Review

The Less Known Cyclins—Uncovered

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Abstract: Cyclins belong to a group of proteins that are cyclically produced and destructed in a cell. Cyclins are a family of proteins that are a key component of the cell cycle regulating system, which level of expression depends on the phase of the cycle. Cyclins regulate the activity of cyclin-dependent kinases (Cdk), thanks to which they influence the length of individual phases of the cell cycle and also determine whether the cell can enter the next life stage. Proper expression of cyclins plays an important role in processes such as proliferation, transcription, DNA repair and cell differentiation. However, dysregulation of their expression is one of the most important disorders leading to the development of different types of cancer, which suggests that cyclins can be defined as a prognostic marker. Currently, we may distinguish >10 members of the cyclins family participating in the division of human cells. The group of less known cyclins includes C, F, G, H, I, J, K, L, M, O, T and Y cyclins. The present report demonstrates the current state of knowledge considering less known cyclins and their role in normal and cancer cells.

Keywords: cyclins; cell cycle; cancer

1. Introduction

The cell cycle is a process in which a series of biophysical and biochemical changes take place. In cell division, two daughter cells are produced and contain identical genetic material as the parent cell. Progress of the cell cycle is determined by the activity of two classes of regulatory proteins: cyclins and cyclin-dependent kinases (Cdks). Cyclins belong to the group of proteins that are necessary for the proper course of all life stages [1]. The main feature of cyclins is its variable concentrations depending on the phase of the cell cycle (Figure 1). In turn, Cdks are present in the cells throughout all cell cycle phases in an inactive form. Their activation is a result of the connection with the appropriate cyclin. Cyclin/Cdk complex affects the length of individual phases, and also determines whether the cell can enter the next phase. The division into mitotic cyclins and a group of G1 phase cyclins are commonly known. Mitotic cyclins include A and B cyclins, while D and E can be assigned as G1 phase cyclins. In turn, the group of less known cyclins includes C, F, G, H, I, J, K, L, M, O, T and Y cyclins. Cyclins have been known as regulators of the cell cycle for a long time, but recent studies also indicate their important role in the process of carcinogenesis. Maintaining the correct expression of cyclins is crucial not only for normal cell proliferation but also plays a significant role in other cellular processes like transcription, DNA repair and cell differentiation. Disruption of these proteins may lead to abnormal cell proliferation and cancer progression, thus cancer is often called a cell cycle disease [2,3]. Dysregulation of the cell's life cycle is one of the most common variables during tumor development. Cell cycle progression is a highly ordered and strictly regulated process involving many control points, which disruption may result in uncontrolled cell divisions. Therefore, understanding the molecular mechanisms of the cell-division cycle abnormalities in cancer may provide important information on how normal cells undergo malignant transformation and how new treatment strategies can be designed [4].
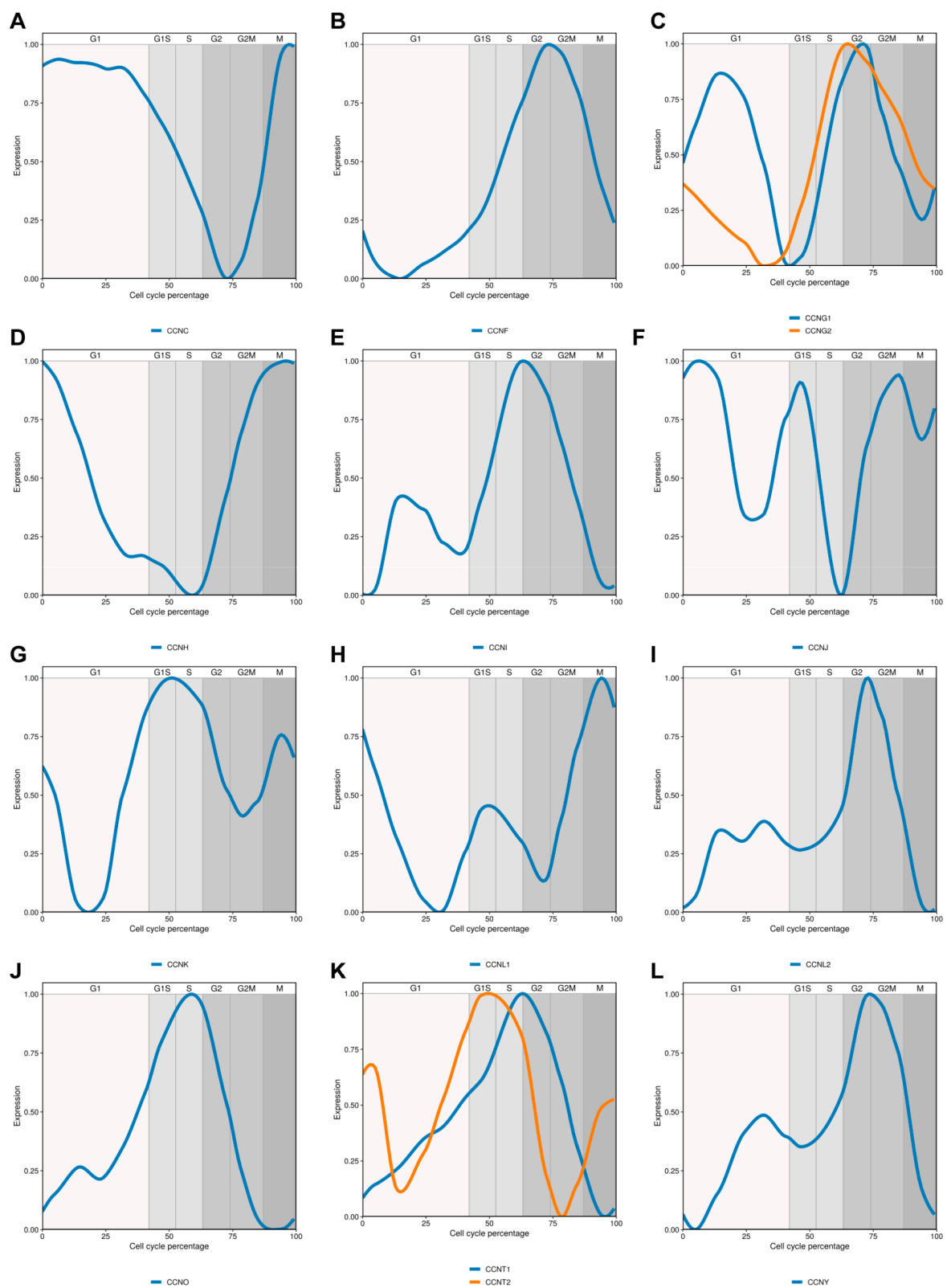
Figure 1. Expression patterns of the less-known cyclins. The data were obtained from endoDB (a database of endothelial cell transcriptomics data). The graphs show cyclin expression in human lung tumor endothelial cells. (**A**) cyclin C (**B**) cyclin F (**C**) cyclin G1 and G2 (**D**) cyclin H (**E**) cyclin I (**F**) cyclin J (**G**) cyclin K (**H**) cyclin L (**I**) cyclin M (**J**) cyclin O (**K**) cyclin T1 and cyclin T2 (**L**) cyclin Y.

2. Cyclin C

Cyclin C is a protein encoded by the CCNC gene, which is located in position 16.2 on chromosome 6. The cyclin belongs to the subfamily of transcriptional cyclins. It was first isolated as a G1 growth factor along with cyclins D and E [5,6]. It consists of 283 amino acids, while its molecular weight is 33.2 kDa [5,6]. Cyclin C contains two 5 α-helix cyclin boxes. It has no additional carboxyl and amino α-helical regions on the C-terminal domain. The N-terminal domain is not included in the α-helix cyclin box and is mobile. Human cyclin C binds to Cdk8 through HC α-helix and activates it [7].

