Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i5.6419

COMPREHENSIVE ANALYSIS OF CDCA8 IN COLON ADENOCARCINOMA INCLUDING EXPRESSION, METHYLATION, MUTATIONS, AND PROGNOSTIC SIGNIFICANCE

Muhammad Imran[1], Imtiaz Ali Soomro[2], Kiran Nazish[3], Naheed Bano[4], Muhammad Abbas[5], Muhammad Khizer Hayat[6], Habibullah Janyaro[7*], Usama Ahmed[8], Hafeez Ullah[9], Muhammad Salman Hameed[10]

[1]Department Of Animal Sciences, KBCMA College Of Veterinary And Animal Sciences, Narowal , Pakistan
[2]Department Of Surgery, Peoples University Of Medical And Health Sciences Nawabshah, Pakistan
[3]Department Of Veterinary Epidemiology And Public Health SBBUVAS Sakrand, Pakistan
[4]Department Of Zoology, Wildlife & Fisheries, MNS-University Of Agriculture Multan, Pakistan
[5]1st Affiliated Hospital Of Hebei North University Hebei Province, China
[6]Center For Animal Diagnostics, Chughtai Lab Lahore, Pakistan
[7]Department Of Veterinary Surgery, SBBUVAS, Sakrand, Pakistan
[8]Department Of Medicine, School Of Biomedical Engineering, Shenzhen University Medical School, Shenzhen 518060, PR China
[9]Department Of Microbiology, Abasyn University Peshawar, Pakistan
[10]National Key Laboratory of Green Pesticide, International Joint Research Center For Intelligent Biosensor Technology And Health, CentralChina Normal University, Wuhan 430079, P.R. China

***Corresponding Author:** Habibullah Janyaro
*Email Address: Janyaroh@Gmail.Com

ABSTRACT

In the current study, the role of cell division cycle-associated 8 (CDCA8) in colon adenocarcinoma (COAD) was analyzed through comprehensive expression and methylation analysis, genetic mutation inquiry, and prognostic assessment. Utilizing the UALCAN database, CDCA8 expression analysis revealed significant overexpression in carcinogenic cells compared to normal control samples, suggesting its involvement in COAD proliferation. Further examination of CDCA8 expression across various clinical parameters showed significant upregulation in different cancer development stages, racial groups, genders, and age classes within COAD patients, highlighting its critical role in cancer proliferation. Validation using the GEPIA2.0 tool confirmed that CDCA8 was highly expressed in COAD compared to normal controls. Additionally, analysis of CDCA8 expression across different cancer stages revealed dysregulation in all four stages, with the highest expression in stage I and the lowest in stage III. The study also investigated the promoter methylation level of CDCA8, finding a significant association between COAD samples and normal controls. Analysis of promoter methylation across various clinical parameters showed significant variations, with distinct methylation patterns observed across cancer stages, racial groups, genders, and age groups. Overall

survival (OS) and disease-free survival (DFS) analyses using the KM plotter tool demonstrated that low CDCA8 expression was associated with shorter OS compared to high CDCA8 expression. In terms of DFS, COAD patients with higher CDCA8 expression experienced better DFS than those with low CDCA8 expression. Further validation of CDCA8 expression against survival data indicated that high CDCA8 expression was associated with better OS and DFS in COAD. Lastly, mutational assessment using the cBioPortal platform showed no significant mutations in COAD samples. Overall, these findings highlight the complex role of CDCA8 in COAD pathogenesis, underscoring its potential as a prognostic biomarker and therapeutic target in COAD management.

Keywords: Colon adenocarcinoma, Diagnosis, Treatment, Biomarker

Introduction

Cancer remains the leading cause of mortality worldwide, presenting significant health-related and socio-economic challenges (1, 2). Current cancer treatments include surgery, chemotherapy, radiotherapy, and immunotherapy (3, 4). Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in both men and women, affecting over 1.4 million individuals and causing approximately 693,900 deaths annually (5). Approximately 60% of CRC patients are diagnosed with localized and distant metastases, categorized as stage IV, which has a 5-year survival rate ranging from 12.5% to 70.4%, and a poor prognosis compared to over 90% for stage I (6). Recently, there has been a trend toward younger age at diagnosis of CRC (7). Over the last decade, CRC incidence rates increased by 22% and CRC mortality rates increased by 13% among adults under 50 years old in the USA (8). These facts highlight the urgent need to develop early molecular biomarkers for CRC. CRC is a heterogeneous, multifactorial disease, with approximately 35% of cases attributed to genetic factors. Genome-wide association studies have identified around 50 associated loci (9). Additionally, smoking, alcohol consumption, low physical activity, obesity, and environmental factors have been linked to increased CRC risk (10). Currently, chemotherapy, including anti-cancer drugs and compounds, is primarily used in advanced stages of the disease or as an adjuvant therapy after surgery in cases of lymph node metastasis (11, 12). Surgery combined with chemotherapy and radiotherapy is still considered the best approach for treating most patients at stages III and IV. However, these treatments are often associated with severe adverse reactions and chemo-resistance (13).

