A

	126	127N	127C	128N	128C	129N	129C	130N	130C	131N	131C
TMT11-1	Ref										
TMT11-2	Ref										
...											
TMT11-11											

TMT11-labeled Samples → bRPLC → Fractionation/Concatenation

24 fractions 5% of peptide mass → **Proteome**

12 fractions 95% of peptide mass — IMAC

Phosphoproteome

Flow-through, **IP** 4 fractions → **Acetylome**

Quantification / Identification

LC-MS/MS analysis

B

% sequence coverage of each protein vs. TMT-10 plex experiment number
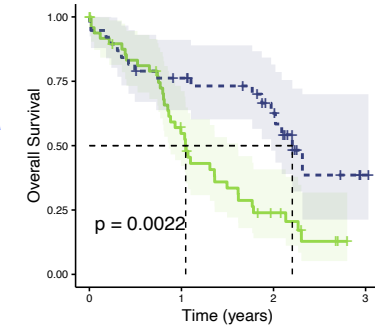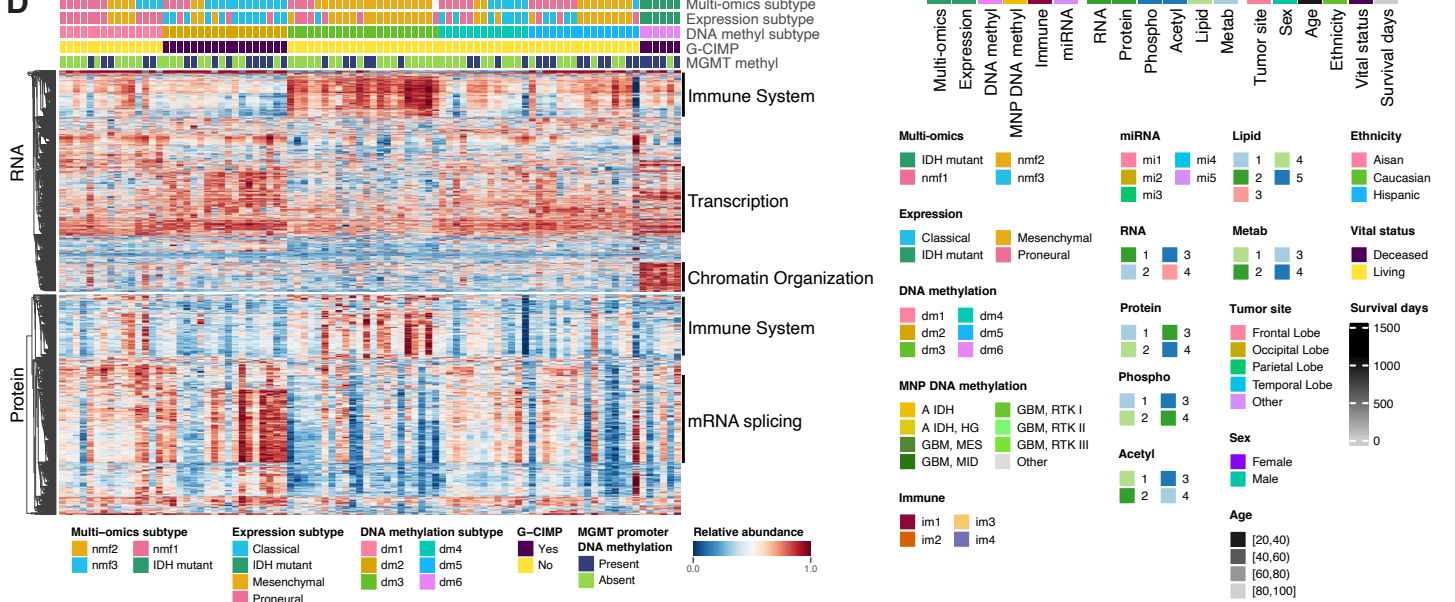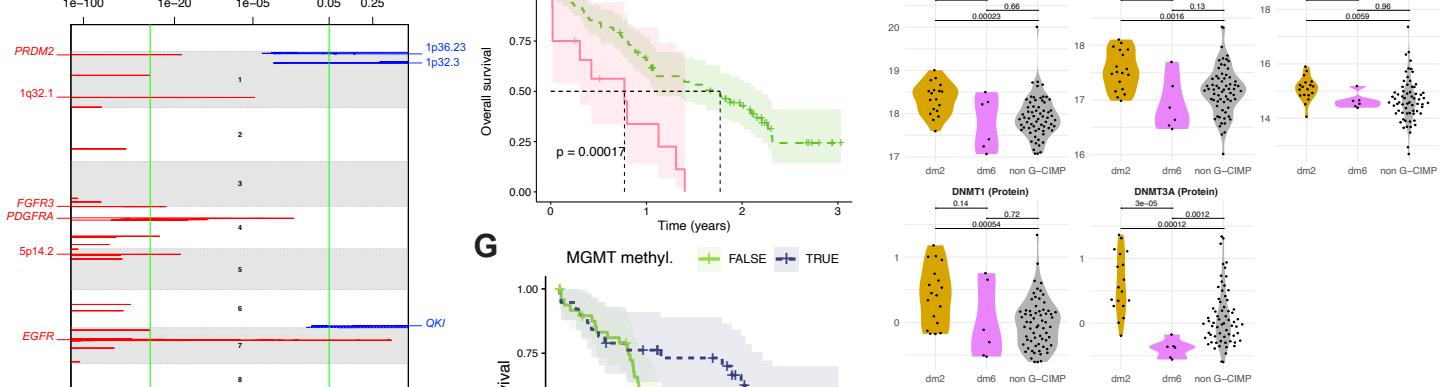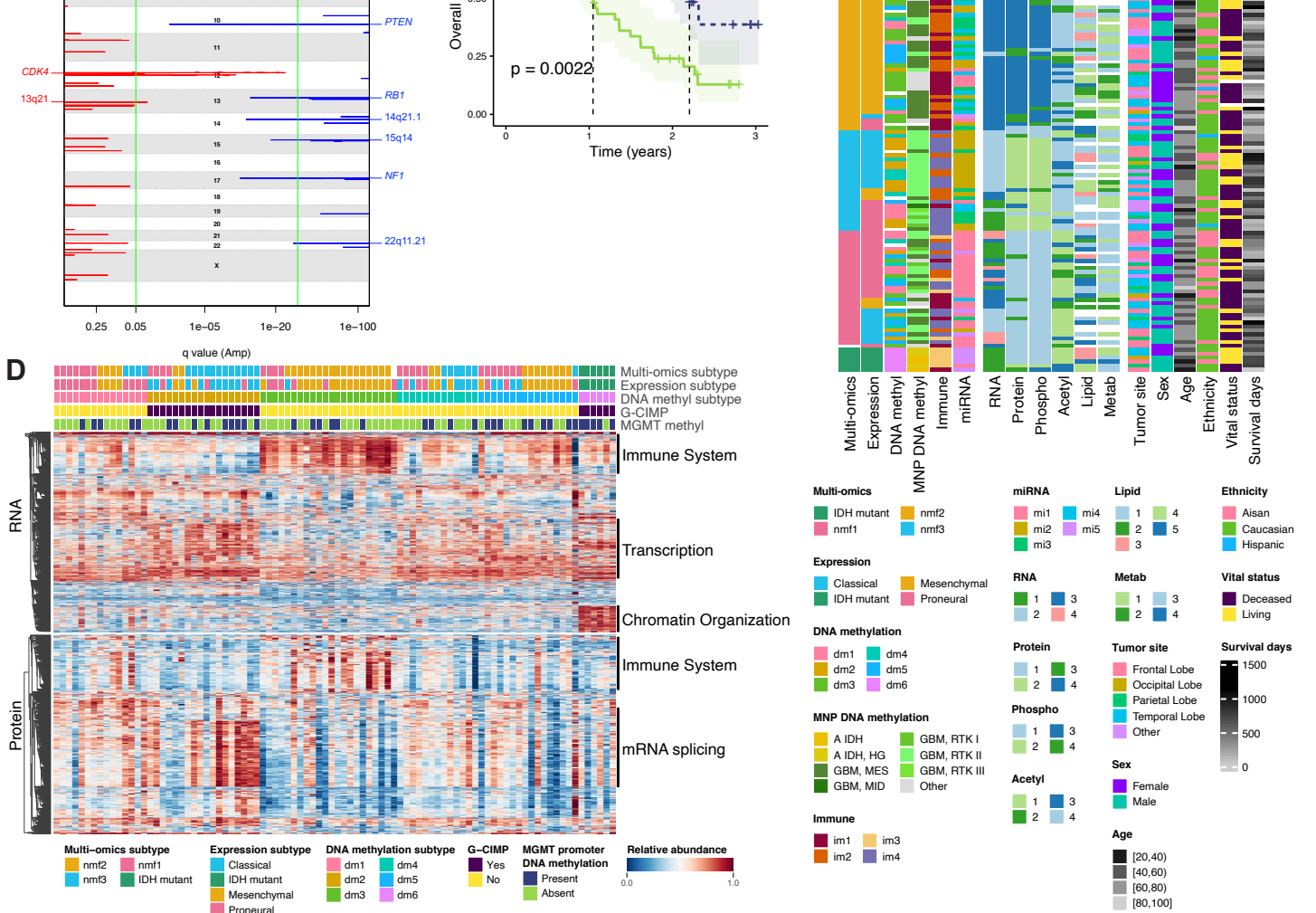
C

