

Figure S1 Study flowchart.

Table S1 The 14 RNA m5C methylation regulators enrolled in this study

m5C regulators	Type
<i>TRDMT1</i>	Writers
<i>NSUN1</i>	Writers
<i>NSUN2</i>	Writers
<i>NSUN3</i>	Writers
<i>NSUN4</i>	Writers
<i>NSUN5</i>	Writers
<i>NSUN6</i>	Writers
<i>NSUN7</i>	Writers
<i>ALYREF</i>	Readers
<i>YBX1</i>	Readers
<i>TET1</i>	Erasers
<i>TET2</i>	Erasers
<i>TET3</i>	Erasers
<i>ALKBH1</i>	Erasers

Table S2 CNV frequency of m5C regulators in TCGA-LUAD

Gene	Gain	Loss
<i>NSUN1</i>	4.324324324	5.94594595
<i>ALKBH1</i>	1.801801802	4.86486486
<i>TET2</i>	1.981981982	3.42342342
<i>NSUN5</i>	2.522522523	3.06306306
<i>NSUN4</i>	6.126126126	2.52252252
<i>TRDMT1</i>	2.702702703	2.52252252
<i>NSUN6</i>	2.702702703	2.52252252
<i>NSUN3</i>	5.585585586	1.98198198
<i>NSUN2</i>	13.69369369	1.8018018
<i>YBX1</i>	7.387387387	1.8018018
<i>ALYREF</i>	10.81081081	1.44144144
<i>TET1</i>	3.243243243	1.44144144
<i>TET3</i>	2.342342342	1.44144144
<i>NSUN7</i>	4.684684685	1.08108108

CNV, copy number variation; TCGA-LUAD, The Cancer Genome Atlas lung adenocarcinoma cohort.

Table S3 Clinical characteristics of the patients in the TCGA-LUAD and the GSE72094 cohort

Characteristics	TCGA-LUAD	GSE72094
n	522	441
Age		
≤65 years	241	127
>65 years	262	294
Unknow	19	21
Gender		
Female	280	240
Male	242	202
Stage		
I	279	265
II	124	69
III	85	63
IV	26	17
Unknow	8	28
T		
T1	172	–
T2	281	–
T3	47	–
T4	19	–
Unknow	3	–
N		
N0	335	–
N1	98	–
N2	75	–
N3	2	–
Unknow	12	–
M		
M0	353	–
M1	25	–
Unknow	144	–
Mutation		
EGFR		
Mutation		47
Wild		395
KRAS		
Mutation		154
Wild		288
TP53		
Mutation		111
Wild		331

TCGA-LUAD, The Cancer Genome Atlas lung adenocarcinoma cohort.

Table S4 Spearman correlation analysis of the 14 m5C regulators

From	To	Cor	P value	Weight
<i>TET1</i>	<i>TET2</i>	0.661743558	4.34E-76	3.970461348
<i>TET1</i>	<i>TET3</i>	0.544926884	3.06E-47	3.269561301
<i>TET1</i>	<i>ALKBH1</i>	0.250946716	5.55E-10	1.505680297
<i>TET1</i>	<i>TRDMT1</i>	0.311450679	7.93E-15	1.868704076
<i>TET1</i>	<i>NSUN3</i>	0.576112033	8.05E-54	3.456672195
<i>TET1</i>	<i>NSUN4</i>	0.329586303	1.62E-16	1.977517817
<i>TET1</i>	<i>NSUN6</i>	0.478985473	2.14E-35	2.873912835
<i>TET1</i>	<i>NSUN7</i>	0.335594184	4.21E-17	2.013565101
<i>TET2</i>	<i>TET3</i>	0.465789154	2.54E-33	2.794734922
<i>TET2</i>	<i>ALYREF</i>	-0.243438883	1.84E-09	1.460633296
<i>TET2</i>	<i>YBX1</i>	-0.243353803	1.87E-09	1.46012282
<i>TET2</i>	<i>TRDMT1</i>	0.357936995	2.15E-19	2.14762197
<i>TET2</i>	<i>NOP2</i>	-0.197848508	1.17E-06	1.187091047
<i>TET2</i>	<i>NSUN3</i>	0.699749267	1.58E-88	4.198495604
<i>TET2</i>	<i>NSUN4</i>	0.329682267	1.59E-16	1.978093604
<i>TET2</i>	<i>NSUN5</i>	-0.299809698	8.39E-14	1.798858185
<i>TET2</i>	<i>NSUN6</i>	0.432603482	1.74E-28	2.595620893
<i>TET2</i>	<i>NSUN7</i>	0.404451996	8.76E-25	2.426711977
<i>TET3</i>	<i>NOP2</i>	0.274301369	1.03E-11	1.645808215
<i>TET3</i>	<i>NSUN2</i>	0.313999629	4.66E-15	1.883997774
<i>TET3</i>	<i>NSUN3</i>	0.43530397	7.35E-29	2.611823817
<i>TET3</i>	<i>NSUN4</i>	0.235522735	6.25E-09	1.413136409
<i>TET3</i>	<i>NSUN6</i>	0.421756083	5.11E-27	2.5305365
<i>TET3</i>	<i>NSUN7</i>	0.274787916	9.45E-12	1.648727495
<i>ALKBH1</i>	<i>ALYREF</i>	0.193981745	1.91E-06	1.163890471
<i>ALKBH1</i>	<i>NSUN4</i>	0.266840392	3.84E-11	1.601042351
<i>ALKBH1</i>	<i>NSUN6</i>	0.187111572	4.40E-06	1.122669435
<i>ALKBH1</i>	<i>NSUN7</i>	0.191851004	2.48E-06	1.151106025
<i>ALYREF</i>	<i>YBX1</i>	0.404640807	8.29E-25	2.427844841
<i>ALYREF</i>	<i>NOP2</i>	0.399336235	3.79E-24	2.396017408
<i>ALYREF</i>	<i>NSUN2</i>	0.366117417	2.80E-20	2.196704503
<i>ALYREF</i>	<i>NSUN5</i>	0.488305836	6.44E-37	2.929835015
<i>YBX1</i>	<i>NOP2</i>	0.234600394	7.18E-09	1.407602366
<i>YBX1</i>	<i>NSUN2</i>	0.206088969	4.05E-07	1.236533812
<i>YBX1</i>	<i>NSUN7</i>	-0.195919248	1.50E-06	1.175515486
<i>TRDMT1</i>	<i>NSUN3</i>	0.277259403	6.05E-12	1.663556421
<i>TRDMT1</i>	<i>NSUN6</i>	0.276129986	7.42E-12	1.656779917
<i>TRDMT1</i>	<i>NSUN7</i>	0.186003201	5.03E-06	1.116019207
<i>NOP2</i>	<i>NSUN2</i>	0.401768722	1.89E-24	2.410612334
<i>NOP2</i>	<i>NSUN5</i>	0.377251562	1.58E-21	2.263509372
<i>NSUN2</i>	<i>NSUN5</i>	0.403146217	1.28E-24	2.418877304
<i>NSUN2</i>	<i>NSUN6</i>	0.196965583	1.31E-06	1.181793496
<i>NSUN3</i>	<i>NSUN4</i>	0.261138589	1.02E-10	1.566831532
<i>NSUN3</i>	<i>NSUN5</i>	-0.190912011	2.78E-06	1.145472065
<i>NSUN3</i>	<i>NSUN6</i>	0.427830452	7.81E-28	2.566982714
<i>NSUN3</i>	<i>NSUN7</i>	0.324232799	5.25E-16	1.945396793
<i>NSUN4</i>	<i>NSUN6</i>	0.262270365	8.44E-11	1.573622189
<i>NSUN4</i>	<i>NSUN7</i>	0.246962976	1.05E-09	1.481777855
<i>NSUN6</i>	<i>NSUN7</i>	0.376461356	1.95E-21	2.258768134

