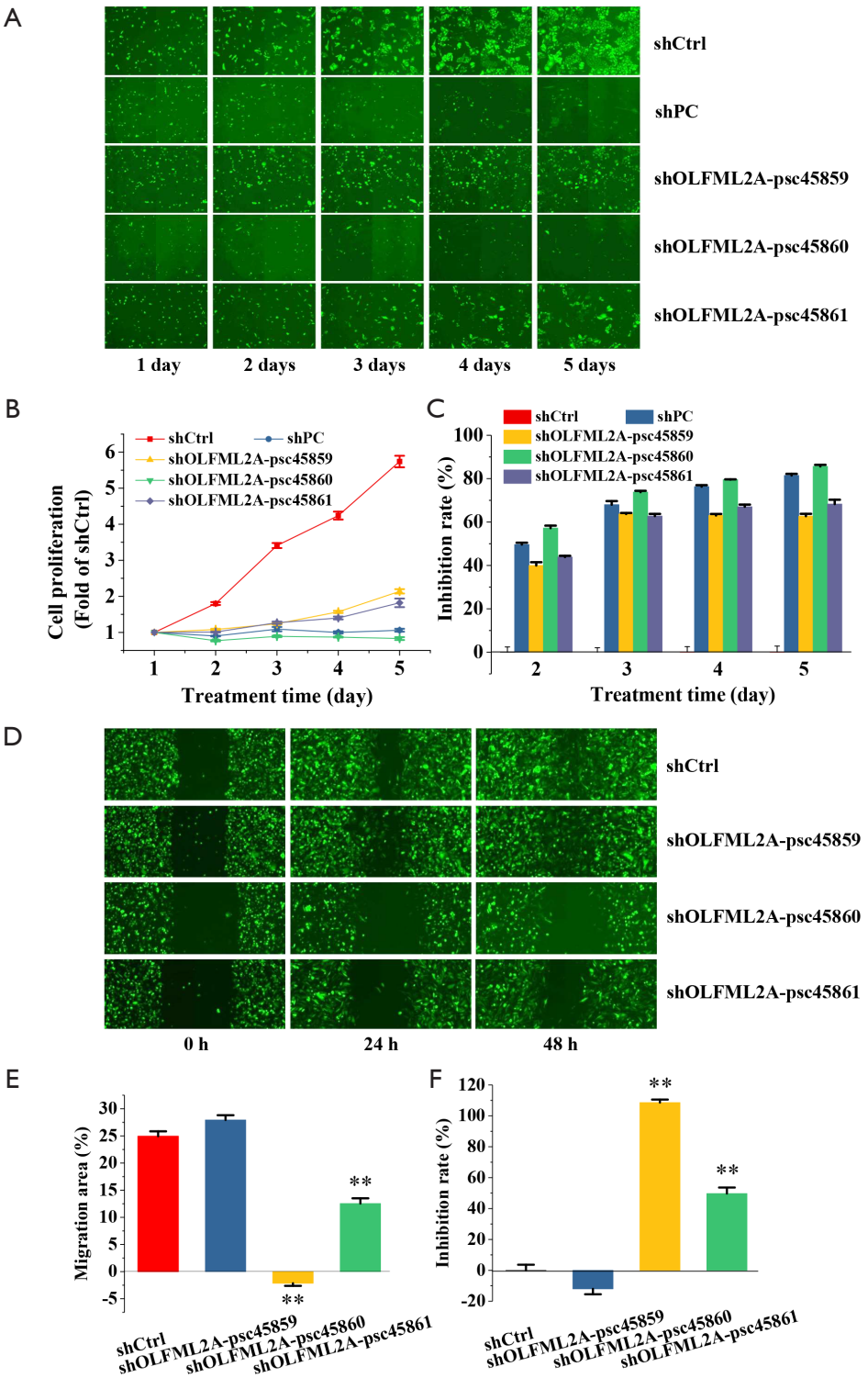

Figure S1 sh*OLFML2A* inhibited cell proliferation and migration. (A) Representative images of cell proliferation from the Celigo assay (×50 magnification). (B) Cell proliferation curve. (C) Inhibition ratio of cell proliferation. (D) Representative images of wound-healing from the Celigo assay (×50 magnification). (E) Cell migration rate when scratches were produced at 48 h. (F) Cell migration inhibition ratio when scratches were produced at 48 h. *P<0.05, **P<0.01 *vs.* shCtrl group. sh*OLFML2A*, shRNA targeting *OLFML2A*.

