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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.
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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.
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WEBSITE
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К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman** (**Кириллица**), ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ,რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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TRANSCRIPTOME ANALYSIS REVEALED THE MOLECULAR SIGNATURES OF CISPLATIN-FLUOROURACIL COMBINED CHEMOTHERAPY RESISTANCE IN GASTRIC CANCER

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Abstract.

Background: Gastric cancer (GC) is among the top five malignant tumors worldwide in terms of morbidity and death. Chemotherapy is the primary treatment for unresectable or advanced postoperative GC. Chemotherapy resistance developed against cisplatin-fluorouracil (CF) combined chemotherapy is one of the most common clinical issues in patients with GC, leading to poor prognosis.

Materials and methods: Two different methods were used to analyze GSE14210, and two gene sets were obtained. The first method involved performing the traditional difference analysis (adjusted p-value < 0.05, |log2FC|>= 1) by Network Analyst to obtain gene set 1, followed by conducting gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis on the obtained gene set. The second method involved using iDEP to make the weighted gene co-expression network analysis (WGCNA) and performing GO and KEGG enrichment analysis, to obtain gene set 2. Thereafter, the STRING database and Cytoscape were used to construct Protein–Protein Interaction (PPI) networks, screen core clusters, and hub genes of the two gene sets. Furthermore, the hub genes were verified in GSE14210 by the survival analysis method of the Kaplan–Meier plotter database. Finally, we analyzed the mRNA expression of the hub genes by UALCAN and the protein expression of the same by Human Protein Atlas (HPA). Three real hub genes with the same mRNA expression as that of protein were identified, including CENPB, MTA1, and GCNT3. Finally, we performed single gene GO and KEGG enrichment analyses to explore the possible mechanisms of action of these three genes. **Results:** The mRNA and protein expressions of CENPB, MTA1, and GCNT3 were upregulated in CF-resistant GC patients, and they were significantly associated with bad overall survival (OS).

Conclusions: CENPB, MTA1 and GCNT3 are expected to be biomarkers with promising clinical applications as potential therapeutic targets for patients with refractory GC treated with CF combined chemotherapy.

Key words. Gastric cancer, Cisplatin-Fluorouracil combined chemotherapy, WGCNA, PPI, Survival analysis.

Introduction.

Gastric cancer (GC), one of the most malignant human cancers with increasing incidence worldwide, ranks among the top five malignant tumors in terms of morbidity and mortality [1-46,2,44]. The clinical efficacy of conventional therapies to treat GC is limited [33], and the median overall survival for advanced-stage GC is approximately 8 m [8]. Currently, chemotherapy is the main treatment for unresectable or advanced postoperative GC. However, its efficacy is compromised by the development of chemo-resistance in the patient, which severely affects the patient's prognosis [27]. The mechanisms of chemo-resistance in GC include the inhibition of apoptosis signal pathway [41], loss of cell cycle checkpoint control [40], accelerated cell proliferation and autophagic flux [42], enhanced DNA damage repair [23], upregulation of multidrug resistance-associated proteins [17,25,45], activated cancer stem cell (CSC) and epithelial-mesenchymal transformation (EMT) [5,12], reduced/increased drug uptake/outflow [21], drug degradation [44], amplification and upregulation of oncogenes [36], and epigenetic modifications [3].

Several molecules are involved in GC drug resistance. Chen et al. reported that the overexpression of miRNA-200c can inhibit the expression of Bcl-2 and Bax and render SGC7901/DDP cells sensitive to cisplatin and 5-FU [8]. Wang et al. discovered that the downregulation of microRNA-17–5p inhibits cisplatin resistance of GC cells by targeting p21 [35]. The downregulation of microRNA-147 and microRNA-193–3p increases the chemosensitivity of GC cells to 5-fluorouracil by directly targeting PTEN [19,30]. Hang et al. reported that by upregulating lncRNA AK022798 expression, Notch 1 downregulates the expression of caspase-8 and caspase-3 and inhibits the extrinsic apoptosis pathway, thereby leading to cisplatin resistance in GC cells [17]. However, the detailed underlying mechanisms of chemotherapy resistance remain unelucidated to date.

Platinum drugs are the largest class of drugs currently used in cancer treatment, with the major ones being cisplatin, carboplatin, and oxaliplatin. The anti-tumour mechanism of platinum drugs can be carried out in four stages, including drug entry into cells, drug activation, Pt–DNA complex formation, cell cycle arrest, and apoptosis [15]. Platinum-based drugs are the most widely used in cancer treatment [24,31], but several tumors are completely resistant to these drugs and do not respond clinically [7]. CF-based chemotherapy resistance is a widely encountered postoperative clinical issue in patients diagnosed with GC, resulting in poor prognosis [20,26]. The key step to developing a treatment to prevent or overcome chemotherapy resistance is to understand the evolution of

tumors at the molecular level to overcome the cytotoxic effect of chemotherapy. Therefore, an important step is to identify the molecules that cause CF resistance in patients with GC to prevent and treat their drug resistance.

Bioinformatics, a new discipline formed by the combination of life science and computer science, studies the collection, processing, storage, dissemination, analysis, and interpretation of biological information. By comprehensively utilizing biology, computer science, and information technology, bioinformatics reveals the biological mysteries created by numerous complex biological data. Currently, high-throughput microarray technology and bioinformatics analysis are used to identify differences in gene expression between chemosensitive and chemoresistant tissues, analyze the differential expression genes (DEGs), and identify the drug resistance and cancer progression pathways.

The current study is based on the following technical route (Figure 1): Herein, not only the traditional differential analysis and clustering methods but also the weighted gene co-expression network analysis (WGCNA) were used. Using various bioinformatics analytical methods, we aim to identify the molecules associated with CF drug resistance more accurately and comprehensively, determine a direction toward a possible targeted therapy for CF-resistant GC patients, and provide biomarkers for patients with GC to apply CF combined chemotherapy.

Materials and Methods.

