

## Supplementary data

**Table S1** Enriched pathways identified by Reactome among DEGs in indicated clusters.

Subclusters	Top 10 most relevant pathways	P values	FDR	Involved genes
<b>Cluster 2</b> (Figure 1E)	Response of EIF2AK1 (HRI) to heme deficiency (R-HSA-9648895)	4.60e-12	7.78e-10	ATF3 CHAC1 DDIT3
	Cellular responses to stress (R-HSA-2262752)	6.53e-09	4.59e-07	ATF3 CHAC1 DDIT3 CDKN1A DEDD2
	Cellular responses to external stimuli (R-HSA-8953897)	8.20e-09	4.59e-07	ATF3 CHAC1 DDIT3 CDKN1A DEDD2
	Transcriptional activation of p53 responsive genes (R-HSA-69560)	1.08e-07	3.56e-06	CDKN1A
	Transcriptional activation of cell cycle inhibitor p21 (R-HSA-69895)	1.08e-07	3.56e-06	CDKN1A
	ATF4 activates genes in response to endoplasmic reticulum stress (R-HSA380994)	2.13e-07	5.95e-06	ATF3 DDIT3
	Transcriptional Regulation by TP53 (R-HSA-3700989)	3.35e-07	8.05e-06	ATF3 DDIT3 CDKN1A PMAIP1
	PERK regulates gene expression (R-HSA-381042)	4.91e-07	1.03e-05	ATF3 DDIT3
	Response of EIF2AK4 (GCN2) to amino acid deficiency (R-HSA-9633012)	7.33e-07	1.32e-05	ATF3 DDIT3
	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest (R-HSA-6804116)	3.94e-06	6.31e-05	CDKN1A
<b>Cluster 3 and 4</b> (Figure 1E)	TP53 Regulates Metabolic Genes (R-HSA-5628897)	1.36e-04	0.006	PTEN
	Regulation of PTEN mRNA translation (R-HSA-8943723)	2.60e-04	0.006	PTEN
	PTEN Regulation (R-HSA-6807070)	3.32e-04	0.006	PTEN
	Regulation of PTEN gene transcription (R-HSA-8943724)	0.001	0.017	PTEN
	PIP3 activates AKT signaling (R-HSA-1257604)	0.002	0.017	PTEN
	Iron uptake and transport (R-HSA-917937)	0.002	0.017	FTH1
	PTEN Loss of Function in Cancer (R-HSA-5674404)	0.002	0.017	PTEN
	Intracellular signaling by second messengers (R-HSA-9006925)	0.003	0.018	PTEN
	Transcriptional Regulation by MECP2 (R-HSA-8986944)	0.003	0.018	PTEN
	Transcriptional Regulation by TP53 (R-HSA-3700989)	0.007	0.033	PTEN
<b>Cluster 1</b> (top 5 genes, Figure 2E)	Regulation of HSF1-mediated heat shock response (R-HSA-3371453)	3.50e-09	6.34e-07	DNAJB1 HSPH1 DEDD2
	Cellular response to heat stress (R-HSA-3371556)	8.48e-09	7.63e-07	DNAJB1 HSPH1 DEDD2
	Attenuation phase (R-HSA-3371568)	1.36e-08	8.19e-07	DNAJB1 HSPH1 DEDD2

	HSF1-dependent transactivation (R-HSA-3371571)	3.38e-08	1.52e-06	DNAJB1 HSPH1 DEDD2
	HSF1 activation (R-HSA-3371511)	2.15e-06	5.50e-05	HSPH1 DEDD2
	Cellular responses to stress (R-HSA-2262752)	2.20e-06	5.50e-05	DNAJB1 HSPH1 DEDD2 PSME1
	PTEN Regulation (R-HSA-6807070)	2.31e-06	5.50e-05	PSME1 PTEN
	Cellular responses to external stimuli (R-HSA-8953897)	2.50e-06	5.50e-05	DNAJB1 HSPH1 DEDD2 PSME1
	PIP3 activates AKT signaling (R-HSA-1257604)	2.69e-05	5.37e-04	PSME1 PTEN
	Intracellular signaling by second messengers (R-HSA-9006925)	4.59e-05	8.27e-04	PSME1 PTEN

