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Review

The crosstalk between non-coding RNAs and cell-cycle events: A new frontier in cancer therapy

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The cell cycle comprises sequential events during which a cell duplicates its genome and divides it into two daughter cells. This process is tightly regulated to ensure that the daughter cell receives identical copied chromosomal DNA and that any errors in the DNA during replication are correctly repaired. Cyclins and their enzyme partners, cyclin-dependent kinases (CDKs), are critical regulators of G- to M-phase transitions during the cell cycle. Mitogenic signals induce the formation of the cyclin/CDK complexes, resulting in phosphorylation and activation of the CDKs. Once activated, cyclin/CDK complexes phosphorylate specific substrates that drive the cell cycle forward. The sequential activation and inactivation of cyclin-CDK complexes are tightly controlled by activating and inactivating phosphorylation events induced by cell-cycle proteins. The non-coding RNAs (ncRNAs), which do not code for proteins, regulate cell-cycle proteins at the transcriptional and translational levels, thereby controlling their expression at different cell-cycle phases. Deregulation of ncRNAs can cause abnormal expression patterns of cell-cycle-regulating proteins, resulting in abnormalities in cell-cycle regulation and cancer development. This review explores how ncRNA dysregulation can disrupt cell division balance and discusses potential therapeutic approaches targeting these ncRNAs to control cell-cycle events in cancer treatment.

INTRODUCTION TO CELL CYCLE

The cell cycle is a highly regulated process that involves a series of coordinated events to duplicate genetic material and produce two identical daughter cells. It consists of four distinct stages: the growth phase (G1), DNA replication phase (S), preparation for division phase (G2), and the division phase (M or mitosis). Progression through the cell cycle is tightly controlled by a group of proteins known as cyclins, which bind to and activate a class of serine-threonine kinases called CDKs. CDKs, once activated, phosphorylate themselves and other essential proteins to drive the cell cycle forward.[1] CDK-cyclin complexes play a key role in regulating the cell cycle. CDKs are typically expressed continuously throughout the cell cycle, while cyclin expression varies at different stages.[1,2] The activity of CDK-cyclin complexes is further modulated by numerous CDK inhibitors (CKIs) that inhibit their activation, acting as brakes on cell-cycle progression when conditions are unfavorable.[3]

Throughout evolution, the number of CDKs and cyclins has increased. For example, the budding yeast *Saccharomyces cerevisiae* has six conserved CDKs and 22 cyclins, while human cells have 20 CDKs and 29 cyclins.[4,5] In *S. cerevisiae*, CDKs such as Cdc28 (mammalian CDK1) and Pho85 (mammalian CDK1) interact with multiple cyclins and are sufficient to drive the cell cycle.[6,7] In contrast, humans have six homologs of Cdc28 (CDK1, CDK2, CDK3, CDK4, CDK6) and Pho85 (CDK5, CDK14, CDK15, CDK16, CDK17, CDK18) to perform similar functions.[8,9] This increased complexity allows for precise regulation at each stage of the cell cycle by forming various cyclin/CDK combinations. To ensure the proper progression of the cell cycle and prevent the propagation of genetic errors during cell division, various checkpoints are in place. These checkpoints include the G1-S checkpoint at the G1- to S-phase transition, the intra-S-phase checkpoint during DNA synthesis, the G2/M checkpoint as the cell transitions from G2 (after DNA replication) to the mitotic M phase for division, and the spindle assembly checkpoint (SAC), which ensures proper chromosome segregation to prevent aneuploidy.

The G1-S checkpoint serves as a critical gatekeeper that oversees the transition from the pre-replicative G1 phase to the replicative S phase in the cell cycle. Its primary function is to determine whether a cell is

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adequately prepared to enter the S phase for DNA replication or if it should exit the cell cycle and enter a state of quiescence. Importantly, this checkpoint is equipped to detect DNA damage, and, in the presence of damaged DNA, it halts the cell's progression from G1 to S. This pause in the cell cycle allows time for the necessary repairs to be made to damaged DNA.[10,11] In cases where the DNA damage is irreparable, cells may choose to enter a state of senescence (growth arrest) or undergo cell death.[12] Assuming that some DNA with unrepaired damage manages to pass through the G1-S checkpoint and enters the S phase, or if DNA damage occurs during DNA replication within the S phase, the G2/M checkpoint becomes crucial. This checkpoint's role is to prevent cells from entering the process of mitosis (cell division) if there are issues or abnormalities detected in the DNA.[13,14] The S-phase checkpoint monitors the proper progression of DNA replication forks to ensure the smooth and accurate replication of the genetic material.[15,16] It is particularly vigilant in detecting aberrant replication fork structures that expose single-stranded DNA, a condition known as replication stress. When replication stress occurs, it triggers the S-phase checkpoint-mediated replication stress response. This response is essential for preventing genomic instability, a condition that can have profound consequences for normal cell development.[15,17]

The SAC comes into play during the prometaphase of the cell cycle and is responsible for ensuring that the spindle apparatus properly attaches to the kinetochores.[18] Kinetochores are disc-shaped protein structures associated with duplicated chromatids, and their correct attachment is crucial for the orderly separation of sister chromatids during cell division. This process prevents the occurrence of chromosomal gains or losses in daughter cells, a phenomenon frequently observed in cancerous cells.[19] In summary, the progression of the cell cycle is a meticulously orchestrated process, tightly regulated by intricate protein interaction networks. These networks ensure the faithful replication of genomic DNA and its subsequent distribution to daughter cells. Additionally, cell-cycle checkpoints stationed at the exit of each stage serve as vigilant monitors of this process, intervening when necessary to halt the cell cycle in cases of DNA damage or incomplete replication. Dysregulation of the signaling networks that control the cell cycle plays a pivotal role in uncontrolled cell-cycle progression and cell division, contributing to the development of cancerous cells.

NcRNAs: A CRUCIAL ELEMENT IN REGULATINGTHE CELL CYCLE

NcRNAs are emerging as crucial players in the intricate regulation of the cell cycle, complementing the extensive research on protein mutations that influence cell-cycle control in cancer cells. Many proteins involved in cell-cycle progression, DNA repair, and checkpoint responses are frequently found to be mutated in cancer, contributing to the unchecked cell growth characteristic of these cells.[20,21] These mutations, often arising during DNA replication, can lead to genomic instability, ultimately transforming healthy cells into cancerous ones. Furthermore, errors in chromosome segregation during mitosis can result in various chromosome abnormalities, such as abnormal ploidy, chromosome loss, or amplification, frequently observed in cancer cells.[22,23] However, beyond these well-studied protein-level regulations, there exists another layer of upstream control over cell-cycle proteins, primarily composed of ncRNAs.

The ncRNAs wield significant influence over the expression of genes involved in the cell cycle through various mechanisms. They can bind to messenger RNA (mRNA) molecules, hindering their translation; directly govern gene transcription by interacting with DNA-binding and chromatin-modifying proteins; act as molecular scaffolds that facilitate diverse RNA-protein or protein-protein interactions; modulate microRNA (miRNA) activity and their target genes; or function as decoy molecules that disrupt normal protein functions. Despite not encoding any proteins themselves, ncRNAs occupy a substantial portion of the genome and exert control over nearly every cellular process.[24] The dysregulation of ncRNAs has been closely linked to abnormal cell-cycle regulation and the development of cancer.[25,26] These ncRNAs belong to diverse RNA groups and can have either oncogenic or tumor-suppressor roles, depending on the protein-coding genes they regulate. In this review, we will delve into the roles of three distinct types of ncRNAs, namely miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), in establishing an intricate regulatory network that influences various components of the cell-cycle control system. Drawing from recent literature, this review will explore the diverse mechanisms through which ncRNAs regulate the cell cycle and how targeting these ncRNAs therapeutically can exploit vulnerabilities in cancer cells, potentially paving the way for innovative cancer therapies.

