

ORIGINAL ARTICLE

A gene expression signature of *FOXM1* predicts the prognosis of hepatocellular carcinoma

Bic-Na Song^{1,2} and In-Sun Chu^{1,2}

FOXM1 (Forkhead box M1) is a key regulator of tumorigenesis. Previous studies demonstrated that *FOXM1* overexpression was strongly correlated with poor prognosis in various cancers, including hepatocellular carcinoma (HCC). In this study, we examined an association between the gene expression signature of *FOXM1* and HCC patient outcome. The co-expressed gene set of *FOXM1*, which is significantly associated with the prognosis of HCC patients, was identified by analyzing the gene expression profiles of 100 patients with HCC, and this gene set was validated in two independent HCC patient cohorts ($n = 573$). In multivariate analysis, the co-expressed gene set of *FOXM1* was the most significant prognostic factor for overall survival in patients with HCC (hazard ratio = 1.706, 95% confidence intervals = 1.176–2.475, $P = 0.005$). We also analyzed different types of cancer, including pancreatic adenocarcinoma, lung adenocarcinoma, breast carcinoma and bladder urothelial carcinoma, to verify the association between the co-expressed gene set of *FOXM1* and patient prognosis, and we found a consistent prognostic significance, regardless of tumor type. Finally, we identified a putative signaling pathway in which miR-34a acts as an upstream regulator of the *FOXM1-MYC* signaling network; this pathway may be ultimately responsible for the poor prognosis of HCC patients. The prognostic subgroups defined by the gene expression signature of *FOXM1* could help predict high-risk patients and may guide selection of the best treatment strategy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major public health problem; it is the primary malignancy of the liver, one of the most common tumors worldwide, and one of the fastest growing causes of cancer-related death. In 2012, 782,500 new cases of liver cancer were diagnosed, and 745,500 deaths occurred worldwide.¹ Because of the clinical heterogeneity of this malignant disease, precisely predicting the prognosis of HCC patients remains challenging.

With the advent of new technologies over the past decade, many genome-wide expression profiling studies have revealed the existence of biologically distinct subtypes of HCC, with prognostic implications.^{2–4} Furthermore, genome-wide gene expression profiling studies have discovered several genomic predictors for the recurrence or survival of HCC.^{5,6} However, it is currently unknown whether this signature is applicable to the development of new treatments. Recently, a number of putative prognostic markers for HCC, including *FOXM1*, have been proposed in various investigations. Although several studies have shown that *FOXM1* overexpression was associated with poor

outcomes in many types of cancer,^{7–10} its clinical relevance as a prognostic and predictive biomarker is not yet fully understood. Furthermore, no studies have examined the prognostic impact of the co-expressed gene set of *FOXM1* and whether it can provide additional insights on the potential signaling pathway that is responsible for the poor prognosis of HCC patients.

Here we examined an association between the gene expression signature of *FOXM1* and HCC patient outcome using gene expression data sets. We also analyzed four different cancer types to verify the association between the gene expression signature of *FOXM1* and patient outcome. To further validate the utility of the signature, we tested whether the gene expression signature of *FOXM1* could identify the distinct subgroups of patients with different types of cancer in The Cancer Genome Atlas (TCGA) pan-cancer gene expression data set. Through gene-to-gene network and upstream regulator analyses, we also identified a putative signaling pathway composed of *FOXM1*, *MYC* and miR-34a that potentially mediates HCC patient outcome.

¹Korean Bioinformation Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, Korea and ²Department of Bioinformatics, KRIBB School of Bioscience, Korea University of Science and Technology (UST), Daejeon, Korea
Correspondence: Dr I-S Chu, Korean Bioinformation Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon 34141, Korea.
E-mail: chu@kribb.re.kr

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MATERIALS AND METHODS

Patients and gene expression data

Gene expression data sets from the Korean and Fudan HCC cohorts, as reported in previous studies, were acquired from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database.^{6,11} The mRNA-seq and miRNA-seq data sets of HCC patients from the TCGA project were obtained from Cancer Browser (<https://genome-cancer.uscs.edu>). The Korean cohort (GSE16757, $n = 100$) was used as the exploration data set. The Fudan (GSE14520, $n = 242$) and TCGA ($n = 331$) cohorts were used for validation. Supplementary Table 1 shows the pathologic and clinical characteristics of the patients in all three HCC cohorts.