In normal cells, cyclin C is involved in the regulation of the transcription process mainly in two ways. First, cyclin C together with Cdk8, mediator complex subunit 12 (Med12) and mediator complex subunit 13 (Med13) create the Cdk8-dependent kinase module (CKM). CKM is a part of the mediator complex involved in the regulation of the transcription process by phosphorylation of the C-terminal domain (CTD) of RNA polymerase II (RNAPII) [7]. Second, cyclin C in complex with Cdk8 can regulate the transcription process by targeting cycH-Cdk7 of the transcription factor II Human (TFIIH). Triggered by cyclin C, Cdk8 phosphorylates cyclin H, which results in the limitation of TFIIH ability to activate transcription and inhibition of CTD [8]. Moreover, after induction of various stress types, i.e., oxidative stress, osmotic stress, heat shock or ethanol treatment, cycC-Cdk8 affects stress response genes, transcription of which is required for cell survival after injury [9].

Another function of cyclin C in normal cells is a transmission of the oxidative stress signal to the mitochondria by inducing extensive mitochondrial fragmentation. The induced fraction of cyclin C is released from the nucleus into the cytosol, where it activates the mitochondrial Dynamin related protein 1 (Drp1) GTPase. The result is a fragmentation of the mitochondria, which regulates further stress reactions, i.e., mitophagy or apoptosis [10]. Wang et al., 2015 [11] used mouse embryonic fibroblasts (MEF), treated with cisplatin and H_2O_2, which led to the induction of oxidative stress. The result was a translocation of cyclin C from the nucleus to the mitochondria, where it connects to Drp1 and is required to initiate the mitochondrial fission. In the same study, the authors showed that cyclin C is also involved in the regulation of apoptosis. After using cisplatin, the results confirmed that the MEF CCNC $-/-$ cells were characterized by a significant reduction in the Annexin V signal when compared to the wild-type control cells. This suggests that cyclin C results in a cisplatin resistance phenotype and is required for the programmed death in MEF. Simultaneously, after the use of H_2O_2, MEF CCNC $-/-$ cells were more resistant than the control cells [11].

In normal cells, cyclin C in the complex with Cdk3 is also involved in the cell's exit from the G0 phase through phosphorylation of the retinoblastoma protein (Rb), which was proved by Ren and Rollins in their studies on human fibroblasts. The results suggest that the regulation of re-entry into the cell cycle from the G0 phase is closely correlated with the transcriptional machinery. The authors confirmed that phosphorylation of pRb by cycC-Cdk3 allows the exit from G0 phase, but also limits suppression of rRNA synthesis [12]. Furthermore, Miyata et al., 2010 [13] in their studies showed that cyclin C can regulate the G0/G1 transition in human hematopoietic stem/progenitor cells (HSPC). In turn, the silencing of CCNC expression in HSPC results in enhanced expansion and increases their engraftability in immunodeficient mice treated with sublethal doses of radiation [13].

In normal cells, it is assumed that cyclin C also participates in the regulation of G1 and G2 phases. Liu et al., 2010 [13] by studying hematopoietic cell line BAF-B03, showed that cyclin C can cooperate with c-Myc and affects the proliferation of the cells in a cytokine-independent manner, but also participates in the formation of cell clusters. The interaction of cyclin C with c-Myc is responsible for cell proliferation and passage through the G1/S restriction site. In addition, cyclin C together with c-Myc affects the induction of the cdc2 gene, which is a key regulator in the G2/M phase [14].

In turn, Li et al., 2014 [15] showed that the CCNC gene is missing in the subset of acute lymphoblastic leukemia, suggesting that cyclin C deficiency is sufficient to promote tumor

growth. It has been presented that cyclin C controls the level of well-known oncogene Notch1. Cyclin C activates phosphorylation of the Notch1 intracellular domain (ICN1) via CDK 3/8/19 kinases and promotes its degradation. Ablation of cyclin C significantly increased ICN1 levels and enhanced T-ALL progression in vivo [15]. Moreover, Ohata et al., 2006 [16] described cases of osteosarcoma with comparative genomic hybridization (CGH). The results of their studies indicated that transfection with CCNC cDNA caused significant suppression of the osteosarcoma cell lines proliferation. After the mapping of the region commonly deleted in osteosarcoma and transfection assay, they showed that CCNC may be a potential tumor suppressor gene [16].

By contrast, the overexpression of cyclin C was demonstrated in colon adenocarcinoma. Bondi et al., 2005 [17] confirmed the enhanced expression of cyclin C caused by the amplification of its gene in 219 colon cancer cases, which was associated with an unfavorable prognosis [17]. The in vitro experiments showed that high levels of cyclin C/CDK8 complexes are associated with increased proliferation and hyperactivation of the WNT/beta-catenin pathway [18]. Moreover, mutations of the cyclin C and Cdk8 complex were also observed in other tumors, i.e., melanoma and colorectal cancer [19].

Cdk8 and Cdk19 inhibitors are promising anticancer agents. Currently, two compounds received clinical trial approval: SEL120 in patients with Acute Myeloid Leukemia or high-risk Myelodysplastic Syndrome (NCT04021368) and BCD-115 in Women with ER(+) HER2(-) Local Advanced and Metastatic Breast Cancer (NCT03065010).

3. Cyclin F

Cyclin F with a molecular weight of 87 kDa is the largest cyclin. It is a cell cycle protein that in humans is encoded by the CCNF gene located in position 16p13.3. It was first identified in 1994 by Bai et al., 1994 [20] and isolated as a suppressor of the G1/S phase transition deficiency of Saccharomyces cerevisiae CDC4 mutant. Cyclin F is the closest relative to the mitotic cyclins: A and B in terms of expression and structure [20,21]. It also has features common to all cyclins, such as richness in proline, glutamic acid, serine and threonine (PEST) region, the abundance of protein, mRNA level dependent on cell cycle stage and ability to control the cell cycle progression [22]. Cyclin F is expressed in all human tissues at different concentrations depending on the cell cycle stage. In most cells, it shows subcellular localization, mainly in the nucleus (in the S and G2 phases), while in the others occurs only in the cytoplasm (mainly in the G2 phase) [20]. The pattern of expression is very similar to cyclin A. The level of cyclin F begins to increase in the S phase and reaches its peak during the G2 phase. However, it does not bind or activate any of the known Cdks. Cyclin F also differs from other cyclins by its ability to monitor and regulate the cell cycle even without activation [23].

Cyclin F is a unique cyclin because it contains not only the cyclin domain but also the F-box region. This domain is necessary for the binding of S-phase kinase-associated protein 1 (Skp1). It is the component of the ubiquitin ligase protein machinery Skp1-Cul1-F-box (SCF). Skp1 also binds Cullin 1 (Cul1) and RING-box protein 1 (RBX1) to assemble a functional SCF complex. Moreover, RBX1 recruits regulatory protein E2 (E2) for the ubiquitination of target substrates. While other cyclins use the catalytic subunit of Cdk to phosphorylate target substrates, cyclin F uses the F-box domain to promote the ubiquitination of target substrates [22,23].