Proteome   **Phosphoproteome**   **Acetylome**

Figure S1. Integrated Proteomic Workflow and Quality Control, Related to Figure 1.

A) TMT-11 based global proteome, phosphoproteome, and acetylome analysis workflow. The GBM tumors and GTEx normal tissues were analyzed in 11 TMT 11-plex experiments, each with 10 study samples and a common internal reference sample created by pooling all study samples (equal contribution). The TMT11-labeled samples were then fractionated, split (with 5% peptide mass analyzed directly for global proteome), and subjected to tandem enrichment of phosphopeptides and acetylated peptides. Peptides were detected and quantified using information from the TMT-11 MS/MS spectra.

B) Distribution of sequence coverage of the identified proteins with tryptic peptides detected by MS/MS in each TMT-11 plex; whiskers show the 5–95 percentiles. The total numbers of identified proteins in each TMT plex range from 9,992 to 10,572.

C) Robust and precise proteomics platforms. Longitudinal performance was tested by repeated proteome, phosphoproteome and acetylome analysis of aliquots of the same patient-derived xenograft QC samples in standalone TMT-11 plexes, along with the GBM study samples; scatter plots and Pearson correlations comparing individual replicate measurements are shown.

B

Multi-omics subtype
Expression subtype
NMF concensus
NMF concensus score
NMF cluster membership
Immune subtype
Sex
nmf1
nmf2
nmf3

NMF consensus / Multi-omics subtype
nmf1
nmf2
nmf3
IDH mutant

Expression subtype
Proneural
Mesenchymal
Classical
IDH mutant

NMF cluster membership
0.4 0.6 0.8 1

Immune subtype
im1
im2
im3
im4

Sex
Female
Male

NMF coefficient
0 0.5 1

A

q value (Del)
1e-100   1e-20   1e-05   0.05   0.25

PRDM2   1p36.23
                               1p32.3
1q32.1
FGFR3
PDGFRA
5p14.2
                               QKI
EGFR
                               CDKN2A
                               PTEN
CDK4
                               RB1
13q21   14q21.1
                               15q14
                               NF1
                               22q11.21

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X

q value (Amp)
0.25   0.05   1e-05   1e-20   1e-100

C

Multi-omics membership — Non mixed — Mixed
Overall survival
1.00
0.75
0.50
0.25
0.00
p = 0.00017
0   1   2   3
Time (years)

G

MGMT methyl. — FALSE — TRUE
Overall Survival
1.00
0.75
0.50
0.25
0.00
MGMT methyl.
p = 0.0022
0   1   2   3
Time (years)