The four gene expression data sets, which consist of pancreatic adenocarcinoma (PAAD, GSE21501, $n = 132$), lung adenocarcinoma (LUAD, GSE31210, $n = 246$), breast invasive carcinoma (BRCA, GSE20486, $n = 97$), and bladder urothelial carcinoma (BLCA, GSE13507, $n = 165$) samples, were obtained from the NCBI GEO database. Of the 97 patients with BRCA, we only used the 81 patients who had estrogen-receptor-positive tumors.

The TCGA pan-cancer gene expression data set ($n = 9,755$) was obtained from Cancer Browser. This data set is composed of 32 different cancer types. Among these, we focused on five cancer types: HCC (the TCGA cohort mentioned above, $n = 331$), PAAD ($n = 161$), LUAD ($n = 468$), BRCA ($n = 1,055$), and BLCA ($n = 327$). Of the 1,055 patients with BRCA, only 779 patients who had estrogen-receptor-positive tumors were selected. Therefore, a total of 2,066 patient samples were examined in this study (the Pan-cancer cohort, $n = 2,066$).

Clinical data were obtained from the Supplementary Information of the corresponding literature or was requested from the authors. The patients with available survival time data were subjected to statistical analysis.

Statistical analysis

The non-tumor and replicated samples were removed based on the sample annotations attached to each data set. Gene expression profile data, regardless of platform, was separately log₂ transformed and quantile normalized. For the exploration data set, genes were filtered out if they did not have at least a two-fold change relative to the median in more than 5% of the samples. For gene expression profiling from the RNA-seq data set, genes with a value of zero were set to the missing value after log₂ transformation, and genes were filtered out if they had missing data in > 30% of the samples.

To identify the co-expressed gene set of *FOXMI*, we analyzed the gene expression profile data by employing the same procedure

described in a previous study.¹² Briefly, we selected genes that had a significant correlation with the *FOXMI* gene ($P < 0.001$ by Pearson correlation coefficient; $r < -0.4$ or $r > 0.4$). Then, hierarchical clustering analysis was performed using a gene expression data matrix that consisted of *FOXMI* and its correlated genes. We estimated patient prognosis using Kaplan–Meier plots and the log-rank test. The prognostic association between the signature and risk factors was assessed using multivariate Cox proportional hazard regression models. All statistical analyses were performed in the R language environment.

Using the Ingenuity Pathway Analysis (IPA) tool (www.ingenuity.com), gene set enrichment and upstream regulator analyses were performed as described in a previous study.¹³

RESULTS

Baseline characteristics

The baseline characteristics of all eight data sets analyzed in this study are summarized in Table 1. In each data set, overall survival was defined as the number of months from the initial pathological diagnosis of the tumor until the patient was deceased or lost to follow-up. In the Fudan and TCGA cohorts, recurrence-free survival was defined as the time from surgery to the first confirmed recurrence.

Prognostic utility of *FOXMI* and its associated genes on HCC patients in the exploration data set

We first tried to identify a gene set that was highly correlated with *FOXMI* expression, then used that gene set to predict the prognosis of HCC patients. We identified 1,185 genes that were highly correlated with *FOXMI* expression in the exploration data set. Based on hierarchical clustering analysis of the expression patterns of these genes, patients with HCC were divided into two subgroups: *FOXMI*-high (FH) and *FOXMI*-low (FL) (Figure 1a). The survival rate of the FH subgroup was significantly worse than that of the FL subgroup ($P = 0.01$ by log-rank test; Figure 1b).