In normal cells, cyclin F interacts with enzymes important for the synthesis, stability and repair of DNA. D'Angiolella et al., 2013 [22] showed that cyclin F performs important functions in controlling centrosome duplication and prevents genomic instability by promoting the degradation of centriolar coiled-coil protein of 110 kDa (CP110) and ribonucleoside-diphosphate reductase subunit M2 (RRM2). Incorrect centrosome duplication and chromosome aberration contribute to the formation of tumors. As CP110 promotes duplication of centrosomes, cyclin F prevents genomic instability by ensuring that during every cell cycle only a single centrosome duplication event occurs. CP110 proteolysis by SCF with the participation of ubiquitin is crucial for maintaining centrosome homeosta-

sis and mitotic fidelity [24]. Another target for SCF is RRM2, which is a ribonucleotide reductase (RNR) subunit that allows the conversion of ribonucleotides to dNTP, which are then used in DNA synthesis and repair processes. A balanced pool of dNTP is one of the determinants of the replication accuracy, while an increase in their production is necessary for the process of DNA repair (Figure 2). This suggests that cyclin F helps to maintain genome integrity through modulation of RRM2 availability [2,22]. Failure of cyclin F-dependent RRM2 degradation leads to an imbalance in the dNTP pool and increases the frequency of genomic mutations [25]. As was confirmed by Casimiro et al., 2012 [23] RRM2 overexpression increases the probability of lung cancer occurrence in mice. Moreover, elevated RRM2 level is associated with poor prognosis in ovarian, liver, colorectal and breast cancer [23].
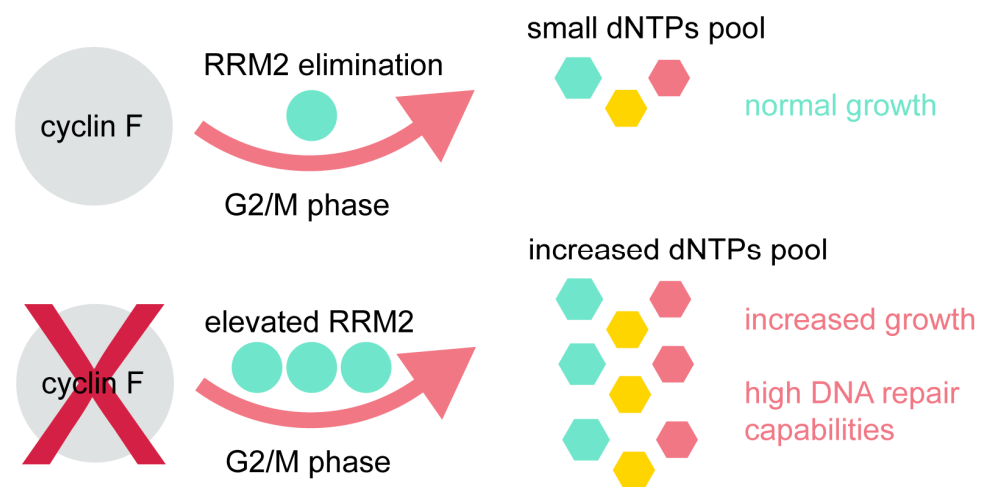

Figure 2. The cyclin F–RRM2 axis is essential for genome stability and DNA repair. The defective elimination of RRM2 drives to elevated DNA pool and increases the cell capability to DNA repair. This can lead to uncontrolled proliferation and drug resistance.

The third substrate of cyclin F is nucleolar and spindle-associated protein 1 (NuSAP). It belongs to the family of microtubule-associated proteins and is required for the spindle assembly process, where its main function is to interact with microtubules and chromatin to ensure stabilization and cross-linking [26]. The absence of NuSAP leads to incorrect spindle formation, erroneous segregation of chromosomes and eventually blocks cell proliferation, whereas an increased level of NuSAP results in mitotic arrest and microtubule formation. Cyclin F helps to control the amount of NuSAP and therefore is essential for proper cell division. Considering all of the above, defective cyclin F may contribute to the formation of the hypermutator phenotype and chromosomal instability through the RRM2, CP110 and NuSAP pathways [22,26].

In the case of DNA damage, the cell activates specific checkpoints to stop proliferation and facilitate DNA repair. Cyclin F in normal cells inhibits the activity of the Myb-related protein B (B-Myb) transcription factor. Klein et al., 2015 [27] performed screening tests for RNA interference involved in ubiquitination processes. Their results show that in normal cells that were not exposed to ionizing radiation (IR) B-Myb-dependent control of cyclin F has little effect on the activation of the transcription process and proliferation of cells. Moreover, in the cells damaged by IR exposition, cyclin F inhibits the activity of B-Myb in the aim to trigger the G2 phase checkpoint. It is, therefore, possible that cyclin F plays an important role in the development of cancer by preventing genomic instability and excessive cell proliferation by B-Myb suppression [27].

Another function of cyclin F in normal cells is its participation in embryogenesis. Tetzlaff et al, 2004 [28]. investigated the role of cyclin F in in vitro and in vivo conditions. For the study, they created mice with complete or conditional deficiency of cyclin F (CycF−/−) and cyclin F-negative MEF. CycF−/− embryos showed a wide range of

problems and developmental defects like lack of complete axial rotation, delay in neural tube closure and delayed brain formation, together with abnormal development of the yolk sac and chorioallantoic placentation. In turn, CycF−/− MEF allowed for assessing the defects in the cell cycle caused by the lack of cyclin F function. The result showed that cyclin F is not the essential factor in the context of MEF viability, but it affects their cell cycle. The cells were characterized by the decreased proliferation rate, slightly altered cell cycle distribution and delayed cell cycle re-entry after the serum starvation [28]. Furthermore, appropriate expression and location of cyclin F play a major role in cell differentiation and carcinogenesis. Fu et al., 2013 [29] showed that the reduction in cyclin F expression is associated with unfavorable prognosis for patients with liver cancer. Decreased expression of cyclin F in poorly differentiated hepatocellular carcinoma (HCC) may contribute to the tumorigenesis and HCC progression. The results confirmed that cyclin F is an independent prognostic marker for the overall survival of patients with liver cancer. Moreover, decreased expression of cyclin F correlated with the size of the tumor, alpha-fetoprotein level in serum and tumor multiplicity. Another way of cyclin F contribution to the maintenance of genomic stability is the reduction of centrophore duplication abnormalities, which additionally proves that a decrease in the level of cyclin F may lead to tumor initiation and progression [29].

Under normal conditions, cyclins have clear subcellular localization patterns. For example, cyclin A in normal cells is located mainly in the nucleus, while in tumor cells, increased translocation to the cytoplasm is observed [30]. The presence of cyclin F was at first confirmed only in the cell nucleus, but later it was also localized in the cytoplasm, where it interacts with ɣ-tubulin [24]. Weng et al., 2012 [31] showed that cyclin A localized abnormally in the cytoplasm in most Hepatitis B virus-associated HCC samples [31], although Fu et al., 2013 [29] came to similar results investigating the subcellular location of cyclin F. The results of these studies are also confirmed by the previous reports on cyclin F [20].

4. Cyclin G

The G type cyclin may be divided into two types [32]. The first is cyclin G1 encoded by the CCNG1 gene, with molecular weight 34 kDa [33]. The second is cyclin G2 encoded by CCNG2, with a molecular weight of 40 kDa [31]. G-type cyclins are able to interact with several proteins from the cyclin-dependent kinase family, such as Cdk2 and Cdk4, but also with serine/threonine-protein phosphatase PP2A-2 catalytic (PP2A) and regulatory subunits (WDB). G-type cyclins (G1 and G2) are crucial factors for tissue differentiation [32]. Cyclin G1 was first identified as one of the first targets of p53 and interacts with several cell cycle regulators, including Mdm2, ADP ribosylation factors (ARF) and Rb [34,35].

In normal cells, cyclin G is involved in the regulation of transcription factor with the properties of a tumor suppressor (p53). Ohtsuka et al., 2004 [36] examined MEF G −/−and MEF G +/+ cells. They treated both cell lines with DNA damaging factors: MMC and ɣ-irradiation. The effect of DNA damage was the activation of the p53 protein, which was dependent on ataxia-telangiectasia mutated (ATM) protein. Increased levels of p53 have been observed in G −/− cells, resulting in cell cycle arrest. In contrast, in G +/+ cells the expression level of p53 was lower [36].

