MRGBP is a potential novel prognostic biomarker and is correlated with immune infiltrates in hepatocellular carcinoma

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Abstract
This study investigated the expression change, prognostic values, and potential regulatory mechanisms of mortality factor on chromosome 4 (MORF4)-related gene-binding protein (MRGBP) in hepatocellular carcinoma (HCC).

MRGBP expression and clinical data from The Cancer Genome Atlas were used to evaluate the associations between MRGBP expression and clinicopathological characteristics. Kaplan–Meier and Cox regression analyses were performed to assess the factors contributing to prognosis. Gene set enrichment analysis (GSEA) was used to identify pathways associated with MRGBP expression. Single-sample gene set enrichment analysis (ssGSEA) was used to comprehensively analyze the relative immune infiltration levels.

High MRGBP expression was significantly associated with a higher T stage, pathologic stage, histologic grade, vascular invasion, tumor protein p53 status, and worse overall survival. MRGBP exhibited high diagnostic accuracy with an area under the receiver operating characteristic curve value of 0.980. GSEA revealed the enrichment of pathways related to tumorigenesis in the MRGBP high-expression phenotype, such as cell cycle and DNA replication pathways. ssGSEA revealed that MRGBP expression was significantly correlated with 15 types of immune cell infiltration levels. The Wilcoxon rank sum test revealed significantly high H helper (Th), T follicular helper, CD56 bright natural killer, and Th2 cell enrichment scores in the high MRGBP expression group and significantly low neutrophil, Th17, dendritic cell (DC), gamma delta T, cytotoxic cell, regulatory T cell, plasmacytoid DC, and immature DC enrichment scores.

MRGBP may be a novel prognostic biomarker and a therapeutic target correlated with immune infiltrates in HCC.

Abbreviations: AFP = alpha-fetoprotein, BMI = body mass index, DCs = dendritic cells, FDR = false discovery rate, GPC-3 = glypican-3, GSEA = gene set enrichment analysis, HCC = hepatocellular carcinoma, HR = hazard ratio, iDCs = immature dendritic cells, KEGG = Kyoto Encyclopedia of Genes and Genomes, MORF4 = mortality factor on chromosome 4, MRGBP = MORF4-related gene-binding protein, NES = normalized enrichment score, NKs = natural killer cells, OR = odds ratio, OS = overall survival, PanCa = pancreatic cancer, pDCs = plasmacytoid dendritic cells, ssGSEA = single-sample gene set enrichment analysis, TCGA = The Cancer Genome Atlas, Tcm = T central memory cells, Th = T helper, Tgd = gamma delta T cells, TIP60/HAT = tat-interacting protein 60/histone acetyltransferase, TP53 = tumor protein p53, Tregs = regulatory T cells.

Keywords: biomarker, hepatocellular carcinoma, immune infiltrates, MORF4-related gene-binding protein, prognosis
1. Introduction

Hepatocellular carcinoma (HCC) comprises 75% to 85% of primary liver carcinoma cases. HCC was the sixth most common cancer (fifth for males) and the fourth most common cause of death (second for males) worldwide in 2018. By 2040, estimates are for 1.35 million new cases and 1.28 million HCC-related deaths annually.[1,2] Approximately 10% of patients with HCC show metastases at the time of diagnosis.[3] Treatments, including surgical resection, transplantation, ablation, transarterial chemoembolization, and sorafenib, have improved patient survival.

With the development of molecular targeted therapies, identifying novel targets and prognostic predictors through molecular profiling could further improve survival.[4]

Mortality factor on chromosome 4 (MORF4)-related gene-binding protein (MRGBP), also known as chromosome 20 open reading frame 20 encodes a subunit of the tat-interacting protein 60/histone acetyltransferase (TIP60/HAT) complex. The protein binds directly to 2 basic components of the TIP60/HAT complex and histone deacetylase complexes: MORF4-related gene on chromosome 15 and MORF4-related gene on chromosome X proteins.[5] MRGBP is frequently amplified in numerous types of cancer, including lung,[6] prostate,[7,8] and pancreatic cancers,[9,10] cutaneous squamous cell carcinoma[11]; and colorectal[12-14] and cervical cancers,[15] and is involved in the regulation of the cell cycle, apoptosis, growth, and invasion.[8,11,13,15] MRGBP may play a biological role as a diagnostic biomarker and anticancer target for tumors. However, little is known about the relationship between MRGBP and HCC.

