

REVIEW ARTICLE

Aberrant G1/S Phase Cyclins in Human Cancer Tissues

Sarminiyy Lenga Gururuloo¹, Doblin Anak Sandai¹, Md Salzihan Md Salleh², Muhammad Asyraf Abduraman¹, Siti Nurfatimah Mohd Shahpudin¹

¹ Advanced Medical and Dental Institute, University Sains Malaysia, 13200 Kepala Batas, Pulau Pinang, Malaysia

² Department of Pathology, School of Medical Sciences, Health Campus University Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Cancers are classified into numeric staging or grading systems to better know the behaviour of cancer. These grading and staging have a strong correlation with the expression of cyclin in the cell cycle because cancer cells drive cell progression by overriding the control of cell regulators. Abnormalities in the cyclins' activity are the hallmark of tumorigenesis. Even though the cyclin D isomers comparatively share similar amino acids, their variety in expression has proven to have a distinctive role in cancer progression and it is the only cyclin that has been widely elucidated in various types of cancer since the late 80's. Likewise, recently cyclin E and cyclin A are also being explored widely for their oncogenesis properties. In the current review, we emphasize insights on the latest findings on G1/S phase aberrant cyclins; D, E and A expressions which are determined using various human tumour tissues.

Keywords: Tissue, Cancer, Cell cycle, Cyclins, Dysregulation

Corresponding Author:

Siti Nurfatimah Mohd Shahpudin, PhD

Email: sitinurfatimah.ms@usm.my

Tel: +604-5622316

INTRODUCTION

Over ten million deaths were recorded in the cancer statistics of the year 2020 by World Health Organization (WHO) (1). Where the most leading cancers are breast cancer followed by lung, colon and rectum, prostate, skin, and stomach cancers. Abnormalities of tumours are classified by grades and stages. There are three grading which is from grade I to III. Grade I tumours appear to be same as normal cells with very low division rate. Whereas in grade II also known as intermediate grade cancer cells are dissimilar to the normal cells and the cell division rate is higher than grade I. In grade III, cells begin to divide rapidly and exhibit abnormal appearance (2). Cancer stages comprises of two types one is the tumor, nodes and metastases (TNM) staging system, the other one is numeric staging system which mostly been used in clinical field (3). This staging and grading of cancer are highly associated in the cell regulator expression for the prognostic and cancer progression. Oncologists' discoveries on the cyclin dependent kinase 1 (CDK1) in yeast and followed by over 13 CDKs (4) and 25 cyclins that homologs in cyclin box has provided enormous insights in the medical and research field today (5). The G1/S phase cyclins which are cyclin D, cyclin E and cyclin A owns protruding responsibility in urging cancer development due to their aberrant expression

throughout the cell (6–10). Hence it is essential to study the expression of cyclins in both mRNA and protein level to have a better view on the abnormal mechanisms. In current review, we emphasis insights on the latest G1/S phase cyclins expression which is determined using various human tumour tissues.

STANDARD G1/S PHASE CYCLINS MECHANISM

Human genome comprises of as a minimum 30 different genes that holds cyclin box, a domain of amino acids which are shared by all cyclins (7,11). Cyclins are specialized proteins which are produced cyclically in each cell cycle phases where it will be degraded once the cell is transitioned from one phase to another. This canonical type of cyclins; D, E, A and B couples with specific CDKs to form a protein complex. Canonical CDKs such as CDK4/6, CDK2 & CDK1 has three binding sites which are called as cyclin-binding domain, ATP-binding domain, and T-loop activator site. Cyclins bind at the cyclin-binding domain of CDKs to form active heterodimer complexes for cell cycle progression (9,12) as in Figure 1. Isomers of D-type cyclins were discovered in the 90's and it was later labelled as the connector between mitogenic signals and cell cycle progression. Upon receiving the mitogenic signals by RAS-RAF-MAPK cascade and transcription of cyclin D gene takes place (13). Subsequently with the activation of cyclin D/CDK4/6 complexes (14), it phosphorylates the retinoblastoma protein family; Rb1, Rb2, and Rb3 also known as pocket proteins. The unphosphorylated Rb-E2F complexes act as G1/S phase transition

