Supplementary Table 1. The association between OPN expression and TAM (CD163) infiltration or PD-L1 expression in human HCC tissues.

		OPN		*P*
		Low(n=131)	High(n=55)	
CD163	Low(n=137)	124	13	<0.001
	High(n=49)	7	42	
PD-L1	Low(n=134)	101	33	0.018
	High(n=52)	30	22	

Chi-square test. $P < 0.05$ was considered statistically significant.

Supplementary Table 2. The association between OPN and clinicopathologic characteristics in HCC.

Variables		OPN expression		
		High (n=55)	Low(n=131)	*P*-value
Sex	Female	9	22	0.943
	Male	46	109	
Age (years)	≥50	27	65	0.948
	< 50	28	66	
HBV status	yes	49	113	0.599
	no	6	18	
Cirrhosis	Yes	44	101	0.663
	No	11	30	
AFP (ng/mL)	>20	35	82	0.893
	≤20	20	49	
ALT(U/L)	>75	3	12	0.397
	≤75	52	119	
Tumor size (cm)	>5	17	38	0.795
	≤5	38	93	
Tumor number	Multiple	8	12	0.279
	Single	47	119	
Tumor capsule	No	30	58	0.200
	Yes	25	73	
Tumor differentiation	Ⅰ + Ⅱ	30	107	**＜0.001**
	Ⅲ + Ⅳ	25	24	
Tumor thrombus	Yes	28	38	**0.004**
	No	27	93	
TNM stage	Ⅰ	45	82	**0.01**
	Ⅱ + Ⅲ	10	49	
BCLC stage	0 + A	8	32	0.134
	B + C + D	47	99	

The analysis was performed using Pearson chi-square test. A *P* value < 0.05 was considered statistically significant. Abbrebiations: HBV, hepatitis B virus; AFP, α-fetoprotein; ALT, alanine transaminase; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer staging system.

Supplementary Table 3. The association between PD-L1 and clinicopathologic characteristics in HCC.

Variables		PD-L1 expression		
		High (n=52)	Low(n=134)	P-value
Sex	Female	11	20	0.306
	Male	41	114	
Age (years)	≥50	26	66	0.927
	< 50	26	68	
HBV status	yes	49	113	0.071
	no	3	21	
Cirrhosis	Yes	15	130	**< 0.001**
	No	37	4	
AFP (ng/mL)	>20	34	83	0.663
	≤20	18	51	
ALT(U/L)	>75	6	9	0.278
	≤75	46	125	
Tumor size (cm)	>5	14	41	0.622
	≤5	38	93	
Tumor number	Multiple	8	12	0.204
	Single	44	122	
Tumor capsule	No	26	62	0.647
	Yes	26	72	
Tumor differentiation	Ⅰ + Ⅱ	33	104	**0.049**
	Ⅲ + Ⅳ	19	30	
Tumor thrombus	Yes	19	47	0.851
	No	33	87	
TNM stage	Ⅰ	34	93	0.597
	Ⅱ + Ⅲ	18	41	
BCLC stage	0 + A	11	29	0.942
	B + C + D	41	105	

The analysis was performed using Pearson chi-square test. A *P* value < 0.05 was considered statistically significant. Abbrebiations: HBV, hepatitis B virus; AFP, α-fetoprotein; ALT, alanine transaminase; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer staging system.

Supplementary Table 4. The association between TAM infiltration (CD163) and clinicopathologic characteristics in HCC.