Furthermore, cyclin G plays an important role in regulating the p53-Mdm2 pathway in normal cells [35]. Xinbin Chen in his research used MEF cells. In the MEF G −/− line, the author observed that Mdm2 is less efficiently phosphorylated by PP2A, which leads to a lower level of stabilization of the p53 protein. In contrast, the MEF G +/+ line restored normal PP2A activity, resulting in better performance in Mdm2 phosphorylation, and thus p53 degradation [37].

In cancer cells, cyclin G plays a dual role in the tumorigenesis process. On the one hand, overexpression[of cyclin G leads to the growth of cancer cells; on the other, its presence affects the suppression of cell proliferation. Elevated expression of cyclin G was observed in colorectal cancer [38]. Perez et al., 2003 [38] studied 90 cases of human rectal and colon

cancer. The authors showed that about 90% of the tissues examined were characterized by overexpression of cyclin G. However, the authors did not observe a correlation between pathological and clinical features and elevated expression of cyclin G [38]. Moreover, overexpression of cyclin G was also observed in breast and prostate cancers [39]. Reimer et al., 1999 [39] examined breast cancer cell lines: MDAMB435, MDAMB436, Hs578t, MCF7, T47D; prostate cancer cell lines: DU145, LNCaP, PC3, ND1; and breast epithelial line (hNMEC) and normal prostate cell lines (NPrEC-1 and NPrEC-2). Using comparative analysis, the authors showed that increased levels of cyclin G expression occur in both types of cancers. In contrast, normal cells of the breast and prostate epithelium showed a lower level of expression of the tested protein. To confirm the conclusions, the authors used immunohistochemistry to analyze the distribution of cyclin G in normal (10 biopsies) and cancer (30 biopsies) tissues of the breast. The results confirmed the observations made during in vitro studies. Cyclin G overexpression has also been shown in human osteosarcoma [39,40]. Skotzko et al., 1995 [41] studied the expression of cyclin G in the MG-63 line. The authors showed that cyclin G is overexpressed in this type of cancer. Furthermore, this protein is crucial for the growth and survival of osteosarcoma cancer cells [41].

On the other hand, cyclin G is also a factor sensitizing embryonic cancer cells to drug-induced apoptosis. Okamoto and Prives in their research on the P19 embryonic cancer line showed that cyclin G influences the sensitivity of cancer cells to apoptosis after using apoptosis inducers, i.e., low serum levels, retinoic acid (RA) and TNF-α. The authors also suggest that cyclin G alone does not affect the sensitivity of cancer cells, but is only an auxiliary factor after using apoptosis inducers [36,42].

In cancer cells, cyclin G has an effect on the negative control of cell proliferation in endometrial cancer in a progesterone-dependent manner. Liu et al. in their research used human endometrial cancer lines (ECC): KLE, HEC-1-B and Ishikawa, which were then treated with progesterone. The authors showed that too low progesterone levels in cell lines contribute to a reduction in cyclin G expression levels. Moreover, hormone deficiency may be associated with ECC cell proliferation and carcinogenesis [43,44].

5. Cyclin H

Cyclin H is a cell cycle protein encoded by the CCNH gene. Its main function is the activation of Cdk7. The interaction between Cdk7 and cyclin H is stabilized by phosphorylation of Cdk7 in its activation segment. However, the complex may also be stabilized by Mat1 [45,46]. Cyclin H together with Cdk7 and Mat1 forms the structure of Cdk activating kinase (CAK), which is a member of the Cdk family and acts as a positive regulator of Cdk1, Cdk2, Cdk4 and Cdk6 through threonine phosphorylation [47].

In normal cells, cyclin H in the CAK complex plays an important role in the regulation of transcription as a module of the TFIIH transcription factor. As the component of TFIIH, CAK phosphorylates serines 5 and 7 of the carboxyl terminus domain of RNA polymerase II, allowing promoter clearance and enabling the transcription initiation. This provides a direct connection between the cell cycle machinery and the regulation of transcription. The CAK complex may also directly phosphorylate transcription factors to regulate gene expression [23,48]. Moreover, the transcription process regulated by the CAK complex affects the differentiation of embryonic cells (ES). Patel et al., 2010 [49] showed that the loss of the function of cyclin H in ES induces the process of their differentiation as the cyclin phosphorylates the Spt5 negative transcription factor leading to its activation. In turn, Spt5 regulates RNA processing and pause transcription [49].

A high level of cyclin H expression is associated with gastrointestinal stromal tumors (GIST). Dorn et al., 2010 [50] based on the cyclin H mRNA level, showed 10-fold increased transcription of cyclin H in GIST compared to normal tissue. These results suggest the important role of cyclin H in the pathogenesis of GIST. The authors showed cyclin H overexpression in 24% of tumors, which was also correlated with the risk of malignancy. In addition, for patients with tumor recurrences and/or metastases, increased expression

of cyclin H was associated with decreased disease-specific survival. The level of expression of cyclin H in GIST varied between high and very high risk concerning specific mortality for this type of cancer, thanks to which it can be used as a prognostic marker [50].

Moreover, the regulation of cyclin H correlates with lower proliferation in diffuse large B-cell lymphoma (DLBCL). Bavi et al. 2008 [51] observed a reduction or lack of expression of cyclin H in 14.5% of DLBCL cases. Simultaneously, reduced expression of cyclin H correlated with lower expression of the cyclins B1, D3 and E, and Ki-67 proliferation marker. Downregulation of cyclin H was significantly associated with poor overall survival, both in the one-dimensional and multifactor analysis with the international predictive index. The authors demonstrated an independent prognostic value of the expression of cyclin H in DLBCL and propose its use as a prognostic marker [51].

Overexpression of cyclin H is also observed in breast cancer. Based on the studies conducted by Patel et al., 2010 [49] it was found that the mRNA levels of cyclin H and Mat1 required for Cdk7 activity are increased in breast cancer, which indicates an increase in CAK complex activity [52].

Inhibition of CDK7 activity seems like reasonable anticancer strategy. The several molecules show good efficiency against cancer cell lines. Two clinical trials conducting CDK7 inhibitors are currently ongoing: Modular Study to Evaluate CT7001 Alone in Cancer Patients with Advanced Malignancies (NCT03363893) and A Study of SY-1365 in Adult Patients with Advanced Solid Tumors (NCT03134638).

6. Cyclin I

Cyclin I is encoded by the CCNI gene localized in position 21.1 on the human chromosome 4. The protein consists of 377 amino acids with a total molecular weight of 42.6 kDa. Cyclin I was first isolated from the human forebrain cortex obtained from an equalized cDNA library. The protein is characterized by the classic cyclin construction, where the N-terminal domain contains a "cyclin box", while the PEST sequence is on the C-terminal domain. The protein has significant structural similarity in the N-terminal domain with cyclins G and E, while in C-terminal only with cyclin G. High expression of cyclin I was demonstrated in postmitotic tissues, for example, heart, brain and skeletal muscle. Furthermore, cyclin I binds to the Cdk5 and activates it. In turn, activated Cdk5 plays a key role in postmitotic neurons, through participation in synaptic signaling, neuron development and migration. Moreover, the protein is a pivotal factor in the process of angiogenesis, cell differentiation and survival [53,54].

Initial research conducted by Nakamura et al., 1995 [53] indicated that there is no relationship between the expression of cyclin I and the regulation of cell cycle as its mRNA level does not fluctuate during the cell cycle [53]. However, the results of Nagano et al., 2013 [54] suggest that cyclin I is involved in the progression of the cell cycle. The authors showed that along with the decrease in the expression of cyclin I, cell proliferation stopped, which was a result of the inhibition of the cell cycle in S and G2/M phases. These results may also suggest that cyclin I participates in control of the DNA replication process [54].