The CDCA8 gene encodes the Borealin/Dasra B protein and is a crucial component of the chromosome passenger complex (CPC) (14, 15). The CPC is a vital structure during cell division, comprising four key parts: INCENP, Survivin, Aurora B, and Borealin/Dasra B (16). CDCA8 is essential for localizing the CPC to the centromere, correcting kinetochore binding errors, and stabilizing bipolar spindles (17, 18). The CPC includes the enzymatic core Aurora-B kinase, the scaffold protein inner centromere protein, CDCA8, and two non-enzymatic surviving subunits (19, 20). Therefore, CDCA8 is a significant factor in mitosis regulation (21, 22). The eight members of the cell division cycle-associated (CDCA) gene family (CDCA1-8) are critical regulators of cell proliferation. Studies have shown that the abnormal expression of CDCAs can cause cancer (19, 23, 24). Specifically, CDCA8 is highly expressed in breast cancer cells, and knockdown of the CDCA8 gene can suppress the survival and growth of cancer cells. Furthermore, higher CDCA8 gene expression is strongly associated with poor prognosis in various cancers. CDCA8 is thus a vital mediator of estrogen-stimulated breast cancer cell growth and survival (25, 26). Research has confirmed that CDCA8 plays a crucial role in mitosis, chromosome segregation, and cancer cell division (27, 28). One study showed that CDCA8 was overexpressed in colorectal cancer, and that depletion of CDCA8 hindered the growth of malignant cells and induced apoptosis (29).

In the ongoing research, our goal was to investigate CDCA8 mutations, expression levels, prognostic implications on survival, and functional perspectives within the context of colon adenocarcinoma (COAD) through bioinformatics analysis. Additionally, we explored the relationship between CDCA8 expression and promoter methylation levels. To accomplish this, we utilized various

databases including The Cancer Genome Atlas (TCGA), the UALCAN platform, the Kaplan-Meier database, the Gene Expression Profiling Interactive Analysis (GEPIA2.0), and cBioPortal. The primary aim of this study was to evaluate CDCA8 expression patterns in COAD and elucidate its potential significance in cancer treatment and prognosis.

Materials and methods

GEPIA2.0 analysis

GEPIA2.0 is a powerful online tool that facilitates survival analysis in cancer research (30). The GEPIA2.0 website allowed us to compare the expression of CDCA8 in tumor tissues versus adjacent normal tissues and generate box plots. By utilizing information from TCGA and GTEx data sets, GEPIA2.0 enables users to evaluate the impact of specific genes on patients' survival across various cancer types. In the current study, GEPIA2.0 was employed to analyze the association between CDCA8 gene expression and prognosis, including overall survival (OS) and disease-free survival (DFS), in colon adenocarcinoma (COAD).

UALCAN analysis

UALCAN (http://ualcan.path.uab.edu/) is an integrative and interactive online resource that can be used to analyze level 3 RNA-seq data and clinical information from 31 different tumors in The Cancer Genome Atlas (TCGA) data set. This portal allows users to examine differences in the expression levels of query genes between tumor and normal samples and to estimate the impact of gene expression levels and clinicopathological characteristics on patient survival (31). In our study, we used the UALCAN database to probe CDCA8 expression levels and promoter methylation status in colon adenocarcinoma (COAD). Additionally, we utilized UALCAN to assess CDCA8 expression and promoter methylation levels across various clinical parameters, including patient race, age, and gender. This comprehensive investigation provided valuable insights into the relationship between CDCA8 expression patterns, promoter methylation, and demographic factors in COAD patients.

Kaplan-Meier Plotter analysis

The Kaplan-Meier (KM) plotter is an essential tool in the domain of survival analysis (32). This online platform harnesses extensive clinical data to evaluate the impact of specific genes on patient survival across different cancer types. Researchers can easily explore the prognostic value of gene expression, identifying potential prognostic biomarkers. KM Plotter's intuitive interface offers Kaplan-Meier survival curves, providing insights into how gene expression correlates with patient outcomes. In this study, the KM plotter tool was utilized to analyze the impact of CDCA8 dysregulation on the overall survival (OS) of cancer patients.

cBioPortal analsysis

cBioPortal (https://www.cbioportal.org/) (33) is a crucial platform for analyzing genetic alterations in cancers. Utilizing large-scale genomics data, it enables researchers to investigate and interpret genomic alterations, including mutations, copy number variations, and mRNA expression changes. The user-friendly interface facilitates in-depth analysis of these alterations across various cancer types, contributing to a better understanding of the molecular landscape and potential therapeutic targets. In the current research, we utilized cBioPortal for mutational analysis of the CDCA8 gene across COAD tumors.

Results

Expression analysis of CDCA8 in COAD based on sample types

CDCA8 expression in COAD and normal control samples was investigated using the UALCAN database (Figure 1). Our findings reveal a significant overexpression of CDCA8 in COAD cancer cells compared to normal control samples. This pronounced upregulation indicates a potential association between CDCA8 expression and the proliferation of COAD cancer cells.

