STUDENT CORNER

Biological Role of CDK 11 and 12 in Cell Cycle and its Function in Tumorigenesis

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ABSTRACT

Uninhibited proliferation and abnormal cell cycle regulation are the hallmarks of cancer. The main role of cyclin dependent kinases is to regulate the cell cycle and cell proliferation. These protein kinases are frequently down regulated or up regulated in various cancers. Two CDK family members, CDK 11 and 12, have contradicting views about their roles in different cancers. For example, one study suggests that the CDK 11 isoforms, p58, inhibits growth of breast cancer whereas, the CDK 11 isoform, p110, is highly expressed in breast tumor. Studies regarding CDK 12 show variation of opinion towards different parts of the body, however there is a consensus that upregulation of cdk12 increases the risk of breast cancer. Hence, CDK 11 and CDK 12 need to be analyzed to confirm their mechanism and their role regarding therapeutics, prognostic value, and ethnicity in cancer. This article gives an outline on both CDKs of information known up to date from Medline, PubMed, Google Scholar and Web of Science search engines, which were explored and thirty relevant researches were finalized.

Keywords: Cyclin-Dependent Kinases; Cancer; Cell Cycle; CDK 11; CDK 12.

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INTRODUCTION

The cell cycle is an essential component of cell-biology that controls cell growth and duplication. Cell cycle control mechanisms by protein phosphorylation involving a highly regulated kinase family called cell cycle regulator or "cyclin dependent kinases (CDKs)". The mechanism of these processes is that cyclins bind to CDKS. As a result, the cyclin/CDK complex phosphorylates a target protein and is then degraded. Development and progression of cancer are usually connected by many changes in the activity of cell cycle regulators. In human, twenty distinct family members of CDKs have been described. CDK 2 plays an important role in replication during S phase[1-5]. However, there does not seem to be much research on other CDKs. For example, two such CDKs are 11 and 12. Research indicates that both CDKs belong to the serine threonine family[6]. There are limited studies on CDK 11 that state that it has important function in cancer cell growth and proliferation[7]. Furthermore, various genetic and epigenetic actions are suspected to cause increased expression of CDK 11 in certain cancers. Especially for breast cancer, CDK 11 is debated to be both over and under expressed[8]. As for CDK 12, it is considered a transcription related kinase that participates in DNA damage response, splicing, cellular differentiation, and pre mRNA processing[9]. Specifically in breast cancer, it is debated to be overexpressed[10]. Therefore, this article will focus on CDK 11 and 12 because of their role in the prognosis of different cancers.

DISCUSSION

The cell cycle is when growing cells replicate their own components and divide into two daughter cells[11]. There are four stages in the cell cycle, which includes G1, S, G2 and M phase[12]. G1 and G2 are resting phases for cell growth. These stages have checkpoints that make sure the cell is prepared to move forward to the next phase. S phase is a stage for DNA replication. M phase is a stage for cell division. These two phases are considered active phases. Dysregulation of different CDKs, such as

CDK11 and 12, can give us a finer understanding on how the cell cycle is affected and how cancer progresses.

CDK 11 has critical roles in different cancers. For example, expression of CDK 11 has major roles in osteosarcoma cell growth[13]. If Cdk11 is inhibited it can reduce the invasion of osteosarcoma cells. Another article states that expression of CDK 11 has a role in melanoma survival by interacting with proto oncogenes, BRAF and nRAS[14]. If CDK11 is inhibited it can cause death of melanoma cells. Therefore, CDK11 is involved in multiple cancers.

CDK11 has three different isoforms: p110, p58, and p46[7]. Each isoform has different roles. The p110 isoform is has a major role in pre mRNA splicing[15]. The p58 isoform has a major role in centrosome maturation and cytokinesis[16]. The p46 isoform has a major role in apoptosis by acting on Ran binding protein and activating caspases[17]. Because of these varying functions of different isoforms CDK 11 has varying effects in different cancers (Table 1).