repressor. Ahead of phosphorylating Rb family by cyclin D, induction of cyclin D degradation takes place in the early S phase subsequent to the elevated cyclin E expression in the late G1 phase (15). Simultaneously, cyclin E/CDK2 complexes form and will phosphorylate the Rb1 to freely release E2F transcription factors. Then, the monomeric cyclin E will undergo ubiquitination process for degradation (16). The free E2F transcription factors induce the transcription of cyclin A, where now the cells can successfully pass through the G1/S phase checkpoint. Throughout the S phase, cyclin A/CDK2 complexes are responsible in phosphorylating many molecules for DNA replication. At the centrosomes, cyclin A is in charge of preventing reduplication of DNA (7). Right after cyclin E degrades and frees CDK2. Cyclin A is ready to form complexes with CDK2 and aids the cell progression through S phase. The common role of cyclin A/CDK2 complexes is to carry out DNA synthesis in the nucleus. Additionally, these complexes also oversee the entry of cells into G2 phase where the cyclin A2-CDK2 complexes relocate to the centrosome sites to activate the cyclin B-CDK1 complexes. Upon completion of S phase, G2 phase and mitosis phase progression will be activated by the cyclin A/CDK1 and cyclin B/CDK1 complexes respectively (17).

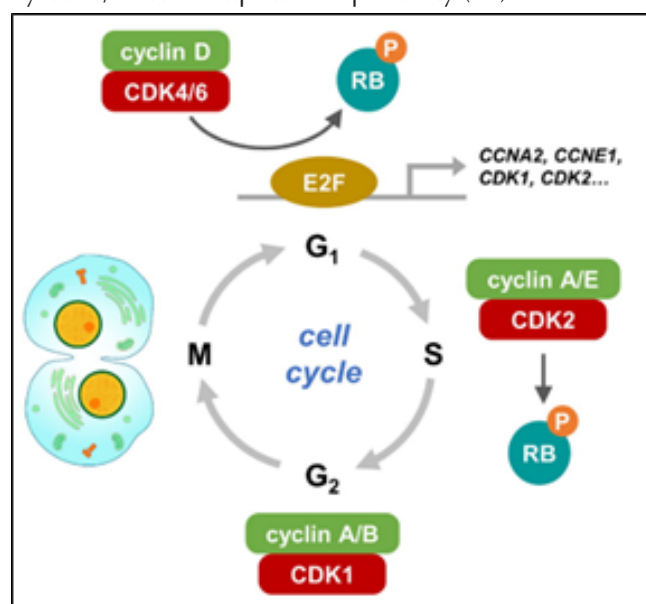


Figure 1: Schematic representation of specific cyclin-CDK complexes. In G1 phase cyclin D binds with CDK4 or CDK6 and in the early S phase, cyclin E binds to CDK2. In the mid to late S phase, cyclin A binds to CDK2. Adapted from (18).

MALFUNCTIONS OF CYCLINS IN CANCERS

Cyclin D

Most of the tumor development are caused by overexpression of cyclin D. Overexpression of cyclin D can lead to two possibilities where the first is when the cyclin D-CDK complex accumulates in the nucleus and runs the excessive cell proliferation mechanism. Next is when the cells progress to S phase, the cyclin D are localized into cytoplasm for degradation. However, due

