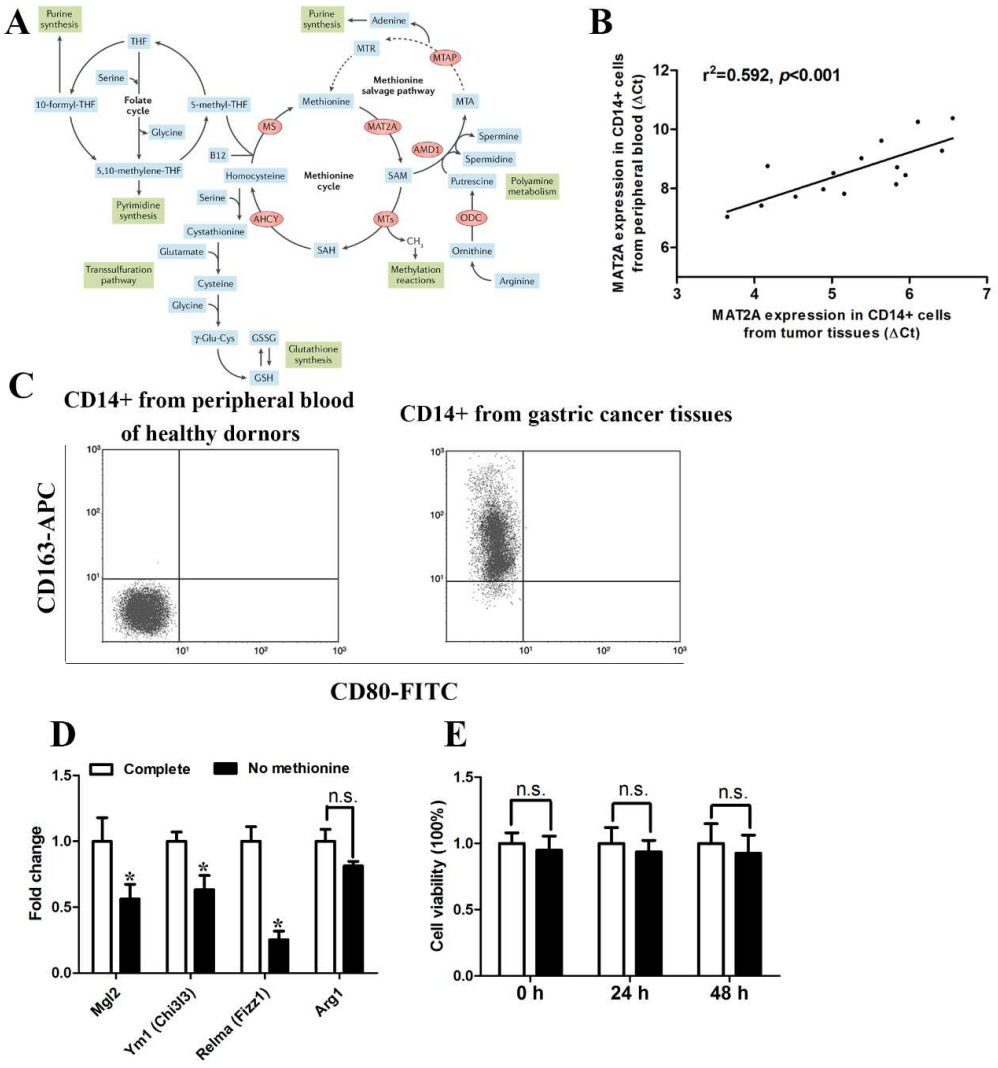
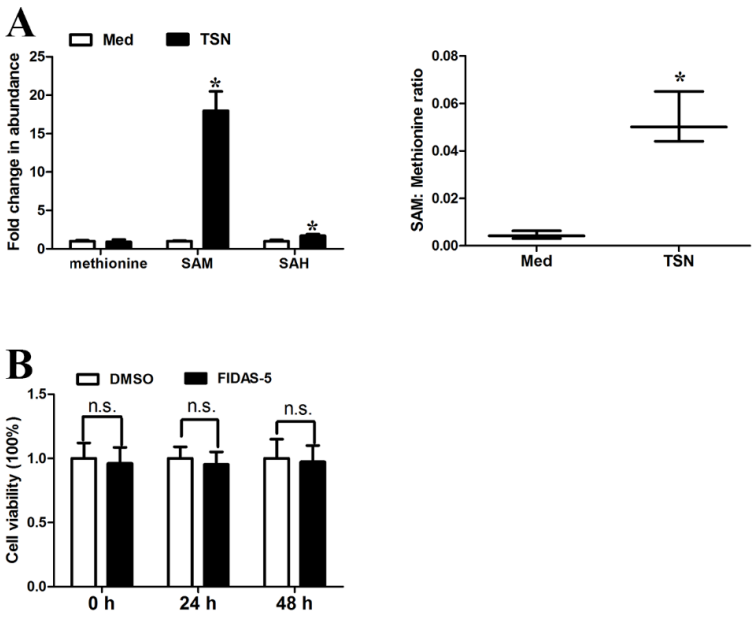