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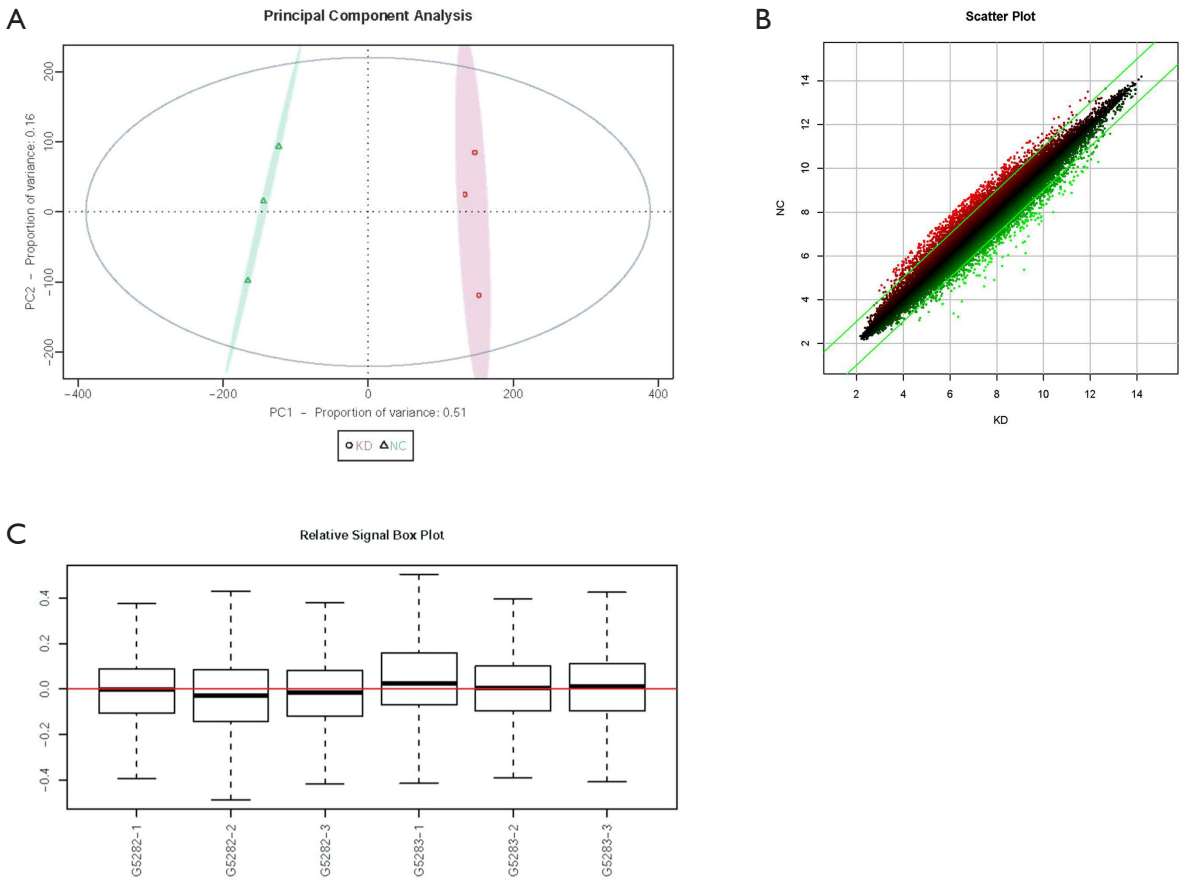

Figure S2 Microarray results determined using Affymetrix GeneChip arrays. (A) Principal component analysis of the microarray. (B) A scatter plot of the microarrays. (C) Relative signal box plot array.

