Cell cycle regulation and hematologic malignancies

Yun Dai\textsuperscript{b,*}, Fengyan Jin\textsuperscript{b,*}, Wei Wu\textsuperscript{c,*}, Shaji K. Kumar\textsuperscript{d}

\textsuperscript{a}Laboratory of Cancer Precision Medicine, The First Hospital of Jilin University, Changchun, Jilin, China; \textsuperscript{b}Department of Hematology, Cancer Center, The First Hospital of Jilin University, Changchun, Jilin, China; \textsuperscript{c}Department of Neurosurgery, The First Hospital of Jilin University, Changchun, Jilin, China; \textsuperscript{d}Division of Hematology, Mayo Clinic, Rochester, MN, USA

Abstract

A complex network precisely regulates the cell cycle through the G\textsubscript{1}, S, G\textsubscript{2}, and M phases and is the basis for cell division under physiological and pathological conditions. On the one hand, the transition from one phase to another as well as the progression within each phase is driven by the specific cyclin-dependent kinases (CDKs; e.g., CDK1, CDK2, CDK4, CDK6, and CDK7), together with their exclusive partner cyclins (e.g., cyclin A1, B1, D1–3, and E1). On the other hand, these phases are negatively regulated by endogenous CDK inhibitors such as p16\textsuperscript{INK4a}, p18\textsuperscript{INK4c}, p19\textsuperscript{INK4d}, p21\textsuperscript{WAF1/CIP1}, and p27\textsuperscript{KIP1}. In addition, several checkpoints control the commitment of cells to replicate DNA and undergo mitosis, thereby avoiding the passage of genomic errors to daughter cells. CDKs are often constitutively activated in cancer, which is characterized by the uncontrolled proliferation of transformed cells, due to genetic and epigenetic abnormalities in the genes involved in the cell cycle. Moreover, several oncogenes and defective tumor suppressors promote malignant changes by stimulating cell cycle entry and progression or disrupting DNA damage responses, including the cell cycle checkpoints, DNA repair mechanisms, and apoptosis. Thus, genes or proteins related to cell cycle regulation remain the main targets of interest in the treatment of various cancer types, including hematologic malignancies. In this context, advances in the understanding of the cell cycle regulatory machinery provide a basis for the development of novel therapeutic approaches. The present article summarizes the pathways as well as their genetic and epigenetic alterations that regulate the cell cycle; moreover, it discusses the various approved or potential therapeutic targets associated with the cell cycle, focusing on hematologic malignancies.

Keywords: Cell cycle, Transcription, Cyclin, Cyclin-dependent kinase, Hematologic malignancy

1. INTRODUCTION

The cell cycle is a defined program that can be divided into four phases—the G\textsubscript{1}, S, G\textsubscript{2}, and M phases—that result in cell division. The passage of cells through these phases is driven by cyclin-dependent kinases (CDKs) and their partner cyclins. These molecules bind to each other to form several specific active heterodimeric cyclin–CDK complexes that play key roles in the regulation of both cell cycle and gene transcription (Fig. 1). Activated CDKs phosphorylate various proteins, thereby driving the entry into and progression through each phase as well as promoting DNA synthesis and mitosis.\textsuperscript{1} The process of cell cycle regulation rigorously follows an empirical rule, that is, the occurrence of an event B is dependent on the completion of the prior event A, to ensure that the cell cycle progresses in an orderly manner. Such control is finely orchestrated through (a) the de novo synthesis (via epigenetic and transcriptional regulation) and turnover (via the ubiquitin–proteasome system, UPS) of cyclins and (b) the phosphorylation (by upstream kinases) and dephosphorylation (by phosphatases) of CDKs, often without a change in their total protein levels. Interestingly, the phosphorylation of certain CDKs could be either activational or inhibitory, which further increases the complexity of cell cycle regulation. A disturbance of cell cycle regulation could lead to or promote the development and progression of cancer. Until the end of the twentieth century, researchers believed that deletion or mutation (gain- or loss-of-function mutations) in tumor-suppressor genes or oncogenes is the sole mechanism via which the “gatekeepers” of the cell cycle could be (in)activated in cancer. Advancements in the understanding of the regulation of gene expression emphasizes a mechanism called epigenetic regulation, which includes several molecular modifications (e.g., DNA methylation and histone methylation and acetylation) that play a key role in the regulation of gene expression; this mechanism is known as (re)programming. In fact, the amplification/overexpression of cyclin and CDK genes or epigenetic silencing/deletion of CDK inhibitor genes is common in nearly all human tumor types,\textsuperscript{2} including various hematologic malignancies (Table 1). For instance, the mutations of CDKs, cyclins, and cell cycle-related oncogenic genes were often observed in several hematologic malignancies (Fig. 2). Over the last several decades, research has provided...
tremendous evidence regarding not only the role of cyclins and CDKs in the regulation of cell division but also in numerous other functions of these genes/proteins in transcription, alternate splicing, DNA damage response (DDR), cell death, cell differentiation, and metabolism, among others, under both physiological and pathological conditions, particularly cancer. In this article, we focused on the fields in which the alterations in cell cycle regulation have been investigated in terms of cyclins and CDKs, focusing particularly on hematologic malignancies.