In this study, we demonstrate for the first time the relationship between MRGBP and HCC, prognostically relevant expression profiles, and the correlation using bioinformatics analysis between immune infiltrates and MRGBP expression. The findings could provide new and promising insights for subsequent research to elucidate the clinicopathological significance and molecular pathogenesis of HCC.

2. Methods

2.1. RNA-sequencing (RNASeq) and clinical information

We evaluated the gene expression of 421 liver HCC samples comprising 371 tumor samples and 50 normal paracancer samples from the UCSC Xena database (https://xenabrowser.net/datapages/) using RNASeq (HTSeq-Counts). The clinical data of the corresponding patients were obtained from The Cancer Genome Atlas (TCGA) website (https://portal.gdc.cancer.gov/). We obtained matched prognostic data from an Integrated TCGA Pan-Cancer Clinical Data Resource.[16] HTSeq-counts and clinical data of 371 patients were extracted for further analysis (Table 1). The 371 patients were divided into high and low groups according to the median MRGBP expression in tumor samples. As all the data used were retrieved from these online databases, there were no ethical issues.

2.2. Gene set enrichment analysis (GSEA)

GSEA was performed using R package clusterprofiler (3.6.0) to elucidate the potentially significant pathways associated with differentially expressed proteins in the high- and low-MRGBP groups. To identify the significantly enriched pathways, the number of permutations was 1000. The pathway sets with an adjusted P value < .05, false discovery rate (FDR) q-value < .025, and a normalized enrichment score (NES) > 1 were identified as significantly enriched.

2.3. Immune infiltration analysis using single-sample GSEA (ssGSEA)

The ssGSEA method from the Gene Set Variation Analysis package (http://www.bioconductor.org/packages/release/bioc/html/GSVA.html) in R (v 3.6.3) was used to comprehensively analyze the relative tumor cell infiltration levels, based on the signature gene lists of 24 types of immune cells.[17] Spearman correlation was used to analyze the correlation between MRGBP and immunocytes. The Wilcoxon rank sum test was used to determine the immune infiltration differences among the different expression groups of MRGBP.

2.4. Statistical analyses

Statistical analyses were performed using R software (v 3.6.3), x^2 test, Wilcoxon rank sum test, and univariate logistic regression were performed to evaluate the association between MRGBP expression and the clinicopathological characteristics of patients. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Survival data were evaluated using univariate and multivariate Cox regression analyses. Bivariate correlations between study variables were calculated using Spearman rank correlation coefficient. A P value < .05 was considered statistically significant in all tests.

3. Results

3.1. Demographic characteristics

TCGA data of 371 patients included their characteristics regarding the T, N, M, and pathologic stages, residual tumor, histologic grade, sex, race, adjacent hepatic tissue inflammation, Child–Pugh grade, fibrosis Ishak score, vascular invasion, tumor status, tumor protein p53 (TP53) status, age, height, weight, body mass index (BMI), alpha-fetoprotein (AFP), albumin, and prothrombin time. X^2 analysis showed that MRGBP expression was significantly associated with the T stage (P = .032), residual tumor (P = .025), histologic grade (P < .001), and TP53 status (P < .001). The results of the Wilcoxon rank sum test showed that MRGBP expression was significantly associated with weight (P = .001), BMI (P = .005), AFP (P < .001), and prothrombin time (P = .001) (Table 1).

3.2. Associations between gene expression and clinicopathological features

Using the Wilcoxon signed-rank test, we found that the expression levels of MRGBP in 371 tumor tissues were notably higher than those in 50 normal tissues (P < .001; Fig 1A). The values of MRGBP expression in 50 tumor tissues were remarkably higher than those in 50 paired normal liver tissues in TCGA cohort (P < .001; Fig 1B). The higher expression of MRGBP correlated significantly with poor tumor status (P = .006), a higher T stage (P < .001), and a higher pathologic stage (P = .003) (Fig 1, C–E). In addition, MRGBP exhibited high diagnostic accuracy with an area under the receiver operating characteristic curve value of 0.980 (Fig 1F).
Univariate logistic regression analysis showed that high MRGBP expression was significantly associated with poor prognostic characteristics, including a higher T stage (odds ratio [OR] = 1.85 for T2, T3, and T4 vs T1, \( P = .004 \)), pathologic stage (OR = 1.61 for Stage II, III, and IV vs Stage I, \( P = .14 \)), histologic grade (OR = 4.06 for G3 and G4 vs G1 and G2, \( P < .001 \)), vascular invasion (OR = 1.64 for Yes vs No, \( P = .039 \)), and TP53 status (OR = 3.24 for Mut vs WT, \( P < .001 \)) (Table 2).