Microarray data:

The Acquired Chemoresistance to CF combined Chemotherapy in GC Patients sample data (Microarray data) was acquired from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo). Expression data were extracted from the dataset (GSE14210). Gene expression data were obtained from 118 tissue samples, including 96 tissue samples from patients with metastatic gastric cancer that were more sensitive to CF combined chemotherapy (Training) and 22 tissue samples from patients with metastatic gastric cancer that did not respond well to CF combined chemotherapy (Acquiredresistant), all of which were collected by endoscopic biopsy.

Identification of DEGs:

NetworkAnalyst (https://www.networkanalyst.ca/NetworkAnalyst/home.xhtml) is an online visual analysis platform for gene expression analysis and meta-analysis [39]. Herein, it was used for DEGs analysis. First, we checked the quality of the gene expression data from GSE14210, then filtered and normalized the data, and finally, used the Limma package to analyze the difference and identify DEGs on training and Acquiredresistant samples.

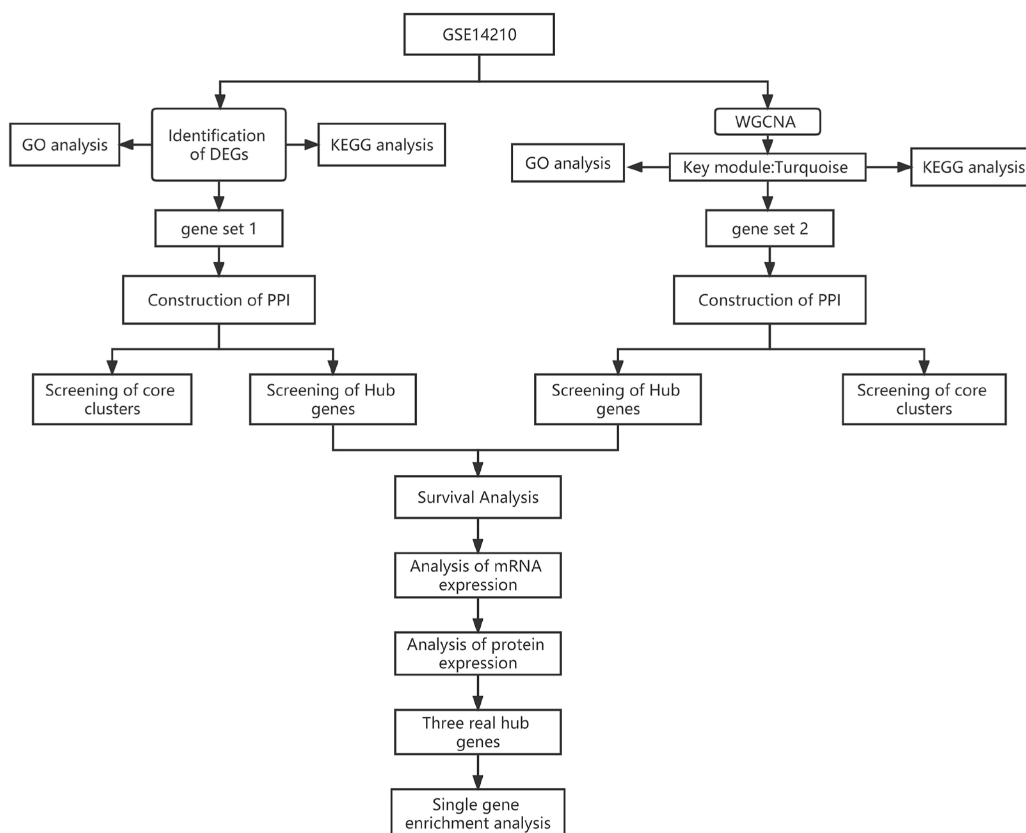

Figure 1. Workflow of this study. *including Identification of DEGs in CF Resistance Samples of GC, Identification of Key Module through Weighted Gene Co-Expression Network Analysis, Screening of Core Clusters and Hub Genes, Prognostic Value of mRNA Expression of hub genes in GC Patients, Expression of mRNA and protein, Single gene enrichment analysis.*

Gene Enrichment Analysis:

Micro-bioinformation cloud platform (www.bioinformatics.com.cn) is an online platform for bioinformatics analysis based on R language, in which gene enrichment analysis is performed based on the data analysis of ClusterProfiler. The ClusterProfiler package depends on the Bioconductor annotation data GO.db and KEGG.db to obtain the maps of the entire gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) corpus [43]. In this study, the Micro-bioinformation cloud platform was used to perform GO and the KEGG enrichment analysis of DEGs. The biological process (BP), molecular function (MF), cellular component (CC), and KEGG pathway were selected as analysis items.

Weighted Gene Co-Expression Network Analysis (WGCNA):

The primary function of WGCNA is to identify gene modules with similar expression patterns, analyze the relationship between gene sets and sample phenotypes, construct regulatory networks among gene sets, and identify key regulatory genes [22]. iDEP (http://bioinformatics.sdstate.edu/idep/) is an online tool based on WGCNA. First, the correlation coefficient between two genes is calculated by using their expression patterns, and then the co-expression network of the genes is constructed based on the obtained correlation coefficient. After building a gene co-expression network, the close degree of gene relationship was demarcated by a soft threshold, and the close relationship was divided into a module. Thereafter, we performed some feature analysis on the module, including endowing it with characteristic values and enriching the genes in the module to explore their functions. Finally, the key module associated with the biological problems was selected based on the expression patterns and functions of the modules.

Construction of Protein-Protein Interaction (PPI) Network:

The STRING (https://cn.string-db.org) database utilizes Textmining, Experiments, Databases, Co-expression, Neighborhood, Gene Fusion, and Co-occurrence as active interaction sources to construct a PPI network [32]. We used this database to construct the PPI network. By setting the minimum interactive score as "the medium confidence (0.400)", the proteins with weak connection with other proteins in the network were excluded to obtain the PPI network of gene set 1 and gene set 2 respectively.

