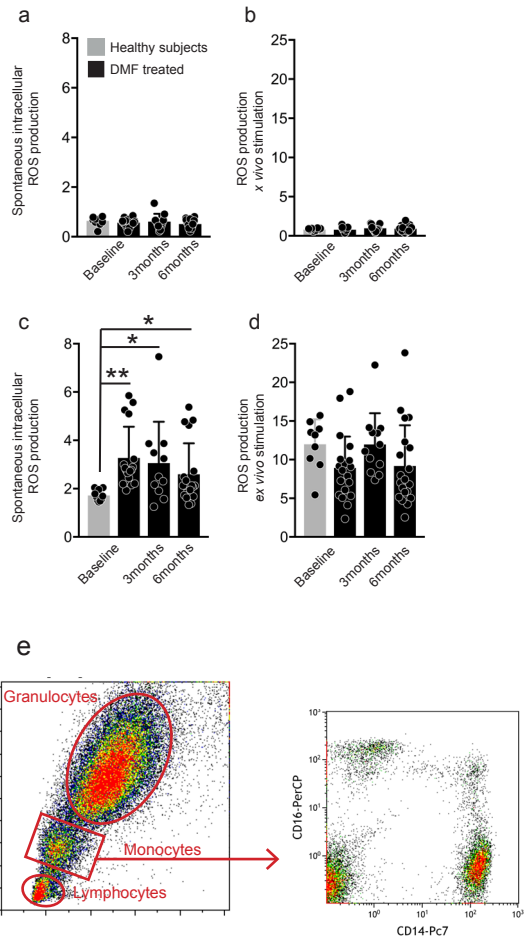


Therapeutic efficacy of dimethyl fumarate in relapsing-remitting multiple sclerosis associates with ROS pathway in monocytes

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Supplementary Fig. 1. ROS generation in granulocytes and lymphocytes. (a, b) ROS generation in lymphocytes from healthy subjects or DMF treated patients. (c, d) ROS generation in granulocytes from healthy subjects or DMF treated patients. (e) Sequential gating strategy. Graphs show means and S.D.. All analysis between healthy controls and patients are performed with Welch's t test. * $P < 0.05$, ** $P < 0.01$

Supplementary Table 1. Canonical pathways affected by differentially expressed genes in CD14+ monocytes after 6 months of treatment with DMF.

Ingenuity Canonical Pathway	-LOG(p-val)	Ratio	Molecules	z-score
Protein Ubiquitination Pathway	3.42	0.042	UBE2D4,PSMD10,DNAJC5,CUL2,PSMB2,BAG1,PSMA5,DNAJC10,UBE2E3,NEDD4L,ANAPC11	NaN
Thiosulfate Disproportionation III (Rhodanese)	3.37	0.667	MOC53,TST	NaN
Mechanisms of Viral Exit from Host Cells	2.84	0.098	VPS25,ACTA2,LMNB1,TSG101	NaN
NRF2-mediated Oxidative Stress Response	2.63	0.042	MGST1,DNAJC5,NRAS,GAB1,ACTA2,DNAJC10,UBE2E3,TXN	NaN
EIF2 Signaling	2.27	0.036	RPL4,NRAS,RPL18A,GAB1,ACTA2,RPL17,RPS25,RPS2	1.342
FAK Signaling	2.17	0.051	NRAS,CAPN11,GAB1,ACTA2,PTEN	NaN
Oxidative Phosphorylation	1.99	0.046	COX8A,SURF1,NDUFA81,ATP5MC3,NDUFA8	2.236
Hypoxia Signaling in the Cardiovascular System	1.90	0.053	UBE2D4,UBE2E3,LDHA,PTEN	NaN
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	1.87	0.029	WNT3A,NRAS,GAB1,CHP1,TLR8,FZD2,FCGR1A,FCGR3A/FCGR3B,PRSS1	NaN
Systemic Lupus Erythematosus Signaling	1.70	0.031	SNRPN,LSMB,NRAS,CD40,GAB1,FCGR1A,FCGR3A/FCGR3B	NaN
NF-kB Signaling	1.65	0.033	CSNK2A2,NRAS,CD40,GAB1,TLR8,TBK1	2.449
UDP-D-xylose and UDP-D-glucuronate Biosynthesis	1.62	0.500	UGDH	NaN
β -alanine Degradation I	1.62	0.500	ALDH6A1	NaN
Role of NFAT in Regulation of the Immune Response	1.60	0.032	NRAS,GAB1,CHP1,FCGR1A,FCGR3A/FCGR3B,GNNG7	NaN
Fc γ Receptor-mediated Phagocytosis in Macrophages and Monocytes	1.59	0.043	ACTA2,FCGR1A,FCGR3A/FCGR3B,PTEN	1.342
Fatty Acid α -oxidation	1.55	0.091	TMLHE,ALDH2	1
Melanoma Signaling	1.55	0.055	NRAS,GAB1,PTEN	NaN
D-myo-inositol (1,4,5,6)-Tetraakisphosphate Biosynthesis	1.54	0.035	PPP1R7,PPTC7,PPP4R1,PPP4C,PTEN	NaN
D-myo-inositol (3,4,5,6)-tetraakisphosphate Biosynthesis	1.54	0.035	PPP1R7,PPTC7,PPP4R1,PPP4C,PTEN	2.236
Prostate Cancer Signaling	1.53	0.041	NRAS,GAB1,NKX3-1,PTEN	NaN
Hereditary Breast Cancer Signaling	1.52	0.035	NRAS,GAB1,REC2,POLR2J,PTEN	NaN
Ovarian Cancer Signaling	1.52	0.035	WNT3A,NRAS,GAB1,FZD2,PTEN	NaN
Colorectal Cancer Metastasis Signaling	1.52	0.028	WNT3A,NRAS,GAB1,TLR8,FZD2,PTGER4,GNNG7	NaN
Huntington's Disease Signaling	1.50	0.028	NSF,DNAJC5,CAPN11,GAB1,POLR2J,GNNG7,NAPB	1.89
Phagosome Maturation	1.48	0.034	NSF,VPS18,ATP6V1C1,TSG101,NAPB	NaN
3-phosphoinositide Biosynthesis	1.46	0.030	GAB1,PPP1R7,PPTC7,PPP4R1,PPP4C,PTEN	2.449
L-carnitine Biosynthesis	1.45	0.333	TM1LHE	NaN
Mouse Embryonic Stem Cell Pluripotency	1.41	0.038	WNT3A,NRAS,GAB1,FZD2	1
3-phosphoinositide Degradation	1.39	0.032	PPP1R7,PPTC7,PPP4R1,PPP4C,PTEN	2.236
Endometrial Cancer Signaling	1.38	0.047	NRAS,GAB1,PTEN	NaN
IL-2 Signaling	1.38	0.047	CSNK2A2,NRAS,GAB1	NaN
D-myo-inositol-5-phosphate Metabolism	1.35	0.031	PPP1R7,PPTC7,PPP4R1,PPP4C,PTEN	NaN
Glioblastoma Multiforme Signaling	1.34	0.031	WNT3A,NRAS,GAB1,FZD2,PTEN	2.236
Phenylethylamine Degradation I	1.33	0.250	ALDH2	1
Molybdenum Cofactor Biosynthesis	1.33	0.250	MOC53	NaN
Paxillin Signaling	1.33	0.035	ITGA2B,NRAS,CAPN11,GAB1,ACTA2	NaN
Integrin Signaling	1.31	0.027	ITGA2B,NRAS,CAPN11,GAB1,ACTA2,PTEN	1.633

Supplementary Table 1. Canonical pathways affected by differentially expressed genes in CD14+ monocytes after 6 months of treatment with DMF.