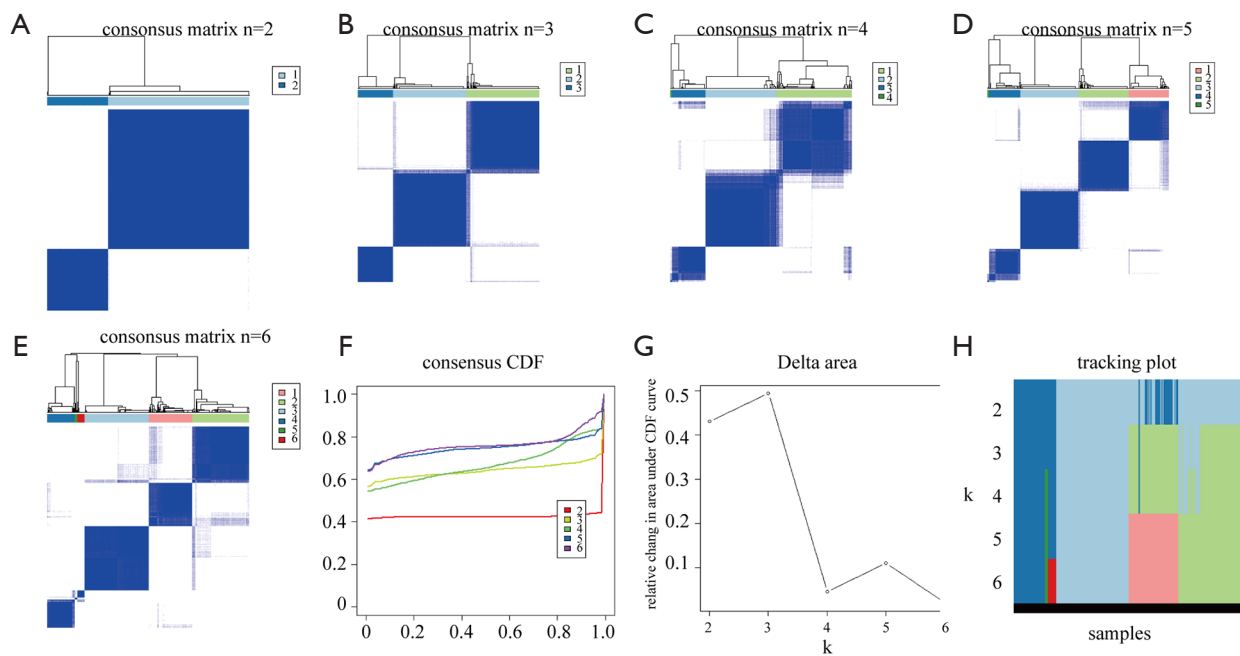


Figure S2 Unsupervised clustering of 14 m5C regulators in TCGA-LUAD. (A-E) Consensus clustering matrix for $k=2-6$, $k=2$ (A), $k=3$ (B), $k=4$ (C), $k=5$ (D), and $k=6$ (E). (F) Consensus clustering CDF for $k=2-6$. (G) Relative change in the area under the CDF curve for $k=2-6$. (H) The tracking plot for $k=2-6$. TCGA-LUAD, The Cancer Genome Atlas lung adenocarcinoma cohort; CDF, cumulative distribution function.