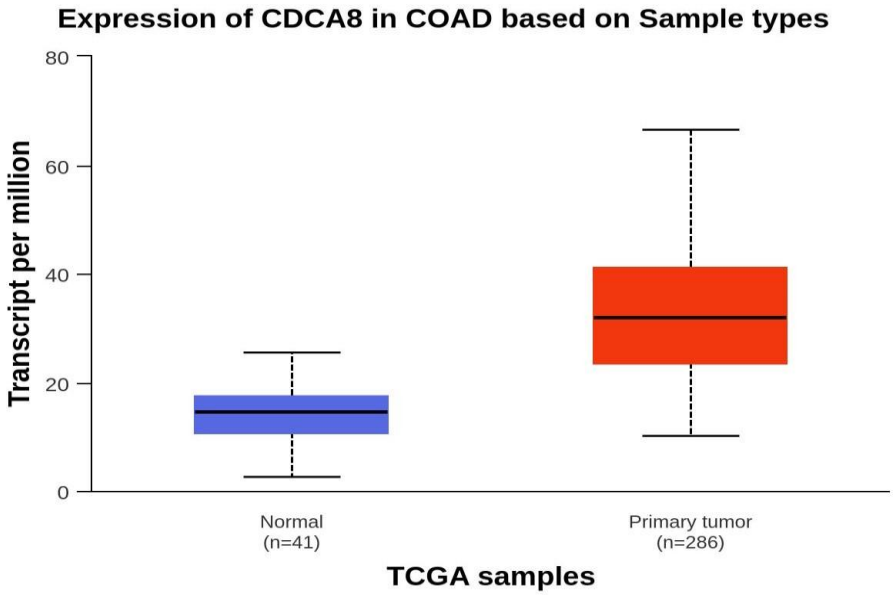

Figure 1: Expression profiling of CDCA8 in COAD and normal tissue samples.

Expression analysis of CDCA8 in COAD cancer divided based on different clinical parameters
Following this, we conducted an evaluation of CDCA8 in COAD samples across various clinical parameters, encompassing cancer stages, patient demographics including race, gender, and age (refer to Figure 2). Initially, we examined CDCA8 expression across different stages of cancer development and observed a significant increase in CDCA8 expression in COAD compared to normal control samples across all stages (Figure 2A). Subsequently, we assessed CDCA8 expression in COAD patients, revealing a substantial upregulation of CDCA8 in each of the three racial groups—Caucasian, Asian, and African American—compared to normal controls (Figure 2B). Furthermore, we investigated CDCA8 expression in COAD patients stratified by gender, which demonstrated a notable elevation of CDCA8 expression in both male and female patients compared to normal controls (Figure 2C). Lastly, we examined the correlation between CDCA8 expression and patient age in COAD. Our findings indicated an increased expression of CDCA8 across various age groups among COAD patients (Figure 2D).

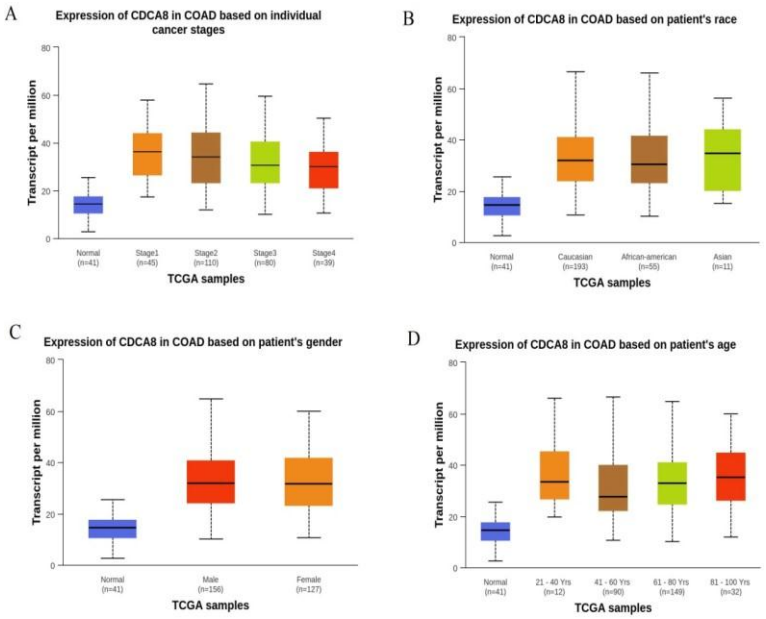

Figure 2: Expression of CDCA8 across different clinical boundaries

Validation of CDCA8 expression in COAD

We utilized GEPIA2 to examine CDCA8 expression in COAD cancer compared to normal tissues. The analysis revealed a significant upregulation of CDCA8 in colon adenocarcinoma (COAD) when compared to normal control samples (refer to Figure 3A). Additionally, we investigated the correlation between CDCA8 expression and different pathological stages using the GEPIA2 database. The results demonstrated a strong association between CDCA8 expression levels and the stages of COAD patients. Notably, CDCA8 exhibited the highest expression in stage I and the lowest expression in stage III among COAD patients (Figure 3B).

