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REVIEW ARTICLE

The Role of Cell Cycle Division 6 (CDC6) in Cancer: Breast Cancer as a Prototype

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Abstract

An increase in cancer-cell division (proliferation) is a distinctive feature of cancer and is acknowledge as a key cell-division checkpoint alteration in cancer cells. Breast cancer is well-known as a heterogeneous disease with variant molecular subtypes, responses to therapy and morphological characteristics, breast malignant cells are identified to deactivate cell-cycle checkpoints to support survival and proliferation. Cell-cycle division 6 (CDC6) plays an important role as a cell-cycle checkpoint, especially between the cell-cycle synthesis phase (S-phase) and the cell-cycle growth 2 phase (G2-phase). Remarkably, CDC6 has complementary performances in tumorigenesis. This review investigates the role of CDC6 in cancer, predominantly concentrating on breast cancer, address the role of participation by tumour suppressor and oncogenes genes in modulating CDC6 and evaluate the possibility of using CDC6 as a target therapeutic approach in cancer treatments.

Keywords

Tumour, Cancer development, Cell cycle, EMT, Progression

Introduction

An instituting hallmark of cancer is a cell-division process that maintains the high demands of cells to proliferate and control both viability and apoptosis [1]. During cancer progression, tumour cells alter the proliferative ability of cells to divide and produce more of cells, which results in mass formation. In response, angiogenesis, which is a phenomenon characterised by releasing cancer-cell growth factors and angiogenetic factors to enhance tumour progression, will be established to supply the required amount of food and energy to this new mass [2]. Another reason for uncontrolled cell division occurring is due to mistakes/errors in cell-cycle regulators biomarkers that are responsible for arranging/adjusting the proliferation process and avoiding any unnecessary divisions that might lead to promoting mass. One of these key cell-cycle regulator biomarkers is CDC6. During the cell-cycle S-phase, CDC6 is usually phosphorylated by cyclin A, and this allows CDC6 to contribute to regulating the replication process of DNA; and therefore, CDC6 can be used as a suitable target therapy to prevent uncontrolled tumour cells proliferation [3,4] (Figure 1).

The proliferating behaviour of tumour cells is controlled by cell-cycle checkpoints, including CDC6. Despite the importance of CDC6 as one of the most effective checkpoints in the cell cycle, the exact role of CDC6 expression in cancer remains controversial and needs extensive study. In this review, we study the role, regulation and significance of CDC6 and its isozymes and splice alternatives in cancer, particularly putting a spotlight on breast cancer (BC). We also highlight the potential use of CDC6 as a therapeutic target.

CDC6 Cell Cycle, DNA Replication, Epithelial Mesenchymal Transition (EMT) and Addiction in Cancer

Cellular replication is a very precise and dangerous process. A cell's ability to replicate its DNA accurately is crucial to its survival, along with the filial transmission of genetic material to the next generation [5,6]. Within this process, CDC6 is an essential gene that makes

