphoma (HL), neuroblastoma and NSCL | [127,128] |
| Taxanes (Paclitaxel, Docetaxel, nanoparticle albumin-bound paclitaxel) | Mitotic spindle | Ovarian, breast, lung, bladder, prostate cancer, melanoma, and esophageal cancer | [127–129] |
| PROTACs | CDK4/6 | Malignant melanoma | [130] |

standard of care [137]. ICEC0942 (CT7001) is another drug that targets CDK7 and disrupts CDK7 mediated phosphorylation of RNA polymerase II particularly affecting genes like RUNX1 in T-cell acute lymphoblastic leukemia (T-ALL) facilitating transcription, to force the cell to exit cell cycle. It is in Phase I/II clinical trials for ER+ breast cancer [122] and Acute myeloid leukemia (AML) [138].

Chalcones are precursors of flavonoids, composed of the chemical scaffold 1,3-diphenyl-2-propen-1-one [139,140]. SKLB-M8, a derivative of natural chalcone Millepachine, is a potent growth inhibitor of various melanoma cancer cell lines which downregulates CDC2 expression and upregulates p53 to promote G2/M cell cycle arrest in A2058 and CHL-1 cells, respectively. SKLB-M8 also downregulates AKT and phosphorylates mTOR, resulting in the induction of apoptosis [124].

*Checkpoint kinase inhibitors*

Cell cycle inhibitors such as CDK and checkpoint kinase inhibitors are often used in combination with chemotherapy to target cell cycle factors for cancer treatment [21,124,140,141]. In addition to CDKs, checkpoint kinases like Aurora A/B and PLKs are other targets for cancer therapy. Promising clinical trial outcomes have been reported, and the first treatment targeting a cell cycle regulator has been approved which has shown quite promising results for treating breast cancers [137]. However, recent research has introduced the possibility of using TTK and PLK4 inhibitors as alternatives to overcome CDK4/6 drug resistance, and further research in this domain could hold great potential for advancement in cancer therapeutics [112,114,142]. BI2536, one of the initial PLK1 inhibitors, inhibits PLK1 and significantly suppresses tumor development *in-vivo* as well as *in-vitro*. Although BI2536 demonstrated a satisfactory safety profile in several clinical trials, its monotherapy application resulted in suboptimal response rates. However, when BI2536 was combined with chemotherapy drugs, synergistic effects were observed. For instance, it enhanced the susceptibility of neuroblastoma cells to the anticancer effects of vincristine, which facilitated cell death by blocking B-cell lymphoma 2 (BCL-2) and cleaving caspases 3 and 9. Furthermore, BI2536 exhibited a synergistic impact with eribulin in neuroblastoma and rhabdomyosarcoma, leading to a reduction in tumor development in *in-vivo* [4]. To modify aberrant ATR expression, four ATR inhibitors M6620 [143], M4344 [144], AZD6738 [145], and BAY1895344 [146] are currently under clinical trials [96,147]. AZD6738 modulates CHK1 phosphorylation, induces ATM-dependent signaling, inhibits homologous recombination repair, and enhances tumor sensitivity to DNA-damaging agents [148]. M6620 significantly reduces the repair of DNA double-strand breaks (DSBs) induced by radiation, leading to increased cell death [149]. M4344 inhibits activation of the ATR signaling pathway, thereby blocking signal transduction from replicative DNA damage. After M4344 treatment, cells undergo replication catastrophe with DNA damage and mitotic defects, leading to cell death [150]. Among all, Adavosertib (AZD1775) which bypasses necessary DNA repair processes, promoting cell death in cancer cells especially those with p53 mutations [151], is in Phase II trials for relapsed small cell lung cancer (SCLC), ovarian cancer, NSCLC, AML, gastric adenocarcinoma, and various advanced solid tumors, that target WEE1 kinase, delaying mitotic entry [125,126]. VX970, which impairs replicative stress tolerance by targeting ATR, is in Phase II trials for recurrent ovarian cancer, primary peritoneal fallopian tube cancer, and metastatic urothelial carcinoma [126,143]. Berzosertib, another potent ATR inhibitor, is currently undergoing Phase I/II clinical trials. When administered in combination with the topoisomerase I inhibitor, topotecan, in small cell lung cancer; cisplatin in neuroendocrine tumors; and benezortib in brain metastases from non-small cell lung cancer, berzosertib significantly enhances the efficacy of chemotherapy. Notably, promising results were observed for high-grade serous ovarian cancer (HGSOC) and chemotherapy-resistant small cell neuroendocrine carcinoma, both of which exhibit elevated levels of replication stress [152]. The drugs LY2606368 and MK-8776, which target CHK1 and regulate replicative stress, are in phase II trials for SCLC, BRCA1/BRCA2-mutated breast, and ovarian cancer [153,154], triple-negative breast cancer (TNBC) [155,156], high-grade serous ovarian cancer (HGSOC), metastatic castration-resistant prostate cancer (CRPC), bladder cancer [157] and advanced solid tumors [158] with homologous recombination repair defects or genetic alterations [159–161]. These drugs have also been tested in phase I—acute leukemia, solid tumors, or lymphoma and phase II—relapsed AML (with or without cytarabine) [126].

