CDC20 as a new therapeutic target for treating ovarian cancer: an integrated bioinformatics analysis

Xiaocui Zhang
China Medical University Shengjing Hospital Nanhu Branch: Shengjing Hospital of China Medical University

Fangfang Bi
China Medical University Shengjing Hospital Nanhu Branch: Shengjing Hospital of China Medical University

Qing Yang (yangqing_sj@126.com)
China Medical Universitry

Research

Keywords: ovarian cancer (OC), CDC20, cancer therapy

Posted Date: March 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-192561/v2

Abstract

Background: There were 313959 cases of newly diagnosed ovarian cancer (OC) and 207252 new deaths for OC in 2020 and OC lacks effective treatment options. Therefore, identifying novel therapeutic targets is imminent. Here, we use an integrated bioinformatics analysis to key genes involved in ovarian cancer and reveal potential therapeutic targets.

Methods: GSE105437, GSE14407 and GSE18520 downloaded from Gene Expression Omnibus (GEO) were used to screen differentially expressed genes (DEGs). Gene ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed to predict the potential functions of the DEGs. Protein-protein interaction network (PPI) was drawn through STRING database and select CDC20 having the highest degrees of connectivity as the potential therapeutic target. Oncomine database and quantitative Real-time RT-PCR (RT-qPCR) of the ovarian tissues were used to validate the mRNA expression of CDC20. We use Gene Set Enrichment Analysis (GSEA) software to explore the potential biological function of CDC20 in OC.

Results: A total of 821 DEGs were obtained, including 497 upregulated genes and 324 downregulated genes. Functional and pathway enrichment analyses indicated the DEGs were mainly involved in DNA-binding transcription activator activity, tubulin binding, microtubule binding, cell cycle, Wnt signaling pathway, p53 signaling pathway, and metabolism changes. Oncomine database analysis and RT-qPCR showed that CDC20 is significantly upregulated in OC tissues. GSEA analysis showed that CDC20 may regulate OC via cell cycle, citrate and TCA cycle, Oxidative phosphorylation and ubiquitin mediated proteolysis pathways.

Conclusion: The results of the present study deduced that CDC20 is overexpressed in OC and may be a promising therapeutic target for the treatment of OC.

1. Background

According to the new cancer statistics, there were 313959 cases of newly diagnosed OC and 207252 new deaths for OC in 2020 [1]. There will be approximately 22530 cancer cases diagnosed and 13980 patients will die from OC due to lack of early diagnosed markers, diagnosis at advanced stage with or without distant metastases, drug resistance and easiness to relapse [2-6]. Therefore, identifying novel therapeutic targets to improve the prognosis of OC patients is imminent.

We use the bioinformatical studies on OC from GEO database to study and explore the detailed molecular mechanisms of OC progression and therapy and reliable and positive new biomarkers and specific targets of OC. In this study, GSE105437, GSE14407 and GSE18520 were chosen from GEO database. First, R was used to merge and normalize the expression data of the three datasets based on batch normalization for the next DEGs screening. Subsequently, GO was used for functional annotation evaluation, and KEGG was used for pathway enrichment evaluation. Then, the PPI network of string database was used to explore the relationship between DEGs, and the molecular interaction between

DEGs and tumorigenesis was found. From the PPI network, CDC20 was chosen as one of the key genes. CDC20, an importance factor in cell cycle, control the chromosome segregation and mitotic progression through interactions between spindle assembly checkpoint (SAC) and anaphase-promoting complex or cyclosome (APC/C) [7]. The knockdown of CDC20 causes different endings, including the arrest of mitosis and subsequent cell death or mitotic slippage [8, 9]. CDC20 expression level was also searched on Oncomine database and verified in patients' ovarian cancer tissue compared to the normal ovarian tissues. In conclusion, CDC20 might be a novel anti-cancer therapeutic target in OC.