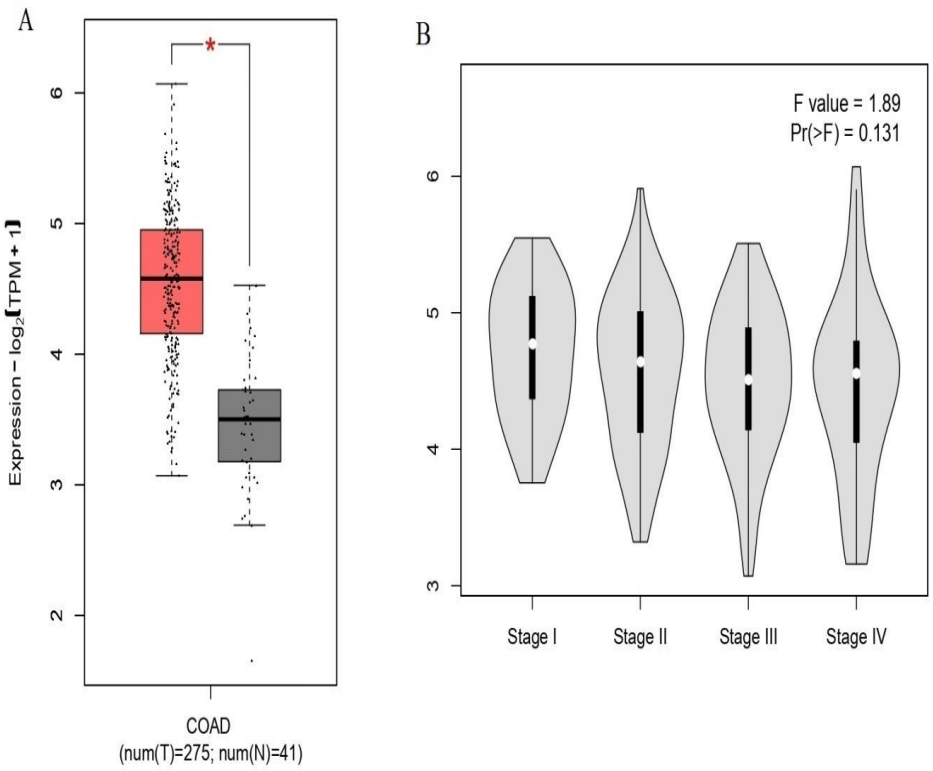

Figure 3: Validation of CDCA8 across different stages of COAD

Promoter methylation of CDCA8 in COAD and normal tissue

Therefore, we examined the differentiation in promoter methylation of CDCA8 between COAD and normal control samples using the UALCAN dataset (refer to Figure 4). Our analysis unveiled a significant variation, particularly hypermethylation, in the promoter methylation levels of CDCA8 in COAD compared to normal control samples. This observation suggests potential epigenetic dysregulation of CDCA8, underscoring its involvement in COAD pathogenesis. Such findings contribute to our understanding of the molecular mechanisms underlying COAD development and propose insights into the role of CDCA8 as a potential biomarker or therapeutic target in COAD management.

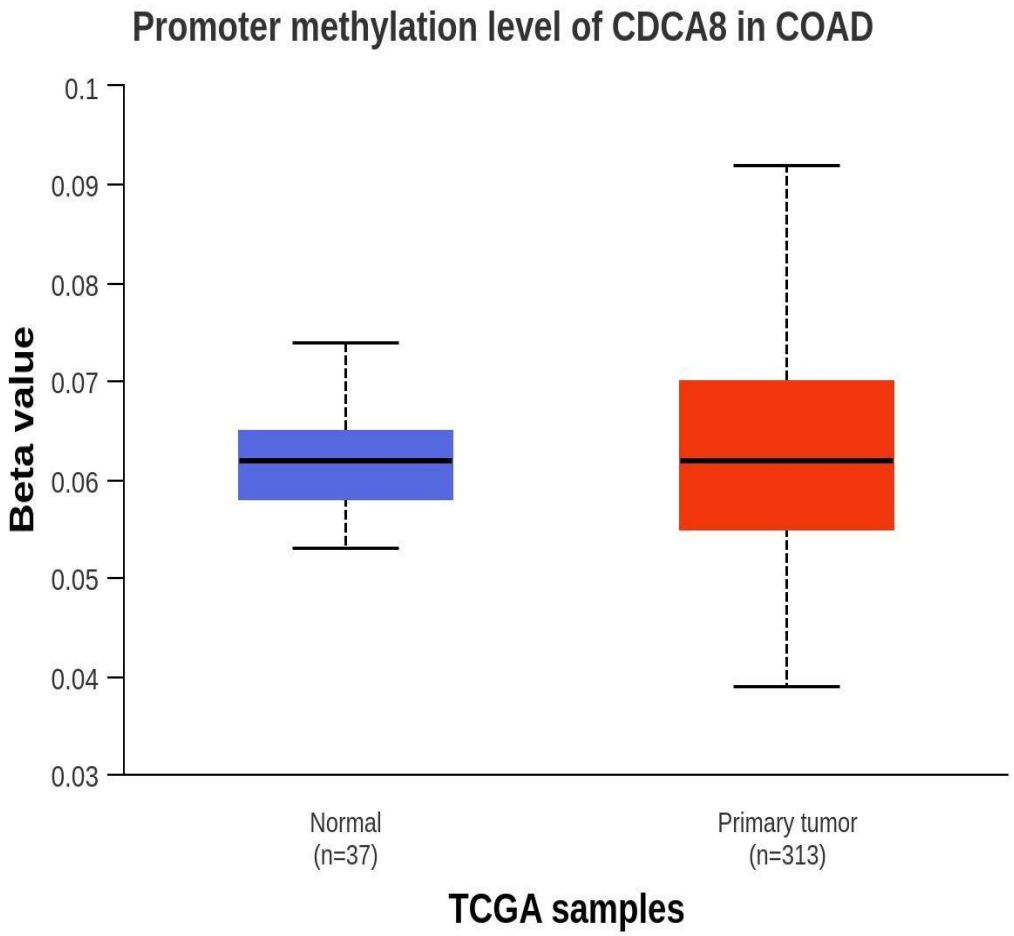

Figure 4: Promoter methylation pattern of CDCA8 in COAD and normal control samples

Promoter methylation of CDCA8 in COAD cancer divided based on different clinical parameters

To further delve into the promoter methylation status of CDCA8 in COAD, we analyzed various clinical parameters (refer to Figure 5). Initially, we examined CDCA8 promoter methylation across different COAD stages in comparison to normal control samples. We observed significant variations among stages, with stage I exhibiting hypomethylation and the remaining stages displaying noticeable hypermethylation (Figure 5A). Subsequently, we investigated CDCA8 promoter methylation in relation to the race of COAD patients. Our analysis revealed hypermethylation in CDCA8 promoter regions across Caucasian and African American groups, whereas hypomethylation was observed in the Asian race group compared to normal control samples (Figure 5B). Following this, assessment of CDCA8 promoter methylation based on patient gender showed gender-specific differences, with both females and males exhibiting hypermethylation (Figure 5C). Finally, we explored CDCA8 promoter methylation with respect to patient age, revealing varying methylation levels across different age groups (Figure 5D). These comprehensive analyses highlight the intricate relationship between CDCA8 promoter methylation and various clinical parameters in COAD, providing insights into the diverse mechanisms underlying CDCA8 expression regulation in COAD pathogenesis.