E

DNMT1 (RNA)
0.047
0.00023   0.66
dm2   dm6   non G-CIMP

DNMT3A (RNA)
0.012
0.0016   0.13
dm2   dm6   non G-CIMP

DNMT3B (RNA)
0.018
0.0059   0.96
dm2   dm6   non G-CIMP

DNMT1 (Protein)
0.14
0.00054   0.72
dm2   dm6   non G-CIMP

DNMT3A (Protein)
3e-05
0.00012   0.0012
dm2   dm6   non G-CIMP

D

Multi-omics subtype
Expression subtype
DNA methyl subtype
G-CIMP
MGMT methyl

RNA
Immune System
Transcription
Chromatin Organization

Protein
Immune System
mRNA splicing

Multi-omics subtype
nmf2
nmf1
nmf3
IDH mutant

Expression subtype
Classical
IDH mutant
Mesenchymal
Proneural

DNA methylation subtype
dm1   dm4
dm2   dm5
dm3   dm6

G-CIMP
Yes
No

MGMT promoter DNA methylation
Present
Absent

Relative abundance
0.0   1.0

F

Multi-omics
Expression
DNA methyl
MNP DNA methyl
Immune
miRNA
RNA
Protein
Phospho
Acetyl
Lipid
Metab
Tumor site
Sex
Age
Ethnicity
Vital status
Survival days

Multi-omics
IDH mutant   nmf2
nmf1   nmf3

Expression
Classical   Mesenchymal
IDH mutant   Proneural

DNA methylation
dm1   dm4
dm2   dm5
dm3   dm6

MNP DNA methylation
A IDH   GBM, RTK I
A IDH, HG   GBM, RTK II
GBM, MES   GBM, RTK III
GBM, MID   Other

Immune
im1   im3
im2   im4

miRNA
mi1   mi4
mi2   mi5
mi3

RNA
1   3
2   4

Protein
1   3
2   4

Phospho
1   3
2   4

Acetyl
1   3
2   4

Lipid
1   4
2   5
3

Metab
1   3
2   4

Tumor site
Frontal Lobe
Occipital Lobe
Parietal Lobe
Temporal Lobe
Other

Sex
Female
Male

Age
[20,40)
[40,60)
[60,80)
[80,100)

Ethnicity
Aisan
Caucasian
Hispanic

Vital status
Deceased
Living

Survival days
0   500   1000   1500

Figure S2. Proteogenomic Characterization and Subtyping of GBM, Related to Figure 1.

A) GISTIC2 copy number variations at and focal level of all tumors with WGS available.

B) Heatmap of multi-omics membership scores of all three multi-omics subtypes for each tumor.

C) Survival Kaplan–Meier curves of mixed-subtype tumors with low multi-omics membership score versus the rest of the tumors.

D) Pathway enrichment analysis of gene expression with differential DNA methylation in promoter regions across all six DNA methylation subtypes.

E) Differentially expressed DNMTs in two G-CIMP subtypes (dm2 and dm6) at both RNA and protein level.

F) Comparison of the clustering results using individual data type, including DNA methylation, miR-NAs, RNAs, proteins, phosphoproteins, acetylproteins, lipids, and metabolites.

G) Survival Kaplan–Meier curves of tumors with different MGMT promoter DNA methylation status.

A

TP53 | TP53BP1 (RNA)
TP53 | TP53BP1 (Protein)
TP53-S315 | TP53BP1 S1099S1106S1109 (Phosphorylation)

N = 68 31 | 51 22 | 68 31 | 50 22 | 44 20

B

TP53

NM_000546

P53_TAD P53 transactivation motif
TAD2 Transactivation domain 2
P53 P53 DNA-binding domain
zinc binding site [ion binding]

other dimerization site [polypeptide binding]
DNA binding DNA binding site [nucleotide binding]
NLS Nuclear localization signal
P53_tetramer P53 tetramerisation motif

C

TP53:X126_splice

Alt splice site
chr17:7675237:C->T
21nt in-frame deletion

C T K A L Q C F M K M K N L A P S Y
TP53

D

TERT RNA
ATRXmut | ATRXmut IDH1mut | IDH1mut | TERTp mut hotspot | TERTp mut not hotspot | WT

Telomere length ratio
ATRXmut | ATRXmut IDH1mut | IDH1mut | TERTp mut hotspot | TERTp mut not hotspot | WT

E

TERT expressing samples with no hotspot mutations

TSS

Sample
C3L-01155
C3L-02041
C3L-03728
C3L-03968
C3N-01515
C3N-01851
C3N-02188
C3N-02786

hotspot mutation

no TERT expression samples

TSS

Sample
C3L-01146
C3L-01155
C3L-02041
C3L-03728
C3L-03748
C3L-03968
C3N-01515
C3N-01798
C3N-01816
C3N-01851
C3N-02188
C3N-02786
C3N-03182
C3N-03473

F

ATRX, IDH1, TP53 mutations: truncating, missense, other

TERTp hotspot	74%
ATRX	10%
IDH1	7%
TP53	32%
TERTp not hotspot	9%
Other	6%

Telomere length ratio
Age

G

IDH1 R222C TERTp mut
ATRX Q1007H TERTp mut
R=0.68, p=7e-15

IDH1 R222C TERTp mut
ATRX Q1007H TERTp mut
R=0.41, p=2.3e-5

Telomere length ratio 2 4 6

ATRX and *IDH1* status: ATRXmut, ATRXmut +IDH1mut, IDH1mut, WT

H

ATRX WT *IDH1* WT

ATRX WT *IDH1* mut

ATRX mut *IDH1* mut

I

	All samples ATRX	ATRX WT samples ATRX
DAXX	0.41	0.61
EZH2	0.5	0.62
SETDB1	0.5	0.69
CBX5	0.46	0.5
TRIM28	0.53	0.59
H2AFX	0.09	0.13
H3F3A	-0.17	-0.26

Pearson's r

Protein level correlation

J

Correlation at RNA level

	ATRX	DAXX	EZH2	SETDB1	CBX5	TRIM28	H2AFX	H3F3A
ATRX		-0.1	0.45	0.06	0.26	0.07	0.05	0.36
DAXX	0.41		0.41	0.11	-0.04	0.28	0.37	0.26
EZH2	0.5	0.62		0.34	0.32	0.46	0.64	0.54
SETDB1	0.5	0.67	0.63		0.27	0.42	0.19	0.33
CBX5	0.46	0.68	0.56	0.75		0.14	0.24	0.29
TRIM28	0.53	0.66	0.53	0.76	0.85		0.57	0.15
H2AFX	0.09	0.18	-0.01	0.18	0.28	0.27		0.33
H3F3A	-0.17	0.03	0	-0.05	0.04	-0.07	0.1	

Correlation at protein level

Pearson's r

Figure S3. Effect of *TP53*, *TERT*p, *IDH1*, and *ATRX* Mutations, Related to Figure 2.