2. Materials And Methods

2.1 Data sources

NCBI-GEO (https://www.ncbi.nlm.nih.gov/geo/) is a free public database of microarray/gene profile and we obtained the gene expression profile of GSE105437, GSE14407 and GSE18520 in ovarian cancer and normal ovarian tissues. The details of each microarray study are provided in Table 1.

2.2 Integration of microarray data and differential expression analysis

Heterogeneity and potential variables are commonly recognized as major sources of bias and variability. The samples of the datasets we recruited for our multiple data sets analysis were handled on different days, in different groups or by different people. Therefore, we first integrated all samples of three data sets to improve the number of samples and avoid generating less reliable results by batch normalization in the R computing environment using sva and limma package [10, 11]. Next, we performed gene differential analysis (|LogFC|>1, adjusted P value (FDR)<0.05) by comparing tumor tissues with normal tissues using limma R package [12]. The integrated dysregulated gene lists were saved for subsequent analysis. In addition, the expression conditions of these DEGs are shown in the heatmap and volcano. Heatmap analysis of the resulting data matrix were performed with R language (version 4.0.2) and pheatmap package (1.0.12), which is available from https://cran.r-project.org/web/packages/pheatmap/.

2.3 Functional enrichment analysis of DEGs

GO [13], KEGG [14] pathway enrichment analyses were performed to predict the potential functions of the DEGs in R using the function of clusterProfiler (version 3.16.1). The top 10 of GO and KEGG pathways were then analyzed and presented in bubble plots. These bubble charts are drawn based on P value by using ggplot2r software package and statistical software R (version 4.0.2). We consider P<0.05 to be statistically significant.

2.4 Protein-protein Interaction

The online database STRING (v11.0, http://www.string-db.org/) was used to visualize the protein-protein Interaction (PPI) between the statistically significant DEG-encoded proteins in the resultant dataset [15]. To avoid an inaccurate PPI network, we used a confidence interaction score≥ 0.9 to obtain the significant PPIs. We downloaded the high-resolution network from the STRING database. And 30 hub

genes with the highest interactions in the network were listed, and a bar plot was drawn to show that in R language (version 4.0.2).

2.5 Gene Set Enrichment Analysis

Gene Set Enrichment Analysis (GSEA) software (Version 4.0.3) (http://www.broad.mit.edu/gsea) was used to explore the potential biological function of CDC20 in OC [16]. GSEA (version 3.0) was run for the KEGG gene sets (c2.cp.kegg.v.7.2.symbols.gmt) [17]. The number of permutations is equal to 1,000 and the phenotype labels were CDC20-high and CDC20-low. FDR <0.25 and NOM P<0.05 was considered as statistical significance.

2.6 Oncomine database extraction

Oncomine database (http://www.oncomine.org, accession number: 2020110263@stu.cmu.edu.cn) is currently the world's largest oncogene-chip database and integrated data-mining platform for the purpose of mining cancer gene information. To date, the database has collected 715 gene expression data sets and 86,733 pieces of cancer tissue and normal tissue sample data. The Oncomine database was applied for differential expression classification for common cancer types, and their respective normal tissues [17-19].

2.7 Ethical statement

This study was carried out in accordance with the standards of the Helsinki Declaration of the World Medical Association [20], and approved by the Ethics Committee of China Medical University. All clinical samples were collected from the Shengjing Hospital of China Medical University with informed consent from all patients .

2.8 Tissue collection

30 cases of primary OC tissue and 30 cases of normal ovarian tissue were used in this study. All samples were collected from the patients undergoing surgical excision at the Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University. No patient received radiotherapy, chemotherapy, or hormone therapy before surgery. The histopathological diagnosis obtained from the Pathology Department according to the criteria of the World Health Organization [21].