DMF: Dimethyl fumarate.

Input gene list was based on differentially expressed genes with p-value < 0.01 and averageRMA > 4.

The table includes all canonical pathways from Ingenuity Pathway Analysis with Fisher's p-value < 0.05.

z-score: the activation z-score is used to infer likely activation states of upstream regulators (z-score > 2 corresponds to activation).

Supplementary Table 2. Canonical pathways affected by differentially methylated genes in CD14+ monocytes after treatment with DN

Ingenuity Canonical Pathway	-LOG(p-val)	Ratio	Molecules	N mol	Group	Cluster	ROS Score
Growth Hormone Signaling	4,15	0,104	PIK3R5,IGF1R,IRS2,RP56KA2,STAT3,PRKCZ,RP56KC1,PRKCB	8	M3 vs. M6	2	0
FLT3 Signaling in Hematopoietic Progenitor Cells	3,99	0,099	PIK3R5,STAT2,IRS2,MAPK13,RP56KA2,STAT3,CREB5,INPP5D	8	M3 vs. M6	1	0
Melanocyte Development and Pigmentation Signaling	2,93	0,078	GNAS,PRKAG2,PIK3R5,IRS2,RP56KA2,CREB5,RP56KC1	7	M3 vs. M6	1	0
Dopamine-DARPP32 Feedback in cAMP Signaling	2,90	0,062	PRKG1,GNAS,PPP1R1B,CSNK1G3,PPM1L,PRKAG2,CREB5,PRKCZ,PRKCB	9	M3 vs. M6	3	0
mTOR Signaling	2,72	0,054	PPM1L,PRKAG2,PIK3R5,RPTOR,IRS2,RP56KA2,PRKCZ,PLD1,RP56KC1,PRKCB	10	M3 vs. M6	1	0
Tec Kinase Signaling	2,70	0,058	LCK,GNAS,GNAS15,PIK3R5,STAT2,IRS2,STAT3,PRKCZ,PRKCB	9	M3 vs. M6	2	0
IL-15 Signaling	2,67	0,081	LCK,PIK3R5,IRS2,IL6,MAPK13,STAT3	6	M3 vs. M6	1	0,17
IL-3 Signaling	2,47	0,074	PIK3R5,IRS2,STAT3,PRKCZ,INPP5D,PRKCB	6	M3 vs. M6	2	0
Gap Junction Signaling	2,45	0,053	PRKG1,GNAS,CSNK1G3,PRKAG2,PIK3R5,IRS2,PRKCZ,GI1C1,PRKCB	9	M3 vs. M6	3	0
Adrenomedullin signaling pathway	2,43	0,053	PPARG,PRKG1,C3,GNAS,GNAS15,PRKAG2,PIK3R5,IRS2,MAPK13	9	M3 vs. M6	1	0
Renin-Angiotensin Signaling	2,43	0,064	PRKAG2,PIK3R5,IRS2,MAPK13,STAT3,PRKCZ,PRKCB	7	M3 vs. M6	2	0
HGF Signaling	2,39	0,063	DOCK1,PIK3R5,IRS2,IL6,STAT3,PRKCZ,PRKCB	7	M3 vs. M6	2	0,14
Synaptic Long Term Depression	2,36	0,056	PRKG1,GNAS,GNAS15,GRID2,PPM1L,IGF1R,PRKCZ,PRKCB	8	M3 vs. M6	3	0
PDGF Signaling	2,34	0,070	PIK3R5,IRS2,STAT3,INPP5D,PRKCB,PDGFRB	6	M3 vs. M6	1	0
Axonal Guidance Signaling	2,30	0,038	GLI2,GNAS,PIK3R5,EPHA3,PRKCZ,ADAMTS2,DOCK1,EPHA6,GNAS15,GLI1,PRKAG2,NFATC2,BMP7,IR15	15	M3 vs. M6	1	0
Superpathway of Inositol Phosphate Compounds	2,29	0,047	ITPK1,MINPP1,LCK,TNS3,PPP1R1B,PPM1H,PIK3R5,IRS2,INPP5D,PDGFRB	10	M3 vs. M6	1	0
G1q Signaling	2,29	0,054	GNAS,GNAS15,PIK3R5,NFATC2,IRS2,PRKCZ,PLD1,PRKCB	8	M3 vs. M6	2	0
Calcium-induced T Lymphocyte Apoptosis	2,29	0,081	LCK,NFATC2,PRKCZ,ORAI1,PRKCB	5	M3 vs. M6	3	0
NGF Signaling	2,28	0,060	PIK3R5,TRIO,IRS2,RP56KA2,CREB5,PRKCZ,RP56KC1	7	M3 vs. M6	1	0
eNOS Signaling	2,27	0,054	AQPS,PRKG1,GNAS,PRKAG2,PIK3R5,IRS2,PRKCZ,PRKCB	8	M3 vs. M6	2	0
Thrombopoietin Signaling	2,26	0,079	PIK3R5,IRS2,STAT3,PRKCZ,PRKCB	5	M3 vs. M6	2	0
UVB-Induced MAPK Signaling	2,26	0,079	PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB	5	M3 vs. M6	2	0
Corticotropin Releasing Hormone Signaling	2,24	0,059	GLI2,GNAS,PRKAG2,MAPK13,CREB5,PRKCZ,PRKCB	7	M3 vs. M6	3	0
CREB Signaling in Neurons	2,23	0,049	GNAS,GNAS15,GRID2,PRKAG2,PIK3R5,IRS2,CREB5,PRKCZ,PRKCB	9	M3 vs. M6	3	0
ERK/MAPK Signaling	2,21	0,049	PPARG,DOCK1,PPM1L,PRKAG2,PIK3R5,IRS2,STAT3,CREB5,PRKCB	9	M3 vs. M6	1	0
3-phosphoinositide Biosynthesis	2,21	0,049	ITPK1,MINPP1,LCK,TNS3,PPP1R1B,PPM1H,PIK3R5,IRS2,PDGFRB	9	M3 vs. M6	1	0
IL-12 Signaling and Production in Macrophages	2,13	0,056	PPARG,PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB,APOD	7	M3 vs. M6	2	0
Role of NFAT in Cardiac Hypertrophy	2,11	0,047	GNAS,PRKAG2,PIK3R5,IGF1R,IRS2,IL6,MAPK13,PRKCZ,PRKCB	9	M3 vs. M6	2	0,11
LXR/RXR Activation	2,07	0,061	ECHS1,C3,NR1H3,IL6,IL1RAPL1,APOD	6	M3 vs. M6	1	0,33
Insulin Receptor Signaling	2,04	0,054	ASIC2,PRKAG2,PIK3R5,RPTOR,IRS2,PRKCZ,INPP5D	7	M3 vs. M6	1	0
IGF-1 Signaling	2,03	0,060	PRKAG2,PIK3R5,IGF1R,IRS2,STAT3,PRKCZ	6	M3 vs. M6	2	0
Nitric Oxide Signaling in the Cardiovascular System	2,01	0,059	PRKG1,PRKAG2,PIK3R5,IRS2,PRKCZ,PRKCB	6	M3 vs. M6	2	0
Endothelin-1 Signaling	1,98	0,048	GNAS,GNAS15,PIK3R5,IRS2,MAPK13,PRKCZ,PLD1,PRKCB	8	M3 vs. M6	2	0
IL-17A Signaling in Airway Cells	1,95	0,067	PIK3R5,IRS2,IL6,MAPK13,STAT3	5	M3 vs. M6	1	0,20
FGF Signaling	1,90	0,065	PIK3R5,IRS2,MAPK13,STAT3,CREB5	5	M3 vs. M6	1	0
Role of NFAT in Regulation of the Immune Response	1,87	0,046	LCK,GNAS,GNAS15,CSNK1G3,PIK3R5,NFATC2,IRS2,ORAI1	8	M3 vs. M6	1	0
Thrombin Signaling	1,87	0,046	GNAS,GNAS15,PIK3R5,IRS2,MAPK13,ARHGFE10,PRKCZ,PRKCB	8	M3 vs. M6	2	0
3-phosphoinositide Degradation	1,86	0,050	ITPK1,MINPP1,TNS3,PPP1R1B,PPM1H,INPP5D,MTMR3	7	M3 vs. M6	1	0
Glioma Signaling	1,84	0,055	PIK3R5,IGF1R,IRS2,PRKCZ,PRKCB,PDGFRB	6	M3 vs. M6	2	0