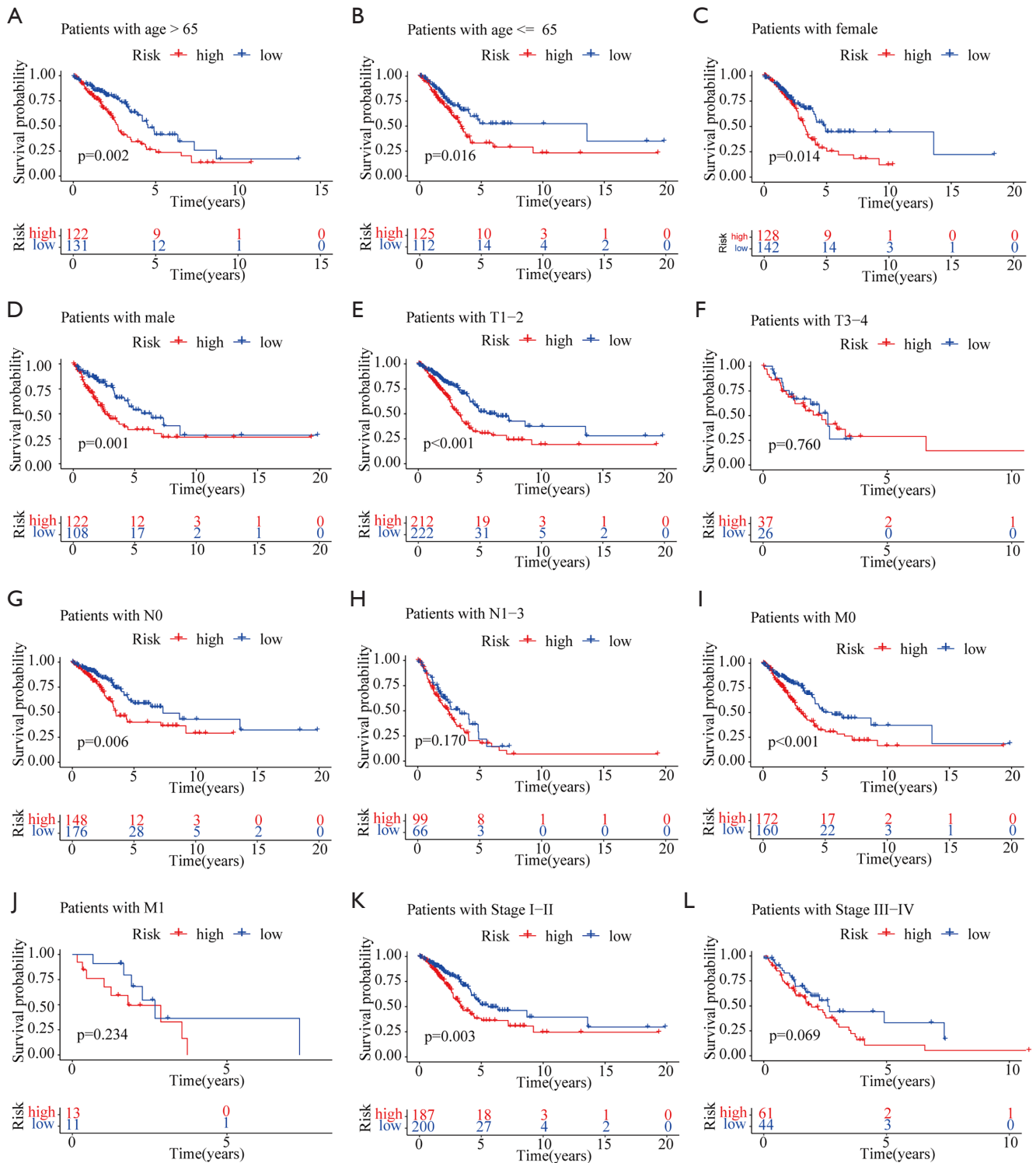


Figure S3 Stratification analysis of m5Csig. (A-L) Kaplan–Meier survival curves for subgroups stratified by different clinical characteristics. Age>65 years (A), age≤65 years (B), female (C), male (D), T1–2 (E), T3–4 (F), N0 (G), N1–3 (H), M0 (I), M1 (J), stage I–II (K) and stage III–IV (L).