2.9 Total RNA extraction and real-time reverse transcription PCR

RNA isolation of ovarian tissue samples were conducted through TRIzol Reagent (Invitrogen, USA). The synthesis of complementary DNA (cDNA) was conducted using PrimeScriptTM RT reagent Kit with gDNA Eraser (Takara), through reverse transcription reaction. Quantitative polymerase chain reaction for CDC20 and GAPDH were conducted in a volume of 20μL using SYBR Premix Ex Taq (Takara) in the ABI 7500 Fast (Life Technologies, Carlsbad, CA, USA). GAPDH was selected as the internal reference gene. The primer sequences were as follows: CDC20 forward 5- AGCAGCAGATGAGACCCTGAGG-3; CDC20 reverse 5-

CAGCGGATGCCTTGGTGGATG-3; GAPDH forward 5- CAGGAGGCATTGCTGATGAT-3; GAPDH reverse 5-GAAGGCTGGGGCTCATTT -3. The relative levels of CDC20 expression were evaluated by the 2-ΔΔCT method using GAPDH as the control.

2.10 Statistical analysis

Statistical analysis was conducted using Graphpad Prism 8. Unpaired t test was utilized for comparing continuous variables between two groups. P-value less than 0.05 was considered to be statistically significant.

3. Results

3.1 Integration of microarray data and identification of DEGs in ovarian cancer.

Three expression profiles (GSE105437, GSE14407 and GSE18520) were obtained from the GEO database. We chose the expression data of normal ovarian epithelial cells and OC epithelial cells. In order to increase the signal and reduce the false positive rate, these data sets are standardized and combined in batches to reduce the variability.

To get differentially expressed genes of three databases, limma package was made to identify DEGs and we set the threshold of (|LogFC|>1, adjusted P value (FDR)<0.05. Finally, we got 821 DEGs, including 497 upregulated genes and 324 downregulated genes. In addition, the volcano (Figure 1A) and heatmap plots (Figure 1B) were drawn to show the expression levels of these DEGs.

3.2 GO function and KEGG pathway enrichment for the DEGs.

To further explore the function of the DEGs, GO function and KEGG pathway enrichment analysis were applied in R using the function of clusterProfiler (version 3.16.1). The top 10 of GO (Figure 2A) and KEGG (Figure 2B) pathways were then analyzed and presented in bubble plots. The detailed results are presented in Table 2 and Table 3.

3.3 PPI network and the selection of CDC20.

According to the information in string database, PPI network of DEGs protein translated in OC was constructed. Confidence score was set more than 0.9 and the high-resolution network picture (Figure 3A) and the details of the network were filtered out. Then R language was used to count the interaction number of each protein in the network and a bar plot was drawn to show 30 genes that had the highest interaction in the network (Figure 3B). As the top 2 proteins, it was identified that many OC-related studies had already well studied CDK1 through literature mining. Therefore, we chose CDC20 as the focus of following analyses.

3.4 Analysis of CDC20 gene in Oncomine database and ovarian cancer tissue.

The mRNA expression of CDC20 in the OC tissue was evaluated through the Oncomine database (Table 4). The results indicated that contrasted with the OC tissues, the CDC20 expression level is significantly decreased in the normal ovarian tissues (P<0.01; Figure 4A-I). For future verification of these results, 30 OC tissues and 30 normal ovarian tissues were evaluated by RT-qPCR. in line with the above results, the expression of CDC20 mRNA in the OC tissues remarkably increases (P<0.001) compared to the normal ovarian tissues (Figure 4J).

3.5 The mechanisms of CDC20 expression in ovarian cancer.

The analysis of single-gene differential expression in biological process research is limited [22]. The expression data of three datasets were used for GSEA to predict the gene set and signal pathway related to CDC20, so as to effectively reveal the biological function of the datasets. CDC20 may function in cell cycle, citrate and TCA cycle, Oxidative phosphorylation and ubiquitin mediated proteolysis (Figure 5A-D).

4. Discussion And Conclusions

Although the treatment technology of ovarian cancer has made great progress, the total mortality of ovarian cancer is the seventh largest cause of death of gynecological malignant tumors [1, 4]. The main causes of OC death are lack of early detection methods, high metastatic tendency and chemotherapy resistance. Therefore, for better treatment of OC, novel specific therapeutic targets should be identified.