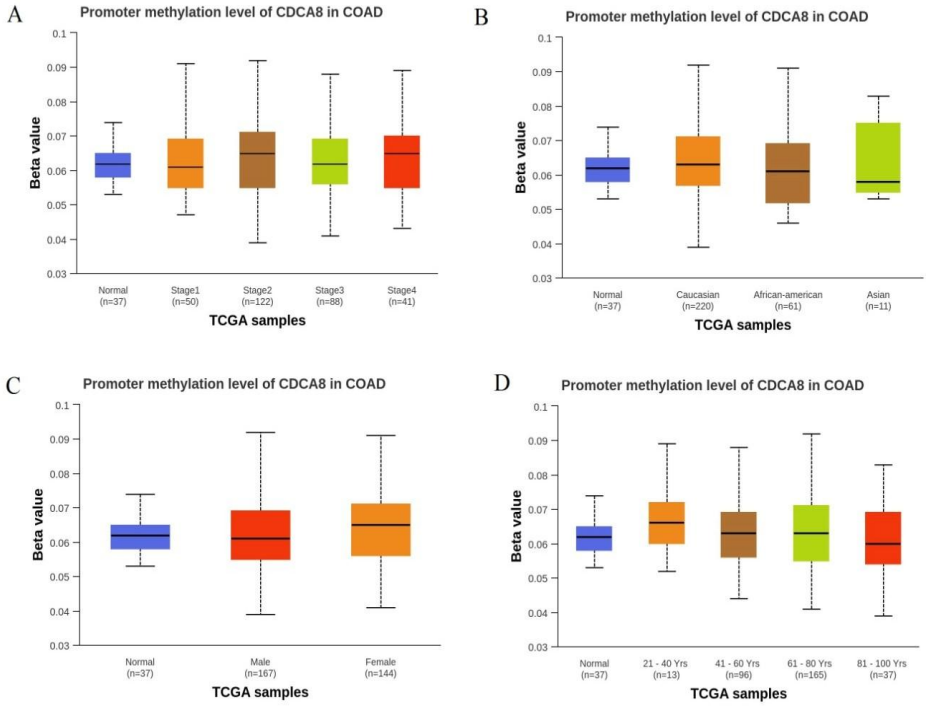

Figure 5: CDCA8 promoter methylation pattern across different clinical parameters

Survival analysis of CDCA8

To further evaluate CDCA8 gene expression in COAD, we conducted an analysis for overall survival (OS) and disease-free survival (DFS) using the KM plotter tool. Our examination revealed a significant association between CDCA8 gene expression and patient survival outcomes in the current study. Specifically, COAD patients with low CDCA8 expression exhibited shorter overall survival compared to those with high CDCA8 expression levels (refer to Figure 6A). Similarly, in the assessment of disease-free survival (DFS), COAD patients with higher CDCA8 expression experienced better DFS relative to COAD patients with low CDCA8 expression. These findings underscore the pivotal role of CDCA8 in influencing the survival outcomes of COAD patients, emphasizing its potential clinical significance as a prognostic marker in COAD management.