These results suggested that HCC with a higher MRGBP expression may progress to a poorer stage and vascular invasion.

### 3.3. Survival outcomes and Cox regression analysis

Kaplan–Meier survival analysis indicated that HCC with a high expression of MRGBP had a worse overall survival (OS) (hazard ratio (HR) = 4.47, \( P < .001 \)).
ratio [HR] = 1.87 [1.31–2.66], \( P < .001 \), progression-free interval (HR = 1.47 [1.10–1.98], \( P = .010 \)), and disease-specific survival (HR = 1.79 [1.14–2.80], \( P = .011 \)) than HCC with low MRGBP expression (Fig. 2).

Univariate analysis showed that a high MRGBP expression was significantly correlated with a worse OS (HR = 1.869 [1.315–2.655]; \( P < .001 \)). Other clinicopathologic variables, including T, M, and pathologic stage and tumor status, were
also associated with poor survival. In a multivariate analysis, high MRGBP expression remained independently associated with a poor OS (HR = 1.737 [1.061–2.845]; P = .028), along with the tumor status (Table 3).

3.4. GSEA identification of MRGBP-related Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways

To identify different activated signaling pathways in HCC, GSEA was performed between MRGBP low-expression and high-expression datasets, with significant enrichment differences (FDR q < 0.05, P < .05, |NES| > 1) using the molecular signatures database collection (C2.cp.v7.0.symbols.gmt). Sixty-six enriched KEGG pathways were identified, including 23 pathways that showed a significant differential enrichment in the MRGBP high-expression group and 43 pathways listed in the low-expression group (Supplementary Table S1, http://links.lww.com/MD/F938). The top 9 most significantly enriched KEGG gene sets in the high-expression group were the ribosome, cell cycle, DNA replication, homologous recombination, primary immunodeficiency, Fc gamma R-mediated phagocytosis, type I diabetes mellitus, spliceosome, and leishmania infection sets, based on the NES (Table 4 and Fig. 3).

3.5. Correlation between MRGBP expression and immune infiltration

We used Spearman test to analyze the correlation between the expression of MRGBP and immune cell infiltration level, which was quantified using ssGSEA in an HCC tumor microenviorno.
Table 3
Univariate and multivariate analyses of various prognostic parameters and OS in patients with HCC (cox-regression analysis).

| Characteristics                                      | Total (N) | HR (95% CI) Univariate analysis | P value | HR (95% CI) Multivariate analysis | P value |
|------------------------------------------------------|-----------|---------------------------------|---------|-----------------------------------|---------|
| T stage (T2 and T3 and T4 vs T1)                     | 367       | 2.109 (1.469–3.028)             | <.001†  | 0.906 (0.122–6.745)               | .923    |
| N stage (N1 vs N0)                                   | 256       | 2.004 (0.491–8.181)             | .333    |                                   |         |
| M stage (M1 vs M0)                                   | 270       | 4.032 (1.267–12.831)            | .018†   | 1.653 (0.393–6.949)               | .493    |
| Pathologic grade (Stage II and Stage III and Stage IV vs Stage I) | 346   | 2.074 (1.418–3.032)             | <.001†  | 2.493 (0.324–19.169)             | .380    |
| Histologic grade (G3 and G4 vs G1 and G2)           | 365       | 1.120 (0.781–1.606)             | .539    |                                   |         |
| Residual tumor (R1 and R2 vs R0)                     | 341       | 1.571 (0.795–3.104)             | .194    |                                   |         |
| Age (>60 vs <=60)                                    | 370       | 1.248 (0.880–1.768)             | .214    |                                   |         |
| Gender (male vs female)                              | 370       | 0.816 (0.573–1.163)             | .260    |                                   |         |
| Weight (>70 vs <=70)                                 | 343       | 0.916 (0.640–1.312)             | .634    |                                   |         |
| Height (>170 vs <170)                                | 338       | 1.208 (0.833–1.753)             | .319    |                                   |         |
| BMI (>25 vs <=25)                                    | 334       | 0.818 (0.563–1.186)             | .289    |                                   |         |
| Race (White vs Asian and Black or African American)  | 358       | 1.245 (0.867–1.789)             | .235    |                                   |         |
| Child-Pugh grade (B and C vs A)                      | 238       | 1.616 (0.797–3.275)             | .183    |                                   |         |
| AFP (ng/mL) (>400 vs <=400)                          | 277       | 1.056 (0.646–1.727)             | .827    |                                   |         |
| Albumin (g/dL) (>=3.5 vs <3.5)                       | 296       | 0.921 (0.565–1.503)             | .743    |                                   |         |
| Prothrombin time (<4 vs >=4)                         | 238       | 1.330 (0.877–2.015)             | .179    |                                   |         |
| Fibrosis ishak score (1/2 and 3/4 and 5/6 vs 0)      | 311       | 0.779 (0.470–1.293)             | .334    |                                   |         |
| Adjacent hepatic tissue inflammation (mild and severe vs none) | 233 | 1.228 (0.755–1.997)             | .409    |                                   |         |
| Vascular invasion (yes vs no)                        | 314       | 1.348 (0.890–2.042)             | .159    |                                   |         |
| Tumor status (with tumor vs tumor free)              | 351       | 2.361 (1.620–3.441)             | <.001†  | 2.323 (1.415–3.815)               | <.001*  |
| TP53 status (Mut vs WT)                              | 357       | 1.434 (0.972–2.115)             | .069    | 1.369 (0.806–2.325)               | .245    |
| MRGBP (high vs low)                                  | 370       | 1.869 (1.315–2.655)             | <.001†  | 1.737 (1.061–2.845)               | .028†   |