to high level of cyclin D content in the cytoplasm, the cyclin D readily phosphorylates the scaffold protein in the cytoplasm to lower the cell adhesion and escalate the cell migration and invasion which indicates that the tumor is undergoing metastatic phase (34). In the search of cyclin D expression in various cancer, epithelial ovarian carcinoma expressed low cyclin D1 protein in the high-grade serous carcinoma (HGSC) which was stated to be main cause of most ovarian cancer (19). Correspondingly, cyclin D1 (CCND1) were inversely proportional to the grades of clear cell renal cell carcinoma patients (ccRCC) where low expression observed in higher grades. However, in comparison with normal adjacent tissue, the expression of cyclin D1 were upregulated in ccRCC (20). The lower cancer grade recorded high CCND1 transcripts and cyclin D1 expression in breast cancer with good prognosis factor (21) was postulated that high mRNA expression of cyclin D1 might be the reason of high protein expression of cyclin D1 (22,23). In contrast, some groups reported that oral cancer (24), oesophageal cancer (25), colorectal cancer (26–29), lung cancer (30), and gastric cancer with upregulated CCND1 indicated reduction in malignancy survival rate and rapid tumour proliferation and spreading throughout the body with the increasing grade of cancer (31). On the other hand, the meta-analysis of breast cancer, digestive system cancers such as gastric cancer, pancreatic ductal adenocarcinoma and rectum adenocarcinoma, excretory system cancers such as pheochromocytoma and paraganglioma, kidney renal papillary cell cancer as well as reproductive system cancers such as ovarian cancer and uterine corpus endometrial carcinoma are reported to have overexpression of CCND2 (31) that leads to tumour metastases. Similarly, overexpression of CCND3 were also found in the bladder cancer (32) and breast cancer (33) however no correlation were found with the tumor prognosis in both cancers. In addition to that, evidence show that positive protein expression in cyclin D2 and D3 can be associated with the phosphorylated Rb expression such in oesophageal cancer (25). In general, despite CCND1 (32), it was stated that these two isoforms, CCND2 and CCND3 also had strong contribution in determining the prognostic outcomes such as overall survival rate (32) in many cancers. From the statement above we understand that cyclin D is not only responsible for cell proliferation, it also has yet to be discovered functions in the cancer progression other than initiating cell proliferation (19) and cell migration (26) correlated to its contradict expression result in different tumor.

Cyclin E

The expression pattern of cyclin E1 were stated to have no correlation with one's sex, age, and tumour location. In meningiomas study, results showed that cyclin E1 expression were found to be overexpressed in grade II compared to grade I (35) likewise was found in the ovarian cancer study (36). Similarly, overexpression

of cyclin E were discovered in colorectal cancer were correlated with occurrence and TNM staging where the higher the staging of TNM, the higher the cyclin E expression were uncovered by comparing to the normal tissues (37). In normal cells, ubiquitin protein ligase (UPL) oversees cyclin E degradation. However, overexpressed of cyclin E1 shortens the G1/S phase (35) because it halts the UPL complex activity concomitantly conducting the Rb-E2F phosphorylation activity which leads to excessive cell proliferation and differentiation (37) those cells undergo premature DNA replication (35). In addition to that, two different studies focusing on osteosarcoma cancer reported overexpression of cyclin E (38,39). However, one of the studies explained that overexpression of cyclin E can be directly correlated with the tumor progression without the Rb-E2F pathway since the study found that the expression of CCNE1 were inversely proportional to the Rb1 protein (39). In another study, it was stated that cyclin E2 had positive expression in the oesophageal cancer tissues but had no correlation with the histological characteristics or grade (25). From the above findings, it is obvious that most of the studies proved that abnormalities in cyclin E expression has strong correlation with the cancer staging and could contribute to tumor progression which is suggested to be a cancer predictive biomarker (36,38).

