

Ingenuity Canonical Pathways	Molecules	-log(p-value)
Superpathway of Cholesterol Biosynthesis	FDFT1,IDI1,HSD17B7,HMGCR,HMGCS1	4.43E+00
Mevalonate Pathway I	IDI1,HMGCR,HMGCS1	3.23E+00
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	IDI1,HMGCR,HMGCS1	2.84E+00
G-Protein Coupled Receptor Signaling	ADRB1,CAMK2D,ADRBK1,RASGRP1,GNAQ,FGFR2,GABBR1,DUSP4,CREB3L4,PTGER2	2.28E+00
Unfolded protein response	CALR,INSIG1,PPP1R15A,DNAJB9	2.15E+00
LXR/RXR Activation	FDFT1,LYZ,LDLR,ACACA,HMGCR,TNFRSF11B	2.10E+00
Calcium Signaling	CALM1 (includes others),CALR,CAMK2D,ATP2A3,MCU,CREB3L4,ASPH	1.97E+00
cAMP-mediated signaling	CALM1 (includes others),ADRB1,CAMK2D,ADRBK1,GABBR1,DUSP4,CREB3L4,PTGER2	1.90E+00
Acetyl-CoA Biosynthesis III (from Citrate)	ACLY	1.84E+00
Cholesterol Biosynthesis I	FDFT1,HSD17B7	1.84E+00
Cholesterol Biosynthesis II (via 24,25-dihydrolanosterol)	FDFT1,HSD17B7	1.84E+00
Cholesterol Biosynthesis III (via Desmosterol)	FDFT1,HSD17B7	1.84E+00
Corticotropin Releasing Hormone Signaling	CALM1 (includes others),NR4A1,GNAQ,JUND,CREB3L4	1.74E+00
Nitric Oxide Signaling in the Cardiovascular System	CALM1 (includes others),ADRB1,HSP90AA1,FGFR2,ATP2A3	1.70E+00
Androgen Signaling	CALM1 (includes others),CALR,GNAQ,HSP90AA1,DNAJB1	1.66E+00
Epoxyqualene Biosynthesis	FDFT1	1.54E+00
GDP-L-fucose Biosynthesis I (from GDP-D-mannose)	GMDS	1.54E+00
Calcium-induced T Lymphocyte Apoptosis	CALM1 (includes others),NR4A1,ATP2A3	1.39E+00
Biotin-carboxyl Carrier Protein Assembly	ACACA	1.37E+00
B Cell Receptor Signaling	ETS1,CALM1 (includes others),MAP3K14,CAMK2D,FGFR2,CREB3L4	1.35E+00

**Supplementary table 1.** Top 20 pathways identified by Ingenuity Pathway Analysis (IPA) containing genes significantly ( $p \leq 0.05$ ) upregulated ( $\geq 1.3$  fold) between poor and good prognostic *BRAF*MT stage II/III CRC in GSE39582.

Ingenuity Canonical Pathways	Molecules	$-\log(p\text{-value})$
Acetyl-CoA Biosynthesis I (Pyruvate Dehydrogenase Complex)	PDHA1,DLAT,DBT,PDHB	5.64E+00
Lipoate Biosynthesis and Incorporation II	LIPT1,LIAS	3.40E+00
L-glutamine Biosynthesis II (tRNA-dependent)	GATB,QRSL1	3.40E+00
Formaldehyde Oxidation II (Glutathione-dependent)	ADH5,ESD	3.40E+00
EIF2 Signaling	RPL22,RPL26L1,SOS1,RPS23,EIF4G3,PPP1CB,RPS27A,RPS15A,EIF2S3,EIF2S1,EIF3M	2.98E+00
TGF- $\beta$ Signaling	JUN,CDC42,SOS1,MAP3K7,VDR,HNF4A,ACVR2A	2.75E+00
Histamine Degradation	ALDH4A1,HNMT,ALDH7A1	2.52E+00
Granzyme B Signaling	CYCS,CASP8,DFFA	2.44E+00
Tetrahydrofolate Salvage from 5,10-methenyltetrahydrofolate	MTHFD1L,GART	2.42E+00
Inflammasome pathway	CASP1,CASP8,CASP5	2.10E+00
Role of PKR in Interferon Induction and Antiviral Response	MAP3K7,CYCS,CASP8,EIF2S1	2.09E+00
PTEN Signaling	SYNJ2,CSNK2A2,GHR,CDC42,SOS1,IGF1R,IGF2R	2.02E+00
Regulation of eIF4 and p70S6K Signaling	SOS1,RPS23,EIF4G3,RPS27A,RPS15A,EIF2S3,EIF2S1,EIF3M	1.96E+00
Tumoricidal Function of Hepatic Natural Killer Cells	CYCS,CASP8,DFFA	1.93E+00
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	AQR,ETS2,SH3GLB1,NR5A2	1.91E+00
Myc Mediated Apoptosis Signaling	YWHAB,SOS1,IGF1R,CYCS,CASP8	1.89E+00
TNFR1 Signaling	JUN,CDC42,CYCS,CASP8	1.85E+00
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	CYCS,CASP8,DFFA	1.79E+00
Dopamine Degradation	ALDH4A1,SULT2A1,ALDH7A1	1.75E+00
CD27 Signaling in Lymphocytes	JUN,MAP3K7,CYCS,CASP8	1.73E+00

