Gene Section

Review

CDC7 (cell division cycle 7)

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Abstract

CDC7 is a serine-threonine kinase that participates in multiple cellular processes, including DNA replication, chromosomal segregation, S phase cell cycle progression, and DNA damage checkpoint. CDC7 is frequently highly expressed in several types of neoplasm, and it has been associated with cancer development and poor clinical outcomes. In different cancer models, functional studies indicated that CDC7 may be an attractive target for antineoplastic therapy, and CDC7 inhibitors have been developed. The present review on CDC7 contains data on DNA/RNA, the protein encoded, and the implication of this gene in cancer cell biology and clinical outcomes.

Keywords
CDC7; DDK; DNA replication; Chromosome segregation; DNA damage checkpoint

Identity

Other names: Hsk1, CDC7L1, HsCDC7, huCDC7
HGNC (Hugo): CDC7
Location: 1p22.1

DNA/RNA

Description

The entire CDC7 gene is approximately 24.9 Kb (start: 91500851 and end: 91525764 bp; orientation: Plus strand). On the NCBI database (https://www.ncbi.nlm.nih.gov/gene), there are 3 transcript variants (exons: 12, coding exons: 11) for CDC7 that encode for the same protein (574 amino acids [aa]): the transcript variant 1 represents the most commonly occurring transcript (transcript length: 3215 bp); the transcript variant 2 presents a different splice site in the 5' UTR (transcript length: 3188 bp), while the transcript variant 3 has different segment for part of its 5' UTR (transcript length: 3316 bp).

On the Ensembl database (http://wwwensembl.org/), there are 3 additional transcript variants for CDC7: one transcript variant has 6 exons (5 coding exons), length of 701 bp, and encode a 157 aa protein, and two transcript variant that encodes no protein (one with 4 exons and length of 729 bp, and other with 4 exons and length of 594 bp).

Protein

Figure 1. Schematic structure of CDC7 protein. (A) The CDC7 protein presents 574 aa and contains a protein kinase domain that is responsible for its activity. The position of amino acids is indicated in the Figure. The 3D reconstitution of CDC7 protein was constructed using Swiss-model platform (https://swissmodel.expasy.org/), and cartoon (B) and surface (C) versions of the protein are illustrated.
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**Figure 2.** CDC7-mediated cell signaling and cellular processes. (A) CDC7 binds to DBF4 (activated complex), which acts in initiation of DNA replication at origins by phosphorylation of MCM (mini-chromosome maintenance) proteins. (B) Upon DNA damage or stress, CDC7 phosphorylates claspin and activates ATR/CHK1 pathway. (C) CDC7 phosphorylates HP1 that promotes cohesion of sister chromatids in mitosis.

**Description**

CDC7 protein consists of 574 aminoacids (aa) with a molecular weight of 64 kDa and has a conserved protein kinase domain (58-574 aa) in the C-terminal region. The schematic representation of the CDC7 protein is illustrated in Figure 1.

**Expression**

Ubiquitous.

**Localisation**

Nucleoplasm, cytokinetic bridge, and mitotic spindle.

**Function**

CDC7 is a serine-threonine kinase that participates in chromosomal DNA replication promoting progression of S phase of the cell cycle, normal chromosomal segregation during mitosis, and checkpoint response to DNA damage (Bousslet and Diffley, 1998; Sawa and Masai, 2009; Takahashi et al., 2008). During DNA synthesis, CDC7 forms a complex with DBF4 (CDC7/DBF4 complex, also known as DDK), which acts in initiation of DNA replication at origins by phosphorylation of MCM (mini-chromosome maintenance) proteins (important components of replicative helicase), and allowing replisome activity (Kim et al., 2003b; Labib, 2010; Matsumoto and Masai, 2013; Sclafani and Hesselberth, 2018). Regarding chromosomal segregation, CDC7 regulates multiple proteins that enable cohesin deposition on DNA (Takahashi et al., 2008) and phosphorylates HP1 that promotes cohesion of sister chromatids in mitosis (Bailis et al., 2003). In addition, it has been described as a relevant role for CDC7 in the monopolar attachment to kinetochores during meiosis (Matos et al., 2008). In checkpoint response to DNA damage, CDC7 is important for ATR - CHK1 activation by phosphorylation of CLSPN (claspin) (Kim et al., 2008; Rainey et al., 2013; Tenca et al., 2007), which leads to inactivation of the anaphase-promoting complex (Yamada et al., 2013). It has been demonstrated that DBF4 are upstream targets of ATM or ATR, and once phosphorylated activates intra-S phase checkpoint, which suppresses DNA replication under stress (Lee et al., 2012). Under high replication stress, CDC7 may trigger apoptosis by CHK1-dependent pathway (Costanzo et al., 2003; Tsuji et al., 2008). The main cellular and molecular functions of CDC7 are illustrated in Figure 2.

