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LETTER TO THE EDITOR

Prognostic role of ring finger and WD repeat domain 3 and immune cell infiltration in hepatocellular carcinoma

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Abstract

We have found that the expression of ring finger and WD repeat domain 3 (RFWD3) is significantly higher in unpaired and paired hepatocellular carcinoma (HCC) tissues than in normal tissues. Moreover, this expression has a significant correlation with the infiltration level of 14 immune cell types and when the detected RFWD3 expression levels were grouped as high and low, a prominent difference was revealed for overall survival, disease-specific survival, and progression-free interval. Through statistical analysis (univariate Cox), we were also able to identify RFWD3 as an independent prognostic element for HCC, with RFWD3 having an ability to accurately predict HCC prognosis (area under the curve of 0.863). Finally, we have generated prognostic nomograms for probabilities of 1-, 3- and 5-year overall survival in HCC *via* integrating the factors of age, pathologic stage, alpha-fetoprotein level, and RFWD3 expression.

Key Words: Hepatocellular carcinoma; Ring finger and WD repeat domain 3; Immune cell infiltration; Bioinformatics

Core Tip: We have discovered that ring finger and WD repeat domain 3 (RFWD3) expression is remarkably higher in tumor tissues compared to corresponding non-tumor tissues, regardless of hepatocellular carcinoma (HCC) tissue type (unpaired or paired). The RFWD3 expression also showed a significant correlation with the infiltration level of 14 immune cell types and was identified as an independent prognostic element in HCC by univariate Cox regression analysis. Our collective findings suggest that RFWD3 has the ability to accurately predict prognosis of HCC.

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TO THE EDITOR

We perused the recently published paper by Liang *et al*[1] with much interest. The authors reported on their assessments of ring finger and WD repeat domain 3 (RFWD3) expression levels in hepatocellular carcinoma (HCC) patients. Their findings included RFWD3 effects on HCC prognosis, the processes of proliferation, invasion and metastasis, and the underlying mechanisms, specifically regulation *via* the Wnt/β-catenin signaling pathway. We have a particular appreciation for these authors' novel investigation into the prognostic implication of RFWD3 in HCC as we have also discovered that the expression of RFWD3 is prominently higher in both unpaired and paired HCC tissues from HCC patients than in their corresponding normal tissues (Figure 1A and B).

According to the current literature, cancer cells, endothelial cells, stromal cells, immune cells, and cancer-associated fibroblasts cells all exist in the tumor microenvironment (TME)[3,4]. While the TME is known to play crucial roles in development, invasion and metastasis of HCC, the immune escape of HCC cells has yet to be fully understood and continues to complicate cancer treatment[5]. Due to the ongoing and well-known limitations of chemotherapy in general, immunotherapies are a hot topic of bench and clinical research. This newly emerging cancer therapy exploits immune cells both inside and outside the TME to target and attack cancer cells; its demonstrated advantages are high specificity and low side-effects[6]. The power of this therapeutic method's potential lies in the fact that different types of immune-related cells serve diverse roles; for HCC, the research into defining and developing those immune cells that inhibit/promote tumor processes has a long way to go[7].

Upon reading the report that Liang *et al*[1] found RFWD3 is able to affect the prognosis of HCC, we tested a hypothesis that the expression of RFWD3 may be associated with immune cell infiltration in HCC. Detailed information is shown in Table 1. Following our initial positive data, we systematically explored the correlation between RFWD3 expression and infiltration level of 24 immune cell types, using a single-sample gene set analysis (also known as ssGSEA) algorithm and Spearman coefficient correlation analysis[8]. We found that RFWD3 expression has a remarkable correlation with the infiltration level of 14 immune cell types (Figure 2A). Among them, RFWD3 expression was positively associated with the infiltration level of T helper (Th) cells in general, Th2 cells in particular, T follicular helper (TFH) cells, T central memory (Tcm) cells, activated dendritic cells (DCs), natural killer (NK) $CD56^{bright}$ cells, and eosinophils (all $P < 0.05$; Figure 2B-H). There were negative associations with cytotoxic cells, DCs, plasmacytoid DCs (pDCs), neutrophils, T gamma delta (Tgd) cells, T regulatory cells (Tregs), and Th17 cells (all $P < 0.05$; Figure 2I-O). We hope our findings will encourage further investigations into RFWD3 as an HCC immunotherapy. Detailed information on this aspect is presented in Table 2.