*Checkpoint inhibitors*

Taxanes (paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel) are the drugs that target mitotic spindle checkpoint by binding to β-tubulin and prevent microtubule depolymerization resulting in mitotic arrest and subsequent cell death [162]. These are approved for the treatment of various cancers, including ovarian cancer, breast cancer, lung cancer, bladder cancer, prostate cancer, melanoma, and esophageal cancer [128,129,163]. Vinca alkaloids (vinblastine and vincristine) also target mitotic spindle assembly causing metaphase arrest during mitosis and are approved for use in a range of cancers, including ALL (acute lymphoblastic leukemia), AML, Hodgkin's lymphoma (HL), neuroblastoma, and NSCLC [127,128]. Another class of SAC inhibitors is MPS1 inhibitors, BAY 1161909 and BAY 1217389, [106,164] are under preclinical trial and have recently entered Phase I clinical trials for treating neuroblastoma [108], medulloblastoma [119], and breast cancer in combination with taxanes [107]. Aurora B inhibitors, AZD1152 [165] and AT9283 also target SAC, and are in Phase II of the trial for AML, multiple myeloma (MM), SCLC, prostate cancer, etc. [118,166,167].

*Proteolysis targeting chimeras (PROTACs)*

PROTACS are bivalent molecules comprising two selective binding moieties ("warheads") to recruit the protein target and an E3 ligase at its ends, thereby, linking them together to bring the target protein in close proximity to the E3 ligase for its ubiquitination-induced degradation [168]. To

combat cancer, PROTACs are used to induce the degradation of tumor-overexpressing oncogenic proteins like CDK2/4/6, WEE1, Aurora A/B as well as E2F1 and CDC20 [169–171]. WEE1-PROTAC (ZNL-20-096) [172], Aurora A-PROTAC (JB170) [173], and CDC20-PROTAC (CP5V) [174] Target upstream regulators of G2/M checkpoint which in turn blocks entry and progression into mitosis. Based on CDK4/6 inhibitors, PROTACs have been developed to target CDK4/6 (BSJ-03-024 [175], BSJ-02-162 [175], and pal-pom [176]), CDK4 only (BSJ-03-132 [175]) and CDK6 only (BSJ-03-123 [177], CP-10 [178], YX-2-107 [179], and Degrader 6 [180]), which have been shown to elicit degradation efficiency and antiproliferative effects in cancerous cells [181].

Developing therapies targeting cell cycle regulators such as CDKs, cyclins, other kinases, and multiple checkpoint proteins could be an effective way to combat cancer with minimal side effects and other diseases caused by re-replication and hyperproliferation leading to abnormal cell growth.

## Emerging Trends and Future Directions

The accomplishment and success story of CDK inhibitors in clinical trials represents the potency of targeting cell cycle proteins for the treatment of cancers. In the ensuing years, compounds that inhibit other cell cycle proteins will be assessed in pre-clinical studies and subsequently on cancer patients (clinical trials). However, despite significant advancements, the efforts of combating solid tumors remain an uphill challenge. One of the roadblocks to this is drug resistance in various cancers that develop over some time. Cancer drug resistance arises due to the intra-tumor heterogeneity resulting from highly diverse genetic, epigenetic, and varying cell cycle dynamics of the cancer cells [182]. As a result of cell cycle heterogeneity, resistant populations of tumor cells persist and proliferate despite the presence of classical chemotherapeutic agents and/or novel targeted drugs. Research has demonstrated that this sub-population of tumor cells adopts a variety of DNA repair mechanisms, reverses or escapes chemical damage to DNA by relying on damaged checkpoints, and avoids apoptosis which eventually results in resistance to a variety of anti-cancerous drugs. In addition to cancer drug resistance, other challenges associated with cancer therapy include a lack of target specificity, an inefficient delivery system, tumor microenvironment (TME), and immune evasion [183], all of which need to be addressed (Fig. 5) to develop an efficient treatment for cancer using methods like Combination therapy and Gene-Based Therapy

### *Combination therapy*

Combination therapy for cancer treatment is a promising approach for several reasons. Firstly, it enhances treatment outcomes and achieves superior therapeutic effects, particularly when a synergistic anticancer activity is achieved [184]. Secondly, it overcomes clonal heterogeneity, which is associated with improved response rates [185]. Additionally, combining drug regimens reduces toxicity, as it allows the usage of individual drugs at reduced dosages while maintaining therapeutic efficacy [184]. Another advantage of combination therapies is reducing the emergence of drug resistance [184]. By targeting several molecular pathways, essential for cancer cell survival and abolishing cellular mechanisms associated with adaptive resistance, combination therapy enables concurrent targeting. In one of the studies, the combination of birinapant with the p38 inhibitor (ralimetinib) restored the sensitivity of LKB1- and KRAS-mutated cell lines [186]. Another study by Mortensen et al. in 2020, investigated the impact of the novel heat shock protein 90 (HSP90) inhibitor (onalespib) on enhancing the activity and reversing the resistance of cisplatin in ovarian and head and neck cancer cells. The results showed that the combination of onalespib and cisplatin restored therapeutic activity and enhanced the anti-proliferative, anti-migratory, and apoptotic effects of the chemotherapeutic drug [187]. In 2020, Shi et al. demonstrated sphingosine kinase 2 (SphK2) mediated regorafenib resistance in hepatocellular carcinoma through NF-kB and STAT3 activation. It was also reported that sensitivity to regorafenib was restored with the combination of regorafenib and the SphK2 inhibitor ABC294640 in both *in-vitro* and xenograft animal models of hepatocellular carcinoma [188]. In 2020, Xu et al. showed that the combination of the HSP90 inhibitor, SNX-2112, with the knockdown of STAT3, is associated with enhanced antiproliferative and apoptotic anticancer activity of cancer stem-like cells in culture and animal models for oesophageal cancer [189].