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A

Ranking	Name	| Z-Score |	Molecules
1	Integrin	3.357	AKT3, CAV1, GSN, LIMS1, PAK1, PPP1CB, PTK2, RAC1, RAC2, PAK6, RALA, RAP1A, RAP1B, RHOA,TSPAN2, VCL, WASL, WIPF1
2	HGF	3.162	AKT3, ELF4, ELK1, MAP3K7, PRKCE, PRKCH, PTK2, PTGS2, RAC1, PAK1, RAP1A, RAP1B
3	NGF	2.828	AKT3, ELK1, MAP3K7, RAC1, RAP1A, RAP1B, RHOA, RPS6KA3,
4	Ephrin receptor	2.714	AKT3, CFL1, CFL2, EFNA1, GNB4, GNG12, PAK1, PAK6, PTK2, RAC1, RAC2, RAP1A, RAP1B, RHOA, WASL, WIPF1, VEGFA
5	Gβγ	2.646	AKT3, CAV1, GNB4, GNG12, PAK1, PRKACB, PRKCE, PRKCH
6	IL-3	2.646	AKT3, CHP1, ELK1, PAK1, PRKCE, PRKCH, RAC1

B

Figure S3 Top 6 signaling pathways and the molecules regulated by sh*OLFML2A*. (A) The top 6 signaling pathways. (B) The high frequency molecules in all the significant tumor-associated signaling pathways were mapped using Wordart software (https://wordart.com/). The larger the word frequency, the larger the font size is.

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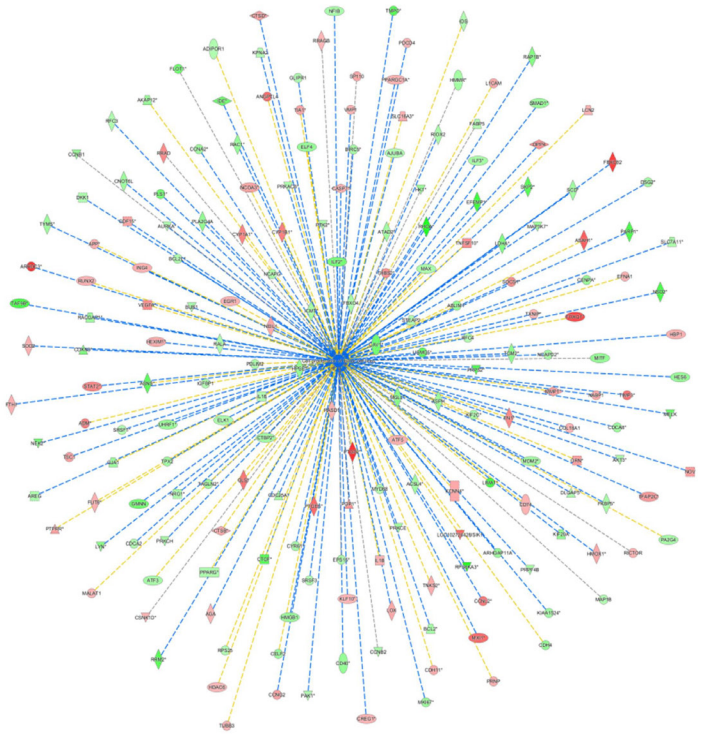
A