CELL CYCLE REGULATION BY ncRNAs DURING THE G1-S TRANSITION

Cell cycle events at the G1-S transition

When a cell receives signals from growth factors or external stimuli, it can commit to initiating replication and move from the G1 phase to the S phase in the cell cycle. This commitment triggers the action of CDKs, including CDK4 and CDK6, along with their partner protein, cyclin D, which play a pivotal role in the transition from G1 to S. Cyclin D binds to CDK4 or CDK6, activating these kinases and enabling them to phosphorylate specific target proteins. These phosphorylation events drive the cell cycle forward. One of the important target proteins of CDK-cyclin complexes is retinoblastoma (RB), along with p107 and p130, collectively known as pocket proteins. These pocket proteins have a role in binding to and regulating the activity of E2F-family transcription factors.[27–30] E2F family members can have either a role in activating transcription (E2F1, E2F2, and E2F3A) or repressing it (E2F3B, E2F4, E2F5, E2F6, E2F7, and E2F8).[31,32]

RB binds to E2F1–3 and inhibits their transcriptional activity. The phosphorylation of Rb by CDK4/6-cyclin D complexes releases its inhibitory effect on which induces E2F1 mediated transcription of genes involved in the G1-S transition.[33–36] For the transcriptional activity of these E2Fs, they require interaction with coactivator proteins from the p300/CBP family.[37] On the other hand, p107 and p130 interact with cytoplasmic E2F4 and 5, transport them to the nucleus, and assemble at promoters to repress transcription.[38]

Phosphorylation of p107 and p130 disrupts their interaction with E2F4 and 5, releasing their inhibitory effect on E2F1–3-responsive genes, leading to their transcription.[38–40] E2F6 forms a potent repressive complex that inhibits the transcription of E2F-responsive promoters,[41] whereas E2F7 is involved in mediating transcriptional repression in response to DNA damage.[42] To ensure a smooth G1-S transition, there is a positive feedback loop in place. E2F-responsive genes, such as cyclin E, complex with CDK2 and phosphorylate and inactivate pocket proteins.[43,44] This inactivation of pocket proteins results in increased E2F1–3 activity, further promoting the transcription of G1-phase cyclins, such as cyclin E, and facilitating cell-cycle progression[44]

REGULATION OF CELL CYCLE EVENTS BY miRNAs DURING THE G1-S TRANSITION IN CANCER

MiRNAs exert their control over gene expression by primarily binding to the 3′ or 5' untranslated regions (UTRs) of mRNAs in the cytoplasm of cells. This binding event triggers mRNA degradation and prevents its translation.[45,46] Further, miRNAs have also inhibited the translation initiation step and thus negatively influence the translation process.[47,48] Over the years, extensive research has focused on understanding the role of miRNAs in cell-cycle regulation. Dysregulation of these miRNAs can lead to abrupt control of the cell cycle, resulting in heightened cell-cycle progression. Many miRNAs have been studied for their involvement in the control and regulation of the cell cycle. Notably, they play a role in regulating the mRNAs of CDKs and cyclins that are essential for the transition from G1 to S phase. For example, miR-6883-5p, miR-149, miR-6785-5p, and miR-4728-5p can bind to the 3′ UTR of CDK4/6 mRNAs, leading to the degradation of these mRNAs.[49] In patients with colorectal cancer, the loss of expression of two of these miRNAs, miR-6883-5p and miR-149, is associated with increased CDK4/6 activity and enhanced cell proliferation. However, when miR-6883-5p and miR-149 are overexpressed in colorectal cancer cells, they downregulate CDK4/6, resulting in stable G1 cell-cycle arrest followed by apoptosis. Moreover, the combined use of miR-6883-5p and miR-149 with CDK4/6 inhibitors and anticancer drugs such as palbociclib, irinotecan, and 5-fluorouracil (5-FU) significantly enhances the anti-proliferative and apoptotic effects of these drugs on tumor cells.[49] This suggests that the loss of tissue-specific miRNAs can disrupt cell-cycle regulation and promote tumor development. Conversely, restoring the expression of these miRNAs can dedifferentiate tumor cells to their original tissue type. Consequently, the combination of targeted drugs with miRNAs holds promise as a therapeutic approach to enhance current cancer treatments and improve outcomes.

Regulation of miRNA expression occurs through various mechanisms, including transcriptional, post-transcriptional, and post-translational processes. p53, a tumor-suppressor protein often referred to as the guardian of the genome, plays a significant role in transcriptionally regulating multiple miRNAs to uphold cell-cycle control. p53 acts as a vigilant monitor of DNA damage and is activated in the G1 phase by the checkpoint protein kinase ataxia telangiectasia mutated (ATM).[50] The detection of double-strand breaks (DSBs) in DNA triggers a response from a DNA damage sensor complex composed of MRE1, RAD50, and NBS1 (MRN), which in turn activates ATM.[51] ATM then phosphorylates and activates p53, leading to an increase in the transcription of its target gene, the CDK inhibitor p21. Elevated levels of p21 inhibit cyclin-CDK complexes during the G1 phase, preventing cells from entering the S phase.[52,53] In addition to its canonical role, p53 can also regulate the G1-S transition by influencing miRNAs directly, binding to their promoter regions and thereby either activating or repressing their transcription. A prime example is the regulation of miR-149 by p53 in melanoma cells. When melanoma cells experience endoplasmic reticulum (ER) stress, p53 is activated and transcriptionally induces the miR-149 host gene, glypican 1 (GPC1). This host gene co-transcribes miR-149, leading to an increase in miR-149 expression.[54] miR-149, in turn, binds to the 3′ UTR of the enzyme glycogen synthase kinase 3α (GSK3α) and reduces its protein levels. Inhibition of GSK3α leads to the upregulation of its downstream target, Mcl-1. Mcl1 regulates the G1-S transition by binding and destabilizing p18, an inhibitor of the G1-S transition.[55] Mcl-1, a member of the antiapoptotic Bcl-2 family of proteins, plays a crucial role in melanoma cell survival and resistance to therapeutic treatments; inhibition of Mcl-1 not only induces cell-cycle arrest followed by apoptosis but also sensitizes melanoma cells to anticancer agents.[54,56,57]

Moreover, when p53 is activated during cellular quiescence, it triggers the transcription of host genes for miR-27b and miR-455, namely chromosome 9 open reading frame 3 (C9ORF3) and collagen alpha-1 (XXVII) chain (COL27A1) in various cancer cell lines, leading to the upregulation of these miRNAs. miR-27b, in particular, targets cyclin-dependent kinase regulatory subunit 1 (CKS1B), which is a cofactor of Skp2, a component of the ubiquitin-proteasome system. Inhibiting Skp2 activity prevents it from mediating the polyubiquitination of p27, allowing p27 to exert its inhibitory functions on cyclin-CDK complexes and causing cell-cycle arrest. On the other hand, miR-455 inhibits the expression of CDK2-associated cullin domain 1 (CAC1), a protein that interacts with CDK2 and enhances its kinase activity. The inhibition of CDK2 kinase activity by miR-455 prevents CDK2-mediated p27 phosphorylation and polyubiquitination, resulting in the accumulation of p27. Ubiquitination plays a crucial role in regulating the levels and activity of cyclins, CDKs, and their regulators throughout the cell cycle.[58] The growing recognition of the involvement of numerous miRNAs in the ubiquitin-proteolytic machinery suggests that miRNAs can influence the ubiquitination status of cell-cycle regulators by targeting proteins involved in the ubiquitin-proteasome system (UPS). This additional layer of regulation adds complexity to the mechanisms governing ubiquitination pathways during cell-cycle progression, offering valuable insights into the processes underlying cellular homeostasis and the development of cancer.

During the transition from the G1 to S phase, the activities of cyclin A (comprising cyclin A1 and A2) and D-type cyclins (including cyclin D1, D2, and D3) are under the regulation of several tumor-suppressor miRNAs. These miRNAs function by inhibiting the translation of

cyclins and arresting cells in the G1 phase. For instance, in osteosarcoma (OS) cells, miR-449a, and miR-424 interact with different parts of cyclin A2 (CCNA2) mRNA, the former with the 3′ UTR and the latter with the coding region, effectively inhibiting cyclin A2 expression during the G1 phase.[59] Overexpression of miR-449a and miR-424 leads to a significant reduction in cyclin A2 levels, resulting in the inhibition of cell proliferation, cell migration, and colony-forming efficiency in OS cells. Moreover, the downregulation of miR-449a and miR-424 is strongly correlated with the upregulation of cyclin A2 and the promotion of pro-tumorigenic characteristics in OS patients. This suggests that the decreased expression of these miRNAs could be a crucial factor contributing to abnormal cell division in this context.[59]

Another cyclin, cyclin D1, is directly targeted by miR-342, whose reduced expression is observed in various cancers, including leukemia,[60] breast cancer,[61] and gliomas.[62] miR-342 exerts its inhibitory effect on cyclin D1 by binding to its 3′ UTR, thereby suppressing cell proliferation and significantly enhancing the DNA double-strand break and apoptosis induced by imatinib in chronic myeloid leukemia (CML) cells.[60] This implies that miRNAs can disrupt the activity of cyclins, interfere with the formation of CDK-cyclin complexes, and modulate their expression, potentially enhancing the effectiveness of anti-proliferative drugs. Furthermore, there are other miRNAs targeting cyclin D1 and controlling tumor cell proliferation, including the miR-17/miR-20a miRNA cluster, which binds to the 3′ UTR of cyclin D1 and regulates its translation.[63] In breast cancer cells, the binding of miR-17/miR-20a to cyclin D1 mRNA leads to the downregulation of cyclin D1, resulting in G1-phase arrest and the inhibition of cell proliferation.[63] Combining miR-17/miR-20 mimics with the anti-estrogen drug tamoxifen, commonly used for treating patients with estrogen-receptor (ER) α-positive breast cancer, has been shown to increase tumor cell death.[64] Interestingly, cyclin D1 can bind to the promoter of the miR-17/20 cluster and induce its transcription. This upregulation of miR-17/20 acts as a negative feedback loop to control cyclin D expression during G1 progression.[63]

