A

Gene	CGI	% Change in Methylation	FDR
PRIM2	CGI	-0.37	9.54E-07
MEOX1	CGI	-0.34	4.22E-08
PPBP	CGI	-0.28	9.47E-05
PTPN7	CGI	-0.27	3.94E-07
PRF1	CGI	-0.15	1.63E-04
MYO10	CGI	-0.14	3.92E-05
NOD2	CGI	-0.13	3.25E-02
OASL	CGI	-0.11	3.49E-03
PSTPIP1	CGI	-0.11	1.11E-05
DCHS1	CGI	0.11	1.59E-03
TRIP6	CGI	0.16	6.31E-03
ABCA1	CGI	0.18	2.36E-02
SLFN13	CGI	0.20	1.52E-02
TP63	CGI	0.22	5.04E-03
LCK	CGI	0.44	3.48E-05
AIM2	NO_CGI	-0.76	5.21E-07
FCER1A	NO_CGI	-0.55	5.59E-10
CCL5	NO_CGI	-0.53	1.07E-05
ICOS	NO_CGI	-0.43	4.79E-08
ISG20	NO_CGI	-0.27	4.72E-08
CCL3	NO_CGI	-0.27	3.00E-05
IL32	NO_CGI	-0.25	1.31E-02
SRGN	NO_CGI	-0.25	1.06E-05
TRIM69	NO_CGI	-0.23	6.49E-02
S100A8	NO_CGI	-0.22	2.19E-05
EMP1	NO_CGI	-0.21	8.21E-04
ITGB2	NO_CGI	-0.21	1.42E-05
RORC	NO_CGI	-0.18	1.90E-05
IL22	NO_CGI	-0.17	3.39E-05
IKBKE	NO_CGI	-0.16	2.51E-06
IL16	NO_CGI	-0.15	2.31E-10
CCL20	NO_CGI	-0.14	1.55E-04
ITGB7	NO_CGI	-0.13	1.19E-02
ITGAX	NO_CGI	-0.13	1.08E-07
ACPP	NO_CGI	-0.12	1.58E-02
SH2D2A	NO_CGI	-0.12	1.64E-03
CCL22	NO_CGI	-0.11	3.76E-04
TLR3	NO_CGI	0.11	6.47E-04
TNFSF15	NO_CGI	0.12	3.72E-02
IFITM3	NO_CGI	0.18	1.35E-03

B

Molecules in Network	Focus Molecules	Top Functions
AIM2,**CCL3**,**CCL5**,**CCL20**,**CCL22**,CD3,**EMP1**,Fcer1,**FCER1A**,**ICOS**,IFN Beta,IgG,**IKBKE**,**IL16**,**IL22**,IL12 (complex),Interferon alpha,**ISG20**,**ITGAX**,**ITGB2**,Jnk,**LCK**,NFkB (complex),**NOD2**,Nr1h,**OAS**L,P38 MAPK,PI3K (complex),**RORC**,**SH2D2A**,TCR,**TLR3**,**TNFSF15**,**TRIM69**,**TRIP6**	23	Inflammatory Response, Cell-To-Cell Signaling and Interaction, Cellular Movement
ABCA1,**ACPP**,ANXA9,APOC2,COL7A1,**DCHS1**,DGKI,E2F1,estrogen receptor,**IFITM3**,**IL32**,IL1B,KRT34,LILRA5,MAPK1,Mapk,**MEOX1**,MYLK (includes EG:107589),PLA2G3,PLA2G5,POPDC2,**PPBP**,PPT2 (includes EG:100126133),**PRF1**,**PRIM2**,**PTPN7**,RNASE2,**S100A8**,SEPP1,SMARCA4,**SRGN**,TDRD7,TNF,**TP63**,ZNF318	13	Embryonic Development, Hair and Skin Development and Function, Organ Development

