CGC International Journal of Contemporary Technology and Research
ISSN: 2582-0486 (online) Vol.-3, Issue-1 DOI: 10.46860/cgcijctr.2020.12.26.134

CYCLIN D1: As a Risk of Breast Cancer

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Abstract: **Breast cancer is varying group of tumors in terms of disease prognosis. Breast cancer is found as second main cause of death related with cancer. Cyclin D1 (CCND1) is an important regulator of cell cycle. CCND1over expressed in various human cancers like head, oesophageal, neck, squamous, colon, breast, prostateetc. Many studies have conducted to find correlation between polymorphism in CCND1 gene and development of breast cancer. Some studies found certain genotypes related with risk of breast cancer development. Some studies also proposed the role of varying genetic backgrounds in breast cancer development. This review focuses on role of CCND1 polymorphism and possible risk factors associated with breast cancer, which may explicate the breast cancer screening, prevention, and treatments strategies for future use.**

Indexed Terms- : Cyclin D1, breast cancer, polymorphism, cell cycle. **(*Keywords*)**

I. INTRODUCTION

Breast cancer is varying group of tumours in disease prognosis. Breast cancer is found as second main cause of death related with cancer[1].Cell cycle proceeds by the activation of CDK (cyclin dependent kinase)which are controlled by various cyclins and inhibitors of cyclin dependent kinases [2,3].CDK (Cyclin Dependent Kinase) is a heterodimer and made up of catalytic subunit i.e. regulatory subunit known as cyclin and cyclin dependent kinases.

Activity of CDK is generally decided by binding of regulatory cyclin subunit, as positive and negative regulatory phosphorylation [3,4]. Cyclin/CDK complexes phosphorylatethe substrates those are required for progression of cell cycle process. Stimulation of growth factor speed up the cell cycle progression which is requiredonly up to a point in G1 phase of cell cycle. This phase isknown as point of restriction [4].

Ahead of this point, cells are mainly committed to only a simple round of cell proliferation without referring the presence of any mitogen or carcinogens. Progression through the G1 phase needs the activities of D and E type cyclinin relation with their kinase subunits [5]. The D-type Cyclini.e. D1, 2, 3, CDK4 or CDK6 acts as target during cancer formation. Over expression of Cyclin D1 is found as most frequently associated with breast cancer development out of all cyclin families.

Frequency of cyclinD1 variation has been found to be connected with risk of other cancers also including, oral, cervical, oesophageal, urinary bladder, lung, colorectal and prostate[6,7]. The conclusions of these studies were inconsistent in different ethnic groups. To study these encounters in detail, many researches have been executed worldwide to check effect of CCND1 polymorphism and risk for different types of cancer [8,9]. This review shows role of CCND1 as an oncogene for cell division machinery especially in breast cancer cases.

II.CELL CYCLE ASSOCIATION WITH BREAST CANCER DEVELOPMENT

Division of cell is comprises of two successive processes i.e. chromosomes segregation into two different cells and DNA replication. Cell division is divided into two main stages: mitosis i.e. nuclear division phase and inter phase.

Cell cycle progression occurred by activation of cyclindependent kinases (CDKs).Activated CDKand cyclin complexes lead to phosphorylation and then inactivation of retinoblastoma ('RB')protein [10] (fig. 1). The process is regulated by many inhibitors (CKIs), which are divided into two groups known as: cyclin kinase 4 inhibitors (INK4) and CDK inhibitor protein (KIP /CIP).

INK4 groups includes CDKN2A (p16 ARF/p14//INK4A/\),CDKN2B (INK4B /p15), CDKN2C (p18/INK4C/)and CDKN2D (p19/INK4D). These groups are associate with CDK4 & CDK6 and then further interfere its interaction with other subunit of cyclin D. The KIP /CIP group consists ofCDKN1A (p21/WAF1 /CIP1) and CDKN1B (p27/KIP1) which form a trimetric complexes with the G1 transition cyclin dependent kinase. It does not affect the further binding of cyclin [11] (fig. 2).