FDR: False discovery rate; R-HSA-XXXXXXX: Reactome pathway identifiers

**Table S2** Significantly enriched pathways by Reactome of DEGs in cluster 1 of Figure 3B ( $p < 0.05$ ).

Significant pathways	P values	FDR	Involved genes
Toxicity of botulinum toxin type G (botG) (R-HSA-5250989)	0.005	0.06	SYT1
Cargo recognition for clathrin-mediated endocytosis (R-HSA-8856825)	0.007	0.06	SYT1
Protein repair (R-HSA-5676934)	0.007	0.06	MSRA
Signaling by MAPK mutants (R-HSA-9652817)	0.008	0.06	DUSP8
Toxicity of botulinum toxin type B (botB) (R-HSA-5250958)	0.01	0.06	SYT1
Clathrin-mediated endocytosis (R-HSA-8856828)	0.013	0.06	SYT1
Acetylcholine Neurotransmitter Release Cycle (R-HSA-264642)	0.02	0.06	SYT1
Serotonin Neurotransmitter Release Cycle (R-HSA-181429)	0.022	0.06	SYT1
Norepinephrine Neurotransmitter Release Cycle (R-HSA-181430)	0.022	0.06	SYT1
GABA synthesis, release, reuptake and degradation (R-HSA-888590)	0.023	0.06	SYT1
Neurotoxicity of clostridium toxins (R-HSA-168799)	0.026	0.06	SYT1
Dopamine Neurotransmitter Release Cycle (R-HSA-212676)	0.027	0.06	SYT1
Glutamate Neurotransmitter Release Cycle (R-HSA-210500)	0.029	0.06	SYT1
RAF-independent MAPK1/3 activation (R-HSA-112409)	0.029	0.06	DUSP8
TNFR1-induced NF-kappa B signaling pathway (R-HSA-5357956)	0.036	0.06	RNF31
EGFR downregulation (R-HSA-182971)	0.037	0.06	PTPRK
Membrane Trafficking (R-HSA-199991)	0.038	0.06	SYT1
Gluconeogenesis (R-HSA-70263)	0.04	0.06	SLC37A1
Ovarian tumor domain proteases (R-HSA-5689896)	0.045	0.06	OTUB2
Regulation of TNFR1 signaling (R-HSA-5357905)	0.046	0.06	RNF31

FDR: False discovery rate; R-HSA-XXXXXXX: Reactome pathway identifiers

**Table S3** A list of tumor suppressors and oncogenes used in all heatmaps.

Tumor suppressors	Tumor suppressors	Oncogenes	Oncogenes	Oncogenes
NKD2	FTH1	FZD8	TSC22D3	HMOX2
GAS1	NQO1	POU3F2	CDK7	BOLA2B
PTPRK	PSME1	FLII	JDP2	BFAR
PINX1	DNAJB1	NRG2	OTUB2	KDM7A
DDIT4	HSPH1	LDLRAD4	HRAS	LUCAT1
GABARAPL1	MIR1244-3	KLF2	PEAK3	CHORDC1
SQSTM1	MTCH2	PTPRK	PHF1	TXNRD1
DUSP8	IBTK	MAP3K19	RUFY1	HMOX1
DEDD2	RASA3	SLC25A24	CDR2	SRXN1
PAK1IP1	RNF144A	HSPA4L	RRN3	PAK1IP1
ATF3	FRG1	HSP90AA1	SLC37A1	
PMAIP1	NMRAL1	DNAJA1	MSRA	
DDIT3	NINJ1	HSPA6	DUSP8	
CHAC1	TRIB3	BAG3	RNF31	
MXD1	LAIR1	SERPINH1	SYT1	
DNAJB4	PTEN	ZFAND2A	NANOS1	
CDKN1A	EID3	ZNF251	BCL6	
INHBE	OSGIN1	CLU	CYP19A1	
IFI27L1	IFI27L2	WNT11	EPHB1	