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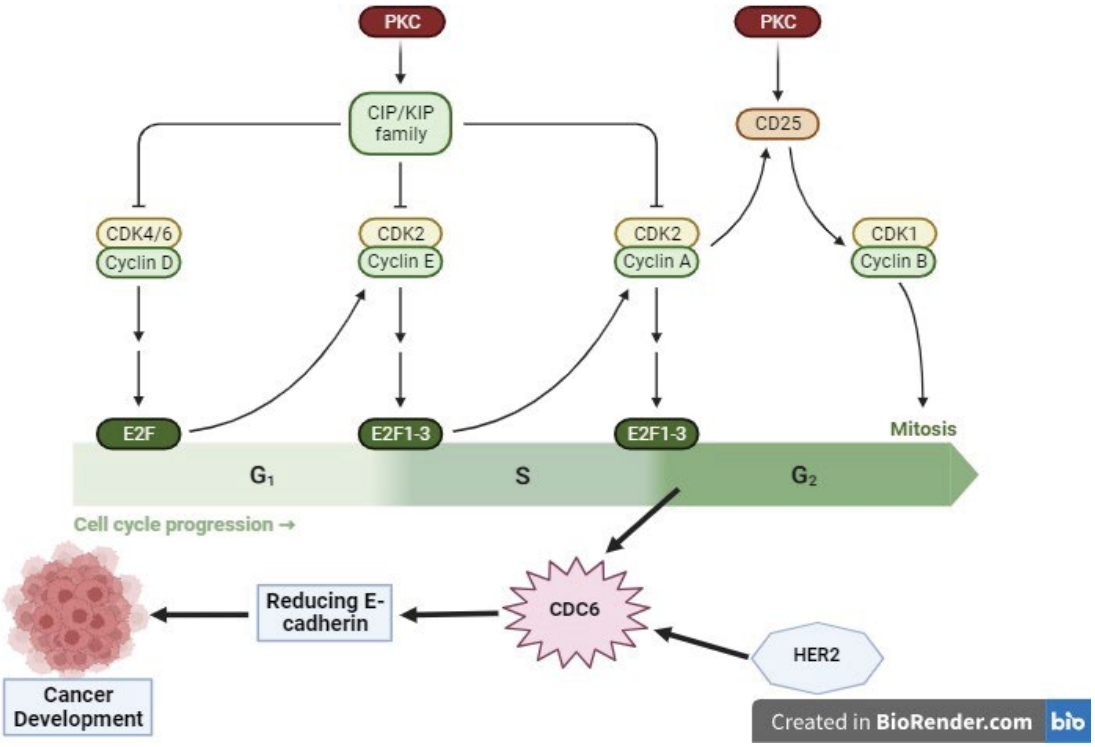

Figure 1: The role of CDC6 in cell cycle and mechanism involvement in tumour progression.

a contribution to the replication checkpoint factors that precisely manage the DNA-replication and cell-proliferation processes [7-9]. To illustrate that, in the cell-cycle process, CDC6 has been found to play a crucial role in regulating S-phase eatery via controlling the loading of mini-chromosome maintenance complex loading, which has been identified as a primary pre-requested step to initiate DNA replication [10,11]. Therefore, CDC6 is an essential primary gene that contributes to the cell-cycle process, and modifications of CDC6 are strongly associated with carcinogenic behaviour. In carcinogenic conditions, tumour mutations are accompanied by genetic instability, which boosts the (uncontrolled) dysregulation of the DNA-replication process of these cells and forms new unfavourable cell masses [12]. Moreover, CDC6 has also been shown to play a significant role in E2F pathways by creating a suitable environment for merging/connecting Yap1 complexes on the E2P pathway via regulating the replication cellular factor in the cell cycle [13] (Figure 1).

Besides the key role of CDC6 in the cell cycle, CDC6 has also been reported to play an essential role in epithelial mesenchymal transition (EMT), which is also indicated as a tumour hallmark, a process enacted by performing as a molecular switch regulator for E-cadherin levels [14]. According to a previous study, oncogenic CDC6 interacts similarly to E-cadherin inhibitors SNAIL1/2 and ZEB1/2, which connect themselves directly to the CDH1 promoter's E-box and regulate E-cadherin expression [15,16]. Likewise, our group has investigated the role of CDC6 in breast cancer (BC) and the results indicate that CDC6 plays a fundamental role in the EMT process by associating negatively with E-cadherin, while being positively associated with N-cadherin (major factors in EMT), at transcriptomic and proteomic levels by correlation [2,17] (Figure 1). The EMT process is always accompanied by advanced tumour types that are characterised by boosting migratory and invasiveness behaviours [2]. Together, these behaviours are responsible for promoting and encouraging tumour-cell metastasis by leaving their primary side and migrating forwards to lymphatic vessels and establishing another cancer site. This highlights the importance of CDC6 in tumour development.

In the early stages of malignancies conditions, CDC6 level has been observed to strongly elevate what has been suggested/speculated is the contribution of CDC6 over expression as one of the main driver genes involved in tumour development [16,18]. Additionally, CDC6 gene amplification has also been reported in significant quantities in studied tumour samples [10]. Although CDC6 gene amplification is mainly perceived and shown to be a separate event, it is speculated that CDC6 amplification might also occur as an indirect consequence of another event, as CDC6 has been found to be amplified concurrently with *ERRB2* (HER2) amplification [13]. This could be explained by the neighbourhood of the gene locus between the CDC6 gene and the *ERRB2* (HER2) gene, which is considered to be one of the most frequent genes involved in cancerous development and aggressive behaviour [19]. Nevertheless, oncogene behaviour activation has been demonstrated to be associated with gene amplification. Moreover, the E2F/Rb cascade proportionally controls