B

Characters	Molecules involved in the proliferation of tumor cells
Inhibited	ABLIM1, ACSL4, ADIPOR1, AJUBA, AKAP12, AKT3, AREG, ARHGAP11A, ASNS, ASPH, ATAD2, ATF3, AURKA, BCL2, BCL2L1, BIRC5, BUB1, CAV1, CCNA2, CCNB1, CCNB2, CD40, CDC25A, CDCA2, CDCA8, CDH4, CDKN3, CELF2, CENPA, CNOT6L, CTBP2, CTGF, CYR61, DKK1, DLGAP5, DSG2, EFEMP1, ELF4, ELK1, EPS15, FABP5, FBXO4, FKBP5, FLOT1, GJA1, GLIPR1, GMNN, HES6, HK1, HMGB1, HMMR, HPSE, ICMT, IDE, IDS, IGFBP1, IL18, ILF2, ILF3, KIAA1524, KIF20A, KIF2C, KPNA2, LDHA, LIMA1, LYN, MAP1B, MAP3K7, MAX, MDM2, MELK, MGLL, MITF, MKI67, MMP1, MYD88, NABP1, NCAPD2, NCAPG, NEK2, NFIB, NRG1, NSD2, PA2G4, PAK1, PARP1, PDLIM2, PLA2G4A, PLS1, PPARG, PRKACB, PRKCE, PRKCH, PRPF4B, PRPS2, PTK2, RAC1, RACGAP1, RALA, RAP1B, RFC3, RFC4, RHOA, RIOX2, RPS25, RPS6KA3, RRM2, SCD, SKP2, SLC7A11, SMAD1, SRSF1, SRSF3, STEAP2, TAF9B, TAGLN2, TGM2, TIMP3, TMPO, TPX2, TYMS, UHRF1, USMG5
Activated	ADM, AGA, ANGPTL4, APP, ARRDC3, ASAH1, ATF5, CASP7, CCNG2, CCNL2, CD74, CDH11, COL18A1, CREG1, CSNK1D, CTSB, CTSD, CYP1A1, CYP1B1, DPP4, EFNA1, EGR1, FBXO32, FN1, FOXQ1, FTH1, FUT8, GDF15, GLS, GRN, HBP1, HDAC6, HEXIM1, HMOX1, IL1B, ING4, KCNN4, KLF10, L1CAM, LCN2, LOC102724428/SIK1, LOX, MALAT1, MXI1, NCOA3, NEIL1, NOV, PDCD4, PDP1, PPARGC1A, PRNP, PTGES, PTGS2, PTPRR, RASD1, RICTOR, RRAD, RRAGB, RUNX2, SLC16A3, SOCS1, SOD2, SP110, STAT2, TFAP2C, THBS2, TIA1, TNFSF10, TNKS2, TSC1, TUBB3, TXNIP, VEGFA, VMP1

C

Figure S4 The top function: the cell proliferation of tumor cell lines and the high-frequency molecules in all the significant functions. Cell proliferation of tumor cell lines was the top function (A), and the molecules involved in this function are listed (B). (C) The high-frequency molecules in all of the significant functions were mapped by Wordart software (https://wordart.com/). The larger the word frequency, the larger the font size. * indicated the potential key genes.

https://dx.doi.org/10.21037/atm-22-757

A

Characters	NUPR1 target molecules in dataset
Inhibited	AKAP12, ANP32E, APOBEC3B, AREG, ARHGAP11A, ARHGEF26, ASOM, ATF3, AURKA, BUB1, C3orf58, CCNA2, CCNB2, CDC23, CDC25C, CDCA2, CDCA3, CDCA8, CKAP2L, CYR61, EXTL2, FANCD2, FAM173B, FCF1, GINS1, KIF11, KIF20A, KIF23, KIF2C, KNL1, LMNB1, LRP8, MGLL, MKI67, MMD, MPO, MTFR2, MYD88, BFIB, NSL1, OSBPL6, PARP1, PM20D2, PMP22, POLA2, POLE2, RFX5, RLPL2, SHROOM3, SKP2, SPAG5, SPC25, SPIN4, SRSF1, TDRKH, UAP1
Activited	ADM, BTG2, FUCA1, GBP2, GDF15, LHFOL2, LOC102724428/SIK1, MT1X, PCTP, PFKB4, PRNP, TMEM158, TOLLP, TRIB1