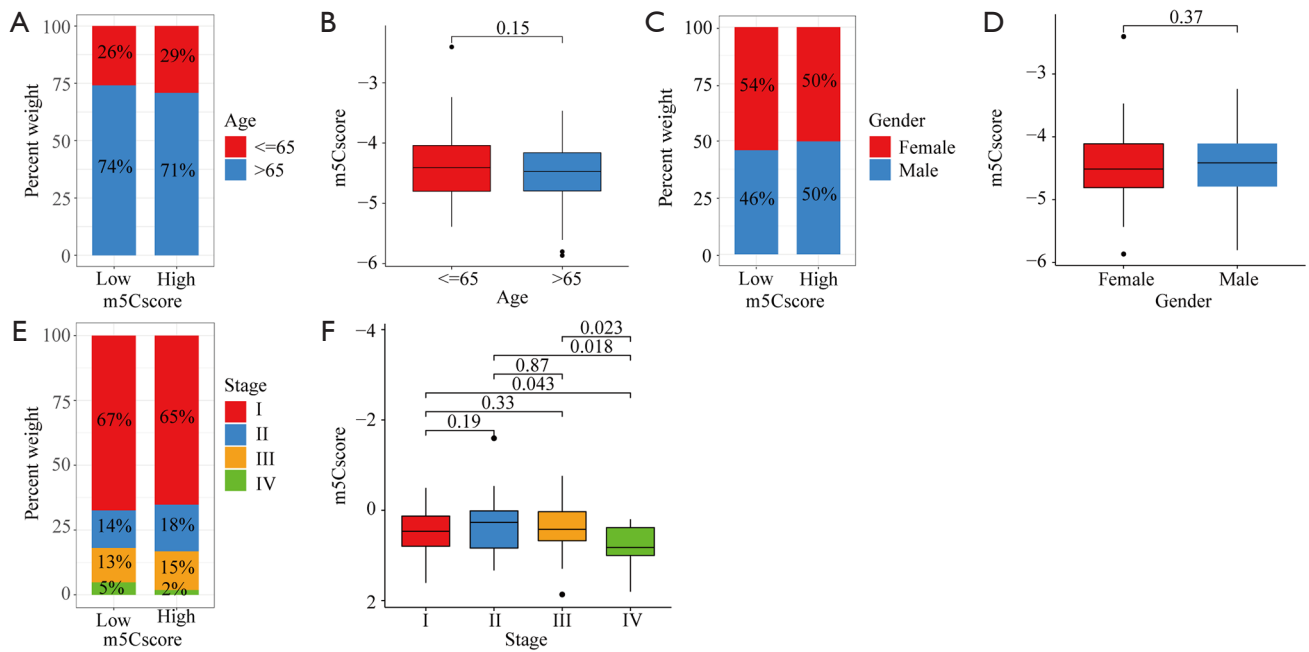


Figure S4 Clinical characteristics between high- and low-risk groups in GSE72094. (A-F) The proportion and distribution of different clinical characteristics between high- and low-risk groups in GSE72094: age 65/>65 years (A,B), female/male (C,D), stage I/II/III/IV (E,F).

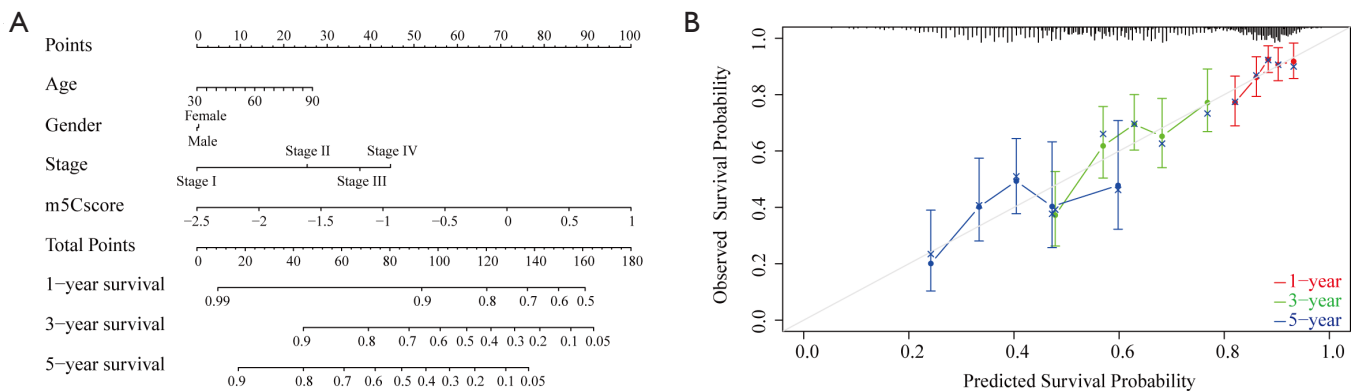


Figure S5 Building and validating the nomogram in the TCGA database. (A) Nomogram based on age, gender, stage, and m5Cscore. (B) Calibration to assess the consistency between the predicted and the actual OS at 1-, 3- and 5 years. TCGA, The Cancer Genome Atlas; OS, overall survival.

