The importance of CDC27 in cancer: molecular pathology and clinical aspects

Golnaz Ensieh Kazemi-Sefat1, Mohammad Keramatipour2, Saeed Talebi3, Kaveh Kavousi1, Roya Sajed1, Nazanin Atieh Kazemi-Sefat5 and Kazem Mousavizadeh1,6*

Abstract

Background: CDC27 is one of the core components of Anaphase Promoting complex/cyclosome. The main role of this protein is defined at cellular division to control cell cycle transitions. Here we review the molecular aspects that may affect CDC27 regulation from cell cycle and mitosis to cancer pathogenesis and prognosis.

Main text: It has been suggested that CDC27 may play either like a tumor suppressor gene or oncogene in different neoplasms. Divergent variations in CDC27 DNA sequence and alterations in transcription of CDC27 have been detected in different solid tumors and hematological malignancies. Elevated CDC27 expression level may increase cell proliferation, invasiveness and metastasis in some malignancies. It has been proposed that CDC27 upregulation may increase stemness in cancer stem cells. On the other hand, downregulation of CDC27 may increase the cancer cell survival, decrease radiosensitivity and increase chemoresistancy. In addition, CDC27 downregulation may stimulate efferocytosis and improve tumor microenvironment.

Conclusion: CDC27 dysregulation, either increased or decreased activity, may aggravate neoplasms. CDC27 may be suggested as a prognostic biomarker in different malignancies.

Keywords: Anaphase-Promoting complex–cyclosome, CDC27 protein, Cell cycle, Neoplasms, Upregulation, Downregulation, Tumorigenesis

Background

Neoplastic cells usually form by cellular transformation. This is a stepwise process which disturbs the harmonies between factors that regulate the cell cycle. The cell cycle transition, error-free chromosome duplication, segregation and finally exit of mitosis are ensured by the well timed activation of ubiquitination enzymes [1]. One of the most important ubiquitination enzymes is Anaphase-Promoting complex or cyclosome (APC/C). CDC27 is one of the core components of Anaphase Promoting complex/cyclosome.

CDC27 in Anaphase Promoting complex (APC/C)

APC/C is composed of two specific sub-complexes: catalytic sub-complex and tetratricopeptide repeat (TPR) suprahelix sub-complex which the latter has scaffolding role [2, 3]. TPR suprahelix sub-complex orchestrates the position of substrate recognition sites in APC/C to perform ubiquitination [2, 4]. Human conserved canonical TPR subunits of APC/C including CDC27 (APC3), CDC16 (APC6) and CDC23 (APC8) consist of TPR motifs and have a quasi-symmetrical structure [4].

Human studies about the role of CDC27 in cancer pathogenesis and its clinical importance are relatively few. Therefore, collecting the current knowledge and recent insights about this molecule in human may help better understanding its role in cancer and depicting the road map for future investigations.
**CDC27** gene has 33 specific exons and undergoes alternative splicing that leads to multiple transcripts including 22 different mRNAs. Thirteen spliced mRNAs are supposed to translate to functional proteins. CDC27 main functional isoforms are coded by 19 exons and consist of 830 and 824 amino acids respectively with two TPR domains. The N-terminal domain has 5 TPR motifs and C-terminal domain has 9 motifs [5] (Fig. 1, Additional file 1: Table S1).

More than 16,494 **CDC27** variants have been recorded in human genome ensemble database, from which 1994 variants are on exons. Analyzing the distribution of variants on **CDC27** gene by calculating the variant density (frequency of variants per 100 bp sequence length) has shown that the 6th exon has the most variant density (Additional file 2: Figure S1, Additional file 1: Table S1, Fig. 1).

Eleven **CDC27** pseudogenes have been discovered on chromosomes 2, 14, 20, 21, 22 and Y [6]. The processed pseudogenes contain the complete cDNA sequence of **CDC27** from exon 3 to 14.