Cyclin A

Cyclin A isoforms has a strong role in cell cycle especially in DNA replication and segregation of chromosome, this is because according to the catalytic activity of cyclin A/CDK2, it is proven to be crucial in the centrosome duplication process as well as in the segregation of sister chromatid in the S phase (40). The overexpression of cyclin A protein reported in many studies could be due to the reduction of cyclin A protein degradation activity causing the accumulation of protein in the cell (23) as the basic operation of cyclins is to be synthesized when needed and degraded once the role is done. Latest meta-analysis finding on the role of cyclin A2 (CCNA2) in colon homeostasis and colorectal cancer (CRC) revealed that the expression of cyclin A2 in the patients was heterogenous and two main cases were observed. First, up-regulation of CCNA2 transcripts observed in cancer patients with primary tumour of CRC. On the contrary, compared to primary tumour, metastases tumours in CRC had lower CCNA2 transcripts expression. Which means, expression of CCNA2 were higher in stage I and II and lower in stage III and IV (40). Apart from transcripts or mRNA expression, the protein expression of cyclin A2 were also stated to express highly in early stages than later stages of colorectal (III and IV) (40) and likewise results were obtain in colorectal adenocarcinoma in a study done previously and stated that metastasis colon cancer has lower cyclin A2 expression than primary tumor (41). Similar pattern of cyclin A2 overexpression were found in rectal cancer (23) and breast cancer (42) and were correlated with poor prognosis (23,42) and decreasing rate of local recurrence (23). However, one

findings explored that abnormal cyclin A expression had no statistical correlation with prognostic values associating with cancer stages although the results showed higher cyclin A expression in squamous cell carcinoma than adenocarcinoma in non-small cell lung cancer (NSCLC) (43). Therefore, different expression of cyclin A2 in cancers exhibited essential predictive characteristic which was correlated with overall survival rate of patients and thus suggested to be a good diagnostic markers (17) in cancers.

Most of the papers that were reviewed in current study were widely investigated in the expression of D, E and A with gold standard method, IHC (17,19,22,26,38,40,42,44). IHC is convenient to perform due to its straightforward method and rapid result generation (20). However, this method is limited to only study on the protein expression and not the mRNA expression in tissues. Correspondingly, a meta-analysis study conducted with qualified findings from year 1995 to 2017 in cyclin D1 expression in various cancer found out that most of the test were only done with IHC and relatively lesser in RT-PCR or mRNA (22,23,37,40,42,45) study (46). Transcription and translation are the primary strides of protein synthesis. Cells acts as controller and keep in check of genes that should and should not transcribe and translate (47). Next, postulation from the few studies stating that high expression in transcripts/mRNA cyclins could have strong correlation to the high expression of proteins of cyclins (22,23,42) in cancer shows a compelling justification to the need of more mRNA expression studies in cancer. Hence, the exploration of mRNA expression in various study could be a prominent prognostic biomarker to treat cancers.

CONCLUSION

In spite of the study restricted mostly protein expression and very few mRNA expression, current study demonstrated that low protein expression of cyclin D1 in ovarian cancer, breast cancer and clear cell renal cell carcinoma (ccRCC) as well as low mRNA expression of cyclin D1 in breast cancer were explored in the increasing grading of cancer had good prognosis. In contradictory, elevated of cyclin D1 expression were found in higher grading of cancer with reduction of malignancy survival rate in oral cancer, gastric cancer, colorectal cancer, lung cancer, and oesophageal cancer. The cyclin D2 was also overexpressed in breast cancer, gastrointestinal cancer, excretory organ cancer and reproductive organ cancer leading the tumor to invade and spread. Even though, cyclin D3 exhibited high expression as cyclin D1 and cyclin D2 in bladder and breast cancer, no correlations were found with tumour prognosis value. The pattern of cyclin E expression in meningiomas, ovarian cancer, colorectal cancer and osteosarcoma tumour was upregulated in higher cancer grade compared to the lower ones and upregulation of cyclin E shorten the G1 phase by ubiquitination

process. However, esophageal cancer did not show any correlation with the grade although it had positive cyclin E expression. For cyclin A2 expression, the pattern was from high in early stage of colon cancer, rectal cancer, breast cancer, and squamous cell carcinoma (NSCLC). All of these cancer with high expression of cyclin A in early stage showed poor prognosis except NSCLC. In a nutshell, we can see that the abnormalities in expression G1/S phase cyclins in most of the cancer had strong correlation with cancer grades and prognostic values. We also found out that more studies are needed to significantly justify the protein and gene amplification of the G1/S phase cyclins to paves better understanding on the precise molecular role of these crucial regulatory proteins in cancer for better cancer treatment in future. Therefore, to affirm the prognostic significance of cyclin D, E and A levels in different malignancies, well-designed studies based on cancer forms and diverse target both mRNA and protein in expression study are advised.