Validation of the gene expression signature of *FOXMI* on HCC patient survival using the independent cohorts

To validate our findings, we used gene expression profile data from an independent cohort of HCC patients. The gene expression profile data of the Fudan cohort (Affymetrix

Table 1 Characteristics of data sets and patients included in this study

Data set	Data source	Platform description	GEO platform ID	No. of patients
Korean cohort	GSE16757	Illumina Human-6 v2.0	GPL6102	100
Fudan cohort	GSE14520	Affymetrix Human Genome U133A Array	GPL571/GPL3921	242
TCGA cohort	^a	Illumina RNA-seq	NA	331
PAAD	GSE21501	Agilent-014850 Whole Human Genome Microarray	GPL4133	102
LUAD	GSE31210	Affymetrix Human Genome U133 Plus 2.0 Array	GPL570	226
BRCA	GSE20486	Illumina HumanHT-12 V3.0	GPL6947	81
BLCA	GSE13507	Illumina Human-6 v2.0	GPL6102	165
Pan-cancer cohort	^a	Illumina RNA-seq	NA	2,066

Abbreviations: BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; GEO, National Center for Biotechnology Information's Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo/); LUAD, lung adenocarcinoma; PAAD, pancreatic adenocarcinoma.

^aUCSC Cancer Genome Browser (<https://genome-cancer.ucsc.edu>).

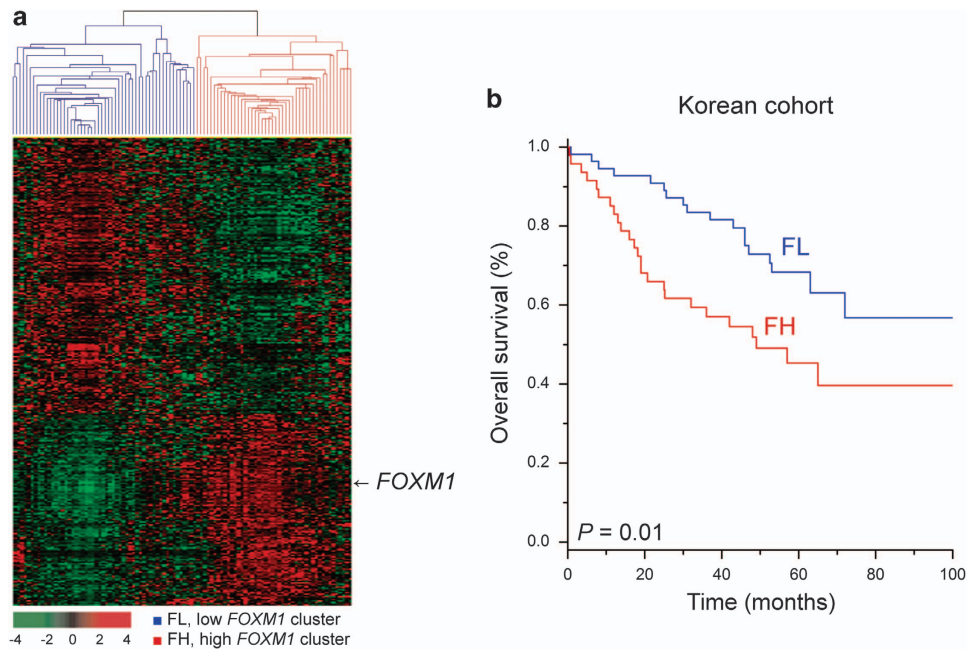


Figure 1 Gene expression patterns of the co-expressed gene set of *FOXM1* and the overall survival of HCC patients in the exploration data set ($n=100$). (a) Gene expression patterns of *FOXM1* and its associated genes. A total of 1,185 genes with expression patterns that highly correlated with *FOXM1* were selected for cluster analysis. The patients were divided into two subgroups: *FOXM1*-high (FH) and *FOXM1*-low (FL). (b) Kaplan–Meier plot of the overall survival of HCC patients, stratified by the co-expressed gene set of *FOXM1*. The survival rate of the FH subgroup was significantly worse than that of the FL subgroup ($P=0.01$ by log-rank test).

microarray platform) does not contain all of the gene symbols in the exploration data set (Illumina microarray platform). For this reason, we selected the 826 genes that overlapped with the 1,185 genes derived from the exploration data set. Applying the same procedure employed in the previous result, the patients in the Fudan cohort were divided into two subgroups (FH and FL). The FH subgroup in the Fudan cohort also had significantly worse survival than the FL subgroup ($P=0.002$ by log-rank test, Figure 2a). Furthermore, we also estimated the recurrence-free survival of each subgroup to assess whether the co-expressed genes could identify patients at high risk for recurrence. The recurrence rate was significantly higher in the FH subgroup than the FL subgroup ($P=0.03$ by log-rank test; Figure 2b). The survival analysis was further validated with the TCGA RNA-seq data set ($P=0.001$ for the survival rate and $P=0.01$ for the recurrence rate by log-rank test; Figure 2c and d). Taken together, these results demonstrate that the gene expression signature of *FOXM1* is a robust prognostic indicator of HCC patient outcome.