Figure 1. Cyclins and cyclin-dependent kinases (CDKs) involved in the regulation of both the cell cycle and gene transcription. (A) In mammalian cells, cell cycle regulatory CDKs drive intraphase progression and interphase transition during the cell cycle via the formation of complexes with their corresponding cyclins. These complexes include (a) cyclin C–CDK3, which promotes G0–G1 transition (or G0 exit) in an RB-dependent manner; (b) cyclin D–CDK4/6, which primarily functions in the late G1 phase before entry to the S phase via the RB-E2F pathway, in which the genetic and epigenetic alterations are extremely frequent in cancer; (c) cyclin E–CDK2, which stimulates entry into and progression through the S phase; (d) cyclin A–CDK2, which takes over the function of cyclin E–CDK2 in the late S phase; and (e) cyclin A–CDK1, which is formed before mitosis and is an event likely required for progression through the late G2 phase and entry to the M phase followed by the formation of the cyclin B–CDK1 complex that promotes mitosis. (B) Transcription-regulatory CDKs, also via the formation of complexes with their cyclin partners, govern the entire process of gene transcription, including initiation primarily by the cyclin H–CDK7 complex, elongation almost exclusively and termination largely by the cyclin T–CDK9 complex, and RNA splicing by the cyclin L–CDK11 complex. In addition, the cyclin C–CDK8/19 and cyclin K–CDK12/13 complexes are also involved in transcriptional regulation, although they most likely control the expression of a specific set of genes. Several CDKs (e.g., neural CDK5 and, probably, CDK18) and cyclins (e.g., cyclin F), which bind to other proteins rather than the corresponding cyclins or CDKs, are categorized beyond these two relatively well-defined groups but play important roles in various physiological and pathological processes, particularly cancer, including hematologic malignancies.

Table 1

| Cyclin-CDK complexes and CDK inhibitors in hematologic malignancies. |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Cyclin-CDK | Function | Disease | CDK inhibitor | Inhibitor status |
| B-CDK1 | G2-M, mitosis | MM: B1↑ (aneuploidy?) | Flavopiridol/alfacidib: AML | Phase II |
| A-CDK2 | S | AML (M2, M3): A1↑ | | |
| E-CDK2 | G1-S | | | |
| C-CDK3 | G0-G1 | | | |
| D-CDK4/6 | G1 | MM: D1↑ (11;14), D2↑ (due to MYC↑), D3↑ (8;14) | PD0332991/palbociclib: MM, MCL | Approved |
| | | MCL: D1↑ | LEE011/ribociclib: ALL | Approved |
| | | MLL-r AML: CDK6↑ | LY2835219/abemaciclib: ? | Approved |
| | | MM: CDK5↑ | SCH77965/dinaciclib: MM | Phase I |
| | | T-ALL: CDK7↑ | THZ1/THZ2: T-ALL | Pre-clinical |
| | | | C77001: AML | Phase I |
| | | | SY-1365: ? | Phase I |
| | | | Bi-1347: AML | Pre-clinical |
| | | | FLavopiridol/alociclib: CLL, MM | Phase II |
| | | | SCH77965/dinaciclib: CLL, MM | Phase II |
| | | | KL-1/KL-2: ? | Preclinical |
| H-CDK7 | CAK; Transcription initiation (TFIIH) | C-CDK8/19 | | |
| | | | M-CDK10 | |
| | | | L-CDK11 | |
| | | | K-CDK12/13 | |
| | | | ?: (β-catenin↑) | |
| | | | CLL | |
| | | | MM: P-TEFb↑ (Mcl-1↑) | |
| | | | Lymphoma (?: SEC↑ (MYC↑) | |
| | | | FL: CDK10↑ | |

AML: acute myeloid leukemia; CAK: CDK activating kinase; CDK: cyclin-dependent kinase; CCL: chronic lymphocytic leukemia; DDR: DNA damage response; FL: follicular lymphoma; MCL: mantle cell lymphoma; MLL-r: mixed-lineage leukemia rearrangement; MM: multiple myeloma; P-TEFb: positive transcription elongation factor b; SEC: super elongation complex; T-ALL: T-cell acute lymphoblastic leukemia; TFIIH: transcription factor II human (general transcription factor). G0, G1, S, G2, and M indicate different cell cycle phases.
Figure 2. Genetic alterations in cell cycle regulatory genes in hematologic malignancies. Using the cBioPortal for Cancer Genomics platform, genetic abnormalities were analyzed as follows. (A) The frequency of genetic alterations was examined in 24 data sets involving various hematologic malignancies, including (1) diffuse large B-cell lymphoma (DLBCL; TGCA); (2) DLBCL (TGCA Pan-Cancer); (3) mantle cell lymphoma (MCL; IDIBIPS 2013); (4) non-Hodgkin’s lymphoma (NHL; BCGSC 2013); (5) diffuse large B-cell lymphoma (DLBCL; Broad 2012); (6) DLBCL, not otherwise specified (DLBCLNOS; DFCI); (7) acute lymphoblastic leukemia (ALL-phase II; TARGET 2018); (8) DLBCLNOS (Duke 2017); (9) mature B-cell neoplasm (MBN; MDACC 2013); (10) primary central nervous system lymphoma (PCNSL; Mayo Clinic); (11) cutaneous T-cell lymphoma (CTCL; Columbia 2015); (12) multiple myeloma (MM; Broad); (13) acute myeloid leukemia (AML; TCGA Pan-Cancer); (14) AML (TCGA); (15) AML (TCGA pub); (16) NHL (bog sci 2011); (17) AML (TARGET 2018); (18) ALL (St. Jude, Nat Gen); (19) chronic lymphocytic leukemia (CLL; IUOPA 2015); (20) CLL (Broad 2013); (21) ALL (St. Jude 2015); (22) CLL and small lymphocytic lymphoma (CLLSSL; Nat Genet 2011); (23) histiocytic leukemia (HIST; COBI 2019); and (24) myelodysplastic syndrome (MDS; Tokyo). (B) The frequency of the mutations of each cell cycle regulatory gene in various hematologic malignancies included in all the studies described above, with mutations further functionally categorized as inframe, missense, and truncated, either as putative driver or with unknown significance, as well as other mutations, was assessed. Among all of the cell-regulatory genes considered, the genes that were most frequently altered (>1%) at the genetic level were CDKN2A (7.0%), CDKN2B (6.0%), MYC (4.0%), RB1 (2.2%), CDKN1B (1.4%), CCND1 (1.1%), and CCND2 (1.1%).
2. CYCLINS

In mammals, over 20 members of the cyclin family have been identified. All cyclins share a region of approximately 150 amino acids called the cyclin box, which interacts with CDKs. G1 (C, D, and E) and mitotic (A and B) cyclins form distinct categories that are directly involved in cell cycle regulation, whereas cyclins H, K, L (L1 and L2), and T (T1, T2a, and T2b) are categorized beyond these two groups. Cyclin F does not bind to CDKs but to multiple other proteins, including those involved in cell cycle regulation, such as the CDK inhibitor p27kip1. As a substrate receptor of 1 of 69 human SCF ubiquitin ligase complexes, cyclin F interacts with all three activators of the E2F transcription factor family and leads to their degradation via UPS during the late S and G2 phases, which prevents premature S-phase entry.

