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Review

The Role of G1/S Phase Cyclins in Colorectal Cancer: A Review

Hawbash M. Rahim[1,2*], Omer Ates[1], Fahmi H. Kakamad[3,4], Marwan N. Hassan[4], Berun A. Abdalla[4], Hiwa O. Abdullah[4], Shvan H. Mohammed[4], Rawezh Q. Salih[4], Fakher Abdullah[5]

1. *Department of Medical Biology, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey*
2. *Smart Health Tower, Madam Mitterrand Str, Sulaimani, Kurdistan, Iraq*
3. *College of Medicine, University of Sulaimani, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq*
4. *Kscien Organization, Hamdi Str, Azadi Mall, Sulaimani, Kurdistan, Iraq*
5. *Kscien Organization (Europe office), Verboomstraat 175b, 3082 jj Rotterdam, Netherlands*

[*] ***Corresponding author***: *hawbash.mhamad96@gmail.com (H.M. Amin). Mamostayan City, Building C7, Apartment 54, Zip code: 46000, Sulaimani, Iraq*

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Abstract

Colorectal cancer is a highly prevalent cancer with a high mortality rate. Although the colorectal carcinogenesis mechanism is not fully understood yet, it has been proven that most cancers result from the accumulation of genetic mutations, mostly in the genes responsible for cell cycle regulation, leading to uncontrolled and excessive cell growth. Hence, cyclins may have a significant role in cancer development and progression. Although many studies have been carried out on the expression of these cyclin proteins to indicate their role in colorectal cancer development and their correlation with patient outcome, the currently available data is quite controversial; thus, no certain conclusions can be made. This review article summarizes current knowledge regarding the role of G1/S cyclins, such as cyclin D, E, and A, in colorectal cancer and discusses their potential as prognostic biomarkers and therapeutic targets. Hence, it may provide the groundwork for future research.

1. Introduction

1.1 Epidemiology of colorectal cancer

Colorectal cancer (CRC) is a type of cancer that usually develops in the cell lining of parts of the large intestine, such as the colon and rectum, which has the ability to become metastatic and invade other parts of the body [1]. Colorectal cancer is the third most prevalent cancer type, and, despite the appearance of better diagnostic methods and a better understanding of molecular mechanisms leading to CRC, it is one of the most severe cancers that has the highest tendency to exhibit metastatic disease, associated with poor results and a high death ratio [2]. The statistics of CRC in 2020 show that it is responsible for 10% of cancer cases and fatalities, with above 1.8 million new cases and 935,000 mortalities related to CRC occurring annually [3]. Colorectal cancer incidence rates vary widely across regions and countries; however, it has been observed that the number of cases is about 3 times higher in developed countries versus

developing countries [4]. Globally, the incidence rate of CRC is continuously increasing, and the prevalence of CRC is expected to double by 2040 [5].

1.2. Risk factors for CRC

Several risk factors have been linked to the development of CRC, including age, family history, diet, physical inactivity, smoking, and alcohol consumption. The risk of CRC development increases with age, as nine-tenths of cases occur in individuals older than 50 [6]. A family history of CRC, especially in first-degree relatives, is also a significant risk factor. The increase in CRC incidence has also been attributed to the rapid move towards westernized diet and lifestyle, such as a diet high in saturated fats, low in vegetables and fruits, and high in red and processed meats, as they have been linked to an increased risk of CRC [1,7].

1.3. Genetic parameters associated with CRC

Colorectal cancer is a complex condition that results from a combination of environmental and genetic factors. While most CRCs are sporadic, up to 30% of cases are attributed to hereditary factors, and genetic factors play a critical role in the development of CRC [8]. Several genetic syndromes, such as Lynch syndrome and familial adenomatous polyposis, have been linked to increased CRC risk. Genetic testing is recommended for people with a family history of CRC or other related cancers to identify those at risk and provide appropriate surveillance and management [9].