CDC7 kinase, functioning in collaboration with cyclin-dependent kinase CDK2, is a crucial and rate-limiting factor for initiating DNA replication [54]. However, CDC7 is not essential for the cell division of various cell types, as CDK1 can take over to continue the cell division cycle. CDC7 and CDK1 perform functionally equivalent roles during the G1/S transition, and the presence of at least one of these kinases is necessary for S-phase entry [9,54]. These findings provide insight into the intricate molecular coordination of the cell cycle, and the combination of CDC7 and CDK1 inhibitors could be a potent new strategy for combating cancer [52–54]. A recent combinatorial strategy involving Poly (ADP-ribose) polymerase (PARP) inhibitors and the inhibition of two major cell cycle checkpoint pathways, specifically the DNA damage checkpoints (ATM-CHK2-TP53) and DNA replication stress checkpoints (ATR-CHK1-WEE1), demonstrates synergistic effects in increasing the frequency of DNA errors, compromising the DNA repair machinery, and disrupting the cell cycle. This approach consequently enhances the mortality rate of cancer cells exhibiting DNA repair deficiency or PARP inhibitor resistance [190]. Although cocktail treatments with two or more drugs can often yield additional or synergistic therapeutic effects, they may have their challenges like the possibility of drug-drug interactions and severe side effects. Furthermore, differences in pharmacokinetic profiles among drugs may raise significant concerns and limitations.

### *Gene-based therapy*

Gene-based therapies have proven to be a vital component of precision medicine by utilizing techniques such as gene inhibition, addition, replacement, or editing [191]. This approach has demonstrated considerable success in the

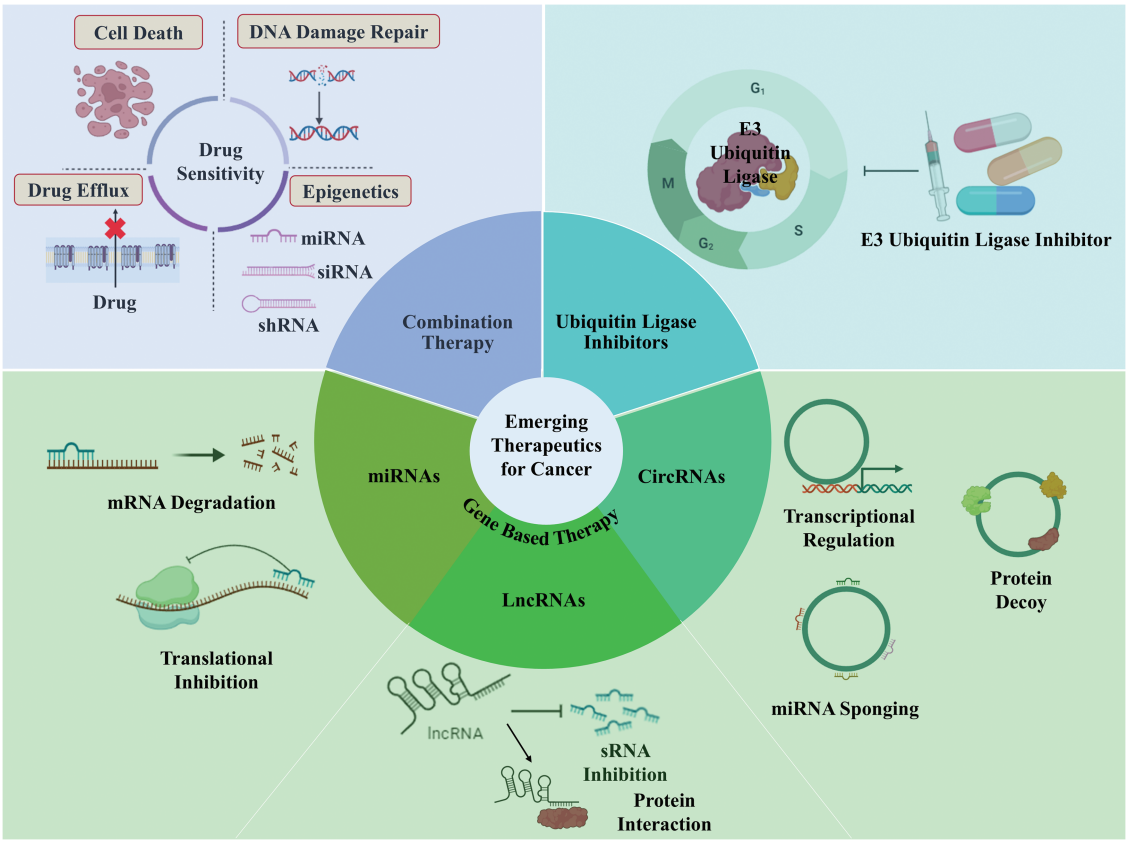


**FIGURE 5.** Emerging therapeutics to target cell cycle regulators in cancer. Combination therapy is codelivery of small drugs to overcome cancer drug resistance by inhibiting drug efflux pump hence decreased drug efflux, promoting apoptosis and DNA damage repair. Ubiquitin ligase inhibition, specially E3 inhibition is a more specific interference which ensures the target specificity and also, deubiquitinase inhibitors has also been recognised as a promising therapeutic option. Gene therapy involving inhibition of oncogenic RNA (miRNA, lncRNA, circRNA, and siRNAs) or overexpression of tumor suppressive RNAs to modulate expression of target gene is one of the promising fields in cancer research with minimum side effects. miRNA ensures target gene inhibition either by degrading the target gene or by inhibiting the translation of gene whereas lncRNA and circRNAs can either regulate cell cycle proteins by directly targeting the gene or protein or indirectly via miRNA sponging (Created using BioRender graphics).