Therefore, cyclin F belongs to the family of cell cycle regulatory cyclins, although it acts primarily in an indirect manner.

Cyclins A and B are known as mitotic cyclins as they are upregulated in the late G2 or G2/M phase and undergo proteolysis in the M phase. Unlike cyclin B, which interacts with CDK1 during mitosis, the cyclin A–CDK1 complex forms before mitosis and is likely required for progression through the late G2 phase. Thus, although cyclin A acts at the G2/M transition, evidence indicates that it binds and activates CDK2 primarily in the S phase. Overexpression of cyclin A in the G1 phase leads to accelerated entry into the S phase, thereby suggesting that this cyclin is involved in transformation. Although cyclin A1 is detected in normal CD34+ hematopoietic progenitor cells, the highest levels of cyclin A1 are observed in acute myeloid leukemia (AML), particularly at the promyelocyte (M3) and myeloblast (M2) stages. Moreover, transgenic cyclin A1-overexpressing mice develop AML, although with low frequency, likely via the regulation of WT1 expression. In patients with AML, high levels of cyclin A1 are associated with poor prognosis, and this cyclin may serve as an immunogenic targetable antigen in AML stem cells.

Cyclin A is mandatory for the downregulation of anaphase-promoting complex or cyclosome (APC/C), a complex of at least 11 proteins (including cullin and RING subunits) that constitutes an E3 ubiquitin ligase, which marks cell cycle regulatory proteins for degradation via UPS. Considering the predominant role of APC/C in cell cycle regulation, its gene mutation or dysfunction is speculated to be one of the major reasons for the misregulation of the cell cycle as well as the transformation of cells in certain types of tumors.

B-type cyclins associate with CDK1 to form the classical mitotic cyclin–CDK complex. Cyclin B is synthesized in the S phase and accumulates together with CDK2, following which this cyclin is then ubiquitinated and degraded via UPS, thereby allowing the cell to exit from mitosis. Cellular localization of the cyclin B–CDK1 complex is strictly cell cycle-dependent. Although this complex accumulates in the cytoplasm during the G2 and S phases, it translocates to the nucleus and binds to the mitotic spindle during mitosis.

Different family members of the B-type cyclins (i.e., cyclin B1 and B2) have distinct functions. Upon mitotic entry, cyclin B1–CDK1 promotes chromosome condensation, nuclear membrane dissolution, mitotic asters assembly, and Golgi breakdown, whereas cyclin B2–CDK1 only induces Golgi disassembly. Cyclin B1 accumulates in the nucleus at prophase and then translocates to the condensed chromatin, spindle microtubules, centrosomes, and chromatin during prometaphase. Moreover, the localization of cyclin B1 to the chromatin, centrosomes, and kinetochores during mitosis is controlled by distinct sequence elements. Exit from mitosis is characterized by the rapid degradation of cyclin B. Cells with a defect in mitotic cyclin B expression or degradation mechanism easily become aneuploid, which refers to the presence of an abnormal number of chromosomes (e.g., ≤45 or ≥47 chromosomes instead of the usual 46) in a cell. Aneuploidy originates from the improper separation of chromosomes between the two daughter cells during cell division. The cyclin B/CDK2 checkpoint is often defective in malignant cells, leading to uncontrolled M-phase entry and aneuploidy with either missing or extra chromosomes. In fact, aneuploidy is common in several types of hematologic malignancies. For example, trisomies typically involving odd-numbered chromosomes 5, 7, 9, 11, 13, and 15 represent one of the primary cytogenetic abnormalities in multiple myeloma (MM), leading to a hyperdiploid karyotype. Researchers currently believe that primary genetic events, including aneuploidy and chromosome translocations, are associated with the development of the asymptomatic precursor states of MM (e.g., monoclonal gammopathy of undetermined significance and smoldering MM) and probably with the symptomatic disease as well.

Three cyclin D molecules (i.e., D1, D2, and D3) bind to CDK4 or CDK6 and function mainly in the late G1 phase. The cyclin D–CDK4 or –CDK6 complex phosphorylates RB, thereby restraining the latter’s inhibitory effects on E2Fs and other related transcription factors. In turn, RB controls the activity of other cell cycle regulatory elements such as Skp2 (the rate-limiting component of the Skp1/Cullin/F-box protein (SCF) complex, an E3 ubiquitin ligase), which triggers degradation of the CDK inhibitor p27kip1 and thereby activates cyclin E–CDK2. Then, activated CDK2 induces RB phosphorylation, followed by E2F-dependent Skp2 expression. Although all three cyclin Ds act in the late G phase, just before entry into the S phase, cyclin D1 represents the major form of D-type cyclins in most cell types. Cyclin D1 notably has various cell cycle-independent functions. For example, cyclin D1 regulates microRNA biogenesis by the induction of Dicer, a central regulator of miRNA maturation. Moreover, the cyclin D1–CDK4 complex is involved in the regulation of glucose metabolism in post-mitotic cells.