**Regulation of cell cycle by CDC27**

The ubiquitin-mediated proteolysis is one of the main mechanisms of cell cycle regulation. The APC/C and the SCF (SKP1–CUL1–F-boxprotein) complexes are two ubiquitin ligases responsible for the specific ubiquitylation of many of cell cycle regulators [7]. Substrates from mid-M phase to the end of G1 phase are targeted by APC/C, whereas degradation of substrates from late G1 to early M phase is mediated by SCF ligases [8].

**CDC27** can regulate mitosis and chromosome segregation by controlling APC/C activity in cyclins degradation. During mitosis, **CDC27** accumulates in spindle microtubules, spindle poles and centrosomes [9] as well as chromosome arms and kinetochores [10].

In normal mitosis, interactions between some proteins and **CDC27** may inhibit substrate binding to APC/C which regulates the timing of mitosis [10–12]. As an example, Early mitotic inhibitor 1 (Emi1) can inhibit APC activation. It has been revealed that **CDC27** links Emi1 to APC/C core [13–15]. These negative regulations of APC/C prevent chromosome missegregation [16].

**CDC27** at the G2/M transition interacts with **CDC20** (Fig. 2) and regulates ubiquitination and finally, proteolysis of proteins such as Securin and cyclin B to allow chromosome segregation [17, 18]. Securin is a regulator of cell cycle progression from metaphase to anaphase and in dephosphorylated form is one of the APC/C targets. When securin is triggered by APC/C,
separase (that until then was inactivated by securin) degrades sister chromatid cohesions to synchronize faithful chromosomal segregation and ploidy stability [19].

CDC27 at the M/G1 transition [17] interacts with CDH1 (Fig. 2) and prepares all changes required for mitotic exit and transition into G1. Residual securin and cyclin B are targeted for degradation, as are CDC20 and CDC5, which put an end to the pattern of proteins required for mitosis [20].

It has been demonstrated that CDC27 expression modulates CDKN1A (p21: a cyclin-dependent kinase inhibitor in cell cycle) quantity and by this mechanism can control ID1 (as a regulator of G1/S transition during cell cycle) expression and G1 to S phase arrest/transition status [21–23].

CDC27 and CDC16 at S phase by degradation of the putative initiator proteins of DNA synthesis cause exclusively one time DNA replication per cell cycle in the yeast. Conversely, CDC27 or CDC16 mutants cause DNA to be over replicated [24]. This finding in human cell line models has not been investigated.

Mechanisms suggested for the CDC27 regulation
Wide range of mechanisms could regulate activity of gene products at different levels [25]. Transcriptional and post-transcriptional regulations by several mechanisms are important pieces of cancer genetics puzzle. Furthermore, gene product’s activity can be changed independently of RNA level due to translational and posttranslational modifications [26].

Here we mention the known evidence about CDC27 regulatory factors in different levels from transcription to post translational modifications that may reveal the big gap of knowledge in this field.

One of the most recognized transcription factors in the regulation of CDC27 expression is C/EBPdelta [27]. C/EBPdelta (CCAAT/enhancer binding protein delta) is a transcription factor that may play role in many biological processes such as proliferation, differentiation, growth arrest, metabolism, motility, inflammation and other immune responses [28].

In post transcriptional stage, the most important microRNAs which may have regulatory role in CDC27 are miR-218-2 and miR-27a. CDC27 expression is a
downstream target of miR-218-2 and miR-27a. Over-expression of miR-218-2 and miR-27a lead to CDC27 downregulation [29, 30]. In the case of cancer, expression of various microRNAs is out of regulation and this directly affects the expression of key proteins during tumorigenesis [31].

In the translational step, heterogeneous nuclear ribonucleoprotein E1 (hnRNP E1) can regulate the translation of CDC27 [32]. hnRNP E1 which is encoded by PCBP1 (poly (rC)-binding protein gene) is an RNA binding protein that preferably binds to mRNA of genes which have tandem polycytosine motifs such as 3′-UTR of CDC27 mRNA [32, 33].

The most important post translational modification in CDC27 is phosphorylation. CDC27 during mitosis in a phosphorylation-dependent manner can regulate APC/C activity. Various kinases such as casein kinase II (CKII), cyclin dependent kinase (CDK1) and Polo-like kinase (PLK1) phosphorylate CDC27 especially at Threrone/Serine-Proline motifs [32, 34–37]. It has been suggested that TGF-β/Smad3 also can phosphorylate CDC27. Cis/trans isomerization of the phosphorylated CDC27 induces conformational changes that regulates CDC27 activity [38, 39].