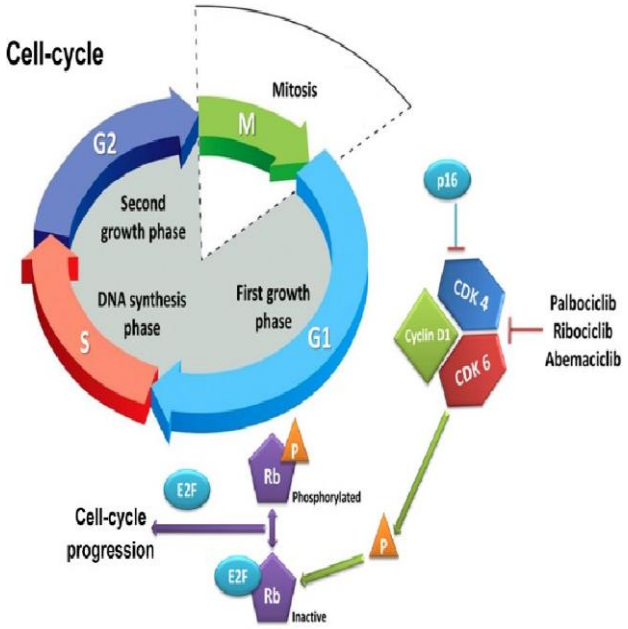

FIG1. The role of Cyclin D1 in cell cycle regulation

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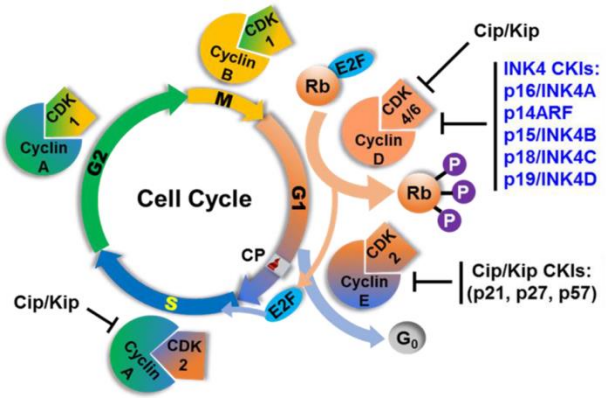

FIG 2.Association of cyclin kinase 4 inhibitors (INK4) and CDK inhibitor protein (KIP /CIP) in cell cycle regulation as well as breast cancer development

Loss of expression of CDKN1B is also important in breast cancer development and is associated with poor prognosis of disease and high tumour grade [12].Some studies noted the importance of CDKN1B C79T polymorphism withrisk of breast cancer risk [11,13].

CCND1is a member of Dtype cyclins which control G1 cell cycle phase. Increased expression of CCND1 prolongs this phase, and disturbs normal control oncell cycle. This enhances the development as well as progression of breast cancer[14]. In some studies it is found that CCND1 is related with other cancers like colorectal, gastric, breast, prostateetc.[15].

III.CYCLIN D1(CCND1)

Cyclin D1 protein is encoded by the CCND1 gene. It is present on long arm of chromosome no. 11q13. Cyclin D1 protein is important forproliferation, differentiation, and transcriptionof cell [16].Many studies observed a linkage between the CCND1 870A allele and elevated risk of development of breast cancer [11,16].

Cyclin D1 acts by phosphorylation that leads to inactivationof RB protein in connection with CDK4 (cyclin dependent kinase 4), which promote the transcription factor (TF) release known as E2F from RB (retinoblastoma protein). This will start the process of DNA synthesis[17].Over expression of cyclin D1 result in phosphorylation of retinoblastoma (RB) and then uncontrolled growth of cells[17].

Cyclin D1 is present mainly in two forms i.e. cyclin D1a & cyclin D1b. Cyclin D1b form is devoid of residues which are required for its export through nucleus. Cyclin D1b ispresentin nucleus, with an increased transforming capacity as comparison tocyclin D1a, which is a nuclear oncoprotein[18].Polymorphisms in CCND1 don't lead to the change in amino acid but it enhances the expression of cyclin D1b, an alternative transcript encoding [16].

CCND1 gene isone of the most over expressed oncogenes in breast carcinoma. Around45-50% of IDC (invasive ductal carcinomas) occurs due to over expression of only this oncoprotein [14]. Alteration in CCND1 gene is the very first step in breast cancer formation. Polymorphism in CCND1 has also been found in correlation with breast cancer progression [19].

IV. CYCLIN D1 ASSOCIATION WITH CLINICOPATHOLOGICAL PARAMETERS

In clinicopathological parameters like tumor size, grade, lymph nodes (LN) status and expression of estrogen, progesterone receptors (ER and PR) Her2/neu etc. was studied by many researchers. Tumor grade, size as well as lymph node (LN) status was notfound correlated with expression of Cyclin D1 in some studies [20,21]. Positive expression of estrogen and progesterone found significantly correlated with cyclinD1 expression in previous studies especiallyin invasive breast carcinoma[21,22]. These results pointed out the role of estrogen and progesterone receptor mediated role of cyclin D1 [23].

