High CENPM mRNA expression and its prognostic significance in hepatocellular carcinoma: a study based on data mining

Zeng-hong Wu and Dong-liang Yang*

Abstract

Background: Hepatocellular carcinoma (HCC) is a high mortality disease, the fifth most general cancer worldwide, and the second leading to cancer-related deaths, with more than 500,000 new patients diagnosed each year. First, the high expression of centromere M (CENPM) in mammary gland tissue of b-catenin transformed mice was identified.

Materials and methods: In our study, we evaluated the expression of CENPM in hepatocellular carcinoma based on data obtained from an online database. Multivariate analysis showed that the expression of CENPM and M classification was an independent prognostic factor for patients with hepatocellular carcinoma.

Results: Survival analysis showed that patients with high CENPM had a worse prognosis than patients with low CENPM (P < 0.01). A multivariate Cox regression hazard model showed that B cells, CD8+ T cells, macrophages, and dendritic cells infiltrated by immune cells were statistically significant in liver cancer (P < 0.05). Using the network, the 50 most frequently changed neighbor genes of CENPM were shown, and the most common change was RAD21 (18.3%).

Conclusion: Our study found that the expression of CENPM was significantly increased in patients with hepatocellular carcinoma, and it was related to a variety of clinical characteristics, its correlation with the level of immune infiltration and poor prognosis, so CENPM can be used as a useful prognosis for patients’ markers and HCC.

Keywords: Hepatocellular carcinoma, Centromere protein M, Data mining, Prognosis

Background

Hepatocellular carcinoma (HCC), a high mortality disease which is the fifth most general cancer in the world and the second most common lead to cancer-related deaths, with over 500,000 new patients diagnosed each year [1, 2]. Viral hepatitis and nonalcoholic steatohepatitis are the most common causes of cirrhosis and approximately 80% of cases develop to HCC [3]. Due to the recurrence of HCC the prognosis of HCC remains discouraging and the 5-year overall survival rate which is only 34 to 50% [4]. Despite the rapid development of advanced medical technology, there are still no useful curable strategies for HCC patients [5]. Byeno et al. [6] reported that based on long-term survival data, serum OPN and DKK1 levels in patients with liver cancer can be deemed as novel biomarkers that show prognostic useful for liver cancer. Other serum markers, such as alpha-fetoprotein (AFP) and alkaline phosphatase (ALP or AKP), are proverbially used in clinical, but they lack sufficient sensitivity and specificity [7]. Therefore, finding useful biomarkers is indispensable for diagnosis and treatment for HCC patients.

Post-transcriptional modifications are essential for tumorigenesis and development. Centromere protein M (CENPM; otherwise called PANE1, CENP-M and
C22orf18), which encodes a kinetic protein, binds to spindle microtubules to regulate chromosomal separation during cell division [8]. Expression of the PANE1 gene was found preferentially in immune cells involving tumor tissues and tumor derived cell lines and leukemias and lymphomas [9]. Brickner et al. [10] found highly expressed in B lineage chronic lymphocytic leukemia (B-CLL) cells and resting CD19 (+) B cells, may be a potential therapeutic target for B-CLL. Bierie et al. [9] also demonstrated that human CENPM transcript cRNA was detected only in vivo or in vitro in activated B cells and T cells. These studies suggested CENPM may play critical role in tumor immune response and may be deemed to therapeutic target for immunotherapy. However, the role of CENPM in HCC prognostic remains unclear. In our study, we evaluated the expression of CENPM in HCC based on data from an online database to further understand the biological pathway of CENPM related to the pathogenesis of HCC. In addition, we also analyzed the connection between CENPM expression and clinical features as well as the correlation of its expression with immune infiltration level in HCC comes an online tumor infiltrating immune cells analysis tool.

Materials and methods

Data collection

Information on RNA-sequencing data (424 tissues, workflow type: HTSeqCounts) and comparative clinical data (377 patients, data format: BCR XML) were identified and got from the level 3 (standardized FPKM) of the TCGA-HCC cohort. Use boxplots to imagine expression differences for discrete variables [11]. The clinical factors included gender, stage, age, grade, T-phase, M-phase, N-phase, survival status and number of days of survival. Data analysis were checked by R (version 3.5.3) and R Bioconductor software packages.