We next combined the clinical data from the Korean and Fudan cohorts (total $n=321$) and assessed the prognostic association between the co-expressed gene set of *FOXM1* and other known clinical and pathologic factors for HCC using univariate Cox regression analyses. In addition to tumor size, Tumor-Node-Metastasis (TNM) stage, and Barcelona Clinical Liver Cancer (BCLC) stage, all of which are already well-known risk factors, the co-expressed gene set of *FOXM1* was a significant indicator for overall survival (Supplementary Table 2). We also applied multivariate Cox regression analyses

to verify the independent utility of the gene set. Importantly, the co-expressed gene set of *FOXM1* was the most important independent prognostic factor for overall survival (HR = 1.706, 95% CI = 1.176–2.475, $P=0.005$; Supplementary Table 2).

Prognostic utility of the gene expression signature of *FOXM1* in different types of cancer

Because the dysregulated expression and function of *FOXM1* are not confined to certain types of cancer,¹⁴ we next asked whether the co-expressed gene set of *FOXM1* was associated with the prognosis of patients with different types of cancer. From the NCBI GEO database, we selected the gene expression data sets of four cancers and identified 2,689, 4,211, 760 and 1,349 co-expressed genes of *FOXM1* in pancreatic adenocarcinoma (PAAD), lung adenocarcinoma (LUAD), breast invasive carcinoma (BRCA) and bladder urothelial carcinoma (BLCA), respectively. We did not include other cancer types in this study because we could not identify a sufficient co-expressed gene set of *FOXM1* in their data sets (due to a limited sample size or an inadequate follow-up time). Consistent with our previous result, survival analysis revealed that the co-expressed gene set of *FOXM1* was a significant predictor of overall survival in patients with different types of cancer (each $P<0.05$ by log-rank test, Figure 3). This finding strongly demonstrates that the gene expression signature of *FOXM1* has prognostic significance, regardless of tumor type.