Cyclin D1 is highly expressed in several tumor types (e.g., breast cancer), including hematologic malignancies (e.g., mantle cell lymphoma and MM), often without the amplification or mutation of the cyclin D1 gene (CCND1) itself. In these cases, D1 levels are regulated via various other mechanisms. For example, alterations in the RB gene in cancer may secondarily cause the upregulation of cyclin D transcription, thus indicating an RB-dependent feedback loop. As cyclin D dysregulation is mostly prominent in MM carrying IGH rearrangement, cyclin D genes are directly involved in chromosome translocations, resulting in the fusion of these genes to the IGH enhancer on chromosome 14 [e.g., t(11;14) for cyclin D1 and t(6;14) for cyclin D3]. Moreover, the overexpression of cyclin D2 is also frequent in MM, mostly likely due to the activation of other transcriptional factors such as MYC.

Cyclin E accumulates at the G1/S boundary of the cell cycle, where it stimulates functions associated with entry into and progression through the S phase. In normal cells, cyclin E levels are finely regulated to ensure that peak cyclin E–CDK2 kinase activity occurs only for a short interval near the G1/S boundary. The cyclin E–CDK2 complex becomes active during the S phase, following which it is rapidly ubiquitinated and degraded via UPS. Cells overexpressing cyclin E progress much faster through the G1 phase and into the S phase, but the time required for DNA synthesis remains normal. Furthermore, cyclin E
levels are regulated by environmental factors, including transforming growth factor-β (TGF-β) and irradiation, which is partly mediated by small proteins known as CDK inhibitors. Cyclin E overexpression delays progression through the early phases of mitosis and causes aberrant mitosis, thereby resulting in the dysregulation of mitotic progression. The poor prognostic implications of cyclin E overexpression, which leads to high cyclin E levels throughout the cell cycle, have been observed in a variety of human cancers. However, the direct association between cyclin E overexpression and tumorigenesis remains poorly understood. In this context, the cyclin E–CDK2 complex phosphorylates and inactivates the RB protein or leads to genomic instability via the generation of aneuploid cells.

Although the cyclin E–CDK2 complex controls the progression from the G1 phase to the S phase, cyclin A, another cyclin that interacts with CDK2, is able to compensate for the loss of cyclin E function. However, the exact time point at which CDK2 “switches” from cyclin E to cyclin A binding during the cell cycle is unclear. In cyclin E-defective cells, cyclin A can take over the function of cyclin E in the S phase. Moreover, cyclin E plays a critical role in the duplication of centrosomes, whereas cyclin A is important for centrosome amplification in G2-arrested cells, irrespective of cyclin E. As a consequence, bifurcations in CDK2 activity determine whether cells immediately commit to the next cell cycle or enter a transient state of quiescence as they exit mitosis.

3. CYCLIN-DEPENDENT KINASES

Early studies on the control of mitosis provided the first evidence about the existence of factors called M- and S-phase-promoting factors. The key element of S-phase-promoting factor was initially believed to be cdc2. Later, a group of cdc2-related kinases were characterized and named CDKs because they all bind to their corresponding cyclins for activation. Similar to cyclins, more than 20 CDKs have been identified in mammalian cells. However, only some cyclin–CDK complexes are known to be involved directly in cell cycle regulation, whereas other similar complexes participate in multiple cell cycle-independent processes such as mRNA transcription and splicing.

Three cdc2-related proteins—cdc2 (i.e., CDK1), CDK2, and CDK3—that were able to replace deficient cdc28 function in budding yeast were originally isolated. CDK1 was initially characterized as an M phase-specific histone H1 kinase and is the only essential member of the CDK subfamily that drives cell cycle progression. The function of this CDK is irreplaceable by its closest homolog, CDK2. Although CDK1 shares several similarities in sequence and structure with CDK2 and CDK4, the structure of cyclin B–CDK1 complex displays a relatively relaxed specificity for residues adjacent to the phosphorylation site, thereby suggesting that its activation segment is relatively more flexible than that of its close relatives. CDK1 is phosphorylated at tyrosine 15 and threonine 14 by Wee1 and dephosphorylated by CDC25A. However, the function of these phosphorylations of CDK2 is less clear than those of CDK1. For example, the inhibitory phosphorylation of CDK2 plays a role in S-phase entry and centrosome duplication but may not be required for DDR. In the S phase, tyrosine 15 and threonine 14 phosphorylations of CDK2 directly regulate cyclin E degradation and are essential for the maintenance of genome stability; however, failure of these phosphorylations to inhibit CDK2 during replication stress results in irreparable DNA damage.

Unlike CDK1 and CDK2, which act after cells enter the cell cycle, CDK3 interacts specifically with cyclin C to drive the exit from the G0 phase, a quiescent (resting) state, by phosphorylating RB1 at serine 807/811 during the G0–G1 transition. In addition, CDK3 may promote G1–S transition, probably by involving the activation of E2F1, E2F2, and E2F3 in an RB1-independent manner.

Two other CDKs that bind to cyclin D at the G1 phase are CDK4 and CDK6. These two CDKs have recently become the focus of anticancer research, primarily because they form a complex with cyclin D1. Mice lacking cyclin D1 are completely resistant to breast cancer driven by ErbB-2 (HER2). Moreover, the development of mammary tumors induced by ErbB-2 is prohibited by the inactivation of CDK4, thereby underlining the role of the cyclin D1–CDK4 complex in breast cancer. Because aberrations of the p16–cyclin D–CDK4–RB pathway are common in most cancers, the development of selective CDK4 inhibitors has launched promising efforts to target tumors displaying either cyclin D1 overexpression (e.g., breast cancer, mantle cell lymphoma, MM) or CDK4 amplification (e.g., liposarcoma). In addition, cyclin D-dependent CDK4/6 phosphorylates various substrates (e.g., RB1 and its relatives RB1 and RB1L2, SMAD2, SMAD3, FOXM1, and ME3) that form a central node in a signaling network that governs the overall transcriptional and other biological responses to the activation or inhibition of the kinases. Due to their essential
role in cell cycle progression, cyclin D–CDK4 and cyclin D–
CDK6 complexes represent one of the most important
therapeutic targets, particularly for the treatment of breast
cancers that often overexpress cyclin D1.  As a result, CDK4/6
inhibitors (e.g., palbociclib, abemaciclib, and rebociclib), in
combination with hormone therapy, have been approved to
treat hormone receptor-positive, HER2-negative metastatic breast
cancer.  