CXCR4 Signaling	1,84	0,049	DOCK1,GNAS,GNAS15,PIK3R5,IRS2,PRKCZ,PRKCB	7	M3 vs. M6	2	0
JAK/Stat Signaling	1,81	0,062	PIK3R5,STAT2,IRS2,IL6,STAT3	5	M3 vs. M6	1	0,20
Prolactin Signaling	1,81	0,062	PIK3R5,IRS2,STAT3,PRKCZ,PRKCB	5	M3 vs. M6	2	0
GNRH Signaling	1,81	0,049	GNAS,GNAS15,PRKAG2,MAPK13,CREB5,PRKCZ,PRKCB	7	M3 vs. M6	3	0
Role of Tissue Factor in Cancer	1,80	0,054	LCK,GNAS15,PIK3R5,IRS2,MAPK13,RP56KA2	6	M3 vs. M6	1	0
Natural Killer Cell Signaling	1,80	0,054	LCK,PIK3R5,IRS2,PRKCZ,INPP5D,PRKCB	6	M3 vs. M6	2	0
Fc Epsilon RI Signaling	1,79	0,053	PIK3R5,IRS2,MAPK13,PRKCZ,INPP5D,PRKCB	6	M3 vs. M6	2	0
NF-kB Activation by Viruses	1,73	0,059	LCK,PIK3R5,IRS2,PRKCZ,PRKCB	5	M3 vs. M6	2	0
LPS-stimulated MAPK Signaling	1,73	0,059	PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB	5	M3 vs. M6	2	0
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	1,73	0,059	GNAS,GNAS15,PRKAG2,PRKCZ,PRKCB	5	M3 vs. M6	3	0
B Cell Receptor Signaling	1,72	0,043	APBB1P,PIK3R5,NFATC2,IRS2,MAPK13,CREB5,INPP5D,PRKCB	8	M3 vs. M6	1	0
CCR3 Signaling in Eosinophils	1,72	0,051	GNAS,PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB	6	M3 vs. M6	2	0
Breast Cancer Regulation by Stathmin1	1,71	0,043	GNAS,PPM1L,PRKAG2,PIK3R5,IRS2,ARHGFE10,PRKCZ,PRKCB	8	M3 vs. M6	2	0
Aldosterone Signaling in Epithelial Cells	1,71	0,046	ASIC2,DNAJC5,DNAJC8,PIK3R5,IRS2,PRKCZ,PRKCB	7	M3 vs. M6	2	0
PAK Signaling	1,69	0,058	ARHGAP10,PIK3R5,IRS2,EPHA3,PDGFRB	5	M3 vs. M6	1	0
fMLP Signaling in Neutrophils	1,69	0,050	GNAS,PIK3R5,NFATC2,IRS2,PRKCZ,PRKCB	6	M3 vs. M6	2	0
IL-6 Signaling	1,67	0,050	PIK3R5,IRS2,IL6,IL1RAPL1,MAPK13,STAT3	6	M3 vs. M6	1	0,17
CDK5 Signaling	1,67	0,057	GNAS,PPP1R1B,PPM1L,PRKAG2,MAPK13	5	M3 vs. M6	3	0
Adrenomedullin signaling pathway	1,66	0,029	C3,MAPK14,KCNQ2,PIK3R5,KCNN2	5	BL vs. M3	1	0,20
p70S6K Signaling	1,66	0,050	PPM1L,PIK3R5,IRS2,PRKCZ,PLD1,PRKCB	6	M3 vs. M6	2	0
P2Y Purigenic Receptor Signaling Pathway	1,64	0,049	PRKAG2,PIK3R5,IRS2,CREB5,PRKCZ,PRKCB	6	M3 vs. M6	2	0
ErbB Signaling	1,62	0,055	PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB	5	M3 vs. M6	2	0
PI3K Signaling in B Lymphocytes	1,61	0,048	C3,NFATC2,IRS2,PRKCZ,INPP5D,PRKCB	6	M3 vs. M6	3	0
AMPK Signaling	1,60	0,041	GNAS,PPM1L,PRKAG2,PIK3R5,RPTOR,IRS2,MAPK13,CREB5	8	M3 vs. M6	1	0
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monoc	1,60	0,054	DOCK1,PRKCZ,PLD1,INPP5D,PRKCB	5	M3 vs. M6	3	0
Huntington's Disease Signaling	1,59	0,039	DNAJC5,GNAS15,PIK3R5,IGF1R,DNM3,IRS2,CREB5,PRKCZ,PRKCB	9	M3 vs. M6	1	0
Role of Pattern Recognition Receptors in Recognition of Bacteria	1,55	0,047	C3,PIK3R5,IRS2,IL6,PRKCZ,PRKCB	6	M3 vs. M6	2	0,17
Cardiac Hypertrophy Signaling	1,50	0,039	GNAS,GNAS15,PRKAG2,PIK3R5,IGF1R,IRS2,IL6,MAPK13	8	M3 vs. M6	1	0,13
UVA-Induced MAPK Signaling	1,50	0,051	PIK3R5,IRS2,MAPK13,RP56KA2,RP56KC1	5	M3 vs. M6	1	0
G Beta Gamma Signaling	1,50	0,051	GNAS,GNAS15,PRKAG2,PRKCZ,PRKCB	5	M3 vs. M6	3	0
Type II Diabetes Mellitus Signaling	1,49	0,046	PPARG,PRKAG2,PIK3R5,IRS2,PRKCZ,PRKCB	6	M3 vs. M6	2	0
Xenobiotic Metabolism Signaling	1,48	0,037	AHRR,PPM1L,PIK3R5,IRS2,IL6,MAPK13,CYP2B6,PRKCZ,PRKCB	9	M3 vs. M6	1	0,11
G-Protein Coupled Receptor Signaling	1,45	0,036	GNAS,GNAS15,HTR7,PRKAG2,PIK3R5,IRS2,STAT3,CREB5,PRKCB	9	M3 vs. M6	1	0
NF-kB Signaling	1,45	0,041	LCK,PIK3R5,IGF1R,IRS2,PRKCZ,PRKCB,PDGFRB	7	M3 vs. M6	2	0
Opioid Signaling Pathway	1,43	0,038	LCK,GNAS,PRKAG2,GRK5,RP56KA2,CREB5,PRKCZ,PRKCB	8	M3 vs. M6	3	0
Paxillin Signaling	1,42	0,049	DOCK1,ACTN2,PIK3R5,IRS2,MAPK13	5	M3 vs. M6	1	0
Neuropathic Pain Signaling In Dorsal Horn Neurons	1,42	0,049	PRKAG2,PIK3R5,IRS2,PRKCZ,PRKCB	5	M3 vs. M6	2	0
Phospholipase C Signaling	1,42	0,038	LCK,GNAS,NFATC2,CREB5,ARHGFE10,PRKCZ,PLD1,PRKCB	8	M3 vs. M6	3	0
Relaxin Signaling	1,41	0,044	GNAS,GNAS15,PRKAG2,PIK3R5,IRS2,PRKCZ	6	M3 vs. M6	2	0
Production of Nitric Oxide and Reactive Oxygen Species in Macro	1,40	0,040	PPM1L,PIK3R5,IRS2,MAPK13,PRKCZ,PRKCB,APOD	7	M3 vs. M6	2	0
Sperm Motility	1,40	0,048	PRKG1,GNAS,PRKAG2,PRKCZ,PRKCB	5	M3 vs. M6	3	0
Signaling by Rho Family GTPases	1,37	0,037	GNAS,CDH18,GNAS15,PIK3R5,IRS2,ARHGFE10,PRKCZ,PLD1	8	M3 vs. M6	1	0
Glucocorticoid Receptor Signaling	1,35	0,033	PRKAG2,PIK3R5,NFATC2,TAT,IRS2,IL6,MAPK13,STAT3,KRT20,TSC22D3	10	M3 vs. M6	1	0,10
Systemic Lupus Erythematosus Signaling	1,35	0,039	SNRPN,LCK,PIK3R5,NFATC2,IRS2,INPP5D	7	M3 vs. M6	1	0,14
Hepatic Cholestasis	1,34	0,042	PRKAG2,NR1H3,IL6,IL1RAPL1,PRKCZ,PRKCB	6	M3 vs. M6	3	0,17
p38 MAPK Signaling	1,33	0,046	IL1RAPL1,MAPK13,RP56KA2,CREB5,RP56KC1	5	M3 vs. M6	1	0
Synaptic Long Term Potentiation	1,31	0,046	GNAS15,PRKAG2,CREB5,PRKCZ,PRKCB	5	M3 vs. M6	3	0