**Homology**

The CDC7 gene and protein are highly homologous among different species, as shown in Table 1.

| % Identity for: Homo sapiens CDC7 | Symbol | Protein | DNA |
|----------------------------------|--------|---------|-----|
| vs. P.troglodytes CDC7           | 97.7   | 98.6    |     |
| vs. M.mulatta CDC7               | 96.9   | 97.8    |     |
| vs. C.lagus CDC7                 | 90.6   | 92.9    |     |
| vs. B.taurus CDC7                | 89.4   | 90.8    |     |
| vs. M.musculus Cdc7              | 81.4   | 83.2    |     |
| vs. R.norvegicus Cdc7            | 81.5   | 81.9    |     |
| vs. G.gallus Cdc7                | 69.8   | 74.1    |     |
| vs. X.tropicalis cdc7            | 66.9   | 68.3    |     |
| vs. D.rerio cdc7                 | 63.7   | 60.6    |     |
| vs. A.gambiae AgaP_AGAP002110    | 40.0   | 43.8    |     |

Table 1. Comparative identity of human CDC7 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

**Mutations**

**Somatic**

A total of 272 unique samples presenting CDC7 mutations were found among the 36154 tested samples reported in COSMIC (Catalogue of Somatic
Mutations in Cancer; http://cancer.sanger.ac.uk/cancergenome/projects/ cosmic. The mutations p.N31Tfs*51 ([c.92del] large intestine, n=16; stomach, n=4; lung, n=1; and biliary tract, n=1) and p.L28* ([c.83T>A], liver, n=4; prostate, n=3; skin, n=3; lung, n=2; soft tissue, n=1; and glioma, n=1) were the most frequent. In agreement, 315 out of 46651 (0.7%) tested samples presented CDC7 genetic alterations (mutations, amplifications, deep deletions, and multiple alterations), as reported in cBioPortal (http://www.cbioportal.org). The distribution of somatic mutations was 122 missense substitutions, 51 truncating, 1 inframe, and 2 other mutations (a total of 176 mutated samples [0.4%]). Interestingly, p.N31Tfs*51 mutation was observed in 15 out of 176 mutations in stomach adenocarcinoma, uterine endometrioid carcinoma, colon cancer, and others. Indeed, somatic mutations in CDC7 have been reported in colorectal and gastric cancer, but its biological relevance is still poorly elucidated (Greenman et al., 2007).

**Implicated in**

**Adrenocortical carcinoma**

Data mining of gene expression revealed positive regulation of genes involved in DNA damage and cell cycle pathways in samples from adrenocortical carcinoma patients, including CDC7, their higher levels were associated with worse overall survival (Subramanian and Cohen, 2019).

**Bladder cancer**

In order to identify candidate genes associated with cisplatin-resistant bladder cancer cells, sensitive and cisplatin-resistant cell lines were used for microarray analysis to determine the differential expression of significant genes in resistance. A total of 18 genes, including CDC7, were significantly upregulated in cisplatin-resistant cell lines (Kim et al., 2016).

**Breast Cancer**

In breast cancer, high CDC7 expression had been reported (Bonte et al., 2008; Zografos et al., 2019), and associated with the development of aggressive disease, including ERBB2 (HER2) overexpression, triple-negative subtypes, accelerated cell cycle progression, disrupted tumor differentiation, genomic instability, increased NPI score, and reduced disease-free survival (Rodriguez-Acebes et al., 2010). Using tissue microarray of a cohort of 2197 highly characterized breast carcinomas, CDC7 expression was found in 1088 samples (57%), of which 228 samples exhibited moderate or strong expression. High CDC7 levels were also related to medullary histotype, high tumor grade, estrogen receptor-negative status, high Ki67 expression; overexpression of TP53 and CDKN2A; and amplification of HER2, MYC, MDM2, CCND1, and ESR1, unfavorable tumor phenotype, and poor prognosis (Choschzick et al., 2010).

In triple negative breast cancer cellular models, the dual CDC7/CDK9 inhibitor (PHA-767491) synergizes with tyrosine kinase inhibitors to overcome resistance to EGFR -targeted therapy (McLaughlin et al., 2019): combined inhibition of EGFR and CDC7/CDK9 reduced cell proliferation accompanied by apoptosis induction, G2/M cell cycle arrest, and DNA replication inhibition. Due to the rarity of male breast cancer (MBC), serum protein alterations have not been extensively studied. Using two-dimensional gel electrophoresis (2-DE) and matrix-assisted laser desorption/ionization time mass spectrometry (MALDI-TOF MS), a panel of differentially expressed serum proteins were identified, which included the high CDC7 expression in MBC patients (Zografos et al., 2019).