1.4. The progression of CRC

Uncontrolled and excessive cell growth through the cell cycle is the defining characteristic of cancer. CRC development usually has a multi-step progression that begins as a benign tumor, which will progress into adenomatous polyps and likely become malignant. Furthermore, during this period, it provides an opportunity for diagnosis and in-depth prognosis of the disease [10]. The colorectal carcinogenesis mechanism is still not fully understood. Still, it has been proven that most cancers result from the accumulation of genetic mutations, mostly in the genes responsible for cell cycle regulation [11]. The inactivation of tumor suppressor genes is stated to be the first genetic event in CRC carcinogenesis, especially p53 which is the most mutated tumor suppressor gene found in 50% of various cancers and 75% of tumors [12].

2. An overview of the eukaryotic cell cycle

The cell cycle is known as a sequence of events that results in the production of two genetically identical daughter cells out of one mother cell through the duplication of the mother cell's DNA and the division of its cytoplasm. The eukaryotic cell cycle includes 2 primary phases; a) the interphase, in which the cell grows, replicates DNA, and prepares to divide, and b) the Mitotic (M) phase, in which the cell undergoes cell division. Further breakdown of the phases includes G1, S, G2, and M, with G0 describing the resting phase outside the cell cycle [13].

Over many years, a significant amount of time and resources have been dedicated to comprehending the processes that govern the cell cycle. As a result of these efforts, a detailed but not yet finished understanding has been reached, revealing that the cell cycle in eukaryotic cells is finely tuned and regulated by cyclins and cyclin-dependent kinases (CDKs) that serve as promoters of growth signals and kinase inhibitors that act as suppressors of growth signals [14]; together, they ensure accurate completion of each phase of the cell cycle. The activation of CDK enzymes by cyclins regulates and controls the progression of the cell cycle, enabling the cell to enter the cell cycle and progress through the different phases [15].

2.1. Cyclins

Cyclins act as key regulatory proteins in the eukaryotic cell cycle and are responsible for controlling proper cell proliferation, DNA replication, and chromosome segregation. As their name suggests, these cyclins continuously undergo synthesis and degradation throughout different stages of the cell cycle. To date, 8 families of cyclins and 11 sub-types (A, B1-2, C, D1-3, E, F, G, and H) have been identified [16]. However, five mammalian cyclin classes directly participate in cell cycle regulation: cyclin A, B, C, D, and E [17].

Depending on their role and when they are expressed throughout the cell cycle, there are 4 classes of cyclins which include G1 cyclins; which control the entry of the cell into the cell cycle, G1/S cyclins, S cyclins, and M cyclins; which control the cell cycle transitions. During different phases of the cell cycle, the concentration of each cyclin subtype fluctuates. The progression of the cell cycle requires the activation and inactivation of many cellular proteins. Cyclins alone do not have any enzymatic activity, and for them to be able to control and drive the cell cycle, they have to bind to a family of enzymes called CDKs and form an activated complex [18]. The concentration of cyclins is controlled by a complex network of feedback loops involving different protein members. Each group of cyclins has a distinct preference for binding with CDK family members, which leads to the phosphorylation of a unique set of proteins [19].

2.2. Cyclin-dependent kinases

Cyclin-dependent kinases are a protein family of serine/threonine kinases that are activated by non-enzymatic cyclin proteins. The CDKs family is reportedly composed of 20 subtypes across the eukaryotic kingdom, named CDK1 to CDK20, but only 8 of them are present in humans. Activated CDKs have the ability to control and regulate the different stages of the eukaryotic cell cycle by phosphorylating different types of target cellular proteins. Cyclin-dependent kinases alone are inactive, but when they bind and form a complex with cyclins, it makes them an activated enzyme capable of attaching phosphate groups to modify target proteins, making them either more or less active. Cyclin-dependent kinases are also regulated by CDK inhibitors, which can act as tumor suppressors. Even though the cyclin concentration fluctuates across the different stages of the cell cycle, these CDKs are expressed consistently during all stages. Abnormalities in either CDKs or partner cyclins in any of the phases activate a signal that leads to a cell cycle halt until the problem is resolved [20,21].