Importantly, we agree with the finding of Liang *et al*[1] that indicates higher RFWD3 expression is related to worse overall survival (OS) in HCC. We have found that OS, disease-free survival, and progression-free interval were prominently shorter in HCC patient tissues with high RFWD3 expression than in those with low RFWD3 expression (all $P < 0.05$; Figure 3A-C). Our further statistical analysis *via* univariate Cox regression identified RFWD3 as an independent prognostic element for HCC (Table 3). Generation of the receiver operating characteristic curve showed that RFWD3 has the ability to accurately predict prognosis in HCC (area under the curve of 0.863). Finally, we generated prognostic nomograms for probabilities of 1-, 3- and 5-year OS in HCC *via* integrating the factors of age, pathologic stage, alpha-fetoprotein level, and RFWD3 expression; each element was assigned a score according to its contribution to survival (Figure 3E).

Ultimately, our new findings highlight that the research of Liang *et al*[1] is worthy of attention and that subsequent efforts to build upon it, such as our related discoveries, may promote the next generation of effective and safe therapeutics, such as immunotherapies.

Table 1 Detailed statistical results of differential expression of ring finger and WD repeat domain 3 in hepatocellular carcinoma and normal tissues

Gene	Group	*n*	Minimum	Maximum	Median	IQR	Lower quartile	Upper quartile	Mean	SD	SE
RFWD3	Normal	50	0.504	1.504	0.98	0.251	0.883	1.133	1.013	0.208	0.029
	Tumor	374	0.62	3.5	1.544	0.755	1.245	2	1.647	0.559	0.029
	Normal	50	0.504	1.504	0.98	0.251	0.883	1.133	1.013	0.208	0.029
	Tumor	50	0.707	2.939	1.577	0.716	1.204	1.92	1.578	0.521	0.074

RFWD3: Ring finger and WD repeat domain 3; IQR: Interquartile range; SD: Standard deviation; SE: Standard error.

Table 2 Detailed information on the statistical correlation between ring finger and WD repeat domain 3 expression and immune cell infiltration

Gene	Immune cell type	Pearson's correlation coefficient	Pearson's *P* value	Spearman's correlation coefficient	Spearman's *P* value
RFWD3	Th2 cells	0.499	< 0.001	0.501	< 0.001
	Th cells	0.434	< 0.001	0.436	< 0.001
	Cytotoxic cells	-0.304	< 0.001	-0.314	< 0.001
	DCs	-0.281	< 0.001	-0.304	< 0.001
	pDCs	-0.261	< 0.001	-0.261	< 0.001
	Neutrophils	-0.210	< 0.001	-0.214	< 0.001
	TFH cells	0.226	< 0.001	0.213	< 0.001
	Tcm cells	0.187	< 0.001	0.164	0.002
	Tgd cells	-0.105	0.043	-0.142	0.006
	Tregs	-0.155	0.003	-0.121	0.019
	aDCs	0.141	0.006	0.114	0.027
	NK $CD56^{bright}$ cells	0.128	0.013	0.112	0.031
	Th17 cells	-0.170	< 0.001	-0.110	0.033
	Eosinophils	0.077	0.135	0.106	0.041
	Macrophages	0.096	0.063	0.071	0.171
	Th1 cells	0.090	0.081	0.064	0.214
	iDCs	-0.034	0.507	-0.061	0.241
	Mast cells	-0.053	0.309	-0.060	0.247
	CD8 T cells	-0.047	0.368	-0.058	0.260
	T cells	-0.013	0.796	-0.033	0.522
	Tem cells	0.085	0.100	0.020	0.704
	B cells	0.033	0.525	0.017	0.744
	NK cells	0.035	0.494	-0.012	0.810
	NK $CD56^{dim}$ cells	0.020	0.699	-0.001	0.979

aDCs: Activated dendritic cells; DCs: Dendritic cells; iDCs: Immature dendritic cells; NK: Natural killer; pDCs: Plasmacytoid dendritic cells; RFWD3: Ring finger and WD repeat domain 3; Tcm: T central memory; Tem: T effector memory; TFH: T follicular helper; Tgd: T gamma delta.