**Clear cell renal cell carcinoma**

Ghatalia et al. (Ghatalia et al., 2016) analyzed the gene expression of kinases paired samples from primary and metastatic tumor tissues and found that CDC7 is more expressed in metastatic tumors. Using the Cancer Genome Atlas (TCGA) data, the authors also observed an association between high CDC7 expression and reduced metastasis-free survival (Ghatalia et al., 2016). DISEASE

**Cervical intraepithelial neoplasia**

Using microarray analysis, CDC7 was found among highly expressed genes in high-grade squamous cervical intraepithelial lesions (Suman and Mishra, 2018).

**Colorectal cancer**

Bonte et al. (Bonte et al., 2008) reported a high CDC7 expression in 8 of out 10 cases of colorectal cancer. In agreement, Chen et al. (Chen et al., 2013) reported a significantly higher CDC7 mRNA and protein expression in samples from 39 colorectal patients compared to their tumor-adjacent normal colorectal tissues. Analysis of 1800 colorectal carcinomas, by immunohistochemistry and tissue microarray, showed that CDC7 was highly expressed. Of note, CDC7 expression was significantly associated with TP53, suggesting that CDC7 may be a potential target in a subset of tumors with high TP53 expression (Melling et al., 2015). In contrast, loss of CDC7 expression was significantly associated with high tumor stage and grade, but was not related to nodal status. In multivariate survival analysis, strong CDC7 expression was an independent marker of improved patient survival (Melling et al., 2015).
**Esophageal squamous cell carcinoma**

CDC7 is highly expressed in esophageal squamous cell carcinoma (ESCC) tissues, and that CDC7 knockdown inhibits cell proliferation, migration, and invasion, and induces apoptosis in ESCC cells. In addition, downregulation of CDC7 also partially enhances the chemosensitivity of ESCC cells to cisplatin and 5-fluorouracil, indicating that CDC7 may serve as a potential therapeutic target in ESCC (Cao and Lu, 2019).

**Glioblastoma**

Inhibition of CDC7 by inhibitor PHA-767491 significantly reduced cell viability, proliferation, migration, invasion, and tumorigenesis, and induced apoptosis in glioblastoma models (Erbayraktar et al., 2016; Li et al., 2018). Li et al. (Li et al., 2018) identified that CDC7 expression was enhanced and functionally necessary for proliferation in glioblastomas, and its high expression was associated with poor prognosis.

**Head and neck squamous cell carcinoma**

Human papillomavirus (HPV) is associated with a subset of head and neck squamous cell carcinoma (HNSCC) that can harbor HPV DNA and it was suggestive that there are biological and clinical differences between HPV positive (HPV +) and negative (HPV -) HNSCC. Slobos et al. (Slobos et al., 2006), comparing gene expression profiles of HPV+ and HPV- tumors, found 91 genes differentially expressed, including high CDC7 expression in HPV+ HNSCC.

**Hematological neoplasms**

Hess and colleagues (Hess et al., 1998) identified the sequence of encoding human gene CDC7 and reported its overexpression in several types of cancers, including hematological neoplasms. Latterly, it was confirmed by Bont et al. (Bonte et al., 2008) in additional leukemia cellular models. In chronic lymphocytic leukemia (CLL), CDC7 was expressed and activated in lymph node biopsies. A similar finding was also observed in an in vitro model that partially recapitulates lymph node proliferation centers of CLL. These data suggested a potential role for CDC7 in the aberrant lymph node microenvironment (Natoni et al., 2011).

In addition, high CDC7 expression was associated with poor prognosis in patients with diffuse large B-cell lymphoma (DLBCL) (Hou et al., 2012b; Hou et al., 2011; Krawczyk et al., 2009). In DLBCL cell lines, CDC7 silencing combined with rituximab synergistically increased apoptosis (Hou et al., 2012a).

The dual CDC7/CDK9 inhibitor, PHA-767491, also induced cell death on a panel of multiple myeloma cell lines and primary patient samples alone or in combination with drugs currently used in the clinics, including the TP53 mutant cells that developed resistance to dexamethasone, melphalan, and doxorubicin. PHA-767491 had the same effect on primary myeloma cells from patients who relapsed with progressive refractory disease. These data suggested that the mechanisms leading to chemoresistance in myeloma may not affect the activity of a dual CDC7/CDK9 inhibitor, thus supporting further evaluation of CDC7 and CDK9 targeting in multiple myeloma (Natoni et al., 2013).

In acute myeloid leukemia (AML), the dual CDC7/CDK9 inhibitor, PHA-767491, downregulated MCL1 and sensitized AML cell lines and primary AML blasts to BCL2 inhibitors, ABT-737 and ABT-199 (O’Reilly et al., 2018).

