Genes & Cancer
3(11-12) 649–657

DOI: 10.1177/1947601913479022
http://ganc.sagepub.com
SAGE

Cyclins and Cell Cycle Control in Cancer and Disease

Mathew C. Casimiro, Marco Crosariol, Emanuele Loro, Zhiping Li, and Richard G. Pestell

Abstract

Cyclin D1 overexpression is found in more than 50% of human breast cancers and causes mammary cancer in transgenic mice. Dysregulation of cyclin D1 gene expression or function contributes to the loss of normal cell cycle control during tumorigenesis. Recent studies have demonstrated that cyclin D1 conducts additional specific functions to regulate gene expression in the context of local chromatin, promote cellular migration, and promote chromosomal instability. It is anticipated that these additional functions contribute to the pathology associated with dysregulated cyclin D1 abundance. This article discusses evidence that examines the functional roles that cyclin D1 may play in cancer with an emphasis on other cyclin family members that also may contribute to cancer and disease in a similar fashion.

Keywords: cyclins, cyclin D1, migration, CIN, stem cells

Introduction

The cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases controlling progression through the cell cycle.[1] The regulatory subunits of the CDKs, known as cyclins, form complexes with their catalytic partner to function as checkpoint kinases of specific proteins that regulate progression through the cell cycle. The cyclin-CDK complexes govern a linear progression of events that lead cells from a resting state (G_0), growth phase (G_1), through DNA replication (S), and finally to cell division (M). Abnormalities that occur in any of the phases initiate a signal that triggers a cell cycle arrest until the issue is resolved. There are some 11 cyclins found in human cells, many having subfamily members (e.g., D-type cyclin D1, D2, and D3). Cyclins partner with associated CDKs and assembly factors to affect their canonical roles in cell cycle checkpoint regulation. Several cyclins exhibit noncanonical roles that may be kinase independent. This review is focused on new and emerging roles for cyclin D1 and includes other cyclins that function in a similar manner.

Cyclin Functions in Cell Migration

Cyclin D1 plays an important role in cell cycle progression through the association with CDK4 and CDK6, which phosphorylate and inactivate the retinoblastoma protein pRb, leading to the expression of a subset of proliferation-associated E2F target genes.[2,3] In addition to this canonical pRB-dependent effect in cell cycle progression, cyclin D1 functions in cellular migration, DNA damage response and repair, and chromosome stability.[4-8] Metastasis is a major cause of death in cancer patients. Cellular migration is essential for tumor metastasis. Macrophages, fibroblasts, and epithelial cells have enhanced adhesion and reduced migration after depletion of cyclin D1.[9-11] The cyclin $D1^{K112E}$ mutant that fails to activate CDK4 or CDK6 does not increase cell migration as the wild-type cyclin D1 protein. This suggests that cyclin D1 induction of cell migration is a CDK-dependent function.[10,11] Some CDK4/CDK6 substrates have roles in cell adhesion, cell migration, and cytoskeletal remodeling. Phosphorylation of these substrates such as filamin A[12] and Ral GEF Rgl2[13] by cyclin D1–CDK4 contributes to enhanced cell detachment and motility.

Cyclin D1 binding of $p27^{Kip1}$ contributes to cellular migration. $p27^{Kip1}$ has effects on cell migration in either a Rac- or a RhoA-dependent manner through inhibition of RhoA.[14] Introduction of $p27^{Kip1}$ rescued the cellular migratory defect of cyclin $D1^{-/-}$ cells. Cyclin D1 cannot induce migration following $p27^{Kip1}$ knockdown. This suggests that cyclin D1 association with $p27^{Kip1}$ may contribute to cyclin D1 functions in cell migration independent of CDK4/CDK6.[11] In addition, cyclin D1 promotes cellular migration by firstly binding $p27^{Kip1}$ and thereby inhibiting Rho GTPase activity and secondly by transcriptional upregulation of ROCKII and thrombospondin (TSP-1). The frequent amplification and overexpression of cyclin D1 in cancer cells[15,16] and its upregulation by mitogenic growth factors, cytokines, ECM proteins, and other genes,[17] which are important in malignant development, suggest that cyclin D1 may have a central role in mediating the invasion and metastasis of cancer cells by controlling Rho/ROCK signaling and expression of TSP-1.[10]

Alternate noncanonical roles for cyclins continue to be discovered; they have important implications for their role in cancer and metastasis. The traditional role for cyclin A2 is in the somatic cell cycle at 2 critical points, when it

Thomas Jefferson University, Philadelphia, PA, USA

Corresponding Author:
Richard G. Pestell, Department of Cancer Biology, The Kimmel Cancer Center, Thomas Jefferson University, 233 South 10th Street, Suite 1050, Philadelphia, PA 19107, USA
(Email: Richard.pestell@jefferson.edu).

activates CDK2 at the onset of DNA replication and when it activates CDK1 during G_2-M transition. During S phase, cyclin A2 is mostly located in the nucleus, where it regulates the initiation and progression of DNA synthesis.[18] Cyclin A2 localizes to the centrosomes in the cytoplasm, where it binds to the poles of mitotic spindles in a CDK-independent manner. In recent studies, cyclin A2 regulated cytoskeletal organization and cell migration independently of its binding to CDK.[19] Depletion of cyclin A2 causes a change in the distribution of actin filaments and an increase in cell migration. Cyclin A2 interacts with, and activates, RhoA, an actin regulator, which in turn negatively regulates migration. In addition, metastatic cancer cells show less cyclin A2 expression than nonspreading tumor cells.[19]

Cyclins in the Regulation of Transcription

As well as having defined roles in cell cycle progression, many cyclins also regulate gene transcription and mRNA processing. Over the last 20 years, a large body of work has implicated cyclin D1 in transcriptional regulation.[20] Cyclin D1 physically associates with more than 30 other transcription factors[20] and regulates the transcriptional activity of estrogen receptor and androgen receptor.[21-23] The histone acetyltransferases P/CAF, p300, and AlB1 bind to cyclin D1.[23,24] Chromatin immunoprecipitation (ChIP) demonstrated cyclin D1 association within target gene promoters, correlated with deacetylation of histone (H3), in particular at H3 lysine 9. Deacetylation of H3 Lys9 was restored upon the reintroduction of cyclin D1, with concomitant recruitment of HDAC1/HDAC3.[17] Thus, cyclin D1 is recruited in the context of local chromatin to specific target genes.[25-27] Cyclin D1 recruitment to genomic DNA was also associated with the shuttling of the histone acetyltransferase p300/CBP to regulate genes governing DNA damage repair signaling.[26] Cyclin D1 was shown to regulate the activity of p300 in a kinase-independent manner. As p300 is regarded as a transcriptional co-integrator, cyclin D1 was proposed as a regulator of gene transcription through co-occupancy with p300 at target DNA binding sites.[26]

Protein-coding genes are transcribed by the transcriptional machinery, a multicomplex protein composed of transcription factors (TFIIB, -D, -E, -F, and -H), the Mediator complex, and RNA polymerase II (RNAPII).[28] The Mediator complex is conserved in eukaryotes and bridges the gap between transcription factors and RNAPII.[29,30] Mediator is required for the transcription of all yeast RNAPII genes.[31] Several cyclins are involved in the phosphorylation of the largest subunit of RNAPII to regulate transcription: cyclin C–CDK8, cyclin H–CDK7, cyclin T–CDK9, and cyclin K–CDK12 or CDK13. Phosphorylation of RNAPII occurs in the heptapeptide ($YS_2PTS_5PS_7$) repeats, referred to as the carboxy terminal domain (CTD).[32] A series of phosphorylation events at S_2, S_5, and S_7 of the CTD affects the transcriptional cycle from initiation to elongation and termination.[33,34] Cyclin C–CDK8 associates with Mediator proteins Med12 and Med13 to form a subcomplex that interacts with the core Mediator complex to repress activated transcription and does so through phosphorylating the RNAPII CTD and the cyclin H subunit of TFIIH.