Table S5 Network edges of the 14 m5C regulators

From	To	Cor	P value	Color	Weight
<i>TET2</i>	<i>NSUN5</i>	-0.29981	8.39E-14	#6495ED	1.7988582
<i>TET2</i>	<i>ALYREF</i>	-0.243439	1.84E-09	#6495ED	1.4606333
<i>TET2</i>	<i>YBX1</i>	-0.243354	1.87E-09	#6495ED	1.4601228
<i>TET2</i>	<i>NOP2</i>	-0.197849	1.17E-06	#6495ED	1.187091
<i>YBX1</i>	<i>NSUN7</i>	-0.195919	1.50E-06	#6495ED	1.1755155
<i>NSUN3</i>	<i>NSUN5</i>	-0.190912	2.78E-06	#6495ED	1.1454721
<i>TRDMT1</i>	<i>NSUN7</i>	0.1860032	5.03E-06	Pink	1.1160192
<i>ALKBH1</i>	<i>NSUN6</i>	0.1871116	4.40E-06	Pink	1.1226694
<i>ALKBH1</i>	<i>NSUN7</i>	0.191851	2.48E-06	Pink	1.151106
<i>ALKBH1</i>	<i>ALYREF</i>	0.1939817	1.91E-06	Pink	1.1638905
<i>NSUN2</i>	<i>NSUN6</i>	0.1969656	1.31E-06	Pink	1.1817935
<i>YBX1</i>	<i>NSUN2</i>	0.206089	4.05E-07	Pink	1.2365338
<i>YBX1</i>	<i>NOP2</i>	0.2346004	7.18E-09	Pink	1.4076024
<i>TET3</i>	<i>NSUN4</i>	0.2355227	6.25E-09	Pink	1.4131364
<i>NSUN4</i>	<i>NSUN7</i>	0.246963	1.05E-09	Pink	1.4817779
<i>TET1</i>	<i>ALKBH1</i>	0.2509467	5.55E-10	Pink	1.5056803
<i>NSUN3</i>	<i>NSUN4</i>	0.2611386	1.02E-10	Pink	1.5668315
<i>NSUN4</i>	<i>NSUN6</i>	0.2622704	8.44E-11	Pink	1.5736222
<i>ALKBH1</i>	<i>NSUN4</i>	0.2668404	3.84E-11	Pink	1.6010424
<i>TET3</i>	<i>NOP2</i>	0.2743014	1.03E-11	Pink	1.6458082
<i>TET3</i>	<i>NSUN7</i>	0.2747879	9.45E-12	Pink	1.6487275
<i>TRDMT1</i>	<i>NSUN6</i>	0.27613	7.42E-12	Pink	1.6567799
<i>TRDMT1</i>	<i>NSUN3</i>	0.2772594	6.05E-12	Pink	1.6635564
<i>TET1</i>	<i>TRDMT1</i>	0.3114507	7.93E-15	Pink	1.8687041
<i>TET3</i>	<i>NSUN2</i>	0.3139996	4.66E-15	Pink	1.8839978
<i>NSUN3</i>	<i>NSUN7</i>	0.3242328	5.25E-16	Pink	1.9453968
<i>TET1</i>	<i>NSUN4</i>	0.3295863	1.62E-16	Pink	1.9775178
<i>TET2</i>	<i>NSUN4</i>	0.3296823	1.59E-16	Pink	1.9780936
<i>TET1</i>	<i>NSUN7</i>	0.3355942	4.21E-17	Pink	2.0135651
<i>TET2</i>	<i>TRDMT1</i>	0.357937	2.15E-19	Pink	2.147622
<i>ALYREF</i>	<i>NSUN2</i>	0.3661174	2.80E-20	Pink	2.1967045
<i>NSUN6</i>	<i>NSUN7</i>	0.3764614	1.95E-21	Pink	2.2587681
<i>NOP2</i>	<i>NSUN5</i>	0.3772516	1.58E-21	Pink	2.2635094
<i>ALYREF</i>	<i>NOP2</i>	0.3993362	3.79E-24	Pink	2.3960174
<i>NOP2</i>	<i>NSUN2</i>	0.4017687	1.89E-24	Pink	2.4106123
<i>NSUN2</i>	<i>NSUN5</i>	0.4031462	1.28E-24	Pink	2.4188773
<i>TET2</i>	<i>NSUN7</i>	0.404452	8.76E-25	Pink	2.426712
<i>ALYREF</i>	<i>YBX1</i>	0.4046408	8.29E-25	Pink	2.4278448
<i>TET3</i>	<i>NSUN6</i>	0.4217561	5.11E-27	Pink	2.5305365
<i>NSUN3</i>	<i>NSUN6</i>	0.4278305	7.81E-28	Pink	2.5669827
<i>TET2</i>	<i>NSUN6</i>	0.4326035	1.74E-28	Pink	2.5956209
<i>TET3</i>	<i>NSUN3</i>	0.435304	7.35E-29	Pink	2.6118238
<i>TET2</i>	<i>TET3</i>	0.4657892	2.54E-33	Pink	2.7947349
<i>TET1</i>	<i>NSUN6</i>	0.4789855	2.14E-35	Pink	2.8739128
<i>ALYREF</i>	<i>NSUN5</i>	0.4883058	6.44E-37	Pink	2.929835
<i>TET1</i>	<i>TET3</i>	0.5449269	3.06E-47	Pink	3.2695613
<i>TET1</i>	<i>NSUN3</i>	0.576112	8.05E-54	Pink	3.4566722
<i>TET1</i>	<i>TET2</i>	0.6617436	4.34E-76	Pink	3.9704613
<i>TET2</i>	<i>NSUN3</i>	0.6997493	1.58E-88	Pink	4.1984956

Table S6 Network nodes of the 14 m5C regulators

ID	Group	Color	Shape	Frame	P value	Size
<i>TET1</i>	Erasers	#E41A1C	Circle	Purple	0.3330402	8
<i>TET2</i>	Erasers	#E41A1C	Circle	Green	0.0678145	8
<i>TET3</i>	Erasers	#E41A1C	Circle	Purple	0.5008091	8
<i>ALKBH1</i>	Erasers	#E41A1C	Circle	Green	0.5460156	8
<i>ALYREF</i>	Readers	#FF7F00	Circle	Purple	0.0153939	10
<i>YBX1</i>	Readers	#FF7F00	Circle	Purple	0.0826999	8
<i>TRDMT1</i>	Writers	#999999	Circle	Green	0.0032905	12
<i>NSUN1</i>	Writers	#999999	Circle	Purple	0.0081617	12
<i>NSUN2</i>	Writers	#999999	Circle	Purple	0.1333446	8
<i>NSUN3</i>	Writers	#999999	Circle	Green	0.4098382	8
<i>NSUN4</i>	Writers	#999999	Circle	Green	0.0124132	10
<i>NSUN5</i>	Writers	#999999	Circle	Purple	0.4902566	8
<i>NSUN6</i>	Writers	#999999	Circle	Green	0.1342394	8
<i>NSUN7</i>	Writers	#999999	Circle	Green	0.0045582	12