Supplemental Figure S1. (A) Methionine is an essential sulfur-containing amino acid

that is catabolized and recycled in a series of metabolic reactions termed the methionine cycle. (B) The correlation between MAT2A mRNA levels was measured in $CD14^+$ cells isolated from tumor tissues and from paired peripheral blood of 15 GC patients. The ΔCt values (normalized to β-actin) were subjected to Spearman rank-correlation analysis. (C) FACS dot plots depicting CD80 and CD163 expression

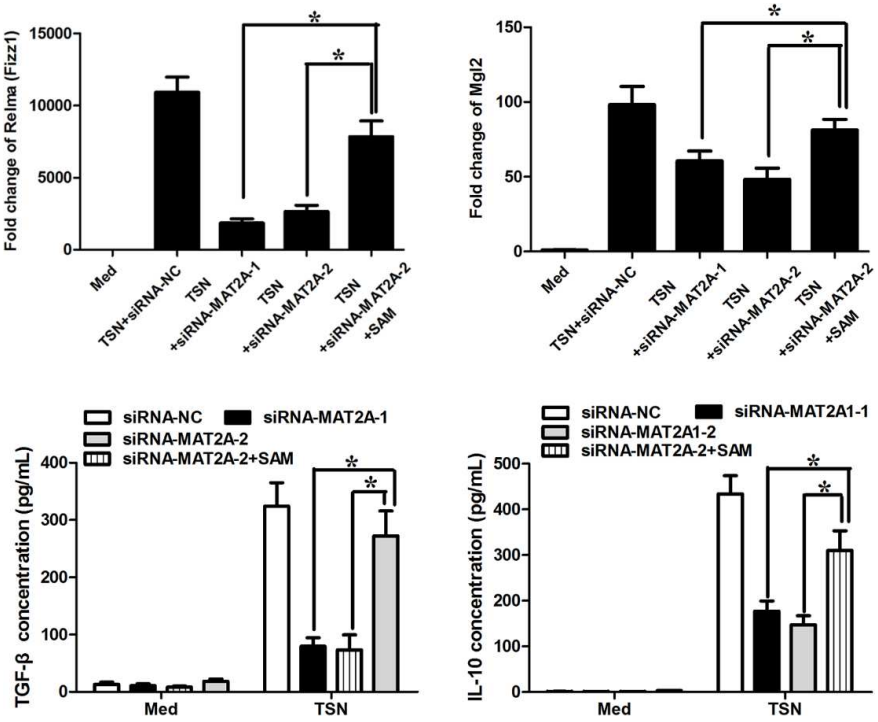
in $CD14^+$ cells purified from peripheral blood of healthy donors or gastric cancer tissues of GC patients.

(D) qPCR analysis of the M2-associated genes Relma, Mgl2 and Ym1 after 24 h methionine starvation. (E) Cell viability determined with CCK8 assay in the presence or absence of 48-h methionine starvation. Values normalized to that of control.