Recently, bioinformatics is developing rapidly and microarray and sequencing data is getting more and more popular, which provide a platform for exploring the general genetic changes of tumor, identifying DEGs, and clarifying the molecular mechanism of tumor diagnosis, treatment and prognosis [23]. Therefore, GSE105437, GSE14407 and GSE18520 were downloaded from the GEO databases, from which 821 DEGs were identified, and GO function and KEGG pathway enrichment analysis showed the DEGs were mainly enriched in some vital pathways and functions, whose abnormalities may cause tumor progression and drug resistance. Activations of gene transcription such as HIF-1, STAT-3, PAX3, c-MYB, TGF-β can promote cancer progression in aspects of immune responses, hematopoiesis, neurogenesis, angiogenesis, cell survival, glucose metabolism and invasion, which can be used as therapeutic targets in OC [24-27]. Tubulin is the important component of microtubules that are an important therapeutic target in tumor cells [28]. Paclitaxel as a tubulin inhibitor is the first-line drug for treating OC, but as many as 80% of patients will eventually relapse and become paclitaxel resistant, which may cause treatment failure and poor prognosis of ovarian cancer [29-32]. Therefore, to find new targets for treatment is imminent. Cell cycle is the basic process of cell division, which is closely related to the orderly expression of related genes, cyclin-dependent kinases (CDKs), cell cycle divisions (CDCs), the tumour suppressor p53 and so on, whose abnormalities contribute to carcinogenesis and tumor progression and drugs target for these can be used to treat various cancer [33, 34]. Wnt signaling pathway can be implicated in OC stemness, carcinogenesis of many OC subtypes by regulating cell growth and apoptosis, and attaches great importance to chemoresistance, which can be targeted for chemo-sensitization in OC [35, 36]. Chen,

M.W., et al. reported that the Wnt signaling pathway regulates ovarian cancer cells growth, progression, and migration through interaction with STAT3 and miRNA-92 [37]. P450 are a series of metabolic enzymes that can regulate many processes such as anticancer drugs' pharmacokinetics. Recent studies have shown that individual forms of P450 play a role in the resistance of anticancer drugs [38, 39]. Downie, D., et al. reported that P450 enzymes are overexpressed in OC and can be markers of prognosis [40]. p53 is a famous tumor suppressor gene, which can regulate the cell cycle and avoid the occurrence of cancer. It is jokingly called "the guardian of genome". Generally, p53 gene mutation happens in more than 50% of cancer patients [41]. Chen, Y.N., et al. reported that microRNA let-7d-5p-HMGA1-p53 signaling pathway rescues OC cell apoptosis and restores chemosensitivity in ovarian cancer [42]. Metabolic reprogramming is a marker of malignancy. There are a lot of metabolic heterogeneity between cancer cells and normal tissues, but almost no metabolic activity is limited in tumors. The metabolic phenotype and metabolic dependence keep changing during the development of cancer from precancerous tissue to local invasion and metastasis [43, 44]. These findings help us better understanding the possible mechanisms in OC development, progression, and therapy.

Furthermore, a PPI network was drawn based on the DEGs, from which 30 hub genes that had the highest interactions in the network were identified. By literature mining, it was identified that many OC-related studies had already well studied CDK1. Therefore, CDC20 was selected for further research as a key gene in OC. Previous studies have suggested that CDC20 could function as tumor oncogene [45-51]. However, there lacks works done to explore CDC20 expression level, protein level and related molecular mechanisms in OC. Initially, we used Oncomine database to verify the CDC20 mRNA expression levels between OC and normal ovary tissues. What's more, we examined the levels of CDC20 mRNA in normal OC tissues and normal ovarian tissues from patients in our hospital. All results indicated CDC20 expression in normal ovarian tissues was lower than that in OC tissues. Next, we predict gene sets and signaling pathways associated with CDC20 using the expression data of three datasets in GSEA software. CDC20 may function in cell cycle, citrate and TCA cycle, oxidative phosphorylation and ubiquitin mediated proteolysis. As SAC target, and APC/C E3 ubiquitin ligase co-activator involving in metaphase and anaphase transition during mitosis, the significance of CDC20 in cell cycle regulation is obvious [7]. The tricarboxylic acid (TCA) cycle is the final metabolic pathway and also the center of carbohydrate, lipid and amino acid metabolism. Oxidative phosphorylation is accompanied by ATP production in biological oxidation, including two types of phosphorylation: metabolite linked phosphorylation and respiratory chain linked phosphorylation. TCA cycle and oxidative phosphorylation are two main process in cells to produce energy, and metabolic reprogramming causes tumorigenesis. From this aspect, controlling cancer energy metabolism becomes a potential treatment. Besides, APC/C^{CDC20} as an E3 ubiquitin ligase can also promote substrate ubiquitination and their subsequent degradation by the proteasome, which can regulate metabolic signaling pathways, transcription factors, and metabolic enzymes [52]. These show that CDC20 attaches great importance to OC and can be a specific target to treat OC.