treatment of various diseases including neuromuscular diseases and liver metabolic diseases as well [192]. Furthermore, the integration of multi-omics has significantly enhanced our comprehension of the molecular mechanisms associated with tumorigenesis and tumor development, leading to the identification of numerous potential oncological targets. RNA therapeutics, or RNATx, represent a promising approach for treating diseases by targeting or utilizing RNA molecules for therapeutic purposes.

*MicroRNAs (miRNAs/miRs)*

miRNAs are small non-coding RNA molecules that help to maintain homeostatic cell signaling and have been shown to regulate the translation of nearly >60% of total genes including genes involved in cell cycle regulation as well. This is achieved by either repressing translation or destabilizing mRNA of cell cycle proteins. Multiple miRNAs have been found to be aberrantly expressed in cancer due to mutations in genes involved in their biogenesis or dysregulated cell signaling [193,194]. Although miRNAs are dysregulated in nearly every disease, many of them are depleted in cancers. Depleted miRNAs are often classified as tumor-suppressive miRNAs. Restoring these tumor-suppressive miRNAs, such as miR-34a or let-7, can inhibit tumor growth *in-vivo* and prevent essential oncological processes like invasion, migration, and metastasis. miR-34a, in particular, has been extensively studied for its tumor-suppressive role in cancer. It contributes to p53 function by targeting multiple p53 inhibitors, including histone deacetylases SIRT1 and HDAC1, and MTA2, which deacetylates p53, thereby increasing the transcriptional activity of p53 [195–197]. miR-34a can also induce p53 activation by directly targeting MDM4, a strong p53 transactivation inhibitor [198]. miR-34a also suppresses a S-phase oncogenic factor CDC-10 dependent transcript 2 (Cdt2) and leads to suppression of cervical cancer cells [199]. Due to these anti-cancer properties, miR-34a was the first tumor-suppressive miRNA to be investigated as an anti-cancer agent in clinical trials; however, the study was terminated due to severe immune-related side effects [200]. To address these challenges, a miRNA delivery strategy using an endosomal escape agent DUPA-nigericin was developed which resulted in decreased cell proliferation *in-vitro* and delayed tumor growth *in-vivo*. Thus, miR-34a is one such example of a tumor-suppressive miRNA that has shown immense promise towards cancer suppression and treatment [201]. Apart from miR-34a, there are other miRNAs mentioned in Table 2A, which could prove to be quite potent in combating cancers.

**TABLE 2**

**Status of small RNAs in cancer and their target cell cycle regulators**

| Cancer type | Non-coding RNA | Expression | Cell cycle regulators-target genes | Reference |
|---|---|---|---|---|
| **A. Micro RNAs** | | | | |
| Glioblastoma | miR-34a | Downregulated | Cyclin D1, Cyclin E2, CDK4/6 | [202] |
| | miR-375 | Downregulated | SLC31A1 | [203] |
| | miR-126 | Downregulated | MDM2-P53, PI3K-Akt | [204] |
| | miR-370-3p | Upregulated | MGMT | [205] |
| | miR-200a-3p | Downregulated | Gαi1-AKT | [206] |
| Lung adenocarcinoma | miR-224 | Upregulated | p21 | [207] |
| Non-small cell lung cancer | miR-330 | Downregulated | E2F1 | [208] |
| | miR-193a-3p | Downregulated | Cyclin D1 | [209] |
| | miR-144 | Downregulated | Cyclin E1/E2 | [210] |
| Small cell lung cancer | miR-17-5p | Upregulated | Rb12 | [211] |
| | miR-25 | Upregulated | Cyclin E2, CDK2 | [212] |
| Lung cancer | miR-506 | Downregulated | CDK1, CDK4 | [213] |
| | miR-143 | Downregulated | CDK1, CDK4 | [213] |
| | miR-214-3p | Downregulated | CDK6 | [211] |
| | miR-155 | Upregulated | p53 | [214] |
| Breast cancer | Let-7 | Downregulated | RAS, HMGA2 | [215] |
| | miR-937-5p | Upregulated | CDK1, Cyclin A2, B1, D1 | [216] |
| Prostate cancer | miR-34a | Downregulated | CD44 | [217] |
| Pancreatic cancer | miR-200c | Downregulated | ZEB1 | [218] |
| | miR-488 | Downregulated | ERBB2, Cyclin A/B, CDK 1/2 | [219] |
| Brain cancer | miR-17 | Upregulated | CD133 | [220] |
| Colon cancer | miR-451 | Downregulated | COX-2 | [221] |
| Cervical cancer | miR-34a | Downregulated | Cdt2 | [199] |
| | miR-17 ~ 92 | Downregulated | Cdt2 | [222] |
| | miR-497-5p | Downregulated | CBX4 | [223] |
| | miR-372 | Upregulated | CDK2, Cyclin A1 | [224] |
| Ovarian cancer | miR-490-3p | Downregulated | CDK1 | [225] |
| Bladder cancer | miR-934 | Upregulated | CDK6 | [226] |
| | miR-3619 | Upregulated | CDK2 | [227] |
| Colorectal cancer | miR-4746 | Downregulated | Cyclin D1 | [228] |
| Acute myeloid leukemia | miR-582-3p | Downregulated | Cyclin B | [229] |
| Esophageal squamous cell carcinoma | miR-200b | Downregulated | CDK2, PAF | [230] |
| Gastric cancer | miR-31 | Downregulated | EZH2 | [231] |
| **B. Long non coding RNAs** | | | | |
| Hepatocellular carcinoma | LINC01419 | Upregulated | Ku80 | [232] |
| | Lnc00312 | Downregulated | Cyclin B1 | [233] |
| Breast cancer | ERINA | Upregulated | E2F1 | [234] |
| Cervical cancer | PITPNA-AS | Upregulated | c-MET | [235] |
| | NCK1-AS1 | Upregulated | CDK1, CDK6 | [236] |
| Oral squamous cell carcinoma | CCAT1 | Upregulated | Cyclin D1, CDK4 | [237] |
| Colorectal cancer | NR2F2-AS1 | Upregulated | Cyclin D1 | [238] |
| | SNHG4 | Upregulated | CDK1 | [239] |
| Pancreatic cancer | ABHD11-AS1 | Upregulated | Cyclin E | [240] |
| | GAS5 | Downregulated | p27Kip1 | [241] |