Screening of Core clusters and Hub Genes:

The PPI network built on the STRING database was sent to Cytoscape analysis software, and MCODE and CytoHubba plug-ins were used to screen core clusters and hub genes. The setting parameters of the MCODE plug-in were as follows: degree cut-off = 2, node score cut-off = 0.2, k-core = 2, and maximum depth = 100. We used 12 algorithms in the CytoHubba plug-in: MCC, DMNC, MNC, Degree, EPC, BottleNeck, EcCentricity, Closeness, Radiality, Betweenness, Stress, ClusteringCoefficient to obtain the hub genes. Each algorithm selected 10 genes with the highest score, and the intersection of 12 results was used to obtain the hub genes.

Survival Analysis:

Kaplan-Meier Plotter (http://kmplot.com/analysis/) database is based on the gene chips and RNA-seq data of public databases such as GEO, EGA, and TCGA, which integrate gene expression information with clinical prognostic values to conduct meta-analysis and research on survival-related molecular markers [4]. Using the Kaplan-Meier Plotter database, the genes significantly associated with the overall survival time (OS) were selected.

Analysis of mRNA expression:

The publicly available cancer genomics databases (TCGA, MET500, CPTAC, and CBTTC) can be conveniently accessed through UALCAN (http://ualcan.path.uab.edu) for analyzing cancer genomics data. It is based on PERL-CGI and provides high-quality graphics using javascript and CSS [6]. Herein, the target gene was input into the home page of the UALCAN website, and its mRNA expressions were derived in the case of GC and paracarcinoma tissues.

Analysis of protein expression:

The Human Protein Atlas (https://www.proteinatlas.org) aims to draw all human protein in cells, tissues, and organs by integrating various omics technologies, including antibody-based imaging, mass spectrometry-based proteomics, transcriptomics, and systems biology [10]. In the current study, immunohistochemical imaging was performed to directly compare the protein expression of genes between normal human tissues and GC tissues.

Single gene enrichment analysis:

We used the STRING database to systematically annotate the biological functions of the 10 genes interacting with each hub gene, construct a PPI network, and analyze the GO and KEGG gene enrichment of each hub gene.

Statistical analysis:

GraphPad Prism and R software were used for graphic drawing and statistical analysis (v8.0, R v4.1.0). In particular, data input and screening, network construction and module detection, module and phenotype data association, identification of important genes, network interaction analysis, export of network interactions data and network visualization were performed using R combined with Cytoscape software. mRNA expression analysis was performed using the Mann Whitney U test combined with UALCAN, and protein expression analysis was performed using the Mann Whitney U test combined with The Human Protein Atlas, and the effect of hub gene level on overall survival was performed using Cox regression combined with Kaplan-Meier plots.

Results.

Identification of DEGs in CF resistance samples:

The sample data (GSE14210) of acquired chemical resistance of patients with GC to CF combined chemotherapy were downloaded from the NCBI-GEO database. By extracting the expression data from this dataset, we finally obtained the gene expression data of 118 tissue samples, of which 96 tissue samples from patients with metastatic gastric cancer that were more sensitive to CF combined chemotherapy (Training) and 22 tissue samples from patients with metastatic gastric cancer that did not respond well to CF combined chemotherapy (Acquiredresistant). Then, we used NetworkAnalyst online analysis tool to identify DEGs. Firstly, uploading the data

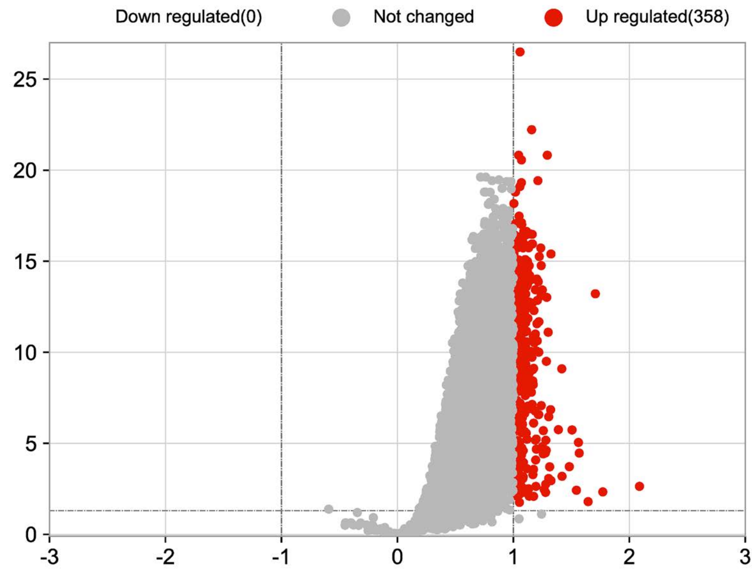

Figure 2. The DEGs. *358 DEGs were up-regulated in the GSE14210.*

Figure 3. The GO and KEGG enrichment analysis of the 358 DEGs. *(A) BP (biological process) results. (B) CC (cellular component) results. (C) MF (molecular function) results. (D) KEGG pathway results.*

and checking the quality of the gene expression data, the results showed that the data was microarray gene expression data, including 118 samples and 22,277 genes were detected, of which 20,375 can be matched, with a matching degree of 91.5%. The Box-plot showed that the data has been normalized. Finally, after filtering the data, we used the Limma software package to identify DEGs and found that there were 10,256 DEGs (adjusted p-value < 0.05) between Acquiredresistant and Training, among which 358 DEGs (gene set 1) were markedly up-regulated (log2FC>= 1) (Figure 2).

Function and pathway enrichment analysis of DEGs:

To obtain the biological explanation of the DEGs, we used the micro-bioinformation cloud platform to perform GO and KEGG enrichment analysis of DEGs, and selected the top 10 with the most statistical significance (the lowest p-value) to plot (Figures 3A-D). These DEGs were primarily concentrated in 16 biological processes, including humoral immune response, neutrophil activation involved in immune response, small molecule catabolic process, and mainly located in eight cell components, such as endoplasmic reticulum lumen, collagen-containing extracellular matrix, secretory granule lumen, and mainly involved in the oxidoreductase activity, chemokine receptor binding, ligand-activated transcription factor activity, and other 50 molecular functions. In terms of the KEGG enrichment pathway, these DEGs were mainly clustered in 15 pathways, such as Lysosome, IL-17 signaling pathway, and Peroxisome.