Supplementary Table 2. Canonical pathways affected by differentially methylated genes in CD14+ monocytes after treatment with DMF.

DMF: Dimethyl fumarate; BL: baseline; M3: 3 months after initiation of DMF treatment; M6: 6 months after initiation of DMF treatment.

Input gene list was based on genes associated with differentially methylated probes that displayed $\Delta b > 5\%$ methylation change and $p\text{-value} < 0.001$.

The table includes all canonical pathways from Ingenuity Pathway Analysis with Fisher's $p\text{-value} < 0.05$ and number of molecules ≥ 5

ROS score indicates % overlap with a list of assembled known ROS genes:

ACADL	CD83	ELK1	HADHB	IL6	MYC	SDHB	TNC
ACADM	CD84	EPHA2	HBEGF	INHBA	MYD88	SDHC	TNFAIP8
ACADS	CDC14C	ETFDH	HCAR2	IRAK1	NAIP	SDHD	TNFRSF11A
ACADVL	CDC45	FADD	HGF	IRAK4	NCF2	SERPINA1	TNS1
ACAT1	CDHR1	FAR1	HIF1A	IRF1	NCF4	SHC1	TOLLIP
ACO1	CDKN1A	FAR2	HIF1A-AS1	IRF2	NFE2L2	SHC3	TPI1
ACO2	CDKN1B	FAR2P2	HLA-A	IRF3	NFE2L2	SIRPA	TRAF2
ACOT9	CDKN2B	FCGR1A	HLA-B	IRF9	NFIX	SIRPD	TRAJ22
ACSL1	CES1	FCGR3B	HLA-C	ITGA2	NFKB1	SLC25A20	TRAJ30
ACSL3	CES2	FCGRT	HLA-DOA	ITGA7	NKAPL	SLC27A2	TRAV13-1
ACSL4	CES3	FDXR	HLA-DRB1	ITGAX	NOD1	SLC7A11	TRAV38-1
ACSL5	CES4A	FGF13	HLA-F	ITGB4	NOG	SMAD1	TRAV4
ACSL6	CES5A	FH	HLA-L	JUN	NOS2	SMAD2	TRBJ2-3
ADH7	CLEC12B	FMO5	HMGCL	JUNB	NOX1	SMAD3	TRBV5-1
AGER	CLEC4A	FN1	HMGCS2	KLHDC10	NOX3	SMAD5	TRGV5
ALDH3A1	CLEC4C	FOS	HMOX1	KLHL1	NOX4	SMAD7	TXN2
APOBEC1	CLEC4E	FOXP3	HSP90AA1	LAX1	NOX5	SMAD9	TXNRD1
APOL3	CLEC5A	FPR1	HSPA1A	LCNL1	NOXA1	SOD1	TXNRD2
APOOL	CLEC6A	FPR2	ICAM1	LOC100287651	NOXO1	SOD2	TXNRD3
APP	CLEC7A	FPR3	IDH2	LPL	NPL	SOD3	UGT1A1
ARHGEF18	CLUH	FST	IDH3A	LTBP1	NQO1	SORBS1	VASP
ARHGEF7	COL1A2	FTL	IDH3B	LTBP2	OGDH	SOS1	VAV1
ATG4A	CPT1A	FYN	IDH3G	LTBP2	OLR1	SP1	VAV2
BCL2	CPT2	G6PD	IFI27L1	LY6G6D	OXCT1	SQSTM1	VAV3
BDH1	CRAT	GAS2L3	IFNA1	LY6H	PC	SRXN1	VEGFA
BLVRB	CS	GBP1	IFNAR1	LY9	PCK2	SSTR3	XDH
BMP4	CSF2	GCDH	IFNAR2	MAFF	PDCD7	STAT1	ZYX
BRAF	CTH	GCLC	IFNB1	MAFG	PDGFB	SUCLG1	
CAMK2N1	CXCL10	GCLM	IFNG	MAL	PDHA1	SUCLG2	
CAPNS1	CXCL11	GGT1	IFNG-AS1	MAOA	PDP2	TAP1	
CASP8	CXCL9	GK2	IFNGR1	MAP2K3	PDPR	TBK1	
CAT	CYBA	GPD2	IFNGR2	MAP2K6	PECR	TBRG4	
CAV1	CYBB	GPX1	IGDCC4	MAPK12	PGD	TCL1B	
CAV2	CYP1A1	GPX2	IGHD	MAPK14	POLDIP2	TERT	
CAV3	CYP2A6	GPX3	IGKV1D-39	MAPK15	PPARD	TGFA	
CBR1	CYP4A11	GRB2	IGKV1D-8	MAPK8	PRDX1	TGFB1	
CBR3	DECR1	GSR	IGKV1OR-3	MDFI	PRDX6	TGFB2	
CBS	DLD	GSTA1	IGLV8-61	MDH2	PREX1	TGFB2-AS1	
CCL5	DLST	GSTA2	IL10	ME1	PSMB9	TGFBR1	
CCND1	DNAJB1	GSTA3	IL10RB	MET	PTGER1	TGFBR2	
CCR6	DOCK2	GSTA4	IL12A	MGST1	PTGR1	TGFBR3	
CD11c	DUOX1	GSTM2	IL12B	MGST3	PTK2	THBS1	
CD14	DUOX2	GSTM3	IL15	MKI67	PXN	TIAM2	
CD19	DUOXA1	GSTM4	IL17A	MLYCD	RAC1	TIRAP	
CD1E	DUOXA2	GSTM5	IL17D	MMP1	RAC2	TLR2	
CD38	ECHS1	GSTP1	IL17RE	MMP12	SCP2	TLR4	
CD40	ECI1	GSTT1	IL19	MPST	SDHAF2	TLR5	
CD47	EGR1	GSTT2	IL1A	MST1R	SDHAP1	TLR6	
CD5	EHHADH	HADH	IL1B	MT1X	SDHAP2	TLR9	
CD69	EIF2AK2	HADHA	IL23A	MTFR1	SDHAP3	TMEM8B	