A) Boxplots showing RNA, protein and phosphosite abundance for *TP53* and *TP53BP1* in *TP53*-WT tumors (blue; n=68) and *TP53*-mutated tumors (red; n=31).

B) The lolliplot of *TP53* mutations in **Figure 2C**.

C) IGV screenshot of RNA supporting reads for alternative splice site associated with *TP53* X126_ splice mutation.

D) *TERT* RNA expression in proposed telomere genotypes. *TERT*p mutations are associated with stable *TERT* expression (left). Telomere length ratio (WGS tumor telomere length / WGS blood normal telomere length) in proposed telomere genotypes (right).

E) Variant allele frequency of mutations in *TERT*p region found in tumors not carrying *TERT*p hotspot mutations but expressing *TERT* RNA (upper panel) and in tumors not carrying *TERT*p hotspot mutations and no expressing *TERT* RNA (bottom panel). For the upper panel mutations with > 10% VAF are shown, for the bottom panel mutations with > 5% VAF are shown. Triangles indicate hotspot genomic position 1295113 and 1295135 (-124 and -146 bp from TSS labeled by the dashed line).

F) Overview of genetic alterations in *TERT*p hotspot and not hotspot positions, mutations in *ATRX*, *IDH1* and *TP53*. Telomere length ratio in tumor/blood normal is indicated on top, patient age is indicated in the bottom.

G) *ATRX* and *IDH1* mutational effect on *ATRX* RNA and protein levels. *IDH1* R132H mutations affect ATRX protein only (left). Neither *ATRX* nor *IDH1* mutations are associated with reduced DAXX protein expression (right). The missense *ATRX* mutant, Q1007H, residing outside of the SNF2 and helicase domains, had normal RNA and protein expression. We noticed that other gene mutations also led to altered ATRX protein levels, including significantly decreased ATRX protein in *IDH1* R132H mutants, even though the *ATRX* RNA level itself appeared unchanged

H) Immunohistochemistry staining for ATRX protein in FFPE sections of *ATRX* WT and *IDH1* WT tumor (positive), *ATRX* WT and *IDH1*mut tumor (negative), and in *ATRX*mut and *IDH1*mut tumor (negative). IHC staining confirmed low ATRX expression in *IDH1* mutants regardless of *ATRX* mutational status. Scale bars: 100 µm.

I) WT ATRX protein is better correlated with its complex partners than if WT and mutant combined together.

J) ATRX complex members showed high correlation of their abundance in protein but not in RNA across all tumors.

A

EGFR | EGFR | EGFR | EGFR-S1166 | PDGFRA | PDGFRA | PDGFRA | PDGFRA-S1070

CNV (log2(Ploidy/2)) | RNA (log2) | Protein | Phosphorylation

EGFR status
N = 53 29 16

PDGFRA status
N = 84 12 2

Status
- WT
- MUT
- SV
- SV & MUT

B

C3L-01040 C3N-03186 C3N-00661 C3L-01146 C3N-01192

FGFR3 | TACC3 | FGFR3 | TACC3

RNA

Protein

WT Fusion WT Fusion
N = 94 5 94 5

FGFR3

Protein length 100 | 200 | 300 | 400 | 500 | 600 | 700 | 800

e17

- IGc2 Immunoglobulin C-2 Type
- IG Immunoglobulin
- Ig2_FGFR Second immunoglobulin (Ig)-like domain of fibroblast growth factor (FG ...
- other FGF binding site [polypeptide binding]
- other ligand binding site [chemical binding]
- IG_like Immunoglobulin like
- Ig3_FGFR-2 Third immunoglobulin (Ig)-like domain of fibroblast growth factor rece ...
- PKc_like Protein Kinases, catalytic domain
- Pkinase_Tyr Protein tyrosine kinase
- other ATP binding site [chemical binding]

C3L-01040
C3N-03186
C3N-01192
chr4:1806934
C3N-00661
chr4:1806924
C3L-01040
chr4:1806971

C

FDR = 0.11 | FDR < 0.01

PLCG1 | PLCG1-Y783

Protein | Phosphorylation

N = 53 46

GAB1 | GRB2

Protein | Protein

N = 53 46

EGFR Status
- WT
- Altered

D

SOX9 | GAB1 | IDH1 R132H

EGFR Altered C3L-01327 | EGFR Altered C3L-01048 | IDH1 mutant C3L-02041

EGFR WT C3L-01149 | EGFR WT C3L-01146 | IDH1 WT C3L-03390

E

CD68 | CD163 | CD3 | PD-1 | PD-L1

im1

im1 C3L-01142 | im1 C3L-01046 | im1 C3L-01046 | im1 C3L-01142 | im1 C3L-01142

im4

im4 C3L-03390 | im4 C3L-01061 | im4 C3L-03390 | im4 C3L-03390 | im4 C3L-01061

F

im1 | im2 | im3 (IDH mut) | im3 (IDH WT) | im4

CD68

im1 C3L-01142 | im2 C3N-01515 | im3 C3L-02041 | im3 C3L-01157 | im4 C3L-03390

CD3

im1 C3L-01046 | im2 C3N-01515 | im3 C3L-02041 | im3 C3L-03387 | im4 C3L-03390

Figure S4. CNV, RNA, Protein and Phosphosite Level Change in Samples with Different RTK Alterations, and Immunohistochemistry Staining Results, Related to Figures 2, 3 and 4.