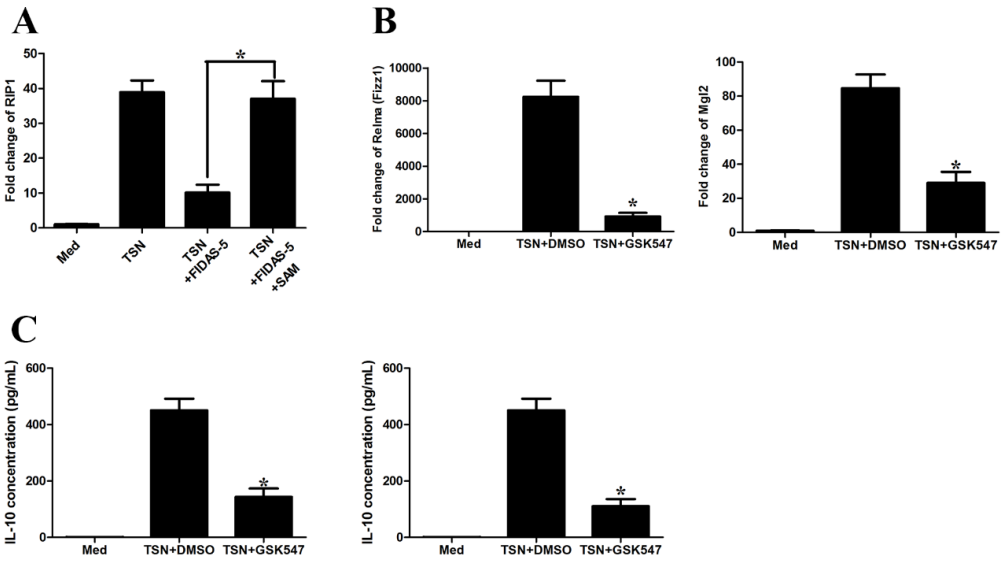


Supplemental Figure S2. $CD14^+$ cells were isolated from peripheral blood of healthy donors. $CD14^+$ Cells were left untreated or treated with supernatant (TSN) from BGC823 cells for 20 h. (A) (Left) LC–MS was used to determine the abundance of methionine cycle metabolites in $CD14^+$ cells purified from tumor tissues 48 h after

methionine starvation. Values were normalized to that in the absence of TSN. (Right) Ratio of SAM to methionine levels in $CD14^+$ cells. (B) Cell viability determined with CCK8 assay in the presence or absence of FIDAS-5 treatment. Values normalized to that of control.