**Supplementary table 2.** Top 20 pathways identified by Ingenuity Pathway Analysis (IPA) containing genes significantly ( $p \leq 0.05$ ) downregulated ( $\geq 1.3$  fold) between poor and good prognostic *BRAF*MT stage II/III CRC in GSE39582.

Ingenuity Canonical Pathways	Molecules	-log(p-value)
Cell Cycle Control of Chromosomal Replication	MCM3,MCM6,PCNA,CDT1,ORC6,ORC1	3.84E+00
ATM Signaling	GADD45A,MAPK9,MDM2,TLK1,MAPK13,CREB5,NBN,CCNB1	3.54E+00
Role of IL-17A in Psoriasis	CXCL3,CXCL1,CXCL5	2.73E+00
Adipogenesis pathway	ATG5,FOXO1,BMPR1A,SETDB1,FZD6,FBXW7,SOX9,SAP30,HIF1A	2.73E+00
p53 Signaling	CCNG1,PCNA,GADD45A,PPP1R13B,PERP,MDM2,HIF1A,BCL2	2.57E+00
Role of IL-17A in Arthritis	CXCL3,MAPK9,CXCL1,CXCL5,MAPK13,MAP2K1	2.51E+00
ErbB Signaling	FOXO1,PAK2,MAPK9,HBEGF,MAPK13,EREG,MAP2K1	2.31E+00
Unfolded protein response	INSIG1,VCP,HSPA6,DNAJB9,BCL2	2.26E+00
Molecular Mechanisms of Cancer	TFDP1,GNA12,MAPK9,MDM2,HIF1A,MAPK13,NBN,BCL2,FOXO1,NF1,BMPR1A,PAK2,FZD6,ADCY7,MAP2K1,RASA1	2.22E+00
IL-17A Signaling in Airway Cells	CXCL3,MAPK9,CXCL1,CXCL5,MAPK13,MAP2K1	2.21E+00
NRF2-mediated Oxidative Stress Response	MGST1,DNAJC9,VCP,DNAJA4,MAPK9,DNAJC10,DNAJB9,FKBP5,ENC1,MAP2K1	2.15E+00
GADD45 Signaling	PCNA,GADD45A,CCNB1	2.13E+00
Mouse Embryonic Stem Cell Pluripotency	IL6ST,SOX2,ID1,BMPR1A,FZD6,MAPK13,MAP2K1	2.13E+00
Paxillin Signaling	ARF6,PAK2,ITGA6,MAPK9,MAPK13,ITGB6,PTPN12	2.02E+00
Hypoxia Signaling in the Cardiovascular System	UBE2G1,MDM2,HIF1A,LDHA,CREB5	1.95E+00
Role of IL-17F in Allergic Inflammatory Airway Diseases	CXCL1,CXCL5,CREB5,MAP2K1	1.95E+00
Prostate Cancer Signaling	FOXO1,TFDP1,MDM2,CREB5,MAP2K1,BCL2	1.85E+00
Cdc42 Signaling	CDC42BPA,WASL,PAK2,MAPK9,MAPK13,HLA-F,RASA1	1.81E+00
IL-17A Signaling in Gastric Cells	MAPK9,CXCL1,MAPK13	1.80E+00
Role of JAK family kinases in IL-6-type Cytokine Signaling	IL6ST,MAPK9,MAPK13	1.80E+00

**Supplementary table 3.** Top 20 pathways identified by Ingenuity Pathway Analysis (IPA) containing genes differentially expressed (2-fold;  $p < 0.05$ ) between poor (disease free survival <5 years) and good prognostic *BRAF*MT stage II CRC (disease free survival >5 years) in E-MTAB-863 and E-MTAB-864.