Positive and negative feedback loops, where proteins regulated by miRNAs also control the transcription of those miRNAs, play crucial roles in maintaining the balance of the cell cycle, particularly during the transition from G1 to S phase. Disruptions in these feedback loops can lead to the activation of oncogenic signaling pathways and contribute to tumor development and growth. One example is the p53-miR-34a feedback loop, which is vital for ensuring the stability and turnover of the tumor-suppressor protein p53. p53 acts as a transcription factor for miR-34a, which, in turn, targets sirtuin 1 (SIRT1), an enzyme that deacetylates p53. This deacetylation promotes p53's ubiquitination and degradation by MDM2/MDMX. When miR-34a levels increase due to p53-mediated upregulation, SIRT1 levels decrease, leading to enhanced p53 acetylation and stability. Stabilized p53, in turn, further increases miR-34a transcription, creating a feedback loop that keeps SIRT1 suppressed and p53 activated. This promotes cell-cycle arrest and apoptosis in cells.[65] The downregulation of miR-34a has been associated with various tumor types, and its constitutive expression can induce G1-phase arrest in cancer cells.[66–68]

Additional examples of feedback loops include miR-532-E2F1, miR-183-E2F1, and miR-223-E2F1 loops, disruption of which can drive tumor growth and resistance to therapy. In these loops, the tumor-suppressor miR-532 is transcriptionally repressed by its target protein E2F1, which is often highly expressed and associated with tumor growth, particularly in gastric cancer.[69,70] miR-532 reduces E2F1 expression by directly interacting with specific binding sites in E2F1's 3′ UTR. Suppression of E2F1 inhibits the G1-S transition, contributing to G1-phase arrest in gastric cancer cells. E2F1, in turn, possesses binding motifs within the promoter region of the gene that houses miR-532. When E2F1 binds to these motifs, it inhibits miR-532 transcription, keeping E2F1 expression high and promoting tumor cell proliferation and growth.[69] Moreover, combining miR-532-3p mimics with chemotherapy drugs such as 5-FU or cisplatin significantly enhances apoptotic cell death in colorectal cancer cells.[71]

Similarly, miR-183 plays a role in negatively regulating its transcription factor, E2F1. When miR-183-5p is expressed in breast cancer cells, it leads to the downregulation of E2F1, resulting in cell-cycle arrest at the G1 phase. Intriguingly, genetic knockdown of E2F1 results in an increase in both mature miR-183 and pri-miR-183, indicating that E2F1 promotes its own negative autoregulation to maintain turnover during G1 progression.[72] Furthermore, E2F1 acts as a transcriptional repressor of miR-223, which possesses a 3′ UTR-binding site for E2F1.[73] During the process of granulopoiesis, miR-223 overexpression is induced by CCAAT/enhancer-binding protein (C/EBP) α, a myeloid-specific transcription factor that facilitates cell-cycle arrest, allowing cells to terminally differentiate. miR-223 plays a crucial role in regulating the functions of C/EBPα, particularly in suppressing cell-cycle progression and promoting cell-cycle exit. In cases of abnormal E2F1 expression, such as in acute myeloid leukemia (AML), miR-223 is consistently downregulated, blocking the normal differentiation process by inhibiting cell-cycle exit and thereby promoting uncontrolled cell division.[73] Taken together, these studies emphasize the critical role of miRNAs in regulating E2F1, a frequently overexpressed cell-cycle protein in various human cancers. Disruptions in the miRNA-mediated regulation of E2F1 can have a profound impact on its diverse range of cell-cycle regulatory functions, ultimately leading to genomic instability and the development of tumors.

The role of miRNAs in cancer is closely tied to their regulation of E2F transcription factors. Depending on the specific E2F target and miRNAs involved, miRNAs can either activate or suppress the transcription of genes controlled by E2F. Dysregulation of miRNAs in cancer disrupts the balance of oncogenic and tumor-suppressive E2F activities, leading to uncontrolled cell proliferation. For instance, in hepatocellular carcinoma (HCC), miR-302a/d directly targets E2F7, inhibiting downstream pathways such as AKT1-p27Kip1/p21Cip1 and AKT/β-catenin/CCND1. This inhibition causes a delay in the G1- to S-phase transition, reducing proliferation in HCC cells and stemness in liver cancer stem cells.[74] The treatment with miR-302b enhances the sensitivity of HCC cells to 5-FU.[75] Furthermore, in HCC patients, there is a negative correlation between the expression levels of E2F7 and miRNA-302a/d. Patients with high E2F7

expression and low miRNA-302a levels have poorer overall survival and progression-free survival.[74] Similarly, in non-small cell lung cancer (NSCLC) and OS, miR-99a and miR-125a inhibit E2F2, leading to cell-cycle arrest and reduced cell migration.[76,77] The reduced expression of miR-99a and miR-125a in NSCLC and OS correlates with higher E2F2 levels in lung cancer biopsies.[76–78]

Conversely, in pancreatic cancer, miR-17 indirectly suppresses E2F4, promoting cell proliferation and growth. miR-17 binds to the 3′ UTR of E2F4's interacting partner, RB-like protein 2 (RBL2), disrupting the RBL2/E2F4 transcriptional complex and preventing E2F4's gene-repressing activity. High levels of miR-17-5p and low levels of RBL2 are associated with poor prognosis in pancreatic cancer patients.[79] Additionally, inhibiting miR-17 sensitizes pancreatic cancer cells to gemcitabine treatment, suggesting that miRNA mimics could potentially help overcome drug resistance in cancer therapy.[80] In summary, these studies underscore the important role of miRNAs in modulating the E2F family of transcription factors and their target genes, which are critical in controlling cell-cycle progression, particularly the transition from the G1 phase to the S phase. Dysregulation of miRNAs in cancer is linked to aberrant expression of E2F-regulated genes, which correlates with increased cell proliferation. Thus, a comprehensive understanding of miRNAs and their regulatory functions is crucial for elucidating the roles of E2F repressors and activators in orchestrating proper cell-cycle progression. Additionally, Table 1 provides information about other miRNAs involved in the G-phase transition in cancer cells.

The role of lncRNAs during the G1-S transition in cancer

LncRNAs are a class of RNA molecules with lengths ranging from 100 to 10,000 residues. They play a significant role in regulating gene expression in both the nucleus and cytoplasm by interacting directly or indirectly with DNA, RNA, and proteins.[81] During the transition from the G1 phase to the S phase of the cell cycle, lncRNAs exert regulatory control over various E2F proteins, thereby influencing cell proliferation and growth in cancer cells. One example of lncRNA involvement in this process is the c-Myc regulatory lncRNA known as E2F1 mRNA-stabilizing factor (EMS). EMS promotes G1-S cell-cycle progression and facilitates growth in tumor cells by stabilizing E2F1 mRNA. EMS contains a poly-U stretch with 22 uridines, which allows it to bind to RALY, a poly-U binding ribonucleoprotein. The binding of EMS to RALY stabilizes E2F1 mRNA, ensuring its consistent levels throughout the G1 phase.[82]

Furthermore, several lncRNAs directly regulate E2F mRNA to drive G1 progression and facilitate entry into the S phase in cancer. For instance, linc00337, located in the 1p36.31 genomic region, acts as a coactivator of E2F1 mRNA and upregulates E2F1 expression in pancreatic ductal adenocarcinoma (PDAC) cells. This upregulation promotes cell proliferation and growth.[83] High levels of E2F1 have been observed in pancreatic cancer patients, and this correlates strongly with elevated linc00337 expression and poor survival rates.[83] Additionally, the inhibition of linc00337 using small hairpin RNA (shRNA) sensitizes breast cancer cells to paclitaxel treatment, suggesting the potential for combining targeted drugs with lncRNA inhibitors to enhance the effectiveness of current cancer treatments.[83] In summary, lncRNAs play a crucial role in regulating the G1-S transition in cancer cells by modulating E2F proteins and their expression. These regulatory mechanisms contribute to the control of cell proliferation and growth in cancer, and targeting specific lncRNAs may hold promise for improving cancer treatment strategies.

In addition to lncRNAs regulating E2F1, E2F1 itself can transcriptionally activate specific lncRNAs, such as SLC16A1-AS1, which is located on chromosome 1 at 1p13.2-p12 and is oriented in an antisense direction relative to metabolic genes, including SLC16A1 and monocarboxylate transporter 1 (MCT1).[80] SLC16A1-AS1 interacts with E2F1 and enhances the expression of SLC16A1/MCT1. This leads to metabolic reprogramming in cancer cells, including increased glycolysis, oxidative phosphorylation, and fatty acid oxidation, as well as enhanced invasiveness in bladder cancer cells. Inhibition of SLC16A1-AS1 or SLC16A1/MCT1 reduces the invasiveness of bladder cancer cells and makes them more sensitive to chemotherapy.[84] This reciprocal regulation between E2F1 and lncRNAs such as SLC16A1-AS1 suggests that targeting downstream lncRNAs regulated by E2F1 could be a promising therapeutic strategy, particularly for tumors that overexpress E2F1. By disrupting this regulatory pathway, it may be possible to inhibit cancer cell invasiveness and enhance their sensitivity to chemotherapy, potentially offering a more effective treatment approach for E2F1-driven tumors.