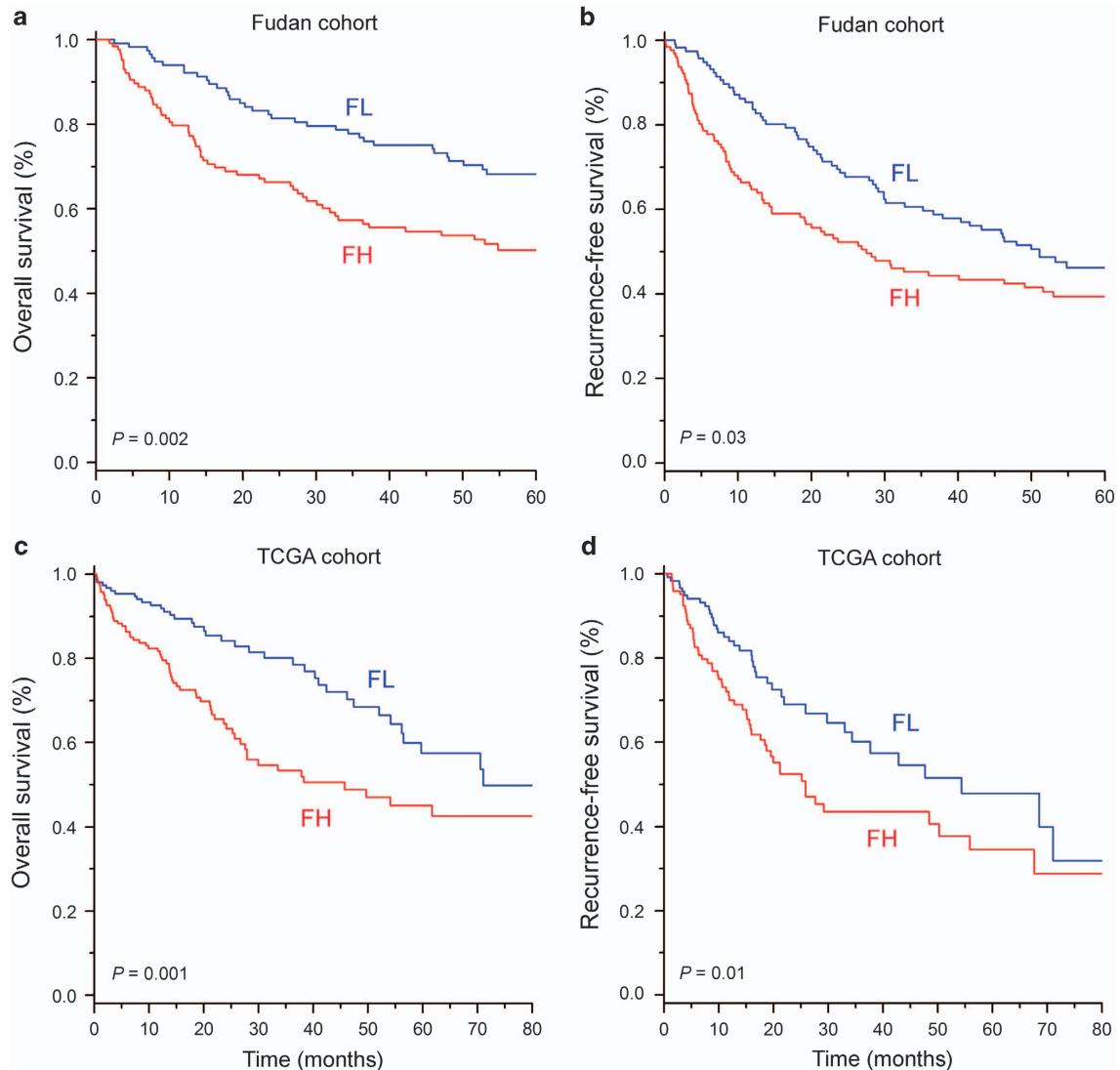


Figure 2 The validation of the gene expression signature of *FOXM1* in independent cohorts. (a) Overall survival and (b) recurrence-free survival in HCC patients, stratified by the co-expressed gene set of *FOXM1*, were estimated in the Fudan cohort ($n=242$). (c) Overall survival and (d) recurrence-free survival were also estimated in the TCGA cohort ($n=331$). FH, *FOXM1*-high; FL, *FOXM1*-low.

Two distinct subgroups of patients with different types of cancer in the Pan-cancer cohort

Having identified two subgroups that show considerable differences in clinical outcomes in the five cancer types, we next examined whether we could identify two subgroups of patients with different cancer types in a large, pooled data set. Therefore, we used a gene expression data set that was generated by merging multiple TCGA RNA-seq data sets, including HCC, PAAD, LUAD, BRCA and BLCA. The co-expressed gene set of *FOXM1* was identified by selecting the genes that highly correlated with *FOXM1* expression in the Pan-cancer cohort. We applied hierarchical cluster analysis to the gene expression data matrix, which consisted of *FOXM1* and its correlated genes, and the results showed that the cancer patients were divided into two distinct subgroups (FH and FL) based on the co-expressed gene set of *FOXM1*, not on the histological cancer type (Supplementary Figure 1). The results based on the gene

expression profile data suggest that *FOXM1* may be a master regulator of expression changes in genes associated with patient survival across cancer types.

Biological insight into the gene expression signature of *FOXM1* that is associated with the prognosis of HCC patients

Gene set enrichment analysis was performed to identify the biological characteristics of the co-expressed gene set of *FOXM1* using the IPA tool. When applying the 1,185 genes obtained from the exploration data set to the IPA tool, genes involved in organismal injury and abnormalities, gastrointestinal disease and hepatic system disease were significantly enriched. Furthermore, genes involved in DNA replication, recombination and repair, such as *BRCA1*, *EXO1*, *POLQ*, *POLD1*, *POLE*, *FANCD2*, *PRKDC* and *PARP1*, were also significantly enriched. These results indicate that the