Weighted Gene Co-Expression Network Analysis (WGCNA):

The key modules of GSE14210 were screened by iDEP based on WGCNA. To transform the network constructed by WGCNA to an approximately scale-free network, the soft threshold was chosen as $\beta = 6$ (scale-free R2 > 0.8). In addition, all selected genes were clustered by using the dynamic tree-cutting algorithm based on the topological overlap matrix (TOM), the min. Module Size (minimum number of genes in the module) was set to 20. Finally, a network of 537 key genes was divided into nine modules (Figure 4A) and the number and expression of genes in each module are shown in Figure 4B. KEGG analysis of the genes within each module reveals that the turquoise module genes are concentrated in seven pathways, including metabolic pathways and drug metabolism (Figure 4C). In terms of GO enrichment, we found that the turquoise module genes were primarily concentrated in 15 biological processes such as the Xenobiotic metabolic process, Hormone metabolic process, and Lipid metabolic process. These are mainly located in 15 cell components, such as Extracellular space, Vesicle, and Extracellular organelle, and mainly involved in the Oxidoreductase activity, acting on the CH–OH group of donors, NAD or NADP as acceptor, and other 15 molecular functions (Figure 4D). Based on the aforementioned findings, we concluded that the turquoise module genes (gene set 2) play critical roles in the CF resistance of GC. Therefore, the 170 genes extracted from the turquoise module were focused on in our further study.

Construction of Protein-Protein Interaction (PPI) Network:

Interaction between proteins is the basis of cellular activities, and research on protein–protein interactions is extremely significant. To explore the core clusters and hub genes that played the most crucial role in modular genes, the STRING database was used to construct the PPI network from gene set 1 and gene set 2, respectively. We utilized Textmining, Experiments, Databases, Co-expression, Neighborhood, Gene Fusion, and Co-occurrence as active interaction sources to construct the PPI network. By setting the minimum interactive score as "the medium confidence (0.400)", the proteins bearing weak connections with other proteins in the network were excluded to obtain the protein interaction network of the module genes.

Screening of Core Clusters and Hub Genes:

First, we sent the PPI network built on the STRING database to Cytoscape analysis software. Then, removing the proteins with weak connections, two more concise PPI networks were obtained (Figures 5A, B). Next, the MCODE plug-in was used to screen the core clusters, and by setting the parameters of the MCODE plug-in as degree cut-off = 2, node score cut-off = 0.2, k-core = 2, and maximum depth = 100, 13 important clusters of gene set 1 and five important clusters of gene set 2 were obtained. The cluster with the highest score in the two gene sets was visualized (Figures 5C, D). In addition, we used 12 algorithms in the CytoHubba plug-in: MCC, DMNC, MNC, Degree, EPC, BottleNeck, EcCentricity, Closeness, Radiality, Betweenness, Stress, and ClusteringCoefficient to obtain the hub genes. Each algorithm selected 10 genes with the highest score, and the intersection of 12 results was adopted to obtain the hub genes. Finally, 78 hub genes were obtained, of which 43 were from gene set 1 and 35 from gene set 2 (Figures 5E, F).

Prognostic Value of mRNA Expression of hub genes in CF-resistant GC Patients:

To further screen the hub genes, the relationship between these 78 hub genes and OS in the microarray data (GSE14210) was explored. The findings reveal that 11 genes were negatively correlated with OS (Figures 6A–K). This implies the upregulation of the mRNA expression of the 11 genes, ACP6, AKT1, ASGR2, BSG, CENPB, CYC1, IDH3B, MTA1, PON3, TLN1, and GCNT3, would lead to compromised OS of GC patients using the CF combined chemotherapy. Therefore, further research mainly focuses on these 11 genes.

Expression of mRNA and protein:

Despite the hierarchical organization of gene expression via the central dogma, the relationship between transcripts and protein expression levels is highly variable in GC. To identify the trend associated with drug resistance, the expression of mRNA and protein must be highly consistent. We used the UALCAN database, which is based on the TCGA database, to explore the mRNA expression of these 11 hub genes in GC. The results reveal that 10 of these genes were overexpressed in GC (Figures 7A–J). Simultaneously, we used the HPA to study the protein expression of these 10 genes and found that compared with normal stomach tissues, only three of them demonstrated higher protein expression in GC tissues (Figures 8A–C). Therefore, these three genes, CENPB, MTA1, and GCNT3, were identified as the real hub genes of CF-resistant GC patients.