**Hepatocellular carcinoma**

Using gene expression data sets, Zhuang et al. (Zhuang et al., 2018) detected that expression of various genes, including CDC7, was increased in hepatocellular carcinoma tissues compared to adjacent normal tissues. CDC7 overexpression was correlated with advanced histological grade and/or vascular invasion, and predicted worse overall and disease-free survival in hepatocellular carcinoma patients (Zhuang et al., 2018). It is important to highlight that the CDC7 inhibitor (PHA-767491) had a synergistic antitumor effect with 5-FU, exhibiting stronger cytotoxicity and inducing significant apoptosis in hepatocellular carcinoma cell lines and xenograft models (Li et al., 2015).

**Lung cancer**

In non-small lung cancer (NSCLC) cell lines and tissue samples, CDC7 expression was highly expressed (Bonte et al., 2008). In agreement, CDC7 was significantly increased in lung adenocarcinoma tissues, as observed by immunohistochemistry and gene expression analysis in lung adenocarcinoma (Cao, 2019). In another study, high CDC7 expression significantly correlates with TP53 mutational status and predicts poor clinical outcomes in lung adenocarcinoma patients. In an experimental lung cancer model, CDC7 was also upregulated by gain-of-function mutant TP53, which induced cell cycle progression and tumorigenesis (Datta et al., 2017).

**Melanoma**

CDC7 gene is located at chromosome 1p22 band, which was identified as a melanoma susceptibility locus with the high frequency of loss of heterozygosity (Walker et al., 2004). In a series of benign and dysplastic nevi, primary cutaneous melanomas and melanoma cutaneous
metastasis samples, CDC7 regulatory subunits, DBF4, were found to be upregulated in malignant tissues (Nambiar et al., 2007), which was associated with shorter relapse-free survival.

In the same study, DBF4 depletion reduced melanoma cell survival and proliferation (Nambiar et al., 2007). Clarke and colleagues (Clarke et al., 2009), using a tissue microarray containing 40 melanomas, 40 Spitz tumors, and 30 nevi reported that invasive melanomas and atypical Spitz nevi exhibited the highest CDC7 expression.

In order to better understand the transcriptional regulation cell cycle checkpoints in melanocytes and melanoma cell lines, Kaufmann et al. (Kaufmann et al., 2008) analyzed global gene expression patterns upon DNA damage induced by ionizing radiation, and most melanoma cell lines (11 of 16) showed significant defects in checkpoints, which included reduced expression of TP53 transcriptional targets, and enhanced expression of proliferation-associated genes. Of note, defective melanomas at checkpoint G1 exhibited higher levels of DNA synthesis-related genes, including CDC7 and CKS1B.

Using a VSV-cDNA library and B16 melanoma tumors, CDC7 was identified (among others) as a potential immunogenic antigen for chemotherapy or immunotherapy (Zaidi et al., 2015).

**Oral squamous cell carcinoma**

Evaluating CDC7 protein expression, by immunohistochemistry, in a cohort of 105 oral squamous cell carcinoma (OSCC) tumors and 30 benign oral tissues, CDC7 overexpression was found in 91% of tumor cases and 1% benign cases (Cheng et al., 2013). In multivariate analysis, CDC7 was an independent marker for overall survival in a cohort of 80 OSCC patients.

In OSCC cell lines, overexpression of CDC7 inhibited genotoxin-induced apoptosis, suggesting that high CDC7 expression increases chemotherapy resistance (Cheng et al., 2013). Yong-Deok and colleagues (Yong-Deok et al., 2015) investigated the expression of inflammation-associated genes in samples from tumor and normal tissue from OSCC patients, in which genetic analysis of functional networks and ontologies identified CDC7 as one of the relevant genes. Pharmacological CDC7 inhibition with XL413 markedly reduced cell viability and proliferation by induction of apoptosis in OSCC cell lines (Jin et al., 2018).

**Ovarian carcinoma**

CDC7 was a strong independent prognostic marker in epithelial ovarian carcinoma and CDC7 targeted inhibition leads to specific tumor cell death. In a cohort of 143 cases of ovarian cancer, increased levels of CDC7 protein were significantly associated with reduced tumor differentiation, advanced clinical stage, genomic instability, and accelerated cell cycle progression (Kulkarni et al., 2009). Moreover, CDC7 predicted disease-free survival, regardless of age, tumor grade and stage. CDC7 downregulation by siRNA in ovarian cancer cells (SKOV-3 and Caov-3) resulted in high levels of apoptosis (Kulkarni et al., 2009).

**Pancreatic cancer**

In a cohort of 73 pancreatic adenocarcinoma patients, including 24 controls, CDC7 was highly expressed in pancreatic adenocarcinoma compared to benign pancreatic tissue, as observed by immunohistochemistry (Huggett et al., 2016). CDC7 depletion using siRNA and PHA-76749, a CDC7 small molecule inhibitor, in pancreatic cancer cellular models (Capan-1 and PANC-1), resulted in marked apoptotic cell death. Using human pancreatic cell lines (Capan-1, BxPC3, and PANC-1), the preclinical efficacy of another CDC7 inhibitor, MSK-777, was reported (induction of cell cycle arrest in G1/S and apoptosis) (Skoura et al., 2013). Taken together, these results indicated that CDC7 is a potential target and may be used as a complementary diagnosis marker to predict responses in pancreatic adenocarcinoma.