A) The comparison of CNV, RNA and protein expressions and phosphosite level between *EGFR* altered and WT samples (left panel) and *PDGFRA* altered and WT samples (right panel). We did not find expression differences between samples having a sole SV event versus those with dual mutation and SV events, suggesting EGFR upregulation in GBM is largely due to SV, as associated with CNV amplification, rather than mutationally driven, which is different from other tumor types, such as lung cancer (Cancer Genome Atlas Research Network, 2014). We also found nine samples in which *EGFR* SV co-occurred with *PDGFRA* or *FGFR3* SV, while 13 samples with either *PDGFRA* or *FGFR3* alteration did not show any alterations in *EGFR*. For *PDGFRA*, two out of three mutations overlap with SV events. Only one sample with mutation in *PDGFRA* had high *PDGFRA* RNA and protein expression. For EGFR, n=53 (WT), 29 (SV), and 16 (SV and MUT); for PDGFRA, n=84 (WT), 12 (SV), and 2 (SV and MUT).

B) The comparison of RNA and protein expression of FGFR3 and TACC3 between samples with and without FGFR3-TACC3 fusion and the breakpoints found in *FGFR3* from RNA-Seq data (n=94 and 5, respectively). Five samples with FGFR3-TACC3 fusions with an intact FGFR3 kinase domain. Three samples which are protein expression outliers in FGFR3 are marked by larger circles.

C) The comparison of PLCG1, GAB1, and GRB2 protein expression and PLCG1-Y783 phosphosite level between *EGFR* altered (n=53) and WT (n=46) samples.

D) Immunohistochemistry staining for SOX9 and GAB1 expression in *EGFR* altered and WT tumors is concordant with the mass spectrometry findings. Positive *IDH1* R132H staining of the *ATRX* WT and *IDH1* mutant tumor shown in **Figure 2H**. Scale bars: 100 µm.

E) Immunohistochemistry staining for CD68, CD163, CD3, PD-1, PD-L1 in tumors of different immune subtypes is concordant with the mass spectrometry and gene expression analyses. Scale bars: 100 µm.

F) Immunohistochemistry staining for CD68 and CD3 in tumors of all four immune subtypes is concordant with the mass spectrometry and gene expression analyses. Scale bars: 100 µm.
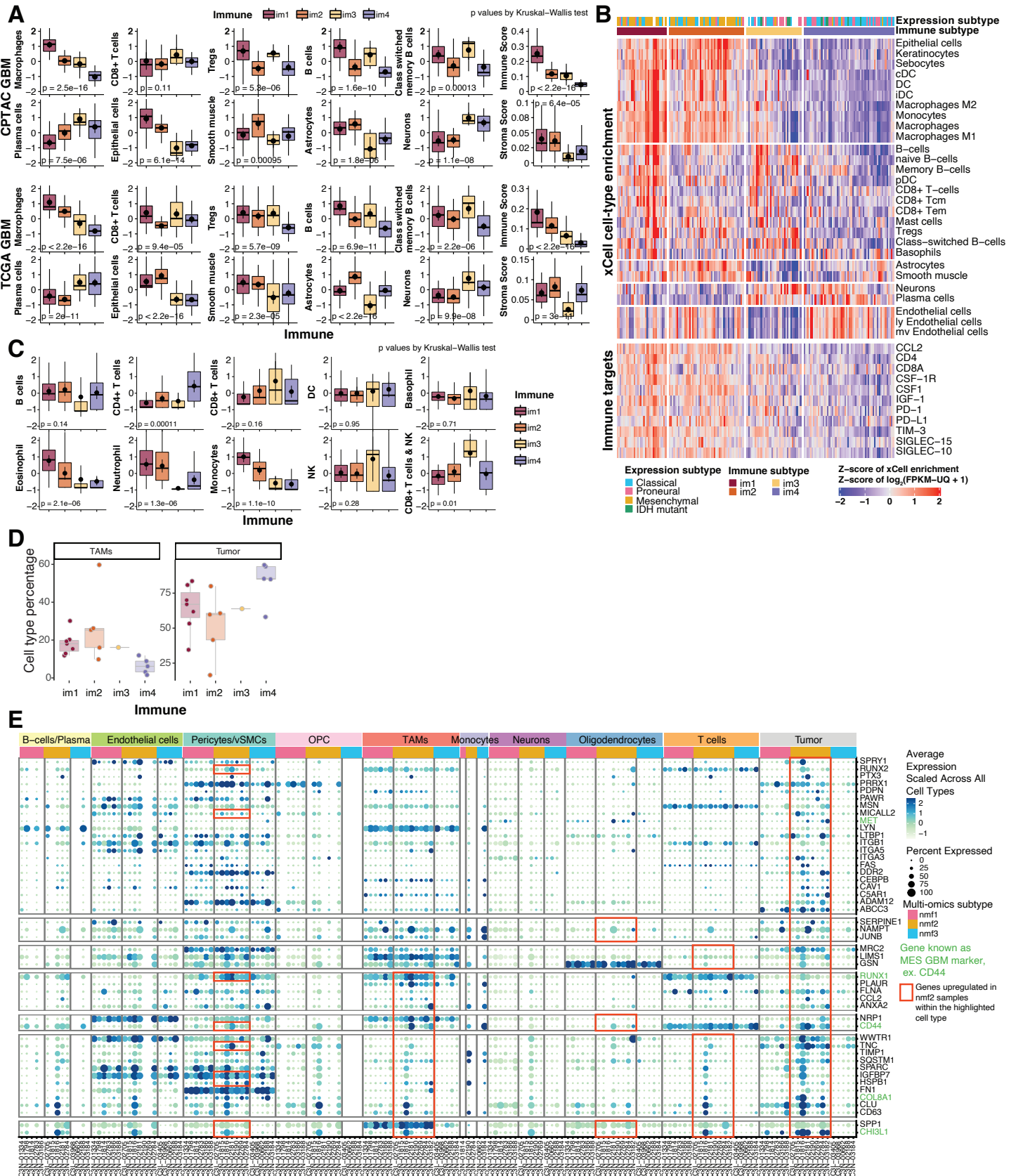
Figure S5. Distinct Immune Marker Expression Ascertains Immune Subtypes, Related to Figure 4.

A) The distributions of xCell cell type enrichments, immune scores, and stroma scores among the 4 immune subtypes in the CPTAC GBM cohort and TCGA GBM cohort. For CPTAC, n=30 (im1), 28 (im2), 9 (im3), and 32 (im4); for TCGA, n=32 (im1), 48 (im2), 35 (im3), and 59 (im4).

B) The 4 immune subtypes identified by the consensus clustering on the cell type enrichment in the TCGA GBM study.