Up regulation of CDC27 phosphorylation may increase its activity and sensitivity to mitotic checkpoints inhibition [20]. On the other hand, CDC27 dephosphorylation leads to increasing chromosomal instability and production of multinucleated cells.

It has been shown that different enzymes such as PP1 (Protein phosphatase1) dephosphorylate CDC27 [10]. Also, dissociation of CDC20 from CDC27 causes inhibition of CDC27 phosphorylation [40]. CDC27 dephosphorylation has an important role in TGF beta superfamily signaling [36, 41]. In addition, CDC27 dephosphorylation during mitosis leads to raised level of cyclin B and sister chromatid segregation prohibition [24].

CDC27 in cancer

Generally, the malignancy related genes are classified as oncogenes (OG) or tumor suppressor (TSG) genes. Loss of function in TSGs and gain of function in OGs are the main suggested origins of tumorigenesis.

It has been suggested that CDC27 play role either like a tumor suppressor gene or oncogene in different neoplasms [27, 42]. Divergent variations in CDC27 DNA sequence and alterations in transcription of CDC27 have been detected in different solid tumors and hematological malignancies.

Investigations about CDC27 level or sequence alterations in cancer, its involvement in processes such as apoptosis, epithelial to mesenchymal transition (EMT), stemness and efferocytosis and its association to cancer prognosis and treatment response may help to better understand cancer mechanisms and more efficiently manage malignancies in future.

**CDC27 expression alterations and consequences in cancer**

Alterations in CDC27 level and its suggestive effects have been described in different malignancies (Table 1). The vast majority of cancers indicated moderate to strong expression of CDC27 protein including colorectal, testis, thyroid, gastric cancers and lung adenocarcinoma [42–45]. It has been suggested that CDC27 may contribute in the activation of oncogenic pathways [42]. Therefore, upregulation of CDC27 may enhance tumorigenesis.

CDC27 protein level in Non-hodgkin's lymphomas, prostate, glioma, breast cancer and renal cell carcinomas was very low or absent in some samples [45]. It has been proposed that CDC27 may also act as a tumor suppressor gene [27]. Therefore, downregulation of CDC27 or loss of function mutations in this gene may suppress its inhibitory effects on tumorigenesis.

Generally, CDC27 overexpression leads to proliferation, tumor formation, migration and invasion, and knock down of CDC27 gene inhibits these functions [43].

CDC27 overexpression is in harmony with the tumor size, TNM (tumor (T), nodes (N), and metastases (M)) stage and distant metastasis in colorectal cancer (CRC). These findings reveal evidence for the relation of CDC27 expression to tumor progression and poor patient's survival [23].

Enhanced expression of CDC27 protein was in agreement with the relative expression of EMT biomarkers in gastric cancer tissues and was correlated with clinicopathological properties such as TNM stage and lymph node metastasis [43].

**CDC27 downregulation may play a crucial role in carcinogenesis and drug resistance in glioma. Increased chemoresistancy of glioma cells to beta-lapachone (β-lap, as an antineoplastic agent) has been attributed to CDC27 downregulation** [29]. Downregulation of CDC27 in glioma, as a core component of APC/C, leads to inadequate ubiquitination of securin and various cyclins such as cyclinA1/2, cyclinB1, and cyclinD1 and their elevated expression at protein level. Consequently, delay in the G0/G1 phase transition occurs [29].

In breast cancer patients, immunohistochemical evaluations of CDC27 along with securin are the valuable prognostic biomarkers after lymph node examination. Downregulation of CDC27 combined with overexpression of securin have potential to predict 5-year overall survival of the patients [46]. In triple negative breast cancer cell lines, CDC27 downregulation due to miR-27a
overexpression is associated with poor response to radiotherapy [30].