**Papillary thyroid carcinoma**

Fluge et al. (Fluge et al., 2006) studied gene expression profile using cDNA microarray in papillary thyroid carcinoma samples, including 7 clinically aggressive carcinomas, 10 differentiated thyroid papillary carcinomas, and normal thyroid tissues, which were confirmed by RT-PCR, in situ hybridization and immunohistochemistry. Patients with aggressive and poorly differentiated thyroid carcinoma were specifically characterized by the marked positive regulation of several genes related to cell proliferation, including CDC7 (Fluge et al., 2006).

**Salivary gland tumor**

Jaafari-Ashkavandi et al. (Jaafari-Ashkavandi et al., 2019) reported high CDC7 expression in malignant salivary gland tumors compared to pleomorphic adenomas, and its positive correlation with tumor differentiation in samples from 15 cystic adenoid carcinomas, 12 mucoepidermoid carcinomas, 14 pleomorphic adenomas, and 5 normal salivary glands (total 46 patients and donors).
Uterine leiomyosarcoma

Barlin and colleagues (Barlin et al., 2015) compared the molecular profiles of 23 samples of uterine leiomyosarcoma (ULMS) and 29 samples of normal myometrium (NL) to identify clinically relevant molecular subtypes. Pathway analyses of genes differentially expressed between ULMS and NL samples identified over-representation of cell cycle regulation, DNA repair, and genomic integrity. External validation confirmed differential expression in 31 genes, with 84% overexpressed genes, including CDC7 and other cell cycle regulators (Barlin et al., 2015).

To be noted

Cdc7-deficient mice present embryonic lethality at day 3.5 (Kim et al., 2002). Mice carrying Cdc7 hypomorphic allele (Cdc7+/tg) were born apparently normal, but smaller than their littermates. However, the rate of mortality during postnatal development was 75% within 3 days postpartum. Surviving Cdc7+/tg mice presented a normal life span and body growth retardation compared to their littermates. In addition, male and female Cdc7+/tg mice had impaired spermatogenesis and abnormal oogenesis, respectively (Kim et al., 2003a). Promising results of CDC7 inhibition in cancer models drawn attention for the development of selective pharmacological inhibitors, among which can be mentioned 895 (Menichincheri et al., 2009), PHA-767491 (Natoni et al., 2011), 1H-pyrrolo[2,3-b]pyridines, synthesis and structure activity relationship (Menichincheri et al., 2009), 3-amino pyrimidine analog, pyrrolopyridinone analog, tricyclic CDC7 inhibitor, indazolylpyrimidin-2(1H)-one inhibitor, thienopyrazole-base inhibitor, 2-pyrimidyl-5-amidothiophene, imidazolone-based inhibitor (Sawa and Masai, 2009), NMS-1116354 (Colotta et al., 2010), TAK-931 (Iwai et al., 2019; Kurasawa et al., 2020), and XL413 (Koltun et al., 2012). The main cellular effects triggered by CDC7 inhibitors in the neoplasm models are: the late S-phase progression, reduced cell proliferation, DNA damage checkpoint activation, and apoptosis (Iwai et al., 2019; Kurasawa et al., 2020; Sawa and Masai, 2009). Clinical studies using CDC7 inhibitors, NMS-1116354 and TAK-931, in patients with solid tumors have been conducted, but the results of the clinical outcomes have not yet been published (https://clinicaltrials.gov/).

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References

Bailis JM, Bernard P, Antonelli R, Allshire RC, Forsburg SL. Hsk1-Dip1 is required for heterochromatin-mediated cohesion at centromeres. Nat Cell Biol. 2003 Dec;5(12):1111-6

Barlin JN, Zhou QC, Leitao MM, Bisognia M, Olivera N, Shih KK, Jacobsen A, Schultz N, Tap WD, Hensley ML, Schwartz GK, Boyd J, Qin LX, Levine DA. Molecular subtypes of uterine leiomyosarcoma and correlation with clinical outcome. Neoplasia. 2015 Feb;17(2):183-9

Bonte D, Lindvall C, Liu H, Dykema K, Furge K, Weinreich M. Cdc7-Ddb1 kinase overexpression in multiple cancers and tumor cell lines is correlated with p53 inactivation. Neoplasia. 2008 Sep;10(9):920-31

Boussset K, Diffley JF. The Cdc7 protein kinase is required for origin firing during S phase Genes Dev 1998 Feb 15;12(4):480-90

Cao JX. miR888 regulates cancer progression by targeting multiple targets in lung adenocarcinoma Oncol Rep 2019 Jun;41(6):3367-3376