2.3. The essential role of CDK/cyclin interactions in cell cycle control

The interaction between cyclins and CDKs is crucial for the regulation of the cell cycle. Each type of cyclin is produced and broken down at particular stages of the cell cycle and will bind to specific CDKs, which will in turn either activate or inactivate specific proteins that will drive the cycle through the different stages. Hence, different cyclin/CDK complexes are active at different the cell cycle stages, and their activities are tightly regulated by various mechanisms [17].

Cyclin D, which mostly belongs to G1 phase cyclins, is involved in the entry of a cell into the cell cycle and prepares transition into the S phase in response to environmental signals or growth factors. Cyclin D binds to and activates CDK4 and CDK6 as the cell leaves the resting phase (G0), which phosphorylates tumor suppressor protein Rb and relieves its inhibition function. It also induces the synthesis of cyclin E. Cyclin C is a less understood cyclin that has been reported to be also involved in controlling a cell's entry into the cell cycle (G1) via binding to various CDKs (1/2/3). Cyclin E (G1/S cyclins) participates in the G1/S transition by activating CDK2 and pushing cells past a restriction point into the S phase. Cyclin A (S cyclins) is a multi-phase cyclin that appears in the S phase, binds with CDK2 to initiate complete DNA replication, and also binds to CDK1 through the G2 phase. Cyclin B belongs to M cyclins and is shown to be active through G2 and M phases. Later it will bind to CDK1 to form a complex that controls the cell's entry and exit into and out of mitosis and cytokinesis [17,22,23].

The importance of cyclin/CDK interactions in cell cycle regulation has been confirmed by knockout studies. For instance, a new threshold model of cell cycle control has been proposed based on the results of cyclin and CDK-knockout studies. Moreover, dysregulation of cyclin/CDK interactions has been implicated in cancer development and progression, and CDK inhibitors have emerged as a promising class of drug for cancer treatment [24]. Overall, understanding the complex interplay between cyclins, CDKs, and CDK inhibitors is essential for gaining insights into the molecular mechanisms of cell cycle regulation and developing novel cancer therapies.

3. Cell cycle control and cancer

The process of cell division is closely monitored and controlled by various mechanisms that have evolved over time. The cell cycle is regulated by checkpoints that function as surveillance mechanisms for DNA, preventing the spread of genetic errors during cell division. These checkpoints can either pause the cell cycle or force the cell to stop dividing or undergo apoptosis if there is irreversible DNA damage [25]. Alterations in any of the different components or machinery that control the decisions in the cell cycle can cause an imbalance that allows cells to acquire an excessive cell growth ability. Hence, cyclins may have a significant role in cancer development and progression. Mutations linked to cancer can disrupt cell cycle regulation, making it difficult for cells to exit the cycle and leading to unchecked cell division. The difference in cyclins' concentration in a specific phase of the cell cycle makes them a good candidate for prognostic markers of cancer research [22,23].

Recent evidence indicates that the majority of functions that regulate the cell cycle are critical for the survival of cancer cells. In cancer cells, the checkpoint related to DNA damage is often compromised, enabling uninterrupted cell division in spite of the build-up of genetic errors. Whereas mutation rarely occurs in the replication stress checkpoint genes as many cancers rely heavily on checkpoint function to endure high levels of replication stress [25].

Several cyclin abnormalities have been reported in several types of cancer, especially in cyclins A, E, and D. Multiple causes are likely to bring forth the oncogenic properties of these cyclins, for instance, gene amplification, chromosomal translocations, and protein overexpression [11].