In squamous cell cervix carcinoma, CDC27 downregulation was correlated with a poor radio-responsiveness status and treatment failure. It has been shown that reduced expression of CDC27 in irradiated SiHa cell line (cervical cancer cell line) promotes cell survival. Conversely, higher expression of CDC27 in irradiated C33A (cervical cancer cell line) compared to SiHa cell line causes more cell death [47]. Irradiated CNE-1 cells (nasopharyngeal carcinoma cells) showed decreased level of CDC27, which suggested CDC27 is a part of mechanism of radiosensitivity [48].

It is important to consider that the vast majority of CDC27 mRNA isoforms are not protein coding. Therefore, gene expression profile may suggest false positive in the upregulation results, and measurement of protein would be required to confirm CDC27 induction.

**CDC27 as a potential prognostic biomarker in cancer**

CDC27 has been suggested as a prognostic biomarker in some cancers. Discovering potential biomarkers for assessing treatment response is a valuable indicator to differentiate between responder patients and those who are at risk of treatment failure. This information helps clinicians to change their strategies to other modalities in order to decrease the rate of toxicity and other side effects in clinical settings. Biomarkers are also useful for predicting the prognosis and survival [49].

Considering CDC27 as a potential prognostic biomarker, there are a number of obstacles that this potential biomarker must surpass before it can be applied in the clinic. CDC27 at mRNA level has heterogeneous behavior in some malignancies such as breast cancer. As it was mentioned, CDC27 also has several isoforms at RNA and protein level. Therefore, additional studies may be necessary to determine which CDC27 isoform in which tumor subtype has the strongest association with prognosis. Subsequent evaluations may involve validation of the original findings, including analytic validity, clinical validity, and clinical utility [50].

**CDC27 germline and somatic variants**

It has been proposed that some germline variants in CDC27 may increase the susceptibility to cancers (Table 2). In breast cancer, homozygous or heterozygous rs11570443 (CT or CC) along with homozygous rs12601027 (TT) in CDC27 have an association with the risk of cancer [51]. The rs11570443 is a Variant of Uncertain Significance (VUS) and is located upstream to the CDC27 promoter which may have a regulatory function. However, the basic mechanism of this relationship is not clarified.

In another study which was about the role of 1084 functional germline variants in breast cancer, rs764792 in CDC27 was correlated with the risk of high-grade breast cancer. However, this association was not significant after Bonferroni correction for multiple testing [52].

| Neoplasm                        | CDC27 expression changes | Effect                                      | References |
|---------------------------------|--------------------------|---------------------------------------------|------------|
| Gastrointestinal cancers        |                          |                                             |            |
| Tumoral rectum or colon tissue  | Upregulation             | CRC progression, patient's survival         | [23]       |
| Breast cancer                   |                          |                                             |            |
| Human breast cancer tissues     | Downregulation           | Prognostic biomarker                        | [46]       |
| Human breast cancer tissues     | Upregulation             | Potential to explain disease recurrence     | [32]       |
| Negative breast cancer cell lines (TNBC) (MDA-MB-435 and MDA-MB-231) | Downregulation           | Radio-responsiveness                        | [30]       |
| SCC of cervix                   |                          |                                             |            |
| Irradiated SiHa                 | Downregulation           | Radio-responsiveness status and treatment failure | [47]       |
| Gloma                           |                          |                                             |            |
| Human glia cell lines and glioma tissue | Downregulation | Chemoresistance to β-lap                    | [29]       |
| Lung cancer                     |                          |                                             |            |
| Lung adenocarcinoma             | Upregulation             | Cell cycle progression and tumor progression | [82]       |
| Non-small cell lung carcinoma cell line (EGFR-overexpressing H1299 cells) | Downregulation | Tumor progression                           | [44]       |
| Bladder cancer (BC)             |                          |                                             |            |
| Cisplatin sensitive human BC cell line (T24) and cisplatin resistant BC cell line (T24R2) | Upregulation | Metastasis and recurrence of progressive BC | [83]       |

IHC immunohistochemistry, SCC squamous cell carcinoma

Table 1 CDC27 RNA expression changes in different neoplasms
In addition to germline variants, several important functional somatic variants, including gene fusions, in CDC27 have been reported in different malignancies. Most of them are between TPR5 and TPR6 motifs and some are classified as Tier 1 (Table 3).