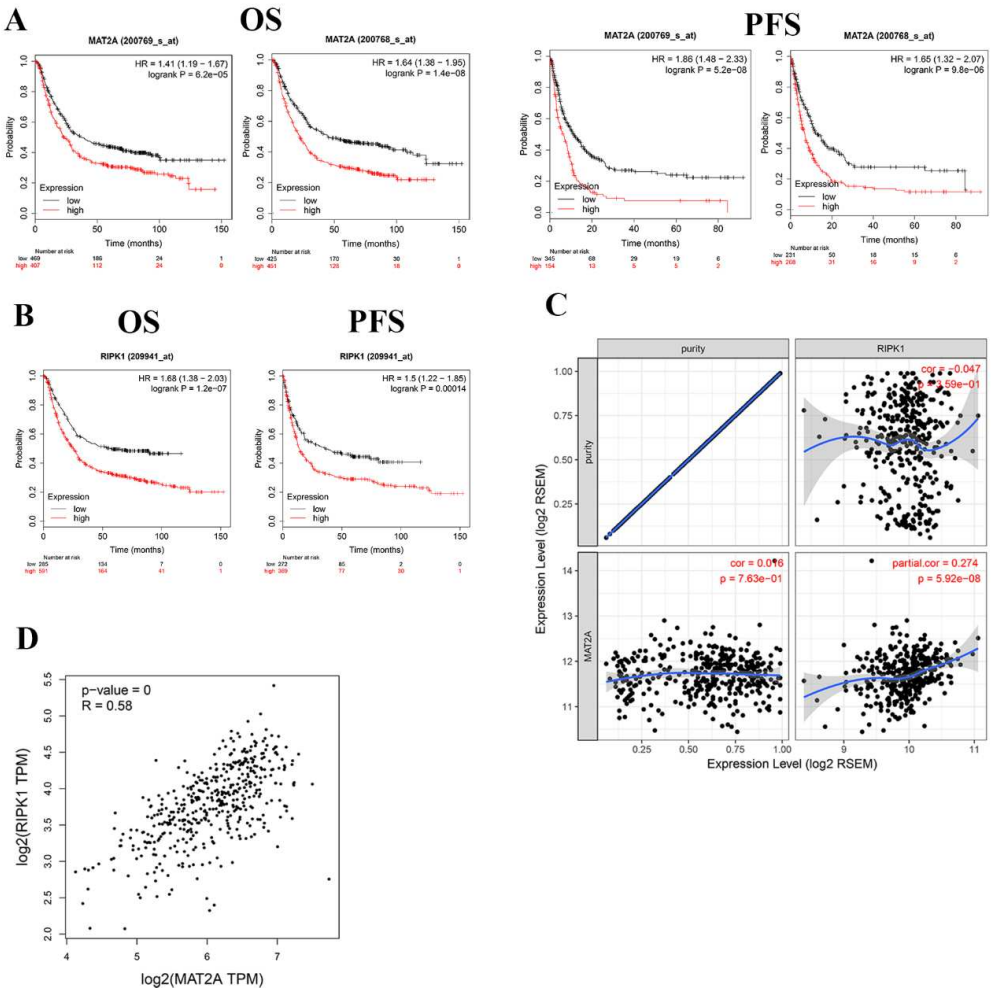


Supplemental Figure S3. $CD14^+$ cells transfected with siRNA-NC or siRNA-MAT2A were left untreated or treated with MGC803 TSN for 28 hours in the presence or absence of SAM supplementation (500 μM). qRT-PCR analysis of the M2-associated genes Mgl2 and Relma (Fizz1). ELISA analysis of IL-10 and TGF-β production.