Regarding cyclin D, it has been reported that overexpression of the protein is involved in the development of many cancers [26]. Cyclin D1 (CCND1 gene) expression has been shown to be decreased in high-grade epithelial ovarian carcinoma in comparison to lower grades [27]. Similarly, the expression of cyclin D1 was found to be inversely proportional to the grade of clear cell renal cell carcinoma (ccRCC), with higher grades being associated with lower expression of the protein. Whereas cyclin D1's expression is upregulated in ccRCC in comparison to normal tissues [28]. High D1 expression was also observed in low-grade breast cancer, associated with a good prognosis [29]. On the other hand, some investigations have reported that upregulated cyclin D1 expression in lung cancer [30], esophageal cancer [31], oral cancer [32], and gastric cancer, indicate rapid tumor proliferation, survival rate reduction, and increased invasiveness and cancer grade [33]. Additionally, a meta-analysis study has shown overexpression of cyclin D2 (a cyclin D isomer, CCND2 gene) in digestive system cancers (such as pancreatic rectum adenocarcinoma, ductal adenocarcinoma, and gastric cancer), breast cancer, excretory system cancers (such as ovarian cancer, kidney renal papillary cell cancer, pheochromocytoma, and paraganglioma), to be associated with a higher frequency of tumor metastasis. Similarly, upregulation of cyclin D3 (CCND3 gene) has also been observed in breast cancer [33] and bladder cancer [34]; however, in both cancers, the protein's expression did not seem to be correlated to tumor prognosis. From the above findings, we may conclude that the expression results contradict in different types of cancer.

On the expression of cyclin E, an article studying meningiomas showed that cyclin E1 (CCNE1 gene) expression was upregulated in grade II compared to grade I tumors [35]. The same observation was made in an ovarian cancer investigation [36]. Ubiquitin protein ligase oversees cyclin E1 breakdown in normal cells. However, overexpression of cyclin E1 makes the G1/S phase shorter, resulting in excessive cell division and undergoing premature DNA replication [10,35]. Moreover, two investigations reported overexpressed cyclin E in osteosarcoma cancer [37,38]. Regarding cyclin E2, it has been stated that the protein is overexpressed in tissues of esophageal cancer; however, no correlation has been found between this upregulation and the cancer's grade or histological characteristics [31].

The expression of cyclin A protein in different cancers has been investigated in multiple studies, which mostly reported its upregulation and the accumulation in the cell [39]. Cyclin A2 (CCNA2 gene) was found to be overexpressed in breast cancer and was linked with poor prognosis [40]. However, according to a single study, abnormal expression of cyclin A2 had no statistically significant correlation with cancer stage or patient outcome, although their findings revealed lower cyclin A2 expression in adenocarcinoma in non-small cell lung cancer (NSCLC) than squamous cell carcinoma [41]. Overall, it can be said that cyclin A2 expression in cancers exhibits prognostic features correlated with overall patient survival [42].

It is worth noting that most of the mentioned investigations studied protein expression, and only a few have analyzed mRNA expression through reverse transcriptase polymerase chain reaction (RT-PCR). Hence there is a need for more research to analyze the expression of the mRNAs of specific cyclins in particular cancer types to understand prognostic values and also exploit their functions to bring forward new cancer treatment methods.

4. The importance of studying proteins involved in cell cycle regulation in different cancers

In cancer patients, cyclins could be potential anti-cancer therapeutic targets. Several studies demonstrate that the suppression or knockdown of cyclin D1 and cyclin E1 genes could induce apoptosis and reduce excessive growth and invasiveness of some cancer cell lines [16,43]. Some studies conducted on mice embryos report that the disruption of a cyclin D or E gene might not usually be lethal to the cells, despite obvious abnormalities in the tissues. This could mean that another sub-type of cyclin D or E might compensate for the loss of its sub-type by reacting with the associated CDK protein; this property might cause resistance to targeted therapies that inhibit cyclin expression. On the other hand, the knockdown of cyclin A2 will result in embryonic lethality closely post-implantation, indicating a lack of compensating counterpart [44].