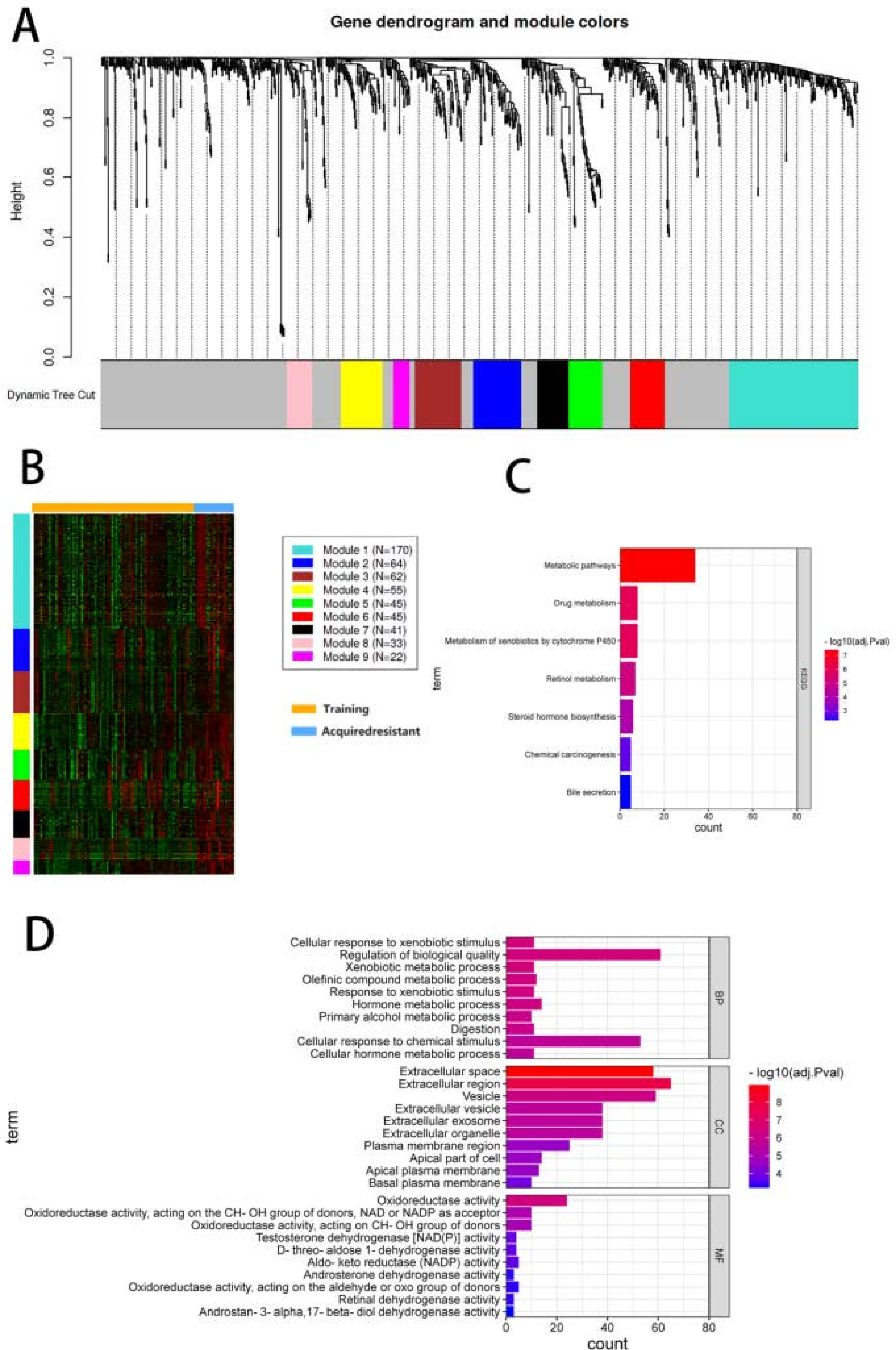

Figure 4. WGCNA. *(A) the dynamic tree-cutting algorithm based on the topological overlap matrix (TOM) divides the genes in GSE14210 into nine modules. (B) The genes contained in each module and their expression in GSE14210. (C) KEGG enrichment results of genes in turquoise module. (D) GO enrichment results of genes in turquoise module.*

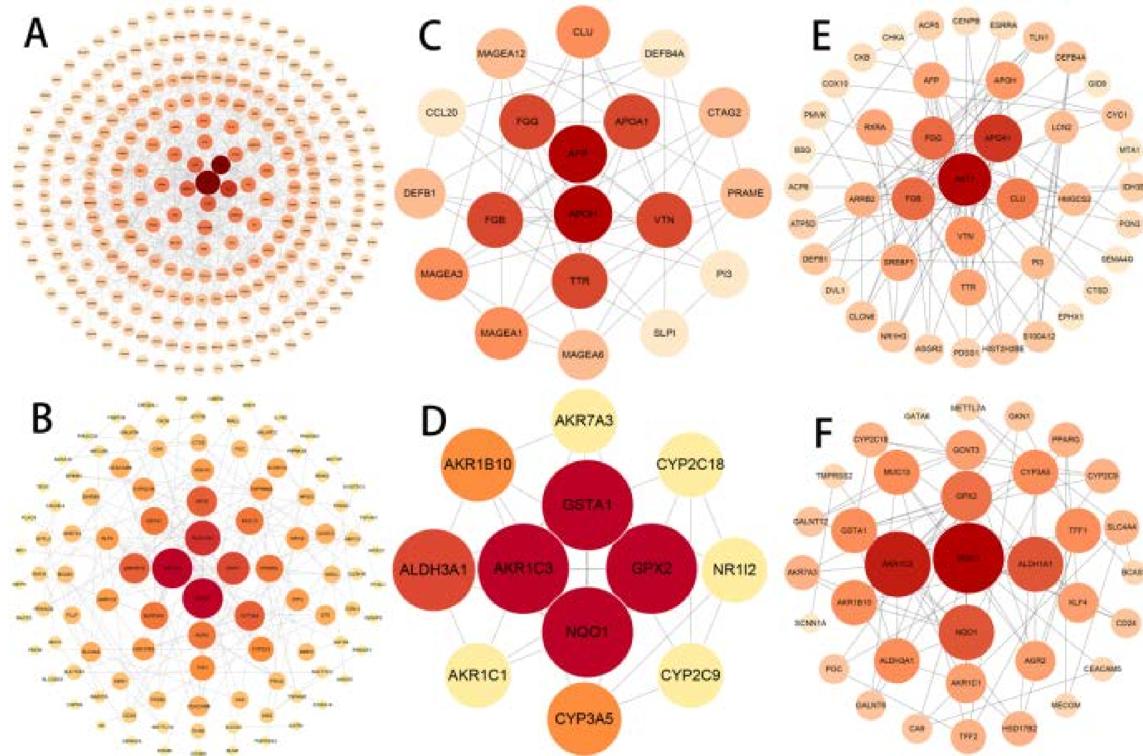

Figure 5. Construction of PPI Network and Screening of Core Clusters and Hub Genes through Cytoscape analysis software. *(A) PPI Network of the 358 DEGs. (B) PPI Network of genes in turquoise module. (C)the cluster with the highest score in gene set 1. (D) the cluster with the highest score in gene set 2. (E) The hub genes of gene set 1. (F) The hub genes of gene set 2.*

Single gene enrichment analysis:

To explore the possible mechanism of the three hub genes regulating CF resistance in GC, we introduced the hub genes separately into STRING to construct the PPI network (Figures 9A–C) and for functional enrichment analysis (Figures 9D–H). Consulting the research related to tumor drug resistance revealed that CENPB may regulate the progress of the cell cycle through CENPA, CENPC, CENPE, INCENP, and APITD1 (Figure 9I). Moreover, MTA1 may regulate the Notch signaling pathway through HDAC1, and HDAC2 (Figure 9J), and GCNT3 may regulate metabolic pathways through B3GNT3, B3GNT6, C1GALT1, C1GALT1C1, and ST3GAL1(Figure 9K), to lead to drug resistance.