Cao JX, Lu Y. Targeting CDC7 improves sensitivity to chemotherapy of esophageal squamous cell carcinoma Onco Targets Ther 2018 Dec 20;12:63-74

Chen HJ, Zhu Z, Wang XL, Feng QL, Wu Q, Xu ZP, Wu J, Yu XF, Qian HL, Lu Q. Expression of huCdc7 in colorectal cancer World J Gastroenterol. 2013 May 28;19(20):3130-3

Cheng AN, Jiang SS, Fan CC, Lo YK, Kuo CY, Chen CH, Liu YL, Lee CC, Chen WS, Huang TS, Wang TY, Lee AY. Increased Cdc7 expression is a marker of oral squamous cell carcinoma and overexpression of Cdc7 contributes to the resistance to DNA-damaging agents Cancer Lett 2013 Sep 1;337(2):218-25

Choschzick M, Lebeau A, Marx AH, Tharun L, Terracciano H, Heilenkötter U, Jaenicke F, Bokemeyer C, Simon R, Sauter G, Schwarz J. Overexpression of cell division cycle 7 homolog is associated with gene amplification frequency in breast cancer Hum Pathol. 2010 Mar;41(3):358-65

Clarke LE, Fountaine TJ, Hennessy J, Bruggerman RD, Clarke JT, Mauger DT, Helm KF. Cdc7 expression in melanomas, Spitz tumors and melanocytic nevi J Cutan Pathol 2009 Apr;36(4):433-8

Costanzo V, Schechter I, Lupardus PJ, Cimprich KA, Gottesman M, Gautier J, An ATR- and Cdc7-dependent DNA damage checkpoint that inhibits initiation of DNA replication Mol Cell 2003 Jan;11(1):203-13

Datta A, Ghatak D, Das S, Banerjee T, Paul A, Butti R, Gorain M, Ghuwalewala S, Roychowdhury A, Alam SK, Das P, Chatterjee R, Dasgupta M, Panda CK, Kundu GC, Roychowdhury S. p53 gain-of-function mutations increase Cdc7-dependent replication initiation EMBO Rep 2017 Nov;18(11):2030-2030

Erbayraktar Z, Alural B, Erbayraktar RS, Erkan EP. Cell division cycle 7 kinase inhibitor PHA-767491 hydrochloride suppresses glioblastoma growth and invasiveness Cancer Cell Int 2016 Nov 18;16:88

Ermoli A, Bargiotti A, Brasca MG, Ciavolella A, Colombo N, Fachini G, Isaaci A, Menichincheri M, Molinari A, Montagnoli A, Pillan A, Rainoldi S, Sirtori FR, Sola F, Thieffine S, Tibolla M, Valsasina B, Volpi D, Santocanale C, Vanotti E. Cell division cycle 7 kinase inhibitors: 1H-pyrrolo[2,3-b]pyridines, synthesis and structure-activity relationships J Med Chem 2009 Jul 23;52(14):4380-90

Atlas Genet Cytogenet Oncol Haematol. 2020; 24(10)
Füle Ø, Bruland O, Akslen LA, Lillevang JR, Varhaug JE. Gene expression in poorly differentiated papillary thyroid carcinomas Thyroid 2006 Feb;16(2):161-75

Ghataial P, Yang ES, Lasseigne BN, Ramaker RC, Cooper SJ, Chen D, Sudarshan S, Wei S, Guru AS, Zhao A, Cooper T, Della Manna DL, Naik G, Myers PM, Compagno G, Kinzssi E. Gene Expression Profiling of Metastatic Clear Cell Renal Cell Carcinoma Tissue Identifies Potential New Therapeutic Targets PLoS One 2016 Aug 30;11(8):e0160924

Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, Davies H, Teague J, Butler A, Stevens C, Edkins S, O'Meara S, Vastrik I, Schmidt E, Avis T, Barthorpe S, Bhamra G, Buck G, Choudhury B, Clements J, Cole J, Dickens E, Forbes S, Gray K, Halliday K, Harrison R, Hills K, Hinton J, Jenkinson A, Jones D, Menzies A, Mironenko T, Perry J, Raine K, Richardson D, Shepherd R, Small A, Tofts C, Varian J, Webb T, West S, Widaa S, Yates A, Caihil DP, Louis DN, Goldstraw P, Nicholson AG, Brasseur F, Looijenga L, Weber BL, Chiew YE, DeFazio A, Della Manna DL, Naik G, Myers PM, Compagno G, Kinzssi E. Gene Expression Profiling of Metastatic Clear Cell Renal Cell Carcinoma Tissue Identifies Potential New Therapeutic Targets PLoS One 2016 Aug 30;11(8):e0160924