As cancer cells are highly reliant on cell cycle control regulatory pathways, these processes can be considered targets for anti-cancer agents [25]. Hence, it is essential to study key players in cell cycle control mechanisms in normal tissues in comparison to different cancer tissues; this can guide us to develop more specific and effective drugs for cancer control. For this purpose, the exploitation of several cell cycle control pathways has been described, such as:

Forced exit from the cell cycle: Continued proliferation of cancer cells is essential for tumor growth. Cyclin-dependent kinase activity is the primary driver of cell cycle progression, and in various cancers, increased activity of CDKs has been frequently described; this makes them potential anti-cancer targets [45]. Cyclin-dependent kinase inhibitors can have the potential to stop continued cell cycle progression and force cancer cells to go into a senescent state and permanently come out of the cell cycle, preventing tumor growth as a result [46].

Excessive DNA damage generation: Exploiting cancer dependence on cell cycle regulatory pathways either through chemotherapy or radiation, can lead to extreme levels of genome instability; thus cause cancer cell death more so than normal cells [47]. This exploit is yet the most effective cancer management method [25]; however, it also induces DNA damage in healthy cells and harms them in the process.

Inducing uncontrolled cell cycle progression: This is the exact opposite of forcing the exit of cancer from the cell cycle; instead, this method promotes CDK activity and puts cell cycle progression into overdrive. Cyclin-dependent kinase inhibitors delay or halt the cell cycle till specific conditions are fulfilled. It is believed that cancer cells become highly dependent on these CDK inhibitors to stop DNA damage propagation [48]. In line with this, a CDK inhibitor such as p21 is very uncommonly mutated in human cancer [49]; meanwhile, WEE1 CDK inhibitor is expressed at high levels in different types of cancer [50]. Hence, targeting these two CDK inhibitors can potentially compromise the ability of cancer cells to prevent DNA damage propagation, thereby leading to the generation and accumulation of excessive levels of DNA damage and thus inducing cancer cell death.

5. G1/S cyclins in CRC

As CRC is one of the top causes of cancer-related mortality, and, as previously mentioned, its incidence is increasing. Therefore, there is a need to identify new biomarkers and therapeutic targets for early diagnosis and management of CRC. G1/S cyclins, such as cyclin D1, cyclin E, and cyclin A, have been reported to play a critical role in regulating the cell cycle, and their dysregulation has been linked to the development and progression of CRC.

Studying G1/S cyclins in CRC can help in the diagnosis of the disease. The expression levels of cyclin D1, cyclin E, and cyclin A have been shown to be altered in CRC, and these alterations are associated with the clinicopathological features of the disease, such as tumor size, stage, and grade [51]. Therefore, the analysis of G1/S cyclin expression levels can help in the diagnosis and prognostication of CRC.

Deregulation or overexpression of cyclin D1 will disturb the cell cycle and will likely cause further deregulation and mutations in the DNA replication phase, which might lead to tumor formation and malignancy. In more than one-third of CRC cases, cyclin D1 has been reported to be upregulated [44,52]. Multiple review studies indicate that a common single nucleotide polymorphism in the CCND1 gene (G870A) (rs9344) might be a risk factor for CRC, especially amongst Caucasians and Asians [52,53]. However, it is also mentioned in other studies that no associations have been found between the CCND1 gene polymorphism and CRC risk [54]. Multiple investigations have been conducted to evaluate cyclin D1's prognostic significance. Although several studies report them as a useful prognostic marker for CRC, the exact significance is still not determined [55]. Some studies report cyclin D1 as a poor prognosis indicator of CRC [34,52,56,57]. A meta-analysis of 22 studies with a total of 4,150 patients found that overexpression of Cyclin D1 was significantly associated with poor overall survival in CRC

patients [51]. Some other reports describe them as good indicators of CRC [58]. A recent study in 2023 investigated cyclin D1 expression in 495 surgically removed CRC tissues and stated that the protein is overexpressed in 78.6% of cases, in which the expression was described as a favorable prognostic indicator [59]. Meanwhile, other studies show no prognostic significance [51,60,61].