The cyclin H–CDK7–Mat1 (CDK-activating kinase [CAK]) complex binds TFIIH and is the principal S_5 kinase that eases promoter clearance and enables the transition to transcription initiation, hence providing a direct link between the cell cycle machinery and transcription regulation.[35-39] The cyclin H–CDK7–Mat1 complex also interacts directly with transcription factors to regulate their function. Using mouse embryonic fibroblasts (MEFs) and 3T3-L1 cells, phosphorylation of PPARγ by CDK7 blocks lipogenesis.[40]

In humans, cyclin T (T1, T2, and T2b) and CDK9 associate to form a complex termed PTEFb, which phosphorylates CTD S_2 of RNAPII to regulate productive transcription elongation.[41-43] Like cyclin H, the level of cyclin T does not oscillate during the cell cycle, suggesting that these cyclins perform necessary functions that are not cell cycle stage specific.[44-47] Cyclin T1 expression is regulated during T-cell activation.[48-51] Cyclin T–CDK9 are important regulators of several cellular processes including lymphoid development.[52] Overexpression of cyclin T is sufficient to induce foci and colony formation in NIH 3T3 cells *in vitro* and induces tumor growth in Nu/Nu mice *in vivo*.[52] Cyclin T likely contributes to lymphomas derived from B- and T-cell lineages possibly through the inhibition of apoptosis.

Cyclin K binds CDK12 and CDK13, likely in 2 separate complexes to regulate the phosphorylation of S_2 and S_5 of the RNAPII CTD.[53,54] In human cells, depletion of CDK12 results in a marked reduction of CTD S_2 phosphorylation. The net effect on gene expression is a downregulation in a modest number of genes; however, these genes have key roles in the DNA damage response (DDR): FANCI, FANCD2, ATR, and BRCA1.[53] Consistent with the role in regulating the DDR, depletion of cyclin K–CDK12 results in sensitivity to DNA damaging agents and increased γ-H2AX foci.[53] Cyclin L (L1 and L2) is closely related to cyclin K, cyclin T1, and cyclin T2. Cyclin L binds CDK11 and interacts with the family of SR splicing proteins to regulate splicing.[55-57] Cyclin L is a candidate oncogene in head and neck cancer.[58]

Cyclins in the Regulation of Stem Cells

Considerable interest has been given to the hypothesis that stem cells are a central and critical determinant in cancer initiation, maintenance, and recurrence following treatment. The last several years have seen this hypothesis gain in popularity due to a growing body of evidence implicating breast cancer stem cells (BCSCs) as responsible for the origin and maintenance of tumors.[59,60] The

model proposes that due to the increased longevity of stem cells, they have the propensity to accumulate genetic lesions that could transform the stem cell from a highly controlled and regulated cell to a deregulated abnormal BCSC. The next section will highlight roles for cyclins in stem cells.

Mice lacking cyclin D1 are viable and show deficiencies that are restricted only to a limited set of tissues. Cyclin D1–null animals have hypocellular retinas due to abnormalities in retinal progenitor cell proliferation and retinal cell death.[61-63] The abnormality is predicted to be caused by a protracted cell cycle in retinal progenitor cells and early cell cycle exit.[64] Cyclin D1–null animals also display defects in mammary gland development; cyclin D1–null females are defective in lobuloalveolar development during pregnancy and cannot lactate.[61,62] Cyclin D1–null mice are resistant to breast cancer induced by Neu and Ras oncogenes. However, animals that are lacking cyclin D1 remain fully sensitive to other oncogenic pathways of the mammary epithelium, driven, for example, by c-Myc or Wnt-1.[65-67] Thus, a cyclin D1–targeted therapy could be highly effective in the treatment of human breast cancers in which the primary driver is the Ras oncogenic pathway. The requirement of cyclin D1 in normal mammary gland development appears to be kinase independent.[68] *Cyclin D1*^{K112E} knockin to the cyclin D1 allele rescued the female mammary gland defect; however, the knockin animals were still resistant to ErbB2-induced tumorigenesis.[69] To explain this puzzling discrepancy, the Hinds laboratory conducted a systematic analysis of the progenitor cell pools in the mammary gland that are dependent on cyclin D1.[68] There are 3 fundamental epithelial cell types in the mammary tissue: luminal, myoepithelial, and alveolar cell types that arise during pregnancy and undergo cell death following the cessation of lactation. All 3 cell types are thought to arise from precursor progenitor cells with self-renewal properties. One type of stem/progenitor cell can be identified with cell surface markers CD24^{med}/CD29^{HI} or CD24^{+}/CD49f^{HI}; a second type is reported to be able to establish a fully functional mammary gland upon transplantation (parity-identified mammary cells: PI-MEC).[70-75] An analysis on the cyclin D1$^{KE/KE}$ mutant confirmed that the resistance to ErbB2-driven tumorigenesis is linked to near total absence of the PI mammary cells, making those progenitor cells the likely target for ErbB2-induced tumorigenesis. Cyclin D1 kinase activity is therefore required for mammary progenitor cells' self-renewal and activity. Recently, acute, conditional ablation of cyclin D1 using a floxed model demonstrated the requirement for cyclin D1 in tumor maintenance.[76] In an MMTV-ErbB2 mammary carcinoma model, deletion of cyclin D1 resulted in reduced tumor cell proliferation and increased cellular senescence, suggesting that the continued presence of cyclin D1 is required to maintain tumor growth in ErbB2-induced mammary carcinomas.

Cyclins appear to have specific and nonredundant roles in stem cell function. Cyclin C was originally cloned from a screen in *Saccharomyces cerevisiae* conducted to identify factors that could rescue G_1 cyclin deficiency.[77,78] Subsequently, cyclin C has been shown to promote the progression from G_0 quiescence to G_1 and does so in part by binding CDK3 to phosphorylate pRB.[79] Recently, an interesting role for cyclin C has been uncovered in the inhibition of hematopoietic stem progenitor cell (HSPC) quiescence.[80] Cyclin C expression was induced upon cytokine activation in HSPCs from human cord blood. siRNA to cyclin C increased the quiescent HSPC population, increased the long-term colony-forming ability, and increased the engraftment capacity.

Cyclin A overexpression correlates with poor prognosis in breast cancer, contributes to prostate cancer invasion and metastasis, and may contribute to colorectal carcinogenesis.[81-83] Cyclin A levels increase at S-phase onset. Cyclin A binds to the partners CDK1 and CDK2 and phosphorylates targets that regulate DNA replication (e.g., MCM7).[84,85] The cyclin A–CDK complex remains high through mitosis, where it functions to initiate chromosomal condensation and nuclear membrane dissolution.[86-88] Cyclin A is redundant in fibroblast cell proliferation but is essential for embryonic and hematopoietic stem cells.[89]

Elevated cyclin H is associated with very high-risk gastrointestinal stromal tumors, and reduced or absent cyclin H expression correlates with lower proliferation in B-cell lymphoma.[90,91] The transcriptional regulation elicited by the CAK complex (cyclin H–CDK7–Mat1) impacts embryonic stem (ES) cell differentiation. The complex activates CDK1, CDK2, CDK4, and CDK6 through phosphorylation of the T-loop.[92-94] Loss of cyclin H function in ES cells induces the differentiation of ES cells and expansion defects of the inner cellular mass in blastocysts.[95] Cyclin H represses ES differentiation possibly through phosphorylation of the negative elongation factor Spt5, an event required for the repressive effect of Spt5 on differentiation.[95] CDK7 phosphorylates Spt5 *in vitro*, and downregulation of Spt5 leads to the same induction of the differentiation program elicited by the loss of cyclin H.[95,96] This is likely transcriptionally regulated since Spt5 regulates RNA processing and transcriptional pausing at sites proximal to the promoter.