Variables		TAM infiltration		
		High (n=49)	Low(n=137)	*P*-value
Sex	Female	8	23	0.941
	Male	41	114	
Age (years)	≥50	26	66	0.557
	< 50	23	71	
HBV status	yes	44	118	0.511
	no	5	19	
Cirrhosis	Yes	10	135	**< 0.001**
	No	39	2	
AFP (ng/mL)	>20	30	87	0.777
	≤20	19	50	
ALT(U/L)	>75	4	11	0.976
	≤75	45	126	
Tumor size (cm)	>5	17	38	0.360
	≤5	32	99	
Tumor number	Multiple	8	12	0.142
	Single	41	125	
Tumor capsule	No	24	64	0.785
	Yes	25	73	
Tumor differentiation	Ⅰ + Ⅱ	28	109	**0.002**
	Ⅲ + Ⅳ	21	28	
Tumor thrombus	Yes	26	40	**0.003**
	No	23	97	
TNM stage	Ⅰ	38	21	**< 0.001**
	Ⅱ + Ⅲ	11	116	
BCLC stage	0 + A	7	33	0.152
	B + C + D	42	104	

The analysis was performed using Pearson chi-square test. A *P* value < 0.05 was considered statistically significant. Abbrebiations: HBV, hepatitis B virus; AFP, α-fetoprotein; ALT, alanine transaminase; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer staging system.

Supplementary Table 5. Univariate and multivariate analyses of Overall survival (OS) in HCC.

Features	Overall Survival			
	Univariate *P*	Multivariate		
		HR	95% CI	*P*
Sex				
Male vs. Female	0.266			NA
Age				
>50 vs. ≤50	0.582			NA
HBsAg				
Positive vs. Negative	0.260			NA
ALT				
>75U/L vs. ≤75U/L	0.474			NA
AFP				
20ng/ml vs. ≤20ng/ml	0.070			NA
Liver cirrhosis				
Yes vs. No	0.654			NA
Tumor size				
>5cm vs. ≤5cm	**0.002**	**1.787**	**1.141 ~ 2.800**	**0.011**
Tumor thrombus				
Yes vs. No	**< 0.001**	**1.811**	**1.155 ~ 2.840**	**0.010**
Tumor number				
multiple vs. single	**0.003**	1.700	0.920 ~ 3.140	0.090
Tumor encapsulation				
Yes vs. No	0.053			NA
Tumor differentiation				
III + IV vs. I + II	**0.006**	1.227	0.735 ~ 2.051	0.434
TNM stage				
II + III vs. I	0.169			NA
BCLC stage				
B + C + D vs. 0 + A	**0.024**	1.168	0.599 ~ 2.279	0.648
OPN expression				
High vs. Low	**0.002**	**1.654**	**1.054 ~ 2.594**	**0.028**
CD163 expression				

High vs. Low	**0.037**	0.557	0.272 ~ 1.139	0.109
PD-L1 expression				
High vs. Low	**< 0.001**	**2.609**	**1.667 ~ 4.082**	**< 0.001**

Univariate analysis, Cox proportional hazards regression model. Bold values indicate $p<0.05$.

Abbrebiations: HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; ALT, alanine transaminase; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; HR, hazard ratio; NA, not adopt.

Supplementary Table 6. Univariate and multivariate analyses of Recurrence-free survival (DFS) in HCC.

Features	Time to Recurrence			
	Univariate *P*	Multivariate		
		HR	95% CI	*P*
Sex				
Male vs. Female	0.348			NA
Age				
>50 vs. ≤50	0.730			NA
HBsAg				
Positive vs. Negative	**0.05**	1.482	0.762 ~ 2.882	0.246
ALT				
>75U/L vs. ≤75U/L	0.976			NA
AFP				
20ng/ml vs. ≤20ng/ml	0.120			NA
Liver cirrhosis				
Yes vs. No	0.570			NA
Tumor size				
>5cm vs. ≤5cm	**0.002**	**1.701**	**1.118 ~ 2.587**	**0.013**
Tumor thrombus				
Yes vs. No	**0.006**	1.472	0.973 ~ 2.228	0.067
Tumor number				
multiple vs. single	**0.039**	1.211	0.640 ~ 2.292	0.555
Tumor encapsulation				
Yes vs. No	**0.027**	1.398	0.938 ~ 2.085	0.100
Tumor differentiation				
III + IV vs. I + II	**0.003**	1.291	0.806 ~ 2.066	0.288
TNM stage				
II + III vs. I	0.242			NA
BCLC stage				
B + C + D vs. 0 + A	**0.040**	1.307	0.728 ~ 2.346	0.370
OPN expression				
High vs. Low	**0.006**	1.449	0.955 ~ 2.198	0.081