(Continued)

**Table 2 (continued)**

| Cancer type | Non-coding RNA | Expression | Cell cycle regulators-target genes | Reference |
|---|---|---|---|---|
| Thyroid carcinoma | ENST00000606790.1 | Upregulated | CDC25C | [242] |
| Esophageal squamous cell carcinoma | PCAT1 | Upregulated | Cyclin B1, CDC2 | [243] |
| Bladder cancer | LOC572558 | Downregulated | Akt, MDM2, p53 | [244] |
| Prostate cancer | LINC00304 | Upregulated | Cyclin A1 | [245] |
| **C. Circular RNAs** | | | | |
| Gastric cancer | $CircRHOBTB_3$ | Downregulated | p21 | [246] |
| Bladder cancer | Circ0058063 | Upregulated | CDK6 | [247] |
| | CircGLIS3 | Upregulated | Cyclin D1 | [248] |
| Breast cancer | Circ0006014 | Upregulated | CDK2, CDK6, NTRK2 | [249] |
| | Circ0006528 | Upregulated | MAPK, ERK | [250] |
| Hepatocellular carcinoma | CircSP3 | Upregulated | CDK4 | [251] |
| | Circ0079929 | Downregulated | PI3K, AKT, Cyclin B | [252] |
| Osteosarcoma | Circ001621 | Upregulated | CDK4, MMP9 | [253] |
| Head and neck squamous cell carcinoma | Circ0032822 | Upregulated | E2F3 | [254] |
| Chronic myeloid leukemia | F-circBA1 | Upregulated | CDC25B | [255] |
| Colorectal cancer | CircIFT80 | Upregulated | β catenin | [256] |

In one of the studies performed by Hsu et al., the effective role of a microRNA miR-31-5p in an Oxaliplatin (OXA)-resistant colorectal cancer (CRC) cells both *in-vitro* and *in-vivo* has been shown. Oxaliplatin is currently used in first-line chemotherapy to treat Stage III and Stage IV metastatic CRC. They showed that the upregulated expression of FOXC1 and miR-31-5p inhibited LATS2 expression, which led to OXA resistance. They further showed that the knockdown of miR-31-5p results in cancer cell apoptosis, decreased cell proliferation, and enhanced chemosensitivity [257].

*Long non-coding RNAs (lncRNAs)*

LncRNAs are stake targets due to their capacity to regulate a wide range of oncogenic molecular networks in a cell. These RNAs play a crucial role in controlling gene expression both in the nucleus and cytoplasm by interacting directly or indirectly with DNA, RNA, and proteins [258]. Dysregulated lncRNA expression has been linked with adverse outcomes for cancer patients (Table 2B). When lncRNAs are deregulated during the G1 phase, cells become more susceptible to uncontrolled mitogenic growth and defects in the G1-S transition [258,259].