In sporadic vestibular schwannoma, the mutations in CDC27 were clustered in cDNA position 754–796, corresponding to amino acids 252–266, between TPR5 and TPR6. This region is important for protein–protein interactions. In this tumor, CDC27 variants (including p.G265D/rs7350889) were suggested as possible drivers of tumorigenesis [53].

The CDC27 tumor-specific and coding somatic variants in calcifying fibrous tumor of the pleura were suggested to have a role in the tumorigenesis and molecular pathogenesis of this cancer [54]. The rs79201963, rs199899451, rs775321736 and rs796538886 variants are classified as Tier 1 using CGI prediction software tool (Cancer Genome Interpreter) [55]. In Osteosarcoma, (OS) pathogenic p.E6G CDC27 Tier 1 somatic mutation was suggested to have an important role in regulating OS tumor cell division and suggested as potential biomarker for OS [56]. CDC27-OAT intrachromosomal fusion between CDC27 as a cell cycle regulator and OAT (ornithine aminotransferase, an enzyme which produces ornithine) in aggressive prostate tumors was identified in some patients [57].

The importance of somatic variants of CDC27 in the pathogenesis of cancer also have been suggested in other malignancies including the Follicular thyroid cancer [58], colon cancer [59], EGFR/KRAS/ALK-negative lung adenocarcinoma [60], Testicular germ cell tumors (TGCT) [61] and FLT3-ITD Sorafenib-Resistant Acute Myeloid Leukaemia. [62]. Several CDC27 variants have been detected in Prostate cancer [63], Relapsed B-Cell Precursor Acute Lymphoblastic Leukemia [64], Duodenal adenocarcinoma [65] and Adrenocortical carcinoma [66], but their role in tumorigenesis is unknown. In a recent study in gastric cancer, it was shown that CDC27 somatic

| Variant Coordinates (hg19) | dbSNP rs number | cDNA/Protein (NM_001114091) | Exon/intron position | Neoplasm | CGI classification | References |
|---------------------------|-----------------|-----------------------------|----------------------|----------|--------------------|------------|
| 17-45267537-T-C           | rs11570443      | c.-999A>G                   | 2 KB Upstream        | Breast cancer | NA                | [51]       |
| 17-45203468-C-T           | rs12601027      | c.2179–2142G>A             | Intron 16            | Breast cancer | Not protein-affecting | [51]       |
| 17-45257617-T-C           | rs764792        | c.103+1311A>G              | Intron 2             | Breast cancer | Not protein-affecting | [52]       |

Table 2 The germline variants in CDC27 associated to cancer susceptibility

| dbSNP rs number | cDNA/protein (NM_001114091) | Exon/intron position; TPR domain | Effect/Neoplasm | CGI classification | References |
|-----------------|-----------------------------|---------------------------------|-----------------|--------------------|------------|
| rs7201963       | c.1549G>G;A.p.E517K         | 17 Exon12;TPR6                  | Tumorigenic roles in calcifying fibrous tumor of the pleura | Tier 1 | [54] |
| rs7709560       | c.644T>G;p.L215W             | Exon6                           |                | Passenger          | Tier 1 |
| rs199899451     | c.505A>G;p.K169*             | Exon6                           |                | Not protein-affecting | NA |
| rs796969472     | c.1801C>G;p.Q601E            | Exon14;TPR8                    |                | Tier 1             | [54] |
| rs775321736     | c.1795G>G;p.A599T            | Exon14;TPR8                    |                | Tier 1             | [54] |
| rs796538886     | c.1459T>G;p.C487G            | Exon12;TPR5                    |                | Tier 1             | [54] |
| rs79610899      | c.794G>G;p.G265D            | Exon7                           |                | Tier 1             | [54] |
| rs62077729      | c.17A>G;p.E6G               | Exon1;TPR1                     | Potential biomarker for Osteosarcoma | Tier 1 | [56] |
| rs74628496      | c.705T>G;p.I235I            | Exon7                           | Tumorogenesis/molecular pathogenesis of colon cancer | Tier 1 | [59] |
| rs747953129     | c.510A>G;p.T167T            | Exon6                           |                | NA                 | Polymorphism | Passenger |
| rs77679852      | c.449C>G;p.S150Y           | Exon4                           |                | NA                 | Polymorphism | Passenger |
| rs193069147     | c.704T>C;p.I235T            | Exon7                           |                | Tier 1             | [56] |
| rs200611688     | c.818C>G;p.A273G            | Exon7                           | Tumorigenesis/potential therapeutic targets in lung adenocarcinoma | NA | Polymorphism | Passenger |
| –              | c.1304G>G;p.S434I          | Exon9                           | Unknown roles in Adrenocortical carcinoma | Tier 1 | [66] |
| rs200940073     | c.1341C>T;p.S14V           | Exon12;TPR6                    |                | Tier 1             | [54] |
| rs202052665     | c.1504T>G;p.Y502H          | Exon12                           |                | Tier 1             | [54] |

