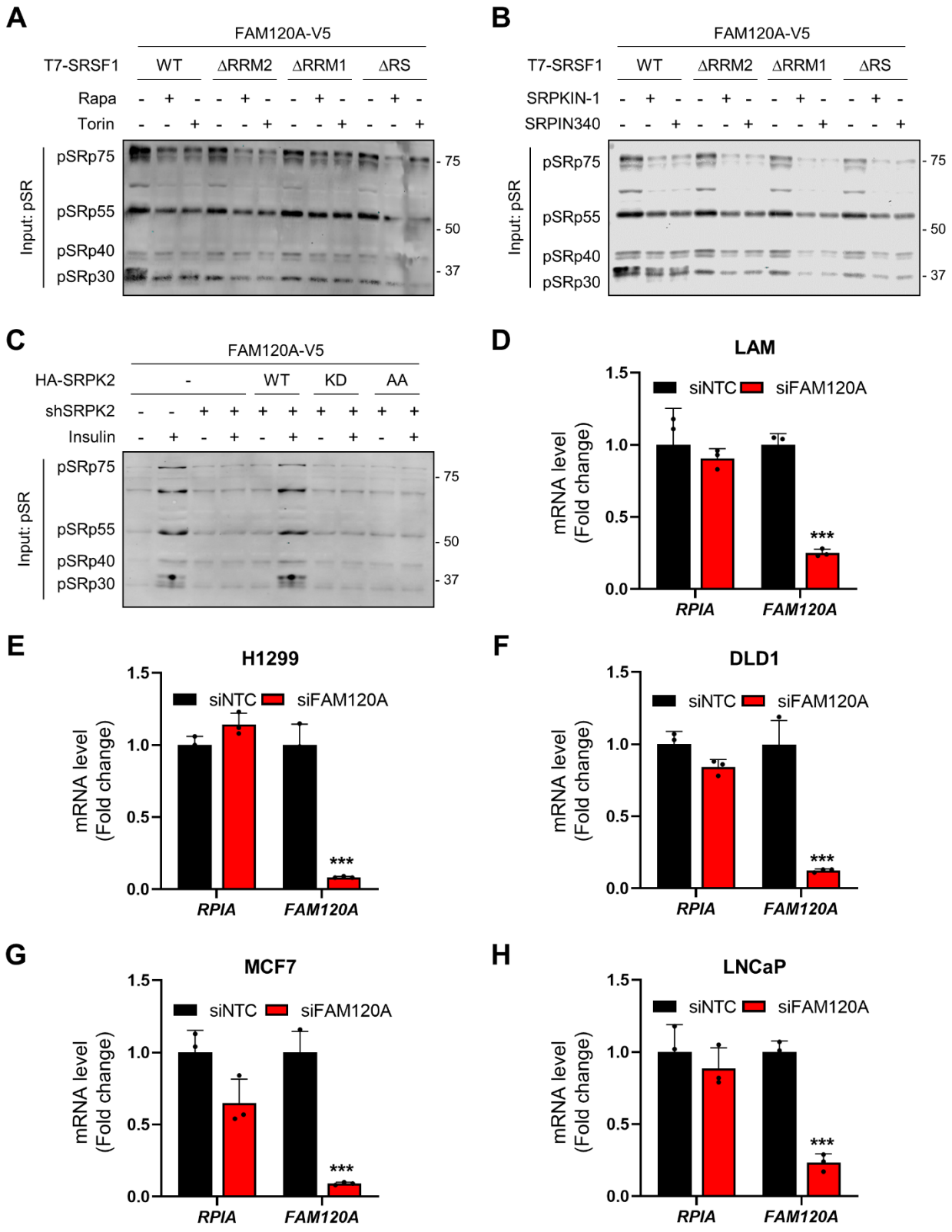
Supplemental Figure S1 (Related to Figures 1 and 2)



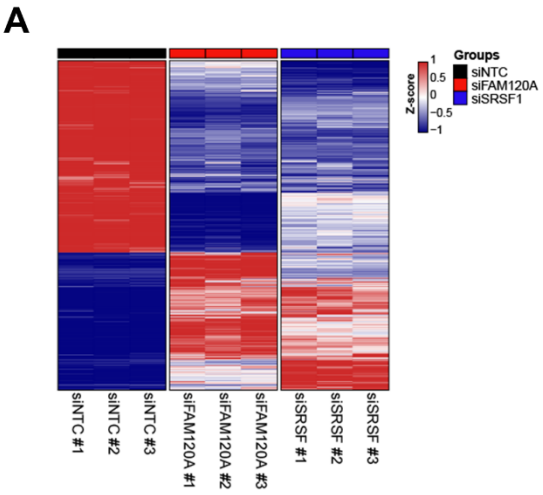
Supplemental Figure S1. Confirmation of SR protein phosphorylation and additional qPCR analysis of *FAM120A* knockdown cells (Related to Figures 1 and 2).