Discussion.

GC ranks as the third leading cause of cancer-related deaths worldwide, with more than one million new cases and 769,000 deaths annually [2,44]. Owing to the atypical and insidious nature of the early clinical symptoms of GC, >60% of patients already have local or distant metastases at the time of diagnosis. Consequently, the 5-year OS rate for patients with GC with local and distant metastases drops sharply to 30% and 5%, respectively [33]. Currently, the gold standard for diagnosing gastric cancer diagnosis is pathological tissue biopsy performed under gastroscopy [29]. However, the invasive nature of the diagnosis has limited its use in mass screening for GC. Therefore, the discovery of new highly sensitive and specific biomarkers is extremely essential for the diagnosis of tumors, monitoring of tumor recurrence and metastasis, and assessing prognosis. CF-associated chemotherapy resistance is one of the most encountered postoperative clinical complications in patients diagnosed with GC, resulting in poor prognosis [20,26]. We hope to identify the molecules associated with CF drug resistance more accurately and comprehensively through various bioinformatics analyses, determine a possible direction of the targeted therapy for CF-resistant GC patients, and provide biomarkers for GC patients to use CF combined chemotherapy.

The current study uses not only the traditional differential analysis and clustering methods but also the weighted gene co-expression network analysis method. Through the use of various bioinformatics analysis methods, the molecules associated with CF drug resistance can be searched for more accurately and comprehensively. The primary result of this study is that both the mRNA and protein expressions of CENPB, MTA1, and GCNT3 are upregulated in CF-resistant GC patients, and they are significantly associated with bad OS. In addition, the findings reveal that CENPB may regulate the process of the cell cycle, MTA1 may regulate the Notch signaling pathway, and GCNT3 may regulate metabolic pathways to lead to drug resistance.

In this study, the network of 537 key genes was divided into 9 modules by WGCNA. KEGG analysis of the genes within each module revealed that the turquoise module genes were mainly concentrated in seven pathways, including metabolic pathways and drug metabolism. GO enrichment analysis of the genes within each module revealed that the turquoise module genes were mainly distributed in 15 cellular components, such as Extracellular space, Vesicle, Extracellular organelle, etc., and were mainly concentrated in 15 biological processes, such as Xenobiotic metabolic process, Hormone metabolic process,