During the transition from the G1 to S-phase of cell cycle, lncRNAs exert regulatory control over various E2F proteins, influencing cell proliferation and growth in the cancer cells. For instance, lncRNA regulating c-Myc (E2F1 mRNA-stabilizing factor; EMS) is involved in this process. lncRNAs can also directly regulate the E2F mRNA for G1 to S-phase transition. Linc00337, located in the 1p36.31 genomic region, has been reported to coactivate E2F1 mRNA and upregulate its expression leading to cancer progression in pancreatic ductal carcinoma [260]. Additionally, in breast cancer inhibition of linc00337 using small hairpin RNA (shRNA) sensitizes the cancer cells to paclitaxel and hence can be used as a combination therapy to overcome the drug resistance [260]. Apart from E2Fs, lncRNAs can also regulate the cell cycle by targeting cyclin-CDK complexes during G1 progression. They transcriptionally regulate CDK encoding genes as well as directly interact with cyclin and CDKs, affecting the protein phosphorylation and stability. LncRNAs also act as a scaffold that brings together multiple proteins involved in CDK regulation. In stress conditions, the CDC28 lncRNA recruits Hog1 (a stress-activated protein kinase) to CDC28 which in turn helps in recruiting chromatin structure remodelling (RSC) complex, resulting in increased CDC28 transcription and more efficient cell cycle progression upon stress [261]. Another lncRNA, DILA1 has been reported to interact directly with cyclin D1, preventing its phosphorylation at Thr-286. This in turn stabilizes cyclin D1 by suppressing its glycogen synthase kinase 3β (GSK3β)-mediated ubiquitination-dependent degradation. Stabilization of cyclin D1 promotes inactivation of pRb by phosphorylating at Ser-780 which in turn promotes G1/S cell cycle progression. Furthermore, high DILA1 expression is associated with poor prognosis and tamoxifen resistance in breast cancer patients [262]. lncRNA RP11-624L4.1 directly interacts with CDK4 and stabilizes its expression leading to the upregulation of CDK4/6-cyclin D1-Rb-E2F1 pathway, promoting G1 cell cycle progression in nasopharyngeal carcinoma (NPC) cells [263]. Several other lncRNAs have also been reported to be differentially expressed in different cancers (Table 2B) [264–266]. Some of which are hypomethylated and highly expressed in tumors whereas others are hypermethylated and expressed in lower levels in cancers. The S-phase exclusive lncRNAs; LINC00704, LUCAT1, and MIAT, have been reported to be essential for cancer development. Loss-of-function of these lncRNAs accumulates the cells in the G1 phase while decreasing the proportion of cells in the G2/M phase [267–270]. LINC00704 accelerates the cell cycle and contributes to

proliferation in nasopharyngeal carcinoma cells by regulating ETS1/CDK6 axis [271] and in papillary thyroid carcinoma by regulating miR-204-5p/HMGB1 axis [268]. LncRNA LUCAT1 also called as SCAL1 has found to be over-expressed [270] in a variety of cancers including choroidal melanoma [265], breast [272], ovarian [273], cervical [274], thyroid [266], and kidney [270] where it contributes to proliferation of ovarian cancer cells by regulating miR-199a-5p expression [275]. LncRNA LUCAT1 contributes to cell proliferation and migration in human pancreatic ductal adenocarcinoma via sponging miR-539 [276]. Hypoxia-induced regulation of PTBP1 by lncRNA LUCATI modulates cancer cell viability and chemotherapy response [277].

Many lncRNAs can also function as competing endogenous RNAs (ceRNAs) by sequestering miRNAs that target cell cycle regulators which could modulate cell proliferation. In thyroid cancer lncRNA MIAT functions as ceRNA to target EZH2 by sponging miR-150-5p [278]. lncRNA H19 (lncH19) regulate E2F1 level by sponging miR-29a in renal cell carcinoma [279].

*Circular RNAs (circRNAs)*

circRNAs are non-coding, single-stranded, covalently closed circular RNA that differ from traditional linear RNA. Majorly, circRNAs are derived from back splicing of pre-mRNA [280,281]. High-throughput RNA sequencing and circRNA bioinformatics analysis studies have identified thousands of circRNAs in eukaryotes which show tissue and lineage-specific expression [282–284]. Recent studies have shown the emerging roles of circRNA in transcription regulation, miRNA sponging, and protein decoys [285,286]. These circRNA are observed to be dysregulated in many diseases including cancers [287]. Most of the research has been done on the function of circRNAs in solid tumors, where they have been identified as either oncogenes or tumor suppressors [288–291] (Table 2C). Recently, the role of circRNA in tumor progression by regulating cell cycle factors was explored. circRNAs regulate the cell cycle gene expression either indirectly by sponging miRNA or lncRNA involved in cell cycle regulation or by directly interacting with the regulator proteins. CircMYLK has been found to be significantly upregulated in laryngeal squamous cell carcinoma (LSCC). Gain-of-function of circMYLK elevates cyclin D1 levels by sponging miR-195 facilitating LSCC cell proliferation and G1/S cell cycle transition [292]. A CCND1 derived circular RNA, circ-CCND1 is significantly upregulated in LSCC and, is associated with aggressive clinical features with adverse prognosis. circ-CCND1 interacts with HuR protein to stabilize CCND1 mRNA promoting CCND1 translation by sponging miR-646, hence, promotes LSCC tumorigenesis [293]. Another study reported the up-regulated circRNA; circPUM1 which leads to an increase of cyclin D1 and Bcl-2 expression by sponging miR-326 thereby, facilitating cell proliferation, migration, and invasion of lung adenocarcinoma [294]. In 2019, Li et al. reported upregulation of hsa_circ_000984 in NSCLC tissues and cell lines, which exerts oncogenic effects by regulating the expression levels of β-catenin, c-Myc, and cyclin D1, thereby activating Wnt/β-catenin pathway [295]. Also, circ-CMPK1/miR-302e/cyclin D1 signaling pathway has been reported to play a significant role in NSCLC, and can be targeted to develop an effective treatment [291]. In CRC, circ5615 is significantly up-regulated exhibiting an oncogenic role. Silencing of circ5615, leads to sponging of miR-149-5p and upregulation of tankyrase, (a regulator of β-catenin stabilization), thereby inducing β-catenin and cyclin D1 expression [290]. Silencing of hsa_circ_0035483 increases gemcitabine sensitivity and inhibits tumor growth in renal cancer cells via regulation of miR-335/CCNB1 axis [289]. hsa_circ_0136666 upregulates CDK6 expression by sponging miR-1299 to induce G2/M phase transition and promote breast cancer cell proliferation [296]. However, most of the circRNAs have been reported to play oncogenic role, some of them inhibit the cell cycle transition via diverse molecular mechanisms (Table 2C). For example, circNR3C1 has been found to be significantly downregulated in bladder cancer and its upregulation can significantly suppress cell proliferation and cell cycle progression by sponging miR-27a-3p, thereby inhibiting cyclin D1 expression [297].