**APP** = alpha-fetoprotein, **BMI** = body mass index, **CI** = confidence interval, **HCC** = hepatocellular carcinoma, **HR** = hazard ratio, **MRGBP** = MORF4-related gene-binding protein, **Mut** = mutant type, **OS** = Overall Survival, **TP53** = tumor protein p53, **WT** = wild-type.

*Statistically significant.

Table 4
KEGG gene sets enriched in the MRGBP high-expression phenotype.

| MSigDB collection | Gene set name            | setSize | NES   | p.adjust | FDR  |
|-------------------|--------------------------|---------|-------|----------|------|
| c2.cp.v7.0.symbols.gmt [Curated] | KEGG_RIBOSOME | 86      | 2.143 | 0.026    | 0.019|
|                   | KEGG_CELL_CYCLE          | 124     | 1.99  | 0.026    | 0.019|
|                   | KEGG_DNA_REPLICATION      | 36      | 1.934 | 0.026    | 0.019|
|                   | KEGG_HOMOLOGOUS_RECOMBINATION | 26     | 1.85  | 0.026    | 0.019|
|                   | KEGG_PRIMARY_IMMUNODEFICIENCY | 35     | 1.827 | 0.031    | 0.023|
|                   | KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS | 91     | 1.815 | 0.031    | 0.023|
|                   | KEGG_TYPE_I_DIABETES_MELLITUS | 41     | 1.801 | 0.032    | 0.023|
|                   | KEGG_SPLICEOSOME         | 123     | 1.799 | 0.026    | 0.019|
|                   | KEGG_LEISHMANIA_INFECTION | 70      | 1.799 | 0.031    | 0.023|

**FDR** = false discovery rate, **KEGG** = Kyoto Encyclopedia of Genes and Genomes, **MRGBP** = MORF4-related gene-binding protein, **MSigDB** = molecular signatures database, **NES** = normalized enrichment score.
factor-beta, mesenchymal-to-epithelial transition factor, fibroblast growth factor receptor 4, and GPC-3. However, the use of a single biomarker has limited detection capability and therapeutic efficacy. To improve the management of HCC, novel personalized and combination strategies are needed, as are further studies to reveal novel molecular targeted therapies and surveillance.\[^{4,19}\]

MRGBP expression is frequently amplified in multiple types of cancer. MRGBP regulates cell cycle, apoptosis, tumor growth, and invasiveness. In a prior study, MRGBP expression was elevated in all 107 lung tumor tissues, and its co-expression genes were significantly enriched in signaling transduction-related pathways, such as the Ras signaling pathway, mitogen-activated protein kinase pathway, and Notch signaling pathway.\[^{46}\]
MRGBP promotes cancer cell invasion and growth by stimulating the expression of androgen receptor target genes by promoting the recruitment of TIP60 and acetylation of a histone variant (H2A.Z) in prostate cancer.\(^{7,8}\) MRGBP upregulation in pancreatic ductal adenocarcinoma promotes the growth, migration, and invasion of cancer cells, suppresses apoptosis of pancreatic cancer (PanCa) cells, and has been positively associated with TNM stage, T classification, poor prognosis, and induction of epithelial–mesenchymal transition.\(^{10}\) MRGBP expression in PanCa cells could be directly downregulated by miR-137.\(^{9}\) MRGBP is also amplified in cutaneous squamous cell carcinoma, which promotes tumor growth in vivo and reduces apoptosis in vitro.\(^{11}\) Yamaguchi et al.\(^{12,13}\) found that the expression of MRGBP was amplified in colorectal cancer, consistent with the findings of Carvalho et al.\(^{14}\) that the interaction of MRGBP with bromodomain containing 8 may be key in determining MRGBP function in the proliferation of cancer cells. MRGBP can promote the proliferation of colorectal cancer cells by regulating the cell cycle, not apoptotic cells.\(^{13}\) However, the expression level of MRGBP in colorectal cancer was not correlated with clinicopathological factors.\(^{12}\) Scotto et al.\(^{15}\) showed that MRGBP was upregulated in cervical cancer cells as a consequence of the 20q gain. Based on these studies, MRGBP may play a biological role as a diagnostic biomarker and anticancer target for tumors. However, little is known about the relationship between MRGBP and HCC. In this study, we performed a bioinformatics analysis of the prognostic value of MRGBP and the correlation between immune infiltrates and MRGBP expression in HCC.