Statistical analysis

R statistical software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) was used for all statistical analyses. Wilcoxon rank-sum test was used to perform the differential expression analysis of RFWD3 between HCC samples and corresponding

Table 3 Univariate Cox regression analysis in hepatocellular carcinoma

Characteristics	Total, *n*	Univariate analysis	
		Hazard ratio (95%CI)	*P* value
Pathologic stage	349		
I	173		
II	86	1.417 (0.868-2.312)	0.164
III	85	2.734 (1.792-4.172)	< 0.001
IV	5	5.597 (1.726-18.148)	0.004
Child-Pugh grade	240		
A	218		
B	21	1.595 (0.757-3.361)	0.219
C	1	2.138 (0.294-15.544)	0.453
Fibrosis Ishak score	214		
0	75		
1/2	31	0.935 (0.437-2.002)	0.864
3/4	28	0.698 (0.288-1.695)	0.428
5/6	80	0.737 (0.410-1.325)	0.308
Histologic grade	368		
G1	55		
G2	178	1.162 (0.686-1.969)	0.576
G3	123	1.185 (0.683-2.057)	0.545
G4	12	1.681 (0.621-4.549)	0.307
RFWD3	373	1.557 (1.148-2.110)	0.004

CI: Confidence interval; RFWD3: Ring finger and WD repeat domain 3.

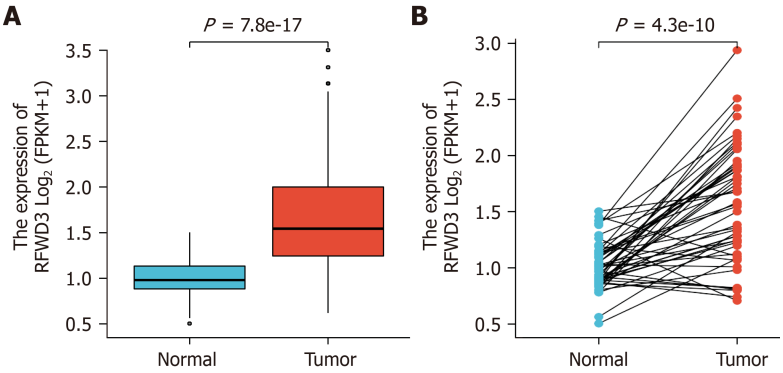

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Figure 1 Differential expression levels of ring finger and WD repeat domain 3 in hepatocellular carcinoma and normal tissues. A: Non-paired hepatocellular carcinoma (HCC) and normal samples; B: Paired HCC and normal samples. Data source: mRNA-Seq data from the Genotype-Tissue Expression project (GTEx) of The Cancer Genome Atlas processed through the Toil process in the UCSC Xena database. (https://xenabrowser.net/datapages/)[2].

normal samples, with results demonstrated by the "ggplot2" R package[10]. Survival analysis was carried out by log-rank test and univariate Cox regression. The association between RFWD3 expression and immune cell infiltration were performed by Spearman and Pearson analysis. Positive values of correlation coefficient indicate positive correlation, negative values indicate negative correlation.