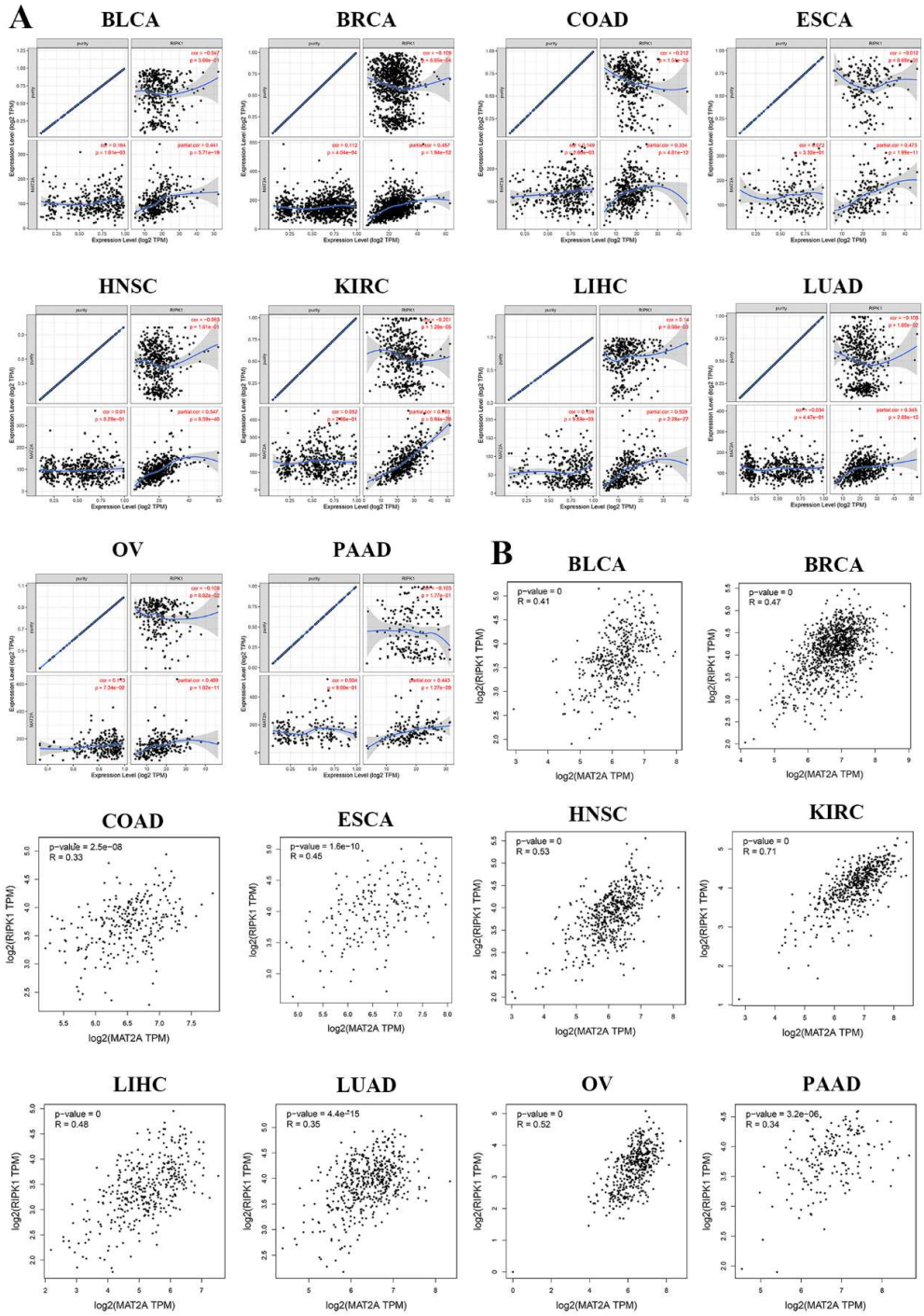


Supplemental Figure S4. (A) $CD14^+$ cells were left untreated or treated with BGC823 TSN for 20 hours in the presence or absence of FIDAS-5 treatment (10 μM) or SAM supplementation (500 μM). qRT-PCR analysis of RIP1. (B,C) $CD14^+$ Cells were left untreated or treated with supernatant (TSN) from MGC803 cells for 20 h in the presence or absence of RIP1 inhibitor (GSK547, 50 nM). (B) qRT-PCR analysis

of the M2-associated genes Mgl2 and Relma (Fizz1). (C) ELISA analysis of IL-10 and TGF-β production.

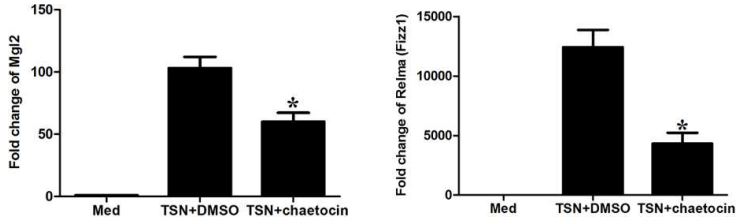


Supplemental Figure S5. (A) A higher expression level of MAT2A is correlated with a significantly poorer OS (p<0.05) and PFS (p<0.05) in GC according to data from the KMPlot database. (B) A higher expression level of RIP1 is correlated with a significantly poorer OS (p<0.05) and PFS (p<0.05) according to data from the KMPlot database. The HRs and p values were calculated with log-rank tests. (C) Scatterplots of correlations between MAT2A expression and RIP1 expression adjusted by purity according to TIMER (http://cistrome.org/TIMER/) in STAD. (D) Correlation results between MAT2A and RIP1 according to GEPIA (http://gepia.cancer-pku.cn/) in STAD.



Supplemental Figure S6. (A) Scatterplots of correlations between MAT2A expression and RIP1 expression adjusted by purity according to TIMER

(http://cistrome.org/TIMER/) in BLCA (bladder urothelial carcinoma), BRCA (breast invasive carcinoma), COAD (colon adenocarcinoma), ESCA (esophageal carcinoma), HNSC (head and neck cancer), KIRC (kidney renal clear cell carcinoma), LIHC (liver hepatocellular carcinoma), LUAD (lung adenocarcinoma), OV (ovarian cystadenocarcinoma), PAAD (pancreatic adenocarcinoma). (B) Correlation results between MAT2A and RIP1 according to GEPIA (http://gepia.cancer-pku.cn/) in BLCA, BRCA, COAD, ESCA, HNSC, KIRC, LIHC, LUAD, OV, PAAD.



Supplemental Figure S7. $CD14^+$ Cells were pretreated with histone

methyltransferase inhibitor (chaetocin, 0.5 μM) for 1h before left untreated or treated with supernatant (TSN) from MGC803 cells for 20 h. qRT-PCR analysis of the M2-associated genes Mgl2 and Relma (Fizz1).

Supplemental Table S1. Clinicopathological characterisitcs of 32 GC patients

Characterisitcs	Number of patients (%)
Patients	32
Gender	
Male	21 (65.63%)
Female	11 (34.37%)
Age (years)	38 to 69, mean 57.32
Tumor size (cm)	1.32 to 14, mean 3.46
Lymph node metastasis (N stage)	
N0	9 (28.13%)
N1	6 (18.75%)
N2	10 (32.15%)
N3	7 (21.87%)
Depth of invasion (T stage)	
T1	6 (18.75%)
T2	7 (21.88%)
T3	13 (40.63%)
T4	6 (18.75%)
Histology	
well and morderately	15 (46.88%)
Poorly and others	17 (53.12%)
Perineural Invasion	

Negative	20 (62.50%)
Positive	12 (37.50%)
Lymphovascular invasion	
Negative	24 (75.00%)
Positive	8 (25.00%)
Gross type	
EGC	3 (9.38%)
Borrmann type I	2 (6.25%)
Borrmann type II	6 (18.75%)
Borrmann type III	15 (46.87%)
Borrmann type IV	6 (18.75%)

Abbreviations: EGC, early gastric cancer;TNM, tumor-nodes-metastasis,based on the American Joint Committee On Cancer/International Union Against Cancer Staging Manual(8th editon, 2016).

