

Supplementary Materials

Screening for lipid metabolism-related genes and identifying the therapeutic potential of ACACA for ER stress-related progression in hepatocellular carcinoma

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Supplementary Table 1. Sequence used in the manuscript

Name	Sequence (5' to 3')	
GAPDH	Forward	GGAGCGAGATCCCTCCAAAAT
	Reverse	GGCTGTTGTCATACTTCTCATGG
PPAR- γ	Forward	GGAAGACCACTCGCATTCCTT
	Reverse	GTAATCAGCAACCATTGGGTCA
FASN	Forward	GGAGGTGGTGATAGCCGGTAT
	Reverse	TGGGTAATCCATAGAGCCCAG
C/EBP- β	Forward	CTTCCTCTCCGACCTCTTCG
	Reverse	AGGCTCACGTAACCGTAGTC
ACACA	Forward	CTCCCGATTCATAATTGGGTCTG
	Reverse	TCGACCTTGTTTTACTAGGTGC

Supplementary Table 2. Antibodies used in this study

Antibody	Catalog Number	Company	Dilution	Application
Anti-human GRP78	ab32618	Abcam	1:200/1:1000	IHC/ WB
Anti-human XBP1	381720	Zenbio	1:500	WB
Anti-human PERK	C33E10	CST	1:1000	WB
Anti-human IRE1a	14C10	CST	1:1000	WB
Anti-human ATF6	BS6476	Bioworld	1:10000	WB
Anti-human FASN	C29G5	CST	1:1000	WB
Anti-human ACC1	21923-1-AP	Proteintech	1:100/1:1000	IHC/WB
Anti-human β -actin	66009-1-Ig	Proteintech	1:10000	WB
Anti-human GAPDH	GB15004-100	Servicebio	1:3000	WB

Supplementary Table 3. The most significant terms of GO and KEGG enrichment analyses (Top 5)

Ontology	ID	Description	GeneRatio	P value	P.adjust
BP	GO:0008202	steroid metabolic process	37/130	6.09e-35	8.06e-32
BP	GO:0010876	lipid localization	41/130	6.63e-35	8.06e-32
BP	GO:0016042	lipid catabolic process	35/130	5.75e-32	4.67e-29
BP	GO:0006631	fatty acid metabolic process	37/130	1.1e-31	6.67e-29
BP	GO:0016125	sterol metabolic process	27/130	1.26e-30	6.15e-28
CC	GO:0034358	plasma lipoprotein particle	11/131	4.06e-16	4.66e-14
CC	GO:1990777	lipoprotein particle	11/131	4.06e-16	4.66e-14
CC	GO:0032994	protein-lipid complex	11/131	1.11e-15	8.53e-14
CC	GO:0034364	high-density lipoprotein particle	9/131	8.55e-14	4.92e-12
CC	GO:0005811	lipid droplet	11/131	6.67e-11	3.07e-09
MF	GO:0005319	lipid transporter activity	15/131	4.58e-13	1.88e-10
MF	GO:0005496	steroid binding	12/131	6.24e-12	1.28e-09
MF	GO:0016705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	14/131	3.16e-11	4.33e-09
MF	GO:0004497	monooxygenase activity	11/131	1.77e-10	1.78e-08
MF	GO:0008395	steroid hydroxylase activity	8/131	2.17e-10	1.78e-08

KEGG	hsa03320	PPAR signaling pathway	17/101	1.53e-17	3.36e-15
KEGG	hsa04979	Cholesterol metabolism	14/101	6.9e-16	7.59e-14
KEGG	hsa00564	Glycerophospholipid metabolism	14/101	1.09e-11	7.97e-10
KEGG	hsa00600	Sphingolipid metabolism	10/101	6.7e-10	3.69e-08
KEGG	hsa04975	Fat digestion and absorption	9/101	1.88e-09	8.29e-08

Supplementary Table 4. Drug-Gene interactions for the 5core-DFRGs

Gene	Drug	Approved	Indication	Interaction score
ACACA	[125I]C3A (HUMAN)	No		2.282942228
	SQ007-5	No		2.282942228
	C3A	No		2.282942228
	OLUMACOSTAT GLASARETIL	No		1.141471114
	ORYZATENSIN	No		2.282942228
	C3A RECEPTOR AGONIST	No		2.282942228
	FLPLAR	No		2.282942228
	COMPOUND 4	No		2.282942228
	CASOXIN C	No		2.282942228
	AC-RHYPLWR	No		2.282942228
	EU-DTPA-HC3A	No		2.282942228
	ALBUTENSIN A	No		2.282942228
	COMPOUND 21	No		2.282942228
	FLTCHAAR	No		2.282942228
	E7	No		2.282942228
	WWGKKYRASKLGLAR	No		2.282942228
	FIRSOCOSTAT	No		0.570735557