ACKNOWLEDGEMENTS

The authors acknowledge the assistance provided by the Short-Term Grant (304/CIPPT/6315244). We would like to also thank Dr. Mowaffaq Adam for his unconditional guidance for writing this paper.

REFERENCES

- World Health Organization. Cancer [Internet]. 2020 [cited 2021 Oct 5]. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>
- Cancer Research UK. Cancer grading | Cancer Research UK [Internet]. 2017 [cited 2021 May 2]. Available from: <https://www.cancerresearchuk.org/about-cancer/what-is-cancer/cancer-grading>
- Cancer Research. Stages of cancer – Cancer Research UK. 2014 [cited 2021 May 2];8(1):13–22. Available from: <https://www.cancerresearchuk.org/about-cancer/what-is-cancer/stages-of-cancer>
- Lim S, Kaldis P. Cdks, cyclins and CKIs: Roles beyond cell cycle regulation. *Dev*. 2013;140(15):3079–93.
- Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. Minireview: Cyclin D1: Normal and abnormal functions. *Endocrinology*. 2004;145(12):5439–47.
- Sherr CJ, Sicinski P. The D-Type Cyclins: A Historical Perspective. 2018. 1–26 p.
- Martínez-Alonso D, Malumbres M. Mammalian cell cycle cyclins [Internet]. Vol. 107, *Seminars in Cell and Developmental Biology*. Elsevier; 2020. p. 28–35. Available from: <https://doi.org/10.1016/j.semcdb.2020.03.009>
- Stamatakis M, Palla V, Karaikos I, Xiomeritis K, Alexiou I, Pateras I, et al. Cell cyclins: Triggering elements of cancer or not? *World J Surg Oncol*. 2010;8:1–8.
- Bitar S Al, Gali-Muhtasib H. The Role of the Cyclin Dependent Kinase Inhibitor p21cip1/waf1 in Targeting Cancer: Molecular Mechanisms and Novel Therapeutics Samar. *Cancers (Basel)*. 2019;11(1475):1–21.
- Johansson M, Persson J. Cancer Therapy: Targeting Cell Cycle Regulators. *Anticancer Agents Med Chem*. 2012;8(7):723–31.
- Quandt E, Ribeiro MPC, Clotet J. Atypical cyclins: the extended family portrait [Internet]. Vol. 77, *Cellular and Molecular Life Sciences*. Springer International Publishing; 2020. p. 231–42. Available from: <https://doi.org/10.1007/s00018-019-03262-7>
- Chou J, Quigley DA, Robinson TM, Feng FY, Ashworth A. Transcription-associated cyclin-dependent kinases as targets and biomarkers for cancer therapy. *Cancer Discov*. 2020;10(3):351–70.
- García-Reyes B, Kretz AL, Ruff JP, Karstedt S von, Hillenbrand A, Knippschild U, et al. The emerging role of cyclin-dependent kinases (CDKs) in pancreatic ductal adenocarcinoma. *Int J Mol Sci*. 2018;19(10):9–11.
- Peyressat M, Prével C, Pellerano M, Morris C. M. Targeting cyclin-dependent kinases in human cancers: From small molecules to peptide inhibitors. *Cancers (Basel)*. 2015;7(1):179–237.
- Zhang J, Su G, Lin Y, Meng W, Lai JKL, Qiao L, et al. Targeting cyclin-dependent kinases in gastrointestinal cancer therapy. *Discov Med*. 2019;27(146):27–36.
- Obaya AJ, Sedivy JM. Regulation of cyclin-Cdk activity in mammalian cells. *Cell Mol Life Sci*. 2002;59(1):126–42.
- Brcic L, Heidinger M, Sever AZ, Zacharias M, Jakopovic M, Fediuk M, et al. Prognostic value of cyclin A2 and B1 expression in lung carcinoids. *Pathology*. 2019;51(5):481–6.
- Mok MT, Zhou J, Tang W, Zeng X, Oliver AW, Ward SE, et al. CCRK is a novel signalling hub exploitable in cancer immunotherapy. *Pharmacol Ther* [Internet]. 2018;186(March):138–51. Available from: <https://doi.org/10.1016/j.pharmthera.2018.01.008>
- Soares N, Illeis F, Silva DB, Baiocchi G, Alves MR, Augusto F, et al. Downregulation of AGR2 , p21 , and cyclin D and alterations in p53 function were associated with tumor progression and chemotherapy resistance in epithelial ovarian carcinoma. 2018;(November 2017):3188–99.
- Wang Q shui, Li F, Liao Z qiang, Li K, Yang X liu, Lin Y yu, et al. Low level of Cyclin-D1 correlates with worse prognosis of clear cell renal cell carcinoma patients. *Cancer Med*. 2019;8(9):4100–9.
- Ortiz AB, Garcia D, Vicente Y, Palka M, Bellas C, Martin P. Prognostic significance of cyclin D1 protein expression and gene amplification in invasive breast carcinoma. *PLoS One [Internet]*. 2017;12(11):e0188068. Available from: <https://doi.org/10.1371/journal.pone.0188068>