LncRNAs are also known to exert regulatory control over other members of the E2F family at various levels. For example, E2F3 is regulated by the lncRNA RBAT1, which can enhance its oncogenic functions. RBAT1 functions by recruiting the RNA-binding protein heterogeneous nuclear ribonucleoprotein L (HNRNPL) to the promoter region of E2F3, thereby activating its transcription. This activation of E2F3 by RBAT1 leads to the G1-S-phase transition and accelerates tumor formation in retinoblastoma (RB) and bladder cancer cells.[85] Another E2F family member, E2F4, is recruited by the lncRNA Linc00337 to stimulate the transcription of Xklp2 (TPX2), a nuclear proliferation-related protein involved in spindle assembly and mitosis. Upregulation of TPX2 due to E2F4 activation generates resistance to the chemotherapy drug cisplatin and inhibits drug-induced apoptosis in esophageal squamous cell carcinoma (ESCC) cells.[86] These findings underscore the significant role that lncRNAs play in tightly controlling E2F family members during the cell cycle, a process critical for maintaining tissue homeostasis. Disruption of this delicate balance can lead to cellular dysfunction and contribute to the development of cancer. In summary, lncRNAs are involved in the regulation of E2F family members, including E2F3 and E2F4, and their activities in the cell cycle. Dysregulation of these processes can have important implications for cancer development and treatment resistance. Understanding the intricate interactions between lncRNAs and E2F proteins contributes to our knowledge of the molecular mechanisms underlying cancer progression.

Many lncRNAs function as competing endogenous RNAs (ceRNAs) by sequestering miRNAs that target cell-cycle proteins, thereby

Table 1. The role and associated mechanisms of ncRNAs during the G to M progression in cancer

	ncRNAs			
miRNAs	Cell-cycle phase	Molecular target(s)	Mechanism	Role in cell-cycle control in cancer
miR-26a-5p[171]	G1	3′ UTR of DNMT3A	DNMT3A inhibition decreases SFRP1 methylation and increases its expression	arrests cell at G1-phase and inhibits stem cell-like properties of NSCLC
miR-1-3p[172]	G1	3′ UTR of E2F8	E2F8 inhibition decreases NF-κB and STAT-3	arrests cell at G1-phase and induce LUAD apoptosis
miR-20b-5p/miR-106a-5p[173]	G1	3′ UTRs of p21, cyclins D1, D2, and E2F1	downregulation of p21/CDK/E2F1 pathway promotes G1-S transition	oxidative stress inhibits miR20/miR106, induces G1-S arrest, suppressing DNA synthesis and cell proliferation
miR-934[174]	G1	3′ UTRs of Ube2n	UBE2N inhibition attenuates CDK6 degradation, leading to its accumulation	CDK6 increase by miR-934 promotes bladder cancer tumor growth
miR-127-3p[175]	G1	3′ UTRs of SKP2	SKP2 repression increases p21, downregulates cyclins A, E, and CDK2 leading to RB activation, which suppresses E2F and Myc transcription	inhibits KSHV-driven oncogenic transformation and proliferation and induces G1 cell-cycle arrest
mir-4746[176]	G1	3′ UTR of cyclin D1	promotes cyclin D1 degradation	cyclin D1 inhibition promotes G1 arrest in CRC cells
lncRNAs				
LINC01419[177]	G1	DNA repair protein Ku80	directly binds to Ku80 and promotes DNA repair	lncRNA knockdown induces DNA damage and G1 arrest and sensitizes HCC cells to doxorubicin
ERINA[178]	G1	E2F1	ERINA interaction with E2F1 prevents E2F1 binding to RB, which increases its expression	E2F1 increase promotes G1-S transition and palbociclib resistance in ER+ breast cancer cells
PITPNA-AS[179]	G1	c-MET	sponges miR-876-5p, increasing the expression of its target c-MET and downstream CDK2, CDK4, CDK6, and cyclin D	promotes G1 transition and proliferation in cervical cancer cells
CCAT1[180]	G1	Wnt	sponges miR-181a, upregulating its target Wnt and downstream cyclin D1 and CDK4	activation of Wnt/β-catenin signaling promotes proliferation of OSCC cells
NR2F2-AS1[181]	G1	cyclin D1	promotes cyclin D1 expression	NR2F2-AS1 siRNA induces G0/G1 arrest in CRC cells
ABHD11-AS1[182]	G1	cyclin E	sponges miR-1231, upregulating its target cyclin E	ABHD11-AS1 knockdown decrease cyclin E and induces G1 arrest in PC cells
GAS5[183]	G1	$p27^{Kip1}$ E2F1	GAS5 interacts with E2F1 and enhances E2F1 binding to the $p27^{Kip1}$ promoter, increasing its transcription	$p27^{Kip1}$ increase induces G1 arrest and inhibits proliferation in PC cells
CircRNAs				
CircRHOBTB$_3$[184]	G1	p21	sponges miR-654-3p, upregulating its target p21	p21 upregulation induces G1-S arrest and inhibits GC growth
Circ0000877[185]	G1	MAP4K4	sponges miR-370-3p, upregulating its target MAP4K4	MAP4K4 activates the Hippo pathway, facilitating the progression of diffuse large B cell lymphoma
Circ0058063[186]	G1	CDK6	represses miR-145-5p activity, which upregulates its target CDK6	CDK6 activation promotes G1-S transition and bladder cancer cell proliferation
Circ0006014[187]	G1	CDK2 CDK6 NTRK2	sponges miR-885-3p, upregulating its targets CDK2, CDK6 and NTRK2	promotes G1-S progression and growth in breast cancer cells
CircSP3[188]	G1	CDK4	binds and inhibits miR-198, upregulating its target CDK4	CircSP3 silencing induces G1 arrest and inhibits HCC cell proliferation
Circ_001621[189]	G1	CDK4 MMP9	sponges miR-578, upregulate its target genes CDK4 and MMP9	promotes OS cells proliferation and migration
CircGLIS3[190]	G1	cyclin D1	sponges miR-1273f, upregulating its target gene SKP1 and promoting SKP1 downstream cyclin D1	cyclin D1 upregulation is associated with G0/G1 transition and enhanced bladder cancer cell proliferation

DNMTs, DNA methyltransferase; SFRP1, secreted frizzled-related protein 1; LUAD, lung adenocarcinoma; Ube2n, ubiquitin-conjugating enzyme 2N (ube2n); KSHV, Kaposi's sarcoma-associated herpesvirus; ERINA, estrogen-inducible lncRNA; c-MET, mesenchymal-epithelial transition factor; GAS5, growth-arrest-specific transcript 5; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; NTRK2, neurotrophic receptor tyrosine kinase 2; MMP9, matrix metallopeptidase 9; CRC, colorectal cancer; HCC, hepatocellular carcinoma; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; GC, gastric cancer; OS, osteosarcoma; ESCC, esophageal squamous cell carcinoma.

modulating cell proliferation. For instance, lncRNA H19 (lncH19) acts as a sponge for miR-29a, which targets E2F1. By sponging miR-29a, lncH19 indirectly regulates E2F1 expression in clear cell renal cell carcinoma (ccRCC).[87] Overexpression of lncH19 in breast cancer cells promotes cell proliferation and resistance to tamoxifen, a drug used in the treatment of hormone receptor-positive breast cancer.[88,89] Another example is lncRNA renal cancer-associated transcript 1 (lncRCAT1), which acts as a sponge for miR-214. miR-214 directly targets E2F2 and promotes its degradation. Ectopic expression of lncRCAT1 decreases miR-214 levels, increasing E2F2 stability and promoting cell proliferation in renal cancer cells.[90] Similarly, lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) binds to miR-495 and prevents its inhibitory interaction with E2F3 mRNA. This leads to the stabilization of E2F3 and promotes cell proliferation, migration, and invasion in melanoma cells.[91] Silencing NEAT1 sensitizes tumor cells to radiotherapy[92] and various anticancer drugs, including cisplatin,[93], paclitaxel,[94] gemcitabine,[95] and sorafenib.[96] lncRNA cancer susceptibility candidate 9 (CASC9) acts as a ceRNA for miR-145, indirectly regulating E2F3 expression. This miR-145 sponging by CASC9 induces E2F3 expression, leading to increased proliferation, invasion, and epithelial-mesenchymal transition (EMT) in retinoblastoma (RB) cells.[97]

In summary, lncRNAs play a crucial role in indirectly controlling E2F target proteins vital for G1 cell-cycle progression by acting as ceRNAs and sequestering inhibitory miRNAs. Dysregulation of these lncRNAs can lead to hyperactivation of these proteins and their downstream signaling pathways, resulting in an imbalance in the cell cycle and contributing to cancer development. Studying the functions of these novel lncRNAs provides insights into an upstream layer of regulation that modulates E2F-dependent signal transduction pathways associated with cell-cycle progression and cancer. Additional examples include lncRNAs such as small nucleolar RNA host gene 16 (SNHG16), LINC00607, and LINC00284, which regulate E2F activity by sponging miRNAs targeting E2F family members. SNHG16 is a lncRNA that binds to miR-98, a miRNA that targets E2F5. By sequestering miR-98, SNHG16 indirectly enhances the expression and activity of E2F5, thereby promoting specific cellular processes associated with E2F5's function.[98] LINC00607 is another lncRNA that acts as a sponge for miR-607. miR-607 normally targets E2F6, a member of the E2F transcription factor family. When LINC00607 binds to and sequesters miR-607, it indirectly leads to increased levels of E2F6, affecting the downstream cellular processes controlled by E2F6.[99] Similarly, LINC00284 functions as a ceRNA by binding to miR-3127, which is a miRNA that targets E2F7. By acting as a sponge for miR-3127, LINC00284 indirectly upregulates E2F7 expression and influences cellular processes governed by E2F7.[100] In summary, lncRNAs play a crucial role in indirectly controlling E2F target proteins vital for G1 cell-cycle progression by acting as ceRNAs and sequestering inhibitory miRNAs. Dysregulation of these lncRNAs can lead to hyperactivation of these proteins and their downstream signaling pathways, resulting in an imbalance in the cell cycle and contributing to cancer development. Studying the functions of these novel lncRNAs provides insights into an upstream layer of regulation that modulates E2F-dependent signal transduction pathways associated with cell-cycle progression and cancer.