GSEA enrichment

Gene Set Enrichment Analysis (GSEA) created a list of all gene permutations related to CENPM expression. The samples were then divided into a high CENPM group and a low CENPM group as training sets to distinguish potential functions and use GSEA to clarify significant survival differences. Genome replacement is performed multiple times with each exam. The degree of expression of CENPM was used as a phenotypic marker. Normalized enrichment scores (NES) and nominal P-values have been used to classify the pathways of enrichment in each phenotype.

Immune infiltrates analysis

TIMER [12] is a comprehensive database for the systematic study of immune infiltration in various malignant tumor types. The abundance of immune infiltrates (CD8+ T cells, B cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells) was evaluated by our statistical methods and has been estimated using pathology Methods evaluated it. The network also enables users to explore the clinical relevance of one or more tumor immune subpopulations and has the flexibility to correct multiple covariates in a multivariate Cox proportional hazard model. Meanwhile, we contrast the differential level of CENPM between tumors and normal on all TCGA tumors.

UALCAN and c-BioPortal analysis

UALCAN [13] is a user-friendly intelligent network asset for analyzing, discovering cancer data and in-depth analysis of TCGA gene expression information. One of the highlights of the portal is that it allows users to found between biomarkers or computer approval of potential genes of interest, and to evaluate genes in different clinical subgroups (such as gender, age, race, tumor grade, etc.) expression. cBioPortal [14] is an online free asset that can visualize, analyze, and download large-scale cancer transcription datasets. The portal included 245 cancer studies. The tab biological interaction network of CENPM and its co-expressed genes was got, and neighboring genes with altered frequencies were contained.

TargetScan analysis

TargetScan [15] is a web for predicting potential biological targets of miRNAs. TargetScanHuman deems that the match to human 3’UTR and its orthologs is estimate by a UCSC genome-wide adjustment. As an alternative, they are ranked according to their predicted conservative positioning possibilities. FunRich [16] is a tool designed to process varieties of gene/protein datasets, in spite of the organism, and used for functional enrichment analysis. We used FunRich tools for miRNA enrichment analysis, including analysis of biological pathways, biological processes (BP), cellular components (CC) and molecular functions (MF).

Statistical analysis

Scatter plots and paired plots visualize the differences between normal and tumor samples. Use delete ways to handle disappeared data, and if any individual value is disappeared, the data will exclude the full sample. The relationship between clinical factors and CENPM was used by logistic regression, Wilcoxon rank sum test, and Kruskal test. Multivariate Cox analysis was used to assess the effect of CENPM expression on survival and other clinical factors (such as age, gender, stage, distant metastasis). Benjamini–Hochberg’s means of converting P values to FDR.
Results

Patients’ characteristics

The TCGA database contains 377 patients. The clinical and pathological properties of these samples are shown in Table 1. The middle age at diagnosis in TCGA was 53 years old (range 16–90 years) and median finally contact for subjects was 28.0 months (range 0–122.5 months). Meanwhile, follow-up for subjects conformed 129 (34.2%) alive and 248 (65.8%) death patients. Our study cohort included 122 (32.4%) female and 255 (67.6%) male patients. Stage I was located in 175 patients (46.4%), stage II in 87 (23.1%), stage III in 86 (22.8%) and stage IV in 5 (1.3%). Tumor stage was found T1 in 185 patients (49.1%), T2 in 95 (25.2%), T3 in 81 (21.5%) and T4 in 13 (3.4%). Node stage contained N0 in 257 (68.2%) and N1 in 4 (1.1%), 4 of 377 (1.1%) cases had distant metastases. All the subjects were adenomas or adenocarcinomas.