CD163 expression				
High vs. Low	0.067			NA
PD-L1 expression				
High vs. Low	**< 0.001**	**2.004**	**1.319 ~ 3.046**	**< 0.001**

Univariate analysis, Cox proportional hazards regression model. Bold values indicate $p<0.05$. Abbrebiations: AFP, α-fetoprotein; HBsAg, hepatitis B surface antigen; ALT, alanine transaminase; TNM, tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; HR, hazard ratio; NA, not adopt.

Supplementary Table 7. List of cytokines differentially expressed between Hep3B-OPN/Macrophages co-cultures and Hep3B-control/Macrophages co-cultures using a RayBio Human Cytokine Antibody Array.

Cytokines	Hep3B-OPN/co-culture	Hep3B-control/co-culture	Fold change
POS	8856.0000	8856.0000	
NEG	0.0000	0.0000	
ENA-78	16892.1667	19982.1586	0.8454
G-CSF	128.1667	116.7918	1.0974
GM-CSF	1384.1667	793.4255	**1.7445**
GRO	16448.6667	27919.7508	0.5891
GRO-a	4874.6667	15999.7116	0.3047
I-309	179.6667	175.0359	1.0265
IL-1alpha	166.1667	151.3742	1.0977
IL-1beta	263.6667	276.9633	0.9520
IL-2	148.1667	125.4374	1.1812
IL-3	557.1667	568.1843	0.9806
IL-4	146.6667	170.0306	0.8626
IL-5	117.1667	116.7918	1.0032
IL-6	185.1667	130.4427	1.4195
IL-7	250.6667	228.2748	1.0981
IL-8	23598.1667	22578.5758	1.0452
IL-10	243.1667	275.5982	0.8823
IL12-p40	447.6667	438.9550	1.0198
IL-13	115.1667	99.0455	1.1628
IL-15	368.1667	348.8585	1.0553
IFN-gamma	220.1667	180.0413	1.2229
MCP-1	771.6667	5618.1383	0.1374
MCP-2	659.6667	728.3558	0.9057
MCP-3	360.1667	236.0103	**1.5261**
M-CSF	1056.1667	580.4702	**1.8195**
MDC	394.6667	415.7483	0.9493
MIG	209.1667	168.2105	1.2435
MIP-1-delta	4789.6667	6819.8799	0.7023
RANTES	829.1667	1363.5816	0.6081
SCF	667.1667	414.8382	**1.6083**
SDF-1	369.1667	354.7739	1.0406
TARC	339.1667	408.4678	0.8303
TGF-beta 1	591.1667	387.5255	1.5255
TNF-alpha	10.6667	87.6697	0.1217
TNF-beta	288.6667	180.0413	**1.6033**
EGF	1094.1667	367.0598	**2.9809**
IGF-1	408.1667	367.5148	1.1106

Angiogenin	7915.6667	7142.9532	1.1082
Oncostatin M	1540.1667	1348.1105	1.1425
TPO	278.1667	223.2694	1.2459
VEGF	854.1667	772.9490	1.1051
PDGF-BB	255.6667	2841.0731	0.0900
Leptin	235.6667	195.5124	1.2054

Supplementary Table 8. Primer sequences used in the study.