Table S7 Significant GO terms for DEGs among the 3 clusters

Ontology	ID	Description	Gene ratio	Bg ratio	P value	P adjust	q value	Gene ID	Count
BP	GO:002220	Innate immune response activating cell surface receptor signaling pathway	10/309	116/18,670	2.31E-05	0.000253	0.000203	PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	10
BP	GO:002220	Innate immune response activating cell surface receptor signaling pathway	10/309	116/18,670	2.31E-05	0.000253	0.000203	PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	10
BP	GO:002218	Activation of innate immune response	10/309	142/18,670	0.000129	0.001176	0.000941	PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	10
BP	GO:0045089	Positive regulation of innate immune response	10/309	214/18,670	0.003088	0.019615	0.015698	PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	10
BP	GO:0071356	Cellular response to tumor necrosis factor	11/309	291/18,670	0.009446	0.053699	0.042975	PSMB2/PSMA5/TRAIP/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	11
BP	GO:0033209	Tumor necrosis factor-mediated signaling pathway	11/309	167/18,670	0.000109	0.001016	0.000813	PSMB2/PSMA5/TRAIP/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9	11
BP	GO:0050658	RNA transport	10/309	193/18,670	0.001452	0.010146	0.00812	ALYREF/RAN/NUP37/EIF5A/EIF4A3/CPSF3/SLBP/NUF2/MAGOH/NUP93	10
BP	GO:0051236	Establishment of RNA localization	10/309	196/18,670	0.001628	0.011174	0.008943	ALYREF/RAN/NUP37/EIF5A/EIF4A3/CPSF3/SLBP/NUF2/MAGOH/NUP93	10
BP	GO:0008380	RNA splicing	26/309	469/18,670	8.22E-08	1.89E-06	1.52E-06	YBX1/ALYREF/PPIH/SNRNP40/SNRPC/DNAJC8/EIF4A3/PHF5A/SF3A3/CELF2/SF3B5/CTNNB1/PPP1R8/POLR2G/CPSF3/ZPR1/CIRBP/LSM10/PPIL1/STRAP/PRPF19/LSM2/MAGOH/SNRPF/SNRPD1/SNRPB	26
BP	GO:0000398	Mrna splicing, via spliceosome	23/309	379/18,670	9.47E-08	2.09E-06	1.67E-06	YBX1/ALYREF/PPIH/SNRNP40/SNRPC/DNAJC8/EIF4A3/PHF5A/SF3A3/CELF2/SF3B5/CTNNB1/POLR2G/CPSF3/CIRBP/PPIL1/STRAP/PRPF19/LSM2/MAGOH/SNRPF/SNRPD1/SNRPB	23
BP	GO:0006402	Mrna catabolic process	20/309	364/18,670	3.07E-06	4.07E-05	3.26E-05	YBX1/PSMB2/MRTO4/PSMA5/EIF4A3/PSMD14/PSMB1/PSMC3/PSMD2/POLR2G/PSMB7/CIRBP/PSMA7/PSMA4/PSMD9/LSM2/SERBP1/RPL18A/UBA52/MAGOH	20
BP	GO:0051028	Mrna transport	9/309	152/18,670	0.000985	0.007171	0.005739	ALYREF/NUP37/EIF5A/EIF4A3/CPSF3/SLBP/NUF2/MAGOH/NUP93	9
CC	GO:0034709	Methylosome	4/313	12/19,717	2.79E-05	0.000242	0.000161	PRMT1/SNRPF/SNRPD1/SNRPB	4
CC	GO:0034708	Methyltransferase complex	7/313	113/19,717	0.002186	0.009912	0.006616	PHF19/RUVBL2/PRMT1/EZH1/SNRPF/SNRPD1/SNRPB	7
CC	GO:0005689	U12-type spliceosomal complex	6/313	27/19,717	3.41E-06	3.89E-05	2.59E-05	YBX1/PHF5A/SF3B5/SNRPF/SNRPD1/SNRPB	6
CC	GO:0097525	Spliceosomal snrnp complex	10/313	99/19,717	3.94E-06	4.29E-05	2.86E-05	PPIH/SNRNP40/SNRPC/PHF5A/SF3A3/SF3B5/LSM2/SNRPF/SNRPD1/SNRPB	10
CC	GO:0005732	Small nucleolar ribonucleoprotein complex	5/313	28/19,717	7.11E-05	0.000547	0.000365	SNRNP40/POP7/RRP9/FBL/SNRPF	5
CC	GO:0097526	Spliceosomal tri-snrnp complex	5/313	42/19,717	0.000513	0.003022	0.002017	PPIH/LSM2/SNRPF/SNRPD1/SNRPB	5
CC	GO:0022624	Proteasome accessory complex	4/313	24/19,717	0.000515	0.003022	0.002017	PSMD14/PSMC3/PSMD2/PSMD9	4
CC	GO:1902911	Protein kinase complex	7/313	109/19,717	0.001779	0.008554	0.00571	CCNB1/CDK1/CCNA2/CCNB2/CDK2/CKS1B/PCNA	7
CC	GO:0032040	Small-subunit processome	4/313	38/19,717	0.003006	0.012624	0.008426	UTP18/UTP11/RRP9/FBL	4
CC	GO:0005759	Mitochondrial matrix	16/313	469/19,717	0.003551	0.014758	0.009851	MRPL11/MRPL37/CCNB1/RAD51/NUDT1/CDK1/MRPS7/DTYMK/MRPS15/MRPS16/MRPL51/MRPL12/MRPL15/PARK7/MTFHD2/HSD17B10	16
CC	GO:0032153	Cell division site	4/313	68/19,717	0.022932	0.071185	0.047513	CEP55/RACGAP1/KIF20A/ANLN	4