CENPM expression and clinical factors

Scatter plot showing difference in CENPM expression among normal and tumor samples (P < 0.01), we then use paired plot to demonstrated the CENPM expression between normal and tumor from the same patients and the results was significant difference (P < 0.01) Fig. 1a, b. The outcomes suggested that the expression of CENPM was significant difference. The expression of CENPM correlated significantly with the patient grade (P < 0.01), clinical stage (P < 0.01) and T-classification (P < 0.01) Fig. 1d–f. Univariate analysis utilizing logistic regression uncovered that CENPM expression as a clear-cut ward variable was related to poor prognostic clinicopathologic factors (Table 2). CENPM expression in HCC as appreciably connected with grade (OR = 1.76; 95% CI 0.94–3.42, G1 vs. G3), stage (OR = 1.96; 95% CI 1.16–3.32, I vs. III) and T-classification (OR = 2.04; 95% CI 1.24–3.40, T1 vs. T3) indicated that patients with low CENPM expression are inclined to advance to a further advanced stage than those with high CENPM expression.

Survival and multivariate analysis

Survival analysis found that HCC with CENPM-high had a worse outcome than that with CENPM-low (P < 0.01) Fig. 1c. The univariate analysis suggested that CENPM linked essentially to stage (HR = 1.70; 95% CI 1.36–2.05; P < 0.01) and T-classification (HR: 1.64; 95% CI 1.35–2.01; P < 0.01) Table 3. Multivariate analysis showed that the expression of CENPM (HR = 1.03, P = 0.044) and M classification (HR = 1.38, P = 0.023) were independent prognostic factors for patients with HCC Table 3.

GSEA analysis

To identify useful pathways that may be differentially initiated in liver cancer, we performed a GSEA analysis between low and high CENPM expression datasets. We chose the most abundant signaling pathway, depending on the standardized enrichment score (NES) Table 4. The results showed that CENPM high expression differentially enriched cell cycle, DNA replication, RNA degradation, certain cancers, phagocytosis, P53 signaling pathway and purine metabolism Fig. 2.

| Clinical characteristics | Total (377) | % |
|-------------------------|------------|---|
| Age at diagnosis (year)  | 53 (16–90) | 14.6 |
| Futime (month)          | 280 (0–122.5) | 47.7 |
| Gender                  |            | 32.4 |
| Female                  | 122        | 67.6 |
| Male                    | 255        | 13 |
| Stage                   |            | 32.9 |
| I                       | 175        | 46.4 |
| II                      | 87         | 23.1 |
| III                     | 86         | 22.8 |
| IV                      | 5          | 1.3 |
| NA                      | 24         | 6.4 |
| Grade                   |            | 3.4 |
| G1                      | 55         | 14.6 |
| G2                      | 180        | 96.7 |
| G3                      | 124        | 12.4 |
| G4                      | 13         | 3.4 |
| NA                      | 5          | 1.3 |
| T-classification         |            | 3.4 |
| T1                      | 185        | 49.1 |
| T2                      | 95         | 25.2 |
| T3                      | 81         | 21.5 |
| T4                      | 13         | 3.4 |
| TX                      | 1          | 0.3 |
| NA                      | 2          | 0.5 |
| M-classification         |            | 72.1 |
| M0                      | 272        | 72.1 |
| M1                      | 4          | 1.1 |
| MX                      | 102        | 30.5 |
| N-classification         |            | 1.1 |
| N0                      | 257        | 68.2 |
| N1                      | 4          | 1.1 |
| NX                      | 115        | 30.5 |
| NA                      | 1          | 0.3 |
| Status                  |            | 34.2 |
| Alive                   | 129        | 65.8 |
| Death                   | 248        | 65.8 |
Immune infiltrates related to CENPM in HCC

The correlation between CENPM in liver cancer expression and the abundance of immune infiltrates was statistically significant ($P < 0.01$, Fig. 3a). A multivariate Cox proportional hazard model showed that B-cells, CD8+ T cells, macrophages, and dendritic cells infiltrated by immune cells were statistically significant in liver cancer ($P < 0.05$), indicating that these immune cells significantly affect the prognosis, it is worth further research and exploration Table 5. At the same time, the expression of CENPM was also statistically significant ($P < 0.05$). Finally, we compared CENPM expression between various tumors and normal tissues. The results showed that CENPM was overexpressed in various cancers ($P < 0.05$, Fig. 3b).