The major effects have been studied on isoforms p110 and p58. The p110 isoforms effects show that overexpression causes cancer cell growth. For example, in esophageal squamous cell carcinoma cancer cell growth is majorly associated with expression of cdk11 (p110)[18] . The mechanism as to how this works is unknown (Figure 1). Furthermore, the p110 isoform is highly expressed in breast tumor tissue[8]. However, the mechanism for this is also unknown. On the other hand, the p58 isoform inhibits the growth of breast cancer[19]. This is done by inhibiting mRNA levels of VGEF that reduces angiogenesis of tumor cells. The P58 isomer seems to have other roles besides cancer such as maturation of testis in mice[20]. It also has a role in apoptosis of neuronal cells after being affected by Lipopolysaccharide[21]. Due to these varying studies, there is a need to have an overall understanding on what affect CDK 11 has on different cancer cell tissues (Figure 2a, b).

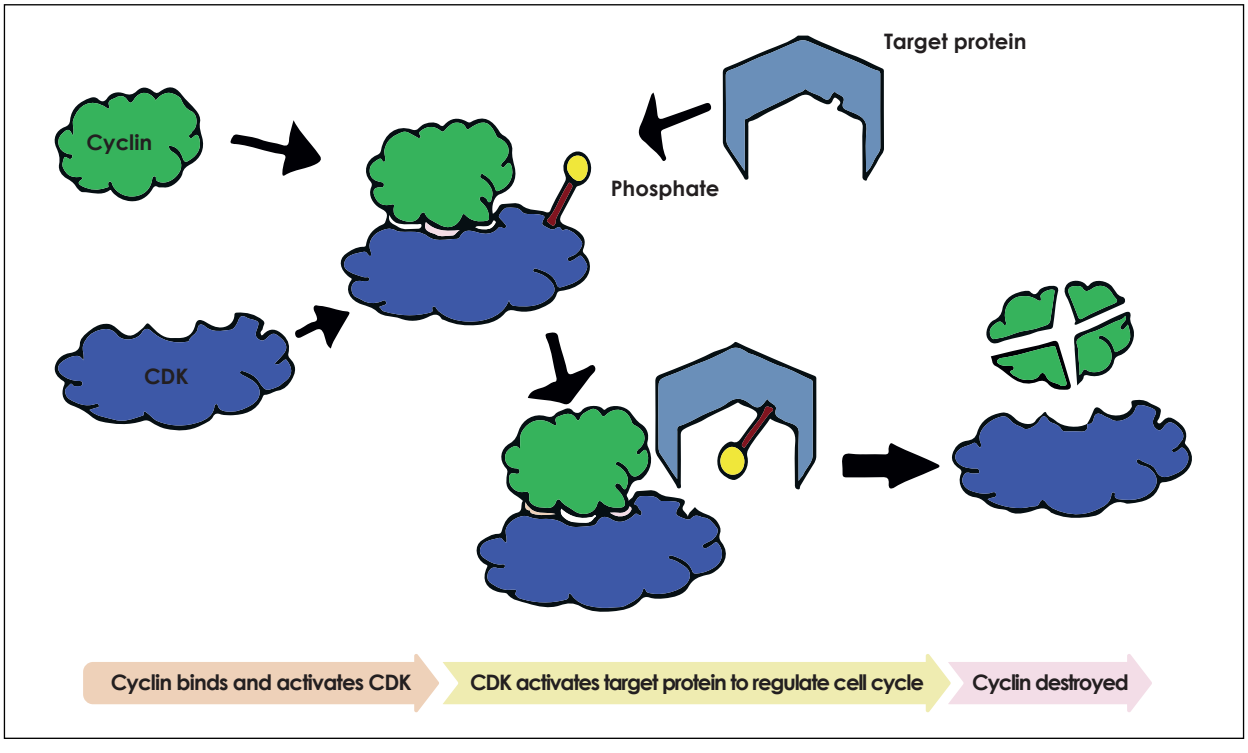

Figure 1: Mechanism of action of CDK with cyclins.