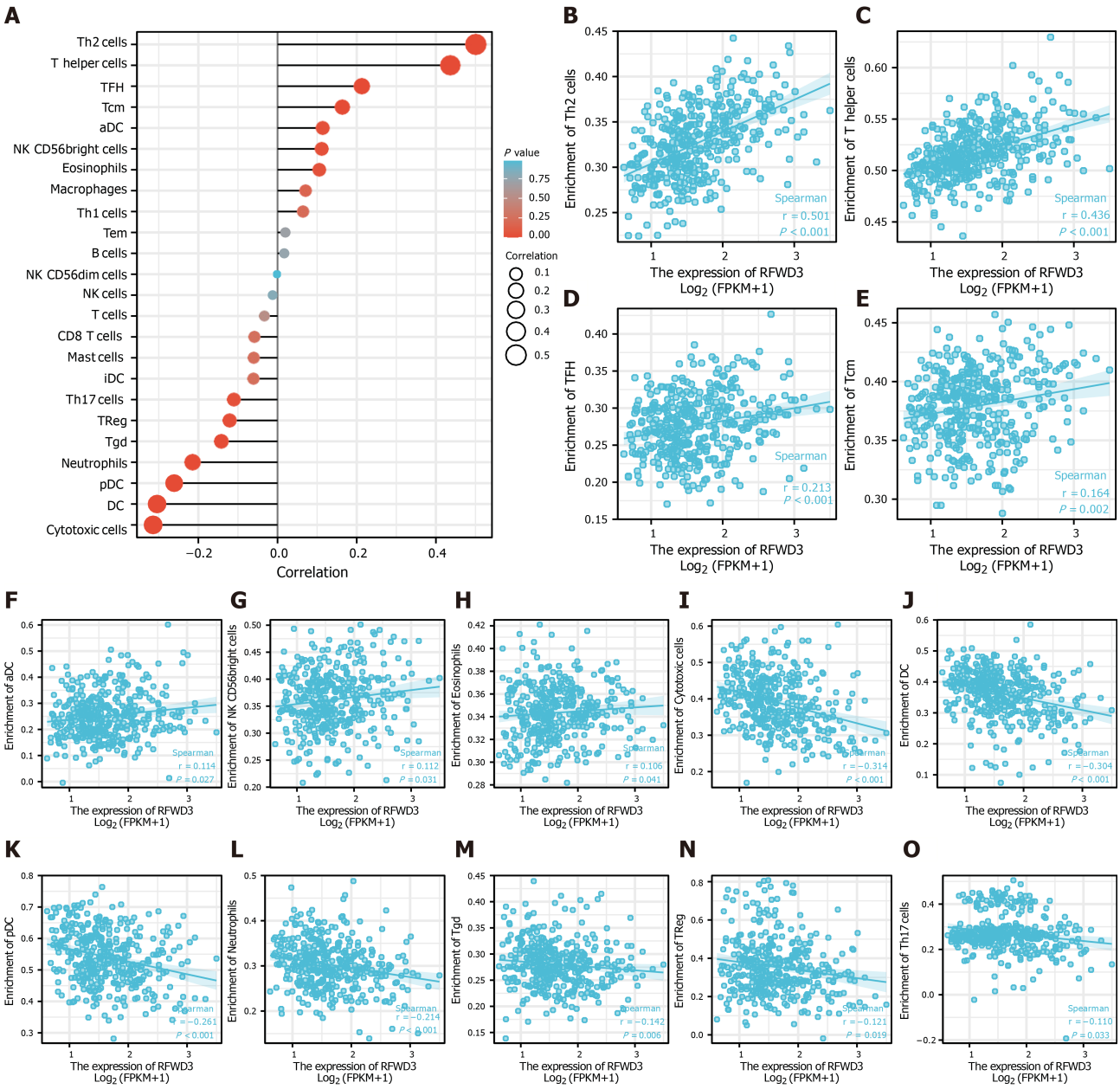

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Figure 2 Correlation analysis of ring finger and WD repeat domain 3 expression and immune cell infiltration in hepatocellular carcinoma.
A: Lollipop plot manifesting the correlation between ring finger and WD repeat domain 3 (RFWD3) expression and the infiltration level of 24 immune cell types; B-H: The infiltration levels of 7 immune cell types have significant positive correlation with RFWD3 expression; B: T helper (Th)2 cells; C: Th cells; D: T follicular helper (TFH) cells; E: T central memory (Tcm) cells; F: Activated dendritic cells (aDCs); G: Natural killer (NK) CD56^{bright} cells; H: Eosinophils; I-O: The infiltration levels of 7 immune cell types have significant negative correlation with RFWD3 expression; I: Cytotoxic cells; J: Dendritic cells (DCs); K: Plasmacytoid dendritic cells (pDCs); L: Neutrophils; M: T gamma delta (Tgd) cells; N: T regulatory cells (Tregs); O: Th17 cells.