CDK5, an atypical CDK, is predominantly expressed in
neurons where it is activated by the non-cyclin proteins p35 and
p39 or their truncated forms p25 and p29.  Interestingly,
although CDK5 was originally considered a neuron-specific
CDK, it has also been found to be expressed at high levels in
several cancer types,  including hematologic malignancies (e.g.,
MM), thereby representing a potential therapeutic target.  
Moreover, CDK5 may serve as a prognostic marker to identify
patients with MM who are most likely to respond to treatment
(e.g., bortezomib).  

CDK6 in complex with D-type cyclins plays a redundant role
with CDK4 in cell cycle regulation (particularly promoting G1–S
transition), and thus, it may be a therapeutic target in cancer
treatment.  However, CDK6 has a distinct role in tumorigenesis
as well under certain circumstances. For example, AML cells
 carrying mixed-lineage leukemia (MLL) rearrangements (e.g.,
MLL-AF9, MLL-AF4, and MLL-AF6) specifically rely on
CDK6, but not on CDK4, to proliferate, thereby suggesting
that CDK6 is a target specifically in MLL-driven leukemia.  
Interestingly, the stabilization of the CDK6 protein by SUMO-
ylation contributes to the progression of some tumors such as
glioblastoma.  

Recent findings suggest that CDK6 has additional
structures and functions beyond cell cycle regulation. For
example, CDK6 physically and functionally interacts with p65
(ReLA), a key component of the NF-κB transcription factor
complex, at defined chromatin regions and transcriptionally
activates several NF-κB target genes, including the cytokines
and chemokines involved in inflammation and cancer.  Interestingly,
the expression of p21<sup>WAF1</sup>, a specific protein inhibitor of the
enzymatic activity of several CDKs, including CDK4/6, is
regulated by NF-κB in a p53-independent manner.  This event
is associated with G1 arrest and differentiation of hematopoietic
cells, and its disruption may enhance the antitumor activity of
differentiation-inducing agents such as epigenetic HDAC
inhibitors.

Three CDKs, namely, CDK7 (p40<sub>MO15</sub>), CDK8, and CDK9,
have been characterized to control gene transcription. Among
these enzymes, CDK7 is the only kinase that plays dual roles in
the regulation of both the cell cycle and gene transcription. On
the one hand, CDK7 interacts with cyclin H and acts as a CDK-
activating kinase to completely activate nearly all cell cycle
regulatory CDKs (e.g., CDK1, CDK2, CDK4, and CDK6) by
phosphorylating their T loops in a context-specific manner,
such as threonine 161 of CDK1.  CDK7 is required to determine
the cyclin specificity and activation order of CDK1 and CDK2
during the S and G2 phases as well as to maintain the activity of
CDK4 as cells exit quiescence and progress to G1 through the
restriction (R) point.  On the other hand, CDK7 is a key component of
the general transcription factor TFIIH (CDK7/

The general transcriptional machinery to sustain the oncogenic
state, represents a novel approach to treat several cancer types,
including T-cell acute lymphoblastic leukemia, triple-negative
breast cancer, and glioma, which may be particularly
addictive to transcription. 

CDK8, or its paralog CDK19, with whom it shares
approximately 91% sequence homology, is a subunit of the
large Mediator complex (~1.2MDa), which is composed of 25–
30 proteins and acts as a molecular bridge between DNA-binding
transcription factors and RNA polymerase II.  Although CDK8
and CDK19 interact with different partners due to their diverse
C-terminal domains, these two proteins share a particularly high
degree of sequence conservation in two critical regions (i.e., the
kinase and cyclin-binding domains). CDK8 or CDK19 binds to
cyclin C, MED12, and MED13 in a mutually exclusive manner in
the Mediator kinase module, which is involved in regulating the
gene transcription of nearly all RNA polymerase II-dependent
genes.  

CDK19 may form a Mediator kinase module distinct from
the CDK8 module, and therefore, regulate different
transcriptional programs. The cyclin C–CDK8 complex
facilitates the phosphorylation of both serine 2 and serine 5 at
the CTD of RNA polymerase II.  However, CDK8 can perform
either positive or negative functions in transcriptional regulation
during different transcription stages (e.g., preinitiation
and elongation), thus providing a mechanism for responding to
different promoter contexts (e.g., transcription factors or CDK8
module binding).  Unlike CDK7 and CDK9, both of which
govern global gene expression, CDK8 appears to promote only
gene-specific transcription. In this context, CDK8 and CDK19
can act as drivers or suppressors of tumorigenesis in a context-
dependent manner.  CDK8 expression has been detected in 70% of
colorectal cancers and correlated with β-catenin activation,
where CDK8 directly antagonizes the suppression of β-catenin
transcription by the transcription factor E2F1.  As
the suppression of β-catenin by E2F1 contributes to apoptosis,
overexpression of CDK8 (and RB) accounts for reduced rates of
apoptosis and increased cell growth. In tumor cells with CDK8
depletion, CDK19 may be required for cell proliferation and
serve as a regulator of p53 stress response independent of
its kinase activity.  CDK19 knockdown in these cells reduces the
expression of mitogenic genes but activates the genes associated
with cholesterol metabolism and the p53 pathway.