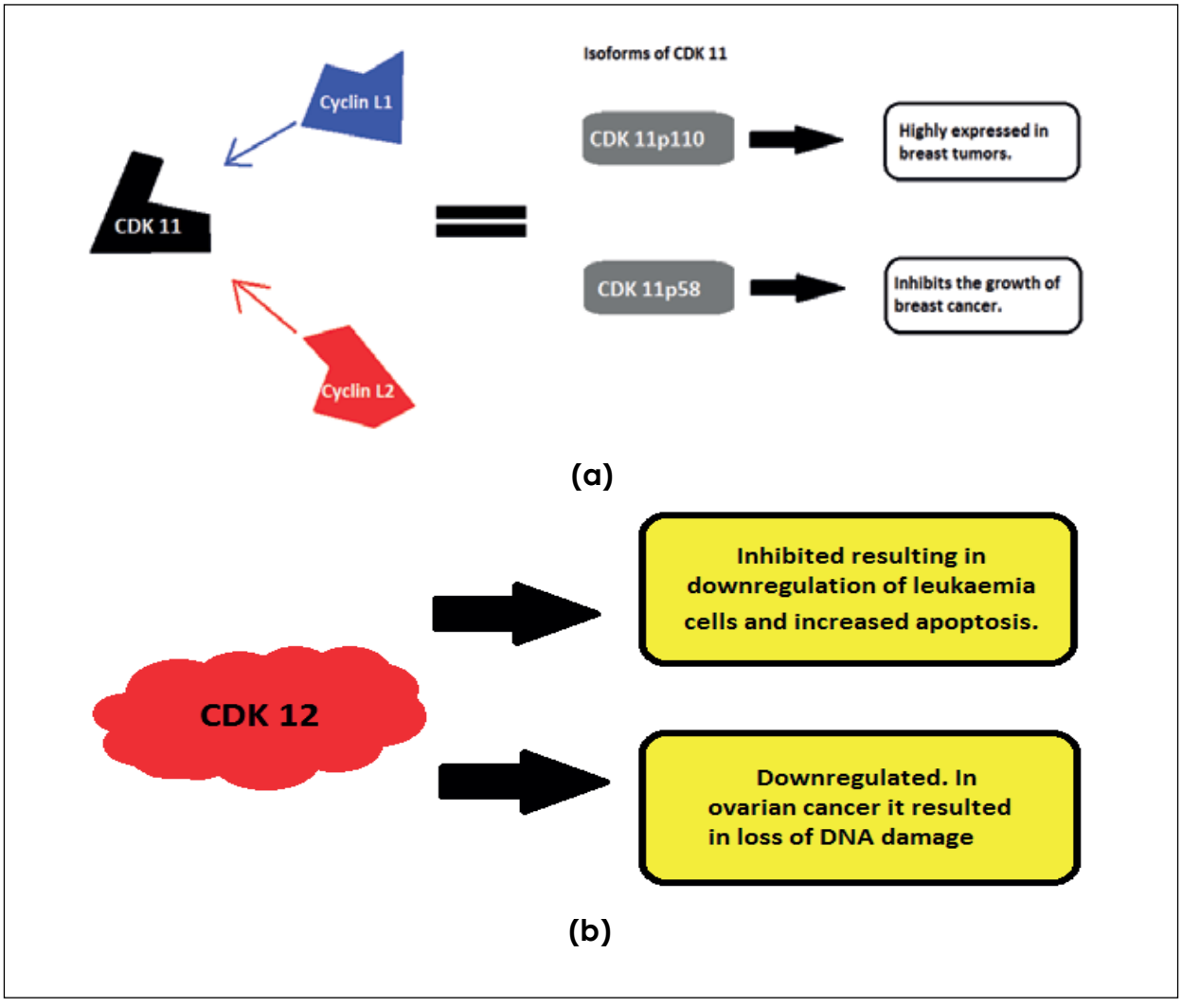

Figure 2: (a) Action of CDK 11 and (b) Action of CDK 12.

Table 1: Studies on CDK 11 and CDK 12 in various cancers.

Study Type	Patient Group	Principle Findings
Clinical Trial[18]	Eight patients with non-small-cell lung carcinoma along with bone metastasis participated.	Out of all the genes responsible for Lung cancer signaling pathways, fibroblast growth factor receptor and CDK12 were the only ones found to be mutated in all eight patients.
Cohort Study[19]	240 patients with ovarian cancer in the late stage.	In the cohort of patients, no genes, ATM, ATR, Chk2 polymorphisms have been found to significantly affect the overall survivaland progression.
Clinical trial[20]	Patients with circulating tumor cells as well as paired leukocytes with metastatic castration resistant prostate cancer.	All patients with metastatic Castration-Resistant Prostate Cancer (mCRPC) also had resistance to Abiraterone acetate or Enzalutamide (primary or acquired). Furthermore genomic gains were observed to be >25% in many genes including CDK12.