Kolun ES, Tshahoko AL, Brown DS, Aay N, Arcalas A, Chan V, Du H, Englstr S, Ferguson K, Franzini M, Gaian A, Holst CR, Huang P, Kane B, Kim MH, Li J, Markby D, Mohan M, Noson K, Plonowski A, Richards SJ, Robertson S, Shaw K, Stott G, Stout TJ, Young J, Yu P, Zaharia CA, Zhang W, Zhou P, Nuss JM, Xu W, Kearney PC. Discovery of XL413, a potent and selective CDC7 inhibitor Bioorg Med Chem Lett 2012 Jun;22(11):3727-31

Kulkarni AA, Kingsbury SR, Tuzdarova S, Hong HK, Loddo M, Rashid M, Rodriguez-Acebes S, Prevost AT, Ledermann JA, Stoeber K, Williams GH. Cdc7 kinase is a predictor of survival and a novel therapeutic target in epithelial ovarian carcinoma Clin Cancer Res 2009 Apr;15(7):2417-25

Labik K. How do Cdc7 and cyclin-dependent kinases trigger the initiation of chromosome replication in eukaryotic cells? Genes Dev 2010 Jun;24(12):1208-19 doi: 10.1101/gad.190910.110

Lee AY, Chiba T, Truong LN, Cheng AN, Do J, Cho MJ, Chen L, Wu X. Dbf4 is direct downstream target of ataxia-telangietasia mutated (ATM) and ataxia telangietasia and Rad3-related (ATR) protein to regulate intra-S-phase checkpoint J Biol Chem 2012 Jan 20;287(4):2531-43

Li Q, Xie W, Wang N, Li C, Wang M. CDC7 dependent transcriptional regulation of RAD54L is essential for tumorigenicity and radio-resistance of glioblastoma Transl Oncol 2018 Apr;11(2):300-306

Li W, Zhao XL, Shang SQ, Chen HX, Chen X. Dual Inhibition of Cdc7 and Cdk9 by PHA-767491 Suppresses Hepatocarcinoma Synergistically with 5-Fluorouracil Cancer Drug Targets 2015;15(3):196-204

Liu ZZ, Cui ST, Tang B, Wang ZZ, Luan ZX. Identification of key biomarkers involved in osteosarcoma using altered modules Genet Mol Res 2016 Aug 26;15(3)

Matos J, Lipp JJ, Bogdanova A, Guillot S, Okaz E, Junqueira M, Shevchenko A, Zachariae W. Dbf4-dependent CDC7 kinase links DNA replication to the segregation of homologous chromosomes in meiosis I Cell 2008 Nov 14;135(4):562-78

Matsumoto S, Masai H. Regulation of chromosome dynamics by Hsk1/Cdc7 kinase Biochem Soc Trans 2013 Dec;41(6):1712-9