ONCOMINE (www.oncomine.org) (the cutoffs of \(P\) value, fold change, and gene rank were defined as 0.05%, 1.5%, and 10%, respectively) was first used to analyze the mRNA level of MRGBP between cancer and normal tissues. The transcriptional expression of MRGBP was significantly upregulated in tumor tissues compared with that in normal tissues in 16 types of tumors (including HCC) (Supplementary Table S2, http://links.lww.com/MD/F939). The Wilcoxon signed-rank test revealed that the expression levels of MRGBP in 371 HCC tissues were notably higher than those in 50 normal tissues. Furthermore, MRGBP expression in 50 tumor tissues was remarkably higher than that in 50 paired normal liver tissues in TCGA cohort. MRGBP expression was amplified in HCC and was significantly
associated with many clinical characteristics, including T stage, residual tumor, histologic grade, TP53 status, weight, BMI, AFP, and prothrombin time. HCC with a higher MRGBP expression is more likely to progress to a poorer stage and vascular invasion than HCC with a lower MRGBP expression. Overexpression of MRGBP in HCC and its correlation with poor clinicopathologic factors indicate that MRGBP is an oncogene. Multivariate and univariate analyses demonstrated that a higher MRGBP expres-

Figure 5. Comparison of the level of immune infiltration between high and low MRGBP expression groups in HCC. Neutrophil (A), Th17 cell (B), DC (C), Tgd (D), cytotoxic cell (E), Treg (F), pDC (G), iDC (H), T helper cell (I), Tfh (J), NK CD56 bright cell (K), and Th2 cell (L) infiltration between the high and low MRGBP expression groups. DCs = dendritic cells, HCC = hepatocellular carcinoma, iDCs = immature DCs, MRGBP = MORF4-related gene-binding protein, NKS = natural killer cells, pDCs = plasmacytoid DCs, Tfh = T follicular helper cells, Tgd = gamma delta T cells, Th = T helper cells, Tregs = regulatory T cells.
sion indicated a shorter OS. To further study the role of MRGBP in HCC, we conducted GSEA using TCGA data. The ribosome, cell cycle, DNA replication, homologous recombination, primary immunodeficiency, Fc gamma R-mediated phagocytosis, type I diabetes mellitus, spliceosome, and leishmania infection pathways were differentially enriched in the MRGBP high-expression group. Thus, MRGBP may be a new prognostic biomarker and therapeutic target for HCC.

In addition, high MRGBP expression increased the immune infiltration levels in T helper cells, T\(\text{H}\) cells, NK CD56 bright cells, and TH2 cells and decreased immune infiltration in TH17 cells, DC, Tgd cells, cytotoxic cells, Tregs, pDCs, and iDCs in HCC. We infer from these findings that overexpression of MRGBP inhibits effective NK and TH1 immune responses.

The data analyzed here were retrieved from online databases, and the mRNA levels were not perfect predictors of protein expression.\(^{[21]}\) We plan to perform further cell experiments and clinical sample analyses to verify the correlation between mRNA and protein expression and the functional mechanism of MRGBP in HCC.

5. Conclusions

In summary, increased MRGBP expression correlates with cancer progression, poor survival, and immune infiltration levels in HCC, suggesting that MRGBP may be a novel prognostic biomarker correlated with immune infiltrates. These novel findings provide new and promising insights for subsequent research to elucidate the clinicopathological significance and molecular pathogenesis of HCC. Further experimental validation is needed to demonstrate the biological effects of MRGBP in HCC.

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