Target	VACO432 ( <i>BRAFV600E</i> )				RKO ( <i>BRAFV600E</i> )				LIM2405 ( <i>BRAFV600E</i> )				HT-29 ( <i>BRAFV600E</i> )			
	Mean	SD	N	P value	Mean	SD	N	P value	Mean	SD	N	P value	Mean	SD	N	P value
SC	1.000000	0.015744	3		1.000000	0.035262	3		1.000000	0.014608	3		1.000000	0.075524	3	
IDI1	0.829299	0.087733	3	0.0295	0.857473	0.063874	3	0.0277	0.727956	0.103091	3	0.0126	0.929155	0.131126	3	0.4629
HMGCS1	0.778222	0.113768	3	0.0287	0.538630	0.145819	3	0.0060	0.316758	0.090746	3	0.002	0.890133	0.041126	3	0.0913
ADRB1	0.619045	0.088908	3	0.0019	0.848141	0.120136	3	0.1036	0.462727	0.094745	3	0.0006	0.833073	0.140335	3	0.1438
PTGER2	0.801242	0.063998	3	0.0064	0.943498	0.075575	3	0.3057	0.658747	0.071621	3	0.0013	0.906784	0.100288	3	0.2678
ADRBK1	0.749069	0.139843	3	0.0366	0.841758	0.037984	3	0.0061	0.498246	0.123861	3	0.0022	0.890065	0.097176	3	0.1967
CAMK2D	0.823838	0.066375	3	0.0111	0.826920	0.043595	3	0.0059	0.573089	0.153268	3	0.0086	0.944775	0.059903	3	0.3772
HSPA5	<b>0.485374</b>	<b>0.173225</b>	<b>3</b>	<b>0.0069</b>	<b>0.197013</b>	<b>0.061246</b>	<b>3</b>	<b>&lt;0.0001</b>	<b>0.213178</b>	<b>0.107679</b>	<b>3</b>	<b>0.0002</b>	<b>0.733968</b>	<b>0.108480</b>	<b>3</b>	<b>0.0252</b>
PPP1R15A	0.767926	0.072728	3	0.0057	0.880523	0.089954	3	0.0989	0.534163	0.181238	3	0.0114	0.922764	0.031236	3	0.1770
DNAJB9	0.857807	0.065351	3	0.0215	0.906884	0.062184	3	0.0871	0.665557	0.144028	3	0.0161	0.921525	0.050664	3	0.2093
INSIG1	0.774294	0.026803	3	0.0002	0.926090	0.125856	3	0.3828	0.451321	0.071155	3	0.0002	0.871335	0.163569	3	0.2838
ATP2A3	0.726593	0.145677	3	0.0319	0.741861	0.160328	3	0.0528	0.691106	0.156560	3	0.0272	0.693824	0.211294	3	0.0774
CALR	0.896125	0.044824	3	0.0193	0.799819	0.183996	3	0.1379	0.717741	0.113224	3	0.0128	0.932426	0.077595	3	0.3406
CALM1	0.829360	0.108812	3	0.0548	0.933955	0.037746	3	0.0912	0.638870	0.129639	3	0.0087	0.998763	0.019691	3	0.9794
HSP90AA1	0.849468	0.079133	3	0.0319	0.990684	0.018992	3	0.7076	0.829432	0.128839	3	0.0849	0.884028	0.070882	3	0.1245
FGFR2	0.652846	0.133605	3	0.0111	0.852635	0.088026	3	0.0546	0.451039	0.106340	3	0.0009	0.750070	0.209704	3	0.1241
NR4A1	0.904344	0.104375	3	0.1916	1.028220	0.048361	3	0.4600	0.749949	0.156150	3	0.0508	0.863488	0.112171	3	0.1553
MCU	0.850547	0.119517	3	0.0983	0.999833	0.038132	3	0.9958	0.681142	0.124057	3	.0115	0.898173	0.134162	3	0.3159
FDFT1	0.666762	0.111441	3	0.0068	0.680179	0.146656	3	0.0213	0.348942	0.116050	3	0.0006	0.809907	0.151129	3	0.1231
MAP3K14	0.775300	0.086065	3	0.0113	0.813820	0.062923	3	0.0111	0.323175	0.154427	3	0.0016	0.764202	0.131510	3	0.0545

**Supplementary table 4. Results of siRNA screen in BRAFMT CRC.** BRAFMT cells were reverse transfected with 10nM of different siRNAs (ON-Targetplus siRNA library, Dharmacon) for 72h and cell viability determined using CellTiter-Glo®. Positive hits were determined using a Student's t-test.