Supplementary Table 3. Canonical pathways affected by differentially methylated genes in CD4+ T-cells after treatment with DMF.

Ingenuity-LOG(p-val)	Ratio	Molecule	mol	Group	Cluster	ROS Score
1D-myo-ii,43	0,294	ITPK1,ITP5		BL vs. M6	1	0
3-phosph2,10	0,190	FYN,PTPN35		M3 vs. M4		0,06
3-phosph1,77	0,168	G6PC2,NL31		BL vs. M6		0,03
3-phosph2,26	0,204	PTPN2,NL29		M3 vs. M4		0
3-phosph2,58	0,197	G6PC2,NL28		BL vs. M6		0
Amyloid F1,83	0,234	PRKACB,#11		BL vs. M6		0,18
Androgen1,49	0,174	PRKACB,C21		BL vs. M6		0,14
Apoptosis1,48	0,183	GAS2,MA17		BL vs. M6		0,29
ATM Sign2,64	0,237	MAP2K4,I22		M3 vs. M5		0
Axonal G1,40	0,157	PRKACB,#62		M3 vs. M5		0,08
Axonal G1,72	0,149	DPYSL2,P159		BL vs. M6		0,05
B Cell Rec1,68	0,166	MAP2K6,I31		BL vs. M6		0,26
BMP sign1,41	0,189	PRKACB,#14		BL vs. M6		0,43
Calcium S1,66	0,183	PRKACB,#30		M3 vs. M5		0
Calcium S2,50	0,189	PRKACB,#31		BL vs. M6		0
Calcium-ii,34	0,194	CALM1 (v12)		BL vs. M6		0,08
cAMP-me1,75	0,179	AKAP12,P36		M3 vs. M5		0
cAMP-me3,52	0,199	AKAP12,P40		BL vs. M6		0
Cardiac P'3,04	0,231	AKAP12,P28		M3 vs. M5		0
Cardiac P'3,73	0,231	AKAP12,P28		BL vs. M6		0
CD28 Sig1,34	0,181	MAP2K4,I23		M3 vs. M5		0,09
CDK5 Sig2,23	0,223	ITGB1,PR121		M3 vs. M5		0
CDK5 Sig2,04	0,202	PRKACB,P19		BL vs. M6		0,05
Colorecta1,33	0,026	JAK1,GAB6		BL vs. M3		0
Corticotrc1,39	0,185	PRKACB,#22		M3 vs. M5		0
Corticotrc1,83	0,185	NOS1,PRF22		BL vs. M6		0
CXCR4 Sig1,59	0,034	DOCK1,PJ5		BL vs. M3		0
D-myo-in1,43	0,294	ITPKB,INP5		BL vs. M6		0
D-myo-in2,29	0,209	PTPN2,NL27		M3 vs. M4		0
D-myo-in2,27	0,194	G6PC2,NL25		BL vs. M6		0
D-myo-in2,29	0,209	PTPN2,NL27		M3 vs. M4		0
D-myo-in2,27	0,194	G6PC2,NL25		BL vs. M6		0
D-myo-in2,17	0,201	PTPN2,NL29		M3 vs. M4		0
D-myo-in2,20	0,188	G6PC2,NL27		BL vs. M6		0
Dopamin1,43	0,209	PRKACB,#14		M3 vs. M5		0
Dopamin3,92	0,284	PRKACB,P19		BL vs. M6		0,05
Dopamin2,13	0,200	PRKACB,#29		M3 vs. M5		0
Dopamin3,41	0,214	NOS1,PRF31		BL vs. M6		0
Ephrin Re1,42	0,030	PAK1,EPH5		BL vs. M3		0
Epithelial1,83	0,197	TCF4,ARP25		M3 vs. M5		0,04
Epithelial1,78	0,181	AKT2,TCF23		BL vs. M6		0,13
Fc Epsilon1,31	0,168	MAP2K6,I20		BL vs. M6		0,15
FcRIIB S1,50	0,194	MAP2K4,I14		BL vs. M6		0,07
FXR/RXR i2,37	0,053	MLXIP1,S15		BL vs. M3		0
G Beta G1,73	0,202	PRKACB,#21		M3 vs. M5		0,05
G Beta G2,20	0,202	PRKACB,#21		BL vs. M6		0,05
GABA Rec3,55	0,286	ADCY2,Uf20		M3 vs. M5		0
Gla12/13,1,91	0,041	CDH18,GJ5		BL vs. M3		0
Gla1 Sign1,71	0,185	PRKACB,#20		BL vs. M6		0,05
Glaq Sign1,35	0,163	AKT2,HTR24		BL vs. M6		0,13
GNRH Sig1,57	0,033	PAK1,MA5		BL vs. M3		0
GNRH Sig1,46	0,180	MAP2K6,I27		M3 vs. M5		0,15
GNRH Sig1,48	0,167	MAP2K6,I25		BL vs. M6		0,28
GP6 Sign1,96	0,042	ITGA2B,G5		BL vs. M3		0
GP6 Sign3,10	0,218	COL4A3,C26		BL vs. M6		0,15
GPCR-Me1,53	0,188	PRKACB,#16		BL vs. M6		0
Hepatic C1,68	0,174	MAP2K4,I25		BL vs. M6		0,20
Hereditar1,54	0,184	NPM1,AR26		M3 vs. M5		0
HGF Sign2,71	0,052	DOCK1,PJ6		BL vs. M3		0
HIPPO sig1,36	0,198	SMAD2,V16		M3 vs. M5		0,25
HIPPO sig2,80	0,235	SMAD2,P19		BL vs. M6		0,21
Huntingt2,02	0,167	MAP2K4,I39		BL vs. M6		0,05
Iz-Adren1,33	0,181	PRKACB,#15		BL vs. M6		0
IL-15 Prox3,07	0,375	PTK2,PRK9		BL vs. M6		1
IL-15 Sign1,45	0,188	IL15RA,A115		BL vs. M6		0,47
IL-17A Sig1,68	0,200	MAP2K4,I15		BL vs. M6		0,33
IL-22 Sign1,83	0,292	MAP2K4,I7		BL vs. M6		0,14
IL-6 Sign1,32	0,167	MAP2K6,I21		BL vs. M6		0,29
ILK Sign1,41	0,030	DOCK1,GJ5		BL vs. M3		0
Insulin Re1,46	0,169	PRKACB,P23		BL vs. M6		0,04
Leukocyte1,46	0,159	MAP2K4,I31		BL vs. M6		0,23
Melanin2,60	0,242	MAP2K6,I16		BL vs. M6		0,06
Molecular2,13	0,171	MAP2K4,I62		M3 vs. M5		0,21
Molecular1,94	0,154	MAP2K4,I56		BL vs. M6		0,21
Netrin Sig3,88	0,327	PRKACB,R17		M3 vs. M5		0
Netrin Sig3,84	0,308	PRKACB,R16		BL vs. M6		0
Neuroin1,2,14	0,178	MAP2K4,I49		M3 vs. M5		0,24
Neuroin1,1,52	0,153	MAP2K4,I42		BL vs. M6		0,38
Nitric Oxi1,72	0,188	PRKACB,#19		BL vs. M6		0,05
nNOS Sig3,04	0,295	NOS1,CA113		BL vs. M6		0
nNOS Sig2,03	0,300	SMTB2,RV9		M3 vs. M5		0
nNOS Sig1,78	0,267	NOS1,CA18		BL vs. M6		0
Opioid Sig2,63	0,195	MAP2K6,I42		M3 vs. M5		0,07
Opioid Sig2,92	0,186	MAP2K6,I40		BL vs. M6		0,10
Pavillin Sig2,12	0,046	DOCK1,PJ5		BL vs. M3		0
Phototr2,15	0,270	PRKACB,C10		BL vs. M6		0
PI3K/AKT 1,91	0,041	JAK1,FOX5		BL vs. M3		0,20
PI3K/AKT 1,73	0,195	ITGB1,GA24		M3 vs. M5		0,08
PPAR α /R1,34	0,160	MAP2K6,I26		BL vs. M6		0,31
Productio1,80	0,170	MAP2K4,I30		BL vs. M6		0,20
Protein K12,36	0,176	PRKACB,P60		M3 vs. M5		0,03
Protein K12,93	0,170	PRKACB,P58		BL vs. M6		0,09
PTEN Sig1,94	0,203	ITGB1,M24		M3 vs. M5		0,17
PXR/RXR i2,41	0,255	PRKACB,#13		BL vs. M6		0,08
Rac Sign1,46	0,188	ITGB1,M22		M3 vs. M5		0,27
Rac Sign2,21	0,197	MAP2K4,I23		BL vs. M6		0,48
RAR Actv1,97	0,175	MAP2K4,I30		BL vs. M6		0,27
Relaxin S1,40	0,167	PRKACB,#23		BL vs. M6		0,13
Renin-Ang1,67	0,181	MAP2K4,I21		BL vs. M6		0,38
Role of Bf2,64	0,250	IFNG,RBL19		M3 vs. M5		0,05
Role of Bf1,33	0,184	RBL2,RBB14		BL vs. M6		0
Role of C1,77	0,236	RPA1,PPP13		M3 vs. M5		0
Role of JA1,73	0,280	MAP2K4,I7		BL vs. M6		0,29
Role of JA2,27	0,348	IFNG,PTP8		M3 vs. M5		0,13
Role of N13,71	0,203	MAP2K6,I40		BL vs. M6		0,08
Role of O:1,99	0,033	FOXO1,GJ7		BL vs. M3		0
Role of P1,41	0,220	MAP2K6,I9		BL vs. M6		0,89
Sertoli Ce2,08	0,180	MAP2K4,I29		BL vs. M6		0,07
Signaling 1,45	0,028	PAK1,CDH6		BL vs. M3		0
Sonic Hed2,07	0,296	PRKACB,P8		BL vs. M6		0
Sperm M1,73	0,202	PNPLA8,P21		M3 vs. M5		0,10
Sperm M1,33	0,173	PRKACB,C18		BL vs. M6		0,11
Superspat1,49	0,273	IMPAD1,I6		BL vs. M6		0
Superspat1,62	0,175	FYN,PTPN37		M3 vs. M4		0,05
Superspat1,60	0,160	G6PC2,NL34		BL vs. M6		0,03
Synaptic I3,44	0,228	GRID2,PLJ4		M3 vs. M5		0
Synaptic I1,75	0,174	NOS1,GR126		BL vs. M6		0
Synaptic I1,75	0,184	PRKACB,P21		BL vs. M6		0
Tec Kinase1,52	0,032	PAK1,JAK5		BL vs. M3		0
Telomera1,79	0,202	HDAC9,H122		M3 vs. M5		0,05
Tight Jun1,60	0,173	PRKACB,C24		BL vs. M6		0,13
Type I Dia2,19	0,048	JAK1,HLA5		BL vs. M3		0,20
Type II Di:1,78	0,038	GAB1,SH:5		BL vs. M3		0
Type II Di:1,36	0,167	MAP2K4,I22		BL vs. M6		0,36