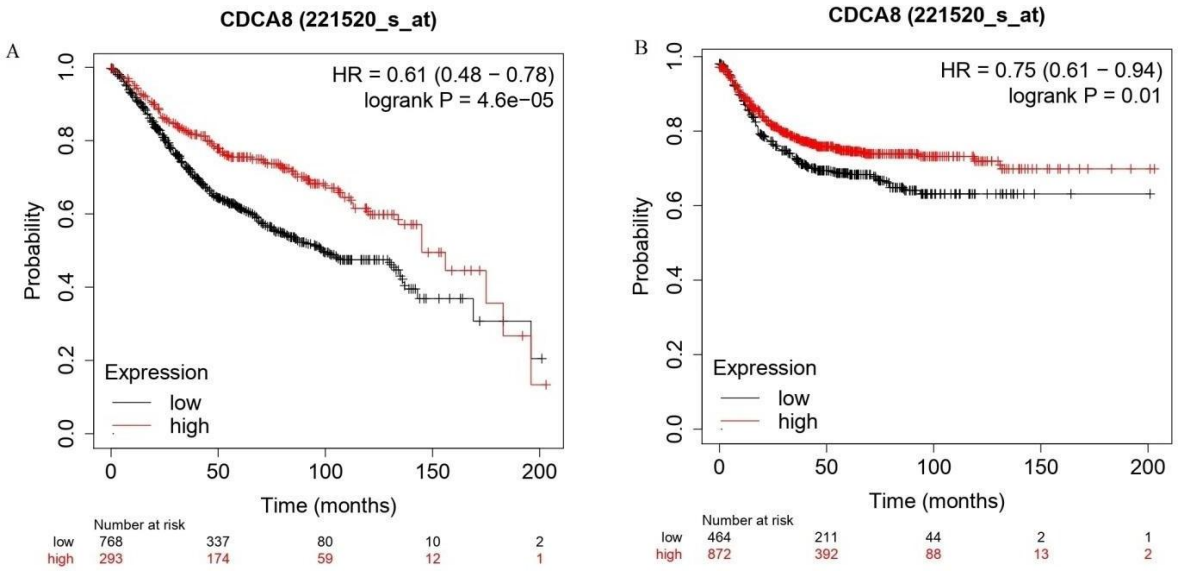

Figure 6: KM survival curve (OS, RFS) of CDCA8 in COAD patients

Prognostic analysis of CDCA8 in COAD

We utilized the GEPIA2.0 database to explore the prognostic significance of CDCA8 expression in COAD cancer progression. COAD patients were stratified into low and high expression groups based on CDCA8 expression levels. In COAD, high CDCA8 expression was correlated with improved overall survival (OS) compared to low CDCA8 expression (refer to Figure 7A). Furthermore, we observed that a high CDCA8 expression level was associated with favorable disease-free survival (DFS) in COAD compared to the low CDCA8 expression group (refer to Figure 7B).

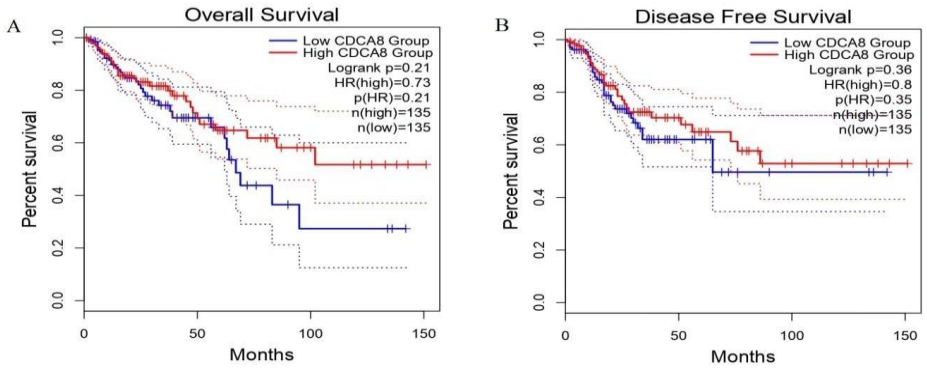

Figure 7: Survival curve (OS, RFS) of CDCA8 in COAD patients

Mutational analysis of CDCA8 in COAD

For the analysis of CDCA8 mutation features, we conducted a comprehensive mutational analysis of CDCA8 in COAD cancer using the cBioPortal dataset. In the current review, no significant mutations of CDCA8 were observed (refer to Figure 8).

Figure 8: Oncoplot of CDCA8 in COAD cancer

Discussion

Colorectal cancer (CRC) is widely understood to develop through a multistep process, starting from aberrant crypt foci, progressing through benign precancerous lesions (adenomas), and eventually culminating in malignant tumors (adenocarcinomas) over an extended period (34). While the majority of CRC cases are sporadic, approximately 20%-30% of CRC patients carry inherited mutations (35, 36). Despite significant advancements in surgical resection for patients with localized disease, the majority of CRC patients eventually experience recurrence and metastasis (37, 38). Current therapeutic approaches, such as chemotherapy, are recommended for CRC treatment; however, these non-surgical interventions have limited efficacy and are ineffective against distant metastasis (39). Consequently, the prognosis for CRC patients remains poor, highlighting the need to focus on future therapeutic strategies to improve clinical outcomes. Immunotherapy has recently emerged as a treatment option for advanced CRC and holds the potential to eradicate the disease by activating immune responses (40).

CDCA8 stands as a crucial regulatory gene in mitosis, playing a pivotal role in various cancer types by promoting cell proliferation and invasion, thus acting as an oncogene (41, 42). Previous studies have highlighted the heightened transcriptional activity of CDCA8 in embryos, embryonic stem cells, and cancer cells, while it either lacks expression or shows minimal expression in normal tissues (43). Consequently, aberrant CDCA8 expression strongly correlates with cancer pathogenesis. Li et al. demonstrated that CDCA8 encodes the protein Borealin/Dasra B, which plays a critical role in regulating postnatal liver development, injury-induced hepatic progenitor-like cell regeneration, and

liver tumorigenesis in mice (44). Earlier research has indicated that upregulated CDCA8 expression plays a significant role in cancer initiation, progression, and transformation. Yu et al. illustrated that CDCA8 induces tamoxifen resistance and enhances cell proliferation by inhibiting apoptosis and promoting cell cycle progression in breast cancer cells (45). Additionally, CDCA8 knockdown has been shown to inhibit cell proliferation and promote cell differentiation in lung cancer, colorectal cancer, and human embryonic stem cells (29, 46, 47).

As illustrated in the aforementioned studies, elevated CDCA8 expression plays a crucial role in various types of cancer. Recently, an increasing number of studies have investigated CDCA8 as a potential prognostic marker. Gu et al. conducted RNA-Seq data analysis and identified CDCA8 as a prognostic gene in kidney renal clear cell carcinoma (48). Additionally, Ci et al. demonstrated that cutaneous melanoma patients with high CDCA8 expression had significantly lower overall survival compared to those with low expression, suggesting CDCA8 as an independent prognostic indicator in cutaneous melanoma (41). Similar findings have been observed in gastric cancer, lung cancer, breast cancer, and colorectal cancer (49, 50). Furthermore, high CDCA8 expression has been associated with poor prognosis in gastric cancer. In pancreatic ductal adenocarcinoma, CDCA8 mediates the upregulation of KIF18B and promotes cancer cell proliferation (51). Depletion of CDCA8 leads to cell cycle arrest at the G2/M stage, increased DNA damage and apoptosis, and enhances the sensitivity of ovarian cancer cells to Cisplatin and Olaparib (52). Through the ROCK signaling pathway, CDCA8 knockdown can inhibit cancer cell proliferation and invasion (41). However, the significance of CDCA8 in COAD has not been fully elucidated.