CDK9 plays an essential role in transcription elongation by
RNA polymerase II in eukaryotes.  CDK9, as a catalytic subunit
with two isoforms (CDK9-p42 and CDK9-p55), partners with
the 87-kDa regulatory subunit cyclin T with three isoforms (T1,
T2a, and T2b), to form a complex known as positive
transcription elongation factor (P-TEFb).  However, CDK9
preferentially binds cyclin T1 to form P-TEFb, which
hyperphosphorylates the CTD (primarily serine 2) of RNA polymerase
II, an event that is essential for transcription elongation. In
addition, P-TEFb phosphorylates negative transcription elongation
factors (N-TEFs), including DRB8-sensitivity inducing factor
(DSIF) and negative elongation factor (NELF), to release the
transcription block (a pause immediately after transcription
initiation) of both N-TEFs present on the hypophosphorylated
forms of RNA polymerase II. Other binding partners of CDK9
include inhibitory HEXIM1 (MAQ1) or HEXIM2 and 7SK
snRNP, which sequester P-TEFb in an inactive complex to inhibit
transcription elongation. After release from the 7SK/HEXIM
complex, P-TEFb becomes active in complexes such as BRD4/P-
TEFb and super elongation complex (SEC).  Moreover,
emerging evidence suggests that CDK9 acts as a signaling hub
for transcriptional control and thus plays essential roles in the
total process of gene transcription, including initiation,
elongation, and termination. In addition, CDK9 plays a role
in rRNA processing via the activation of RNA polymerase II. Interestingly, although mitotic chromosomes have long been
considered to be highly compacted, thereby rendering them
ineligible for transcription, mitotic transcriptional activation is
identified as a key step to control the transcription of genes in
mitosis. In contrast, the inhibition of P-TEFb during mitosis
results in delays in the progression of cell division. These
findings suggest a novel link between the regulation of
transcription and the cell cycle, particularly mitosis.

In normal cells, P-TEFb activity is stringently controlled in a
functional equilibrium to accommodate transcriptional demands
for different biological activities. As a rule in oncogenic
transformation, the upregulation of pro-survival genes in
transformed cells must be sustained by constitutive RNA
polymerase II activity that governs transcription elongation;
here, CDK9 is the primary factor responsible for such
processivity. In this context, transformed cells are addicted to
transcription because of the requirement for the continuous
production of anti-apoptotic proteins, particularly those with
short half-lives (e.g., Mcl-1). Indeed, abnormal activities in the
CDK9-related pathway occur in several human cancers. For
example, the high levels of CDK9 and/or cyclin T1 expression are
observed in several types of hematologic malignancies, including
B- and T-cell precursor-derived lymphomas, anaplastic large cell
lymphoma, follicular lymphomas, and MM. Moreover, strong
nuclear staining for both proteins is observed in Hodgkin and
Reed–Sternberg cells of classical Hodgkin’s lymphoma. In
addition, the P-TEFb complex interacts with the Tat element
of HIV-1 to mediate the latter’s transcription, thereby directly
linking this CDK to the replication pathway of HIV.

Selective CDK9 inhibitors preferentially target malignant cells
in preclinical hematologic tumor models, including leukemia
and MM. Mcl-1, a Bcl-2 family anti-apoptotic protein with an
estimated half-life of <2–3 hours, represents one of the most
important downstream targets for CDK9 inhibition. Moreover,
CDK9 inhibition disrupts the process of cytoprotective
autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adaptor
protein SQSTM1/p62, resulting in an

autophagy, for instance, via the downregulation of the adapter







Consistent with these findings, the inhibition of CDK12 in tumor cells results in gene length-dependent elongation defects, including loss of expression of long (>$45$ kb) genes, most of which participate in DDR.\(^{117}\) The relatively longer length of DDR genes in comparison with that of other genes provides a rationale for the particular susceptibility of DDR genes to CDK12 inhibition. Moreover, CDK12 and CDK13 associate with a large number of splicing factors and positively regulate their expression; depleting either of the kinases could down-regulate gene expression and result in defects in RNA processing without a marked effect on the global CDT phosphorylation of RNA polymerase II.\(^{118}\) Similar to CDK1, CDK12 phosphorylates 4E-BP1 (e.g., threonine 37 and 46), thereby promoting the translation of mTOR-dependent mRNAs, including those required for MYC transformation as well as several other subunits of mitotic and centromere/centrosome complexes.\(^{119}\) This finding suggests the role of CDK12 in maintaining mitotic chromosome stability. Because genomic alterations in CDK12 have been detected in several cancer types, increasing evidence suggests that CDK12 is a potential biomarker and therapeutic target.\(^{120}\)

CDK18 belongs to the PCTAIRE family of CDKs, which includes human CDK16 and CDK17, all of which share a conserved PCTAIRE amino acid sequence in the region for the binding of cyclins. CDK18 was first described as a neuronal kinase that phosphorylates Tau proteins associated with Alzheimer’s disease. However, since then, it has been identified as a regulator of genome stability in other cell types.\(^{121}\) Depletion of CDK18 leads to the accumulation of cells in the early S phase accompanied by an increase in DNA damage and chromosome abnormalities. CDK18 interacts with multiple DNA repair proteins, such as RAD9, RAD17, and TOPBP1, in response to replication stress. Therefore, CDK18 may play a rate-limiting role in replication stress-triggered signaling.

### 4. CONCLUSIONS AND PERSPECTIVES

The cell cycle of normal cells is closely monitored and finely regulated by the cell cycle regulatory machinery via a complicated but well-orchestrated signaling network. Although this network primarily involves CDKs (e.g., CDK1-3 and 4/6) and their partner cyclins (A–E), a variety of CDK inhibitors, DDR-related proteins (those associated with cell cycle checkpoints, DNA repair mechanisms, and apoptosis), and several other related molecules have not been described in our review owing to article length considerations. Because uncontrolled cell proliferation via the cell division cycle represents one of the hallmarks for cancer (including hematologic malignancies), it is not surprising that genetic and epigenetic abnormalities occur most frequently in pathways related to cell cycle regulation and involve CDKs, cyclins, CDK inhibitors, checkpoint kinases, and DNA repair genes, among numerous other genes and proteins. Moreover, many of these pathways can be activated in tumor cells in response to various stimuli and stresses, including chemotherapy, radiation therapy, and targeted therapy, most, if not all, of which impair sensitivity or confer resistance to these treatments. Therefore, these pathways have long been recognized as among the most important targets for cancer treatment. Although few successes in the development of small-molecule inhibitors targeting cell cycle regulatory or related pathways have been achieved, recent progress in the use of CDK4 and CDK6 inhibitors for treating breast cancer has reignited the enthusiasm for the research and development of agents targeting various CDKs and DDR signaling components (e.g., p53, Chk1, Wec1, ATM, ATR, Aurora kinases, and Polo-like kinases). Moreover, an increasing understanding of the roles of CDKs (CDK7–9, CDK12, and, probably, CDK13) in the transcription-regulatory machinery has evoked tremendous interest in novel targeted therapy paradigms, including the ongoing development of inhibitors targeting CDK7, CDK9, and BRD4. Certain cancer types (e.g., MYC-driven tumors, including lymphoma and MM with B-cell origin) proposed to be addicted to transcription, also known as transcriptional dependency, would be particularly susceptible to these agents. Although substantial research remains to be conducted, the future of this field appears extremely exciting and promising.

### ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China (Grant Nos. 81471165, 81670189, 81670190, and 81870160) and the Natural Science Foundation of Jilin Province (Grant Nos. 20190201163JC, 20190201042JC, and 20170622011JC).

### REFERENCES

[1] Hydbring P, Malumbres M, Piotr Sicinski P. Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. *Nat Rev Mol Biol* 2016;17:280–292. 2010.

[2] Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copynumber alteration across human cancers. *Nature* 2010;463:889–905.

[3] Otto T, Sicinski P. Cell cycle proteins as promising targets in cancer therapy. *Nat Rev Cancer* 2017;17:85–115.

[4] Lim S, Kaldis P. Cdks, cyclins and CKIs: roles beyond cell cycle regulation. *Development* 2013;140:3079–3093.

[5] Chlister L, Hoenack C, Calis JJA, et al. Cyclin F regulates cell cycle progression in yeast. *Nat Rev Mol Biol* 1994;4:78–85.

[6] Pagano M, Pepperkok R, Verde F, Ansero W, Draisena G. Cyclin A is required at two points in the human cell cycle. *EMBO J* 1992;11:961–971.

[7] Rumsztycz D, Hengst L, Reed SI. Cyclin A-associated kinase activity is rate limiting for entrance into S phase and is negatively regulated in G1 by p27Kip1. *Mol Cell Biol* 1995;15(8):4347–4352.

[8] Yang R, Nakamaki T, Libbert M, et al. Cyclin A1 expression in leukemia and normal hematopoietic cells. *Blood* 1999;93:2067–2074.

[9] Krug U, Yasmeen A, Beger C, et al. Cyclin A1 regulates WT1 expression in acute myeloid leukemia cells. *Int J Oncol* 2009;34(1):129–136.

[10] Ekberg J, Holm C, Jalili S, et al. Expression of cyclin A1 and cell cycle proteins in hematopoietic cells and acute myeloid leukemia and links to patient outcome. *Eur J Haematol* 2005;75:106–115.

[11] Ochsnerreither S, Majer R, Schmitz T, et al. Cyclin A1 represents a new immunogenic targetable antigen expressed in acute myeloid leukemia stem cells with characteristics of a cancer-testis antigen. *Blood* 2012;119:5492–5501.

[12] Rape M, Kirschner MW. Autonomous regulation of the anaphase-promoting complex promotes mitosis to S-phase entry. *Nature* 2004;432:588–595.

[13] Wang Q, Moyret-Lalle C, Couzon F, et al. Alterations of anaphase-promoting complex genes in human colon cancer cells. *Oncogene* 2003;22:1486–1490.

[14] Nagaraj AB, Kovalenko O, Averal R, et al. Mitotic exit dysfunction through the deregulation of APC/C characterizes cispatin-resistant state in epithelial ovarian cancer. *Clin Cancer Res* 2018;24:4888–4861.

[15] McGowan CH, Russell P, Reed SI. Periodic biosynthesis of the human M-phase promoting factor catalytic subunit p34 during the cell cycle. *Mol Cell Biol* 1990;10:3847–3851.

[16] Gallant P, Nigg EA. Cyclin B2 undergoes cell cycle-dependent nuclear translocation and, when expressed as a non-destructible mutant, causes mitotic arrest in HeLa cells. *J Cell Biol* 1992;117:213–224.

[17] Draviam VM, Orrechea S, Lowe M, Pardi R, Pines J. The localization of human cyclins B1 and B2 determines CDK1 substrate specificity and neither enzyme requires MEK to disassemble the Golgi apparatus. *J Cell Biol* 2001;152:945–958.

www.blood-science.org
[18] Bentley AM, Normand G, Hoyt J, King RW. Distinct sequence elements of cyclin D1 promote localization to chromatin, centrosomes, and kinetochores during mitosis. Mol Biol Cell 2007;18:4847–4858.

[19] Kumar SK, Rajkumar SV. The multiple myelomas: current concepts in cyrogeneic classification and therapy. Nat Rev Clin Oncol 2016;13:640–649.

[20] Kumar SK, Rajkumar SV, Kyle RA, et al. Multiple myeloma. Nat Rev Dis Primers 2017;3:17046.

[21] Yu Z, Wang L, Wang C, et al. Cyclin D1 induction of Dicer governs mitochondrial bioenergetics for radiation-induced DNA repair. Cell Rep 2013;4:4756–4766.

[22] Dai Y, Fan M, Candas D, et al. CDK1 enhances mitochondrial bioenergetics for radiation-induced DNA repair. Cell Rep 2013;15:2056–2063.

[23] Strohmaier H, Spruch CH, Kaiser P, Won KA, et al. Inactivation of hCDC4 can cause chromosomal instability. Nature 2004;428:77–81.

[24] Hanashiro K, Kanai M, Geng Y, Sicinska P, Fukasawa K. Roles of cyclins A and E in induction of centrosome amplification in p53-compromised cells. Oncogene 2007;26:3288–3302.