Supplemental Table S2. Clinical characteristics of 15 GC patients.

Code	Gender	Age (yr)	TNM stage
3	female	47	IIB
12	male	52	IIIA
19	male	44	IIIB
25	female	65	IIA
29	male	60	IIB
33	female	73	IIIA
34	male	53	IIIB
35	male	81	IIIC
36	male	67	IIIB
37	female	74	IIB
38	female	69	IIIB
39	male	55	IIIC

40	male	71	IIB
41	male	66	IIIC
42	female	73	IIB

Supplemental Table S3. Primer sequence used in this study.

PCR Primers	
Gene	sequence
β-Actin-F	5'-GGGAAATCGTGCGTGACATTAAG-3'
β-Actin -R	5'-TGTGTTGGCGTACAGGTCTTTG-3'
CD11b-F	5'-ATCTCTGCTGGCTTTCCAGT-3'
CD11b-R	5'-ATGCTGTGCTGTCCTCTCTG-3'
RBPj-F	5'-CGGCCTCCACCTAAACGAC-3'
RBPj-R	5'-TCCATCCACTGCCCATAAGAT-3'
MS4A4A-F	5'-CTGGGAAACATGGCTGTCATA-3'
MS4A4A-R	5'-CTCATCAGGGCAGTCAGAATC-3'
CD51-F	5'-GCTGTCGGAGATTTCAATGGT-3'
CD51-R	5'-TCTGCTCGCCAGTAAAATTGT-3'

CD39-F	5'-CCATCCTTGGCTTCTCCTCTAT-3'
CD39-R	5'-CCACGCCTGTGTCATTCTCCT-3'
Camkk2-F	5'-CATGAATGGACGCTGC-3'
Camkk2-R	5'-TGACAACGCCATAGGAGCC-3'
PFKFB3-F	5'-CTCGCATCAACAGCTTTGAGG-3'
PFKFB3-R	5'-TCAGTGTTTCCTGGAGGAGTC-3'
NLRC4-F	5'-GCGGAGGTGGGAGATATG-3'
NLRC4-R	5'-CGTAGAAGGTTTGGAACA-3'
EphB4-F	5'-GGATCGCATTCAGCCAAAGT-3'
EphB4-R	5'-ACTGTCTAAGGCTGTGGCAT-3'
Clever-1-F	5'-CTGTGTCCTGGTCCTCTGC-3'
Clever-1-R	5'-CGCAACGTTTAGACCGTACC-3'
LAMP2a-F	5'-CACCGTCCTTGTGCCCATAGCGGT-3'
LAMP2a-R	5'-AAACACCGCTATGGGCACAAGGAC-3'
ATP6V0d2-F	5'-TGCGGCAGGCTCTATCCAGAGG-3'
ATP6V0d2-R	5'-CCACTGCCACCGACAGCGTC-3'
RIP1-F	5'-CCTGCTGGAGAAGACAGACC-3'
RIP1-R	5'-CATCATCTTCCCCTCTTCC-3'
ICER-F	5'-ATGGCTGTAACTGGAGATGAA-3'
ICER-R	5'-GTGGCAAAGCAGTAGTAGGA-3'
NRP2-F	5'-GACTCCAAGCCCACGGTAGA-3'
NRP2-R	5'-TGGTTGTCTCTTCGCTCTTCAC-3'
MGLL-F	5'-ACAAGTCAGGTCAGGCTTCA-3'
MGLL-R	5'-AAGTGGGGCCTTTCATAGCT-3'
Lgr4 -F	5'-GCCTGAATGGGCTAAATCAA-3'
Lgr4 -R	5'-CCTTTCTCCTGTGCCACACT-3'
LILRB2-F	5'-ACCCCCTGGACATCCTGATCAC-3'
LILRB2-R	5'-TGGAGTCTCTGTACCCTCC-3'
ERK5-F	5'-GCCTGTGTGTCCAGATGTTG-3'
ERK5-R	5'-CAGGCTGCAGAGTCAGATCA-3'
NDRG2-F	5'-CCCTGTGTTCCCTTTGGGAT-3'
NDRG2-R	5'-GTGAGGCCTGTTAGCTTGTG-3'
FABP4-F	5'-TTTCCTTCAAACTGGGCGTG-3'
FABP4-R	5'-CATTCCACCACCAGCTTGTC-3'
FoxO1-F	5'-AGGATCCGATGTCACCATGGCCG-3'
FoxO1-R	5'-AAAGGATCCACCATGGCCG-3'
ZEB1-F	5'-GATGACCTGCCAACAGACCA-3'
ZEB1-R	5'-CTTTCACTGCTCCTCCCTGG-3'
ITGA4-F	5'-TTCCAGAGCCAAATCCAAGAGTAA-3'
ITGA4-R	5'-AAGCCAGCCTTCCACATAACAT-3'
S1PR1-F	5'-CAGCAAATCGGACAATTCCT-3'
S1PR1-R	5'-GCCAGCGACCAAGTAAAGAG-3'
Siglec-10-F	5'-GTGACCGTTGTCTGCTTGTTTTCC-3'
Siglec-10-R	5'-CCAGGCTCTGGAGGAGCAGTT-3'