Cohort study[21]	556 patients of ovarian carcinoma, 760 patients of breast carcinoma as well as 401 patients of prostate carcinoma.	An increased prevalence of interstitial gains is associated with CDK12 inactivation. Tandem duplication results in regular gains in CDK12 mutated ovarian tumors.
Clinical trial[22]	2 patients diagnosed with breast adenoid cystic carcinoma with eterogeneous morphology associated with triple negative breast cancer area of high grade.	In the second patient, three additional mutations were limited to STAG2, KDM6A, and CDK12 to high-grade triple – negative breast cancer.
Cross sectional[23]	105 gnomically annotated breast cancers.	Highly phosphorylated kinases associated with amplicon have been identified, CDK12, PAK1, PTK2, RIPK2, and TLK2.
Case Control[24]	Immediately after surgical resection, 18 parts of breast tumor samples with adjacent normal tissues were collected. No patients were treated before operation.	In each of the tested breast tumor tissue samples, CDK11p110 was highly expressed as to the normal tissues ($p<0.01$). Various histological staining characteristics showed high levels of expression of CDK11p110, mainly in BT-474, MCF-7, and MDA-MB-468 cells.
Case control[25]	A total of 78 samples of epithelial ovarian cancer.	CDK11 levels in metastatic samples (average 2.08, $p< 0.01$), recurrent samples (average 2.269, $p<0.01$) were significantly higher than in primary samples (average 1.207)
Case Control[26]	For tissue microarrays, 250 FFPE blocks of breast cancer tissues and ANCT have been collected. Thus, 2 tissue cores for breast cancer and 2 ANCT cores from the FFPE blocks of the same patient.	CDK11 levels in metastatic samples (average 2.08, $p< 0.01$), recurrent samples (average 2.269, $p<0.01$) were significantly higher than in primary samples (average 1.207)

CDK 12 is responsible for responding to DNA damage, splicing, pre-mRNA processing, cellular development, and cellular differentiation[27]. CDK 12 has contrary views on its function. In one article, inhibiting it resulted in downregulation of leukemia cells and increased apoptosis[28]. However, in a study on serous ovarian cancer, downregulation of CDK 12 resulted in loss of DNA damage repair[29]. Down regulation had caused expression of tandem repeats in a patient. This evidence emphasizes that it has varying opinion on different areas of the body. In terms of breast cancer, the consensus seems to be that it increases the chances of breast cancer. According to Mertens et al, amplification of cdk12 is one of the causes to somatic mutations in breast cancer[29]. The pathology to CDK 12 and breast cancer is unclear. Tien et al hinted that CDK12 has a role in alternative splicing of mRNA strands, which is considered a factor to invasive cells in breast cancer[10]. However, it is important to reassure these results because some articles state that cdk12 has a role in tumor suppression[27].

CDKs give a better understanding towards the cell cycle and cancer. If studies figure out where each CDK is over or under expressed during cancer then this information can give clues to provide better treatment such as CDK inhibitors. Even though studies have been done on cdk11 and 12, several of them contradict each other. More studies must be done to confirm certain findings (Figure 3). Moreover, certain studies must be done to see whether certain CDKs being expressed have an ethnic relevance or not. In conclusion, there is information about CDKs, but there are many gaps to be filled.