	PF-05175157	No		1.141471114
	SB290157	No		1.141471114
	CLESACOSTAT	No		0.570735557
	YSFKPMPLAR	No		1.141471114
	JR14A	No		2.282942228
	COMPOUND 17	No		2.282942228
APOC3	PEGASPARGASE	Yes		0.25003653
	ALPROSTADIL	Yes	sexual dysfunction , erectile dysfunction	0.081533651
	TREPROSTINIL	Yes	Antihypertensive Agents; Antithrombotic Agents	0.208363775
	BUTAPROST (FREE ACID FORM)	No		0.312545662
	AFP-07	No		1.875273973
	SELEXIPAG	Yes	antihypertensive agent	0.937636986
	FK-788	No		1.875273973
	TAPROSTENE	No		1.875273973
	TG6-129	No		0.468818493
	BERAPROST	No	antihypertensive agent	0.468818493
	EP 157	No		1.875273973

	PROTEASE INHIBITOR	No		0.187527397
	BMY 45778	No		1.875273973
	ILOPROST	Yes	antihypertensive agent	0.156272831
	MRE-269	No		0.625091324
	RITONAVIR	Yes		0.208363775
	BAY-73-1449	No		1.875273973
	[3H]ILOPROST	No		1.875273973
	CAY10441	No		1.875273973
	VOLANESORSEN	Yes		0.937636986
	CARBACYCLIN	No		0.234409247
	TEI-9063	No		1.875273973
	ESUBERAPROST	No		0.937636986
	FR181157	No		1.875273973
	EPOPROSTENOL	Yes	Antihypertensive Agents; Platelet Aggregation Inhibitors	0.468818493
	CICAPROST	No		0.468818493
	U46619	No		0.208363775
	RO3244794	No		1.875273973
LCAT	MEDI6012	No		21.00306849

	PREDNISOLONE	Yes	corticosteroid,antiinflammatory agent	0.750109589
	TESTOSTERONE	Yes	sexual dysfunction, hormone replacement	0.538540218
	TESTOSTERONE PROPIONATE	Yes		2.625383562
	STREPTOZOCIN	Yes		0.456588446
LPA	ROSUVASTATIN	Yes	antihypecholesterolemic agent	2.187819635
	ASPIRIN	Yes	NSAID,antithrombotic,anticoagulant	0.372394831
PON1	SIMVASTATIN	Yes	antidyslipidaemic agent, anticholesterolaemic agent, antihypertensive agent	2.100306849
	QUERCETIN	Yes		0.664654066

Supplementary Table 5. Druggable categories for the 5 core-DLRGs

Category	Matching gene count	Matching gene(s)
Transporter	2	LCAT, PON1
Druggable genome	5	ACACA, APOC3, LCAT, LPA, PON1
Enzyme	4	ACACA, APOC3, LCAT, PON1
Protease	1	LPA

Supplementary Table 6. Correlation between ACACA and the clinicopathological features of HCC patients

Variable	Patient (<i>n</i> = 85)	ACACA expression		χ^2/Z	<i>P</i>
		Low (<i>n</i> = 30)	High (<i>n</i> = 55)		
Gender				0.157	0.692
Female	22	7	15		
Male	63	23	40		
Age (years)				0.943	0.332
< 60	54	17	37		
≥ 60	31	13	18		
History of hepatitis				0.003	0.955
No	28	10	18		
Yes	57	20	37		
History of cirrhosis				0.614	0.433
No	49	19	30		
Yes	36	11	25		
AFP level				5.058	0.08
Low	36	8	28		
Moderate	20	10	10		
High	29	12	17		
Clinical stages				3.167	0.075
I / II	61	18	43		

III / IV	24	12	12		
Tumor size (cm)				1.08	0.583
< 5	29	11	18		
5~10	40	12	28		
≥ 10	16	7	9		
Degree of differentiation				2.16	0.34
High	31	14	17		
Moderate	39	12	27		
Low	15	4	11		