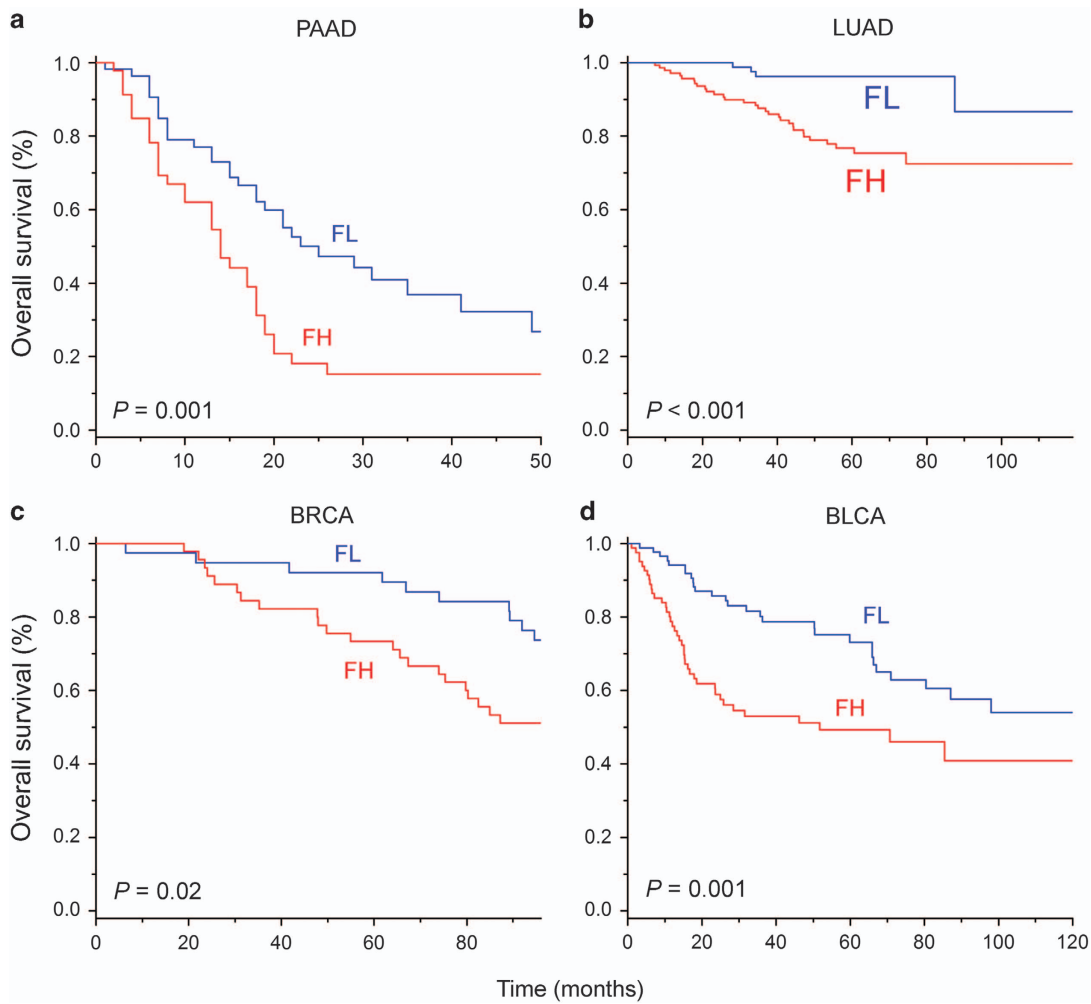


Figure 3 Kaplan–Meier plots showing differences in overall survival for patients diagnosed with different types of cancer based on the gene expression signature of *FOXM1*. Data from (a) PAAD, (b) LUAD, (c) BRCA and (d) BLCA are shown. FH, *FOXM1*-high, FL, *FOXM1*-low.

biological processes associated with the DNA repair system might be closely linked to the poor prognosis of HCC patients (Supplementary Figure 2).