Another function of cyclin I in normal cells is the protection of podocytes from apoptosis after mitosis. As proven by Griffin et al., 2006 [55] maintaining the correct expression of cyclin I is extremely important for the proper functioning of podocytar cells and thus preventing the progression of kidney diseases and glomerulosclerosis. However, other studies showed that cyclin I $-/-$ cells are more susceptible to apoptosis in vitro and in vivo. This is related to the p21Cip1/Waf1 inhibitor, which action is regulated by cyclin I; p21Cip1/Waf1 interacts with procaspase-3 preventing its activation, which precludes the initiation of the apoptosis execution-phase [55]. In turn, elevated levels of cyclin I are associated with the final arrest of the growth of cardiomyocytes. Liu et al., 2007 [56] used 2-day-old cardiomyocytes and cardiomyocytes isolated from 13-day-old postnatal hearts of mice to assess the changes in cyclin I expression profile along with aging. It demonstrated that the expression level of cyclin I was significantly higher in 13-day-old cardiomyocytes. After studying the expression pattern of cyclin I in the H9c2 cell line (rat myoblasts), it was

found that the expression of cyclin was relatively low during the growth phase and increased in the growth arrest/differentiation stop phase, which confirms the results of the previous studies [56].

In addition, in the case of cancer cells, expression of cyclin I is correlated with proliferative activity and angiogenesis. As indicated by research carried out by Li et al., 2015 [57] increased cyclin I expression may promote the development of cisplatin resistance in cervical cancer (CC). The authors showed that cyclin I is overexpressed in CC cells resistant to cisplatin chemotherapy. They also confirmed that the increased level of cyclin I expression stimulates the growth of tumor cells in vitro and enhances the resistance of the tumor cells to cisplatin in vivo. This is probably due to the antiapoptotic action of cycI-Cdk5 [57]. However, overexpression of cyclin I may also promote tumor development by its participation in the angiogenesis process. Cybulski et al., 2012 [58] confirmed the association of cyclin I with vascular endothelial growth factor (VEGF) and 2 VEGF receptor (VEGFR-2), which in turn leads to angiogenesis, providing epithelial ovarian cancer cells a proliferative advantage. Moreover, elevated VEGFR-2 expression results in faster disease progression and is associated with shorter survival [58].

7. Cyclin J

Cyclin J was originally observed in a yeast two-hybrid screen for embryonic proteins that interact with Cdk2. Although the amino acid sequence of cyclin J most resembles that of the A-type cyclins, it lacks the destruction box and other consensus motifs identified in all mitotic cyclins. Cyclin J is a protein encoded by the CCNJ gene, which is localized in position q24.1 on the human chromosome 10 [59].

In normal cells, cyclin J mRNA exists in the embryo before cellularization but, as opposed to other cyclins, is not present in late embryogenesis. Kolonin et al., 2000 [60] showed that cyclin J is identified in the early embryo as a form of an active complex with Cdk2. During later embryonic development both cyclin J and the associated kinase activity are decreased before downregulation of cyclins A, B, B3 and E occurs. To study the importance of cyclin J in the syncytial embryo, the authors used peptide aptamers with the ability to specifically inhibit Cdk2 activity and applied them into embryos. The results showed that both peptide aptamers and cyclin J antibodies inhibit divisions in the early embryos [60].

In normal cells, cyclin J is localized in early embryos and ovaries, where it regulates their normal development. Atikukke et al., 2014 [61] studied ovarian mutants Drosophilia melanogaster CycJ−/−, Armi−/− and CycJ−/− Armi−/− [61]. The authors confirmed that no changes in the structure were observed in the CycJ−/− ovaries. This suggests that cyclin J is not essential for oogenesis. However, in Armi−/− ovaries they showed alterations in a structure such as ovarian malformations and only two egg chambers production. Double mutants were unable to produce eggs. Changes in their structure were also observed, i.e., the production of only one egg chamber, which contained various germline cells in excess [61].

In the case of cancer cells, Venturutti et al., 2016 [62] further implicate that the inhibition of CCNJ favors the reduction in proliferation of breast (BC) and gastric cancers (GC) cells in vitro and promotes chemosensitivity to trastuzumab and lapatinib in BC model [62]. In the previous research, it was also demonstrated that cyclin could be a novel prognostic marker of HCC and acute myeloid leukemia (AML) [63,64].

In the further in silico analysis, it was demonstrated that CCNJ is the target of miRNA-146a (miR-146a). Moreover, cell mitosis occurring during oncogenesis and embryogenesis is controlled by CCNJ. In the case of cisplatin (DDP)-resistant lung cancer cell lines, A549 and SPC-A1 transfection with miR-146a followed by treatment with DDP resulted in an intensified response to DDP by inducing cell cycle arrest and apoptosis [65,66].

8. Cyclin K

Cyclin K is a cell cycle protein. In humans, it is encoded by the CCNK gene, which can be found on chromosome 14q32.2. The protein is the most closely related to human cyclins C and H, which are members of the transcriptional cyclin family. The gene encoding human cyclin K was first isolated as a restoration of cell cycle progression (CPR) due to its participation in shaping the phenotype of the yeast Saccharomyces cerevisiae [67,68]. It also can limit lethality due to the deletion of the G1 cyclin genes, such as Ceroid-Lipofuscinosis, Neuronal 1 (CLN1), Ceroid-Lipofuscinosis, Neuronal 2 (CLN2) and Ceroid-Lipofuscinosis, Neuronal 3 (CLN3) [68]. Cyclin K binds to several cyclin-dependent kinases: Cdk9, Cdk12 and Cdk13, and activates them [69,70].

Cyclin K was initially considered as an alternative Cdk9 subunit [69]. However, later studies showed that it also binds to Cdk12 and Cdk13 (Figure 3). Both complexes (cycK-Cdk12 and cycK-Cdk13) are involved in the regulation of the transcription process but on different principles. They regulate transcription and post-transcriptional mRNA modifications by phosphorylation of the CTD of RNAPII and other transcription regulators, like negative extension factor (NELF), 5,6-dichloro-1-D-ribofuranosylbenzimidazole (DRB) or DRB sensitivity inducing factor (DSIF) [70]. Additionally, Lin et al., 2002 [67] showed that cyclin K activates the transcription process only when it is attached to RNA, suggesting that cycK-Cdk9 may be required by RNA-related proteins to their transcriptional activity [71]. However, Mori et al., 2002 [71] suggest that the cyclin K gene may be activated by a transcription factor with p53 tumor suppressor properties after treatment with adriamycin, ultraviolet radiation or gamma radiation [67,69,71]. The p53 protein is involved in the regulation of many cellular processes, in particular the activation of DNA repair mechanisms, regulation of the cell cycle and the induction of apoptosis in response to DNA damage [67].

The transcription regulators of the Cdk and cyclin families also participate in DNA repair and genome stability. Blazek et al., 2012 [70] showed that the expression of several DNA damage response genes, including some key players involved in maintaining genomic stability, depends on cycK-Cdk12. At least for breast cancer type 1 susceptibility protein (BRCA1), ataxia telangiectasia and Rad3-related protein (ATR) and Fanconi anemia, complementation group I (FANCI) regulation is at the transcriptional level. Cells that did not contain the cycK-Cdk12 induced spontaneous signaling of DNA damage as was indicated by the accumulation of 53BP1 and γ-H2AX outbreaks and an increased number of cells in the G2/M phase. Cells depleted of cycK-Cdk12 were sensitive to various DNA damaging factors, including camptothecin, mitomycin C and etoposide [72]. This sensitivity of the cells to various types of DNA damage is consistent with the proposed role of this complex in the DDR pathway and maintaining genomic stability [72,73].