NA not available, VUS Variant of Uncertain Significance

Table 3 The somatic variants in CDC27 associated to cancer progression
mutations may be independently associated with peritoneal metastasis [67].

Usually, mutations in CDC27 are loss of function mutations. Therefore, it is expected that the germline or the somatic mutations, including point mutations or deletions, in CDC27 may decrease the activity or the level of this protein in the cell.

It is important to consider that the variants on CDC27 pseudogenes may produce false positive findings, specifically in sequencing by next generation sequencing (NGS) technologies [68]. Therefore, all detected variants by whole exome sequencing (WES) or whole genome sequencing (WGS), specifically between exons 3 to 14, must be confirmed by sanger sequencing to exclude false positive variants. Generally, the variant density of reported variants on exons 3 to 14 is more than other CDC27 exons which some may be due to the variants on the pseudogenes.

**CDC27 variations and cancer mutational signatures**

Mutagenesis due to cellular DNA damage and impaired repair mechanisms leave mutational signature or distinctive imprint on the cancer genome.

The somatic and germline variations in CDC27 in esophageal squamous cell carcinomas (ESCC) were key regulators that have been suggested to affect mutational processes. In this malignancy, association between cancer signatures and germline polymorphisms of CDC27 was significant. Somatic amplification of CDC27 was correlated with lower rate of C > A substitution, the higher activity of Signature 1, and decreased activity of Signature 2. Patients with Signature 1 showed low burden of overall somatic single nucleotide variants (SNVs). Inversely, higher burden of SNVs was significantly associated with CDC27 deletions [69].

**CDC27 may play role in apoptosis, stemness, efferocytosis and EMT**

The involvement of the cell cycle proteins in apoptosis shed light on the potentially common pathways between apoptosis and mitosis. The role of CDC27 in apoptosis has been evaluated in the Jurkat cells (T cell leukemia cell line). The cleavage of CDC27 by caspase-3-like enzyme in the Fas signaling cascade subsequently avoids the ubiquitin ligase function of APC. Therefore, cyclins A and B stay intact and prevent cell cycle progression [70].

Apoptosis or programmed cell death is attenuated in cancers. Accordingly, cells become immortal and this is one of the most important underlying mechanisms of tumorigenesis, metastasis and drug resistance in cancer [71]. Therefore, suppression of apoptosis by aberrant signaling pathways in most cancers may lead to increased CDC27 activity and cell cycle progression.

Cancer stem cells (CSCs) are subpopulations of cells inside a tumor that possess characteristics related to normal stem cells such as self-renewal and differentiation, but they have some deviations from normal stem cells. For instance, CSCs have altered gene expression profiles and are resistant to conventional radiotherapy and chemotherapy. Therefore, CSCs are the origin of the cancer resistance and the reason of cancer recurrence. Targeting CSCs is one of the most important areas of cancer treatment, but due to lack of specific and sensitive biomarkers for these cells, usage of this strategy is challenging [72].

ID1 and p21 are two proteins that are correlated with self-renewal capacity of cancer stem cells. The possibility of relation between CDC27 expression in CSCs and stemness features in colorectal cancer has been evaluated. Results demonstrated that modulation of ID1 by CDC27 is one of the proposed mechanisms of p21 expression regulation. For that reason, CDC27 can be a potential therapeutic target of CSCs, but more investigations are needed to confirm this possibility [23].