In addition to E2Fs, CDK-cyclin complexes are also tightly controlled by lncRNAs during G1 progression. The regulation of cyclin-CDK complexes is frequently disrupted in cancer due to the deregulation of lncRNA activity. The mechanisms through which lncRNAs regulate CDK-cyclin complexes can vary. In some cases, lncRNAs act as transcriptional regulators, modulating the expression of genes that encode CDKs or their regulatory molecules. In other cases, lncRNAs can directly interact with CDKs or cyclins, affecting their protein phosphorylation and stability or acting as scaffolds that bring together multiple proteins involved in CDK regulation and facilitate their interactions. Below, we discuss some examples of lncRNA-mediated regulation of CDK-cyclin complexes.

During osmotic stress, the stress-activated protein kinase (SAPK) p38-Hog1 induces the transcription of the Hog1-dependent lncRNA CDC28, which is present in an antisense orientation to the CDC28 gene, the yeast homolog of CDK1. The CDC28 lncRNA recruits Hog1 to CDC28, thereby attracting the chromatin structure remodeling (RSC) complex. The RSC complex induces changes in chromatin architecture, resulting in increased CDC28 transcription and more efficient cell-cycle progression after stress.[101] Another example involves the lncRNA DILA1, which interacts directly with cyclin D1 at its Thr286 site and prevents its phosphorylation at Thr286. This inhibition of phosphorylation stabilizes cyclin D1 by suppressing its glycogen synthase kinase 3β (GSK3β)-mediated ubiquitination-dependent degradation. Subsequently, cyclin D1 stabilization promotes the Ser780 phosphorylation of RB, inactivating it and promoting G1-S cell-cycle progression and tamoxifen resistance in breast cancer cells.[102] Furthermore, high DILA1 expression is associated with overexpressed cyclin D1 and poor prognosis in tamoxifen-treated breast cancer patients.[102] Another example includes the lncRNA RP11-624L4.1, which directly interacts with CDK4 and stabilizes its expression. CDK4 stabilization upregulates the CDK4/6-cyclin D1-Rb-E2F1 pathway, promoting G1 cell-cycle progression in nasopharyngeal carcinoma (NPC) cells. RP11-624L4.1 is highly expressed in NPC cells and is associated with poor clinicopathological features in NPC patients.[103] These examples illustrate how lncRNAs play a role in the regulation of key cell-cycle components and their impact on various cellular processes, including cell-cycle progression and cancer development.

Several other lncRNAs facilitate the interaction of mRNA-binding proteins with target mRNAs, thereby regulating their stability. This post-transcriptional regulation plays a key role in controlling the expression of cell-cycle genes. For instance, the lncRNA DNA methylation-deregulated and RNA m6A reader-cooperating lncRNA (DMDRMR) stabilizes CDK4 mRNA by acting as a cofactor for the RNA-binding protein insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3). IGF2BP3 binds to m6A-modified sites on mRNA.[104] DMDRMR facilitates the binding of IGF2BP3 to the m6A-modified sites on CDK4 mRNA, enhancing the stability of CDK4 mRNA. The increased expression of CDK4 promotes the transition from G1 to S

phase and cell proliferation in ccRCC cells. Furthermore, high expression levels of both DMDRMR and IGF2BP3 exhibit a strong positive correlation and are associated with poor survival in ccRCC patients.[104] Table 1 summarizes some other lncRNAs involved in the G-phase transition in cancer cells. These findings collectively support the idea that lncRNAs play a critical role in regulating the activity of CDKs during the cell cycle. Aberrant lncRNA expression is most associated with adverse outcomes for cancer patients and disruptions in the G1-S-phase transition. When lncRNAs are deregulated during the G1 phase, cells become more susceptible to uncontrolled mitogenic growth and defects in the G1-S transition.

THE ROLE OF circRNAs DURING G1-S TRANSITION IN CANCER

circRNAs are single-stranded, highly stable, covalently closed RNA molecules that regulate gene expression either by acting as miRNAs sponges or by affecting mRNA and protein stability.[105] Many genes specific to the cell cycle are post-transcriptionally regulated by circRNAs, and disruption of this regulation can lead to cancer by accelerating cell division rates or inhibiting normal cell-cycle controls. Growth factor signaling pathways regulate circRNAs to activate cell-cycle regulators, modulating cell proliferation and survival.[106] For example, activation of the epidermal growth factor receptor (EGFR) signaling pathway induces the expression of circRNA hsa_circ_0000190, also known as C190, in NSCLC cells. C190 acts as a sponge for CDK4 and CDK6-targeting miRNA miR-142, resulting in the upregulation of CDK4 and CDK6 and enhanced cell proliferation. Additionally, C190 overexpression induces the expression of several cell-cycle-regulatory proteins, including CDK1 and CDK6, and promotes RB hyperphosphorylation and extracellular signal-regulated kinase (ERK) phosphorylation, which are associated with tumor cell growth and survival.[104] The estrogen hormone signaling pathway, critical for the growth and development of many tissues in the body, induces the expression of multiple circRNAs. Estrogen treatment in ER-positive breast cancer cells induces circPGR, which, in turn, induces cell proliferation and tumorigenesis. Mechanistically, estrogen-induced circRNA, circPGR acts as a ceRNA to sponge miR-301a, which targets CDK6, CDK1, and the DNA damage repair protein CHEK2. The upregulation of cell-cycle genes promotes the transition from G1 to S phase and cell growth in breast cancer cells. Treatment of cancer cells with circPGR-targeting antisense oligonucleotides (ASOs) suppresses the growth of ER-positive breast cancer cells.[107] Another circRNA, circRACGAP1, functions similarly by sponging miR-144, which directly targets the cell-cycle protein CDKL1. Silencing circRACGAP1 in NSCLC cells increases miR-144-mediated CDKL1 suppression, leading to cell-cycle arrest in the G1 phase and inhibition of cell proliferation. Moreover, circRACGAP1 knockdown sensitizes NSCLC cells to gefitinib treatment, suggesting that targeting oncogenic circRNAs could be an effective strategy against drug-resistant tumors.[108] Overall, the mechanism of circRNA-mediated sponging of miRNAs represents an important aspect of post-transcriptional gene regulation during the cell cycle and has significant implications for our understanding of cellular processes and disease development.

Some circRNAs act as scaffolds for the assembly of protein complexes, facilitating protein-protein interactions and modifications during the G1 phase. For instance, the circRNA circZFR directly interacts with single-stranded DNA-binding protein 1 (SSBP1) and promotes its assembly onto CDK2/cyclin E1 complexes. Activation of CDK2/cyclin E1 leads to the phosphorylation and inactivation of RB at ser807 and ser608, abolishing its inhibitory effect on E2F1. The activation of E2F1, in turn, induces the transcription of E2F-regulated genes, promoting the G1-S transition and the proliferation of cervical cancer cells.[109] Another example involves circ-0075804, which interacts with the RNA-binding protein heterogeneous nuclear ribonucleoprotein K (HNRNPK) to enhance the stability of E2F3 mRNA in retinoblastoma (RB) cell lines. The upregulation of E2F3 stimulates proliferation in RB cells.[110] Conversely, E2F proteins can regulate circRNAs to promote proliferation in tumor cells. E2F1 and EIF4A3 can bind to the promoter of circSEPT9 and increase its transcription. circSEPT9, in turn, enhances proliferation, migration, and invasion of triple-negative breast cancer (TNBC) cells and is strongly correlated with advanced clinical stage and poor prognosis in TNBC patients.[111] These examples highlight the diverse roles of circRNAs in regulating protein interactions and cell-cycle progression during the G1 phase as well as the bidirectional interactions between E2F proteins and circRNAs in promoting cancer cell proliferation.