Cyclins in DNA Damage and Genomic Instability

Genomic DNA is continually subject to insults by damaging ionizing radiation, chemical carcinogens, and reactive oxygen species generated by cellular metabolism.[97,98] In addition, cells are sensitized to errors from DNA replication during S phase. In order to maintain genomic integrity, the cell has several preventative mechanisms relayed through the DDR pathway. Defects in the DDR can lead to genomic instability and cancer. Several cyclin-CDK complexes are implicated in the DDR.[99]

Cyclin D1 abundance was shown to determine the DDR, assessed using

γ-H2AX and a comet assay.[6] Cyclin D1 was shown to be recruited to the sites of DNA damage, requiring the carboxy terminal exon 5, and to bind directly to RAD51 (a recombinase that drives the homologous recombination process).[6] In a subsequent proteomic screening of cyclin D1, interacting proteins revealed a pool of DNA repair proteins; among them, the most notable was also RAD51. Irradiation of cells stimulated cyclin D1 binding to RAD51 and aided RAD51 recruitment to DNA damage foci in a process that was BRCA2 dependent.[6] This finding was consistent with a prior finding that cyclin D1 bound BRCA1.[100]

Reduction of cyclin D1 levels in different types of human cancer cells (mantle cell lymphoma, breast cancer, squamous cell carcinoma, and colorectal cancer) led to the impaired recruitment of RAD51 to the damaged DNA, thus increasing the sensitivity of the cells to radiation. MEFs lacking cyclin D1 showed increased sensitivity to ionizing radiation, which is rescued upon the reintroduction of cyclin D1. This proved to be a kinase-dependent process since the expression of the cyclin $D1^{K112E}$ point mutant and the use of specific CDK4 and CDK6 inhibitors had no effect on the radiation sensitivity. While radiation induces comparable levels of DNA damage in both cyclin D1 control and cyclin D1–depleted cells, the amount of unrepaired DNA after radiation is higher in the cyclin D1–depleted cells.

Cyclin F is unique among the cyclins in that it contains both a cyclin and F-box domain. It does not bind or activate a known CDK and like most cyclins oscillates through the cell cycle. F-box proteins are components of SCF complexes (SKP1–Cullin–F-box); hence, cyclin F acts as a phosphorylation-dependent ubiquitin ligase.[101-103] Cyclin F localizes to centrosomes and the nucleus.[104] In the cytoplasmic compartment, cyclin F targets centriolar coiled-coil proteins of 110 kDa (CP110) for degradation. CP110 promotes centrosome duplication; therefore, cyclin F inhibits genomic instability by ensuring that a single centrosome duplication event occurs once per cell cycle.[105,106] Additionally, cyclin F degrades nucleolar and spindle-associated protein 1 (NuSAP1) to regulate the correct mitotic spindle architecture.[107] A nuclear role for cyclin F relates to its regulation of RRM2 (ribonucleotide reductase family member 2).[106] RRM2 catalyzes the conversion of ribonucleotides to dNTPs necessary for replication and DNA repair. Failure of cyclin F to degrade RRM2 leads to imbalances in the dNTP pool and increased frequency of genomic mutations. Overexpression of RRM2 leads to lung cancer in mice, and elevated RRM2 in ovarian, colorectal, liver, and breast cancers is associated with poor prognosis.[108-112]

Downregulation of the cyclin G2 transcript has been linked to various cancers including the thyroid and oral cavity.[113,114] Cyclin G1 and cyclin G2 share 53% amino acid identity; however, cyclin G1 lacks the protein-destabilizing PEST domain.[115] The cyclin G1 gene has a p53 binding site and is induced in a p53-dependent manner.[116] The cyclin G2 gene is a transcriptional target of the p53 homolog, p63.[117] Both cyclin G1 and G2 are induced following DNA damage and maintain p53-dependent cell cycle arrest.[118,119] Both cyclin G1 and cyclin G2 enhance G_2-M checkpoint regulation. In the case of cyclin G1, it may promote or inhibit cell arrest or apoptosis; in the case of cyclin G2, cell cycle arrest is thought to occur through the inhibition of cyclin B1–Cdc2.[120-124]

Cyclins in the Regulation of Chromosomal Instability

Chromosomal instability (CIN) is a prevalent feature widely shared by cells from solid tumors and is considered a hallmark of cancer.[125,126] CIN can be caused by multiple mechanisms and results in an abnormal chromosomal complement. Whether CIN is a cause or a consequence of cancer is a highly debated topic; however, CIN does occur early in cancer development and is associated with poor prognosis.[127] Cyclin D1 is overexpressed in the majority of human breast tumors. Several lines of evidence suggest that, although cyclin D1 is required for tumorigenesis, cyclin D1 conveys a number of cyclin D1 kinase-independent functions. Further, several lines of evidence suggest that the oncogenic function of cyclin D1 may not correlate with its ability to phosphorylate pRB. In this regard, cyclin D1 overexpression does not correlate with pRB phosphorylation or the proliferative marker Ki67 in human breast cancer.[128-132]

Based on a significant number of publications from our laboratory, and others, we had proposed an alternative mechanism by which cyclin D1 may drive tumorigenesis by inducing CIN.[133] Early studies showed that cyclin D1 did not induce aneuploidy in rat embryonic fibroblasts.[134] A subsequent study on mouse primary hepatocytes showed that transiently expressing cyclin D1 induced abnormal mitosis, accumulation of supernumerary centrosomes, defects in the mitotic spindle, and aneuploidy.[135] Copy number changes in cyclin D1 have been proposed as a biomarker for CIN in bladder cancer.[135] Cyclin D1 gene amplification was only seen in CIN-positive bladder cancer samples and correlated with tumor grade. Our studies, using ChIP of cyclin D1 followed by sequencing (ChIP-Seq), demonstrated that gene regulatory elements bound by cyclin D1 are enriched for genes that govern CIN.[8] Using mammary epithelial-targeted transgenics, the CIN genetic signature[136] was enriched through cyclin D1 overexpression and reduced through the induction of mammary gland–targeted, inducible cyclin D1 antisense.[8] FACS and spectral karyotyping demonstrated that chromosomal duplication was induced by cyclin D1 within 5 cellular divisions. Furthermore, in our studies of 2,254 patients, we showed that cyclin D1 expression correlates with the induction of CIN in luminal B breast cancer.[8] These studies suggest that cyclin D1

promotes CIN as a direct consequence of inducing expression of the mitotic transcriptional program regulated by cyclin D1.