UALCAN and c-BioPortal analysis in HCC

In the age subgroup (normal age (21–40 years), normal age (41–60 years), normal age (61–80 years) and normal age (81–100 years)), among patients with liver cancer CENPM has substantially higher transcription levels than healthy individuals. Analysis in the weight subgroup; gender subgroup; ethnicity subgroup; tumor grade subgroups analysis also showed significantly higher CENPM in HCC patients (Fig. 4). In order to determine the
biological interaction network of CENPM in liver cancer, we used the network in the "Network" tab in cBioPortal, showing the 50 most frequently changed neighbor genes in CENPM, and the most common change was RAD21 (18.3%) (Fig. 5 and Table 6).

miRNAs related to CENPM
According to the online database, the top 3 of the 2081 miRNA families are hsa-miR-1307-5p, hsa-miR-449b-3p, and hsa-miR-6778-5p related to the gene CENPM. The conserved sites of the miRNA family that are widely conserved in vertebrates Fig. 6a. Using the Funrich database to explore the function of the identified 2081 miRNAs. BP are significantly enriched in the regulation of nucleobases, signal transduction, cell communication, transport, regulation of gene expression, and organogenesis. CC are mainly concentrated in the nucleus, cytoplasm, Golgi apparatus, endosome, actin cytoskeleton and early endosome. The MF are mainly transcription factor activity, transcription regulation activity, protein serine, GTPase activity and ubiquitin-specific protease activity, rich biological pathways in the ErbB receptor signaling network, TRAIL signaling pathway, Glypican pathway, and syndecan-1 mediated signaling events and signal transduction events mediated by hepatocyte growth factor receptor (c-Met) Fig. 6b–e.

Discussion
In this work, we performed a detailed assessment of CENPM expression in hepatocellular carcinoma based on the TCGA database and explored its relationship with clinicopathological features, survival, function, immune infiltration, and expression differences. Understanding whether higher expression biomarkers in tumors are directly related to hepatocellular carcinoma can help us understand the mechanism of the observed clinical survival patterns. In our findings, the significant expression of CENPM suggests that CENPM may play an important role in regulating cancer progression. This should draw attention to current views on the improvement of liver cancer, and may reveal potential biomarkers or indicators to determine prognosis.

CENPM is an indispensable centromere protein involved in centromere assembly, which regulates mitochondrial protein assembly and chromosome segregation [17]. Huang et al. [18] cloned and identified the cDNA sequence of porcine PANE1, and found that porcine PANE1 gene was expressed differently in seven different tissues, with the highest expression in lymph nodes and the lowest expression in kidney. Until now, the expression of CENPM and its potential prognostic effect on hepatocellular carcinoma has not yet been investigated, our outcomes showed that the expression of CENPM in hepatocellular carcinoma was related to advanced clinical pathologic factors (grade, clinical stage, T-classification), survival time, and poor prognosis. Univariate analysis uncovered that CENPM expression as a clear-cut ward variable was related to poor prognostic clinicopathologic factors and M-classification may play an indispensable role in the inclined to advance to a further advanced stage. The univariate and multivariate analysis also suggested CENPM still remained freely connected with OS and recommended that CENPM may act as a potential prognostic biomarker of prognosis and therapeutic target in hepatocellular carcinoma, but more researches needed to conduct for further study. In addition, we further analyzed various clinicopathological features of HCC samples using the UALCAN database, and all of them showed high transcription of CENPM.