the regulation of the CDC6 gene [20]. To achieve this, dysregulated CDC6 expression may also originate from the over expression of E2P proteins, which has been linked to cancers [20,21]. In reality, it has been demonstrated that Rb disruption correlates with a poor prognosis and a more rapid rate of neoplastic transformation in KRAS-activated cells. As a result of its location within the Rb cascade, CDC6 has the capacity to prove the effect of its transcriptional regulation and, subsequently, the cascade's downstream effects, which suggest a role for CDC6 in carcinogenesis [18,22].

The Influence of CDC6 in Cancer

Although current studies have demonstrated that elevation of CDC6 biomarker levels are usually accompanied by several types of advanced cancers, the exact role of CDC6 in cancer development remains controversial and needs to be further clarified. Initially, the CDC6 gene is one of the main gene checkpoint members that are included in the cell-cycle process, which aims to control cell proliferation and apoptosis [23]. Additionally, it has been found that dysregulation in CDC6 expression contributes to carcinogenic activity in a variety of malignancies and may serve as a diagnostic and prognostic biomarker for associated tumours [24,25]. Abnormal expression of CDC6 has been shown to be associated with poor patient outcomes in cancers, including brain tumour [25], hepatocellular carcinoma [24], gastric cancer [26,27], lung cancer [28], ovarian cancer [29] and prostate cancer [30,31] (Table 1).

The expression levels of CDC6 variants are pointedly elevated in tumour cells that are well-differentiated, and this correlates with a remarkably shorter survival time (Table 1). It appears that CDC6 expression positively regulates the activity of the phosphoinositide 3-kinases-AKT signalling pathway, which is speculated to play a role of CDC6 in tumour development by enhancing the ability of malignant cells to survive, proliferate, migrate, invade and metastasise [23,32-34]. Therefore, investigating the role of CDC6 in both the early and cancer-development stages is promising to prevent metastasis and increase the possibility of survival for cancer patients.

The Important of CDC6 in BC

Because there are different molecular subtypes of BC, there are differences in the CDC6 quantity requirements. To illustrate this, aggressive BC subtypes (triple negative BC (TNBC) and HER2) need more CDC6 expression to the less aggressive BC subtypes (luminal BC). Meanwhile, luminal B cells (moderately aggressive behaviour) exhibit significantly increased amounts of CDC6 in order to increase proliferative tumour cells' behaviour and block apoptosis, while luminal A tumours (less aggressive behaviour) mostly demonstrate normal levels of CDC6, showing a relatively slight effect on growth and viability in a CDC6-deprived environment [17,35].

CDC6 Expression in BC

Inspection of Breast Cancer Gene-expression Miner v4.5 (http://bcgenex.centregauducheau.fr) revealed a negative correlation with the expression of CDC6 mRNAs [36]. Remarkably, in mRNA levels, CDC6 is strongly associated with poor prognostic clinic-pathological factors in BC, including: Larger tumour size, present of nodal stage, high-grade tumours, oestrogen receptor (ER) negativity, progesterone receptor (PR) negativity and human epidermal growth factor receptors (HER2) positivity (all $p < 0.05$) [17].

Among BC biological subtypes, CDC6 mRNA expression is indicated to present more with aggressive molecular BC subtypes, including HER2-enriched BC and basal-like BC (TNBC), and it is significantly associated with poor survival, especially in BC patients who have ER negativity [35]. Likewise, Luminal-B BC patients show much better expression of CDC6 compared to luminal-A BC patients, and this indicates a worse prognosis for the patient (Figure 2A and Figure 2B). When investigating BC patients' survival, CDC6 high mRNA expression is observed to associated with a high mortality rate and poor patient outcomes using both the METABRIC and Kaplan Meier (KM) Plotter (https://kmplot.com/

Table 1: Key role and clinical outcome of CDC6 in different cancers.