In recent years, considerable progress has been made in the clinical application of RNA-based therapeutics, primarily through the use of antisense oligonucleotides and small interfering RNAs, with several gaining FDA approval for the treatment of conditions such as Duchenne muscular dystrophy and Spinal muscular atrophy [192]. Nevertheless, there are various limitations associated with RNA therapeutics, including challenges related to RNA delivery, stability, immunogenicity, and off-target effects. These issues need to be addressed before the development of RNA therapeutics for cancers [298]. Currently, several RNA-based potential treatments are in clinical trials and developmental pipelines. Despite all the limitations, non-coding RNA-based therapies hold significant potential in the treatment of cancer. These therapies aim to utilize non-coding RNAs, such as miRNAs, lncRNAs, circRNAs, and small interfering RNAs (siRNAs), to modulate gene expression and control various cellular processes specially cell cycle pathways involved in cancer development and progression. One strategy involves the use of anti-miRNA oligonucleotides and siRNAs to specifically target and inhibit oncogenic miRNAs or key cancer-related genes, thereby reducing tumor growth and promoting cancer cell death [299]. On the other hand, certain tumor-suppressive miRNAs or lncRNAs can be therapeutically delivered to restore their normal function and inhibit cancer. The most challenging task is their effective and accurate delivery mechanism [300]. Moreover, RNA-based therapies can be designed to target specific signaling pathways implicated in cancer, providing a precise and personalized treatment approach. In addition to RNA therapy, alternative gene therapy approaches, such as recombinant protein therapy utilizing appropriate plasmids for genetic correction, have emerged as viable options for the successful targeted delivery of the protein of interest [301].

*Targeting ubiquitin ligase system*

Ubiquitin ligase system is one of the most implicated systems which involve ubiquitylation of cellular targets leading to control of numerous cellular functions. In cell cycle, ubiquitination mechanism is involved in timely degradation

of protein for the transition of cell from one phase to another in most regulated manner (Fig. 3). The deregulation of the components of this elaborated system leads to disease conditions like cancer. Researches over the decades has shown that alteration in the ubiquitin system in cancer can be exploited for the molecular diagnostics and development of novel therapeutics [57,302,303].

APC is one of the major E3 ubiquitin ligases involved in the regulation of timely cell cycle progression by forming two E3 ubiquitin ligase complexes, $APC^{CDC20}$ and $APC^{CDH1}$. Recent studies have revealed that CDH1 functions as a tumor suppressor, while CDC20 may act as an oncoprotein [304–307] to promote the development and progression of human cancers, making it a potential target for therapeutics. In 2015, Zhang et al., have identified a compound "331" which inhibits CDC20 expression by upregulating miR-494 to induce cell death in glioma cells without any cytotoxic effect in astrocytes [306]. Another natural ligand-based drug ZINC000004098930 has been shown to target and inhibit CDC20, which has shown promising results for TNBC-targeted treatment [308]. A new apcin-based inhibitor for CDC20, designed by replacing the pyrimidine group with substituted thiazole-containing groups, shows improved antitumor activity [102]. A MAD2 inhibitor, M21-1, also inhibits CDC20 activity by disrupting the CDC20-MAD2 interaction, and consequently, the assembly of the mitotic checkpoint complex increasing the sensitivity of cancer cells to antimitotic drugs in myeloid cell leukemia-1 (MCL-1) [309]. Moreover, a triterpene mixture extracted from the mushroom *Poria cocos*, polyporenic acid C, can downregulate the expression of CDC20 in some cancer cells and inhibit cancer metastasis [307]. Cdt2 is an essential S-phase regulator protein that forms an E3 ubiquitin ligase system in association with its partner CRL4 to regulate cellular processes like re-replication, DNA damage repair, and proliferation [310–314]. Despite its crucial role, it is amplified in around 37 cancer types. NEDD8 targeting drug MLN4924 inhibits the $CRL4^{Cdt2}$ complex formation, leading to DNA re-replication by stabilizing Cdt1 in S-phase, triggering checkpoint activation, apoptosis, and senescence in cancer cells [315]. miR-34a and miR-17~92 can also suppress the expression of Cdt2 protein to inhibit $CRL4^{Cdt2}$ complex formation in cervical cancer cells, thereby suppressing the tumor progression [199,222]. MDM2 is a regulator of p53 and is implicated in the regulation of diverse cellular processes including cell cycle, apoptosis, senescence, and DNA repair [316]. Multiple small molecules have been reported to target MDM2 but none of them showed any promising results in clinical trials [317–319]. Recently another small molecule, AMG-232, a piperidinone-based compound, has been reported to act by binding to the p53 binding pocket in MDM2 [320], which results in the inhibition of p53-MDM2 complex formation. So far in clinical trials, the drug is showing modest safety and tolerability with similar but milder side effects than previous MDM2 inhibitors [321]. Apart from this, other accessory proteins that are involved in maintaining the ubiquitin system have also been observed to be aberrantly expressed during cancer and can be targeted for therapeutic intervention of cancer. MK-1775, a potent small-molecule inhibitor targeting the WEE1 protein, is currently under development for clinical trials in solid tumors [322–324]. A CDC25 inhibitor, NSC663284 derivative 6 has shown anti-proliferative effects in colon and colorectal carcinoma [325,326]. Deubiquitinase molecules (DUBs) have shown significant influence in regulating the specific substrates contributing to cancer progression. Therefore, targeted inhibition of DUBs is a therapeutic strategy for cancer treatment. Knockdown of USP3 leads to suppression of CDC25A, causing a delay in cell cycle progression [327]. Knockdown of USP21, USP39, USP7, and OTUB1 leads to downregulated FOXM1's transcription activity hence halting the cell cycle in breast cancer [328–331]. Targeting ubiquitin ligase can be a potential therapeutics to deal with drug resistance. However, it may exhibit certain limitations in addressing the same. Firstly, the diversity of the ubiquitin ligase system impedes a comprehensive understanding of their functions and corresponding target genes. Secondly, E3 ubiquitin systems possess the capacity to bind to multiple oncogenes. A single E3 not only interacts with one oncogene or tumor suppressor gene but also has the potential to engage with multiple oncogenes or tumor suppressor genes simultaneously.