We next conducted upstream regulator analysis of the 1,185 genes to uncover potential upstream regulators of the molecular signature based on a co-expressed gene set of *FOXM1*. An examination of the enriched genes revealed the involvement of several important activated regulators; the strongest overrepresentation of these regulators was the predominant activation of *MYC* (Figure 4). The downstream effectors of *MYC*, such as *E2F1*, *SUZ12*, *EZH2* and *PARP1*, were previously reported to be associated with tumor aggressiveness and metastasis,^{15–17} indicating that *MYC* is a key factor associated with the gene signature of *FOXM1*. Although the expression of *MYC* downstream genes is higher in the FH subgroup than in the FL subgroup, the expression of *MYC* is not altered in either the FH or FL subgroups, suggesting that *MYC* activation might not be driven by changes in gene expression levels, but by other mechanisms, such as amplifications or translocations.¹⁸ *FOXM1* was also a predominant regulator, and it was interconnected with another

gene network hub that included *MYC* (Figure 4). All of the satellite genes in the gene network participate in the cell cycle, cellular growth and proliferation, and the DNA repair system, which corresponds to the well-known activities of *FOXM1* and *MYC*.^{18,19} These results indicate that activation of the *FOXM1*-*MYC* signaling network may be a key event associated with a poor prognosis in HCC.

To identify an upstream regulator of the *FOXM1*-*MYC* signaling network, we used the path-exploring function of the IPA tool and observed the functional connectivity between *MYC* and miR-34a; *MYC* is a downstream effector of miR-34a (Figure 4). miR-34a is reported as a direct transcriptional target of p53, and it is frequently downregulated in various types of cancer,^{20–22} including HCC.²¹ In the TCGA cohort, the expression level of miR-34a was significantly lower in the FH subgroup than in the FL subgroup ($P < 0.001$ by two-sample *t*-test; Supplementary Figure 3).

In addition, the close examination of gene networks revealed that *CDK1* was a common downstream effector controlled by *FOXM1*, *MYC* and miR-34a (Figure 4). *CDK1* has previously been reported to play an important role in cell cycle regulation.²³