Supplementary Table 3. Canonical pathways affected by differentially methylated genes in CD4+ T-cells after treatment with DMF.

DMF: Dimethyl fumarate; BL: baseline; M3: 3 months after initiation of DMF treatment; M6: 6 months after initiation of DMF treatment.
 Input gene list was based on genes associated with differentially methylated probes that displayed delta b > 5% methylation change and p-value < 0.001.
 The table includes all canonical pathways from Ingenuity Pathway Analysis with Fisher's p-value < 0.05 and number of molecules \geq 5.

Supplementary Table 4. Functions affected by differentially methylated genes in CD4+ T-cells after treatment with DMF.

Categories	Diseases or Functions Annotation	P-val	Molecules	N mol	Group
Hematological System Development and Function, Tissue Morphology	Quantity of mononuclear leukocytes	3,90E-02	CDK6,CHST2,CXCL18		BL vs. M3
Cell Death and Survival	Apoptosis of B lymphocytes	1,65E-02	BCL11A,BCL2A1,B26		BL vs. M6
Cell Death and Survival	Apoptosis of B-lymphocyte derived cell lines	1,65E-02	BCL2A1,BCR,BLK,(24		BL vs. M6
Cell Death and Survival	Apoptosis of leukocyte cell lines	4,56E-02	BCL2A1,BCR,BLK,(32		BL vs. M6
Cell Cycle	Arrest in G1 phase	2,01E-02	BCR,DCN,FOXO1,(8		BL vs. M6
Cell Cycle	Arrest in G1 phase of B-lymphocyte derived cell lines	6,35E-03	BCR,FOXO1,GRID:6		BL vs. M6
Infectious Diseases	Bacterial Infections	2,86E-02	CASP1,CASP4,CSK 5		BL vs. M6
Cell Death and Survival	Cell death of B-lymphocyte derived cell lines	1,65E-02	BCL2A1,BCR,BLK,(25		BL vs. M6
Cell Death and Survival	Cell death of leukocyte cell lines	1,53E-02	ANTXR1,BCL2A1,E39		BL vs. M6
Cellular Movement, Hematological System Development and Function	Cell movement of naive lymphocytes	1,21E-02	BACH2,CCL20,CX6		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Cell proliferation of leukocyte cell lines	3,27E-02	ABL2,BTCR,EBF1,LY7		BL vs. M6
Cellular Development, Hematological System Development and Function	Commitment of lymphocytes	6,35E-03	DTX1,EBF1,IL6,PA 6		BL vs. M6
Cell Death and Survival	Delay in apoptosis of phagocytes	1,59E-02	CASP1,CASP4,IL6, 5		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of B lymphocytes	Development of B lymphocytes	2,19E-02	ADAM10,AFF1,AK28		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of B-1 lymphocytes	Development of B-1 lymphocytes	1,71E-03	AKT2,BTCR,EBF1,LY7		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Development of bone marrow-derived macrophages	4,00E-02	AKAP13,CAV1,FOXO8		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of follicular B lymphocytes	Development of follicular B lymphocytes	1,17E-02	ADAM10,AKT2,BT7		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of marginal-zone B lymphocytes	Development of marginal-zone B lymphocytes	6,35E-03	ADAM10,AKT2,BT6		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of plasma cells	Development of plasma cells	2,86E-02	BACH2,CXCL12,DIC5		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Differentiation of myeloid progenitor cells	4,84E-02	BTK,FIP1L1,IL15,IL6		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of naive lymphocytes	Differentiation of naive lymphocytes	4,55E-02	AHR,BCL6,EFNB2, 12		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of pro-B lymphocytes	Differentiation of pro-B lymphocytes	4,00E-02	BLK,EBF1,ETV6,LY8		BL vs. M6
Cell-To-Cell Signaling and Interaction, Inflammatory Response	Immune response of leukocyte cell lines	4,84E-02	APP,CD38,FOXO1, 6		BL vs. M6
Cell Cycle	Interphase of leukocyte cell lines	1,35E-02	BCR,CXCL12,FOXO8		BL vs. M6
Cell Death and Survival	Killing of leukocyte cell lines	4,00E-02	CD22,EXOC2,IL15, 6		BL vs. M6
Cellular Movement, Hematological System Development and Function	Migration of naive lymphocytes	7,63E-03	BACH2,CXCL12,CX5		BL vs. M6
Hematological System Development and Function, Lymphoid Tissue Morphology	Morphology of lymph follicle	8,88E-03	BACH2,EP515,FN1 6		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Osteoclastogenesis of macrophages	4,42E-02	CAST,CAV1,DICER 9		BL vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Osteoclastogenesis of phagocytes	4,17E-02	CAST,CAV1,DICER 10		BL vs. M6
Cell Morphology	Polarization of Th17 cells	2,86E-02	AHR,CD36,IL15,IL5		BL vs. M6
Hematological System Development and Function, Hypersensitivity	Quantity of mast cells	1,68E-02	BCL2A1,CASP1,CA12		BL vs. M6
Hematological System Development and Function, Hematopoiesis	Quantity of pre-B lymphocytes	2,30E-02	AFF1,AKAP13,ARF 24		BL vs. M6
Cell Signaling, Small Molecule Biochemistry	Synthesis of nitric oxide	3,61E-02	ALOX5,APP,BDNF, 17		BL vs. M6
Connective Tissue Disorders, Immunological Disease, Inflammatory Response	Systemic juvenile idiopathic arthritis	2,81E-02	ASAP1,ATP2B1,CA14		BL vs. M6