Table 4 Gene sets enriched in phenotype high

| Gene set name                               | Size | NES   | NOM P-val | FDR q-val |
|---------------------------------------------|------|-------|-----------|-----------|
| KEGG_CELL_CYCLE                             | 124  | 2.13  | 0.000     | 0.002     |
| KEGG_DNA_REPLICATION                        | 36   | 2.08  | 0.000     | 0.002     |
| KEGG_RNA_DEGRADATION                        | 56   | 2.06  | 0.000     | 0.002     |
| KEGG_BLADDER_CANCER                         | 40   | 1.94  | 0.000     | 0.010     |
| KEGG_NON_SMALL_CELL_LUNG_CANCER            | 54   | 1.78  | 0.008     | 0.029     |
| KEGG_THYROID_CANCER                         | 29   | 1.78  | 0.030     | 0.030     |
| KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS       | 93   | 1.80  | 0.006     | 0.028     |
| KEGG_P53_SIGNALING_PATHWAY                  | 65   | 1.86  | 0.000     | 0.018     |
| KEGG_PURINE_METABOLISM                      | 152  | 2.10  | 0.000     | 0.002     |

NES: normalized enrichment score; NOM: nominal; FDR: false discovery rate. Gene sets with NOM P-val < 0.05 and FDR q-val < 0.25 are considered as significant.

To identify differential signaling pathways in liver cancer, GSEA analysis results show that cell cycle, DNA replication, RNA degradation, some cancers, phagocytosis, P53 signaling pathway and purine metabolism are differentially enriched in CENPM high expression phenotype. CENPM may influence cell cycle, DNA replication, RNA degradation then controls the begins and development...
of cancer cells. Kim et al. [19] was identified CENPM as a key gene that mediates the anti-cancer effect of garlic and cisplatin on bladder cancer, and showed that patients with low CENPM expressed better progression-free survival than patients without high expression. Studies also found the CENPM genes encode a human minor histocompatibility antigen expressed by tumor cells [9, 10]. Yu et al. [20] found CENPM could as AFP-related diagnostic biomarkers in HCC and validate the results using quantitative real-time PCR. Our study for the first time investigated the CENPM mRNA expression and its prognostic significance in hepatocellular carcinoma. Chen et al. [21] demonstrated that LHX6 can inhibit the proliferation, invasion and migration P53 signaling pathways during hepatocarcinogenesis. Qin et al. [22] found that P53-stabilizing and activating RNA can strengthen the interaction between hnRNP K and P53, which ultimately leads to the accumulation and transactivation of P53. So CENPM may play a role via P53 signaling pathway and more researches needed to conduct in the future.

Fig. 2 Enrichment plots from gene set enrichment analysis (GSEA)
Previous studies demonstrated that human CENPM transcript cRNA was only detected in activated B- and T-cells either in vivo or in vitro. These studies suggested CENPM may play important role in tumor immune response so we used an online tool to analysis immune infiltrates correlation with CENPM in HCC. Multi-variable Cox proportional hazard model showed that B cells, CD8+ T cells, macrophages and dendritic cells of immune infiltrates statistically significant ($P < 0.05$) in HCC indicating that these immune cells significantly affecting the prognosis. A latest study showed CD8+, CD68+ and FoxP3+ immune cells were associated with HCC, particularly in the invasive margin [23]. Macrophages not only promote the proliferation, colony formation and migration of HCC cells, but also maintain tumor growth and metastasis by secreting hepatocyte growth factor (HGF) [24]. Pang et al. [25] proposed that fusion of dendritic cells (DC) with tumor cells can effectively activate anti-tumor immunity in the body and affect tumor progression [26]. These studies indicate that CENPM may play an important role in tumor immune response and can be a good therapeutic target for immunotherapy.

![Fig. 3 Immune infiltrates correlation with CENPM in HCC. a Correlation between CENPM in HCC expression and abundance of immune infiltrates ($P < 0.05$); b CENPM expression between various tumor and normal tissue](image)