In some studies it was notes that low tumor grade, estrogen, progesterone receptor (positive) and Ki67 expression showed statistically significant correlation with cyclin D1[23]. However lymph node status, tumor size and Her2/neu expression were not associated with cyclin D1 expression[23].Some studies found positive correlation of cyclin D1 with lymph node status and negative correlation with Her2/neu and p53 expression especially in luminal B type tumors. However, the expression of cyclin D1 was missing in basal type of tumor cells [24].

Over expression of cyclin D1 has been linked with breast cancer that over express human epidermal growth factor receptor 2 which are generally estrogen receptor (ER) negative. Firstly, it was recommended that CD Kinase function of CCND1 solely leads to its progression into G1 phase. This process caused cell differentiation and lead to its potential of on cogenicity. However, proof from several clinical studies fails to upkeep this hypothesis, and therefore, a different CDK-independent function resulting in carcinogenesis had been suggested[25].

CCND1 is over expressed mainly in those breast cancer cells which show estrogen positive receptors. It has been recommended that alteration in transcriptionvia its action on estrogen receptormay be responsible for carcinogenic potential of CCND1 in breast cancer. This proposition is governed by various outcomes which show connection between CCND1 and estrogen receptor that activates estrogen regulated genes in estrogennegative cases [26]. Although CCND1 gene amplification connectsvery well with increased expression of estrogen protein which suggests some other mechanisms (like p53, p21cip1 pathway) may also contribute to increase cyclin D1 over expression [27].

V. CYCLIN D1 POLYMORPHISMS AND BREAST CANCER RISK

It has been reportedin many studies that the CCND1 gene is found over expressed in about 20% of breast cancerpatients[14, 18]. In exons 4, there is substitution from G to A (rs603965) nt870. Some studiesreported that CCND1 forms an alternative protein known as transcript b.Some researchers also evaluated that transcriptb was not a goodfactor of retinoblastoma (RB)activation or inactivation and henceenhanced cell transformation as compared to transcripta[18].

Till date, different studies revealed the role of the CCND 1 as riskof breast carcinoma. But the results remain disputable[28].Cui et al.(2012)found AA genotype of the cyclin D1 polymorphism was associated with risk of breast cancer development [29]. However, few studies did not find any association with genotype GA of CCND 1 and risk of breast cancer [30]. Some studies found that AA genotype of cyclin D1 polymorphism were significantly related with breast carcinoma development in Caucasians women, but not in Asian women [31]. These results showed that allelic polymorphisms may increase the breast cancer risk. This effect may differ by ethnicity. Results of some studies are shown in table 1.

Yaylim et al. (2009) reported that frequencies of AG, AA, and GG genotypes were 48.4%, 28.1% and 23.4% respectively in healthy controls, and 21.1%, 39.5% and 39.5% resply in breast cancer patients [30]. Statistical significant difference of distribution of percentage frequency of CCND 1 genotype was found among breast cancer patients and control cases. Their findings indicated that patients having AG genotype have reduced risk of breast cancer [30].

In contrast, Bedewy et al. (2013) found that breast cancer patients with GG genotype produce high amount of transcript b, while patients with AA genotype produce more transcript ‘a’ [32]. In a study, it was noted that there was a statistical significant variation in the genotype frequency distribution between breast cancer patients and controls. These findings suggest that CCND 1 polymorphism association with breast cancer susceptibility. These findings were consistent with previous findings suggested CCND 1genotype association with breast cancer development [33, 34].

Some large scale case control studies of breast cancer observed no correlation between CCND 1 polymorphism and risk of development of breast cancer [28]. Shah et al. found that cyclin D1 polymorphism confer breast cancer in young women of China [33]. These results revealed that patients with AA and AG genotypes were at high risk for breast cancer in contrast those having GG genotype [32, 35].

Some studies associated the cyclin D1 GG genotype with elevated risk of breast cancer but results remain controversial [16]. Some researchers evaluated that, breast cancer breast cancer patients having GG genotype whose relatives suffered from any kind of cancer history showed two fold times greater occurrence of breast cancer than those with AG and AA genotype as compare to controls (p=0.073) [30].