In tumor cells, it is suggested that cyclin K can be a prognostic marker. Works of Schecher et al., 2017 [74] revealed that the depletion of cyclin K in prostate cancer cells results in apoptosis and inhibits tumor cell proliferation, which is caused by the cell cycle arrest in the G2/M phase. It was also shown that cyclin K, by regulating Aurora B kinase, causes cell cycle block and apoptotic cell death by inducing a mitotic catastrophe in prostate cancer cells [74].
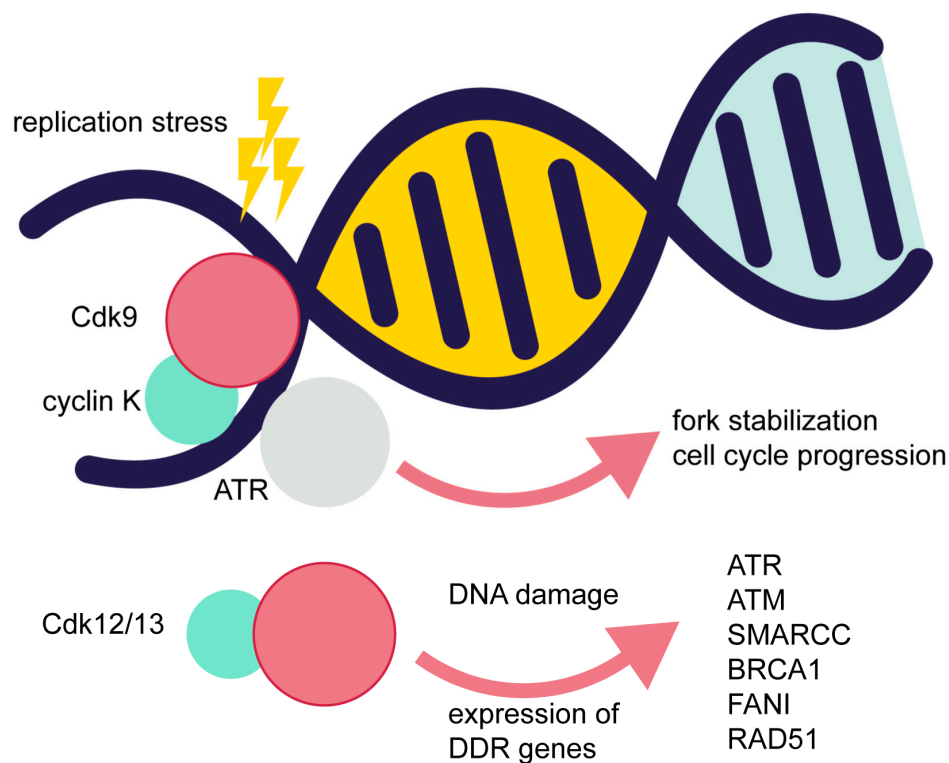
Figure 3. During the replication stress, the cyclin dependent kinase 9 (Cdk9) accumulates on chromatin and reduces the amount of single-strand breaks. Cdk9 in complex with cyclin K interacts with ataxia telangiectasia and Rad3-related protein (ATR) and other damage response proteins and provides genome stability. In the presence of DNA damage, cyclin K/Cdk12/13 complexes induces the expression of DNA damage response genes.

9. Cyclin L

Cyclin L occurs in two forms: cyclin L1 encoded by the CCNL1 gene located on human chromosome 3 at position q25.31 and cyclin L2 encoded by the CCNL2 gene located on human chromosome 1 at position p36.33 [75]. Cyclin L is the first example of cyclin, which on the N-terminal domain contains a cyclin box, while on the C-terminal domain, the domain rich in alternating arginine and serine residues (RS domain), which is characteristic for serine and arginine-rich (SR) proteins. The RS domain mainly participates in RNA splicing, processing and transport. In terms of the structure, cyclin L is most similar to cyclin K [76,77].

Human cyclins L1 and L2 have a different level of expression in various normal cells and tissues, and in tumor cells. Both forms are located in the cell nucleus [78]. Cyclin L binds and activates Cdk11, more specifically its isoform p110. Moreover, L1 and L2 cyclins may be divided into two groups. The first is the longer isoforms of L-α cyclin containing the cyclin box on the N-terminal domain, and the RS domain at the C-terminus, while shorter L-β cyclin isoforms have only the cyclin domain [75,78].

In normal cells, human L-α cyclin is involved in the regulation of pre-mRNA splicing. The L-α cyclin through the RS domain is involved in the splicing of the β-globin pre-mRNA and the E1A reporter gene. Loyer et al., 2008 [75] using the dual reporter system, showed that cyclin L1/2α and β contribute to the growth of constitutive splicing, whereas the complex of cyclin L and Cdk11p110WT intensified splicing even further. Using the second E1A minigene construct, which generates pre-mRNA, the authors demonstrated that Cdk11 p110 complexes with cyclin L1α, L2α and L2β influence the choice of an alternative splicing site [75,79].

The studies indicate the overexpression of cyclin L in head and neck cancers [79–81]. Redon et al., 2002 [80] in their research used several cell lines: CAL 27 (squamous cell carcinoma

of the tongue), FaDu (lower throat cancer) and CAL 33 (squamous cell carcinoma of the tongue). They showed that in all three types of cancer only cyclin L gene is overexpressed. They concluded that the level of cyclin L is elevated in differentiated primary tumors, resulting in an increase in the number of proliferating cells [80]. Sticht et al., 2005 [81] studied a collection of 280 cases of squamous cell carcinoma of the head and neck (HNSCC), i.e., squamous carcinoma of the mouth (OSCC), squamous cell carcinoma of the throat (PSCC) and squamous cell carcinoma of the larynx (LSCC), in search for a molecular marker corresponding to lymph nodes metastases. Their results show that elevated levels of L1 cyclin expression occur in HNSCC with locoregional lymph node metastases and independently of the anatomy and T-stage of the primary tumor. They also showed that a higher level of CCNL1 gene amplification was associated with shorter survival [81]. Amplification of the CCNL1 gene in squamous cell carcinoma was also examined by Muller et al., 2006 [79] In their studies, they showed a higher level of cyclin L expression in HNSCC. Cyclin L was located mainly in the nucleus of the head and neck malignant tumor cells. The authors suggest that overexpression of the CCNL1 gene can influence the splicing pattern of particular genes, and L1 cyclin itself may play a key role in RNA processing and contribute to HNSCC progression [79].

In turn, in the case of HCC cyclin L2 overexpression is observed. Yang et al. 2004 [76] confirmed that the increase in cyclin L2 expression in the SMMC 7721 cells causes inhibition of cell proliferation and contributes to the induction of apoptosis. Overexpression of L2 cyclin effectively counteracts SMMC 7721 antiapoptotic mechanisms, leading to an imbalance between cell cycle progression, apoptosis and cell proliferation. The researchers also observed that cyclin L in cancer cells regulates the expression of proapoptotic and antiapoptotic proteins. The results of their studies show that with the elevated L2 cyclin expression in the SMMC 7721 line, there is an increase in expression of such proteins as p53 and Bax and a decrease in the expression of Bcl-2, which results in programmed cell death [76]. Cyclin L1 is also amplified in cervical cancer and is associated with poor prognosis [78].

10. Cyclin M

Encoded by the CCNM gene, cyclin M is characterized by strong homology in sequence to the transcriptional cyclin L [82]. This recently discovered cyclin binds and activates Cdk10. In normal cells, cyclin M together with Cdk10 plays an important role in the ciliogenesis process. As was confirmed by Guen et al., 2017 [83] cycM-Cdk10 regulates ciliogenesis by modulating actin dynamics. Actin network reorganization occurs through phosphorylation of protein kinase N2 (PKN2) and activation of the RhoA pathway. The cyclin M and Cdk10 complex bind to the N-terminal domain of PKN2, which is responsible for binding to RhoA. The phosphorylation of two residues, T121 and T124, promotes the binding and stabilization of RhoA, resulting in actin polymerization and repression of primary cilia formation [83,84].