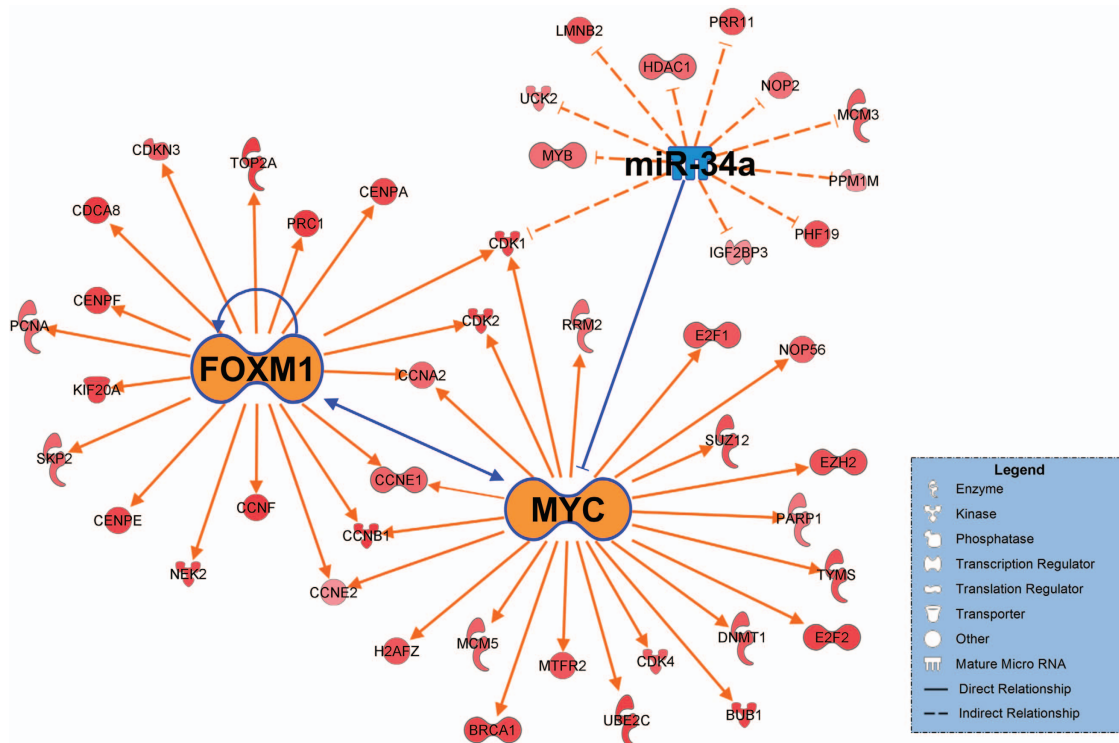


Figure 4 The putative signaling pathway composed of *FOXM1*, *MYC* and miR-34a. Upregulated genes in the *FOXM1*-high (FH) subgroup are indicated in red. The intensity of color is indicative of the degree of overexpression. Orange- or blue-colored elements indicate predicted activation or inhibition, respectively. Each line and arrow represents the functional and physical interactions between the genes and the direction of regulation reported in the literature. The networks were generated using the Ingenuity Pathways Analysis tool (www.ingenuity.com).

Thus, *CDK1* activation might account for the poorer prognosis of the FH subgroup than the FL subgroup. Among the other satellite genes in the gene network, *CCNB1* and *CCNE1*, which have been shown to play critical roles in cancer progression,^{12,13} were identified as common downstream effectors of *FOXM1* and *MYC*. Taken together, these results suggest that the complicated molecular interactions of multiple gene networks are associated with the poor prognosis of HCC patients.

DISCUSSION

FOXM1 (Forkhead box M1) is one of the most commonly overexpressed genes in various cancer types, based on genome-wide gene expression profile analysis. In addition, it has been shown that the overexpression of *FOXM1* is associated with aggressive tumor features and with the eventual prognosis of cancer patients, including those with HCC.⁷ Importantly, the prognosis of patients may be affected not only by the overexpression of *FOXM1* but also by other genes associated with its expression. Here we identified two distinct subgroups of cancer patients based on the gene expression signature of *FOXM1*. Survival analysis revealed a significant survival difference between the cancer patient subgroups. Finally, we identified a putative signaling pathway that might be responsible for the poor prognosis of HCC patients.

FOXM1, a major oncogenic transcription factor, plays an essential role in the regulation of a wide spectrum of biological

processes, suggesting that it has a fundamental role in tumor development and progression.²⁴ Although an association between the overexpression of *FOXM1* and patient prognosis has been observed in several studies,²⁵ the prognostic relevance of a co-expressed gene set of *FOXM1* has not been demonstrated. Through an estimation of prognosis using a co-expressed gene set of *FOXM1*, we discovered that an expression signature of *FOXM1* and its associated genes has prognostic significance in various cancer types. By applying hierarchical cluster analysis to the gene expression profile data from a pool of five different cancer types from the TCGA RNA-seq data set, we showed the presence of two subgroups based on a co-expressed gene set of *FOXM1*, regardless of tumor type. These data suggested that the gene expression signature of *FOXM1* could be used as a potential prognostic and predictive indicator in various cancers.

Gene network analysis of the gene expression signature of *FOXM1* identified a putative signaling pathway composed of *FOXM1*, *MYC* and miR-34a; this pathway is associated with the poor prognosis of HCC. Among several upstream candidates, *FOXM1* and *MYC* were revealed as the two predominant regulators of the overexpressed genes in the FH subgroup, which is consistent with previous studies that show their regulatory role in HCC patients with poor prognosis.^{7,26} miR-34a, an upstream regulator of *MYC*, was reported as a tumor suppressor gene by targeting many oncogenes related to

proliferation, apoptosis and invasion. A recent study suggested that miR-34a directly targets *FOXM1* and *MYC* via binding the 3' untranslated regions in liver cancer cells,²⁷ which indicates that expression changes in miR-34a might be a critical factor for the diagnosis of HCC patients.

By applying the co-expressed gene set of *FOXM1*, we were able to divide individuals with cancer into two subgroups that showed a significant difference in their clinical outcomes. These findings support the notion that *FOXM1* is a key regulator of genes associated with patient survival in various types of cancer. Furthermore, the good or poor prognostic subgroups defined by the gene expression signature of *FOXM1* could be exploited for use as a diagnostic tool to predict high-risk patients and to improve treatment responses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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