MF	GO:0140097	Catalytic activity, acting on DNA	22/309	213/17,696	2.42E-11	1.13E-08	9.70E-09	RAD51/RFC2/MCM6/NME1/MCM2/FEN1/MCM4/CDC45/DCLRE1B/POLE3/GINS1/RAD54L/RUVBL2/UNG/EME1/HMGA1/TOP2A/PCNA/MCM7/RFC4/GINS2/PTGES3	22
MF	GO:0003688	DNA replication origin binding	9/309	24/17,696	1.40E-10	3.25E-08	2.80E-08	MCM6/MCM2/ORC1/MCM4/CDC6/CDC45/ORC6/MCM7/MCM10	9
MF	GO:0016887	Atpase activity	27/309	434/17,696	1.24E-08	1.53E-06	1.32E-06	KIF2C/RAD51/RFC2/MCM6/KIF4A/MCM2/MCM4/ABCC6/CDC45/ATP6V1F/EIF4A3/OLA1/KIF18B/KIF20A/KIF23/GINS1/RAD54L/PSMC3/RUVBL2/KIF11/TOP2A/KIF11/MCM7/RFC4/GINS2/GET3/DDX49	27
MF	GO:0008017	Microtubule binding	20/309	246/17,696	1.31E-08	1.53E-06	1.32E-06	BIRC5/MTUS1/KIF2C/GAPDH/PLK1/KIF4A/FAM83D/DRG1/RACGAP1/KIF18B/KIF20A/KIF23/PRC1/KIF11/PSRC1/NUSAP1/RCC2/KIF11/DPYSL2/SKA1	20
MF	GO:0015631	Tubulin binding	23/309	336/17,696	2.73E-08	2.54E-06	2.19E-06	BIRC5/MTUS1/KIF2C/GAPDH/PLK1/KIF4A/NME1/FAM83D/DRG1/RACGAP1/KIF18B/KIF20A/KIF23/CCT5/PRC1/STMN1/KIF11/PSRC1/NUSAP1/RCC2/KIF11/DPYSL2/SKA1	23
MF	GO:0003697	Single-stranded DNA binding	13/309	113/17,696	8.77E-08	5.84E-06	5.02E-06	YBX1/RAD51/MCM6/NABP2/NME1/MCM2/MCM4/CDC45/RAD51AP1/PRIM1/POLR2G/MCM7/MCM10	13
MF	GO:0008094	DNA-dependent atpase activity	13/309	113/17,696	8.77E-08	5.84E-06	5.02E-06	RAD51/RFC2/MCM6/MCM2/MCM4/CDC45/GINS1/RAD54L/RUVBL2/TOP2A/MCM7/RFC4/GINS2	13
MF	GO:0003678	DNA helicase activity	11/309	81/17,696	1.58E-07	9.18E-06	7.90E-06	RAD51/RFC2/MCM6/MCM2/MCM4/CDC45/GINS1/RUVBL2/MCM7/RFC4/GINS2	11
MF	GO:0070182	DNA polymerase binding	6/309	19/17,696	6.05E-07	3.13E-05	2.70E-05	RAD51/NABP2/CDT1/PCNA/PTGES3/FANCI	6
MF	GO:0017116	Single-stranded DNA helicase activity	6/309	20/17,696	8.52E-07	3.61E-05	3.11E-05	RAD51/RFC2/MCM6/MCM2/MCM7/RFC4	6
MF	GO:0043138	3'-5' DNA helicase activity	6/309	20/17,696	8.52E-07	3.61E-05	3.11E-05	MCM6/MCM2/CDC45/GINS1/MCM7/GINS2	6
MF	GO:0004386	Helicase activity	14/309	163/17,696	1.07E-06	3.91E-05	3.37E-05	RAD51/RFC2/MCM6/MCM2/MCM4/CDC45/EIF4A3/GINS1/RAD54L/RUVBL2/MCM7/RFC4/GINS2/DDX49	14
MF	GO:0004298	Threonine-type endopeptidase activity	6/309	21/17,696	1.17E-06	3.91E-05	3.37E-05	PSMB2/PSMA5/PSMB1/PSMB7/PSMA7/PSMA4	6
MF	GO:0070003	Threonine-type peptidase activity	6/309	21/17,696	1.17E-06	3.91E-05	3.37E-05	PSMB2/PSMA5/PSMB1/PSMB7/PSMA7/PSMA4	6
MF	GO:0035173	Histone kinase activity	5/309	17/17,696	8.19E-06	0.000254	0.000219	CCNB1/CDK1/CDK2/CHEK1/AURKB	5
MF	GO:0051082	Unfolded protein binding	11/309	131/17,696	1.90E-05	0.000554	0.000477	PPIH/CCT7/CCT4/TCP1/CCT5/RUVBL2/PPIA/PTGES3/CHAF1A/CCT8/CHAF1B	11
MF	GO:0043021	Ribonucleoprotein complex binding	10/309	133/17,696	0.000116	0.003173	0.002731	PPIH/NME1/SNRPC/EIF5A/EIF4A3/OLA1/UNG/PES1/SNRPD1/SNRPB	10
MF	GO:0003777	Microtubule motor activity	7/309	84/17,696	0.000664	0.017188	0.014792	KIF2C/KIF4A/KIF18B/KIF20A/KIF23/KIF11/KIF11	7
MF	GO:0042393	Histone binding	11/309	197/17,696	0.000711	0.01744	0.015009	MCM2/PHF19/H2AX/NCAPD2/ASF1B/CKS1B/UHRF1/EZH1/HAT1/NPM3/CHAF1B	11
MF	GO:0003735	Structural constituent of ribosome	11/309	202/17,696	0.000874	0.020364	0.017526	MRPL11/MRPL37/MRPS7/MRPS15/MRPS16/MRPL51/MRPL12/MRPL15/RPL39L/RPL18A/UBA52	11
MF	GO:0003684	Damaged DNA binding	6/309	65/17,696	0.000939	0.020841	0.017936	FEN1/DCLRE1B/AUNIP/H2AX/UNG/PCNA	6
MF	GO:0140142	Nucleocytoplasmic carrier activity	4/309	31/17,696	0.001978	0.041893	0.036054	RAN/KPNA2/CSE1L/NUF2	4
MF	GO:0003774	Motor activity	8/309	136/17,696	0.002698	0.054326	0.046754	KIF2C/KIF4A/KIF18B/KIF20A/KIF23/KIF11/KIF11/MYL6B	8
MF	GO:0016891	Endoribonuclease activity, producing 5'-phosphomonoesters	4/309	34/17,696	0.002798	0.054326	0.046754	FEN1/RNASEH2A/POP7/RPP40	4
MF	GO:0008409	5'-3' exonuclease activity	3/309	17/17,696	0.00299	0.055732	0.047965	FEN1/DCLRE1B/CPSF3	3