McLaughlin RP, He J, van der Noord VE, Redel J, Foekens JA, Martens JWM, Smid M, Zhang Y, van de Water B. A kinase inhibitor screen identifies a dual cdc7/CDK9 inhibitor
to sensitize triple-negative breast cancer to EGFR-targeted therapy Breast Cancer Res 2019 Jul 1;21(1):77
Melling N, Muth J, Simon R, Bokemeyer C, Terracciano L, Sauter G, Izbicki JR, Marx AH. Cdc7 overexpression is an independent prognostic marker and a potential therapeutic target in colorectal cancer Diagn Pathol 2015 Jul 25;10:125
Menichincheri M, Bagiotti A, Berthelsen J, Bertrand JA, Bossi R, Ciavolella A, Ciria A, Cristiani C, Croci V, D' Alessio R, Fasolini M, Fiorentini F, Forte B, Iasacchi A, Martina K, Molinari A, Montagnoli A, Orsini P, Orzi F, Pesenti E, Pezzetta D, Pillan A, Poggesi I, Roletto F, Scolaro A, Tató M, Tibolla M, Valsasina B, Varasi M, Volpi D, Santocanale C, Vanotti E. First Cdc7 kinase inhibitors: pyrrolopyridinones as potent and orally active antitumor agents 2. Lead discovery
Nambiar S, Mirhomamadsadegh A, Hassan M, Meta R, Marin A, Alaoui A, Tannapfel A, Hengge UR. Identification and functional characterization of ASK/Dbf4, a novel cell survival gene in cutaneous melanoma with prognostic relevance Carcinogenesis 2007 Dec;28(12):2501-10
Natani A, Coyne MR, Jacobsen A, Rainey MD, O'Brien G, Healy S, Montagnoli A, Moll J, O'Dwyer M, Santocanale C. Characterization of a Dual CDC7/CDK9 Inhibitor in Multiple Myeloma Cellular Models Cancers (Basel) 2015 Jul 24;5(3):901-18
Natani A, Murillo LS, Kliszczak AE, Catherwood MA, Montagnoli A, Samali A, O'Dwyer M, Santocanale C. Mechanisms of action of a dual Cdc7/Cdk9 kinase inhibitor against quiescent and proliferating CLL cells Mol Cancer Ther 2011 Sep;10(9):1624-34
O'Reilly E, Dhami SPS, Baev DV, Ortuay C, Halpin-McCormick A, Morrell R, Santocanale C, Samali A, Quinn J, O'Dwyer ME, Szegedi E. Repression of Mcl-1 expression by the Cdc7/Cdk9 inhibitor PHA-767491 overcomes bone marrow stroma-mediated drug resistance in AML Sci Rep 2018 Oct 25;8(1):15752
Rainey MD, Harhen B, Wang GN, Murphy PV, Santocanale C. Cdc7-dependent and -independent phosphorylation of Claspin in the induction of the DNA replication checkpoint Cell Cycle 2013 May 15;12(10):1560-8
Rodriguez-Acebes S, Proctor I, Loddo M, Wollenslaeger A, Rashid M, Falzon M, Prevost AT, Sainsbury R, Stoebner K, Williams GH. Targeting DNA replication before it starts: Cdc7 as a therapeutic target in p53-mutant breast cancers Am J Pathol 2010 Oct;177(4):2034-45
Sawa M, Masai H. Drug design with Cdc7 kinase: a potential novel cancer therapy target Drug Des Devel Ther 2009 Feb 6;2:255-64
Scifani RA, Hesselberth JR. O Cdc7 kinase where art thou? Curr Genet 2018 Jun;64(3):677-680 doi: 10.1007/s00037-018-0635-3
Skouras E, Syrigos KN, Sait MW. Preclinical research in treatment of pancreatic cancer JOP 2013 Jul 10;14(4):384-7
Slebos RJ, Yi Y, Ely K, Carter J, Evjen A, Zhang X, Shyr Y, Murphy BM, Cmelak AJ, Burke BB, Nettertville JL, Levy S, Yarbrough WG, Chung CH. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma Clin Cancer Res 2006 Feb 1;12(3 Pt 1):701-9
Subramanian C, Cohen MS. Over expression of DNA damage and cell cycle dependent proteins are associated with poor survival in patients with adrenocortical carcinoma Surgery 2019 Jan;165(1):202-210
Suman S, Mishra A. An interaction network driven approach for identifying biomarkers for progressing cervical intraepithelial neoplasia Sci Rep 2018 Aug 27;8(1):12927
Takahashi TS, Basu A, Bermudez V, Hunwitz J, Walter JC. Cdc7-Drfl1 kinase links chromosome cohesion to the initiation of DNA replication in Xenopus egg extracts Genes Dev 2008 Jul 15;22(14):1894-905
Tenca P, Brotherton D, Montagnoli A, Rainoldi S, Albanese C, Santocanale C. Cdc7 is an active kinase in human cancer cells undergoing replication stress J Biol Chem 2007 Jan 5;282(1):208-15
Tsuiji T, Lau E, Chiang GG, Jiang W. The role of Dbf4/Drfl-dependent kinase Cdc7 in DNA-damage checkpoint control Mol Cell 2008 Dec 26;32(6):862-9
Walker GJ, Indsto JO, Sood R, et al. Deletion mapping suggests that the 1p22 melanoma susceptibility gene is a tumor suppressor localized to a 9-Mb interval Genes Chromosomes Cancer 2004 Sep;41(1):56-64
Yamada M, Watanebe K, Mistrik M, Vesela E, Protivankova I, Mailand N, Lee M, Lukas J, Bartek J. ATR-Chk1-APC/Cdc7-dependent stabilization of Cdc7-ASK (Dbf4) kinase is required for DNA lesion bypass under replication stress Genes Dev 2013 Nov 15;27(22):2459-72
Young-Deok K, Eun-Hyong J, Yeon-Sun K, Kang-Mi P, Jin-Yong L, Sung-Hwan C, Tae-Yun K, Tae-Sung P, Soung Min K, Myung-Jin K, Jong-Ho L. Molecular genetic study of novel biomarkers for early diagnosis of oral squamous cell carcinoma Med Oral Patol Oral Cir Bucal 2015 Mar 1;20(2):e167-79
Zaidi S, Blanchard M, Shim K, et al. Mutated BRAF Emerges as a Major Effector of Recurrence in a Mutine Melanoma Model After Treatment With Immunomodulatory Agents Mol Ther 2015 May;23(5):845-856
Zheng L, Yang Z, Meng Z, Upregulation of BUB1B, CDC7, CDC20, and MCM3 in Tumor Tissues Predicted Worse Overall Survival and Disease-Free Survival in Hepatocellular Carcinoma Patients Biomed Res Int 2018 Sep 30;2018:7897346
Zografos E, Anagnostopoulou AK, Papadopoulou A, Legaki K, Zagouri F, Marinos E, Tsangaris GT, Gazouli M. Serum Proteomic Signatures of Malignant Melanoma Model After Treatment With Immunomodulatory Agents Mol Ther 2015 May;23(5):845-856