c-Maf-F	5'- CAGCAAGGAGGAGGTGATCC-3'
c-Maf-R	5'- GGTTCTTCTCCGACTCCAGG-3'
GCN2-F	5'- TCTCCCAGTCCTTTCTACCTG-3'
GCN2-R	5'- TGTCACTGAAGGCTCAATCTC-3'
ABHD5-F	5'-CCGGCTTCGAGATAAGTCCC-3'
ABHD5-R	5'-GCCAACCAGTTAGCCATCCT-3'
LIF-F	5'-ACAGAGCCTTTGCGTGAAAC-3'
LIF-R	5'-TGGTCCACACCAGCAGATAA-3'
STAT6-F	5'-GTGGTTTAGAAGAGGGGGAATTTT-3'
STAT6-R	5'-ATCTCAACCCCTATCTACCC-3'
STAT1-F	5'-AGTTTGATGTTTGTGGGGATTAATTAG-3'
STAT1-R	5'-ATCCTCAATACTCACTTTTCTCTACA-3'
SLC7A5-F	5'- GCATCG GCTTCACCATCA TC -3'
SLC7A5-R	5'- ACCACCTGCATGAGCTTCTGAC -3'
CD36-F	5'-GAACCACTGCTTTCAAAA ACTGG-3'
CD36-R	5'-GTCCTGAGTTATATTTTCCTTGG-3'
FABP4-F	5'-TTTCCTTCAAACTGGGCGTG-3'
FABP4-R	5'-CATTCCACCACCAGCTTGTC-3'
Fizz1-F	5'-TCGTGGAGAATAAGGTCAAGG-3'
Fizz1-R	5'-AGGAGGCCCATCTGTTCATA-3'
Mgl2-F	5'-AGGCACCCTAAGAGCCATTT-3'
Mgl2-R	5'-CCCTCTTCTCCAGTGTGCTC-3'
Arg-1-F	5'- AGACAGCAGAGGAGGTGAAGAG-3'
Arg-1-R	5'- CGAAGCAAGCCAAGGTTAAAGC-3'
Ym-1-F	5'- CATTCAGTCAGTTATCAGATTCC-3'
Ym-1-R	5'- AGTGAGTAGCAGCCTTGG-3'
MAT2A-F	5'-GACATTGGTGCTGGAGACCA-3'
MAT2A-R	5'-ACTCTGATG GGAAGCACAGC-3'
SHMT2-F	5'-CGAGTTGCGATGCTGTACTT-3'
SHMT2-R	5'-CTGCGTTGCTGTGCTGAG-3'
MTHFR -F	5'-TTTAGGTATGTGAAGTAGGGTAGATGT-3'
MTHFR -R	5'-CAAAAAACTAATAAAAAACCAACAAA-3'
MTR-F	5'-GTTCTGTTTCTCCAGGTCC-3'
MTR -R	5'-GAAGAATCGCATCGCTGC-3'
GLDC-F	5'-GATGCATTCATGAGTATTGCCAAGT-3'
GLDC-R	5'-GTGGACCACTCGGATGAGCTC-3'
RIP1-F	5'-TTCGGGAAGGTGTCCTTGTG-3'
RIP1-R	5'-CATTGTACTCAGCGCGGTTG-3'
Vector construction	
siRNA-MAT2A-1	5'-CACACAAGCUAAAUGCCAA-3'
siRNA- MAT2A-2	5'- CAGUUGUGCCUGCGAAAUA -3'
siRNA-NC	5'- UUCUCCGAACGUGUCACGUTT -3'
siRNA-WDR5-1	5'-GCUGGGAAUAUCCGAUGUATT-3'
siRNA-WDR5-2	5'-GCUCAGAGGAUAACCUUGUTT-3'

RIP1-promoter-F	5'-GCCGAGCTCGAGGGAGTGGACGCTGGAGCAA-3'
RIP1-promoter-R	5'-GCCGCTAGCTCGTCCCGTCACCCTCCTCT-3'

Supplemental Table S4. Information on antibodies.