### Table 5 Multivariate survival model analysis based on TIMER online tool

| Clinicopathologic variable | Coef | HR (95% CI) | P-value | Sig |
|----------------------------|------|-------------|---------|-----|
| Age                        | 0.012| 1.01 (1.00–1.03) | 0.177 |    |
| Gender Male                 | −0.071| 0.93 (0.58–1.50) | 0.769 |    |
| Race Black                  | 1.185| 3.27 (1.18–9.04) | 0.022 * |    |
| Race White                  | −0.032| 0.97 (0.58–1.61) | 0.902 |    |
| Stage II                    | 0.174| 1.19 (0.70–2.02) | 0.522 |    |
| Stage III                   | 0.711| 2.04 (1.24–3.33) | 0.005 ** |    |
| Stage IV                    | 1.434| 4.19 (1.20–14.60) | 0.024 * |    |
| Purity                      | 0.561| 1.75 (0.55–5.58) | 0.343 |    |
| B cells                     | −8.059| 0.00 (0.00–0.09) | 0.036 * |    |
| CD8+ T cell                 | −5.678| 0.003 (0.00–0.50) | 0.026 * |    |
| CD4+ T cells                | −6.886| 0.001 (0.00–1.69) | 0.069 - |    |
| Macrophages                 | 8.002| 2987.33 (11.72–761,175.73) | 0.005 ** |    |
| Neutrophils                 | −1.906| 0.15 (0.00–14,422.16) | 0.745 |    |
| Dendritic                   | 5.098| 163.78 (3.78–7097.75) | 0.008 ** |    |
| CENPM                       | 0.180| 1.20 (1.04–1.38) | 0.012 * |    |

P-value significant codes: $0 \leq *** < 0.001 \leq ** < 0.01 \leq * < 0.05 \leq < 0.1$
To determine the biological interaction network of \textit{CENPM} in liver cancer, we applied the 50 most frequently changed neighbor genes of \textit{CENPM} on the Network tab in cBioPortal, and the most frequent change was \textit{RAD21}. \textit{RAD21} is a nuclear phospho-protein, which becomes hyperphosphorylated in cell cycle M phase. One study found that depletion of \textit{RAD21} resulted in reduced levels of H3K27me3 at the Hoxa7 and Hoxa9 promoters, resulting in enhanced self-renewal of hematopoietic stem and progenitor cells (HSPC) [27]. Recent studies have shown that removing \textit{RAD21} in a background lacking Pds5 can rescue the phenotype observed only in the absence of Pds5 [28]. Our study may provide information on adhesion kinetics in replication fork studies in patients with liver cancer. Our study also used the Targetscan online tool to distinguish \textit{CENPM}-related miRNAs. To check the function of the identified miRNAs, bioenrichment was performed through the Funrich database. It is rich in ErbB receptor signaling network, TRAIL signaling pathway, Glypican pathway, syndecan-1 mediated signaling events and biological pathways of hepatocyte growth factor receptor (c-Met) signaling events. Studies have reported that selective c-Met inhibitors have antitumor activity in HCC and have acceptable safety and tolerability in Child–Pugh A liver function patients [29]. A recent study found that abnormal HGF/c-Met upregulation and activation are often observed in bladder cancer [30]. Studies have also found that metastasis associated with colon cancer 1 (\textit{MACC1}) regulates \textit{PDL1} expression and tumor immunity in gastric cancer (GC) cells through the c-Met/AKT/mTOR pathway [31]. We hypothesized that \textit{CENPM} may regulate the expression of c-Met, leading to the occurrence of HCC, and more related research

![Fig. 4 Boxplot showing relative expression of CENPM in subgroups of patients with HCC (UALCAN)](image1)

![Fig. 5 The network for CENPM and the 50 most frequently altered neighbor genes](image2)

| Table 6 The type and frequency of \textit{CENPM} neighbor gene alterations in HCC (cBioPortal) |
|-----------------|----------|---------|--------|----------|
| **Gene symbol** | **Amplification** | **Homozygous deletion** | **Mutation** | **Total alteration** |
| RAD21          | 17.8     | 0.3     | 0.3    | 18.3     |
| RPS27          | 12.3     | 0.2     | 0.3    | 12.6     |
| AHCTF1         | 9.6      | 0.3     | 2.2    | 12       |
| NUF2           | 11.5     | 0.3     | 0.8    | 12.3     |
| PMF1           | 12       | 0       | 0      | 12       |
is needed. To date, this study demonstrates for the first time the important role of \textit{CENPM} in the prognosis of hepatocellular carcinoma. However, future clinical trials are needed to validate these results and promote the use of \textit{CENPM} in the prognostic evaluation of hepatocellular carcinoma.