Additionally, cyclin M together with Cdk10 is involved in the regulation of the protein C-ets-2 (ETS2) transcription factor. ETS2 participates in osteogenesis and its deregulation was confirmed in many cancer types, including breast cancer [85,86]. The studies conducted by Guen et al., 2013 [87] on MCF7 line (human breast adenocarcinoma) proved that cycM-Cdk10 phosphorylates ETS2, but also positively regulates the degradation of ETS2 by proteasomes [83,86].

In normal cells, mutations in the FAM58A gene cause developmental defects associated with syndactyly, telecanthus, anogenital and renal malformations (STAR) syndrome. Unger et al., 2008 [88] after analyzing patients with STAR syndrome, showed that the activity of the cyclin M and Cdk10 complex is impaired in some tissues in various stages of development [87,88].

There is no study showing the direct effect of cyclin M alteration in cancers; however, CDK10 has been found both overexpressed and downregulated in different cancer types. Low CDL10 expression was associated with poor prognosis in gastric, biliary tract and breast cancer [89–91]. It has been suggested that inactivation of CDK10 in breast cancers

causes MAPK pathway activation. On the contrary, inactivation of CDK10 resulted in decreased tumor growth and increased BCL-2 levels in colorectal cancer [92].

11. Cyclin O

Cyclin O encoded by the CCNO gene is a protein whose molecular weight is 38 kDa. The gene encoding cyclin O is located on the long arm of chromosome 5 at position q11.2. Cyclin O mostly resembles the A- and B-type cyclins. It binds to Cdk1 and Cdk2, which leads to their activation. Cyclin O downregulation blocks the caspase activation [93].

In normal cells, cyclin O is involved in the process of central cell amplification. Funk et al., 2015 [94] researched the functions of cyclin O during deuterostome-mediated centriole amplification of multiciliated cells (MCCs). In the study, it was demonstrated that CCNO expression is limited to MCCs and its deletion in mouse reduces numbers of multiple motile cilia. This is also characteristic of MCCs dysfunctions, like severe hydrocephalus and mucociliary clearance deficits. CCNO−/− MCCs are unable to generate deuterostomes sufficiently so only a few fully functional centrioles that maturate to ciliary basal bodies are created [94].

In normal cells, cyclin O plays a key role in the development of oocytes. Ma et al., 2013 [95] studied mouse oocytes and showed that the highest expression of cyclin O occurs just in the case of these cells. The authors reported that the reduction of cyclin O expression also caused oocyte retention in the germinal vesicle (GV) stage, by CDC2 dephosphorylation. The authors suggest that cyclin O is necessary to resume oocyte meiosis [95].

In normal cells, cyclin O also participates in the normal development of the body. Núnez-Ollé et al., 2017 [96] studied two types of mice: CCNO+/− and CCNO−/−. Studies on mice with cyclin O knockout showed many developmental defects, i.e., hydrocephalus and growth retardation, and decreased ciliary motility in the fallopian tube, which resulted in infertility. Besides, they showed impairment of the central nervous system (CNS), which was manifested in irregularities in the development of the hippocampus and thinning of the cerebral cortex [96].

Cyclin O in cancer cells is overexpressed in gastric cancer (GC). Li et al., 2018 [97] studied 80 patients with stomach cancer. In their studies, they showed that cyclin O is overexpressed in this type of cancer, and also localizes mainly in the cell nucleus. The authors also showed that the reduction of cycO expression in GC cells induces the process of apoptosis, which is associated with inhibition of cell proliferation [97].

12. Cyclin T

Cyclin T exists in two forms: cyclin T1 encoded by the CCNT1 gene and cyclin T2 encoded by CCNT2. In turn, cyclin T2 may be divided into cyclin T2a and T2b, which is the result of alternative splicing. Cyclin T in the N-terminal domain contains the "cyclin box" domain, which binds to the Cdk9 kinase and the C-terminal domain with PEST [98–100]. Similar to cyclin H, the level of cyclin T does not fluctuate during the cell cycle, suggesting that it performs functions that are not specific to the cell cycle. The mRNAs of cyclin T1 and T2 occur in all human tissues. It should be noted that tissues of mesenchymal origin, such as connective tissue, skeletal muscle, myocardial cells, adipocytes, chondrocytes and endothelial cells, and blood and lymphoid tissues, show high levels of cyclin T1 expression. In turn, T2a cyclin is extensively expressed in all cell types, although higher levels occur in some terminally differentiated tissues, such as muscle, blood, lymphoid and connective tissues [99–101].

In humans, cyclin T (T1, T2a, T2b) together with Cdk9 form a complex called positive transcription elongation factor (P-TEFb), which participates in the regulation of transcription by RNA polymerase II [100]. The cyclin T itself, and the P-TEFb complex, plays an important role in normal and cancer cells. In healthy cells, the P-TEFb complex consisting of cyclin T and Cdk9 phosphorylates serine 2 in the CTD domain of RNA polymerase II to regulate the productive prolongation of transcription. Peng et al., 1998 [102] showed that any

of the three cyclin proteins (T1, T2a or T2b) complexed with Cdk9 forms the active molecule P-TEFb, which can phosphorylate CTD RNA polymerase II and cause DDR-sensitive (DNA damage response) transition from unsuccessful to productive elongation [102].

Cyclin T in normal cells, in addition to the transcription process, is involved in the regulation of other cellular processes, such as the differentiation of muscle cells, presentation, and processing of antigen, or cell proliferation. De Luca et al., 2003 [99] confirmed that the high level of cyclin T2a expression occurs in mature muscle cells, while the peak is achieved during in vitro muscle differentiation. These data suggest that the cycT2a-Cdk9 may promote myogenic differentiation by inducing the expression of specific muscle genes [101]. In turn, Leucci et al., 2007 [103] demonstrated that the expression of cycT1-Cdk9 is a pivotal element of B-cell differentiation and activation. The level of the cycT1-Cdk9 grows in B-lymphocytes, and this process takes place through the reaction with the germinal center [104]. However, after the isolation of different T cell populations, the researchers also showed an increase in the expression level of the cycT1-Cdk9. This study confirms the increased expression of the complex in T and B-cells after encountering antigen [103].

Simone et al., 2002 [105] in studies involving human cell lines, and Jurkat and HeLa, showed that cyclin T in the complex with Cdk9 interacts with the Rb protein, which has a fundamental function in regulating the point controlling the transition between G1 and S phase. The role of the Rb protein is based on the transduction of the signal that connects the cell cycle control system with transcription [105]. In turn, phosphorylation of pRb protein mediated by CycT-Cdk9 is necessary for the cell cycle progression, suggesting an important role of the cyclin also in cancer cell proliferation. Moreover, Bellan et al., 2004 [106] observed an imbalance in cyclin T and Cdk9 mRNA levels in several types of hematopoietic tumors, such as follicular lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma and Hodkin's lymphoma cell lines. Additionally, they detected high levels of cyclin T expression in lymphomas derived from B and T cell precursors [106].

13. Cyclin Y

Cyclin Y is encoded by the CCNY gene located on the short arm of chromosome 10 at position p11.21. The protein is one of the most conservative members of the cyclin superfamilies, which are known for their key role in the regulation of the cell cycle and transcription. It binds and activates two cyclin-dependent kinases: Cdk14/PFTK1 and Cdk16 [107–109].

Cyclin Y in normal cells along with Cdk14 influences the transduction of signals in the Wnt pathway by phosphorylation of low-density lipoprotein receptor-related protein 6 (LRP6) (Figure 4). Davidson et al. showed that the complex of cyclin Y with Cdk14 through phosphorylation of LRP6 prevents the degradation of β-catenin, which allows the signal transmission. Wnt receptor phosphorylation and signaling reach the maximum level in the G2/M phase, so as the expression of cyclin Y, which may suggest a relationship between these two elements [110].