Antibody	WB	CHIP	Specificity	Company (catalog number)
RIP1	1:1000	/	Rabbit monoclonal	Abcam (ab106393)
MAT2A	1:1000	/	Rabbit polyclonal	Abcam (ab154343)
WDR5	1:1000	1:200	Rabbit polyclonal	Abcam (ab56916)
β-Actin	1:2000	/	Rabbit polyclonal	Abcam (ab8227)
histone H3	1:1000	/	Rabbit monoclonal	CST (9715S)
H3K4me3	1:1000	1:200	Rabbit polyclonal	Abcam (8580)
H3K27me3	1:1000	/	Rabbit monoclonal	Abcam (ab192985)

Supplemental Table S5. Elution conditions for LC/MS analysis.

	Time (min)	Solvent A (%)	Solvent B1 (%)	Solvent B2 (%)	Flow rate (mL/min)
Sample analysis	Initial	99.90	0.10		0.40
	0.50	99.90	0.10		
	8.50	50.00	50.00		
	8.51	2.00	98.00		
	11.50	2.00	98.00		
Column wash	12.50	2.00		98.00	0.50
	15.50	2.00		98.00	
Column equilibration	16.50	99.90	0.10		0.40
	18.00	99.90	0.10		

Solvent A: 0.1% formic acid in water, Solvent B1: 0.1% formic acid in methanol and Solvent

Supplemental Table S6. Optimized compound-dependent MS parameters using Xevo TQ-S

mass spectrometer.

Analyte	Precursor ion mass (m/z)	Fragment ion mass (m/z)	Dwell time (s)	Cone voltage (V)	Collision Energy (V)	ESI Mode
Methionine	150.00	105.00	0.025	40.00	15.00	Pos
S-adenosylmethionine	399.00	136.00	0.025	62.00	42.00	Pos
S-adenosylhomocysteine	385.00	134.00	0.025	66.00	33.00	Pos

Supplemental Table S7. Regulators of antitumor immunity in tumor-associated macrophages

and relative fold-change in response to TSN in presence or absence of FIDAS-5

Factors	Effect	Ref	Fold-change
CD11b(ITGAM)	antitumor	[1]	2.32
RBPj	pro-tumor	[2]	0.98
MS4A4A	antitumor	[3]	0.72
CD51（ITGAV）	pro-tumor	[4]	0.56
CD39 （ENTPD1）	pro-tumor	[5]	0.49
CaMKK2	pro-tumor	[6]	0.81
PFKFB3	pro-tumor	[7]	0.93
NLRC4	pro-tumor	[8]	0.45
EphB4	pro-tumor	[9]	1.04
Clever-1 (STAB1)	pro-tumor	[10]	0.89
LAMP2a (Lamp2)	pro-tumor	[11]	0.51
ATP6V0d2	antitumor	[12]	0.87
RIP1 (RIPK1)	pro-tumor	[13]	0.16
ICER (CREM)	pro-tumor	[14]	0.81
NRP2 (NRP2)	pro-tumor	[15]	0.94
MGLL	antitumor	[16]	0.88
LGR4	pro-tumor	[17]	0.41
LILRB2	pro-tumor	[18]	0.62
ERK5 (MAPK7)	pro-tumor	[19]	0.96
NDRG2	pro-tumor	[20]	0.83
FABP4	pro-tumor	[21]	0.59
FOXO1	antitumor	[22]	1.21
ZEB1	pro-tumor	[23]	0.67
integrin α4(ITGA4)	pro-tumor	[24]	0.42
S1PR1	pro-tumor	[25]	0.71
Siglec-10	pro-tumor	[26]	0.96
c-Maf (MAF)	pro-tumor	[27]	0.47
GCN2(EIF2AK4)	pro-tumor	[28]	0.49
ABHD5	anti-tumor	[29]	0.44
LIF	pro-tumor	[30]	0.82
STAT6	pro-tumor	[31]	0.58
STAT1	antitumor	[32]	0.52

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