TABLE 1. GENOTYPE DISTRIBUTION OF CYCLIN D1 G870A GENE POLYMORPHISM IN DIFFERENT STUDIES.

S.No	Reference (Country/year)	No. of patients (sample size)	Genotype distribution (%) GG	GA	AA
1	Krippl 2003	497	23	49	28
2	Grieu 2003	339	27	48	25
3	Forsti 2004	223	26	52	22
4	Ceschi 2005	255	23	38	40
5	Shu 2005	1130	19	50	31
6	Naidu 2008	230	25	45	30
7	Onay 2008	1228	30	48	21
8	Justenhoven2009	1143	24	48	28
9	Yaylim 2009	38	39	22	39
10	Canbay2010	78	13	61	26
11	Jeon2010	769	24	47	29
12	Bedewy 2013	30	14	60	26
13	Liu 2014	1232	15	60	26
14	Soleimani 2017	174	21	50	28
15	Thakur 2018	151	33	77	41
16	Akhter 2019	30	14	26	60

In lymph node metastasis, breast cancer cases having the cyclin D1 GG genotype had around two fold increased breast cancer risk as compared with those with the AG and AA geno types.In a study, it was observed that the’‘A’ allele of the CCND 1 polymorphism was weakly related with risk of breast cancer among women ages <45 years[12]. It was also found that CCND1 polymorphism may changes the association of endogenous sex hormone exposure with postmenopausal risk of breast cancer development. Among women with the AA or AG genotype, BMI and WHR, as well as blood levels of testosterone and esterone were positively associated with postmenopausal breast cancer risk. These variables were inversely proportional to risk of breast cancer in women having GG genotype[11].

In addition it was also found that the inverse association between SHBG level and postmenopausal breast cancer risk was restricted only to women carrying the A allele of the CCND 1 polymorphism. Furthermore, CCND 1 polymorphism was also found correlated with a favorable outcome for those women who showed later stages of cancer or negative expression of ER or PR (estrogen and progesterone receptor).

VI. ETHNICITY

Some recent studies reported statistically significant association between CCND1 polymorphism and increased breast cancer risk in carriers of variant 870A allele in Caucasians women and not in Asian women. They proposed that environmental exposures and here dity might also contribute to differences in ethnicity. Although some studies could not found significant result for homozygous A or G alleles [30].Yaylim et al. (2009) found that women with AG genotype have a reduced risk of breast cancer development [36]. Few studies found no relation of GA genotype with development of breast cancer risk.

Further large scale case control breast cancer studies have observed no statistically significant correlation between CCND1 polymorphism and risk of breast cancer on women populations including Singapore, Chinese, Australian, Austrian, German, Finnish and Malaysian populations [28]. On the other side, 'GA' genotype of CCND1 found weak association with risk of breast carcinoma. The A Agenotype and Aallele showed similar prevalence among breast cancer patients and controls [33,34].

VII. CLINICAL RELEVANCE

There are many studies that have suggested, cyclin D1 amplification linkage with poor response of tamoxifen [36,37]. Generally estrogen receptor positive breast tumors show cyclin D1 over expression [38].Transcriptional activity of the estrogen receptor is suggested to be regulated by cyclin D1 in absence of estrogen [39,40]. That is why its expression is also affected by some antiestrogen drugs [41].

There are certain evidences that suggest cyclin dependent kinase, their substrates and regulators as targets of genetic mutation in different kinds of human cancer.These encourage chemical CDK inhibitorsas anti-cancer drugs [36]. Different strategies for therapeutic interferencecan modify CDK activity: targeting the important regulators of CDK activity or interfering the catalytic activity of CDKs. Approaches for the indirect methods include overexpression of CKI, synthesis of peptides which resembles the effects of CKI, decrease level of cyclin, modifications in proteasomal machinery and change in phosphorylated state of CDK and enzymes which regulate it [41].

VIII. CONCLUSION

A large number of studies have pointed out the role of CCND1gene polymorphism in many aspects of breast cancer, but the functional impact of this polymorphism is not fully understood. Further, correlation among the CCND1 polymorphism and expression of transcript variants a and b are required to investigate and how polymorphism is involved in development of breast cancer. In future functional studies may help in explaining the conflicting findings and effect of CCND1 genotypes on tumour behaviour in different cell types.

ACKNOWLEDGMENT

The Authors are grateful to department of biotechnology, Chandigarh College of technology, Landran, 140307, Mohali, Punjab, India for providing help and support

COMPETING INTERESTS: Nil

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