22. Peurala E, Koivunen P, Haapasaari K-M, Bloigu R, Jukkola-Vuorinen A. The prognostic significance and value of cyclin D1, CDK4 and p16 in human breast cancer. *Breast Cancer Res* [Internet]. 2013;15. Available from: <https://doi.org/10.1186/bcr3376>
23. Aamodt R, Jonsdottir K, Andersen SN, Bondi J, Bukholm G, Bukholm IRK. Differences in protein expression and gene amplification of cyclins between colon and rectal adenocarcinomas. *Gastroenterol Res Pract*. 2009;9.
24. Ramos-García P, González-Moles MB, González-Ruiz L, Aydın B, Ruiz-Bvila I, Bravo M, et al. Clinicopathological significance of tumor cyclin D1 expression in oral cancer. *Arch Oral Biol* [Internet]. 2019;99(November 2018):177–82. Available from: <https://doi.org/10.1016/j.archoralbio.2019.01.018>
25. Wang S, Yao Y, Zhang Y, Wang K, Deng Z, Jiang Z, et al. Correlation between the protein expression levels of A-kinase cyclin E2 in esophageal cancer tissues. 2019;(February):1–5.
26. Albasri AM, Elkablawy MA, Ansari IA, Alhujaily AS. Prognostic significance of cyclin D1 overexpression in colorectal cancer: An experience from Madinah, Saudi Arabia. *Asian Pacific J Cancer Prev*. 2019;20(8):2471–6.
27. Kitamura H, Takemura H, Minamoto T. Tumor p16 INK4 gene expression and prognosis in colorectal cancer. *Oncol Rep*. 2019;41(2):1367–76.
28. Fang Y, Liang X, Jiang W, Li J, Xu J, Cai X. Cyclin b1 suppresses colorectal cancer invasion and metastasis by regulating e-cadherin. *PLoS One*. 2015;10(5).
29. Girardi DM, Silva ACB, Rizzo JFM, Coudry RA, Riechelmann RP. Unraveling molecular pathways of poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: A systematic review. *Cancer Treat Rev* [Internet]. 2017;56:28–35. Available from: <http://dx.doi.org/10.1016/j.ctrv.2017.04.002>
30. Fang L, Xu X, Zheng W, Wu L, Wan H. The expression of microRNA-340 and cyclin D1 and its relationship with the clinicopathological characteristics and prognosis of lung cancer. *Asian J Surg* [Internet]. 2021;(xxxx). Available from: <https://doi.org/10.1016/j.asjsur.2021.02.009>
31. Ding Z, Li R, Zhang Q, Wang Y, Jiang Y, Meng Q, et al. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms: A systematic review and meta-analysis. *Cancer Med*. 2019;8(6):2717–29.
32. Shan YS, Hsu HP, Lai MD, Hung YH, Wang CY, Yen MC, et al. Cyclin D1 overexpression correlates with poor tumor differentiation and prognosis in gastric cancer. *Oncol Lett*. 2017;14(4):4517–26.
33. Ding Z. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms : A systematic review and meta-analysis. 2019;(November 2018):1–13.
34. Fusté NP, Ferrezuelo F, Garza E. Molecular & Cellular Oncology Cyclin D1 promotes tumor cell invasion and metastasis by cytoplasmic mechanisms. 2016; Available from: <http://dx.doi.org/10.1080/23723556.2016.1203471>