GO, Gene Ontology; DEGs, differentially expressed genes.

Table S8 Significant KEGG terms for DEGs among the three clusters

ID	Description	Gene ratio	Bg ratio	P value	P adjust	q value	Gene ID	Count
hsa04110	Cell cycle	27/162	124/8,108	4.06E-21	6.33E-19	5.30E-19	<i>CDC20/CCNB1/PLK1/MCM6/CDK1/MCM2/ORC1/CCNA2/CCNB2/MCM4/PKMYT1/CDC6/CDC45/CDK2/MAD2L1/CDC25C/CHEK1/MAD2L2/CDC25A/BUB1/PCNA/ORC6/MCM7/ESPL1/YWHAQ/TTK/BUB1B</i>	27
hsa03030	DNA replication	11/162	36/8,108	5.63E-11	4.39E-09	3.67E-09	<i>RFC2/MCM6/MCM2/FEN1/MCM4/POLE3/RNASEH2A/PRIM1/PCNA/MCM7/RFC4</i>	11
hsa05012	Parkinson disease	23/162	249/8,108	6.51E-10	3.39E-08	2.83E-08	<i>TUBA1C/TUBA1B/TUBB/PSMB2/PSMA5/SDHB/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/PSMB7/PARK7/PSMA7/PSMA4/CYC1/PSMD9/NDUFS6/UBA52/NDUFA12/COX8A</i>	23
hsa05014	Amyotrophic lateral sclerosis	27/162	364/8,108	2.54E-09	9.92E-08	8.30E-08	<i>TUBA1C/TUBA1B/ALYREF/TUBB/PSMB2/PFN1/PSMA5/SDHB/NUP37/BID/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/PSMB7/PSMA7/PSMA4/CYC1/PSMD9/GPX7/NDUFS6/NDUFA12/COX8A/NUP93</i>	27
hsa05016	Huntington disease	24/162	306/8,108	7.31E-09	2.28E-07	1.91E-07	<i>TUBA1C/TUBA1B/TUBB/PSMB2/PSMA5/AP2S1/SDHB/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/POLR2G/PSMB7/PSMA7/PSMA4/CYC1/PSMD9/GPX7/NDUFS6/NDUFA12/COX8A</i>	24
hsa03050	Proteasome	10/162	46/8,108	1.69E-08	4.38E-07	3.67E-07	<i>PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9</i>	10
hsa03040	Spliceosome	16/162	147/8,108	3.12E-08	6.96E-07	5.82E-07	<i>ALYREF/PPIH/SNRNP40/SNRPC/EIF4A3/PHF5A/SF3A3/SF3B5/CTNNB1/PPIL1/PRPF19/LSM2/MAGOH/SNRPF/SNRPD1/SNRPB</i>	16
hsa05020	Prion disease	21/162	273/8,108	9.75E-08	1.90E-06	1.59E-06	<i>TUBA1C/TUBA1B/TUBB/PSMB2/PSMA5/SDHB/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/PSMB7/PSMA7/PSMA4/CYC1/PSMD9/NDUFS6/NDUFA12/COX8A</i>	21
hsa04114	Oocyte meiosis	14/162	129/8,108	2.46E-07	4.11E-06	3.44E-06	<i>CDC20/CCNB1/PLK1/CDK1/CCNB2/PKMYT1/CDK2/MAD2L1/CDC25C/MAD2L2/BUB1/ESPL1/YWHAQ/FBXO5</i>	14
hsa05010	Alzheimer disease	24/162	369/8,108	2.64E-07	4.11E-06	3.44E-06	<i>TUBA1C/TUBA1B/TUBB/PSMB2/GAPDH/PSMA5/SDHB/BID/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/PSMB7/PSMA7/PSMA4/CYC1/PSMD9/NDUFS6/NDUFA12/COX8A/HSD17B10</i>	24
hsa04914	Progesterone-mediated oocyte maturation	12/162	100/8,108	6.19E-07	8.77E-06	7.34E-06	<i>CCNB1/PLK1/CDK1/CCNA2/CCNB2/PKMYT1/CDK2/MAD2L1/CDC25C/MAD2L2/CDC25A/BUB1</i>	12
hsa05022	Pathways of neurodegeneration - multiple diseases	26/162	475/8,108	2.21E-06	2.88E-05	2.41E-05	<i>TUBA1C/TUBA1B/TUBB/PSMB2/PSMA5/SDHB/BID/PSMD14/PSMB1/UQCRH/PSMC3/PSMD2/TUBB6/ATP5MC3/PSMB7/PARK7/PSMA7/PSMA4/CYC1/PSMD9/GPX7/NDUFS6/UBA52/NDUFA12/COX8A/HSD17B10</i>	26
hsa04115	p53 signaling pathway	8/162	73/8,108	9.53E-05	0.001144	0.000957	<i>CCNB1/RRM2/CDK1/CCNB2/CDK2/GTSE1/BID/CHEK1</i>	8
hsa03013	RNA transport	12/162	186/8,108	0.000333	0.003716	0.003109	<i>EIF3I/ALYREF/RAN/TACC3/NUP37/EIF4A3/POP7/RPP40/STRAP/EIF2B3/MAGOH/NUP93</i>	12
hsa05017	Spinocerebellar ataxia	10/162	143/8,108	0.00056	0.005828	0.004876	<i>PSMB2/PSMA5/PSMD14/PSMB1/PSMC3/PSMD2/PSMB7/PSMA7/PSMA4/PSMD9</i>	10
hsa00190	Oxidative phosphorylation	9/162	134/8,108	0.001407	0.013715	0.011475	<i>SDHB/ATP6V1F/UQCRH/ATP6V0B/ATP5MC3/CYC1/NDUFS6/NDUFA12/COX8A</i>	9
hsa04218	Cellular senescence	9/162	156/8,108	0.003963	0.034669	0.029008	<i>CCNB1/CDK1/MYBL2/CCNA2/CCNB2/CDK2/CHEK1/CDC25A/FOXO1</i>	9
hsa03410	Base excision repair	4/162	33/8,108	0.004	0.034669	0.029008	<i>FEN1/POLE3/UNG/PCNA</i>	4
hsa00240	Pyrimidine metabolism	5/162	56/8,108	0.00503	0.041298	0.034554	<i>TK1/RRM2/NME1/DTYMK/NME2</i>	5
hsa00480	Glutathione metabolism	5/162	57/8,108	0.005426	0.042326	0.035414	<i>RRM2/SMS/SRM/GSTO1/GPX7</i>	5

KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.