In our current investigation, we utilized the UALCAN database to explore the expression of CDCA8 in COAD. Consistent analysis across different stages, cancer types, age, gender, and racial groups revealed upregulation of CDCA8 expression. Regarding cancer progression, our study found significantly higher CDCA8 expression levels in COAD tissues compared to normal control samples. Furthermore, using the KM plotter tool, our evaluation indicated that COAD patients with low CDCA8 expression experienced shorter overall survival and worse disease-free survival compared to patients with high CDCA8 expression levels. Our analysis suggests that CDCA8 expression level in tissue serves as an independent poor prognostic factor. Further investigations are warranted to explore the prognostic value of CDCA8 expression in cancer development.

Conclusion

Compared to adjacent normal tissues, COAD tissues exhibited elevated expression levels of CDCA8. Increased CDCA8 levels were associated with poor overall survival (OS), disease-free survival (DFS), and clinical features, including promoter methylation levels and genetic mutations. Therefore, we hypothesize that CDCA8 promotes cancer development through cell cycle regulation. Additionally, CDCA8 may play a potential therapeutic role in COAD-related immunity. Consequently, CDCA8 holds promise as a potential biomarker for early COAD detection and prognostic prediction.

Conflict of interest

None

Acknowledgement

None

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

2. Hameed Y, Usman M, Liang S, Ejaz S. Novel diagnostic and prognostic biomarkers of colorectal cancer: Capable to overcome the heterogeneity-specific barrier and valid for global applications. PLoS One. 2021;16(9).
3. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G. Anastomotic leakage in colorectal cancer surgery. Surg Oncol. 2022;40(101708):24.
4. Sial N, Saeed S, Ahmad M, Hameed Y, Rehman A, Abbas M, et al. Multi-omics analysis identified TMED2 as a shared potential biomarker in six subtypes of human cancer. International Journal of General Medicine. 2021:7025-42.
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):9.
6. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):104-17.
7. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109(8).
8. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.
9. Jia WH, Zhang B, Matsuo K, Shin A, Xiang YB, Jee SH, et al. Genome-wide association analyses in East Asians identify new susceptibility loci for colorectal cancer. Nat Genet. 2013;45(2):191-6.
10. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78-85.
11. Ades S. Adjuvant chemotherapy for colon cancer in the elderly: moving from evidence to practice. Oncology. 2009;23(2):162-7.
12. Xu W, Li H, Hameed Y, Abdel-Maksoud MA, Almutairi SM, Mubarak A, et al. Elucidating the clinical and immunological value of m6A regulator-mediated methylation modification patterns in adrenocortical carcinoma. Oncology Research. 2023;31(5):819.
13. Wu S, Wang X, Chen J, Chen Y. Autophagy of cancer stem cells is involved with chemoresistance of colon cancer cells. Biochem Biophys Res Commun. 2013;434(4):898-903.
14. Usman M, Hameed Y, Ahmad M. Does epstein–barr virus participate in the development of breast cancer? A brief and critical review with molecular evidences. Biomedical and Biotechnology Research Journal (BBRJ). 2020;4(4):285-92.
15. Identification of Key Biomarkers for the Future Applications in Diagnostics and Targeted Therapy of Colorectal Cancer. Current Molecular Medicine. 2022.
16. Carmena M, Wheelock M, Funabiki H, Earnshaw WC. The chromosomal passenger complex (CPC): from easy rider to the godfather of mitosis. Nature reviews Molecular cell biology. 2012;13(12):789-803.
17. Gassmann R, Carvalho A, Henzing AJ, Ruchaud S, Hudson DF, Honda R, et al. Borealin: a novel chromosomal passenger required for stability of the bipolar mitotic spindle. The Journal of cell biology. 2004;166(2):179-91.
18. Sampath SC, Ohi R, Leismann O, Salic A, Pozniakovski A, Funabiki H. The chromosomal passenger complex is required for chromatin-induced microtubule stabilization and spindle assembly. Cell. 2004;118(2):187-202.
19. Phan NN, Wang CY, Li KL, Chen CF, Chiao CC, Yu HG, et al. Distinct expression of CDCA3, CDCA5, and CDCA8 leads to shorter relapse free survival in breast cancer patient. Oncotarget. 2018;9(6):6977-92.
20. Hameed Y. Decoding the significant diagnostic and prognostic importance of maternal embryonic leucine zipper kinase in human cancers through deep integrative analyses. Journal of Cancer Research and Therapeutics. 2023;19(7):1852-64.