Primer name	Sequences	
Primer for qPCR:		
mTNF-α	CAGGCGGTGCCTATGTCTC	CGATCACCCCGAAGTTCAGTAG
mTbx21	AGCAAGGACGGCGAATGTT	GTGGACATATAAGCGGTTCCC
mIFIT1	GCCTATCGCCAAGATTTAGATGA	TTCTGGATTTAACCGGACAGC
mIFIT2	GGAGAGCAATCTGCGACAG	GCTGCCTCATTTAGACCTCTG
mCXCL10	CCAAGTGCTGCCGTCATTTTC	GGCTCGCAGGGATGATTTCAA
mIL-6	CTGCAAGAGACTTCCATCCAG	AGTGGTATAGACAGGTCTGTTGG
mIL-12b	ATGGAGTCATAGGCTCTGGAAA	CCGGAGTAATTTGGTGCTTCAC
mCXCL1	CTGGGATTCACCTCAAGAACATC	CAGGGTCAAGGCAAGCCTC
mPD-1	CAGCTTGTCCAACTGGTCG	GCTCAAACCATTACAGAAGGCG
mPD-L1	GCTCCAAAGGACTTGTACGTG	TGATCTGAAGGGCAGCATTTC
mPD-L2	CTGCCGATACTGAACCTGAGC	GCGGTCAAAATCGCACTCC
mCTLA-4	CATGGTGTCGCCAGCTTTC	GGTAATCTAGGAAGCCCACTGTA
mTIM-3	TCAGGTCTTACCCTCAACTGTG	GGCATTCTTACCAACCTCAAACA
mLAG-3	CTGGGACTGCTTTGGGAAG	GGTTGATGTTGCCAGATAACCC
mArg1	CTCCAAGCCAAAGTCCTTAGAG	GGAGCTGTCATTAGGGACATCA
mIL-10	CTTACTGACTGGCATGAGGATC	GCAGCTCTAGGAGCATGTGG
miNOS	ACATCGACCCGTCCACAGTAT	CAGAGGGGTAGGCTTGTCTC
mIL-1b	GAAATGCCACCTTTTGACAGTG	TGGATGCTCTCATCAGGACAG
mCD206	CTCTGTTCAGCTATTGGACGC	TGGCACTCCCAAACATAATTTGA
hIL-1b	ACCAAACCTCTTCGAGGCAC	AGCCATCATTTCACTGGCGA

hIL-12b	GTGCCCTGCAGTTAGGTTCT	ATGGCAACTTGAGAGCTGGA
hTNF-α	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
hCD206	GCAGGGCCCTCTTAAGAT	AACACGGGAACCAAAGTC
hIL-4	CTCACATTGTCACTGCAAATCG	TGTCTGTTACGGTCAACTCGGT
hCSF1	TCCAGCCAAGATGTGGTGAC	AGTTCCCTCAGAGTCCTCCC
actin	CATGTACGTTGCTATCCAGGC	CTCCTTAATGTCACGCACGAT
Primers for shRNA		
mOPN:		
shRNA-1	CCGGGAGGTCAAAGTCTAGGAGTT TCTCGAGAAACTCCTAGACTTTGAC CTCTTTTTG	AATTCAAAAAGAGGTCAAAG TCTAGGAGTTTCTCGAGAAAC TCCTAGACTTTGACCTC
shRNA-2	CCGGCTCTTAGCTTAGTCTGTTGTT CTCGAGAACAACAGACTAAGCTAA GAGTTTTTG	AATTCAAAAACTCTTAGCTTA GTCTGTTGTTCTCGAGAACAA CAGACTAAGCTAAGAG
shRNA-3	CCGGAGGATGACTTTAAGC AAGAAACTCGAGTTTCTTGC TTAAAGTCATCCTTTTTTG	AATTCAAAAAAGGATGACTTT AAGCAAGAAACTCGAGTTTCT TGCTTAAAGTCATCCT
hCSF1:		
shRNA-1	CCGGTCTCCTGGTACAAGACATAATCTCG AGATTATGTCTTGTACCAGGAGATTTTT	AATTCAAAAATCTCCTGGTACAAGACATA ATCTCGAGATTATGTCTTGTACCAGGAGA
shRNA-2	CCGGAGATCCAGTGTGCTACCTTAACTCG AGTTAAGGTAGCACACTGGATCTTTTTTG	AATTCAAAAAAGATCCAGTGTGCTACCTTA ACTCGAGTTAAGGTAGCACACTGGATCT
p65:		
shRNA-1	CCGGGCCTTAATAGTAGGGTAAGTTCTCG AGAACTTACCCTACTATTAAGGCTTTTTG	AATTCAAAAAGCCTTAATAGTAGGGTAAG TTCTCGAGAACTTACCCTACTATTAAGGC
shRNA-2	CCGGCACCATCAACTATGATGAGTTCTCG AGAACTCATCATAGTTGATGGTGTTTTTG	AATTCAAAAACACCATCAACTATGATGAG TTCTCGAGAACTCATCATAGTTGATGGTG