Overexpression of cyclin B1 has been reported in various human tumors, such as colorectal cancer, non–small cell lung cancer, and head and neck squamous cell carcinoma, and its upregulation is closely associated with poor prognosis in breast cancer.[137-141] In addition, overexpression of cyclin B1 is related to aneuploidy and high proliferation of human mammary carcinomas.[141] In yeast, overexpression of cyclin B1 and cyclin B2 leads to CIN.[142] In eukaryotes, the maturation/M phase–promoting factor (MPF) regulates entry into M phase.[143,144] The MPF complex is composed of cyclin B1 and CDK1 and is sufficient to induce meiotic G_2-M–phase transition in immature oocytes and mitosis of somatic cells.[145-148] Cyclin B1 mediates chromosome condensation and nuclear envelope dissolution; cyclin B2 mediates Golgi disassembly. The major inhibitor of MPF is protein phosphatase 2A/B55 (PP2A-B55).[149,150] MPF suppresses PP2A-B55–dependent inhibition through the Greatwall kinase (Gwl).[150,151] Recently, the definition of MPF has been revised to include Gwl as an essential component, at least in frog and starfish oocytes and possibly somatic cells.[152] Depletion of Gwl results in G_2 arrest in *Drosophila* and human somatic cells, and Gwl is required for MPF activity in the oocyte cytoplasm.[152]

The abundance of the cyclin E transcript and protein is increased in carcinomas of the lung, gastrointestinal tract, and breast in addition to lymphomas and leukemias.[153-159] Increased cyclin E expression occurs in 18% to 22% of breast cancers and has been used as a prognostic marker.[160] A low molecular weight hyperactive version of cyclin E exists in breast cancer and is associated with very poor prognosis.[153,161,162] Cyclin E was thought to be an essential cell cycle regulatory protein involved in promoting the G_1-S–phase transition.[163] Cyclin E binds its catalytic subunit CDK2 and phosphorylates Rb, in a processive event following cyclin D1–CDK4/6, to release E2F transcription factors that regulate genes involved in S-phase progression. However, a cyclin E knockout model demonstrated that mitotic cell division does not require cyclin E1 and E2, challenging the key requirement for cyclin E in S-phase progression. In addition, development in CDK2-null mice was normal, and null fibroblasts demonstrated a normal cell cycle profile. However, these models do underscore several requirements for cyclin E. Endoreplication of placental trophoblast giant cells and megakaryocytes is severely impaired in cyclin E–null mice.[164,165] In addition, null MEFs are resistant to oncogenic transformation, fail to progress from quiescence into S phase, and showed a defect in MCM loading onto replication forks. The absence of these key defects in the CDK2-null mouse may be due to the redundancy offered by cyclin E–CDK1 complexes. Interestingly, the G_0-S phase and replication licensing functions of cyclin E were found to be kinase independent. Aberrant cyclin E expression may be caused by gene amplification, defects in the p16–Rb–cyclin D1 signaling axis, or defects in the ubiquitin-mediated degradation pathway.[166-168] Increased cyclin E abundance may be a consequence of increased proliferation rates since it often correlates with proliferation indices.[169] However, it may itself act as a molecular driver of transformation and do so through CIN. Induction of cyclin E in rat fibroblasts or human epithelial cells caused aneuploidy.[134] In primary human cells, deregulated cyclin E expression and defective p53 led to increased ploidy and genetic instability. In a lung mouse model, high expression of a degradation-resistant cyclin E targeted to the lung frequently caused dysplasia, multiple lung adenocarcinomas, and tumors exhibiting CIN.[170]

Summary

The molecular interplay between the cell cycle, cyclins, and cell function is far from being fully understood. Conceptual advances in the field continue to uncover novel and interesting roles for cyclins in cellular processes that contribute to cancer and disease. In the case of cyclin D1, traditionalists place the protein solely in the RB-E2F signaling axis as a driver of proliferation. However, new functions are emerging that would directly place cyclin D1 as a contributor to cellular transformation and would better explain cyclin D1's role in oncogenesis, particularly in the fields of stem cell regulation, DDR, and chromosomal stability (Figure 1). Uncovering a breast stem cell population that is dependent on cyclin D1 fits well with previous data that suggest that cyclin D1 is a key inhibitor of differentiation. A contribution of cyclin D1 to enhance DNA repair may protect transformed cells from excessive genomic instability and may help protect breast cancer cells when challenged with DNA-damaging therapies. Cyclin D1 promoting whole-genome chromosome instability is a new discovery. This role for cyclin D1 may be particularly important in the

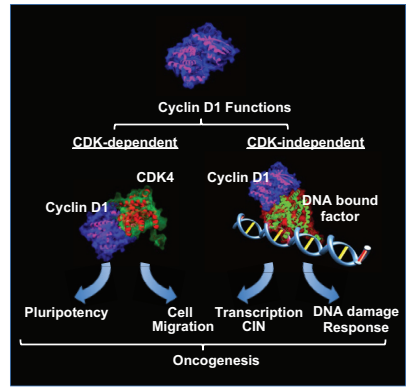

Figure 1. Cyclin D1 forms a holoenzyme through binding CDK4 to elicit kinase-dependent functions that regulate stem cell self-renewal and promote cellular migration. Cyclin D1 functions in a kinase-independent manner to enhance DNA repair and also binds DNA in the context of chromatin to regulate the expression of genes governing CIN. These noncanonical kinase-dependent and -independent functions may contribute to the oncogenic potential of cyclin D1.

15% of breast cancers with clonally selected cyclin D1 amplification in which cyclin D1 may be an early driver of oncogenesis through CIN. Future studies should focus on deciphering the key events that cyclins regulate, which instigate and perpetuate cellular transformation.

Declaration of Conflicting Interests

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

Funding

The author(s) received the following financial support for the research, authorship, and/or publication of this article: This project was funded in part by a grant from the Pennsylvania Department of Health (R.G.P.) and the Breast Cancer Research Foundation (R.G.P.). This project was also funded in part from the Dr. Ralph and Marian C. Falk Medical Research Trust (R.G.P.). The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