Gene Expression	Transactivation of RNA	1,59E-02	CD300LB,CD300L5		BL vs. M6
Cellular Movement, Hematological System Development and Function	Transendothelial migration of lymphocytes	4,07E-02	CAV1,CXCL12,ENF7		BL vs. M6
Cellular Movement, Hematological System Development and Function	Transendothelial migration of mononuclear leukocytes	3,41E-02	CAV1,CCL7,CXCL1 8		BL vs. M6
Cancer	Transformation of B-lymphocyte derived cell lines	4,63E-02	ETV6,FIP1L1,HIP1 5		BL vs. M6
Cell-mediated Immune Response, Cellular Development, Cellular Function and Maintenance	Transition of thymocytes	1,13E-02	BDNF,CHEK1,DOK5		BL vs. M6
Cellular Function and Maintenance	Turnover of cells	2,16E-02	CCL20,CD22,DICE15		BL vs. M6
Cell Morphology, Humoral Immune Response, Immunological Disease	Abnormal morphology of B-1 lymphocytes	1,69E-02	CARD11,CR2,EBF15		M3 vs. M6
Hematological System Development and Function, Immune Cell Trafficking	Accumulation of regulatory T lymphocytes	3,21E-02	EGRF,IFNG,IKKB, 6		M3 vs. M6
Cell-To-Cell Signaling and Interaction, Hematological System Development and Function	Activation of regulatory T lymphocytes	3,10E-02	BACH2,BCL11B,CL9		M3 vs. M6
Cell Death and Survival	Apoptosis of B-lymphocyte derived cell lines	8,61E-03	ABL1,BCL2,BCL2L:27		M3 vs. M6
Cell Death and Survival	Apoptosis of leukocyte cell lines	1,05E-02	ABL1,BCL2,BCL2L:38		M3 vs. M6
Cell Death and Survival	Apoptosis of thymocytes	1,18E-02	ABL1,BBC3,BCL11 29		M3 vs. M6
Cell Cycle	Arrest in G1 phase of B-lymphocyte derived cell lines	4,17E-02	ABL1,BCR,GRID2,15		M3 vs. M6
Cell Death and Survival	Cell death of leukocyte cell lines	2,70E-02	ABL1,BCL2,BCL2L:41		M3 vs. M6
Cell Death and Survival	Cell death of monocyte-derived dendritic cells	1,43E-02	BCL2,BCL2L1,IKKB 6		M3 vs. M6
Cell Death and Survival	Cell death of thymocytes	2,11E-02	ABL1,BBC3,BCL11 31		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Cell proliferation of leukocyte cell lines	2,26E-03	ABCA3,ABL1,ABL254		M3 vs. M6
Cell Death and Survival	Cell viability	2,43E-02	ABL1,ADGRE2,API59		M3 vs. M6
Cell Death and Survival, Hematological System Development and Function	Cell viability of B-lymphocyte derived cell lines	4,18E-02	ABL1,BCL2,BCL2L:14		M3 vs. M6
Cell Death and Survival, Hematological System Development and Function	Cell viability of leukocyte cell lines	3,82E-02	ABL1,BCL2,BCL2L:17		M3 vs. M6
Cellular Function and Maintenance	Cellular homeostasis	4,10E-02	ABL1,ABL2,ADOR/126		M3 vs. M6
Cellular Development, Hematological System Development and Function	Commitment of lymphocytes	1,03E-02	DTX1,EBF1,IL6,PA 6		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of B lymphocytes	Development of B lymphocytes	2,57E-02	ARF1,BCL2,BCL2L:30		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of plasma cells	Development of plasma cells	4,17E-02	CCR2,DICER1,IL21R 5		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Development of pro-B lymphocytes	Development of pro-B lymphocytes	3,75E-02	BLK,FYN,IFNG,LYN 7		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Embryonic Differentiation of pro-B lymphocytes	Differentiation of pro-B lymphocytes	9,17E-03	BLK,EBF1,ETV6,FY 10		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Expansion of hematopoietic progenitor cells	1,20E-02	BCL2L1,EBF1,EOW8		M3 vs. M6
Cell-mediated Immune Response, Cellular Development, Cellular Function and Maintenance	Expansion of thymocytes	1,91E-02	EOMES,IKZF1,LCP 6		M3 vs. M6
Cellular Function and Maintenance	Lymphocyte homeostasis	2,49E-02	ABL1,ABL2,ADOR/114		M3 vs. M6
Antigen Presentation, Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance	Positive selection of thymocytes	3,75E-02	CADM1,ELK4,NF1 7		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function	Proliferation of hematopoietic progenitor cells	4,42E-02	BBC3,BCL2,BCL2L:25		M3 vs. M6
Cellular Development, Cellular Growth and Proliferation	Proliferation of myeloid cells	2,53E-02	CUX1,CYSLTR2,DC23		M3 vs. M6
Cell-mediated Immune Response, Cellular Development, Cellular Function and Maintenance	Proliferation of thymocytes	3,34E-02	BBC3,BLM,EGR3,F 18		M3 vs. M6
Hematological System Development and Function, Hypersensitivity	Quantity of mast cells	1,47E-02	ATF3,CASP1,CASP 13		M3 vs. M6
Cell Cycle	Replication of cells	1,43E-02	CASP1,IFNG,NLRP 6		M3 vs. M6
Connective Tissue Disorders, Immunological Disease, Inflammatory Response	Systemic juvenile idiopathic arthritis	1,38E-02	ASAP1,ATP2B1,DC 16		M3 vs. M6
Cell-mediated Immune Response, Cellular Function and Maintenance	T cell homeostasis	4,33E-02	ABL1,ABL2,ADOR/106		M3 vs. M6
Cellular Function and Maintenance	Turnover of cells	3,19E-02	BCL2L1,CD22,DIC5		M3 vs. M6