[25] Chen S, Pei XY, et al. Interruption of the Ras/MEK/ERK signaling cascade enhances Chk1 inhibitor-induced DNA damage in vitro and in vivo in human multiple myeloma cells. Blood 2008;112:2439–2449.

[26] Dai Y, Chen S, Shah R, et al. Disruption of Src function potentiates Chk1 inhibitor-induced apoptosis in human multiple myeloma cells in vitro and in vivo. Blood 2011;117:1947–1957.

[27] Zhao L, Zhang Y, Chen S, et al. A regimen combining the Wee1 inhibitor AZD1775 with HDAC inhibitors targets human acute myeloid leukemia cells harboring various genetic mutations. Leukemia 2015;29:807–818.

[28] Zhang Y, Chen S, Pei XY, et al. Blockade of histone deacetylase inhibitor-induced G1 arrest and maturation in U937 human myeloid leukemia cells. Cell Cycle 2003;2(5):467–472.

[29] Dai Y, Rahmani M, Grant S. An intact NF-kappaB pathway is required for histone deacetylase inhibitor-induced GI arrest and maturation in U937 human myeloid leukemia cells. Cell Cycle 2013;12(5):847–853.

[30] Dai Y, Rahmani M, Grant S. Blockade of histone deacetylase inhibitor-induced RelA/p65 acetylation and NF-kappaB activation potentiates apoptosis in leukemia cells through a process mediated by oxidative stress, XIAP downregulation, and c-Jun N-terminal kinase 1 activation. Mol Cell Biol 2005;25:3429–3444.
Poss ZC, Ebmeier CC, Taatjes DJ. The Mediator complex and the transcriptional dependencies in cancer.

Cayrol F, Praditsuktavorn P, Fernando TM, et al. THZ1 targeting CKD7 suppresses STAT transcriptional activity and sensitizes T-cell lymphomas to BCL2 inhibitors. Nat Commun 2017;8(14290):1–11.

Wang Y, Zhang T, Kwiatkowski N, et al. CDK7-dependent transcriptional addiction in triple-negative breast cancer. Cell 2015;161:174–186.

Nagaraja S, Vitanza NA, Woo P, et al. Transcriptional addiction in triple-negative breast cancer. Cancer Cell 2014;35:613–627.

Belakavadi M, Fondell JD. Cyclin-dependent kinase 8 positively controls EBNA-positive kinases (CDKs) through phosphorylation of Thr161 and its homologues. EMBO J 1993;12:3111–3121.

Audetat KA, Galbraith MD, Odell AT, et al. A kinase-independent role for CDK9/P-TEFb: more than 20 years of advances since the discovery of the P-TEFb RNA polymerase II carboxyl-terminal domain (CtD) and the CDK9 cofactor 7PAK. J Biol Chem 2013;288:21173–21181.

Husson H, Carideo EG, Neuberg D, et al. Gene expression profiling of follicular lymphoma and normal germinal center B cells using cDNA arrays. Blood 2002;99:282–289.

Iorns E, Turner NC, Elliott R, et al. Identification of CDK10 as an important determinant of resistance to endocrine therapy for breast cancer. Cancer Cell 2008;13:91–104.

Wilkinson S, Croft DR, O’Prey J, et al. The cyclin-dependent kinase PITSLRE/CDK11 is required for successful autophagy. Autophagy 2011;7:1295–1301.

Wilkinson S, Croft DR, O’Prey J, et al. The cyclin-dependent kinase PITSLRE/CDK11 is required for successful autophagy. Autophagy 2011;7:1295–1301.

Petrycki C, Savoian M, Montembault E, Glover DM, Prigent C, Giet R. The PITSLRE/CDK11p58 protein kinase promotes centrosome maturation and bipolar spindle formation. EMBO Rep 2006;7:418–424.

Hu D, Valentine M, Kidd VJ, Lahn JM. CDK11p58 is required for the maintenance of sister chromatid cohesion. J Cell Sci 2007;120:2424–2434.

Hu D, Mayeda A, Trembley JH, Lahn JM, Kidd VJ. CDK11 complexes promote pre-mRNA splicing. J Biol Chem 2003;278:8623–8629.

Wilkinson S, Croft DR, O’Prey J, et al. The cyclin-dependent kinase PITSLRE/CDK11 is required for successful autophagy. Autophagy 2011;7:1295–1301.

Shi J, Feng Y, Goulet AC, et al. The p34cdc2-related cyclin-dependent kinase 11 interacts with the p47 subunit of eukaryotic initiation factor 3 during apoptosis. J Biol Chem 2003;278:5062–5071.

Chen S, Zhou L, Zhang Y, et al. Targeting SQSTM1/p62 induces cargo clearance of multiple subunits of human P-TEFb. Genes Dev 1998;12:755–762.

Burger K, Muhl B, Rohrmoser M, et al. Cyclin-dependent kinase 9 links RNA polymerase II transcription to processing of ribosomal RNA. J Biol Chem 2013;288:21173–21183.

Liang K, Woodfin AR, Slaughter BD, et al. Mitotic transcriptional activation: clearance of actively engaged Pol II via transcriptional elongation in mitosis. Mol Cell 2015;60:435–445.

Chen S, Yuan J, Orlowski R, et al. Positive transcription elongation factor b (P-TEFb) is a therapeutic target in human multiple myeloma. Oncotarget 2017;8:18397–18407.

Franco LC, Morales F, Both S, Gozard C. CDK9: a key player in cancer and other diseases. J Cell Biochem 2017;119:1273–1284.

Wei P, Garber ME, Fang SM, Fischer WH, Jones KA. A novel CDK9-associated C-type cyclin interacts directly with HIV-1 Tat and mediates its high-affinity, loop-specific binding to TAR RNA. Cell 1998;92:451–462.

Chen S, Dai Y, Harada H, Dena P, Grant S. Med-1 down-regulation potentiates ABT-737 lethality by cooperatively inducing Bak activation and Bax translocation. Cancer Res 2007;67:782–791.