References

1. Malumbres M, Barbacid M. Mammalian cyclin-dependent kinases. Trends Biochem Sci. 2005;30:630-41.
2. Musgrove EA, Lee CS, Buckley MF, Sutherland RL. Cyclin D1 induction in breast cancer cells shortens G1 and is sufficient for cells arrested in G1 to complete the cell cycle. Proc Natl Acad Sci U S A. 1994;91:8022-6.
3. Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. Nat Rev Cancer. 2011;11:558-72.
4. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. Cyclin D1: normal and abnormal functions. Endocrinology. 2004;145:5439-47.
5. Li Z, Wang C, Prendergast GC, Pestell RG. Cyclin D1 functions in cell migration. Cell Cycle. 2006;5:2440-2.
6. Li Z, Jiao X, Wang C, *et al*. Alternative cyclin D1 splice forms differentially regulate the DNA damage response. Cancer Res. 2010;70:8802-11.
7. Jirawatnotai S, Hu Y, Michowski W, *et al*. A function for cyclin D1 in DNA repair uncovered by protein interactome analyses in human cancers. Nature. 2011;474:230-4.
8. Casimiro MC, Crosariol M, Loro E, *et al*. ChIP sequencing of cyclin D1 reveals a transcriptional role in chromosomal instability in mice. J Clin Invest. 2012;122:833-43.
9. Neumeister P, Pixley FJ, Xiong Y, *et al*. Cyclin D1 governs adhesion and motility of macrophages. Mol Biol Cell. 2003;14:2005-15.
10. Li Z, Wang C, Jiao X, *et al*. Cyclin D1 regulates cellular migration through the inhibition of thrombospondin 1 and ROCK signaling. Mol Cell Biol. 2006;26:4240-56.
11. Li Z, Jiao X, Wang C, *et al*. Cyclin D1 induction of cellular migration requires p27(KIP1). Cancer Res. 2006;66:9986-94.
12. Zhong Z, Yeow WS, Zou C, *et al*. Cyclin D1/cyclin-dependent kinase 4 interacts with filamin A and affects the migration and invasion potential of breast cancer cells. Cancer Res. 2010;70:2105-14.
13. Fernandez RM, Ruiz-Miro M, Dolcet X, Aldea M, Gari E. Cyclin D1 interacts and collaborates with Ral GTPases enhancing cell detachment and motility. Oncogene. 2011;30:1936-46.
14. Besson A, Gurian-West M, Schmidt A, Hall A, Roberts JM. p27Kip1 modulates cell migration through the regulation of RhoA activation. Genes Dev. 2004;18:862-76.
15. Beroukhim R, Mermel CH, Porter D, *et al*. The landscape of somatic copy-number alteration across human cancers. Nature. 2010;463:899-905.
16. Santarius T, Shipley J, Brewer D, Stratton MR, Cooper CS. A census of amplified and overexpressed human cancer genes. Nat Rev Cancer. 2010;10:59-64.
17. Klein EA, Assoian RK. Transcriptional regulation of the cyclin D1 gene at a glance. J Cell Sci. 2008;121:3853-7.
18. Pagano M, Pepperkok R, Verde F, Ansorge W, Draetta G. Cyclin A is required at two points in the human cell cycle. EMBO J. 2992;11:961-71.
19. Arsic N, Bendris N, Peter M, *et al*. A novel function for cyclin A2: control of cell invasion via RhoA signaling. J Cell Biol. 2012;196:147-62.
20. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. Cyclin D1: normal and abnormal functions. Endocrinology. 2004;145:5439-47.
21. Zwijsen RM, Wientjens E, Klompmaker R, van der Sman J, Bernards R, Michalides RJ. CDK-independent activation of estrogen receptor by cyclin D1. Cell. 1997;88:405-15.
22. Knudsen KE, Cavenee WK, Arden KC. D-type cyclins complex with the androgen receptor and inhibit its transcriptional transactivation ability. Cancer Res. 1999;59:2297-301.
23. Reutens AT, Fu M, Wang C, *et al*. Cyclin D1 binds the androgen receptor and regulates hormone-dependent signaling in a p300/CBP-associated factor (P/CAF)-dependent manner. Mol Endocrinol. 2001;15:797-811.
24. Zwijsen RM, Buckle RS, Hijmans EM, Loomans CJ, Bernards R. Ligand-independent recruitment of steroid receptor coactivators to estrogen receptor by cyclin D1. Genes Dev. 1998;12:3488-98.
25. Hulit J, Wang C, Li Z, *et al*. Cyclin D1 genetic heterozygosity regulates colonic epithelial cell differentiation and tumor number in ApcMin mice. Mol Cell Biol. 2004;24:7598-611.
26. Fu M, Wang C, Rao M, *et al*. Cyclin D1 represses p300 transactivation through a cyclin-dependent kinase-independent mechanism. J Biol Chem. 2005;280:29728-42.
27. Bienvenu F, Barre B, Giraud S, Avril S, Coqueret O. Transcriptional regulation by a DNA-associated form of cyclin D1. Mol Biol Cell. 2005;16:1850-8.
28. Sikorski TW, Buratowski S. The basal initiation machinery: beyond the general transcription factors. Curr Opin Cell Biol. 2009;21:344-51.
29. Kornberg RD. Mediator and the mechanism of transcriptional activation. Trends Biochem Sci. 2005;30:235-9.
30. Malik S, Roeder RG. The metazoan Mediator co-activator complex as an integrative hub for transcriptional regulation. Nat Rev Genet. 2010;11:761-72.
31. Holstege FC, Jennings EG, Wyrick JJ, *et al*. Dissecting the regulatory circuitry of a eukaryotic genome. Cell. 1998;95:717-28.
32. Phatnani HP, Greenleaf AL. Phosphorylation and functions of the RNA polymerase II CTD. Genes Dev. 2006;20:2922-36.
33. Chapman RD, Heidemann M, Hintermair C, Eick D. Molecular evolution of the RNA polymerase II CTD. Trends Genet. 2008;24:289-96.
34. Egloff S, Murphy S. Cracking the RNA polymerase II CTD code. Trends Genet. 2008;24:280-8.
35. Yankulov KY, Bentley DL. Regulation of CDK7 substrate specificity by MAT1 and TFIIH. EMBO J. 1997;16:1638-46.
36. Roy R, Adamczewski JP, Seroz T, *et al*. The MO15 cell cycle kinase is associated with the TFIIH transcription-DNA repair factor. Cell. 1994;79:1093-101.
37. Devault A, Martinez AM, Fesquet D, *et al*. MAT1 ('menage a trois') a new RING finger protein subunit stabilizing cyclin H-cdk7 complexes in starfish and Xenopus CAK. EMBO J. 1995;14:5027-36.
38. Shiekhattar R, Mermelstein F, Fisher RP, *et al*. Cdk-activating kinase complex is a component of human transcription factor TFIIH. Nature. 1995;374:283-7.
39. Adamczewski JP, Rossignol M, Tassan JP, Nigg EA, Moncollin V, Egly JM. MAT1, cdk7 and cyclin H form a kinase complex which is UV light-sensitive upon association with TFIIH. EMBO J. 1996;15:1877-84.
40. Helenius K, Yang Y, Alasaari J, Makela TP. Mat1 inhibits peroxisome proliferator-activated receptor gamma-mediated adipocyte differentiation. Mol Cell Biol. 2009;29:315-23.
41. Price DH. P-TEFb, a cyclin-dependent kinase controlling elongation by RNA polymerase II. Mol Cell Biol. 2000;20:2629-34.
42. Peng J, Zhu Y, Milton JT, Price DH. Identification of multiple cyclin subunits of human P-TEFb. Genes Dev. 1998;12:755-62.
43. Gegonne A, Weissman JD, Lu H, *et al*. TFIID component TAF7 functionally interacts with both TFIIH and P-TEFb. Proc Natl Acad Sci U S A. 2008;105:5367-72.
44. Moiola C, De Luca P, Gardner K, Vazquez E, De Siervi A. Cyclin T1 overexpression induces malignant transformation and tumor growth. Cell Cycle. 2010;9:3119-26.
45. Poon RY, Yamashita K, Howell M, Ershler MA, Belyavsky A, Hunt T. Cell cycle regulation of the p34cdc2/p33cdk2-activating kinase p40MO15. J Cell Sci. 1994;107:2789-99.
46. Tassan JP, Schultz SJ, Bartek J, Nigg EA. Cell cycle analysis of the activity, subcellular localization, and subunit composition of human CAK (CDK-activating kinase). J Cell Biol. 1994;127:467-78.
47. Brown AJ, Jones T, Shuttleworth J. Expression and activity of p40MO15, the catalytic subunit of cdk-activating kinase, during Xenopus oogenesis and embryogenesis. Mol Biol Cell. 1994;5:921-32.
48. Garriga J, Peng J, Parreno, Price, DH, Henderson EE, Grana X. Upregulation of cyclin T1/CDK9