In conclusion, we deduce that CDC20 may be a promising therapeutic target for the treatment of OC. However, continued work will be necessary to define whether CDC20 can produce a marked effect and the exact role and mechanism of it in OC Yet, despite the uncertainty of these mechanism, we believe that CDC20 is an appealing potential therapeutic target for OC patients.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the standards of the Helsinki Declaration of the World Medical Association, and approved by the Ethics Committee of China Medical University. All clinical samples were collected from the Shengjing Hospital of China Medical University with informed consent from all patients.

Consent for publication

Not applicable.

Availability of data and materials

NCBI-GEO: https://www.ncbi.nlm.nih.gov/geo/; accession number: GSE105437, GSE14407 and GSE18520

Oncomine database: http://www.oncomine.org, accession number: 2020110263@stu.cmu.edu.cn

STRING v11.0: http://www.string-db.org/

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by National Natural Science Foundation of China (No.81872125) and Outstanding Scientific Fund of Shengjing Hospital (No. 201704).

Authors' contributions

Xiaocui Zhang downloaded the dataset, analyzed the data, performed the RT-qPCR, and was a major contributor in writing the manuscript. Fangfang Bi collected the ovarian tissues and reviewed the manuscript together with the corresponding author Qing Yang. All authors read and approved the final manuscript.

Acknowledgments

We appreciate the Gene Expression Omnibus and the Oncomine database for the open data and the software of R language and Gene Set Enrichment Analysis.

References

1. Sung, H., et al., *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA Cancer J Clin, 2021.
2. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2019.* CA Cancer J Clin, 2019. **69**(1): p. 7-34.
3. Matulonis, U.A., et al., *Ovarian cancer.* Nat Rev Dis Primers, 2016. **2**: p. 16061.
4. Malvezzi, M., et al., *Global trends and predictions in ovarian cancer mortality.* Ann Oncol, 2016. **27**(11): p. 2017-2025.
5. Eisenhauer, E.A., *Real-world evidence in the treatment of ovarian cancer.* Ann Oncol, 2017. **28**(suppl_8): p. viii61-viii65.
6. Narod, S., *Can advanced-stage ovarian cancer be cured?* Nat Rev Clin Oncol, 2016. **13**(4): p. 255-61.
7. Kapanidou, M., N.L. Curtis, and V.M. Bolanos-Garcia, *Cdc20: At the Crossroads between Chromosome Segregation and Mitotic Exit.* Trends Biochem Sci, 2017. **42**(3): p. 193-205.
8. Wang, L., et al., *Targeting Cdc20 as a novel cancer therapeutic strategy.* Pharmacol Ther, 2015. **151**: p. 141-51.
9. Gu, Q., et al., *CDC20 Knockdown and Acidic Microenvironment Collaboratively Promote Tumorigenesis through Inhibiting Autophagy and Apoptosis.* Mol Ther Oncolytics, 2020. **17**: p. 94-106.
10. Varma, S., *Blind estimation and correction of microarray batch effect.* PLoS One, 2020. **15**(4): p. e0231446.
11. Zhang, X., et al., *Identification of functional lncRNAs in gastric cancer by integrative analysis of GEO and TCGA data.* J Cell Biochem, 2019. **120**(10): p. 17898-17911.
12. Ritchie, M.E., et al., *limma powers differential expression analyses for RNA-sequencing and microarray studies.* Nucleic Acids Res, 2015. **43**(7): p. e47.
13. *Gene Ontology Consortium: going forward.* Nucleic Acids Res, 2015. **43**(Database issue): p. D1049-56.
14. Kanehisa, M., et al., *KEGG: new perspectives on genomes, pathways, diseases and drugs.* Nucleic Acids Res, 2017. **45**(D1): p. D353-d361.
15. Szklarczyk, D., et al., *STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets.* Nucleic Acids Res, 2019. **47**(D1): p. D607-d613.
16. Subramanian, A., et al., *Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles.* Proc Natl Acad Sci U S A, 2005. **102**(43): p. 15545-50.