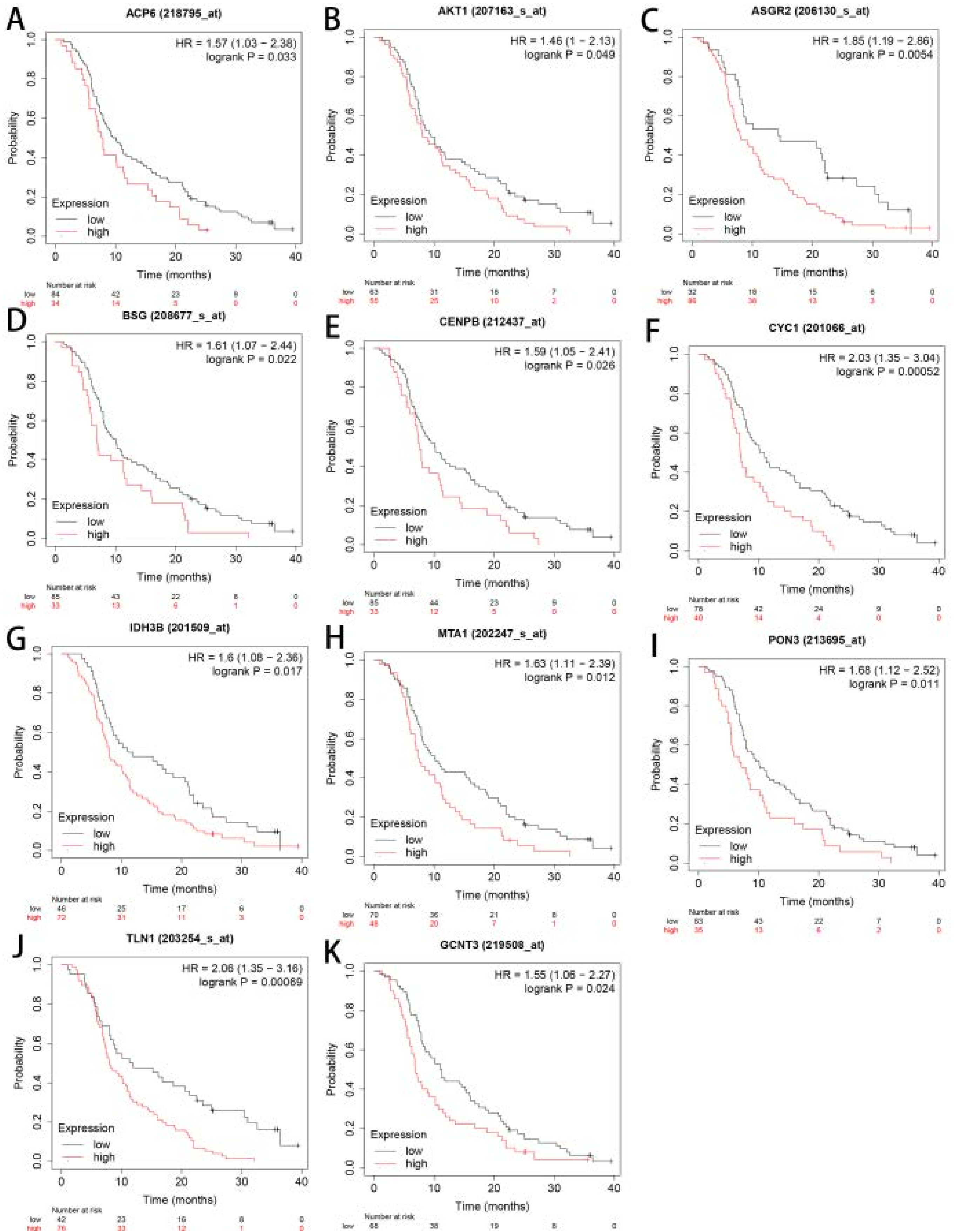

Figure 6. Prognostic value of mRNA expression of distinct hub genes in GC patients using CF combined chemotherapy (Kaplan-Meier Plotter). *(A-K) Up-regulation of ACP6, AKT1, ASGR2, BSG, CENPB, CYC1, IDH3B, MTA1, PON3, TLN1, GCNT3 mRNA expression leads to bad OS of GC patients using CF combined chemotherapy.*

A Expression of ACP6 in STAD based on Sample types
B Expression of AKT1 in STAD based on Sample types
C Expression of ASGR2 in STAD based on Sample types
D Expression of BSG in STAD based on Sample types
E Expression of CENPB in STAD based on Sample types
F Expression of CYC1 in STAD based on Sample types
G Expression of GCNT3 in STAD based on Sample types
H Expression of IDH3B in STAD based on Sample types
I Expression of MTA1 in STAD based on Sample types
J Expression of PON3 in STAD based on Sample types

Figure 7. mRNA expression of distinct hub genes in GC tissues and adjacent normal stomach tissues (UALCAN). *(A-J) mRNA expressions of ACP6, AKT1, ASGR2, BSG, CENPB, CYC1, IDH3B, MTA1, PON3, GCNT3 were found to be over-expressed in primary GC tissues compared to normal samples. ** p<0.01 *** p<0.001.*

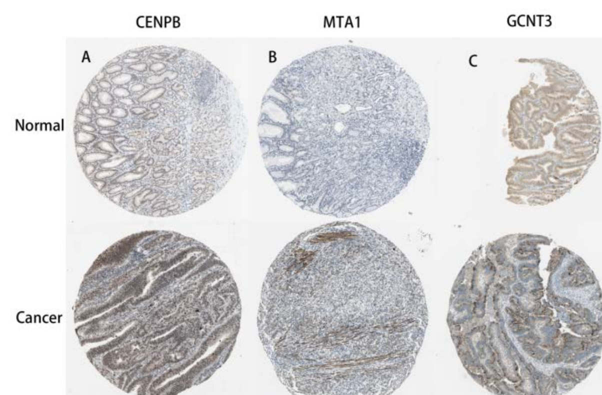

Figure 8. Representative immunohistochemistry images of distinct hub genes in GC tissues and normal stomach tissues (Human Protein Atlas). *(A) CENPB protein was low, and medium expressed in normal stomach tissues, whereas its high expression was observed in GC tissues. (B)Low protein expression of MTA1 was found in normal stomach tissues, while its medium protein expression was observed in GC tissues. (C) Medium protein expression of GCNT3 was observed at normal stomach tissues but its high expression was observed in GC tissues.*