complexes during T cell activation. Oncogene. 1998;17:3093-102.
49. Ghose R, Liou LY, Herrmann CH, Rice AP. Induction of TAK (cyclin T1/P-TEFb) in purified resting CD4(+) T lymphocytes by combination of cytokines. J Virol. 2001;75:11336-43.
50. Herrmann CH, Carroll RG, Wei P, Jones KA, Rice AP. Tat-associated kinase, TAK, activity is regulated by distinct mechanisms in peripheral blood lymphocytes and promonocytic cell lines. J Virol. 1998;72:9881-8.
51. Marshall RM, Salerno D, Garriga J, Grana X. Cyclin T1 expression is regulated by multiple signaling pathways and mechanisms during activation of human peripheral blood lymphocytes. J Immunol. 2005;175:6402-11.
52. Bellan C, De Falco G, Lazzi S*, et al.* CDK9/CYCLIN T1 expression during normal lymphoid differentiation and malignant transformation. J Pathol. 2004;203:946-52.
53. Blazek D, Kohoutek J, Bartholomeeusen K*, et al*. The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. Genes Dev. 2011;25:2158-72.
54. Bartkowiak B, Liu P, Phatnani HP*, et al*. CDK12 is a transcription elongation-associated CTD kinase, the metazoan ortholog of yeast Ctk1. Genes Dev. 2010;24:2303-16.
55. Yang L, Li N, Wang C*, et al*. Cyclin L2, a novel RNA polymerase II-associated cyclin, is involved in pre-mRNA splicing and induces apoptosis of human hepatocellular carcinoma cells. J Biol Chem. 2004;279:11639-48.
56. Dickinson LA, Edgar AJ, Ehley J, Gottesfeld JM. Cyclin L is an RS domain protein involved in pre-mRNA splicing. J Biol Chem. 2002;277:25465-73.
57. Loyer P, Trembley JH, Grenet JA*, et al*. Characterization of cyclin L1 and L2 interactions with CDK11 and splicing factors: influence of cyclin L isoforms on splice site selection. J Biol Chem. 2008;283:7721-32.
58. Redon R, Hussenet T, Bour G*, et al*. Amplicon mapping and transcriptional analysis pinpoint cyclin L as a candidate oncogene in head and neck cancer. Cancer Res. 2002;62:6211-7.
59. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A. 2003;100:3983-8.
60. Dontu G, Abdallah WM, Foley JM*, et al*. In vitro propagation and transcriptional profiling of human mammary stem/progenitor cells. Genes Dev. 2003;17:1253-70.
61. Sicinski P, Donaher JL, Parker SB*, et al*. Cyclin D1 provides a link between development and oncogenesis in the retina and breast. Cell. 1995;82:621-30.
62. Fantl V, Stamp G, Andrews A, Rosewell I, Dickson C. Mice lacking cyclin D1 are small and show defects in eye and mammary gland development. Genes Dev. 1995;9:2364-72.
63. Ma C, Papermaster D, Cepko CL. A unique pattern of photoreceptor degeneration in cyclin D1 mutant mice. Proc Natl Acad Sci U S A. 1998;95:9938-43.
64. Das G, Choi Y, Sicinski P, Levine EM. Cyclin D1 fine-tunes the neurogenic output of embryonic retinal progenitor cells. Neural Dev. 2009;4:15.
65. Yu Q, Geng Y, Sicinski P. Specific protection against breast cancers by cyclin D1 ablation. Nature. 2001;411:1017-21.
66. Rowlands TM, Pechenkina IV, Hatsell SJ, Pestell RG, Cowin P. Dissecting the roles of beta-catenin and cyclin D1 during mammary development and neoplasia. Proc Natl Acad Sci U S A. 2003;100:11400-5.
67. Reddy HK, Mettus RV, Rane SG, Grana X, Litvin J, Reddy EP. Cyclin-dependent kinase 4 expression is essential for neu-induced breast tumorigenesis. Cancer Res. 2005;65:10174-8.
68. Jeselsohn R, Brown NE, Arendt L*, et al*. Cyclin D1 kinase activity is required for the self-renewal of mammary stem and progenitor cells that are targets of MMTV-ErbB2 tumorigenesis. Cancer Cell. 2010;17:65-76.
69. Landis MW, Pawlyk BS, Li T, Sicinski P, Hinds PW. Cyclin D1-dependent kinase activity in murine development and mammary tumorigenesis. Cancer Cell. 2006;9:13-22.
70. Shackleton M, Vaillant F, Simpson KJ*, et al*. Generation of a functional mammary gland from a single stem cell. Nature. 2006;439:84-8.
71. Mack PD, Lester VK, Promislow DE. Age-specific effects of novel mutations in Drosophila melanogaster II. Fecundity and male mating ability. Genetica. 2000;110:31-41.
72. Boulanger CA, Wagner KU, Smith GH. Parity-induced mouse mammary epithelial cells are pluripotent, self-renewing and sensitive to TGF-beta1 expression. Oncogene. 2005;24:552-60.
73. Henry MD, Triplett AA, Oh KB, Smith GH, Wagner KU. Parity-induced mammary epithelial cells facilitate tumorigenesis in MMTV-neu transgenic mice. Oncogene. 2004;23:6980-5.
74. Smith GH, Medina D. Re-evaluation of mammary stem cell biology based on in vivo transplantation. Breast Cancer Res. 2008;10:203.
75. Wagner KU, Boulanger CA, Henry MD*, et al*. An adjunct mammary epithelial cell population in parous females: its role in functional adaptation and tissue renewal. Development. 2002;129:1377-86.
76. Choi YJ, Li X, Hydbring P*, et al*. The requirement for cyclin d function in tumor maintenance. Cancer Cell. 2012;22:438-51.
77. Lew DJ, Dulic V, Reed SI. Isolation of three novel human cyclins by rescue of G1 cyclin (Cln) function in yeast. Cell. 1991;66:1197-206.
78. Leopold P, O'Farrell PH. An evolutionarily conserved cyclin homolog from Drosophila rescues yeast deficient in G1 cyclins. Cell. 1991;66: 1207-16.
79. Ren S, Rollins BJ. Cyclin C/cdk3 promotes Rb-dependent G0 exit. Cell. 2004;117:239-51.
80. Miyata Y, Liu Y, Jankovic V*, et al*. Cyclin C regulates human hematopoietic stem/progenitor cell quiescence. Stem Cells. 2010;28:308-17.
81. Baldini E, Camerini A, Sgambato A*, et al*. Cyclin A and E2F1 overexpression correlate with reduced disease-free survival in node-negative breast cancer patients. Anticancer Res. 2006;26:4415-21.
82. Wegiel B, Bjartell A, Tuomela J*, et al*. Multiple cellular mechanisms related to cyclin A1 in prostate cancer invasion and metastasis. J Natl Cancer Inst. 2008;100:1022-36.
83. Li JQ, Miki H, Wu F*, et al*. Cyclin A correlates with carcinogenesis and metastasis, and p27(kip1) correlates with lymphatic invasion, in colorectal neoplasms. Hum Pathol. 2002;33:1006-15.
84. Rosenberg AR, Zindy F, Le Deist F*, et al*. Overexpression of human cyclin A advances entry into S phase. Oncogene. 1995;10:1501-9.
85. Chibazakura T, Kamachi K, Ohara M, Tane S, Yoshikawa H, Roberts JM. Cyclin A promotes S-phase entry via interaction with the replication licensing factor Mcm7. Mol Cell Biol. 2011;31:248-55.
86. Furuno N, den Elzen N, Pines J. Human cyclin A is required for mitosis until mid prophase. J Cell Biol. 1999;147:295-306.
87. Pagano M, Draetta G. Cyclin A, cell cycle control and oncogenesis. Prog Growth Factor Res. 1991;3:267-77.
88. Gong D, Pomerening JR, Myers JW*, et al*. Cyclin A2 regulates nuclear-envelope breakdown and the nuclear accumulation of cyclin B1. Curr Biol. 2007;17:85-91.
89. Kalaszczynska I, Geng Y, Iino T*, et al*. Cyclin A is redundant in fibroblasts but essential in hematopoietic and embryonic stem cells. Cell. 2009;138:352-65.
90. Dorn J, Spatz H, Schmieder M*, et al*. Cyclin H expression is increased in GIST with very-high risk of malignancy. BMC Cancer. 2010;10:350.
91. Bavi P, Abubaker J, Hussain A*, et al*. Reduced or absent cyclin H expression is an independent prognostic marker for poor outcome in diffuse large B-cell lymphoma. Hum Pathol. 2008;39:885-94.
92. Solomon MJ, Harper JW, Shuttleworth J. CAK, the p34cdc2 activating kinase, contains a protein identical or closely related to p40MO15. EMBO J. 1993;12:3133-42.
93. Poon RY, Yamashita K, Adamczewski JP, Hunt T, Shuttleworth J. The cdc2-related protein p40MO15 is the catalytic subunit of a protein kinase that can activate p33cdk2 and p34cdc2. EMBO J. 1993;12:3123-32.
94. Fesquet D, Labbe JC, Derancourt J*, et al*. The MO15 gene encodes the catalytic subunit of a protein kinase that activates cdc2 and other cyclin-dependent kinases (CDKs) through phosphorylation of Thr161 and its homologues. EMBO J. 1993;12:3111-21.
95. Patel SA, Simon MC. Functional analysis of the Cdk7.cyclin H.Mat1 complex in mouse embryonic stem cells and embryos. J Biol Chem. 2010;285:15587-98.
96. Larochelle S, Batliner J, Gamble MJ*, et al*. Dichotomous but stringent substrate selection by the dual-function Cdk7 complex revealed by chemical genetics. Nat Struct Mol Biol. 2006;13:55-62.
97. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature. 2012;481:287-94.
98. Giglia-Mari G, Zotter A, Vermeulen W. DNA damage response. Cold Spring Harb Perspect Biol. 2011;3:a000745.