Furthermore, some circRNAs act as tumor suppressors by either inhibiting the function of proteins that promote cell-cycle progression or by upregulating inhibitors of cyclin-CDK complexes. For example, circ-Foxo3 forms a ternary complex with CDK2 and p21 in the G1 phase, thereby inhibiting CDK2 activity and impeding cell-cycle progression.[112] CircLAMA3 directly binds to v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN) mRNA and promotes its degradation, reducing its availability at the promoter sequences of target genes, including CDK6. The downregulation of CDK6 arrests cells at the G0/G1 phase, resulting in the inhibition of breast cancer cell proliferation.[113] Furthermore, circCDR1as binds to the DNA-binding domain (DBD) of p53, which is essential for its interaction with MDM2. Inhibition of the p53/MDM2 interaction prevents MDM2-dependent p53 ubiquitination. The expression of p53 leads to G1 growth arrest, suppressing glioma cell proliferation, migration, and colony formation.[114] Table 1 provides information on other circRNAs involved in the G1-phase transition in cancer cells. In summary, the increasing understanding of the role of circRNAs during G1-S progression offers new insights into cell-cycle biology. These studies clearly indicate that circRNA deregulation is expected in the cancer cell cycle and could be harnessed as a potential target for future cancer treatments or for prognostic evaluation.

CELL CYCLE REGULATION BY ncRNAs DURING THE S-M TRANSITION

Cell-cycle events regulating the S-M transition

The S phase encompasses the initiation and completion of DNA replication, followed by the division of the copied DNA into identical daughter cells during the M phase. A-type cyclins and CDK2 start accumulating in the S phase due to E2F-dependent induction of

A-type cyclins and the inactivation of the ubiquitin protein ligase anaphase-promoting complex or cyclosome (APC/C).[115,116] The APC/C is activated by Cdh1 to form the activated complex APC/CCDH1, which tags cyclin A for degradation.[113,114] A-type cyclins and CDK2 play an essential role in initiating the S phase, during which the cell begins DNA replication initiation, referred to as origin firing.[117] During the S phase, the phosphatase CDC25 removes phosphate groups from CDK1, which were induced via phosphorylation by the kinases WEE1 and MYT1.[118–120] Dephosphorylated CDK1 associates with A-type or B-type cyclins, leading to its activation.[117,121] CDK1 phosphorylates multiple CDK1 substrates, promoting entry into mitosis.[122]

ROLE OF miRNAs DURING THE S-M TRANSITION IN CANCER

CDK2 and cyclin A1 are direct targets of miR-372, which binds to their 3′ UTR sequences and promotes their degradation. Overexpression of miR-372 in cervical cancer cells leads to the downregulation of CDK2 and cyclin A1, resulting in cell arrest at the S/G2-phase and inhibiting cell growth.[123] Another miRNA, miR-3619, directly interacts with the cell-cycle inhibitor p21 promoter and the 3′ UTRs of CDK2.[124] Overexpression of miR-3619 induces p21 transcription and reduces CDK2 mRNA stability, leading to growth arrest and the inhibition of metastasis in breast cancer cells. Both miR-3619 and p21 are downregulated in breast cancer patients and are associated with poor clinicopathological features.[124] Moreover, miR-3619 treatment can overcome cisplatin resistance in squamous cell carcinoma cells, suggesting that miR-3619 might prevent cells from developing resistance to cisplatin.[125]

Serum starvation or DNA damage induces the expression of miR-21, which then targets CDC25A mRNA, leading to its degradation. CDC25 plays a crucial role in regulating the S-phase checkpoint and promoting DNA replication during the S phase of the cell cycle.[126] The induction of miR-21 delays the G1-S transition in serum-starved cancer cells and activates the DNA damage-induced G2-M checkpoint after their exposure to ionizing radiation.[127] The activation of the G2-M checkpoint post irradiation by upregulated miR-21 contributes to radiation resistance in breast cancer cells.[128] Furthermore, miR-766 can silence MDM4 mRNA, an inhibitor of p53 activation, and promotes p53 accumulation.[129] p53 is crucial for activating the S-phase checkpoint in response to DNA damage or replication stress.[130,131] Overexpression of miR-766 upregulates p53 and inhibits cell growth by inducing G2/M arrest.[129]

Some miRNAs target the histone-lysine N-methyltransferase enzyme enhancer of zeste homolog 2 (EZH2) to regulate S-phase transition during the cell cycle.[132] EZH2 has been shown to play a role in regulating cell-cycle progression by directly controlling the expression of cell-cycle genes. Ectopic expression of EZH2 and Embryonic Ectoderm Development (EED) increases the number of cells in the S phase.[133] Transfection of miR-31 mimics into gastric cancer cells downregulates EZH2, inducing G2/M arrest and enhancing the chemosensitivity of gastric cancer cells to 5-FU.[132] This suggests that miRNA-mediated regulation of EZH2 and its downstream genes might be an essential mechanism for controlling gene expression during the S phase. Dysregulation of miRNA activity during this process can lead to aberrant EZH2 expression, resulting in uncontrolled cell proliferation. Furthermore, miRNAs act as key regulators of intricate pathways involved in cell fate determination, lineage commitment, and cell function.[134,135] Genetic ablation of the miR-34/449 family, including miR-34a, miR-34b/c, and miR-449a/b/c in mice, prevents the repression of cell-cycle gene expression during differentiation in epithelial cells. Cells typically exit the cell cycle during differentiation to become specialized into distinct cell types. miR-34/449 family knockout mice exhibit upregulated cell-cycle genes and enhanced proliferation in the respiratory epithelium.[136] Some other miRNAs involved in S-phase transition in cancer cells are discussed in Table 2. These studies suggest that miRNAs are crucial regulatory molecules during the S phase that modulate the expression of key regulators involved in cell-cycle progression. The implications of deregulated miRNAs in tumors highlight the importance of understanding the mechanisms underlying miRNA-mediated regulation of cell-cycle progression to develop effective therapeutic strategies.

The role of lncRNAs during the S-M transition in cancer

Many lncRNAs are differentially expressed in different cancer types during the S phase and show alterations in their DNA methylation status.[137] Some lncRNAs are hypomethylated and highly expressed in tumors, while others are hypermethylated and expressed at lower levels. Loss of function of certain S-phase lncRNAs, also known as S-phase cancer-associated transcripts (SCATs), can induce G1- and G2/M-phase arrests, inhibit cell proliferation, and lead to apoptosis.[137] In one study, Yildirim et al. identified more than 900 lncRNAs whose synthesis peaks during the S phase, and over 200 lncRNAs show S-phase-specific expression. Based on their upregulation in the early S phase, the group identified three lncRNAs, LINC00704, LUCAT1, and MIAT, that are essential for normal transition through the S phase. Loss of function of these lncRNAs increases the percentage of cells in the G1 phase while decreasing the proportion of cells in the G2/M phase.[138] Overexpression of these lncRNAs in cancer cells has been associated with enhanced cell proliferation and tumor growth.[139–141]

Another S-phase-induced lncRNA, SUNO1, facilitates cell proliferation through yes-associated protein (YAP)1-mediated transcription of cell-cycle genes.[142] SUNO1 interacts with the transcriptional coactivator DDX5, which influences the recruitment and stabilization of RNA pol II to the WT1 interacting protein (WTIP) promoter, increasing its transcription. WTIP activates YAP1, which, in turn, promotes cell proliferation by enhancing YAP1-mediated transcription of cell-cycle genes. Furthermore, SUNO1 knockdown induces defects in cell-cycle progression, inhibits tumorigenesis, and sensitizes cancer cells to drug-induced DNA damage.[142] Moreover, the lncRNA LOC572558 acts as a tumor-suppressor in bladder cancer cells by reducing Akt and MDM2 phosphorylation and increasing p53 phosphorylation, which is associated with S-phase arrest.[143]

Table 2. The role and associated mechanisms of ncRNAs during the S to M progression in cancer