Cancer types	CDC6 expression	Observation on clinical outcome	References
Brain cancer	High expression	Poor prognosis (oncogenic role)	[25]
Hepatocellular cancer	High expression	Poor prognosis (oncogenic role)	[24]
Gastric cancer	High expression	Poor prognosis (oncogenic role)	[26,27]
Prostate cancer	High expression	Poor prognosis (oncogenic role)	[30,31]
Pancreatic cancer	High expression	Poor prognosis (oncogenic role)	[10]
Lung cancer	High expression	Poor prognosis (oncogenic role)	[28,56]
Ovarian cancer	High expression	Poor prognosis (oncogenic role)	[29]
Breast cancer	High expression	Poor prognosis (oncogenic role)	[17,35]
Colorectal cancer	High expression	Poor prognosis (oncogenic role)	[57]
Bladder cancer	High expression	Poor prognosis (oncogenic role)	[58]
Chronic Myeloid leukaemia	High expression	Poor prognosis (oncogenic role)	[32]

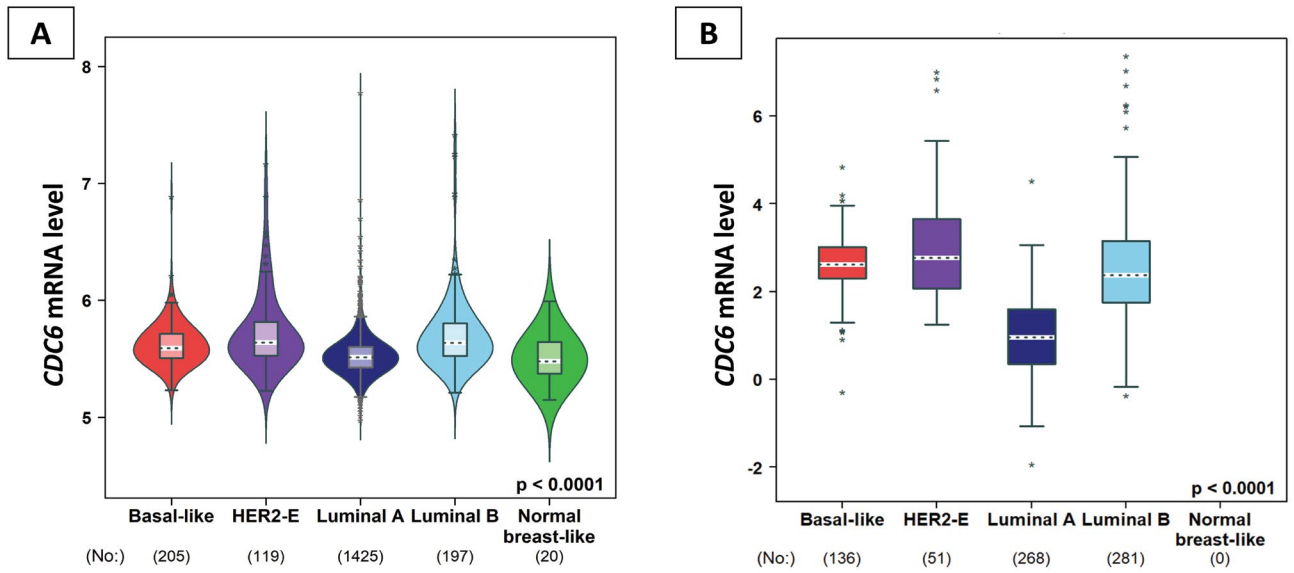

Figure 2: Distribution of mRNA expression of *CDC6* gene in BC molecular subtypes. (A) Distribution of CDC6 mRNA expression in the METABRIC cohort; (B) Distribution of CDC6 mRNA expression in the TCGA cohort.