Supplementary Table 9. Primary antibodies for WB, IHC and IF.

Protein	Concentration	Test	Company
PE anti-mouse FoxP3 Antibody	2.5 μl/ million cells	FCM	BioLegend
FITC anti-mouse CD3 Antibody	5 μl/ million cells	FCM	BioLegend
PerCP/Cy5.5 anti-mouse CD4 Antibody	5 μl/ million cells	FCM	BioLegend
APC anti-mouse CD8 Antibody	5 μl/ million cells	FCM	BioLegend
APC anti-mouse F4/80 Antibody	5 μl/ million cells	FCM	BioLegend
PerCP/Cy5.5 anti-mouse CD11b Antibody	5 μl/ million cells	FCM	BioLegend
PE anti-mouse Ly6c Antibody	2.5 μl/ million cells	FCM	BioLegend
PE anti-mouse CD274 Antibody	2.5 μl/ million cells	FCM	BioLegend
FITC anti-mouse CD45 Antibody	5 μl/ million cells	FCM	BioLegend
PE anti-mouse CD279 Antibody	2.5 μl/ million cells	FCM	BioLegend
PE anti-mouse NK1.1 Antibody	2.5 μl/ million cells	FCM	BioLegend
APC anti-mouse CD19 Antibody	5 μl/ million cells	FCM	BioLegend
FITC anti-human CD45 Antibody	5 μl/ million cells	FCM	BioLegend
PE anti-human CD274 Antibody	2.5 μl/ million cells	FCM	BioLegend
FITC anti-human CD68 Antibody	5 μl/ million cells	FCM	BioLegend
APC anti-human CD163 Antibody	5 μl/ million cells	FCM	BioLegend
FITC anti-human CD206 Antibody	5 μl/ million cells	FCM	BioLegend
AKT	1:2000	WB	Cell Signaling Technology
p-AKT	1:1000	WB	Cell Signaling Technology
ERK	1:2000	WB	Cell Signaling Technology
p-ERK	1:1000	WB	Cell Signaling Technology
P38	1:2000	WB	Cell Signaling Technology
p-P38	1:1000	WB	Cell Signaling Technology
p65	1:1000	WB	Cell Signaling Technology
p-p65	1:500	WB	Cell Signaling Technology
PD-L1	1:1000	WB	Abcam
GAPDH	1:3000	WB	Cell Signaling Technology
LaminB	1:1000	WB	Abcam
OPN	1:1000	WB	Abcam
p-p65	1:25	IF	Cell Signaling Technology
CD8	1:25	IF	BD Bioscience
Tunel	1:50	IHC	Abcam

CD34	1:50	IHC	Abcam
PD-L1	1:50	IHC	Abcam
F4/80	1:25	IHC	Abcam
CD206	1:50	IHC	Abcam
CD4	1:50	IHC	BD Bioscience
CD8	1:50	IHC	BD Bioscience
OPN	1:50	IHC	Abcam
CD163	1:25	IHC	Abcam
cleaved caspase 3	1:100	IHC	Abcam
Ki-67	1:100	IHC	Abcam

Abbreviations: FCM, flow cytometry; WB, western blot; IHC, immunohistochemistry; IF, immunofluorescence