C) The distributions of protein-based CIBERSORT cell type enrichments among the 4 immune subtypes in the CPTAC GBM cohort. N=30 (im1), 28 (im2), 9 (im3), and 32 (im4).

D) snRNA-seq cell type percentage per sample in each immune subtypes.

E) Expression of epithelial–mesenchymal transition genes from different cell types in different snRNA-seq samples. Genes upregulated (Wilcoxon FDR < 0.05 and $\log_2$FC > 0.25) in tumor cells of nmf2 samples. Genes were also tested for significant upregulation in TAMs, T-cells, oligodendrocytes and pericytes/vSMCs; the same thresholds were applied to genes highlighted in red boxes. Dot size denotes the percentage of cells expressing a gene in the given cell type.
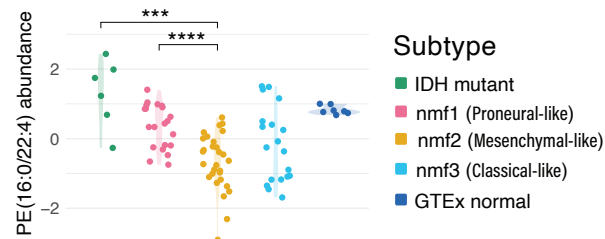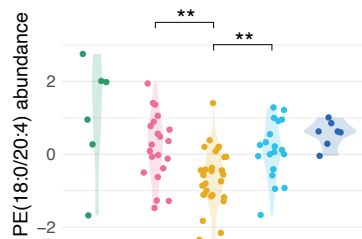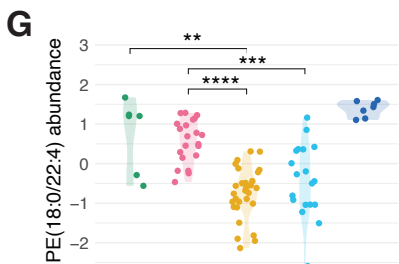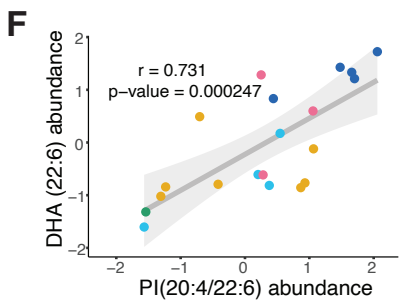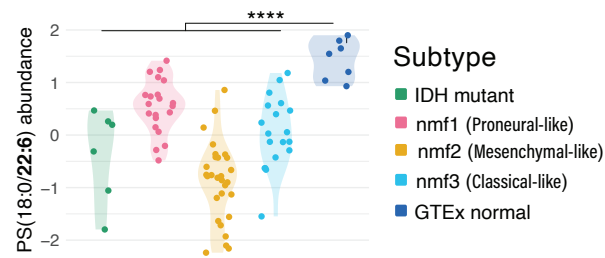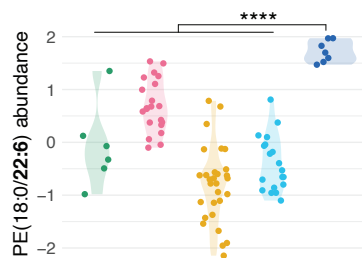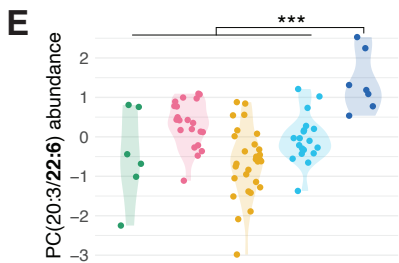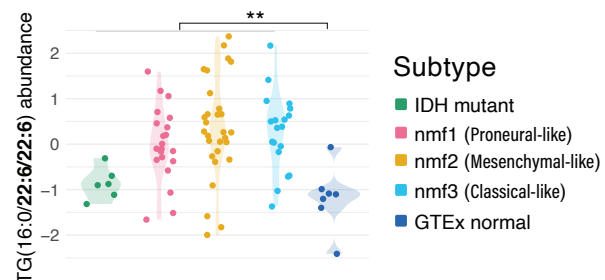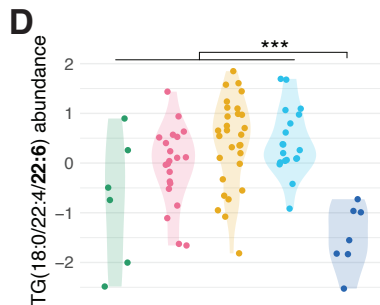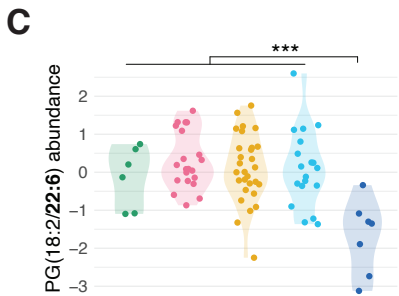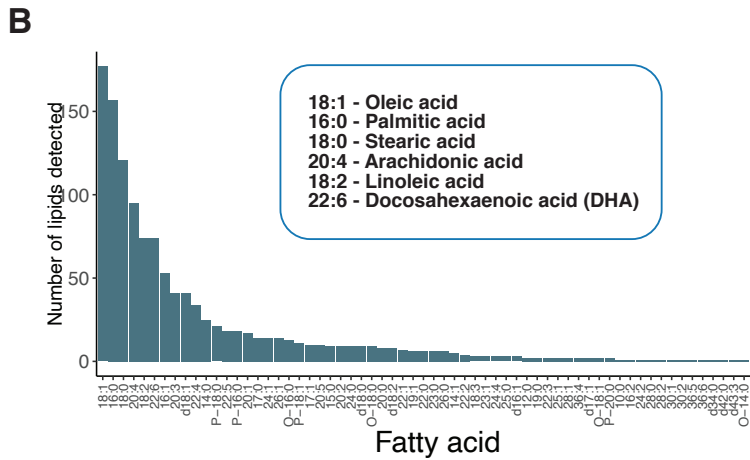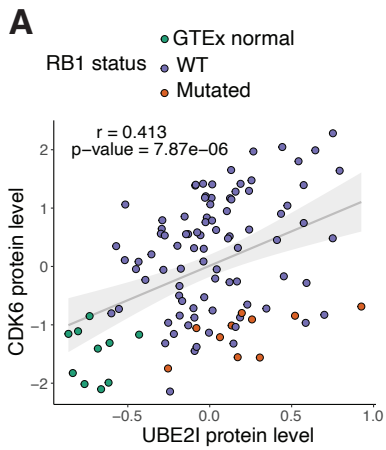
Figure S6. Relations Between H2B Acetylation and SUMOylation Pathway, Related to Figure 5; Additional Lipid Abundance Evidence, Related to Figure 6.