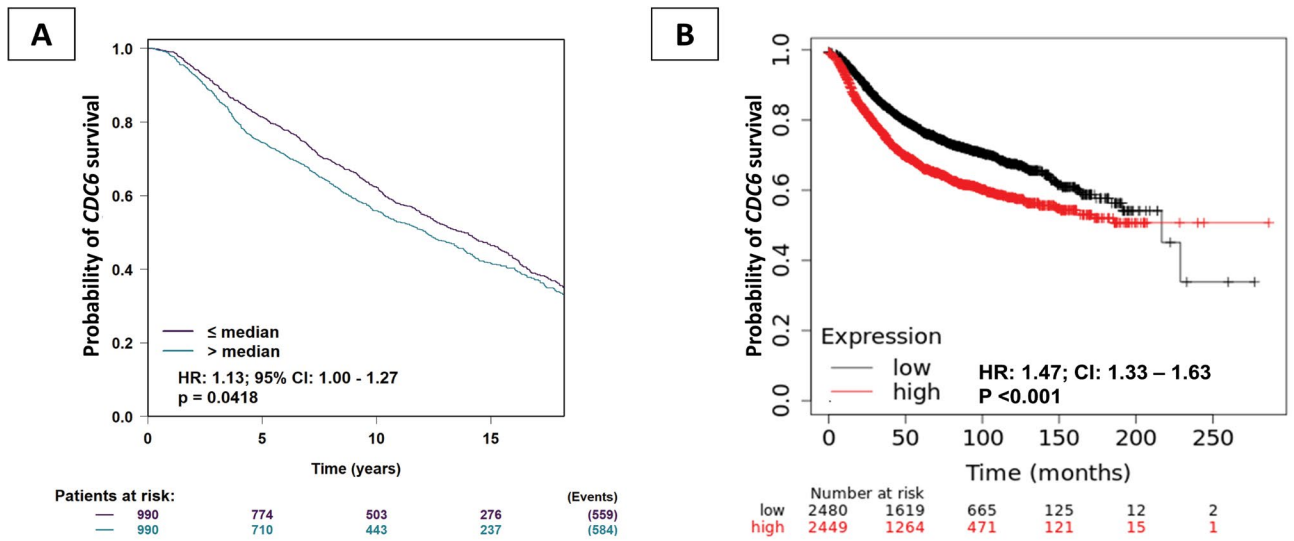

Figure 3: Patients' outcomes of Breast cancer survival on Transcriptomic level. (A) Cumulative breast cancer specific survival (BCSS) of patients stratified by *CDC6* mRNA expression in METABRIC; (B) Cumulative BCSS of patients stratified by *CDC6* mRNA expression in the KM-Plotter cohort.

analysis/) online data sets [37,38] (Figure 3A and Figure 3B). CDC6 immunohistochemistry expression is observed more in the cytoplasm of invasive ductal breast tumours of no special type. Homogeneous expression of CDC6 is present across all histological features in both negative staining BC tissue and positive staining BC tissue (Figure 4A and Figure 4B) [17].

The Contribution of Oncogenes and Tumour Suppressor Genes to CDC6 Regulation of Cancer

The cyclin A/Cdk2 plays a key role in CDC6 phosphorylation by activating CDK phosphorylation sites at the N-terminal consensus, which inhibits the resumption of replication during the S and G2 phases, as well as the translocation of CDC6 through the nucleus to the cytoplasm [39,40]. In the process of DNA replication, locations are recognized and marked by an ATP-dependent origin recognition complex (ORC) for the adherence of replicating components. AAA + ATPase CDC6 and CDC10-dependent transcript 1 (Cdt1) are subsequently attracted to the site (origin of replication) [41-43]. Furthermore, mini-chromosome maintenance/Cdt1 (MCMs/Cdt1) complexes are carried by the DNA through the replication-bound ORC/CDC6 complex's DNA origin to form a pre-replicative complex, also known as replication licensing [44,45].

During cell transformation, the retinoblastoma-E2F transcriptional pathway is typically unstable, resulting in the amplification of genes such as CDC6 and MCM2-7 in cancer cells [46,47]. Operation of their normal regulatory systems can maintain the levels of respective