Apart from CDC27 role in the cell cycle, footprint of this molecule in Efferocytosis has been traced. Efferocytosis is a term for phagocytosis of apoptotic cells [73].

Cancers use this mechanism to make the tumor microenvironment immunotolerant. Elmo1-Dock1-Rac pathway has a major role in efferocytosis. Elmo1 is a non-intrinsic catalytic protein which works as a coordinator between multiple proteins to make the appropriate interactions among them in different cellular processes. One of the proposed binding partners of Elmo1 is CDC27. The exact function of CDC27-Elmo1 is not well defined. It is possible that this interaction makes the Elmo1 ready to be ubiquitinated and degraded by APC via Proteasome [74].

Epithelial to mesenchymal transition (EMT) has a major role in cancer metastasis. EMT explains how cells dedifferentiate and achieve increased invasive and migratory properties [75]. CDC27 by modulating ID1 can downregulate the expression of epithelial markers (ZO-1 and Ecadherin), and adversely upregulate mesenchymal markers (ZEB1 and Snail) to promote metastasis in colorectal cancer cell lines (HCT116 and DLD1). This claim has been confirmed in xenograft mouse model [42]. Furthermore, in gastric cancer tissues, enhanced expression of CDC27 protein was in harmony with the relative expression of EMT biomarkers (E-cadherin, Vimentin and Twist) [43].

Hence, diminished CDC27 activity may improve efferocytosis. Increment in efferocytosis may lead to increased cancer cell survival, decreased radiosensitivity and increased chemoresistance. On the other hand, raised CDC27 activity may promote stemness and EMT which may increase tumorigenesis and metastasis.
**Therapeutic interventions related to CDC27**

The natural and chemical molecules have been vastly studied for finding resources for prevention/treatment of malignancies by different proposed mechanism of actions. For instance, Resveratrol, a natural phytoestrogen, in A549 cells (lung cancer cells) inhibits cells proliferation. Resveratrol downregulates gene and protein expression of CDC27, and these alterations of expression along with some other mechanisms trap cells in G1/S or G2/M phases of cell cycle [76].

Also, in two distinct studies the interaction between Curcumin and CDC27 in various cancer cell types such as medulloblastoma and oral cancer cells has been investigated. Curcumin attachment preferentially to phosphorylated form of CDC27 as a core component of APC/C cross links the dimerized CDC27 molecules, interferes with its function, and eventually leads to cell cycle arrest at G2/M phase. CDC27, especially in phosphorylated form, has been suggested as a biomarker for the evaluation of anti-cancer effects of curcumin [77, 78].

Treating breast cancer cells (MCF10-F) with Etodolac (a member of NSAIDs) alters the expression profile of many genes including CDC27. It has been suggested that NSAIDs arrest the cell cycle at G1 and avoid cell cycle advancement as well as DNA synthesis. This may be one of the explanations for Etodolac inducing cancer cell death [79].

Finally, after treatment of ovarian cancer cells with Eribulin and Paclitaxel (two anti-cancer drugs), expression of CDC27 was decreased at both mRNA and protein...
level. Therefore, CDC27 as an oncogene, is one of the related genes proposed for growth inhibiting action of Eribulin and Paclitaxel on ovarian cancer cells [80]. More investigations are needed to discover the precise underlying molecular mechanisms.

Conclusion

Cell division, genome stability, differentiation, carcinogenesis, autophagy, cell death, as well as energy metabolism can be regulated by APC/C [81]. Most of these functions which are important in cancer pathogenesis may be regulated by CDC27 subunit in APC/C. Alterations in CDC27 at the DNA, RNA and protein levels and post translational modifications may affect cell division. Accordingly, have divergent effects on tumorigenesis, response to treatment and eventually, prognosis and survival of patients (Fig. 3).