A) Scatterplot showing correlation between UBE2I protein level and CDK6 protein level. Pearson's correlation value and p-value are shown. RB1 mutated samples are labeled in dark orange.

B) Frequency of the side chains observed in the detected lipids.

C) Abundance of phosphatidylglycerol PG(18:2/22:6) across multi-omics subtypes and GTEx normal samples. 22:6 is likely DHA. Wilcoxon test *p*-value is labeled.

D) Abundance of 22:6-carrying TGs across multi-omics subtypes and GTEx normal samples. 22:6 is likely DHA. Wilcoxon test *p*-value is labeled.

E) Abundance of 22:6-carrying PC, PE and PS across multi-omics subtypes and GTEx normal samples. 22:6 is likely DHA. Wilcoxon test *p*-value is labeled.

F) Scatterplot showing correlation between DHA abundance and PI(20:4/22:6) abundance. Pearson's correlation value and *p*-value are shown.

G) PEs carrying 22:4 or 20:4 fatty acids are downregulated in nmf2/mesenchymal-like subtype, while PE not containing either of the two FAs is upregulated in IDH1 mutant subtype only.

A

Differential expression significance

Least significant — Most significant

▢ Missing protein expression data
● Phosphosite

▢ Druggable gene (green border)

→ Phosphorylation (blue)
→ Upregulates expression (green)

B

GSK3B | AKT1 | AKT2 | MAPK1 | MAPK3

CNV / RNA / PRO / PHO rows

Substrates PHO

● Outlier (dark green/blue)
● Not outlier (light green/blue)

GSK3B substrates: TSC1, RPTOR, IRS1, EIF4EBP1, CTNNB1, APC
AKT1 substrates: SHC1, RAF1, IRS2, ERRFI1, AKT1S1
AKT2 substrates: IRS2, APC, AKT1S1
MAPK1 substrates: SOS2, SOS1, SCRIB, RPS6KA3, RAF1, MAPK3, IRS2, EIF4EBP1, ADAM17
MAPK3 substrates: SOS2, RPS6KA3, NCOR2, IRS2, ABL1

C

RB1-altered Signature

Transcription-based | Phosphoprotein-based

| | CLUE | | iLINCS | | P100 |

Signature Reverser / Signature Enhancer

CLUE: palbociclib (CDK inhibitor), PP-30, NVP-BEZ235 (MTOR inhibitor), PI-103 (MTOR inhibitor), droxinostat (HDAC inhibitor), LY-294002 (Bromodomain Inhibitor), pyroxamide (HDAC inhibitor), KU-0063794 (MTOR inhibitor), AZD-8055 (MTOR inhibitor), ISOX (HDAC inhibitor), BMS-536924 (IGF-1 inhibitor), GDC-0941 (PI3K inhibitor), PI-828 (PI3K inhibitor), BMS-754807 (IGF-1 inhibitor), OSI-027 (MTOR inhibitor), AT-9283 (Aurora kinase inhibitor), avrainvillamide..., THM-I-94 (HDAC inhibitor), panobinostat (HDAC inhibitor), cytochalasin-b

latrepirdine (Glutamate receptor antagonist), serdemetan (MDM inhibitor), clofarabine (Ribonucleotide reductase inhibitor), BRD-K06217810, isoliquiritigen..., z-leu3-VS (Proteasome inhibitor), pyrrolidine-dit... (NFkB pathway inhibitor), CD-437 (Retinoid receptor agonist), MLN-2238 (Proteasome inhibitor), roscovitine (CDK inhibitor), YM-155 (Survivin inhibitor), PKCbeta-inhibit..., MST-312, importazole, sulforaphane (Anticancer agent), teniposide (Topoisomerase inhibitor), irinotecan (Topoisomerase inhibitor), RITA (MDM inhibitor), SN-38 (Topoisomerase inhibitor), MLN-4924 (NAE inhibitor)

iLINCS: vorinostat (HDAC inhibitor), trichostatin-a (HDAC inhibitor), Pracinostat, JNJ-26854165, palbociclib (CDK inhibitor), XMD-1150 (Leucine rich repeat kinase inhibitor), dacinostat (HDAC inhibitor), Romidepsin, panobinostat (HDAC inhibitor), MLN-0128 (mTOR inhibitor), THM-I-94 (HDAC inhibitor), rifampicin, BRD-K99805333, SB743921, BRD-K83941994, PI-103 (MTOR inhibitor), dasatinib (SRC inhibitor), BRD-K36150982, BRD-K15318079, ZSTK-474 (PI3K inhibitor)

NCGC00166323–01, TW-37 (BCL inhibitor), MLN-4924 (NAE inhibitor), PD-0325901 (MEK inhibitor), gemcitabine (Ribonucleotide reductase inhibitor), Dopamine 3–O–su..., irinotecan (Topoisomerase inhibitor), Dihydroorotate..., BRD-K71947697, Clofarabine, PHA-767491 (CDC inhibitor), Pralatrexate, BRD-K72738889, importazole, mitomycin-c (DNA synthesis inhibitor), Aphidicolin, Floxuridine, SN-38 (Topoisomerase inhibitor), cladribine (Ribonucleotide reductase inhibitor)