## Research Gaps and Challenges

The efficacy of cell cycle-targeted therapies in the future will depend on the development of highly specific, least toxic, and potent compounds, targeting particular vulnerabilities of the cancer cells. Screening methodologies utilizing cell cultures, patient-derived xenografts, and genetically modified mouse models will play a critical role in elucidating synthetic lethal interactions between genomic abnormalities and targeted inhibition of specific cell cycle proteins. Novel therapeutic approaches capable of targeting multiple components within the same pathway, such as microRNAs, may also offer therapeutic advantages. Furthermore, the combination of multiple selective inhibitors may significantly enhance clinical efficacy; however, in numerous instances, combination therapies have resulted in a substantial increase in adverse effects, potentially rendering them intolerable in a significant number of patients. Moreover, a very small percentage of patients had exhibited long-term satisfactory responses for currently available targeted therapies. Consequently, genomic technologies will become crucial diagnostic tools for identifying predictive biomarkers in patient sub-groups. Preclinical research and clinical observations (Table S1) have shown the development of drug resistance, characterized by cancer relapse after an initial positive response. Investigating the mechanisms behind drug resistance will offer valuable insights into how existing compounds are countered, potentially leading to improved treatment strategies for patients who have relapsed or become refractory. Furthermore, this research could aid in designing a combination therapy aimed to prevent cancer cells from developing resistance. Another potential therapeutic approach to address drug resistance could be targeting ubiquitin ligases; however, due to its anticipated severe side effects, it requires extensive research before

progressing to clinical trials. A critical issue that needs to be addressed for the development of cell cycle-specific novel therapeutic formulations is the immunogenic response. Further research is necessary to identify intersections where immune response could complement cell cycle-based novel therapies. Addressing the aforementioned challenges will create opportunities for managing cancer through therapeutic approaches that induce cancer cells to permanently exit the cell cycle.

## Conclusion

The cell cycle machinery, which includes CDKs and cyclin subunits, is tightly regulated by a network of proteins. The past decade has witnessed substantial advancements in their comprehensive role in cancers. For instance, aberrations in CDK4/6, CDK2, and checkpoint proteins such as p53 and Rb, which are crucial for maintaining genomic stability, have been implicated in numerous cancer types. The identification of these aberrations has not only enhanced our mechanistic understanding of cancer biology but also made them highly potent targets for developing cancer therapy. The development of novel compounds through structure-based drug design and high-throughput screening platforms have allowed for the translation of cell cycle studies from bench to bedside. Inhibitors that selectively target CDK4/6, as well as CDK2 and CDK1, are being developed and may offer clinical benefits for certain cancer subtypes specifically. While the first clinical translation of a CDK4/6 selective inhibitor (palbociclib) in breast cancer has been successful, current targeted therapies face the challenge of relatively low response rates and the emergence of drug resistance. To overcome these challenges, novel approaches such as combination therapy, gene therapy, and E3 ubiquitin inhibitors may be employed as valuable therapeutics. Furthermore, a combination of several selective inhibitors may significantly improve clinical efficacy, but it may also increase the risk of adverse effects, limiting their tolerability in many patients. Additionally, developing drugs that target the ubiquitination system represents a promising approach for the treatment of cancer. Although only a limited number of such drugs have been approved by the FDA, a deeper and mechanistic understanding of ubiquitin signalling cascade in regulating cell cycle progression has the potential to expand and enhance current anticancer therapies culminating in improved clinical outcomes. Advances in RNA therapeutics have highlighted the importance of non-coding RNAs (ncRNAs) in cell cycle regulation and their potential as therapeutic targets in cancer. Various strategies have been proposed for harnessing ncRNAs as therapeutic agents, including miRNA mimics that have been tested in clinical trials for cancer treatment. However, other strategies associated with ncRNAs remain in their infancy, therefore, comprehensive investigations are necessary to unlock the potential of ncRNA-based therapeutic agents in targeting cell cycle regulation for advancing future anticancer drug development. Overall, our enhanced understanding of cell cycle control and cancer is guiding current treatments and creating therapeutic opportunities to improve initial treatment with curative intent, either through greater precision or by extending treatment modalities and better-informed treatment decisions that will result in improved outcomes for patients.

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