B

Ranking	Regulator	Molecule Type	Target molecules in dataset
1	ESR1	ligand-dependent nuclear receptor	ABCB9, ABCC3, ABI2, ABLIM1, ADGRG6, ANLN, ANXA4, AREG, ASPM, ATF3
2	RABL6	other	ATXN1, BUB1, CCNA2, CCNB1, CDC25A, CDC25C, DUT, ELF4, FERMT2, HMMR
3	FOXM1	transcription regulator	BIRC5, CAV1, CCNA1, CCNA2, CCNB1, CCNB2, CDC20, CDC25A, CDC25C, CDCA2
4	Vegf	group	AKAP12, ANGPTL4, ASNS, ATF3, AURKA, BAG2, BCL2, BIRC5, BTBD3, BUB1
5	TAL1	transcription regulator	ASPM, BCL2, BTBD3, BUB1, C3, CCNB1, CCNG2, CDKN3, DSG2, GALNT7
6	CSF2	cytokine	ANLN, ATXN1, AURKA, BCL2, BCL2L1, BIRC5, BUB1, C3, CCNA2, CCNB1
7	EP400	other	CCNA2, CDC20, CDC25A, CDCA3, FBXO5, NEK2, PPARG, PSRC1, RCC1, SGO1
8	MYC	transcription regulator	ABCB9, ABCC3, ACSL4, ADIPOR1, ADM, AKAP12, ANXA4, APP, ASNS, ATP13A2
9	SB203580	chemical - kinase inhibitor	APOBEC3B, APOBEC3G, APOL1, ATF3, BCL2, BGLAP, BIRC5, C3, CCNB1, CD40
10	HGF	growth factor	AKAP12, ANGPTL4, ASNS, ATF3, AURKA, BAG2, BCL2, BCL2L1, BIRC5, BUB1

C

Ranking	Regulator	Molecule Type	Target molecules in dataset
1	NUPR1	transcription regulator	ADM, AKAP12, ANP32E, APOBEC3B, AREG, ARHGAP11A, ARHGEF26, ASPM, ATF3, AURKA
2	Tretinoin	chemical - endogenous mammalian	ABLIM1, ADM, AKAP12, ANGPTL4, APP, AREG, ASB2, ASNS, BACE1, BCL2
3	Let-7	microRNA	AURKA, BCL2L1, BUB1, CCNA2, CCNB1, CDC20, CDC23, CDC25A, CDC45, CDCA2
4	CDKN2A	transcription regulator	ATAD2, BCL2, BIRC5, C3, CCNA1, CCNA2, CCNB1, CCNG1, CDC25A, CDC25C
5	TCF3	transcription regulator	ANLN, ATF3, AURKA, BIRC5, BUB1, CA2, CCDC117, CCNA2, CCNB1, CCNB2
6	KDM5B	transcription regulator	ASF1A, AURKA, CAV1, CCNA1, CCNB1, CDCA3, CDIPT, CTGF, DLGAP5, EGR1
7	IKBKB	kinase	ATF3, BCL2, BCL2L1, C3, CCNA2, CTGF, CTSB, CTSF, CYP1B1, EGR1
8	Calcitriol	chemical drug	ABCC3, ABLIM1, ANLN, APP, AREG, ATP10D, ATP2B1, BCAT1, BCL2, BCL2L1
9	Irgm1	other	BUB1, CCNA2, CCNB1, CCNB2, CDCA3, GINS1, KIF20A, MKI67, NCAPG, NEK2
10	5-fluorouracil	chemical drug	ANXA4, BCL2, BCL2L1, BIRC5, BNIP3L, CCNA1, CCNG1, CCT6A, CD40, CYCS

Figure S5 The target molecules of NUPR1 (A) and the top 10 regulators in the inhibitory (B) or activated (C) state. Only the top 10 representative target molecules are shown (in alphabetical order) in cases of more than 10 targets.

