MAPK SIGNALING PATHWAY Phosphaticlylinositol signaling system CAMP O DAG Proliferation, inflammation Heterotorimeric IKK **Chssical MAP kinase** G-protein anti-apoptosis IP₃ pathway Tau 0 Ca2+ STMN1 A NGF RasGRF BDNF MNK1/2^{+p} CREB NT3/4 Scaffold MP1 EGF RafB MEK1 +p ERK FGFR GRB2 - SOS - Ras DNA c-fos 10 Proliferation, MEK2 Sap1a differentiation DNA **→** PDGFR PDGF -Mos c-Myc ► Gap1m $GST\pi$ FLAN JIP3 HSP72 GLK +pTp12/Cot JNK and p 38 MAP ARRB CRKII kinase pathway NFAT-4 Scaffold c-JUN O DNA JunD Hp MLK3 **IP1/2** -p -p Serum, cytotoxic drugs, inadiation, heatshock, PAK1/2 +p MEKK2/3 reactive oxygen species Proliferation. ATF2 lipopolysac charide, and other stress differentiation, PP2CA Elk-1 inflammation Cell MUK p53 signaling p53 cycle Apoptosis MLTK pathway TNF IL1 Sap1a ASK2 FASL GADD153 DAXX O DNA MAX TAB1 TAK1 MEF2C PPAK +p LPS MAPKAPK2+p CREB PP2CB ECSIT GADD45 MEKK4 DNA damage Cdc25B TAO1/2 Wnt signaling pathway ^{+p} NLK **ERK5** pathway

MEK5 +p ERK5

MAPK

MAPKK

MAPKKKK MAPKKK

Proliferation,

differentiation

O DNA

Transcription factor

Serum, EGF, reactive oxygen species,

Srk tyrosinkinase

downstream

MAPK SIGNALING PATHWAY Phosphaticlylinositol signaling system cAMP O DAG Proliferation, Heterotorimeric inflammation anti-apoptosis **Chssical MAP kinase** G-protein IP3 pathway PKA +p Ca2+ В NGF RasGRF CNasGEF BDNF MNK1/2+p CREB NT3/4 Scaffold MP1 RSK2 EGF RafB GRB2 - SOS Raf1 10 Proliferation, Sap1a DNA differentiation DNA PDGF **▶** PDGFR Mos c-Myc NF1 → Gap1m PTP pl20GAP $\mathsf{GST}\pi$ FLAN JIP3 HSP72 JNK and p 38 MAP NFAT-2 ARRB CRKII +p GLK kinase pathway Scaffold NFAT-4 c-JUN O DNA Hp MLK3 JunD Serum, cytotoxic drugs, inadiation, heatshock, **IP1/2** -p -p PAK1/2 +p MEKK2/3 reactive oxygen species Proliferation, differentiation, ATF2 lipopolysac charide, and other stress PP2CA Elk-1 Cell inflammation p53 signaling MUK p53 CASP cycle pathway Apoptosis TNF TRAF2 ASK2 Sap1a FASL +p p38 DAXX O DNA TGFB MAX TAK1 MEF2C O LPS PPAK +p TAB2 -p PP2CB PP5 ECSIT CREB DNA damage MEKK4 MSK1/2 TAO1/2 Wnt signaling **ERK5** pathway pathway Serum, EGF, reactive oxygen species, → MEK5 ^{+p} ERK5 Proliferation, O DNA or differentiation Srk tyrosinkinase downstream Transcription factor MAPKKKK MAPKKK MAPKK MAPK

S4 Fig. Mitogen-activated protein kinase (MAPK) signaling pathway enriched by 47 putative target genes of upregulated miRNAs (A) and 53 putative target genes of downregulated miRNAs (B). Red boxes represent the target genes of miRNAs.