

The Unfolded Protein Response Is Associated with Cancer Proliferation and Worse Survival in Hepatocellular Carcinoma

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Table S1. Member genes of the Unfolded protein response score.

Gene Name	Gene Description
<i>ALDH18A1</i>	aldehyde dehydrogenase 18 family member A1
<i>ARFGAP1</i>	ADP ribosylation factor GTPase activating protein 1
<i>ASNS</i>	asparagine synthetase
<i>ATF3</i>	activating transcription factor 3
<i>ATF4</i>	activating transcription factor 4
<i>ATF6</i>	activating transcription factor 6
<i>ATP6V0D1</i>	ATPase H ⁺ transporting V0 subunit d1
<i>BAG3</i>	BAG cochaperone 3
<i>BANF1</i>	BAF nuclear assembly factor 1
<i>CALR</i>	calreticulin
<i>CCL2</i>	C-C motif chemokine ligand 2
<i>CEBPB</i>	CCAAT enhancer binding protein beta
<i>CEBPG</i>	CCAAT enhancer binding protein gamma
<i>CHAC1</i>	ChaC glutathione specific gamma-glutamylcyclotransferase 1
<i>CKS1B</i>	CDC28 protein kinase regulatory subunit 1B
<i>CNOT2</i>	CCR4-NOT transcription complex subunit 2
<i>CNOT4</i>	CCR4-NOT transcription complex subunit 4
<i>CNOT6</i>	CCR4-NOT transcription complex subunit 6
<i>CXXC1</i>	CXXC finger protein 1
<i>DCP1A</i>	decapping mRNA 1A
<i>DCP2</i>	decapping mRNA 2
<i>DCTN1</i>	dynactin subunit 1
<i>DDIT4</i>	DNA damage inducible transcript 4
<i>DDX10</i>	DEAD-box helicase 10
<i>DKC1</i>	dyskerin pseudouridine synthase 1
<i>DNAJA4</i>	DnaJ heat shock protein family (Hsp40) member A4
<i>DNAJB9</i>	DnaJ heat shock protein family (Hsp40) member B9
<i>DNAJC3</i>	DnaJ heat shock protein family (Hsp40) member C3
<i>EDC4</i>	enhancer of mRNA decapping 4
<i>EDEM1</i>	ER degradation enhancing alpha-mannosidase like protein 1
<i>EEF2</i>	eukaryotic translation elongation factor 2
<i>EIF2AK3</i>	eukaryotic translation initiation factor 2 alpha kinase 3
<i>EIF2S1</i>	eukaryotic translation initiation factor 2 subunit alpha
<i>EIF4A1</i>	eukaryotic translation initiation factor 4A1
<i>EIF4A2</i>	eukaryotic translation initiation factor 4A2
<i>EIF4A3</i>	eukaryotic translation initiation factor 4A3
<i>EIF4E</i>	eukaryotic translation initiation factor 4E
<i>EIF4EBP1</i>	eukaryotic translation initiation factor 4E binding protein 1
<i>EIF4G1</i>	eukaryotic translation initiation factor 4 gamma 1
<i>ERN1</i>	endoplasmic reticulum to nucleus signaling 1
<i>ERO1L</i>	endoplasmic reticulum oxidoreductase 1 alpha
<i>EXOC2</i>	exocyst complex component 2
<i>EXOSC1</i>	exosome component 1
<i>EXOSC10</i>	exosome component 10
<i>EXOSC2</i>	exosome component 2
<i>EXOSC4</i>	exosome component 4
<i>EXOSC5</i>	exosome component 5