17. Xu, W., et al., *Screening of differentially expressed genes and identification of NUF2 as a prognostic marker in breast cancer.* Int J Mol Med, 2019. **44**(2): p. 390-404.
18. Yang, Y., et al., *Identification of metastasis and prognosis-associated genes for serous ovarian cancer.* Biosci Rep, 2020. **40**(6).
19. Rhodes, D.R., et al., *Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles.* Neoplasia, 2007. **9**(2): p. 166-80.
20. *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* Jama, 2013. **310**(20): p. 2191-4.
21. Zhang, C., et al., *Circ-PGAM1 promotes malignant progression of epithelial ovarian cancer through regulation of the miR-542-3p/CDC5L/PEAK1 pathway.* Cancer Med, 2020. **9**(10): p. 3500-3521.
22. Zhang, S., et al., *Long non-coding RNA HOTTIP promotes hypoxia-induced epithelial-mesenchymal transition of malignant glioma by regulating the miR-101/ZEB1 axis.* Biomed Pharmacother, 2017. **95**: p. 711-720.
23. Tao, Z., et al., *Microarray bioinformatics in cancer- a review.* J buon, 2017. **22**(4): p. 838-843.
24. Yu, H. and R. Jove, *The STATs of cancer--new molecular targets come of age.* Nat Rev Cancer, 2004. **4**(2): p. 97-105.
25. Gamero, A.M., H.A. Young, and R.H. Wiltrout, *Inactivation of Stat3 in tumor cells: releasing a brake on immune responses against cancer?* Cancer Cell, 2004. **5**(2): p. 111-2.
26. Bushweller, J.H., *Targeting transcription factors in cancer - from undruggable to reality.* Nat Rev Cancer, 2019. **19**(11): p. 611-624.
27. Koster, M.J., B. Snel, and H.T. Timmers, *Genesis of chromatin and transcription dynamics in the origin of species.* Cell, 2015. **161**(4): p. 724-36.
28. Dumontet, C. and M.A. Jordan, *Microtubule-binding agents: a dynamic field of cancer therapeutics.* Nat Rev Drug Discov, 2010. **9**(10): p. 790-803.
29. English, D.P., et al., *Molecular diagnosis and molecular profiling to detect treatment-resistant ovarian cancer.* Expert Rev Mol Diagn, 2016. **16**(7): p. 769-82.
30. Hansen, J.M., R.L. Coleman, and A.K. Sood, *Targeting the tumour microenvironment in ovarian cancer.* Eur J Cancer, 2016. **56**: p. 131-143.
31. Orzechowska, B.U., et al., *VSV based virotherapy in ovarian cancer: the past, the present and …future?* J Cancer, 2017. **8**(12): p. 2369-2383.
32. Levy, A., et al., *Focal Adhesion Kinase in Ovarian Cancer: A Potential Therapeutic Target for Platinum and Taxane-Resistant Tumors.* Curr Cancer Drug Targets, 2019. **19**(3): p. 179-188.
33. Ingham, M. and G.K. Schwartz, *Cell-Cycle Therapeutics Come of Age.* J Clin Oncol, 2017. **35**(25): p. 2949-2959.
34. Hafner, A., et al., *The multiple mechanisms that regulate p53 activity and cell fate.* Nat Rev Mol Cell Biol, 2019. **20**(4): p. 199-210.