In normal cells, cyclin Y plays an important role in the regulation of the spermatogenesis process. While studying the complex of cyclin Y and Cdk16, Mikolcevic et al., 2012 [108] showed that it is required in the final stages of cell differentiation in the spermatogenesis process. By studying mice with Cdk16 knockout, the authors concluded that they are infertile. Although they contained all cell types at various stages of spermatogenesis, the study of sperm cells showed many irregularities in their structure, which ultimately led to infertility [108].
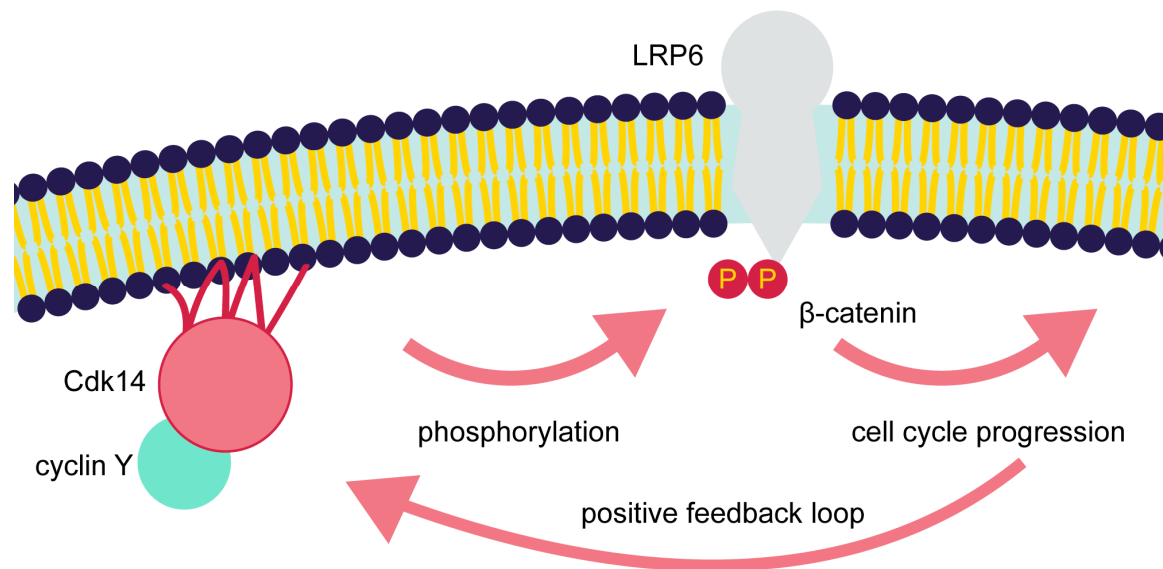
Figure 4. CDK14/cyclin Y complex activates Wnt signaling through LRP6 phosphorylation during the G2/M phase.

Furthermore, the expression of cyclin Y plays a key role in tumorigenesis. Yue et al., 2010 [111] demonstrated that nonsmall cell lung cancer (NSCLC) is characterized by cyclin Y overexpression. Moreover, the expression of cyclin Y positively correlates with the histological subtypes of NSCLC, and the size of the tumor. It was also shown that the decrease in cyclin Y expression in the NSCLC cells leads to inhibition of tumor proliferation and growth [109]. Increased expression of cyclin Y has also been detected in the ovarian tumor. Liu et al., 2016 [112] showed that cyclin Y enhances the proliferation rate, migration and invasion of ovarian cancer cells by regulating the Wnt signaling pathway [112].

Cyclin Y is also overexpressed in glioma and larynx cancer. The studies conducted by Xu et al., 2009 [113] proved that lowering the expression of cyclin Y results in inhibition of cell proliferation and colony formation, and the arrest of cell cycle progression in glioma cells. Tai et al., 2013 [114] came to similar conclusions after studying the expression of cyclin Y in laryngeal cancer [113,114]. Moreover, the overexpression of cyclin Y is observed in breast, colon and liver cancers [109,115,116].

14. Summary

Recent studies have indicated that the role of cyclins is not limited to regulating events directly related to the cell cycle (see Table 1). Newly discovered functions of proteins such as less known cyclins and their involvement in transcription processes, DNA repair or metabolism regulation can, however, be considered as completely "independent of the cell cycle". Fluctuation in the expression of cyclins allows for time-specific control of cell activity and preparation for extremely complex changes occurring during the cell cycle. Abnormal expression of cyclins contributes to the formation of tumors of different types. Tumor cells are characterized by uncontrolled proliferation; therefore, the levels of expression of the proteins regulating the cycle are variable. Expression monitoring can help to estimate the risk of cancer and allows for quick diagnosis. Due to a large amount of new data on cyclins, the current state of knowledge should be considered far from complete and further research on this group of proteins is necessary. This is particularly important in the context of subsequent literature reports concerning cell cycle proteins (such as cyclins, cyclin-dependent kinase inhibitors and Cdks) in cancer therapy and diagnosis.

Table 1. The biological functions of the less-known cyclins in normal cells.

Protein	Function in Normal Cells	References
Cyclin C	RNAPII transcription in complex with Cdk8 Transmission of the oxidative stress Cell's exit from the G0 phase through phosphorylation of the retinoblastoma protein (Rb) in complex with Cdk3 Regulation of G1 and G2 phases	Ježek et al., 2019 [7] Ganesan et al., 2019 [10] Ren et al., 2004 [12] Liu cet al., 1998 [14]
Cyclin F	Synthesis, stability and repair of DNA Transcription Cell proliferation Embryogenesis	D'Angiolella et al., 2010 [24] D'Angiolella et al., 2012 [25] Klein et al., 2015 [27] Klein et al., 2015 [27] Tetzlaff et al., 2004 [28]
Cyclin G	Transcription The p53-Mdm2 pathway	Ohtsuka et al., 2004 [36] Chen et al., 2002 [37]
Cyclin H	Transcription in the CAK complex	Patel et al., 2010 [49]
Cyclin I	Cell cycle Protection of podocytes from apoptosis after mitosis Final arrest of growth of cardiomyocytes	Nagano et al., 2013 [54] Griffin et al., 2006[55] Liu et al., 2007 [56]
Cyclin J	Early embryogenesis in complex with Cdk2 Normal development of the ovaries	Kolonin et al., 2000 [60] Atikukke et al., 2014 [61]
Cyclin K	RNAPII transcription in complex with Cdk9, Cdk12 or Cdk13 DNA repair and genome stability in complex with Cdk12	Mori et al., 2002 [71] Kohoutek et al., 2012 [70] Blazek et al., 2011 [72]
Cyclin L	Regulation of pre-mRNA splicing in complex with Cdk11	Loyer et al., 2008 [75]
Cyclin M	Ciliogenesis proces in complex with Cdk10 Regulation of the protein C-ets-2 (ETS2) transcription factor in complex with Cdk10	Guen et al., 2017[83] Guen et al., 2013 [87]
Cyclin O	Process of central cell amplification Development of oocytes Normal development of the body	Funk et al., 2015 [94] Ma et al., 2013 [95] Núnez-Ollé et al., 2017 [96]
Cyclin T	RNAPII transcription in complex with Cdk9 Differentiation of muscle cells in complex with Cdk9 Presentation and processing of antigen in complex with Cdk9 Cell proliferation in complex with Cdk9 Differentiation and activation B-cell in complex with Cdk9	De Luca et al., 2001 [100] Peng et al., 1998 [102] De Luca et al., 2001 [101] De Falco et al., 2008 [104]
Cyclin Y	Wnt-B-catenin pathway in complex with Cdk14 Spermatogenesis in complex with Cdk16	Davidson et al., 2009 [110] Mikolcevic et al., 2012 [108]

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