ncRNAs				
miRNAs	Cell-cycle phase	Molecular target(s)	Mechanism	Role in cell-cycle control in cancer
miR-497-5p[191]	S	CBX4	binds 3′ UTR of CBX4 and inhibits CBX4-CDK2/cyclin A2 signaling	induces S-phase arrest and inhibits proliferation in cervical cancer cells
miR-490-3p[192]	G2/M	CDK1	binds 3′ UTR of CDK1, inhibits CDK1, Bcl-xL, MMP2/9 and upregulates p53	induces G2/M arrest and inhibits ovarian carcinoma growth
miR-937-5p[193]	S	SOX17	binds 3′ UTR of SOX17. Inhibits SOX17 and its downstream CDK1 and cyclins A2, B1, and D1	promotes S-phase transition and breast cancer cell proliferation
miR-200b[194]	G2	CDK2, PAF	binds 3′ UTR of CDK2 and PAF. Inhibits PAF-mediated Wnt/β-catenin signaling	induces G2 arrest and represses ESCC growth
miR-488[195]	G2/M	ERBB2	binds 3′ UTR of ERBB2. Inhibits ERBB2 and its downstream cyclin A, cyclin B, CDK1, and CDK2	induces G2/M arrest and induces apoptosis in pancreatic tumor cells
miR-148a-3p[196]	G2/M	CDK6	binds 3′ UTR of ERBB2	arrests cells at G2/M, inhibits cell growth and promote apoptosis
miR-582-3p	G2/M	cyclin B2	binds 3′ UTR of cyclin B2	arrests cells at G2/M and inhibits AML proliferation
lncRNAs				
SNHG4[197]	S	CDK1	sponges miR-590-3p, which upregulates its target CDK1	SNHG4 silencing induces S-phase arrest and inhibits CRC growth
NCK1-AS1[198]	S	CDK1 CDK6	sponges miR-6857, antagonizing its ability to repress CDK1 and CDK6	NCK1-AS1 silencing induces S-phase arrest and inhibits cervical cancer growth
Gas5[199]	S	CDK6	negatively regulates CDK6 mRNA expression	induces S-phase arrest and inhibits PC cell proliferation
Lnc00312[200]	G2/M	cyclin B1	downregulates cyclin B1 mRNA translation	induces G2/M arrest and inhibits HCC cell proliferation
HOXD-AS1[201]	S	cyclin B1 cyclin D1	promotes cyclins B1 and D1 protein expression	HOXD-AS1 silencing induces S-phase arrest, inhibits cell number, colony formation, and cell migration
ENST00000606790.1[202]	G2/M	PI3K AKT	inhibits CHK1 and upregulates CDC25C expression	promotes cell proliferation, colony formation, and invasion in thyroid carcinoma cells
PCAT1[203]	G2/M	cyclin B1 CDC2	upregulates cyclin B1 and CDC2	PCAT1 silencing induces G2/M arrest and inhibits ESCC growth
CircRNAs				
Circ0032822[204]	S	E2F3	sponges miR-141, antagonizing its ability to repress oncogenic E2F3	promotes HNSCC cell proliferation and inhibits apoptosis
F-circBA1[205]	G2/M	CDC25B	sponges miR-148-3p, upregulating its target CDC25B	F-circBA1 silencing arrest cells at G2/M and inhibits CML cell proliferation
Circ0079929[206]	S G2/M	PI3K AKT	inhibits PI3K, AKT and cyclin B protein expression	induces S and G2/M arrest and inhibits HCC tumor growth
Circ0006528[207]	G2	MAPK ERK	sponges miR-7-5p, upregulating Raf1, which activates its downstream MAPK/ERK pathway	Circ0006528 silencing induces G2 arrest, triggers apoptosis, and inhibits breast cancer growth
CircIFT80[208]	G2/M	β catenin	sponges miR-142, miR-568, and miR-634, upregulating their target β catenin	loss of CircIFT80 induces G2/M arrest and inhibits tumor progression in CRC

CBX4, polycomb chromobox4; PAF, PCNA-associated factor; ERBB2, Erb-B2 receptor tyrosine-protein kinase 2; SNGH4, small nucleolar RNA host gene 4; NCK1-AS1, NCK1 antisense RNA 1; gas5, growth arrest-specific 5; HOXD-AS1, HOXD cluster antisense RNA 1; PCAT1, prostate cancer-associated transcript 1; AML, acute myeloid leukemia; HNSCC, head and neck squamous cell carcinoma; CML, chronic myeloid leukemia.

Many lncRNAs promote the accumulation of A-type cyclins or CDK2, which are responsible for driving the progression of the cell cycle through the S phase. These lncRNAs play a critical role in driving the progression of the cell cycle through the S phase in tumors. For instance, the androgen-responsive lncRNA LINC00304 promotes the expression of cyclin A1 in prostate cancer cells, thereby increasing their S-phase population and cell proliferation.[144] lncRNA HOXC-AS3 regulates the cell cycle in HCC cells by directly interacting with CDK2 and preventing its inhibitory binding with p21. CDK2 activation promotes RB phosphorylation, increases the number of cells through S phase, and promotes HCC progression.[145] Some lncRNAs act as sponges for miRNAs that regulate the expression of

cell-cycle genes involved in the S to M transition. LINC00346 serves as a sponge for BRD4-targeting miRNA miR-188-3p, which upregulates BRD4 expression and promotes cell proliferation. LINC00346 depletion downregulates BRD4 expression, decreases the cell population in S and G2/M phases, and enhances gemcitabine sensitivity in pancreatic cancer cells.[146]

Furthermore, DNA damage during the S phase induces several lncRNAs that mediate cell-cycle arrest and inhibit cell proliferation. When cells are exposed to DNA damage during the S phase, ATR serine/threonine kinase (ATR) is activated and triggers a cascade of signaling events that activate DNA repair pathways and prevent the accumulation of DNA damage. lncRNA SCAT7 has been shown to bind to and regulate the activity of ATR, thereby modulating the DNA damage response during the S phase. SCAT7 prevents the accumulation of double-stranded breaks in response to DNA-damaging agents such as cisplatin and camptothecin. Mechanistically, SCAT7 regulates ATM and Rad3-related (ATR) activation, a master regulator of the DNA damage response during the S phase, which activates DNA repair pathways to prevent the accumulation of damaged DNA.[147] DNA-damaging agents cause topoisomerase I (Topo I) dysfunction, causing intrinsic DNA damage during replication. SCAT7 promotes proteasome-mediated degradation of Topo I, preventing Topo I-induced DNA damage in tumor cells. Furthermore, combination treatment of cisplatin with SCAT7 inhibition is highly effective in cancers resistant to cisplatin therapy.[148] Some other lncRNAs involved in S-phase transition in cancer cells are discussed in Table 2. Finally, these studies imply that lncRNAs relevant in cell-cycle progression represent a promising class of therapeutic targets, especially in cell-cycle-altered cancers. Due to advances in high-throughput sequencing technologies and bioinformatics, the number of lncRNAs involved in the proliferation of human cancers is growing rapidly. The discovery of new lncRNAs or new functions of existing lncRNAs will further unravel the complex signaling networks that operate during the cell cycle, which may have promising therapeutic implications in cancer treatment.

THE ROLE OF circRNAs DURING THE S-M TRANSITION IN CANCER

Studies have demonstrated that some circRNAs are differentially expressed during the S phase, indicating their involvement in cell-cycle regulation.[149] For instance, circHIPK3 is upregulated in prostate cancer cells compared to normal prostate epithelial cells and facilitates G2/M progression by sponging miR-338-3p. miR-338-3p downregulation upregulates the expression of its target genes, Cdc25B and Cdc2, which are involved in the G2/M transition. Moreover, circHIPK3 knockdown arrests the cell cycle at the G2/M phase, inhibits proliferation, and induces apoptosis in prostate cancer cells.[150] Another example includes circRNA_100876, whose expression increases in OS patients and is strongly associated with poor clinical outcomes. Silencing of circRNA_100876 arrests OS cells at the G2/M phase, increases cell-cycle-related proteins, inhibits cell proliferation, and induces apoptosis.[151] Likewise, aberrant upregulation of circ_0041732 has been observed in breast cancer tissues and cell lines.[152] E2F4, which is frequently overactivated in breast cancer, acts as a transcription factor of circ_0041732.[153] Circ_0041732 binds to miR-541 and acts as a sponge to inhibit miR-541-induced silencing of CDC2 and cyclin B1, thereby affecting the cell cycle in breast cancer. The silencing of circ_0041732 decreases CDC2 and cyclin B1 expression, inducing G2/M arrest and apoptosis in cancer cells.[152] Similarly, circRNA circ_0136666 regulates CDK6 expression by acting as a ceRNA of its targeting miRNA miR-1299. Circ_0136666 overexpression downregulates miR-1299, upregulating its target CDK6, and increases cell proliferation.[154]

Some oncogenic transcription factors regulate the transcription of circRNAs to promote S-phase transition. For example, the Runx family member transcription factor RUNX3, a master regulator of gene expression in developmental pathways, activates circ_0001821 (circPVT1) to promote cell proliferation. Circ_0001821 upregulation in ESCCs contributes to enhanced cell proliferation and tumor growth. Circ_0001821 activation sponges miR-423-5p, upregulating its target mRNA, beta-transducin repeat-containing E3 ubiquitin protein ligase (BTRC). BTRC promotes the ubiquitination and degradation of the nuclear factor κB (NF-κB) inhibitory binding partner, IKBA, thereby activating NF-κB signaling, which is associated with increased cell-cycle progression in ESCC cells. Circ_0001821 knockdown induces G2/M arrest and inhibits ESCC cell proliferation and tumor growth.[155] These studies suggest that circRNAs function as miRNA sponges to modulate the expression of their target genes, which is an important regulatory mechanism during the S-M transition. The complex regulatory networks formed by circRNAs, miRNAs, and miRNA-targeted mRNAs during the cell cycle are crucial for regulating central components of the cell-cycle control system. The deregulation of these circRNAs can affect well-orchestrated cell-cycle signaling pathways, disrupting cell-cycle homeostasis and promoting tumor development.

Furthermore, some circRNAs have been shown to influence signal transduction pathways that regulate the cell cycle. For example, circRNA cZNF292 promotes S phase and G2-M progression in glioma cells by modulating the Wnt/β-catenin signaling pathway. Silencing cZNF292 downregulates the expression of cyclin A, CDK2, β-catenin, p-STAT3 (Tyr705), and p-STAT5 (Tyr694), which is associated with S/G2/M arrest and inhibition of proliferation.[156] Other examples of circRNAs involved in S-phase transition in cancer cells are discussed in Table 2. Figure 1 provides schematics illustrating the role of ncRNAs, including miRNAs, lncRNAs, and circRNAs, in the regulation of cell-cycle events.