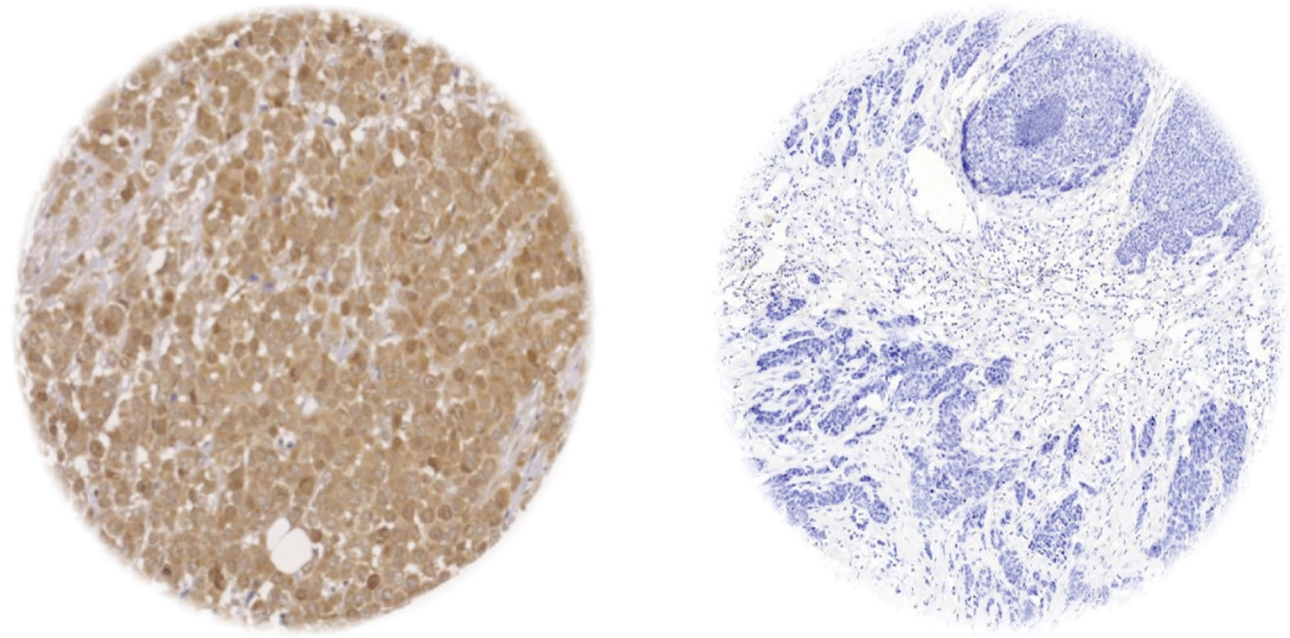

Figure 4: TMAs core CDC6 protein expression. (A) CDC6 weak protein expression in TMAs core; (B) CDC6 strong protein expression in TMAs core.

proteins close to physiological levels, whereas in the same situations, they may reach abnormally high concentrations. Thereby, in a recent study of brain tumour, it was found that 55% of brain tumours had high levels of CDC6 protein [25]. In another recent study it was reported that CDC6 is predominantly elevated in the most severe (advanced) cancer conditions of mantle cell lymphoma including diffuse-large B-cell lymphoma [48]. Cancer-exhibiting MCMs' over expression is increased with CDC6 and Cdt1 expression, and subsequently activates ataxia-telangiectasia mutated/Rad3-related (ATM/ATR) checkpoint pathways (they play a key role in the cellular response to DNA damage), by passing cell-regulatory checkpoints and starting DNA replication again [49]. Furthermore, it has been reported that CDC6 tends to act as a CDK1 inhibitor in the cell-cycle process during the whole M-phase (both M-phase entry and M-phase exit) by constricting CDK1 activity [40].

High CDC6 expression has been demonstrated to contribute to several types of cancers (Table 1). Moreover, recently it has been proven that the expression of CDC6 is controlled by the expression of oestrogen [50], and inhabits methionine-mediated suppression during cell proliferation [51]. Collectively, CDC6 is one of the cell-cycle checkpoint biomarkers involved in DNA replication, and so controlling CDC6 expression could be used as a therapeutic target to prevent cancer development.

Probable Therapeutic Applications

CDC6 has potential as a therapeutic target because it is required for the growth of tumours, particularly increases in breast tumours that are developed and proliferating rapidly, and it is a major biomarker that contributes to the DNA replication process and mRNA synthesis. Moreover, over-replication of DNA is identified in tumour cells once CDC6 is expressed ectopically [52]. Therefore, a CDC6 biomarker could be used as a future therapeutic target therapy to prevent cancer proliferation and development, including invasion and metastasis.