A

ID	Consistency Score	Regulators	Target molecules in dataset	Functions
1	12.73	ADM, Ap1, ATF6, CYP2J2, HMOX1, IL1RN, NOX4, TGM2, and VCAN	APP, FN1, ICAM1, IL1B, PPARG, PROCR, RCAN1, VEGFA	Adhesion of endothelial cells, increased levels of albumin
2	9.07	26s Proteasome, ADM, HMOX1, IL1RN, TNFSF10	BCL2, BCL2L1, BIRC5, IL1B, PPARG, PRNP, PTGS2	Apoptosis of smooth muscle cells, fragmentation of DNA
3	8.85	ANGPT1, E2F2, HSPA5, RBL2	APP, AURKA, BCL2, BCL2L1, BIRC5, BUB1, CCNB1, NEK2, RRM2, SCD	Apoptosis of cervical cancer cell lines, cell death of carcinoma cell lines, fragmentation of DNA
4	8.54	HSPA5, TRG	APP, AREG, BCL2, BCL2L1, BIRC5, CAV1, HSPA8, IL1B, NT5E, SCD	Apoptosis, cell death of tumor cell lines, cell survival, microtubule dynamics
5	7.60	APP, IFNG, IKBKB, IL17A, RELA	DPP4, FCGRT, ICAM1, IL1B, VEGFA	Increased levels of albumin

B

ID	Score	Molecules in Network	Top Diseases and Functions
1	45	APP, ARL6IP6, ARMC9, Aspartyl Protease, C19orf18, C4orf46, C5orf15, CLEC2B, CLIC3, CPED1, EOGT, FAM126B, HINT2, HINT3, HRASLS, LETM2, LHFPL2, LMCD1, MCFD2, METTL25, NAGA, NUP62CL, NXPE3, OLFML2A, Pi3k class III, PIMREG, PNPO, SH3BGRL3, SLC17A5, SPEG, STAC, TCF19, TSPAN12, ZADH2, ZFYVE1	Cellular compromise, organismal injury and abnormalities, skeletal and muscular disorders
2	45	ABLIM1, ANLN, ASL, ATL3, ATP2B1, BZW2, C9orf72, CFAP97, CFL1, CFL2, CHML, DENND4C, DEPDC1B, EFHD2, FBP1, FIGNL1, FLII, G-Actin, GART, GSN, LIMA1, LIMCH1, MELK, OSBPL6, PDZD11, PLEKHA7, Pmca, PPP1CB, PTK2, RAB1A, SH3PXD2A, SMCR8, SORD, TPM3, TPM4	Cellular compromise, cellular assembly and organization, cellular development
3	45	ASAH1, c-Src, CCBE1, CCDC85C, CEP55, CEP128, CEP152, CETN3, CSK, FAM46C, Focal adhesion kinase, HAUS7, MB21D2, MRPS18B, MTHFD1L, NCAPD2, NCAPD3, NCAPG, NCAPH, NEDD1, NEK6, ODF2, PCGF5, PLK4, PM20D2, PSAP, SCLT1, SMG7, SPAG5, TUBGCP3, TUBGCP4, WASHC4, WASHC2A/WASHC2C, ZNF292, ZSWIM8	DNA replication, recombination, and repair, cell cycle, cellular assembly and organization

Figure S6 The top 5 regulator effects (A) and the top networks (B).