Figure S1. 40 genes exhibit differential average methylation between naïve and memory CD4 T cells. (**A**) Change in methylation and FDR values for the 40 differentially methylated genes. (**B**) Top networks (> 10 focus molecules) identified by IPA for 40 genes with differential average methylation between naïve and memory CD4 T cells. Bold genes have differential methylation. Data is representative of ≥ 3 donors.
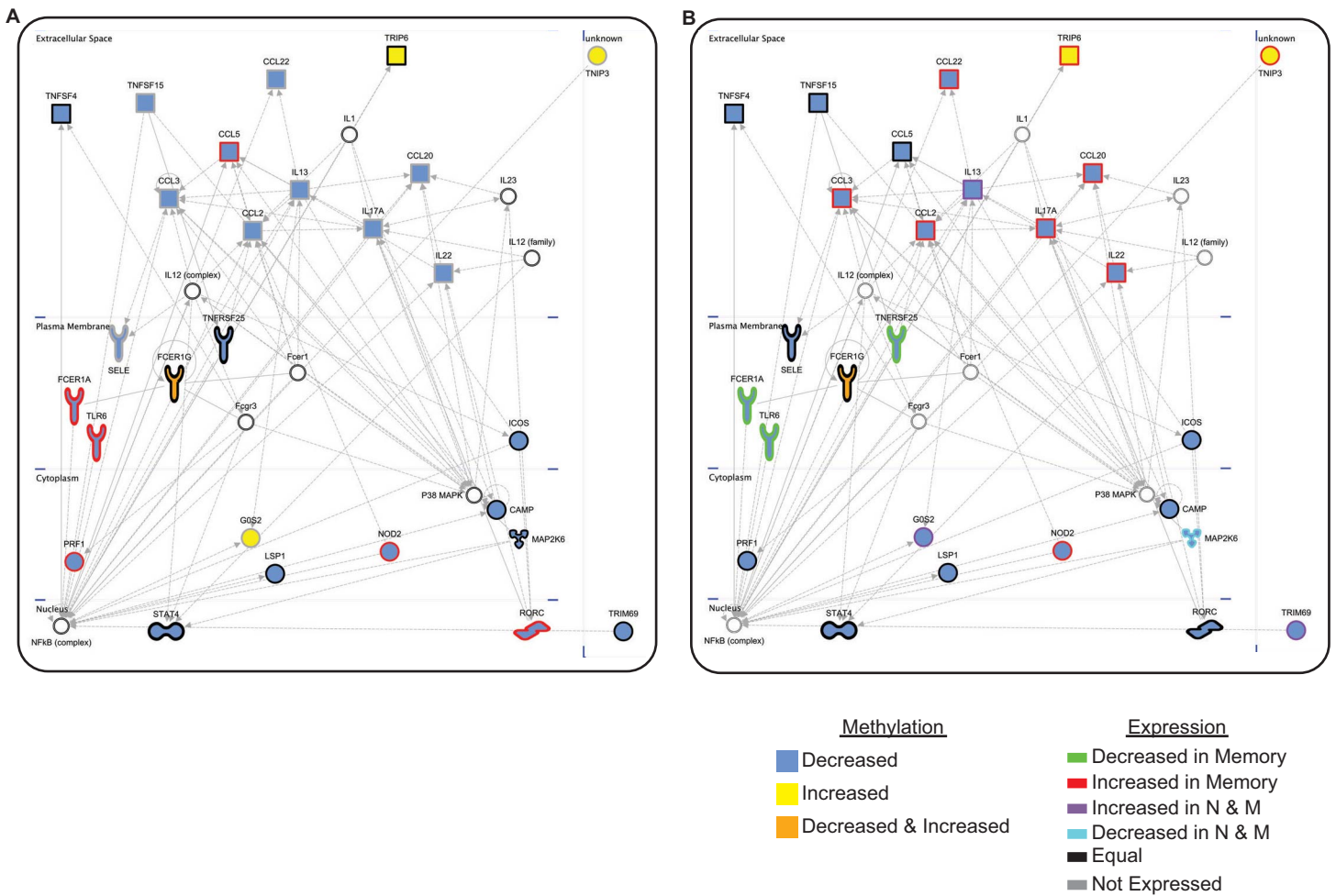
Figure S2. Activation-induced changes in memory CD4 T cells in genes linked to cell-to-cell signaling and cellular movement. Methylation (fill) and gene expression (outline) states for memory CD4 T cells at rest (**A**) and following 48 h of activation (**B**). Unfilled molecules were not targeted in the primer library and thus have no methylation information. Gene expression data for these molecules was not included. Data is representative of ≥ 3 donors.

Gene	Forward Primer	Reverse Primer	CpGs Covered
AIM2	GTCTTACTAACTTTTATATTCTCAGAATGCTAGCTCATATTAGATGTTCAGTGC	CTGGAGCTCTAATTAAGCTTGCTGGTTTGGGTTCTC	12
CCL3	GTGGGCTGACCAAGAAGGTAATAAAGTCTAACTAGTAAAATGAGAAAAATTCAG	CCTTCTGAAGTCTGAAACAAGCTTCTCCTCTTTATAGGCAGCCC	6
CD4	CAAGACAGGTTCTCACTAGTCACTCAGGCTAGAGTGC	CCA CAC CCT AAG CTT GGG CCG GC	16
CD4 Intron	CAC AGA TAC GCC TGC AGG AGA AGC AGC G	CCT CAT GAG ACC GCT AGC ACC AAT TCT TTT CGA ATC C	10
IL17A	GTCAGCCCTCTGAGTTACTAGTAGAGCAGGACAGGG	GGGATGGATGAGTTTAAGCTTGCTATGAGATGGACAAAATG	13
TOX	CTCCAGGTCTTTCGTGGACTAGTCAAGAGCCCTATAGGG	CGC GGC AAG CTT CCG TCG GC	98

Table S1. Primers for luciferase reporter assay cloning.

GENE	CGI	Total CpG	CpG with Increased Methylation at 48 h	CpG with Decreased Methylation at 48 h
CCL2	No CGI	12	0	4
CCL20	No CGI	3	0	0
CCL22	No CGI	10	0	1
CCL3	No CGI	7	0	4
CCL4	No CGI	2	0	0
CCL5	No CGI	6	0	0
IL10	No CGI	6	0	0
IL13	No CGI	18	0	0
IL16	No CGI	25	1	1
IL17A	No CGI	3	0	1
IL17F	No CGI	16	0	0
IL1A	No CGI	2	0	0
IL22	No CGI	8	0	0
IL23A	No CGI	9	0	0
IL24	No CGI	13	0	0
IL32	No CGI	23	4	4
IL8	No CGI	2	0	1
Total		165	5	16

Table SII. Methylation of cytokine promoters in naïve CD4 T cells covered at a minimum read depth of 25 reads. This data is representative of two donors.