CDC6 Inhibitors

Cyclin-dependent kinases (CDKs) have an important role in controlling DNA replication initialization. CDK activity develops from the beginning of S-phase to the beginning of the M-phase, leading to the phosphorylation of licensing factors and preventing the re-licensing [53]. Following the completion of chromosome segregation and DNA duplication, CDKs are blocked and Geminin is degraded in preparation for a new cycle of DNA replication [54]. Genetic variability that results in the over expression or deletion of these proteins has serious implications for genomic stability and cell proliferation. Cell-cycle progression is inhibited when either CDC6 or Cdt1 is deleted because it prevents MCMs joining with chromatin during the G1 phase [55]. Since UCN-01(P53-normal), a pharmacological over expression of CDC25 phosphatase or inhibitor of Chk1, can break the mitotic block, in the current case the mechanism includes the enhancement of checkpoint kinase Chk1. Interestingly, caffeine, an ATM/ATR inhibitor, did not break the mitotic block, indicating that CDC6 may have directly activated Chk1.

The CDC6 inhibitor Chk1/2 inhibitor (AZD7762) is one of the earliest inhibitors to be utilised in xenograft and preclinical models. This inhibitor was selected due to the strong association between CDC6 and androgen receptors (AR) in prostate cancer. A clinical trial revealed that in LNCaP-C4-2b (wild-type p53) and VCaP (mutant p53) cells, the simultaneous treatment of AR with enzalutamide (ENZ) and Chk1/2 inhibition with AZD7762 indicates cooperation with regard to decreased AR/CDC6-ATR-Chk1 signalling, ATM phosphorylation activation and apoptosis [49]. On the other hand, an increase in CDC6 expression is accompanied by a remarkable decrease in ENZ, AZD7762 and activating apoptosis, and thus increases the ability of tumour cells to survival.

A recent *in vitro* model study of prostate cancer conducted by Li J. and et al. investigated a combination of CDC6 target therapies, comprising LINC01088, miR-22 and CDC6, and indicated that the slicing of this drug combination resulted in decreased activity of the PI3K/AKT pathway and prevented prostate cancer cells' growth, as well as a proliferation mechanism [33].

Future Directions in the Role of CDC6 as Therapeutic Target

CDC6 is a potential target and so newer molecules that interfere with the expression or activity of this protein should be developed. Furthermore, the effect of existing therapeutic drugs used in different types of cancer on CDC6 may provide more insights into the role of CDC6 in an anti-cancer effect. The research on CDC6 in BC to date is still very limited, with no extensive studies on CDC6 inhibitors. Moreover, the role of the CDC6 gene itself in BC is still unknown. Our recent study has provided information about the role of CDC6 in BC and its potential as a therapeutic target for breast-cancer treatments. However, no studies have yet focused on demonstrating the possibility of utilising CDC6 as a therapeutic target for BC in animal or human trials. The development of novel CDC6 inhibitors may prove to be an emerging area for the treatment of BC.

Conclusion

Cancer, and especially BC, is still a potentially fatal disease with a poor survival rate, thus prompting a race for better treatment targets and detection, in which CDC6 has possibilities. This study has discussed the participation of CDC6 via various pathways associated with widespread genetic abnormalities. The oncogenic participation of CDC6 may be explained by its involvement in several processes, including cancer-cell proliferation (acting as a key checkpoint in the S-G2 phase in the cell cycle), the E2F pathway, PI3K/AKT pathway, HER2 amplification and EMT process. We have discussed in detail the role that CDC6 cytoplasmic retention plays in senescence induction when it interacts with Cyclin E. This review also conjectures and speculates on the concurrent up regulation of Cyclin A, given that Cyclin E is elevated in the cytoplasm that promotes the oncogenic role of CDC6 within tumour-genesis conditions. If approved, this could theoretically be considered for inclusion in further studies on inducing CDC6 cytoplasmic retention. This could additionally point to a possible mechanism for mortality through suppression of the Cdk2 pathway and cytoplasmic retention of CDC6. Furthermore, Akt kinase, an essential part of the RAS pathway, is a mechanism hypothesised for Cdk2 cytoplasmic distribution. Focusing on a better understanding of CDC6 behaviour and how to take advantage of it could be useful in identifying novel potential therapeutic targets and supporting improved tailoring treatment regimens for BC, and particularly for aggressive subtypes.

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Conflict of Interest

The author declares no conflict of interest.

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Author Contribution

Conception and design: Y.K. Data analysis and interpretation: Y.K. Paper writing: Y.K. The author contributed to revise and approve the final version of the paper.

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