P100: vandetanib (EGFR inhibitor), gefitinib (EGFR inhibitor), afuresertib (AKT inhibitor), kn–62, osi-027, chir99021, imatinib (Bcr–Abl kinase inhibitor), vemurafenib (RAF inhibitor), doxorubicin (Topoisomerase inhibitor), okadaic acid, rolipram (Phosphodiesterase inhibitor), roscovitine (CDK inhibitor), rgfp966, flecainide (Sodium channel blocker), tg101348 (JAK inhibitor), sotrastaurin (PKC inhibitor), regorafenib (FGFR inhibitor), ibrutinib (BTK inhibitor), tbb

gsk525762a (Bromodomain inhibitor), pravastatin (HMGCR inhibitor), dexamethasone (Glucocorticoid receptor agonist), 1271738–62–5, ms–275, jq1–s, bix–01338, dinaciclib (CDK inhibitor), belinostat (HDAC inhibitor), methylstat, crizotinib (ALK RTK inhibitor), verapamil (Calcium channel blocker), ci–994 (HDAC inhibitor), trichostatin a, epz004777 (DNA methyltransferase inhibitor), flavopiridol, bortezomib (NFkB pathway inhibitor), carfilzomib (Proteasome inhibitor), bms-906024

Immuno-high Signature

Transcription-based | Phosphoprotein-based

| | CLUE | | iLINCS | | P100 |

CLUE: PJ-34 (PARP inhibitor), PD-0325901 (MEK inhibitor), PD-184352 (MEK inhibitor), palonosetron (serotonin receptor antagonist), PD-98059 (MEK inhibitor), AZD-7762 (MEK inhibitor), fasudil (PKA inhibitor), AS–703026 (MEK inhibitor), CG-930 (MEK inhibitor), WH–4023 (SRC inhibitor), fatostatin, bosutinib (SRC inhibitor), RHO–kinase–inhi..., SB-202190 (Bromodomain Inhibitor), NSC–23766 (Ras GTPase inhibitor), MEK1–2–inhibito... (MEK inhibitor), Y–27632 (Rho associated kinase inhibitor), HO–013 (PPAR receptor agonist), piperacillin (bacterial cell wall synthesis inhibitor), TWS–119 (Glycogen synthase kinase inhibitor)

MG-132 (Proteasome inhibitor), SA–792728, gemcitabine (PKC activator), BMY–45778 (IP1 prostacyclin receptor agonist), alisertib (Aurora kinase inhibitor), entinostat (HDAC inhibitor), teniposide (Topoisomerase inhibitor), ingenol (PKC activator), etoposide (Topoisomerase inhibitor), ENMD–2076 (Aurora kinase inhibitor), apicidin (HDAC inhibitor), Merck60 (HDAC inhibitor), SA–792987 (PKC inhibitor), HSP90–inhibitor (HSP inhibitor), 7b–cis, KI–8751 (PDGFR/KIT inhibitor), BX-795 (IKK inhibitor), phorbol–12–myri... (PKC activator)

iLINCS: BRD–K63697730, NCGC00166323–01, UNII–CVL1685GPH, AZD2014 (mTOR inhibitor), piperlongumine, MLS002264465, Tioconazole, CHEMBL2133926, Ivermectin, BRD-K79826210, Hexachlorophene, TAK–733 (MEK inhibitor), ZM–39923 (JAK inhibitor), GANT–61 (GLI antagonist), simvastatin (HMGCR inhibitor), BRD–K31856043, Resminostat, MLS002703102, CHEMBL1555451

Pralatrexate, Milciclib (PHA–..., IKK–2–inhibitor... (IKK inhibitor), idarubicin (Topoisomerase inhibitor), PF–03758309 (p21 activated kinase inhibitor), mitoxantrone (Topoisomerase inhibitor), R547 (CDK inhibitor), KPT–330, MLN–2238 (Proteasome inhibitor), MLS000038106, Phorbol Myrista..., pyrvinium–pamoa... (androgen receptor antagonist), CD-437 (retinoid receptor agonist), teniposide (Topoisomerase inhibitor), ingenol (PKC activator), phorbol–12–myri... (PKC activator), palbociclib (CDK inhibitor), 179324–69–7, MG-132 (Proteasome inhibitor)

P100: gsk525762a, gsk126 (EZH2 inhibitor), tbb, bms–906024, rgfp966 (PARP inhibitor), olaparib (PARP inhibitor), sotrastaurin (PKC inhibitor), pravastatin (HMGCR inhibitor), afuresertib (AKT inhibitor), sch 900776, vx–970 (ATR kinase inhibitor), rolipram (phosphodiesterase inhibitor), zebularine (DNA methyltransferase inhibitor), losmapimod (p38 MAPK inhibitor), bafilomycin a1, kn–62, compound e, tg101348 (JAK inhibitor), epz–5687, byl719 (PI3K inhibitor)

ly–294002, ponatinib (Bcr–Abl kinase inhibitor), flecainide (sodium channel blocker), smer–3 (E3 ILigase inhibitor), vandetanib (EGFR inhibitor), cabozantinib (RET tyrosine kinase inhibitor), carfilzomib (proteasome inhibitor), unc–0321, tacrolimus (calcineurin inhibitor), cyclosporine, olmesartan (angiotensin receptor antagonist), okadaic acid (potassium channel blocker), niclosamide (DNA replication inhibitor), pazopanib (KIT inhibitor), gefitinib (EGFR inhibitor), taxol (microtubule inhibitor), isoproterenol, regorafenib (FGFR inhibitor)

CLUE Connectivity Score: -100 to 100
iLINCS Z-score: -20 to 20
P100 Connectivity Score: -1 to 1

Figure S7. Summary of Pathway Alterations of Mesenchymal Tumors Compared to the Other Tumors, Related to Figure 7.

A) Causal explanations for differentially expressed proteomic and phosphoproteomic profiles in mesenchymal tumors versus the rest of the tumors using CausalPath. We highlighted the immune and hypoxia-related interactions enriched in the graph. Genes controlling the immune response might be a potential therapeutic target. Complete result graph is given in **Table S5**.

B) Sample level outlier status for kinase-substrate pairs shown in **Figure 7B**. For kinases (blue) outlier status for four levels of data is shown: CNV, RNA, PRO (protein) and PHO (phosphorylation). For their substrates (green) only PHO outlier status is shown.

C) Drug connectivity analysis using alteration-specific transcriptional (CLUE and iLINCS) and phosphoproteomic (P100) signatures of RB1 altered versus WT tumors and immune-high (im1, im2, and im3) versus immune-low (im4) tumors.