<i>EXOSC9</i>	exosome component 9
<i>FKBP14</i>	FKBP prolyl isomerase 14
<i>FUS</i>	FUS RNA binding protein
<i>GEMIN4</i>	gem nuclear organelle associated protein 4
<i>GOSR2</i>	golgi SNAP receptor complex member 2
<i>H2AFX</i>	H2A.X variant histone
<i>HERPUD1</i>	homocysteine inducible ER protein with ubiquitin like domain 1
<i>HSP90B1</i>	heat shock protein 90 beta family member 1
<i>HSPA5</i>	heat shock protein family A (Hsp70) member 5
<i>HSPA9</i>	heat shock protein family A (Hsp70) member 9
<i>HYOU1</i>	hypoxia up-regulated 1
<i>IARS</i>	isoleucyl-tRNA synthetase 1
<i>IFIT1</i>	interferon induced protein with tetratide repeats 1
<i>IGFBP1</i>	insulin like growth factor binding protein 1
<i>IMP3</i>	IMP U3 small nucleolar ribonucleoprotein 3
<i>KDEL3</i>	KDEL endoplasmic reticulum protein retention receptor 3
<i>KHSRP</i>	KH-type splicing regulatory protein
<i>KIF5B</i>	kinesin family member 5B
<i>LSM1</i>	LSM1 homolog, mRNA degradation associated
<i>LSM4</i>	LSM4 homolog, U6 small nuclear RNA and mRNA degradation associated
<i>MTHFD2</i>	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2
<i>NFYA</i>	nuclear transcription factor Y subunit alpha
<i>NFYB</i>	nuclear transcription factor Y subunit beta
<i>NHP2</i>	NHP2 ribonucleoprotein
<i>NOLC1</i>	nucleolar and coiled-body phosphoprotein 1
<i>NOP14</i>	NOP14 nucleolar protein
<i>NOP56</i>	NOP56 ribonucleoprotein
<i>NPM1</i>	nucleophosmin 1
<i>OBFC2A</i>	nucleic acid binding protein 1
<i>PAIP1</i>	poly(A) binding protein interacting protein 1
<i>PARN</i>	poly(A)-specific ribonuclease
<i>PDIA5</i>	protein disulfide isomerase family A member 5
<i>PDIA6</i>	protein disulfide isomerase family A member 6
<i>POP4</i>	POP4 homolog, ribonuclease P/MRP subunit
<i>PREB</i>	prolactin regulatory element binding
<i>PSAT1</i>	phosphoserine aminotransferase 1
<i>RPS14</i>	ribosomal protein S14
<i>RRP9</i>	ribosomal RNA processing 9, U3 small nucleolar RNA binding protein
<i>SDAD1</i>	SDA1 domain containing 1
<i>SEC11A</i>	SEC11 homolog A, signal peptidase complex subunit
<i>SEC31A</i>	SEC31 homolog A, COPII coat complex component
<i>SERP1</i>	stress associated endoplasmic reticulum protein 1
<i>SHC1</i>	SHC adaptor protein 1
<i>SKIV2L2</i>	Mtr4 exosome RNA helicase
<i>SLC1A4</i>	solute carrier family 1 member 4
<i>SLC30A5</i>	solute carrier family 30 member 5
<i>SLC7A5</i>	solute carrier family 7 member 5
<i>SPCS1</i>	signal peptidase complex subunit 1
<i>SPCS3</i>	signal peptidase complex subunit 3
<i>SRPR</i>	SRP receptor subunit alpha
<i>SRPRB</i>	SRP receptor subunit beta
<i>SSR1</i>	signal sequence receptor subunit 1
<i>STC2</i>	stanniocalcin 2
<i>TARS</i>	threonyl-tRNA synthetase 1
<i>TATDN2</i>	TatD DNase domain containing 2
<i>TSPYL2</i>	TSPY like 2
<i>TTC37</i>	tetratricopeptide repeat domain 37
<i>TUBB2A</i>	tubulin beta 2A class IIa
<i>VEGFA</i>	vascular endothelial growth factor A
<i>WFS1</i>	wolframin ER transmembrane glycoprotein

<i>WIP1</i>	WD repeat domain, phosphoinositide interacting 1
<i>XBP1</i>	X-box binding protein 1
<i>XPOT</i>	exportin for tRNA
<i>YIF1A</i>	Yip1 interacting factor homolog A, membrane trafficking protein
<i>YWHAZ</i>	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta
<i>ZBTB17</i>	zinc finger and BTB domain containing 17

Table S2. Univariate and multivariate analysis with overall survival in the TCGA cohort.

	HR	95%CI		<i>p</i>		HR	95%CI		<i>p</i>	
>60 vs. 60 ≥	1.26	0.89	1.79	0.189						
WHITE vs. Others	1.24	0.87	1.76	0.238						
III/IV vs. I/II	2.40	1.65	3.48	<0.001	*	2.19	1.50	3.20	<0.001	*
G3/G4 vs. G1/G2	1.11	0.78	1.58	0.565						
High vs. Low	1.98	1.39	2.82	<0.001	*	1.59	1.09	2.32	0.016	*

Table S3. Cox regression analysis of cell proliferation-related gene sets.