99. Johnson N, Shapiro GI. Cyclin-dependent kinases (cdks) and the DNA damage response: rationale for cdk inhibitor-chemotherapy combinations as an anticancer strategy for solid tumors. Expert Opin Ther Targets. 2010; 14:1199-212.
100. Wang C, Fan S, Li Z, *et al*. Cyclin D1 antagonizes BRCA1 repression of estrogen receptor alpha activity. Cancer Res. 2005;65:6557-67.
101. Bai C, Sen P, Hofmann K, *et al*. SKP1 connects cell cycle regulators to the ubiquitin proteolysis machinery through a novel motif, the F-box. Cell. 1996;86:263-74.
102. Fung TK, Siu WY, Yam CH, Lau A, Poon RY. Cyclin F is degraded during G2-M by mechanisms fundamentally different from other cyclins. J Biol Chem. 2002;277:35140-9.
103. Cardozo T, Pagano M. The SCF ubiquitin ligase: insights into a molecular machine. Nat Rev Mol Cell Biol. 2004;5:739-51.
104. D'Angiolella V, Donato V, Vijayakumar S, *et al*. SCF(Cyclin F) controls centrosome homeostasis and mitotic fidelity through CP110 degradation. Nature. 2010;466:138-42.
105. Chen Z, Indjeian VB, McManus M, Wang L, Dynlacht BD. CP110, a cell cycle-dependent CDK substrate, regulates centrosome duplication in human cells. Dev Cell. 2002;3:339-50.
106. D'Angiolella V, Donato V, Forrester FM, *et al*. Cyclin F-mediated degradation of ribonucleotide reductase M2 controls genome integrity and DNA repair. Cell. 2012;149:1023-34.
107. Emanuele MJ, Elia AE, Xu Q, *et al*. Global identification of modular cullin-RING ligase substrates. Cell. 2011;147:459-74.
108. Xu X, Page JL, Surtees JA, *et al*. Broad overexpression of ribonucleotide reductase genes in mice specifically induces lung neoplasms. Cancer Res. 2008;68:2652-60.
109. Ferrandina G, Mey V, Nannizzi S, *et al*. Expression of nucleoside transporters, deoxycitidine kinase, ribonucleotide reductase regulatory subunits, and gemcitabine catabolic enzymes in primary ovarian cancer. Cancer Chemother Pharmacol. 2010;65:679-86.
110. Grade M, Hummon AB, Camps J, *et al*. A genomic strategy for the functional validation of colorectal cancer genes identifies potential therapeutic targets. Int J Cancer. 2011;128:1069-79.
111. Satow R, Shitashige M, Kanai Y, *et al*. Combined functional genome survey of therapeutic targets for hepatocellular carcinoma. Clin Cancer Res. 2010;16:2518-28.
112. Kretschmer C, Sterner-Kock A, Siedentopf F, Schoenegg W, Schlag PM, Kemmner W. Identification of early molecular markers for breast cancer. Mol Cancer. 2011;10:15.
113. Ito Y, Yoshida H, Uruno T, *et al*. Decreased expression of cyclin G2 is significantly linked to the malignant transformation of papillary carcinoma of the thyroid. Anticancer Res. 2003;23:2335-8.
114. Kim Y, Shintani S, Kohno Y, Zhang R, Wong DT. Cyclin G2 dysregulation in human oral cancer. Cancer Res. 2004;64:8980-6.
115. Horne MC, Goolsby GL, Donaldson KL, Tran D, Neubauer M, Wahl AF. Cyclin G1 and cyclin G2 comprise a new family of cyclins with contrasting tissue-specific and cell cycle-regulated expression. J Biol Chem. 1996;271:6050-61.
116. Okamoto K, Beach D. Cyclin G is a transcriptional target of the p53 tumor suppressor protein. EMBO J. 1994;13:4816-22.
117. Adorno M, Cordenonsi M, Montagner M, *et al*. A Mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. Cell. 2009;137:87-98.
118. Bennin DA, Don AS, Brake T, *et al*. Cyclin G2 associates with protein phosphatase 2A catalytic and regulatory B' subunits in active complexes and induces nuclear aberrations and a G1/S phase cell cycle arrest. J Biol Chem. 2002;277: 27449-67.
119. Arachchige-Don AS, Dallapiazza RF, Bennin DA, Brake T, Cowan CE, Horne MC. Cyclin G2 is a centrosome-associated nucleocytoplasmic shuttling protein that influences microtubule stability and induces a p53-dependent cell cycle arrest. Exp Cell Res. 2006;312:4181-204.
120. Shimizu A, Nishida J, Ueoka Y, *et al*. CyclinG contributes to G2/M arrest of cells in response to DNA damage. Biochem Biophys Res Commun. 1998;242:529-33.
121. Kimura SH, Ikawa M, Ito A, Okabe M, Nojima H. Cyclin G1 is involved in G2/M arrest in response to DNA damage and in growth control after damage recovery. Oncogene. 2001;20:3290-300.
122. Okamoto K, Prives C. A role of cyclin G in the process of apoptosis. Oncogene. 1999;18:4606-15.
123. Seo HR, Lee DH, Lee HJ, *et al*. Cyclin G1 overcomes radiation-induced G2 arrest and increases cell death through transcriptional activation of cyclin B1. Cell Death Differ. 2006;13:1475-84.
124. Zimmermann M, Arachchige-Don AS, Donaldson MS, Dallapiazza RF, Cowan CE, Horne MC. Elevated cyclin G2 expression intersects with DNA damage checkpoint signaling and is required for a potent G2/M checkpoint arrest response to doxorubicin. J Biol Chem. 2012;287:22838-53.
125. Bakhoum SF, Compton DA. Chromosomal instability and cancer: a complex relationship with therapeutic potential. J Clin Invest. 2012;122:1138-43.
126. Holland AJ, Cleveland DW. Losing balance: the origin and impact of aneuploidy in cancer. EMBO Rep. 2012;13:501-14.
127. Pfau SJ, Amon A. Chromosomal instability and aneuploidy in cancer: from yeast to man. EMBO Rep. 2012;13:515-27.
128. Oyama T, Kashiwabara K, Yoshimoto K, Arnold A, Koerner F. Frequent overexpression of the cyclin D1 oncogene in invasive lobular carcinoma of the breast. Cancer Res. 1998;58:2876-80.
129. van Diest PJ, Michalides RJ, Jannink L, *et al*. Cyclin D1 expression in invasive breast cancer. Correlations and prognostic value. Am J Pathol. 1997;150:705-11.
130. Shoker BS, Jarvis C, Davies MP, Iqbal M, Sibson DR, Sloane JP. Immunodetectable cyclin D(1)is associated with oestrogen receptor but not Ki67 in normal, cancerous and precancerous breast lesions. Br J Cancer. 2001;84:1064-9.
131. Weinstat-Saslow D, Merin MJ, Manrow RE, *et al*. Overexpression of cyclin D mRNA distinguishes invasive and in situ breast carcinomas from non-malignant lesions. Nat Med. 1995;1:1257-60.
132. Montanaro L, Vici M, Donati G, *et al*. Controversial relationship between the expression of the RB pathway components and RB protein phosphorylation in human breast cancer. Histol Histopathol. 2007;22:769-75.
133. Casimiro MC, Pestell RG. Cyclin d1 induces chromosomal instability. Oncotarget. 2012;3:224-5.
134. Spruck CH, Won KA, Reed SI. Deregulated cyclin E induces chromosome instability. Nature. 1999;401:297-300.
135. Nelsen CJ, Kuriyama R, Hirsc B, *et al*. Short term cyclin D1 overexpression induces centrosome amplification, mitotic spindle abnormalities, and aneuploidy. J Biol Chem. 2005;280:768-76.
136. Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet. 2006;38:1043-8.
137. Wang A, Yoshimi N, Ino N, Tanaka T, Mori H. Overexpression of cyclin B1 in human colorectal cancers. J Cancer Res Clin Oncol. 1997;123:124-7.
138. Soria JC, Jang SJ, Khuri FR, *et al*. Overexpression of cyclin B1 in early-stage non-small cell lung cancer and its clinical implication. Cancer Res. 2000;60:4000-4.
139. Hassan KA, Ang K, El-Naggar AK, *et al*. Cyclin B1 overexpression and resistance to radiotherapy in head and neck squamous cell carcinoma. Cancer Res. 2002;62:6414-7.
140. Kawamoto H, Koizumi H, Uchikoshi T. Expression of the G2-M checkpoint regulators cyclin B1 and cdc2 in nonmalignant and malignant human breast lesions: immunocytochemical and quantitative image analyses. Am J Pathol. 1997;150:15-23.
141. Suzuki T, Urano T, Miki Y, *et al*. Nuclear cyclin B1 in human breast carcinoma as a potent prognostic factor. Cancer Sci. 2007;98:644-51.
142. Sarafan-Vasseur N, Lamy A, Bourguignon J, *et al*. Overexpression of B-type cyclins alters chromosomal segregation. Oncogene. 2002;21: 2051-7.
143. Hunt T. Maturation promoting factor, cyclin and the control of M-phase. Curr Opin Cell Biol. 1989;1:268-74.
144. Nurse P. Universal control mechanism regulating onset of M-phase. Nature. 1990;344:503-8.
145. Lohka MJ, Hayes MK, Maller JL. Purification of maturation-promoting factor, an intracellular regulator of early mitotic events. Proc Natl Acad Sci U S A. 1988;85:3009-13.
146. Gautier J, Norbury C, Lohka M, Nurse P, Maller J. Purified maturation-promoting factor contains the product of a Xenopus homolog of the fission yeast cell cycle control gene cdc2+. Cell. 1988;54:433-9.