Cyclin E1 is a cell cycle regulatory protein that is synthesized in G1 and aids in the transition from the G1 phase to the S phase. It has been reported in many types of cancer that the overexpression of cyclin E1 indicates an advanced tumor stage and poor prognosis [10]. Meanwhile, few studies suggest that the knockdown of the CCNE1 gene in murine CRC cells prevents tumor formation and invasiveness [62]. The currently available literature is quite controversial, even suggesting the correlation between survivability and cyclin E1 expression; thus, no certain conclusions can be made.

On the other hand, cyclin A is involved in DNA replication in the S phase. Low expression of cyclin A is associated with multiple types of cancer and also CRC. It is reported that the deletion of its gene results in CRC tumor formation and venous invasion. Cyclin A is reported to be a good prognostic factor [63]. In a recent meta-analysis, heterogenous expression of cyclin A2 was reported, the tumor was upregulated in the primary tumor of CRC, but those associated with metastasis had a lower expression of the protein compared to the primary tumor, indicating lower protein synthesis in higher-stage tumors (III and IV) [64]. Another study reported similar results in colorectal adenocarcinoma [65]. However, another study correlated cyclin A2 overexpression in rectal cancer with poor prognosis [39].

Overall, dysregulation of G1/S cyclins plays a critical role in CRC development and progression, and targeting these proteins may represent a promising therapeutic strategy for the treatment of this disease; however, it has also been postulated that targeted therapy against a single specific pathway of CRC cells might not prove effective due to the activation of compensatory pathways [64].

6. Future perspectives

The identification of G1/S cyclins as critical drivers of CRC has led to the development of targeted therapies that hold promise for the treatment of this disease. However, there is still much that remains to be done in order to fully understand the mechanisms of action of these agents and to optimize their clinical use. Even though there are a heap of studies have been performed on cyclins expression in other cancers, including CRC, the findings seem to be ending up with contradictory conclusions, which could be due to the small pool of epidemiological data, and the pattern of G1/S phase cyclins expression and the interaction among these cyclin members need to be identified.

One area of ongoing research is the development of more specific CDK inhibitors. Currently, available CDK inhibitors target multiple CDKs, which can lead to off-target effects and toxicity. The development of more selective CDK inhibitors that specifically target the G1/S cyclin-CDK4/6 pathway may improve the efficacy and safety of these agents [66].

Another area of research is the identification of biomarkers that can predict response to CDK inhibitors. Several studies have suggested that the expression of certain cyclins and CDKs may be predictive of response to CDK inhibitors [67]. The identification of reliable biomarkers may help to optimize patient selection and improve treatment outcomes.

Additionally, the combination of CDK inhibitors with other targeted therapies is an area of active investigation. For example, preclinical studies have demonstrated the potential benefit of combining CDK inhibitors with EGFR inhibitors in CRC [66]. Further investigation is needed to identify optimal combinations and to understand the mechanisms of synergy between these agents.

Finally, the development of strategies to overcome resistance to CDK inhibitors is an important area of ongoing research. Resistance can be caused by multiple mechanisms, including the upregulation of other cyclins and CDKs, as well as mutations in the CDKs themselves [68]. Developing strategies to overcome resistance will be critical for improving the long-term efficacy of CDK inhibitors in the treatment of CRC.

7. Conclusion

Although many studies have been carried out on the expression of these cyclin proteins to indicate their role in carcinogenesis and their significance as potential prognosis biomarkers in CRC, the absolute significance is yet to be established. Although the literature mostly supports the notion of using cyclins, especially cyclins D and E, as promising tumor biomarkers for the diagnosis and prognosis of patient survivability in CRC cases, further extensive studies are required to establish such a notion, especially amongst different populations to provide a larger pool of epidemiological data. Targeting these proteins represents a promising therapeutic strategy. Further research is also needed here to fully understand their mechanisms of action to optimize their use in the treatment of CRC and to determine whether other types of cyclins compensate for the loss of a selected cyclin gene knockdown.

Declarations

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