Supplementary Table 4. Functions affected by differentially methylated genes in CD4+ T-cells after treatment with DMF.

DMF: Dimethyl fumarate; BL: baseline; M3: 3 months after initiation of DMF treatment; M6: 6 months after initiation of DMF treatment.

Input gene list was based on genes associated with differentially methylated probes that displayed $\Delta b > 5\%$ methylation change and $p\text{-value} < 0.001$.

The table includes all functional annotations from Ingenuity Pathway Analysis with Fisher's $p\text{-value} < 0.05$ and number of molecules ≥ 5 .

Supplementary Table 5. Upstream regulators predicted to explain a pattern of differentially methylated genes in CD4+ T-cells after treatment with DMF.

Upstream Regulator	Molecule Type	P-val	Target molecules in dataset	N mol	Group
NOTCH2	transcription regulator	7,64E-04	DTX1,IL22,IL6,TNF,TSPAN33	5	BL vs. M6
EP300	transcription regulator	2,64E-03	ACOXL,AHI1,AKAP12,ARHGAP24,BCL6,BTK,C36	36	BL vs. M6
WNT3A	cytokine	2,83E-03	IL6,NANOG,RUNX1,RUNX1T1,TNF	5	BL vs. M6
STAT5B	transcription regulator	9,89E-03	ASAP1,BCL6,CASP4,CASP6,CHEK1,EBF16	16	BL vs. M6
CREBBP	transcription regulator	1,31E-02	ACOXL,AHI1,AKAP12,ARHGAP24,BCL6,CA2,C34	34	BL vs. M6
GLI3	transcription regulator	2,21E-02	EBF1,FOXO1,IRF1,KLF13,PAX5,PTCH1,RUNX17	17	BL vs. M6
NOTCH1	transcription regulator	2,70E-02	ADAM19,ASB2,BCL6,IL22,IL6,TNF,TSPAN33	7	BL vs. M6
MAPK8	kinase	3,11E-02	BCL2,DUSP1,EOMES,IFNG,IL6	5	M3 vs. M6
IL17A	cytokine	3,26E-02	BCL2A1,CCL20,CD83,IL22,IL6,RGS13,TNF	7	BL vs. M6
VEGFA	growth factor	3,32E-02	CD1A,EOMES,IFNG,IL6,ITGAV,KLRG1,NFATC28	28	M3 vs. M6
TCF3	transcription regulator	3,39E-02	CDC25B,CIP2A,FOXO1,SERINC5,TMEM184B	5	BL vs. M3
MED1	transcription regulator	3,55E-02	BCL11A,BCL6,EBF1,FOXO1,KLF13	5	BL vs. M6
NOTCH1	transcription regulator	4,40E-02	BCL2,BCL2L1,CFLAR,FLT1,IFNG,IL6,SMARCC1	7	M3 vs. M6
RORC	ligand-dependent nuclear receptor	4,65E-02	CCL20,IL1R1,IL22,IL411,IL6,TNF	6	BL vs. M6

Supplementary Table 5. Upstream regulators predicted to explain a pattern of differentially methylated genes in CD4+ T-cells after treatment with DMF.

DMF: Dimethyl fumarate; BL: baseline; M3: 3 months after initiation of DMF treatment; M6: 6 months after initiation of DMF treatment.

Input gene list was based on genes associated with differentially methylated probes that displayed $\Delta b > 5\%$ methylation change and $p\text{-value} < 0.001$.

The table includes all upstream regulators from Ingenuity Pathway Analysis with $p\text{-value of overlap} < 0.05$ and number of target molecules ≥ 5 .

Supplementary Table 6. Plasma cytokine profile

Marker	Responder		Non-responder		Responder		Non-responder		6months		6months		6months		6months	
	Baseline	±SD	n	±SD	n	6months	±SD	n	Baseline	±SD	n	Baseline	±SD	n	Baseline	±SD
IL17C	0.536	0.625	29	0.365	0.497	29	0.861	0.565	11	0.397	0.474	11	0.176	0.0011	-	-
IL17A	0.235	0.333	29	0.182	0.346	29	0.260	0.257	11	0.079	0.176	11	0.079	-	-	-
CCL28	0.889	0.223	29	0.084	0.397	29	1.171	0.430	11	1.166	0.358	11	1.166	<0.0001	-	-
CDCP1	1.654	0.549	29	1.874	0.519	29	1.563	0.396	11	1.971	0.599	11	1.971	-	-	-
EN-RAGE	1.546	0.485	29	1.148	0.537	29	1.419	0.569	11	1.134	0.331	11	1.134	-	-	-
SLAMF	1.699	0.316	29	1.508	0.495	29	1.691	0.318	11	1.690	0.356	11	1.690	-	-	-
IL12B	4.628	0.759	29	5.130	0.662	29	4.784	0.491	11	5.100	0.364	11	5.100	-	-	-
IL18R	6.841	0.496	29	6.696	0.426	29	6.802	0.281	11	6.891	0.279	11	6.891	0.0081	-	-
CXCL9	5.944	0.973	29	6.500	0.917	29	5.807	0.730	11	6.214	1.001	11	6.214	0.0026	-	-
CCL4	6.229	0.695	29	6.459	0.608	29	6.198	0.501	11	6.364	0.584	11	6.364	-	-	-
TWEAK	8.567	0.328	29	8.407	0.307	29	8.701	0.377	11	8.550	0.319	11	8.550	-	-	-

Supplementary Table 6. Plasma cytokine profile

The table provides statistics (student t-test/ paired t-test) in cytokine levels
Additional Olink information could be found at <https://www.olink.com/>