147. Labbe JC, Capon, JP, Caput D*, et al*. MPF from starfish oocytes at first meiotic metaphase is a heterodimer containing one molecule of cdc2 and one molecule of cyclin B. EMBO J. 1989;8: 3053-8.
148. Gautier J, Minshull J, Lohka M, Glotzer M, Hunt T, Maller JL. Cyclin is a component of maturation-promoting factor from Xenopus. Cell. 1990;60:487-94.
149. Castilho PV, Williams BC, Mochida S, Zhao Y, Goldberg ML. The M phase kinase Greatwall (Gwl) promotes inactivation of PP2A/ B55delta, a phosphatase directed against CDK phosphosites. Mol Biol Cell. 2009;20:4777-89.
150. Mochida S, Ikeo S, Gannon J, Hunt T. Regulated activity of PP2A-B55 delta is crucial for controlling entry into and exit from mitosis in Xenopus egg extracts. EMBO J. 2009;28:2777-85.
151. Vigneron S, Brioudes E, Burgess A, Labbe JC, Lorca T, Castro A. Greatwall maintains mitosis through regulation of PP2A. EMBO J. 2009;28:2786-93.
152. Hara M, Abe Y, Tanaka T, Yamamoto T, Okumura E, Kishimoto T. Greatwall kinase and cyclin B-Cdk1 are both critical constituents of M-phase-promoting factor. Nat Commun. 2012;3:1059.
153. Wingate H, Puskas A, Duong M*, et al*. Low molecular weight cyclin E is specific in breast cancer and is associated with mechanisms of tumor progression. Cell Cycle. 2009;8: 1062-8.
154. Schraml P, Bucher C, Bissig H*, et al*. Cyclin E overexpression and amplification in human tumours. J Pathol. 2003;200:375-82.
155. Fukuse T, Hirata T, Naiki H, Hitomi S, Wada H. Prognostic significance of cyclin E overexpression in resected non-small cell lung cancer. Cancer Res. 2000;60:242-4.
156. Yasui W, Akama Y, Kuniyasu H*, et al*. Expression of cyclin E in human gastric adenomas and adenocarcinomas: correlation with proliferative activity and p53 status. J Exp Ther Oncol. 1996;1:88-94.
157. Erlanson M, Landberg G. Prognostic implications of p27 and cyclin E protein contents in malignant lymphomas. Leuk Lymphoma. 2001;40:461-70.
158. Wolowiec D, Mekki Y, Ffrench P*, et al*. Differential expression of cell proliferation regulatory proteins in B- and T-lineage acute lymphoblastic leukaemias. Br J Haematol. 1996;95: 518-23.
159. Iida H, Towatari M, Tanimoto M, Morishita Y, Kodera Y, Saito H. Overexpression of cyclin E in acute myelogenous leukemia. Blood. 1997;90:3707-13.
160. Keyomars, K, O'Leary N, Molnar G, Lees E, Fingert HJ, Pardee AB. Cyclin E, a potential prognostic marker for breast cancer. Cancer Res. 1994;54:380-5.
161. Porter DC, Zhang N, Danes C*, et al*. Tumor-specific proteolytic processing of cyclin E generates hyperactive lower-molecular-weight forms. Mol Cell Biol. 2001;21:6254-69.
162. Keyomarsi K, Tucker SL, Buchholz TA*, et al*. Cyclin E and survival in patients with breast cancer. N Engl J Med. 2002;347:1566-75.
163. Hwang HC, Clurman BE. Cyclin E in normal and neoplastic cell cycles. Oncogene. 2005;24:2776-86.
164. Geng Y, Yu Q, Sicinska E*, et al*. Cyclin E ablation in the mouse. Cell. 2003;114:431-43.
165. Kollner HJ, Lutterberg C. [The value of functional analysis for orthodontic diagnosis]. Zahn Mund Kieferheilkd Zentralbl. 1988;76: 404-8.
166. Keyomarsi K, Pardee AB. Redundant cyclin overexpression and gene amplification in breast cancer cells. Proc Natl Acad Sci U S A. 1993;90:1112-6.
167. Akama Y, Yasui W, Yokozaki H*, et al*. Frequent amplification of the cyclin E gene in human gastric carcinomas. Jpn J Cancer Res. 1995;86:617-21.
168. Kitahara K, Yasui W, Kuniyasu H*, et al*. Concurrent amplification of cyclin E and CDK2 genes in colorectal carcinomas. Int J Cancer. 1995;62:25-8.
169. Rudolph P, Kuhling H, Alm P*, et al*. Differential prognostic impact of the cyclins E and B in premenopausal and postmenopausal women with lymph node-negative breast cancer. Int J Cancer. 2003;105:674-80.
170. Ma Y, Fiering S, Black C*, et al*. Transgenic cyclin E triggers dysplasia and multiple pulmonary adenocarcinomas. Proc Natl Acad Sci U S A. 2007;104:4089-94.