35. Teeuwssen, M. and R. Fodde, *Wnt Signaling in Ovarian Cancer Stemness, EMT, and Therapy Resistance.* J Clin Med, 2019. **8**(10).
36. Arend, R.C., et al., *The Wnt/β-catenin pathway in ovarian cancer: a review.* Gynecol Oncol, 2013. **131**(3): p. 772-9.
37. Chen, M.W., et al., *The STAT3-miRNA-92-Wnt Signaling Pathway Regulates Spheroid Formation and Malignant Progression in Ovarian Cancer.* Cancer Res, 2017. **77**(8): p. 1955-1967.
38. Rooney, P.H., et al., *The role of cytochrome P450 in cytotoxic bioactivation: future therapeutic directions.* Curr Cancer Drug Targets, 2004. **4**(3): p. 257-65.
39. McFadyen, M.C., W.T. Melvin, and G.I. Murray, *Cytochrome P450 enzymes: novel options for cancer therapeutics.* Mol Cancer Ther, 2004. **3**(3): p. 363-71.
40. Downie, D., et al., *Profiling cytochrome P450 expression in ovarian cancer: identification of prognostic markers.* Clin Cancer Res, 2005. **11**(20): p. 7369-75.
41. Khan, H., et al., *Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions.* Biotechnol Adv, 2020. **38**: p. 107385.
42. Chen, Y.N., et al., *MicroRNA let-7d-5p rescues ovarian cancer cell apoptosis and restores chemosensitivity by regulating the p53 signaling pathway via HMGA1.* Int J Oncol, 2019. **54**(5): p. 1771-1784.
43. Li, Z. and H. Zhang, *Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression.* Cell Mol Life Sci, 2016. **73**(2): p. 377-92.
44. Danhier, P., et al., *Cancer metabolism in space and time: Beyond the Warburg effect.* Biochim Biophys Acta Bioenerg, 2017. **1858**(8): p. 556-572.
45. Paul, D., et al., *Cdc20 directs proteasome-mediated degradation of the tumor suppressor SMAR1 in higher grades of cancer through the anaphase promoting complex.* Cell Death Dis, 2017. **8**(6): p. e2882.
46. Guo, W., et al., *Long non-coding RNA SPRY4-IT1 promotes cell proliferation and invasion by regulation of Cdc20 in pancreatic cancer cells.* PLoS One, 2018. **13**(2): p. e0193483.
47. Zhang, Y., et al., *Inhibition of Cell Survival by Curcumin Is Associated with Downregulation of Cell Division Cycle 20 (Cdc20) in Pancreatic Cancer Cells.* Nutrients, 2017. **9**(2).
48. Zhang, Q., et al., *Cell division cycle 20 (CDC20) drives prostate cancer progression via stabilization of β-catenin in cancer stem-like cells.* EBioMedicine, 2019. **42**: p. 397-407.
49. Wu, F., et al., *Prostate cancer-associated mutation in SPOP impairs its ability to target Cdc20 for poly-ubiquitination and degradation.* Cancer Lett, 2017. **385**: p. 207-214.
50. Kim, Y., et al., *Spindle assembly checkpoint MAD2 and CDC20 overexpressions and cell-in-cell formation in gastric cancer and its precursor lesions.* Hum Pathol, 2019. **85**: p. 174-183.
51. Liu, X., et al., *1-L-MT, an IDO inhibitor, prevented colitis-associated cancer by inducing CDC20 inhibition-mediated mitotic death of colon cancer cells.* Int J Cancer, 2018. **143**(6): p. 1516-1529.

52. Sun, T., Z. Liu, and Q. Yang, *The role of ubiquitination and deubiquitination in cancer metabolism.* Mol Cancer, 2020. **19**(1): p. 146.

Tables And Figures

Mentioned figures and table are not included with this version of the Manuscript.