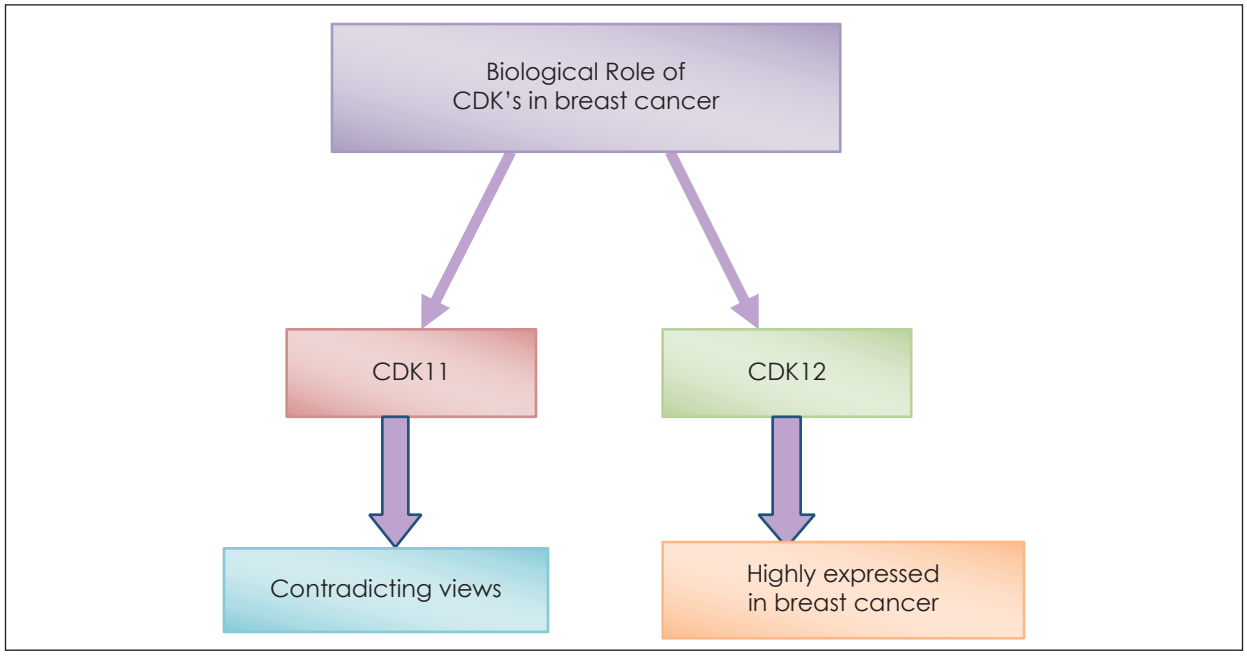

Figure 3: Summarized biological roles of CDK 11 and 12.

CONCLUSION

Studies on CDK 11 and 12 explain that their expression can indicate prognosis for different cancers. These CDKs seem to vary in expression during different cancers. Specifically, for breast cancer, CDK 11 has contradicting views on expression, whereas CDK 12 research seems to lean towards overexpression in breast cancer. Even though this seems to be the trend, findings need to be confirmed on a much larger scale. There could be a chance that ethnicity and region may play a larger role in amounts of expression. Once understood scientist can further act on this information by creating CDK inhibitors to fight cancers. There are already studies on CDK inhibitors, but there has not been much progress. Therefore, cdk11, and 12 must be studied to analyze greater importance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

All authors contributed equally in this write-up.

REFERENCES

1. Malumbres M. Cyclin-dependent kinases. Genome Biol. 2014;15(6):122-132.
2. Malumbres M, Barbacid M. Mammalian cyclin-dependent kinases. Trends Biochem Sci. 2005;30(11): 630-641.
3. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat Rev Drug Discov. 2015;14:130-146.
4. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. BCR. 2016;18(1):17.
5. Lui GYL, Grandori C, Kemp CJ. CDK12: an emerging therapeutic target for cancer. J Clin Pathol. 2018;71 (11):957-962.
6. Zhou Y, Shen JK, Hornicek FJ, Kan Q, Duan Z. The emerging roles and therapeutic potential of cyclin-dependent kinase 11 (CDK11) in human cancer. Oncotarget. 2016;7(26):40846-40859.
7. Zhou Y, Han C, Li D, Yu Z, Li F, Li F, *et al*. Cyclin-dependent kinase 11(p110) (CDK11(p110)) is crucial for human breast cancer cell proliferation and growth. Scientific Rep. 2015;5:10433.
8. PaculováH, Kohoutek J. The emerging roles of CDK12 in tumorigenesis. Cell Div. 2017;12(1):7-17.
9. Tien JF, Mazloomian A, Cheng SG, Hughes CS, Chow CCT, Canapi LT, *et al*. CDK12 regulates alternative last exon mRNA splicing and promotes breast cancer cell invasion. Nucleic Acids Res. 2017;45(11):6698-6716.
10. Hopkins M, Tyson JJ, Novák B, Solomon MJ. Cell-cycle transitions: a common role for stoichi-ometric inhibitors. Mol Biol Cell. 2017;28(23): 3437-3446.
11. Au - Welschinger R, Au - Bendall LJ. Temporal tracking of cell cycle progression using flow cytometry without the need for synchronization. JoVE. 2015(102): e52840.

