Title: Ursodeoxycholic acid inhibits glioblastoma progression via endoplasmic reticulum stress related apoptosis and synergizes with the proteasome inhibitor bortezomib

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Supporting Information

Table S1.	The top	10 up-	and	down-regulated	genes resulting	from	RNA-sea	uencing
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Up/down	Gene	Fold	padj*	GO: biological process (most related three processes)
	Name	Change		
up	CXCL3	92.9601803	0	GO:0070098 chemokine-mediated signaling pathway; GO:0007186 G-
				protein coupled receptor signaling pathway; GO:0006955 immune response
up	STK32A	88.8170292	0	GO:0035556 intracellular signal transduction; GO:0018105 peptidyl-serine
				phosphorylation;
up	BIRC3	69.7645695	0	GO:0007166 cell surface receptor signaling pathway; GO:0007249 I-
				kappaB kinase/NF-kappaB signaling; GO:1990001 inhibition of cysteine-
				type endopeptidase activity involved in apoptotic process
up	LCN2	68.7803266	0	GO:0019730 antimicrobial humoral response; GO:0006915 apoptotic
				process; GO:0006879 cellular iron ion homeostasis degranulation
up	PTX3	67.153736	0	GO:0006954 inflammatory response; GO:0045087 innate immune
				response; GO:0044869 negative regulation by host of viral exo-alpha-
				sialidase activity
up	AKNA	52.4778223	0	GO:0045944 positive regulation of transcription from RNA polymerase II
				promoter
up	ATF3	51.7262096	0	GO:0034198 cellular response to amino acid starvation;
				GO:0030968 endoplasmic reticulum unfolded protein response;
				GO:0006094 gluconeogenesis
up	IL1A	46.8605442	0	GO:0006915 apoptotic process; GO:0008283 cell proliferation;
				GO:0034605 cellular response to heat
up	ADM2	39.9285615	0	GO:0007189 adenylate cyclase-activating G-protein coupled receptor
				signaling pathway; GO:0001525 angiogenesis; GO:0007586 digestion
up	BEX2	37.1963255	0	GO:0006915 apoptotic process; GO:0007049 cell cycle;
				GO:0042981 regulation of apoptotic process
down	TOP2A	0.00100518	0	GO:0030263 apoptotic chromosome condensation; GO:0006974 cellular
				response to DNA damage stimulus; GO:0007059 chromosome segregation
down	MT-	0.00275988	0	GO:0019646 aerobic electron transport chain; GO:0008535 respiratory
	CO3			chain complex IV assembly;
down	MT-	0.00286351	0	GO:0009060 aerobic respiration; GO:0007568 aging;
	CO1			GO:0021549 cerebellum development
down	MT-	0.00308078	0	GO:0042773 ATP synthesis coupled electron transport;
	CO2			GO:0007595 lactation; GO:0006123 mitochondrial electron transport,
				cytochrome c to oxygen
down	ANLN	0.00421259	0	GO:0090521 glomerular visceral epithelial cell migration;

				GO:0002244 hematopoietic progenitor cell differentiation;
				GO:0000281 mitotic cytokinesis
down	MT-	0.00452983	0	GO:0032981 mitochondrial respiratory chain complex I assembly;
	ND6			GO:0042220 response to cocaine; GO:0042542 response to hydrogen
				peroxide
down	MT-	0.00498345	0	GO:0006120 mitochondrial electron transport, NADH to ubiquinone;
	ND5			GO:0032981 mitochondrial respiratory chain complex I assembly;
				GO:0042542 response to hydrogen peroxide
down	CDC20	0.00584008	0	GO:0031145 anaphase-promoting complex-dependent proteasomal
				ubiquitin-dependent protein catabolic process; GO:0051301 cell division;
				GO:0007064 mitotic sister chromatid cohesion
down	MT-	0.00664977	0	GO:0031100 organ regeneration; GO:0015990 electron transport coupled
	CYB			proton transport; GO:0042538 hyperosmotic salinity response
down	CENPF	0.00681404	0	GO:0030154 cell differentiation; GO:0051301 cell division;
				GO:0008283 cell proliferation

*0 was used to represent padj less than 1E-309

Table S2. Recommended symbols for describing synergism or antagonism analyzed with CI method

Range of CI	Symbol	Description
<0.1	+++++	Very strong synergism
0.1-0.3	++++	Strong synergism
0.3-0.7	+++	Synergism
0.7-0.85	++	Moderate synergism
0.85-0.90	+	Slight synergism
0.90-1.10	±	Nearly additive
1.10-1.20	-	Slight antagonism
1.20-1.45		Moderate antagonism
1.45-3.3		Antagonism
3.3-10		Strong antagonism
>10		Very strong antagonism

Table S3. Details of antibodies used

Antibody	Manufacturer	Catalogue number		
CDK2	Cell signaling	#2546		
CDK4	Proteintech	11026-1-AP		
CDK6	Proteintech	14052-1-AP		
cyclinD1	Proteintech	26939-1-AP		
P53	Proteintech	10442-1-AP		
P21	Proteintech	10355-1-AP		
Phospho-Rb	Cell signaling	#2181		
Bcl2	Proteintech	12789-1-AP		
Caspase 3	Proteintech	19677-1-AP		
Parp	Proteintech	13371-1-AP		
AIF	Cell signaling	#5318		

EndoG	Proteintech	22148-1-AP
Rip3	Proteintech	17563-1-AP
β-actin	Proteintech	20536-1-AP
Bid	Cell signaling	#2002
Phospho-JNK	Cell signaling	#4668
Phospho-Erk1/2	Cell signaling	#4370
Phospho-p38	Cell signaling	#4511
MAPK family sampler kit	Cell signaling	#9926
Ubiquitin	Cell signaling	#3936
СНОР	Cell signaling	#5554
IRE1	Cell signaling	#3294
Bip	Cell signaling	#3177
ATF4	Proteintech	10835-1-AP
ATF6	Proteintech	24169-1-AP
p-PERK	Bioss	Bs-3330R
α/β-tubulin	Cell signaling	#2148
GAPDH	Cell signaling	#2118
Anti-mouse IgG	Cell signaling	#7076
Anti-rabbit IgG	abcam	ab205718

Table S4. Quantitative PCR primer sequences

Species	Gene	Forward sequences	Reverse sequences
Homo sapiens	GPADH	GCACCGTCAAGGCTGAGAAC	TGGTGAAGACGCCAGTGGA
Homo sapiens	XBP1 spliced	TCTGCTGAGTCCGCAGCAG	GAAAAGGGAGGCTGGTAAGGAAC
Homo sapiens	ERN1	TCAATGTCGCTGTGGAGACC	ACATACAGAGTGGGGCGTCAG
Homo sapiens	HSPA5	CATCAACGAGCCTACGGCA	AGACACATCGAAGGTTCCGC
Homo sapiens	DDIT3	TTGCCTTTCTCCTTCGGGAC	TGATTCTTCCTCTTCATTTCCAGG
Homo sapiens	ATF4	TCCAACAACAGCAAGGAGGAT	TCCAACGTGGTCAGAAGGTC
Homo sapiens	ATF6	AATCCGCTTGTCAGTCTCGC	GCCTCTGGTTCTCTGACACA



Fig. S1. GBM cells were treated with corresponding concentration of vehicle control (ethanol) for 72 hours, and cell viability was measured using the CCK-8 assay.



Fig. S2. Fluorescence imaging showing AIF translocation after UDCA treatment. LN229 cells were treated with UDCA (800μ M) for 48 h followed by stain with AIF antibody (green) and DAPI (blue).