NcRNA-BASED THERAPEUTICS IN CANCER TREATMENT

NcRNA-based therapeutics hold significant potential in cancer treatment. These therapies focus on utilizing ncRNAs, such as miRNAs, lncRNAs, and small interfering RNAs (siRNAs), to modulate gene expression and control various cellular processes involved in cancer development and progression. One approach involves anti-miRNA oligonucleotides and siRNAs, which can specifically target and inhibit

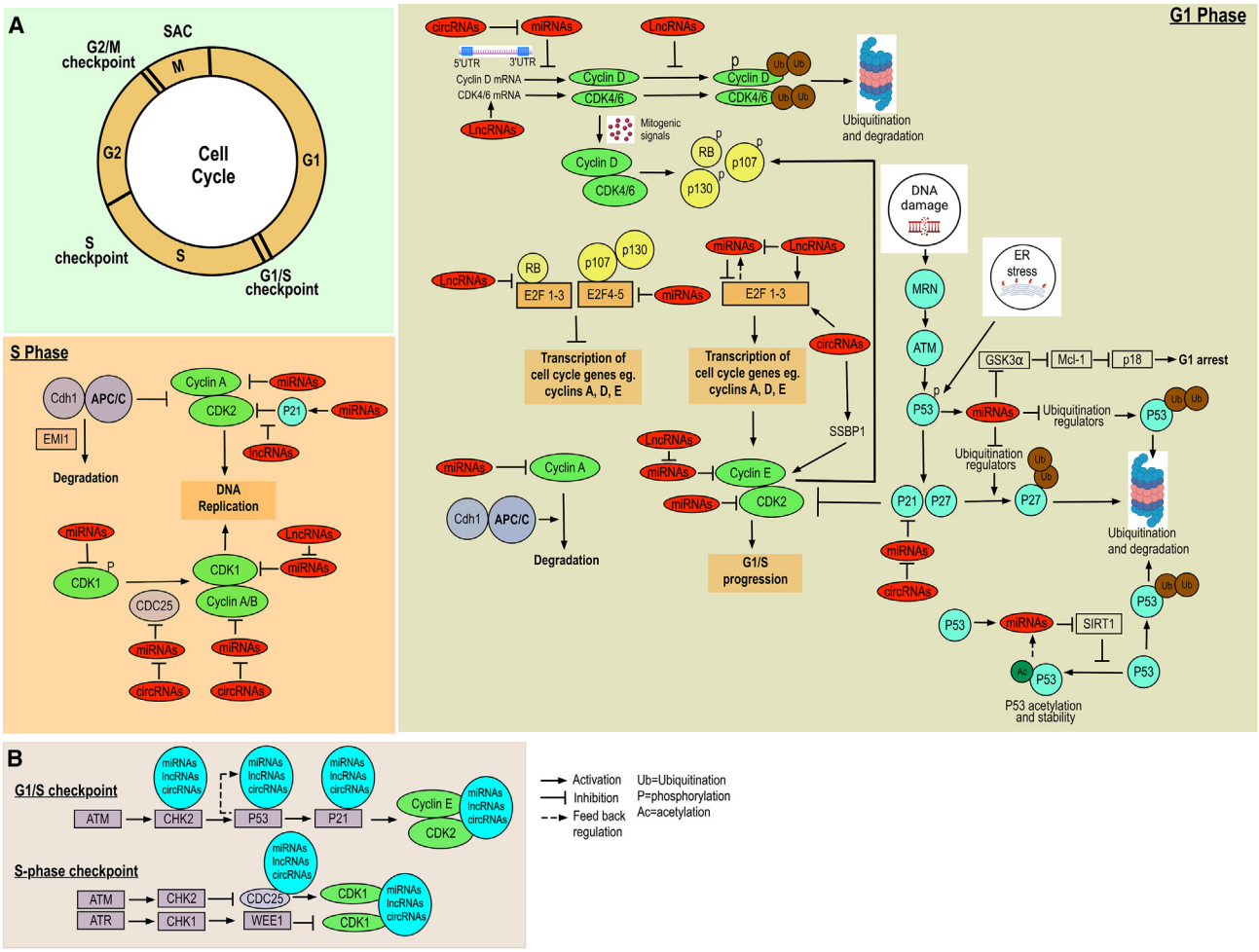

Figure 1. Schematic illustrating a range of ncRNAs, encompassing miRNAs, lncRNAs, and circRNAs, governing major events within the cell cycle

During the progression from G1 to S, CDK4/6 and cyclin D complexes phosphorylate pocket proteins, such as RB, p107, and p130, which release their inhibitory influence on E2F transcription factors, including E2F1–3 or activate transcriptional repressors such as E2F4–5. This, in turn, induces the transcription of cell-cycle genes such as cyclins A, D, and E, promoting G1-S progression. ncRNAs intricately control the expression of CDKs, including CDK4 and CDK6; cyclins A, D, and E; and E2Fs to regulate G1-S progression. Additionally, positive or negative feedback loops exist where cell-cycle proteins under the regulation of ncRNAs control their own transcription by modulating the activity of ncRNAs. During the transition from S to M, A-type cyclin levels rise due to E2F-dependent transcription and the inhibition of their degradation by the anaphase-promoting complex or cyclosome (APC/C). Furthermore, the phosphatase CDC25 dephosphorylates CDK1, which associates with A-type or B-type cyclins for activation. CDK1/2 and cyclin A/B complexes play pivotal roles in facilitating S to M progression. (A) An assortment of ncRNAs regulate the expression of genes involved in various phases of the cell cycle by modulating the activity of CDKs, cyclins, and other crucial regulators. (B) Several signaling pathways oversee cell-cycle checkpoints, including the DNA damage response pathway (G1-S checkpoint) and the SAC pathway (G2/M checkpoint). ncRNAs have the capacity to regulate the expression of proteins involved in these cell-cycle checkpoint signaling pathways.

oncogenic miRNAs or key cancer-related genes, thus reducing tumor growth and promoting cancer cell death.[157–159] Conversely, certain tumor-suppressive miRNAs or lncRNAs can be therapeutically delivered to restore their normal function and inhibit cancer. Additionally, RNA-based therapies can be designed to target specific signaling pathways implicated in cancer, offering a precise and personalized treatment approach. The development of RNA aptamers that bind to specific cancer-related proteins, inhibiting their function, is another avenue of research in this field.[25,160–167] However, this approach also faces several challenges, including (1) specificity and off-target effects, (2) delivery strategies, (3) immune response, (5) resistance mechanisms, and (5) clinical validation. Translating miRNA-based therapies from preclinical studies to clinical trials requires rigorous validation, biomarker identification, and large-scale testing. Clinical trials involving ncRNAs in the context of cancer research have gained significant attention due to the potential of ncRNAs as therapeutic targets and diagnostic biomarkers. However, the majority of these trials aim to explore the role of various ncRNAs, including miRNAs, lncRNAs, and circRNAs, in cancer diagnosis, prognosis, and treatment.[168–170] Overall, ncRNA-based therapeutics

represent a promising and evolving area of cancer treatment, with the potential to offer targeted and effective solutions for various types of cancer.

CONCLUSIONS AND FUTURE DIRECTIONS

A network of ncRNAs tightly regulates each step of the core cell-cycle machinery by modulating central components of the cell-cycle control system, including CDKs and their regulatory cyclin subunits, the E2F family of transcription factors, and downstream cell-cycle genes. Advances in RNA identification and sequencing technologies have led to the discovery and validation of thousands of new ncRNAs with roles in cell-cycle control. These elucidated functions of ncRNAs in cell-cycle regulation underscore their fundamental importance in ensuring the integrity of genetic information and preventing aberrant cell division. It is well established that deregulation of ncRNAs can lead to the loss of cell-cycle control, enabling mutations to bypass cell checkpoints. This, in turn, results in their accumulation within the cell, triggering uncontrolled cell growth and ultimately contributing to cancer development. Numerous studies have provided a rationale for targeting ncRNAs to impede cell division in tumor cells and explore their utility in cancer treatment. Various strategies have been proposed for harnessing ncRNAs as potential therapeutic agents, including ncRNA mimic-based therapeutics, ncRNA inhibitors, ceRNA-based therapeutics, antisense oligonucleotides (ASOs), and ncRNAs as biomarkers for disease progression. While miRNA mimics have been tested in clinical trials for cancer treatment, other strategies and ncRNAs remain to be thoroughly explored for clinical use. Therefore, comprehensive investigations are essential to unlock the potential of ncRNA-based therapeutic agents in targeting cell-cycle regulation and advancing future anticancer drug development. Furthermore, the strong correlation between ncRNA signatures and cancer progression highlights their potential as valuable biomarkers in clinical settings for disease diagnosis.

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AUTHOR CONTRIBUTIONS

A.S.P. and K.B.C., conceptualization, writing – original draft, formal analysis, visualization, manuscript edits; H.C. and R.B., revision and figures preparation; A.K.P. and D.W.C., reading and editing the manuscript; K.B.C., communicating with all the others, study supervision, and acquisition of funding.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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