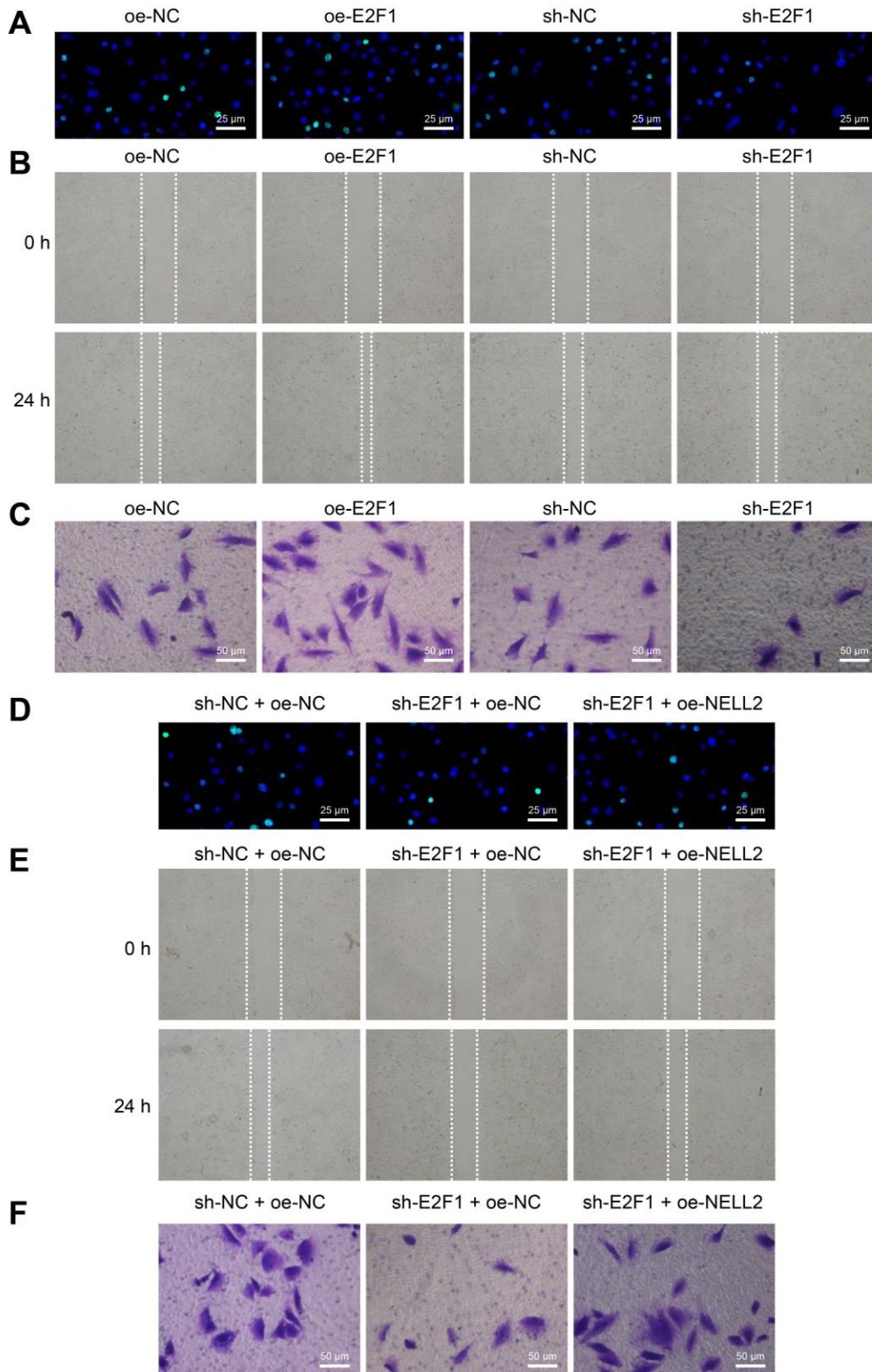


OMTO, Volume 21

Supplemental information

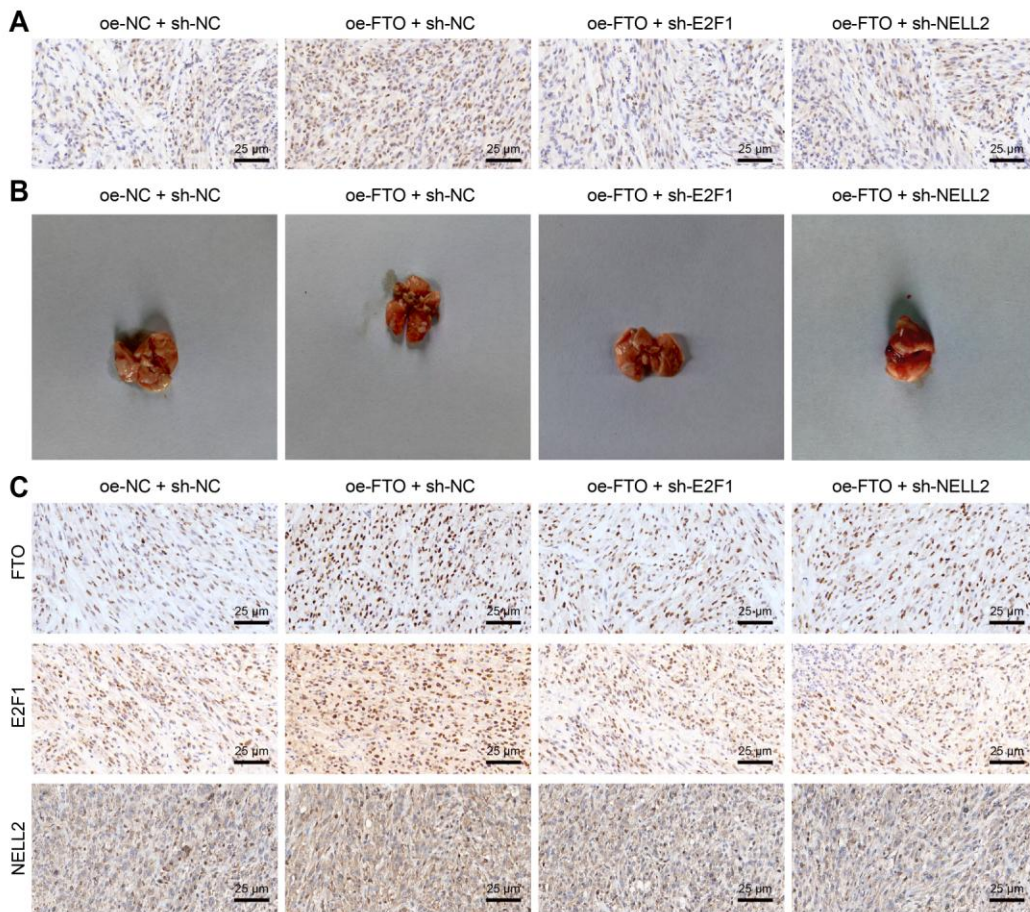
**m6A demethylase FTO induces NELL2 expression
by inhibiting E2F1 m6A modification leading
to metastasis of non-small cell lung cancer**

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Supplementary Figure 1 Representative images of EdU staining, wound healing, and Transwell assays. A: Representative images of EdU staining to detect A549 cell viability in response to overexpression or silencing of E2F1; B: Representative images of wound healing assay to detect the migration of A549 cells in response to overexpression or silencing of E2F1; C Representative

images of Transwell assay to evaluate A549 cell invasion in response to overexpression or silencing of E2F1; D: Representative images of EdU staining to detect the viability of A549 cells in response to the combination of E2F1 silencing and NELL2 overexpression; E: Representative images of wound healing assay to detect the migration of A549 cells in response to the combination of E2F1 silencing and NELL2 overexpression; F: Representative images of Transwell assay to assess the invasion of A549 cells in response to the combination of E2F1 silencing and NELL2 overexpression.



Supplementary Figure 2 Representative images of *in vivo* experiments. A: Representative images of immunohistochemical staining to measure the expression of Ki-67 in the lung tumor tissues of nude mice in response to FTO overexpression alone or its combination with E2F1/NELL2 knockdown; B: Representative images of fluorescence imaging to observe the distribution of extrahepatic metastases in nude mice; C Representative images of immunohistochemical detection of FTO, E2F1 and NELL2 protein positive rates in xenografted tumor tissues.

Supplementary table 1 Bioinformatics analysis for the binding of E2F1 to the promoter of NELL2