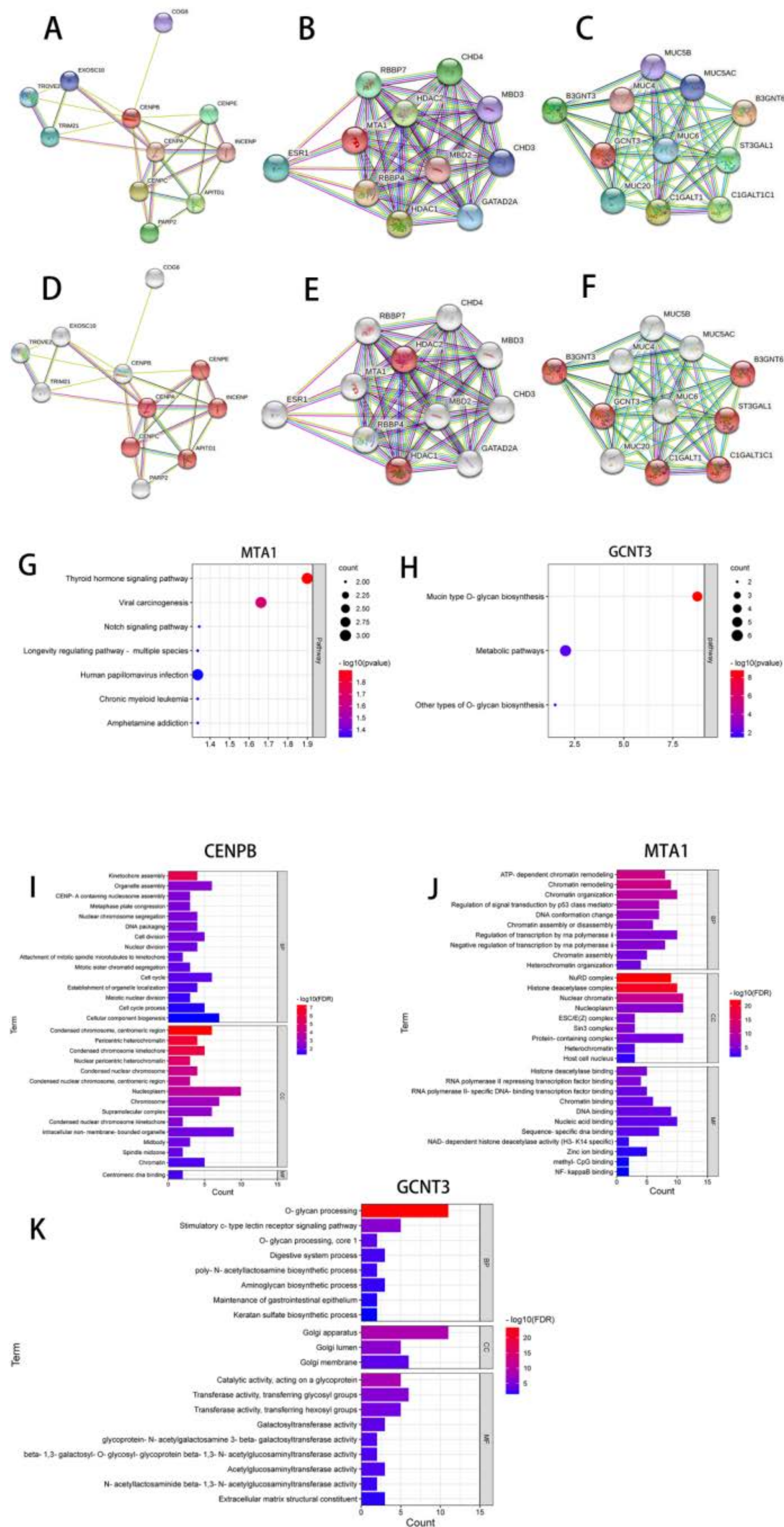

Figure 9. Single gene enrichment analysis through STRING database. *(A-C) PPI network of CENPB, MTA1, GCNT3. (D) Genes related to Cell cycle in CENPB PPI network. (E) Genes related to Notch signaling pathway in MTA1 PPI network. (F) Genes related to Metabolic pathway in GCNT3 PPI network. (G, H) KEGG enrichment results of MTA1 and GCNT3. (I-K) GO enrichment results of CENPB, MTA1, GCNT3.*

and Lipid metabolic process, and were mainly involved in the Oxidoreductase activity, acting on the CH–OH group of donors, NAD or NADP as acceptor, and other 15 molecular functions. The above results suggest that the cluster genes may be mediated by accelerated cell proliferation and autophagic flux [42], enhanced DNA damage repair [23], up-regulation of multidrug resistance-associated proteins [17,25,45], activation of tumour stem cells (CSCs) and epithelial mesenchymal transition (EMT) [5,12], reduction/increase in drug uptake/outflow [21], drug degradation [44], and other modalities leading to resistance to CF combination chemotherapy in gastric cancer patients, which provides a direction for further exploration of the mechanisms of CF combination chemotherapy resistance.

Centromere protein B (CENPB) plays an important role in cell cycle regulation and assists in the vigorous proliferation of cancer cells [9]. El-Desoky et al. reported that using combined antisense oligonucleotides targeting the hTR and mRNA of CENPB on liver cancer cells could be a promising strategy for cancer treatment by concurrently controlling several pathways [13]. Tian et al. suggested that the upregulation of CENPB expression can increase the radio resistance of glioma cells both in vitro and in vivo [34]. IL2RB, CENPB, TP53, and XAGE1A combined biomarker panel holds potential for rapid screening and could improve the diagnosis of early-stage lung cancer, thereby potentially improving its prognosis [37]. Currently, only a few reports are available on the relationship between CENPB and tumor drug resistance. However, we found that CENPB was overexpressed in patients with CF-resistant GC and negatively correlated with OS. If the relationship between CENPB and tumor drug resistance can be further verified, it would provide a new direction for developing strategies to overcome tumor drug resistance.

Reports are available that claim MTA1 overexpression in GC is positively correlated with tumor size, angiogenesis, invasion depth, lymph node metastasis, lymphatic involvement, venous invasion, distant metastasis, recurrence, and advanced clinical stage, and MTA1 overexpression is an independent predictor of adverse OS and DFS [11,18,28,46]. In addition, Yao Y et al. reported that MTA1 is overexpressed in GC, which promotes malignant cell growth by facilitating cell cycle progression through the upregulation of cyclin D1 and accelerates the migration and invasion of human GC cells by regulating fibronectin and MMP2/MMP9 expression [1]. However, no report exists on the relationship between MTA1 and chemotherapy resistance of GC. To investigate whether MTA1 can mediate CF combined chemotherapy resistance of GC through the Notch signalling pathway will be interesting and clinically significant.

GCNT3 (core 2β-1,6-acetylglucosaminyltransferase) is a novel core mucin synthase. Mucins form a barrier impeding drug access to target sites, leading to cancer chemoresistance. Loss of GCNT3 suppresses PC progression and metastasis by downregulating cell cycle genes and β-catenin/MUC4 axis [16]. Increased sensibility to 5-fluoracil in metastatic cells is associated with high levels of GCNT3 [14]. GCNT3 gene knock-out significantly restored the chemical sensitivity of breast cancer cells to natural flavonoid apigenin [38]. Among the three hub genes, only the relationship between GCNT3 and tumor resistance has been explored. However, the relationship between GCNT3 and the drug resistance of GC is unelucidated to date. The current study can provide new and valuable insights to promote further research on the underlying mechanism through which GCNT3 regulates drug resistance in GC.

Despite some significant findings, the current study has some limitations. First, the studied and analyzed data are all from the network database, and the sample size is small. Therefore, the sample size needs to be increased and further conduct in-vivo and in-vitro validation tests need to be conducted. Second, this study suffers from a lack of clinical information, and its potential diagnostic and therapeutic effects have not been evaluated. Further exploration is necessary to determine whether the three real hub genes can be used as a diagnostic marker or a therapeutic target. Finally, because only a few chip data are available on the CF resistance of GC, we found only one chip data aligned with the purpose of this study. Using this single chip data without external dataset verification may lead to one-sided results and a high false positive rate.

Conclusion.

In conclusion, this study suggests that both the mRNA and protein expressions of CENPB, MTA1, and GCNT3 are upregulated in CF-resistant GC patients, and they are significantly associated with bad OS. In addition, CENPB MTA1, and GCNT3 may regulate the processes of the cell cycle, Notch signalling pathway, and metabolic pathway, respectively, to result in drug resistance. This provides a direction for further research on the mechanism of CF resistance, and CENPB, MTA1, and GCNT3 are expected to be biomarkers with promising clinical applications and potential therapeutic targets for GC patients who are refractory to CF combined chemotherapy.

Conflict of interest.

All authors declare no conflicts of interest in this paper.

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