12. Bendris N, Lemmers B, Blanchard JM. Cell cycle, cytoskeleton dynamics and beyond: the many functions of cyclins and CDK inhibitors. Cell Cycle. 2015;14(12):1786-1798.
13. Malumbres M. Cyclin-dependent kinases. Genome Biol. 2014;15(6):122-130.
14. Kalra S, Joshi G, Munshi A, Kumar R. Structural insights of cyclin dependent kinases: implications in design of selective inhibitors. Eur J Med Chem. 2017; 142:424-458.
15. Schmitz ML, Kracht M. Cyclin-dependent kinases as coregulators of inflammatory gene expression. Eur J Med Chem. 2016;37(2):101-113.
16. Chi Y, Huang S, Peng H, Liu M, Zhao J, Shao Z, *et al*. Critical role of CDK11(p58) in human breast cancer growth and angiogenesis. BMC Cancer. 2015;15: 701-711.
17. Zhang K, Zhang M, Zhu J, Hong W. Screening of gene mutations associated with bone metastasis in nonsmall cell lung cancer. J Cancer Res Ther. 2016;12(7):186-190.
18. Guffanti F, Fruscio R, Rulli E, Damia G. The impact of DNA damage response gene polymorphisms on therapeutic outcomes in late stage ovarian cancer. Sci Rep. 2016;6:38142.
19. Gupta S, Li J, Kemeny G, Bitting RL, Beaver J, Somarelli JA, *et al*. Whole Genomic Copy Number Alterations in Circulating Tumor Cells from Men with Abiraterone or Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer. Clin Cancer Res. 2017;23(5):1346-1357.
20. Ekumi KM, Paculova H, Lenasi T, Pospichalova V, Bösken CA, Rybarikova J, *et al*. Ovarian carcinoma CDK12 mutations misregulate expression of DNA repair genes via deficient formation and function of the Cdk12/CycK complex. Nucleic Acids Res. 2015;43(5): 2575-2589.
21. Fusco N, Geyer FC, De Filippo MR, Martelotto LG, Ng CKY, Piscuoglio S, *et al*. Genetic events in the progression of adenoid cystic carcinoma of the breast to high-grade triple-negative breast cancer. Mod Pathol. 2016;29:1292-1305.
22. Mertins P, Mani DR, Ruggles KV, Gillette MA, Clauser KR, Wang P, *et al*. Proteogenomics connects somatic mutations to signalling in breast cancer. Nature. 2016;534:55-62.
23. Zhou Y, Han C, Li D, Yu Z, Li F, Li F, *et al*. Cyclin-dependent kinase 11p110 (CDK11p110) is crucial for human breast cancer cell proliferation and growth. Sci Rep. 2015;5:10433.
24. Liu X, Gao Y, Shen J, Yang W, Choy E, Mankin H, *et al*. Cyclin-Dependent Kinase 11 (CDK11) Is Required for Ovarian Cancer Cell Growth In Vitro and In Vivo, and Its Inhibition Causes Apoptosis and Sensitizes Cells to Paclitaxel. Mol Cancer Ther. 2016;15(7):1691-1701.
25. Chi Y, Huang S, Wang L, Zhou R, Wang L, Xiao X, *et al*. CDK11p58inhibits ERa-positive breast cancer invasion by targeting integrin β3 via the repression of ERa signaling. BMC Cancer. 2014;14(1):577-787.
26. Paculova H, Kohoutek J. The emerging roles of CDK12 in tumorigenesis. 2017;12:7-17.
27. Zhang T, Kwiatkowski N, Olson CM, Dixon-Clarke SE, Abraham BJ, Greifenberg AK, *et al*. Covalent targeting of remote cysteine residues to develop CDK12 and CDK13 inhibitors. Nat Chem Biol. 2016;12 (10):876-884.
28. Popova T, Manie E, Boeva V, Battistella A, Goundiam O, Smith NK, *et al*. Ovarian cancers harboring inactivating mutations in CDK12 display a distinct genomic instability pattern characterized by large tandem duplications. Cancer Res. 2016;76(7):1882-1891.
29. Mertins P, Mani DR, Ruggles KV, Gillette MA, Clauser KR, Wang P, *et al*. Proteogenomics connects somatic mutations to signalling in breast cancer. Nature. 2016;534(7605):55-62.