TF	Pattern name	Source	Sequence name	Start	Stop	Strand	Score	P.value	Q.value	Matched motif
E2F1		database	NELL2	1857	1870	+	11.1613	6.24E-05	0.19	AGAGGGAGGGAGAA
E2F1		database	NELL2	1352	1365	+	10.4919	9.97E-05	0.19	AGGGGGCGCGCGGG
E2F1	m-dataset-801-1	hTFtarget	NELL2	1350	1365	+	18.2273	4.78E-08	0.000182	GCAGGGGGCGCGCGGG
E2F1	m-dataset-803-3	hTFtarget	NELL2	1449	1460	-	19.1974	2.00E-07	0.000775	GGGGCGGGGCGC
E2F1	m-dataset-801-1	hTFtarget	NELL2	1444	1459	-	13.1212	1.68E-05	0.0244	GGGCGGGGCGCTGGAG
E2F1	m-dataset-803-3	hTFtarget	NELL2	1968	1979	-	11.9737	1.80E-05	0.035	AGGGAGGGGCCG
E2F1	m-dataset-801-1	hTFtarget	NELL2	1449	1464	-	12.9545	1.92E-05	0.0244	GCCGGGGGCGGGGCGC
E2F1	m-dataset-803-3	hTFtarget	NELL2	1541	1552	-	10.6842	3.10E-05	0.0402	GAGGTGGAGCTG
E2F1	m-dataset-803-1	hTFtarget	NELL2	1449	1460	-	12.3857	3.33E-05	0.126	GGGGCGGGGCGC
E2F1	m-dataset-801-1	hTFtarget	NELL2	1162	1177	-	11.9848	3.92E-05	0.0373	GGAGATGGAGCCCAGG
E2F1	m-dataset-804-2	hTFtarget	NELL2	1581	1592	+	10.8158	4.16E-05	0.163	CTCCGCACGCC
E2F1	m-dataset-804-1	hTFtarget	NELL2	1412	1424	-	10.7143	4.86E-05	0.187	GCTTCCCGGGCGC
E2F1	m-dataset-801-1	hTFtarget	NELL2	1407	1422	-	11.6061	5.09E-05	0.0388	TTCCGGGCGCGGAGA
E2F1	m-dataset-801-1	hTFtarget	NELL2	1985	2000	-	11.303	6.25E-05	0.0397	GGGGGAGGCGGGGTAA
E2F1	m-dataset-1573-1	hTFtarget	NELL2	1655	1663	-	10.8421	7.50E-05	0.125	GGAGGGAAG
E2F1	m-dataset-805-1	hTFtarget	NELL2	1655	1663	-	10.8421	7.50E-05	0.126	GGAGGGAAG
E2F1	m-dataset-803-1	hTFtarget	NELL2	1407	1418	-	10.3714	8.10E-05	0.154	CGGGCGCGGAGA
E2F1	m-dataset-1573-1	hTFtarget	NELL2	1861	1869	+	10.7237	8.55E-05	0.125	GGAGGGAGA
E2F1	m-dataset-805-1	hTFtarget	NELL2	1861	1869	+	10.7237	8.55E-05	0.126	GGAGGGAGA
E2F1	m-dataset-801-1	hTFtarget	NELL2	1352	1367	+	10.7121	9.03E-05	0.0454	AGGGGGCGCGCGGGTT
E2F1	m-dataset-801-1	hTFtarget	NELL2	1968	1983	-	10.6212	9.53E-05	0.0454	GAGGAGGGAGGGGCCG
E2F1	m-dataset-803-4	hTFtarget	NELL2	501	507	+	10.4286	9.66E-05	0.378	TTTCAA
E2F1	m-dataset-1573-1	hTFtarget	NELL2	1973	1981	-	10.4342	9.80E-05	0.125	GGAGGGAGG
E2F1	m-dataset-805-1	hTFtarget	NELL2	1973	1981	-	10.4342	9.80E-05	0.126	GGAGGGAGG

Supplementary table 2 Cell grouping and transfection

Groups	Plasmids
oe-NC	NC overexpression plasmids
sh-NC	Plasmids shutting NC shRNA
sh-FTO	Plasmids shutting FTO-targeting shRNA
oe-FTO	FTO overexpression plasmids
oe-E2F1	E2F1 overexpression plasmids
sh-E2F1	Plasmids shutting E2F1-targeting shRNA
sh-NC+oe-NC	NC overexpression plasmids and plasmids shutting NC shRNA
sh-E2F1+oe-NC	Plasmids shutting E2F1-targeting shRNA E2F1 and NC overexpression plasmids
sh-E2F1+oe-NELL2	Plasmids shutting E2F1-targeting shRNA and NELL2 overexpression plasmids
oe-FTO+sh-NC	FTO overexpression plasmids and Plasmids shutting NC shRNA
oe-FTO+sh-E2F1	FTO overexpression plasmids and plasmids shutting E2F1-targeting shRNA
oe-FTO+sh-NELL2	FTO overexpression plasmids and plasmids shutting NELL2-targeting shRNA

Note: FTO, fat mass and obesity-associated protein; E2F1, E2F transcription factor-1; NELL2, neural epidermal growth factor-like 2; NC, negative control

Supplementary table 3 Primer sequences for qRT-PCR

Genes	Forward primers	Reverse primers
FTO	5'-ACTTGGCTCCCTTATCTGACC-3'	5'-TGTGCAGTGTGAGAAAGGCTT-3'
E2F1	5'-CCCATCCCAGGAGGTCACCTT-3'	5'-CTGCAGGCTCACTGCTCTC-3'
NELL2	5'-GGTAGCCGTCTCTGCACT CA-3'	5'-TGTAGAAACGGAGCGTG-3'
GUSB	5'-CTCATTGGAATTTTGCCGATT-3'	5'-CCGAGTGAAGATCCCCTTTTTA-3'

Note: FTO, fat mass and obesity-associated protein; E2F1, E2F transcription factor-1; NELL2, neural epidermal growth factor-like 2; GUSB, human functional β -glucuronidase gene