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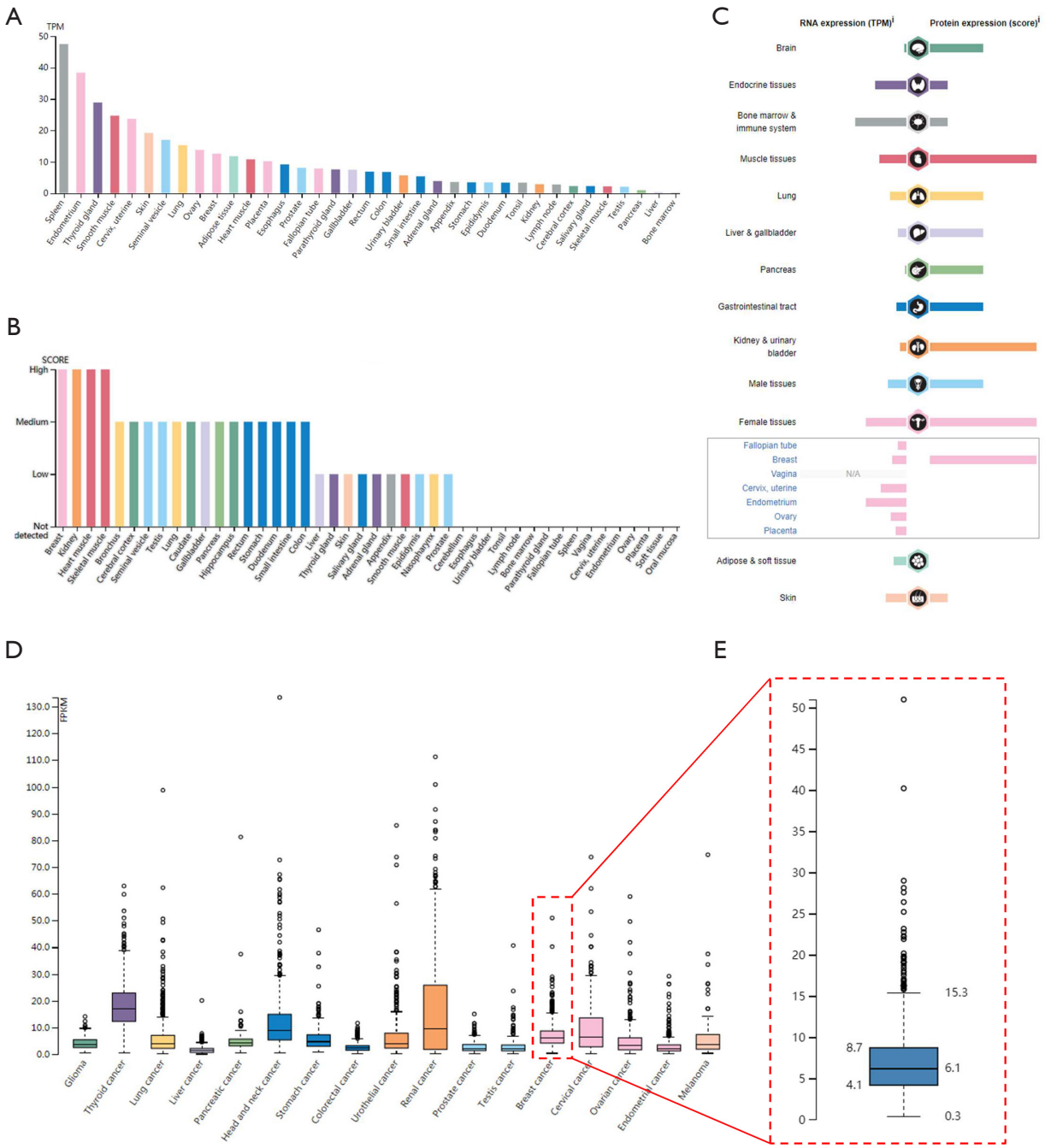

Figure S7 *OLFML2A* gene expression in human tissues or cancers. The protein (A) and mRNA (B) levels of *OLFML2A* in human tissues. (C) *OLFML2A* mRNA expression in different types of human cancers. All the data are available from The Human Protein Atlas (https://www.proteinatlas.org/ENSG00000185585-*OLFML2A*/tissue#gene_information).

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