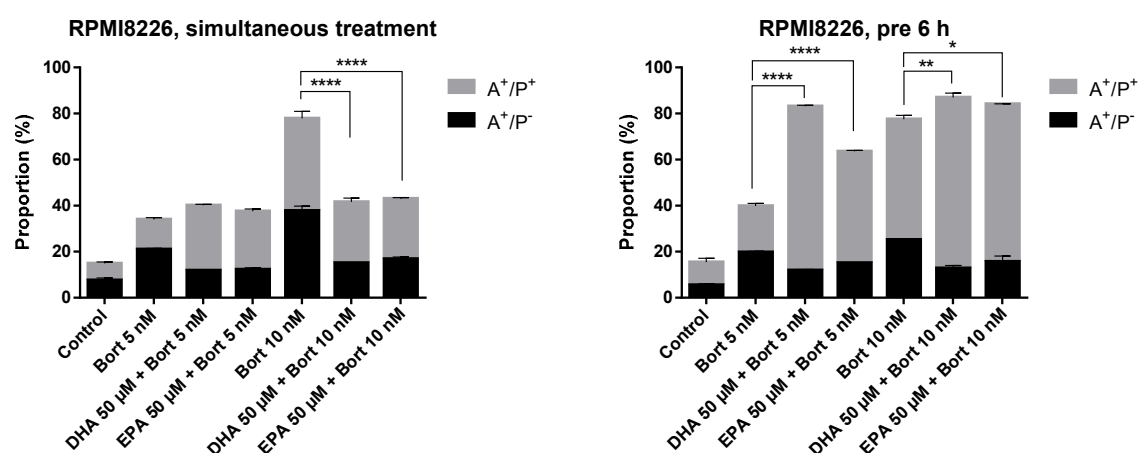
**PAK1IP1**: play a dual role as an oncogene and tumor suppressor in cancer cells.

**Table S4** A list of the metabolites for pathway enrichment analysis using MetaboAnalyst 5.0.

Metabolites-OPM2 (Fig. 4A)		Metabolites-BTZ/100 (Fig. 5B)		
HexP	ASN	HexP	Dihydroxyacetone3P	Hypoxanthine
AMP	Glutathione	AMP	3-Hydroxybutanoic Acid(BHBA)	Fructose 16bisP
GMP	GLN	GMP	Ribulose5P	PEP
IMP	NADP+	IMP	CMP	Adenine
GSSG	NADPH	GSSG	SER	GLN
S-Adenosyl-Methionine	Ornithine	S-Adenosyl-Methionine	Sedoheptulose7P	Guanine
NADH	Glucose	ASN	Ornithine	Orotate
LYS	Orotate	Glutathione	Glucose	N-Carbamoyl-aspartate

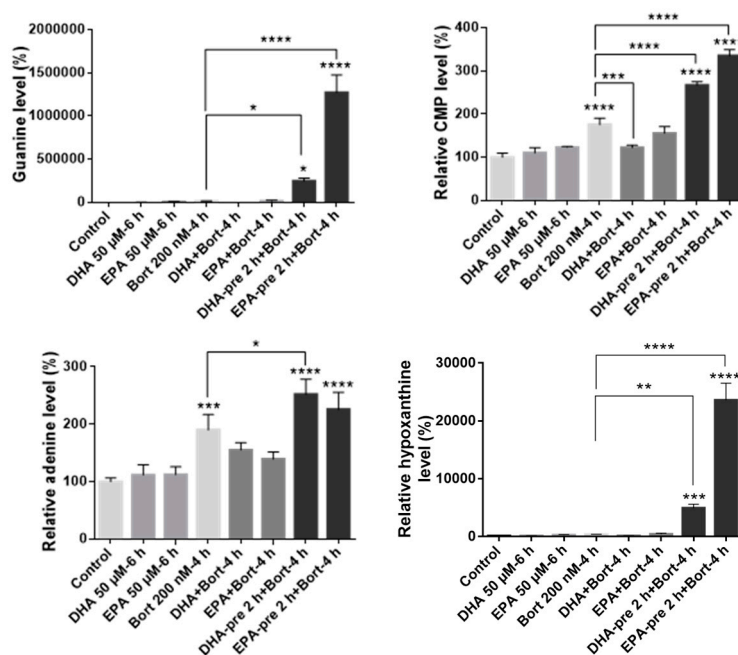
**Table S5** A list for the rest of abbreviations