35. Pereira BJA, Santana Júnior PA de, de Almeida AN, Cavalcante SG, de Melo KCM, de Aguiar PHP, et al. Cyclin E1 expression and malignancy in meningiomas. *Clin Neurol Neurosurg* [Internet]. 2020;190(January):105647. Available from: <https://doi.org/10.1016/j.clineuro.2019.105647>
36. Nakayama N, Nakayama K, Shamima Y, Ishikawa M, Katagiri A, Iida K, et al. Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer. *Cancer*. 2010;116(11):2621–34.
37. Li W, Zhang G, Wang HL, Wang L. Analysis of expression of cyclin E, p27kip1 and Ki67 protein in colorectal cancer tissues and its value for diagnosis, treatment and prognosis of disease. *Eur Rev Med Pharmacol Sci*. 2016;20(23):4874–9.
38. Thanindratarn P, Duan Z, Wei R, Thanindratarn P, Dean DC, Horneck FJ, et al. Cyclin E1 is a prognostic biomarker and potential therapeutic target in osteosarcoma. *J Orthop Res* [Internet]. :0–1. Available from: <http://dx.doi.org/10.1002/jor.24659>
39. Lockwood WW, Stack D, Morris T, Grehan D, O'Keane C, Stewart GL, et al. Cyclin E1 is amplified and overexpressed in osteosarcoma. *J Mol Diagnostics* [Internet]. 2011;13(3):289–96. Available from: <http://dx.doi.org/10.1016/j.jmoldx.2010.11.020>
40. Guo Y, Gabola M, Lattanzio R, Paul C, Pinet V, Tang R, et al. Cyclin A2 maintains colon homeostasis and is a prognostic factor in colorectal cancer. *J Clin Invest*. 2021;131(4).
41. Arsic N et al. A novel function for Cyclin A2: control of cell invasion via RhoA signalling. *J Cell Biol*. 2012;196(1):147–62.
42. Husdal A, Bukholm G, Bukholm IRK. The prognostic value and overexpression of cyclin A is correlated with gene amplification of both cyclin A and cyclin E in breast cancer patient. *Cell Oncol*. 2006;28(3):107–16.
43. Kosacka M, Piesiak P, Porebska I, Korzeniewska A, Dyla T, Jankowska R. Cyclin A and Cyclin E Expression in Resected Non-small Cell Lung Cancer Stage I-IIIa. *In Vivo (Brooklyn)*. 2009;23(4):519–25.
44. Schraml P, Bucher C, Bissig H, Nocito A, Haas P, Wilber K, et al. Cyclin E overexpression and amplification in human tumours. *J Pathol*. 2003;200(3):375–82.
45. Bahnassy A, Zekri A, El-Houssini S, El-Shehaby A, Mahmoud M, Abdallah S, et al. Cyclin A and cyclin D1 as significant prognostic markers in colorectal cancer patients. *BMC Gastroenterol*. 2004;4:22.
46. Moradi Binabaj M, Bahrami A, Khazaei M, Ryzhikov M, Ferns GA, Avan A, et al. The

prognostic value of cyclin D1 expression in the survival of cancer patients: A meta-analysis. *Gene* [Internet]. 2020;728:144283. Available from: <https://doi.org/10.1016/j.gene.2019.144283>

47. Hoopes L. Gene Expression | Learn Science at Scitable. 2008 [cited 2021 May 4]; Nature Education. Available from: <https://www.nature.com/scitable/topicpage/gene-expression-14121669/>