21. Gassmann R, Carvalho A, Henzing AJ, Ruchaud S, Hudson DF, Honda R, et al. Borealin: a novel chromosomal passenger required for stability of the bipolar mitotic spindle. J Cell Biol. 2004;166(2):179-91.
22. Higuchi T, Uhlmann F. Cell cycle: passenger acrobatics: Nature. 2003 Dec 18;426(6968):780-1. doi: 10.1038/426780a.
23. Spruck CH, Strohmaier HM. Seek and destroy: SCF ubiquitin ligases in mammalian cell cycle control. Cell Cycle. 2002;1(4):250-4.
24. Dong Y, Wu X, Xu C, Hameed Y, Abdel-Maksoud MA, Almanaa TN, et al. Prognostic model development and molecular subtypes identification in bladder urothelial cancer by oxidative stress signatures. Aging. 2024;16(3):2591-616.
25. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
26. Hu H, Umair M, Khan SA, Sani AI, Iqbal S, Khalid F, et al. CDCA8, a mitosis-related gene, as a prospective pan-cancer biomarker: implications for survival prognosis and oncogenic immunology. American Journal of Translational Research. 2024;16(2):432.
27. Hindriksen S, Meppelink A, Lens SM. Functionality of the chromosomal passenger complex in cancer. Biochem Soc Trans. 2015;43(1):23-32.
28. Abdel-Maksoud MA, Ullah S, Nadeem A, Shaikh A, Zia MK, Zakri AM, et al. Unlocking the diagnostic, prognostic roles, and immune implications of BAX gene expression in pan-cancer analysis. American Journal of Translational Research. 2024;16(1):63.
29. Wang Y, Zhao Z, Bao X, Fang Y, Ni P, Chen Q, et al. Borealin/Dasra B is overexpressed in colorectal cancers and contributes to proliferation of cancer cells. Med Oncol. 2014;31(11):014-0248.
30. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019;47(W1):W556-W60.
31. Chandrashekar DS, Bashel B, Balasubramanya SAH, Creighton CJ, Ponce-Rodriguez I, Chakravarthi B, et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. Neoplasia. 2017;19(8):649-58.
32. Maciejczyk A, Szelachowska J, Czapiga B, Matkowski R, Hałoń A, Györffy B, et al. Elevated BUBR1 expression is associated with poor survival in early breast cancer patients: 15-year follow-up analysis. J Histochem Cytochem. 2013;61(5):330-9.
33. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-4.
34. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-67.
35. FC DAS, Wernhoff P, Dominguez-Barrera C, Dominguez-Valentin M. Update on Hereditary Colorectal Cancer. Anticancer Res. 2016;36(9):4399-405.
36. Peters U, Bien S, Zubair N. Genetic architecture of colorectal cancer. Gut. 2015;64(10):1623-36.
37. Kerr D. Clinical development of gene therapy for colorectal cancer. Nature Reviews Cancer. 2003;3(8):615-22.
38. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, et al. Colorectal cancer. Lancet. 2010;375(9719):1030-47.
39. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010;78(3-4):237-48.
40. Xiang B, Snook AE, Magee MS, Waldman SA. Colorectal cancer immunotherapy. Discov Med. 2013;15(84):301-8.
41. Ci C, Tang B, Lyu D, Liu W, Qiang D, Ji X, et al. Overexpression of CDCA8 promotes the malignant progression of cutaneous melanoma and leads to poor prognosis. Int J Mol Med. 2019;43(1):404-12.

42. Bi Y, Chen S, Jiang J, Yao J, Wang G, Zhou Q, et al. CDCA8 expression and its clinical relevance in patients with bladder cancer. Medicine. 2018;97(34):0000000000011899.
43. Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. J Clin Oncol. 2014;32(8):774-82.
44. Li L, Li D, Tian F, Cen J, Chen X, Ji Y, et al. Hepatic Loss of Borealin Impairs Postnatal Liver Development, Regeneration, and Hepatocarcinogenesis. J Biol Chem. 2016;291(40):21137-47.
45. Yu D, Shi L, Bu Y, Li W. Cell Division Cycle Associated 8 Is a Key Regulator of Tamoxifen Resistance in Breast Cancer. J Breast Cancer. 2019;22(2):237-47.
46. Hayama S, Daigo Y, Yamabuki T, Hirata D, Kato T, Miyamoto M, et al. Phosphorylation and activation of cell division cycle associated 8 by aurora kinase B plays a significant role in human lung carcinogenesis. Cancer Res. 2007;67(9):4113-22.
47. Dai C, Miao CX, Xu XM, Liu LJ, Gu YF, Zhou D, et al. Transcriptional activation of human CDCA8 gene regulated by transcription factor NF-Y in embryonic stem cells and cancer cells. J Biol Chem. 2015;290(37):22423-34.
48. Gu Y, Lu L, Wu L, Chen H, Zhu W, He Y. Identification of prognostic genes in kidney renal clear cell carcinoma by RNA‐seq data analysis. Mol Med Rep. 2017;15(4):1661-7.
49. Chang JL, Chen TH, Wang CF, Chiang YH, Huang YL, Wong FH, et al. Borealin/Dasra B is a cell cycle-regulated chromosomal passenger protein and its nuclear accumulation is linked to poor prognosis for human gastric cancer. Exp Cell Res. 2006;312(7):962-73.
50. Bu Y, Shi L, Yu D, Liang Z, Li W. CDCA8 is a key mediator of estrogen-stimulated cell proliferation in breast cancer cells. Gene. 2019;703:1-6.
51. Li B, Liu B, Zhang X, Liu H, He L. KIF18B promotes the proliferation of pancreatic ductal adenocarcinoma via activating the expression of CDCA8. J Cell Physiol. 2020;235(5):4227-38.
52. Qi G, Zhang C, Ma H, Li Y, Peng J, Chen J, et al. CDCA8, targeted by MYBL2, promotes malignant progression and olaparib insensitivity in ovarian cancer. Am J Cancer Res. 2021;11(2):389-415.