Abbr.	Description	Abbr.	Description
AKT	Protein kinase B (PKB)	IMP	Inosine monophosphate
AMP	Adenosine monophosphate	JAK2	Janus kinase 2
CDK7	Cyclin-dependent kinase 7	JNK	C-Jun N-terminal kinase
CMP	Cytidine monophosphate	KLF2	Kruppel Like Factor 2
CREB	CAMP response element-binding protein	MAPK	Mitogen-activated protein kinase
EGFR	Epidermal growth factor receptor	MEK1/2	Mitogen-activated protein kinase kinase 1/2
ER	Estrogen receptor	MKK7	MAP-kinase kinase 7
ERBB	Erb-B2 Receptor Tyrosine Kinase	NADPH	Nicotinamide adenine dinucleotide phosphate
ERK	Extracellular-signal-regulated kinase	NF- $\kappa$ B	Nuclear factor-kappa B
GCLM	Glutamate-Cysteine Ligase Modifier Subunit	PI3K	Phosphatidylinositol-3-kinase
GMP	Guanosine monophosphate	PTEN	Phosphatase and tensin homolog
GSR	Glutathione-Disulfide Reductase	STAT3	Signal transducer and activator of transcription 3
HER	(also termed ERBB)	TNFR1	Tumor Necrosis Factor Receptor 1
HSF-1	Heat Shock Transcription Factor-1	WNT	Wingless/Integrated
IKK $\beta$	Inhibitor of NF- $\kappa$ B kinase subunit beta		

**Figure S1**

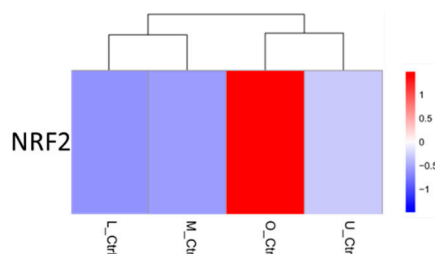
**Figure S1** The effect of DHA/EPA on the chemosensitivity of RPMI8226 cells to bortezomib. RPMI8226 cells were pretreated with 50  $\mu$ M of DHA/EPA for 0 or 6 h and then incubated with bortezomib (5 or 10 nM) for 24 h. Apoptotic cells were determined by Annexin V and PI staining. Data are presented as mean  $\pm$  SD of two treatments. \* $p$  < 0.05, \*\* $p$  < 0.01, \*\*\*\* $p$  < 0.0001.

Figure S2



**Figure S2** The levels of CMP, adenine, hypoxanthine, and guanine upon different treatment in BTZ/100 cell line. RPMI8226-BTZ/100 was pretreated with 50 µM of DHA or EPA for 0 or 2 h and then incubated with bortezomib (200 nM) for 6 h. The levels of CMP, adenine, hypoxanthine, and guanine were determined by metabolomics analysis. Data are presented as mean ± SD of three independent treatments. \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$  when compared with control.

Figure S3



**Figure S3** Heatmap analysis of the expression of NRF2 in four human MM cell lines L363 (L), MM.1S (M), OPM2 (O) and U266 (U).