**Conclusions**

Our study found that the expression of \textit{CENPM} was significantly increased in patients with hepatocellular carcinoma, and was related to a variety of clinical features, its correlation with the level of immune infiltration and poor prognosis, so \textit{CENPM} may become a useful biomarker for the prognosis of patients with liver cancer.

**Abbreviations**

HCC: Hepatocellular carcinoma; CENPM: Centromere protein M; GSEA: Gene set enrichment analysis; TCGA: Cancer genome atlas; GO: Gene ontology; KEGG: Kyoto encyclopedia of genes and genomes; BP: Biological processes; CC: Cellular components; MF: Molecular functions; OS: Over survival.

**Acknowledgements**

Not applicable.

**Authors’ contributions**

WZH designed and analyzed the research study; WZH wrote and revised the manuscript, YDL and WZH collected the data and all authors contributed to final manuscript. All authors read and approved the final manuscript.

**Funding**

This work is not supported by grants.

**Availability of data and materials**

RNA-seq data and corresponding clinical data were acquired from the data portal for TCGA (https://portal.gdc.cancer.gov/).

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.
Competing interests

The authors declare that they have no competing interests.

Received: 1 January 2020  Accepted: 17 August 2020
Published online: 26 August 2020

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
2. Tang Y, Wang H, Ma L, et al. Diffusion-weighted imaging of hepatocellular carcinomas: a retrospective analysis of correlation between apparent diffusion coefficients and histological grade. Abdominal Radiol. 2016;41(8):1539–45.
3. Coskun M. Hepatocellular carcinoma in the cirrhotic liver: evaluation using computed tomography and magnetic resonance imaging. Exp Clin Transplant. 2017;15(Suppl 2):36.
4. Byeon H, Lee SD, Hong EK, et al. Long-term prognostic impact of osteoarthritis after resection for hepatocellular carcinoma in noncirrhotic livers. J Am Coll Surg. 2007;205(1):27–36.
5. Jiao Y, Fu Z, Li Y, Meng L, Liu Y. High EIF2BS mRNA expression and its prognostic significance in liver cancer: a study based on the TCGA and GEO database. Cancer Manag Res. 2018;20(10):6003–144.
6. Byeon H, Lee SD, Hong EK, et al. Long-term prognostic impact of osteopontin and Dickkopf-related protein 1 in patients with hepatocellular carcinoma after hepatectomy. Pathol Res Pract. 2018;214(6):814–20.
7. Shen Y, Bu L, Li R, et al. Screening effective differential expression genes for hepatic carcinoma with metastasis in the peripheral blood mononuclear cells by RNA-seq. Oncotarget. 2017;8(17):27976–899.
8. Renou JP, Bierie B, Miyoshi K, Cui Y, Djiane J, Reichenstein A, Shani M, Hennighausen L. Identification of genes differentially expressed in mouse mammary epithelium transformed by an activated beta-catenin. Oncogene. 2003;22:4594–610.
9. Bierie B, Edwin M, Melenhorst J, et al. The proliferation associated nuclear element (PANE1) is conserved between mammals and fish and preferentially expressed in activated lymphoid cells. Gene Expr Patterns. 2004;4(4):389–95.
10. Brickner AG. The PANE1 gene encodes a novel human minor histocompatibility antigen that is selectively expressed in B-lymphoid cells and B-CLL. Blood. 2006;107(9):3779–86.
11. Krupp J, Jung K. Automated multigroup outlier identification in molecular high-throughput data using bagplots and gemplots. BMC Bioinf. 2017;18:232.
12. Li T, Fan J, Wang B, et al. TIMER: a web server for comprehensive analysis of tumor-infiltrating immune cells. Cancer Res. 2017;77(21):e108–e110110. https://doi.org/10.1158/0008-5472.CAN-17-0307.