At DNA level, both germline and somatic variants may affect CDC27 function and have a role in tumorigenesis. CDC27 dysregulation at RNA level, either upregulation or downregulation, may affect the patient's survival and prognosis. More investigations are needed to discover the exact role of CDC27 in cancer. The advancement of new technologies has made it possible to evaluate the altered function of the product of this gene at single cell level and even at the serial time points of diverse phases of cell cycle.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12935-021-01860-9.

Additional file 1: Table S1. Protein sequence in exons and TPR motifs of CDC27. CDC27 has 19 exons with 14 TPR motifs which are located in two TPR domains. Aminoacid numbers are according to the longest isoform with 830 aminoacids. Six yellow highlighted aminoacids in brackets (at the junction of exon 8 and exon 9) are the difference between the main CDC27 isoform with 824 aminoacids and the second important functional CDC27 isoform with 830 aminoacids. Different exons are colored alternately blue and black. Red colored aminoacids at exon junctions are coded by a codon which has nucleotides on both exons. Purple highlighted aminoacids are common phosphorylation sites in the CDC27 protein which all of them are located between two TPR domains. The structure of the APC3 is consisted of 14 units of the TPR motif, which are organised as follows: dimerization domain (TPR 1 to TPR 7), IR tail binding domain (TPR 8 to TPR 11), and C-terminal domain (TPR 12 to TPR 14).

Additional file 2: Figure S1. The frequency of potentially somatic and germline variants at exons and introns in CDC27 gene. The frequency is calculated as the number of variants per 100 bases in each exon or intron (Number of variants is divided to the exon or intron length and then multiplied by 100). About 588 CDC27 variants were listed in COSMIC (554 variants on exons). This means that potentially somatic cancer variants may compose more than 25% of detected variants on CDC27 exons.

Abbreviations

APC/C: Anaphase-promoting complex or cyclosome; TPR: Tetratricopeptide repeat; Emi1: Early mitotic inhibitor 1; O&c: Oncogenes; TSG: Tumor suppressor; EMT: Epithelial to mesenchymal transition; CRC: Colorectal cancer; β-lap: Beta-lapachone; C/EBPdelta: CCAAT/enhancer binding protein delta; HNRNP E1: Heterogeneous nuclear ribonucleoprotein E1; CKII: Casein Kinase II; CDC7: Cyclin dependent kinase; PLK1: Polo-like-kinase; PIN1: Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; PP1: Protein phosphatase 1; WES: Whole exome sequencing; CGL: Cancer Genome Interpreter; TGCT: Testicular germ cell tumors; OS: Osteosarcoma; OAT: Ornithine aminotransferase; ESCC: Esophageal squamous cell carcinomas; SNV: Single nucleotide variants; CSCs: Cancer stem cells; PTC: Premature Termination Codon; NMD: Nonsense Mediated Decay; TNM: Tumor (T), nodes (N), and metastases (M).

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Authors’ contributions

GEKS, MK, ST, KK, RS, NAKS, KM. GEKS searched, collected the data, designed the figures and wrote the manuscript. KM and MK encouraged the investigation and supervised the project. ST devised the project, suggested the main conceptual ideas and proofed outline. KK and RS provided critical feedback and helped shape the manuscript. NAKS contributed in searching and data collection and helped shape the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the [CGL] repository, [https://www.cancergenomeinterpreter.org]. The datasets generated and/or analysed during the current study are available in the [AceView] repository, [https://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=human&c=Gene&l=CD27]. The datasets generated and/or analysed during the current study are available in the [The Human Protein Atlas] repository, [https://www.proteinatlas.org/ENSG0000004897-CDC27/pathology].

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest for the manuscript entitled “The Importance of CDC27 in Cancer: Molecular Pathology and Clinical aspects”.

Author details

1 Department of Molecular Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Shahid Hemmat Highway, P.O. Box: 14665-354, Tehran 14496-14535, Iran. 2 Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Department of Medical Genetics, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran. 3 Laboratory of Complex Biological Systems and Bioinformatics (CBB), Department of Bioinformatics, Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran. 4 Laboratory of Complex Biological Systems and Bioinformatics (CBB), Department of Bioinformatics, Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran. 5 Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran. 6 Cellular and Molecular Research Center, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.

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