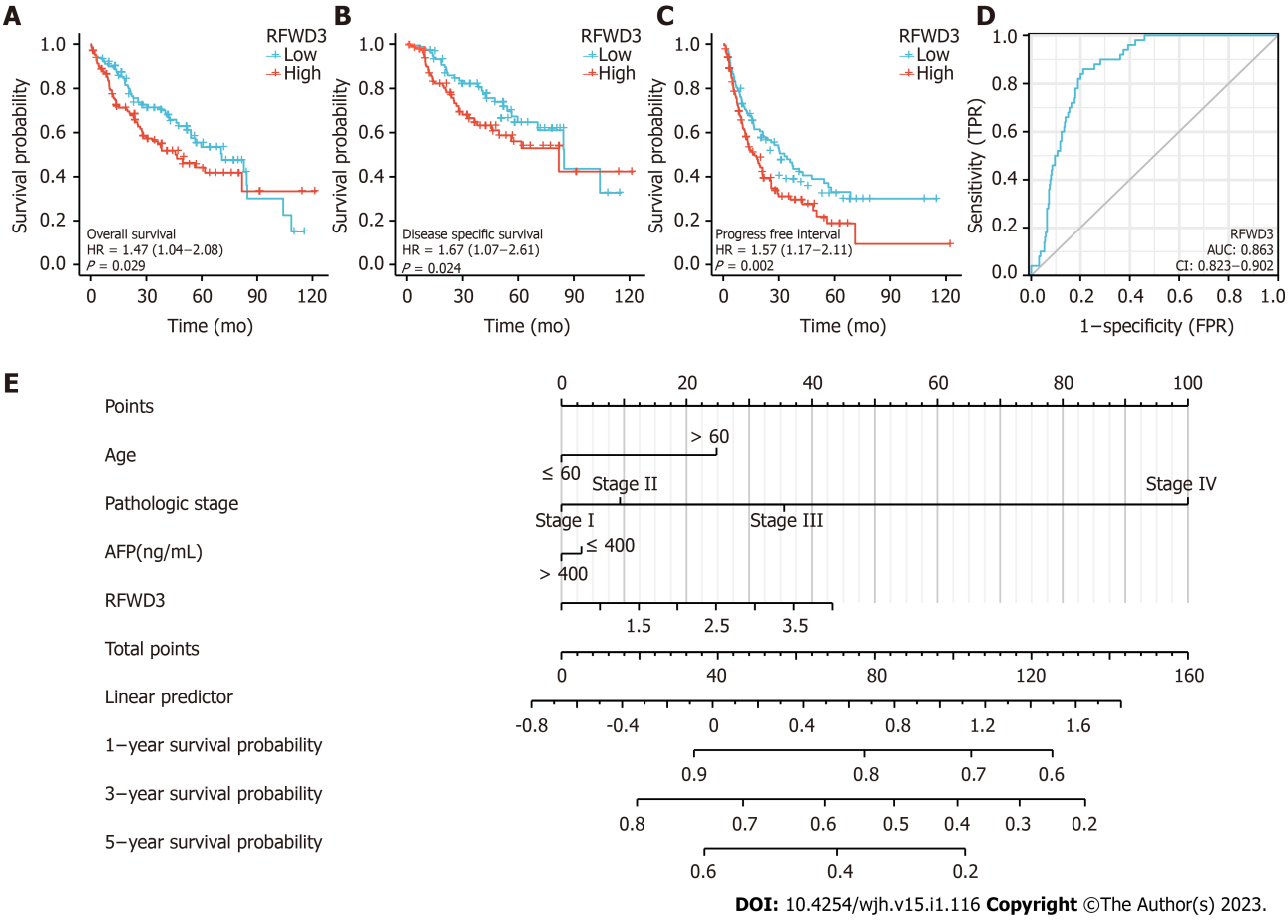

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Figure 3 Survival analysis of ring finger and WD repeat domain 3 in hepatocellular carcinoma and the nomogram for prognosis. A-C: Ring finger and WD repeat domain 3 (RFWD3) expression is related to overall survival, disease-specific survival (B) and progression-free interval (C)[9] in the The Cancer Genome Atlas-liver hepatocellular carcinoma (HCC) data; D: Receiver operating characteristic curves for the RFWD3 gene's prognosis predictive ability. The nomogram can predict 1-, 3- and 5-year overall survival of HCC based on clinicopathological features and the expression of RFWD3.

FOOTNOTES

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