DFS	HR	95%CI		p
UPR	3.45	1.81	6.60	<0.001
E2F	2.53	1.69	3.78	<0.001
G2M	2.58	1.68	3.95	<0.001
MYC v1	3.08	1.90	5.00	<0.001
MYC v2	2.89	1.80	4.65	<0.001
MITOTIC	2.21	1.33	3.69	0.002
MKI67	1.82	1.30	2.54	<0.001
DSS	HR	95%CI		p
UPR	6.21	2.65	14.55	<0.001
E2F	3.65	2.07	6.44	<0.001
G2M	3.86	2.12	7.03	<0.001
MYC v1	4.77	2.46	9.25	<0.001
MYC v2	3.32	1.76	6.27	<0.001
MITOTIC	3.27	1.63	6.55	<0.001
MKI67	2.43	1.53	3.86	<0.001
OS	HR	95%CI		p
UPR	5.67	2.91	11.05	<0.001
E2F	2.73	1.78	4.20	<0.001
G2M	2.85	1.81	4.51	<0.001
MYC v1	3.61	2.17	6.00	<0.001
MYC v2	2.87	1.75	4.72	<0.001
MITOTIC	2.44	1.43	4.16	0.001
MKI67	1.27	1.15	1.42	<0.001

Table S4. List of Software used in analysis.

Software	Version	Reference
R	4.1.0	-
GSEA	4.1.0	Subramanian A, et. al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci U S A. 2005 Oct 25;102(43):15545-50. doi: 10.1073/pnas.0506580102. Epub 2005 Sep 30.
GSVA	1.38.2	Hänzelmann S, et. al. GSVA: gene set variation analysis for microarray and RNA-seq data. BMC Bioinformatics. 2013 Jan 16;14:7. doi: 10.1186/1471-2105-14-7.
Microsoft Excel	16.0	Microsoft Windows 10

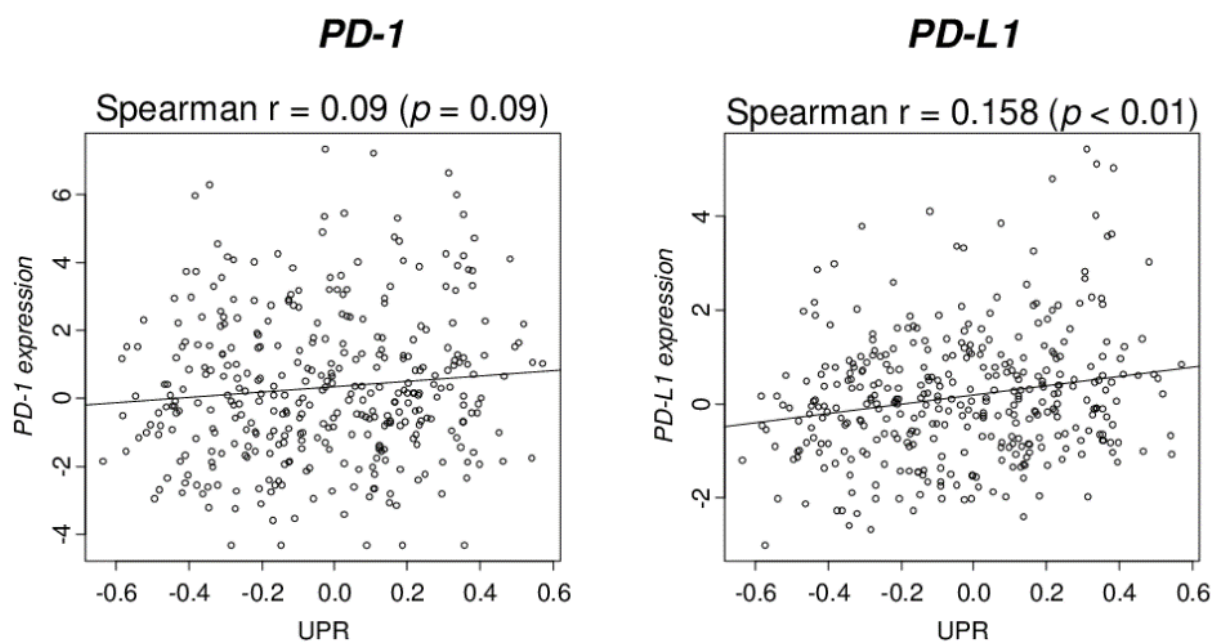


Figure S1. Co-relation curve of PD-1, PDL-1 expressions and UPR score.