13. Chandrashekhar DS, Bashel B, Balasubramanya SAH, Creighton CJ, Rodriguez JP, Chakravarti BSV, Varambally S. UALCAN: a portal for facilitating tumor subgroup gene expression and survival analyses. Neoplasia. 2017;19(8):649–58. https://doi.org/10.1016/j.neo.2017.05.002.
14. Gao et al. Sci. Signal. 2013 & Cerami et al. Cancer Discov. 2012 when publishing results based on cBioPortal. https://doi.org/10.1158/2159-8291.
15. Agarwal V, Bell GW, Nam J, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. eLife. 2015;4:e05005. https://doi.org/10.7554/ eLife.05005.001.
16. Pathan M, Keerthikumar S, Ang CS, Gangoda L, Quek CY, Williamson NA, Mouradov D, Sieber OM, Simpson RJ, Salim A, Bacic A. FunRich: an open access standalone functional enrichment and interaction network analysis tool. Proteomics. 2015;15(15):2597–601. https://doi.org/10.1002/ pmic.201400515.
17. Foltz DR, Jansen LE, Black BE, Bailey AO, Yates JR III. Cleveland DW. The human CENP-A centromeric nucleosome-associated complex. Nat Cell Biol. 2006;8:458–69.
18. Huang H, Deng H, Yang Y, et al. Molecular characterization and association analysis of porcine PANE1 gene. Mol Biol Rep. 2010;37(5):2571–7.
19. Kim WT, Seo SP, Byun YJ, et al. The anticancer effects of garlic extracts on bladder cancer compared to cisplatin: a common mechanism of action via centromere protein M. Am J Chin Med. 2018;46:1–17.
20. Yu Z, Wang R, Chen F, et al. Five novel oncogenic signatures could be utilized as AFP-related diagnostic biomarkers for hepatocellular carcinoma based on next-generation sequencing. Dig Dis Sci. 2018;63:945–57.
21. Chen HQ, Zhao J, LiY, et al. Epigenetic inactivation of LHX4 mediated microcystin-LR induced hepatocarcinogenesis via the Wnt/b-catenin and P53 signaling pathways. Environ Pollut. 2019;252(PT 3):216–26.
22. Qin G, Tu X, Li H, et al. IncRNA PSTAR promotes p53 signaling by inhibiting HnRNP K desUMOylation and suppresses hepatocellular carcinoma. Hepatology. 2019. https://doi.org/10.1002/hep.30793.
23. Ihling C, Naughton B, Zhang Y, et al. Observational study of PD-L1, TGF-β, and immune cell infiltrates in hepatocellular carcinoma. Front Med (Lausanne). 2019(8):16.
24. Dong N, Shi X, Wang S, et al. M2 macrophages mediate sorafenib resistance by secreting HGF in a feed-forward manner in hepatocellular carcinoma. Br J Cancer. 2019;121:22–33.
25. Pang YB, He J, Cui BY, et al. A potential antitumor effect of dendritic cells fused with cancer stem cells in hepatocellular carcinoma. Stem Cells Int. 2019;2019:5680327.
26. Janco JMT, Lamichhane P, Karyampudi L, Knutton KL. Tumor-infiltrating dendritic cells in cancer pathogenesis. J Immunol. 2015;194(7):2985–91.
27. Fisher JB, Peterson J, Reimer M, et al. The cohesin subunit Rad21 is a negative regulator of hematopoietic self-renewal through epigenetic repression of Hoxa7 and Hoxa9. Leukemia. 2016;31(3):712.
28. Carvajal-Maldonado D, Byrum AK, Jackson J, et al. Perturbing cohesin dynamics drives MRE11 nuclelease-dependent replication fork slowing. Nucleic Acids Res. 2019;47(12):294–310.
29. Bouattour M, Raymond E, Qin S, et al. Recent developments of c-met as a therapeutic target in hepatocellular carcinoma. Hepatology. 2017;67:1232–49.
30. Sim WJ, Iyengar PV, Lama D, et al. c-Met activation leads to the establishment of a TGFβ-receptor regulatory network in bladder cancer progression. Nat Commun. 2019;10(1):4349.
31. Tong G, Cheng B, Li J, et al. MACC1 regulates PDL1 expression and tumor immunity through the c-Met/AKT/mTOR pathway in gastric cancer cells. Cancer Med. 2019;8:7044–54.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.