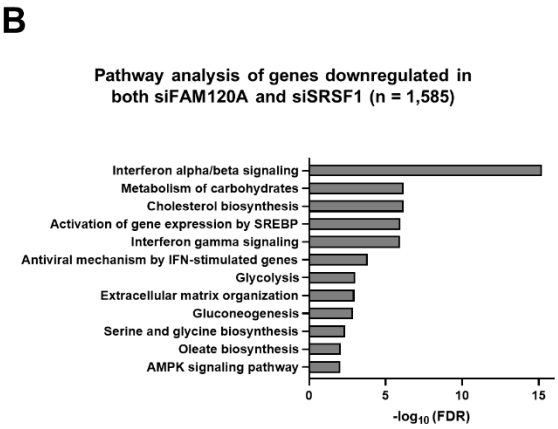
(A, B) Immunoblot analysis of HEK293E cells expressing FAM120A-V5 and T7-SRSF1 (WT or mutants). Cells were treated with torin1 (250 nM), Rapamycin (100 nM) (A) or SRPK inhibitors (SRPKIN-1, 5 μM; SRPIN340, 30 μM) (B) for 4 hr.

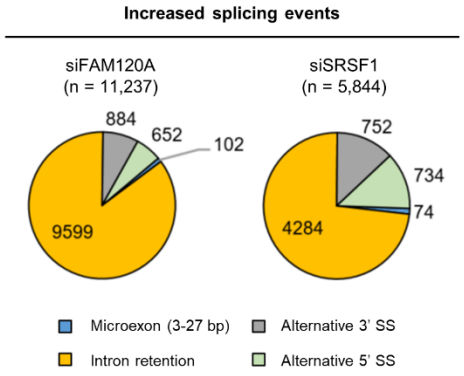
(C) Immunoblot analysis of HEK293E cells expressing FAM120A-V5 and HA-SRPK2 (WT (wild type), KD (kinase dead, SRPK2-K110M), or AA (non-phosphorylatable, SRPK2-S394A/S397A)). Endogenous *SRPK2* was knocked down by shRNA targeting 3'UTR of *SRPK2*. Cells were serum starved overnight followed by insulin (100 nM) stimulation for 4 hr.

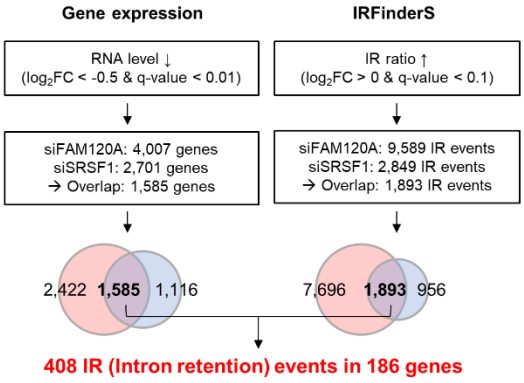
(D-H) QPCR analysis of LAM (D), H1299 (E), DLD1 (F), MCF7 (G), and LNCaP (H) cells transfected with siRNAs targeting *FAM120A* or control. Cells were serum-starved overnight before analysis. N = 3. ***$p < 0.001$.

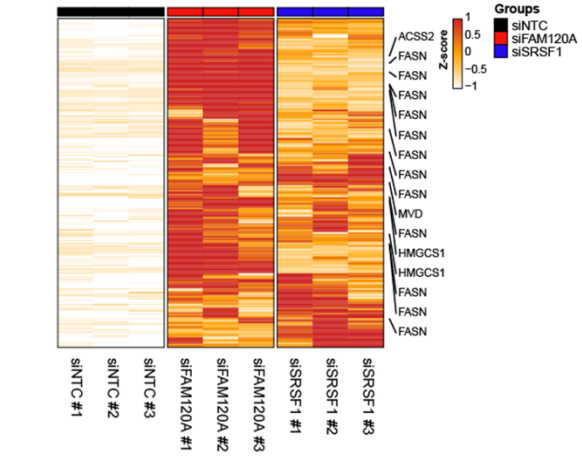
Supplemental Figure S2 (Related to Figure 3)

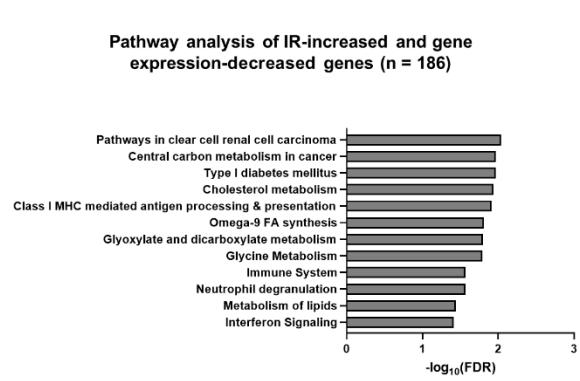












Supplemental Figure S2. Analysis of intron retention in LAM cells knocked down with *FAM120A* or *SRSF1* (Related to Figure 3).

(A) Heatmap of z-scores for differentially expressed gene levels (cutoff: $|Log_2FC| \geq 0.5$, q-value < 0.01; N = 2,895) analyzed from RNA-seq results of LAM cells transfected with siNTC, siFAM120A, or siSRSF1 (GSE229657). Same RNA-seq data are used in Figures 3 and S2.

(B) Pathway analysis of genes from (A) that are significantly downregulated (cutoff: $Log_2FC \leq -0.5$, q-value < 0.01; N = 1,585) by both siFAM120A and siSRSF1.

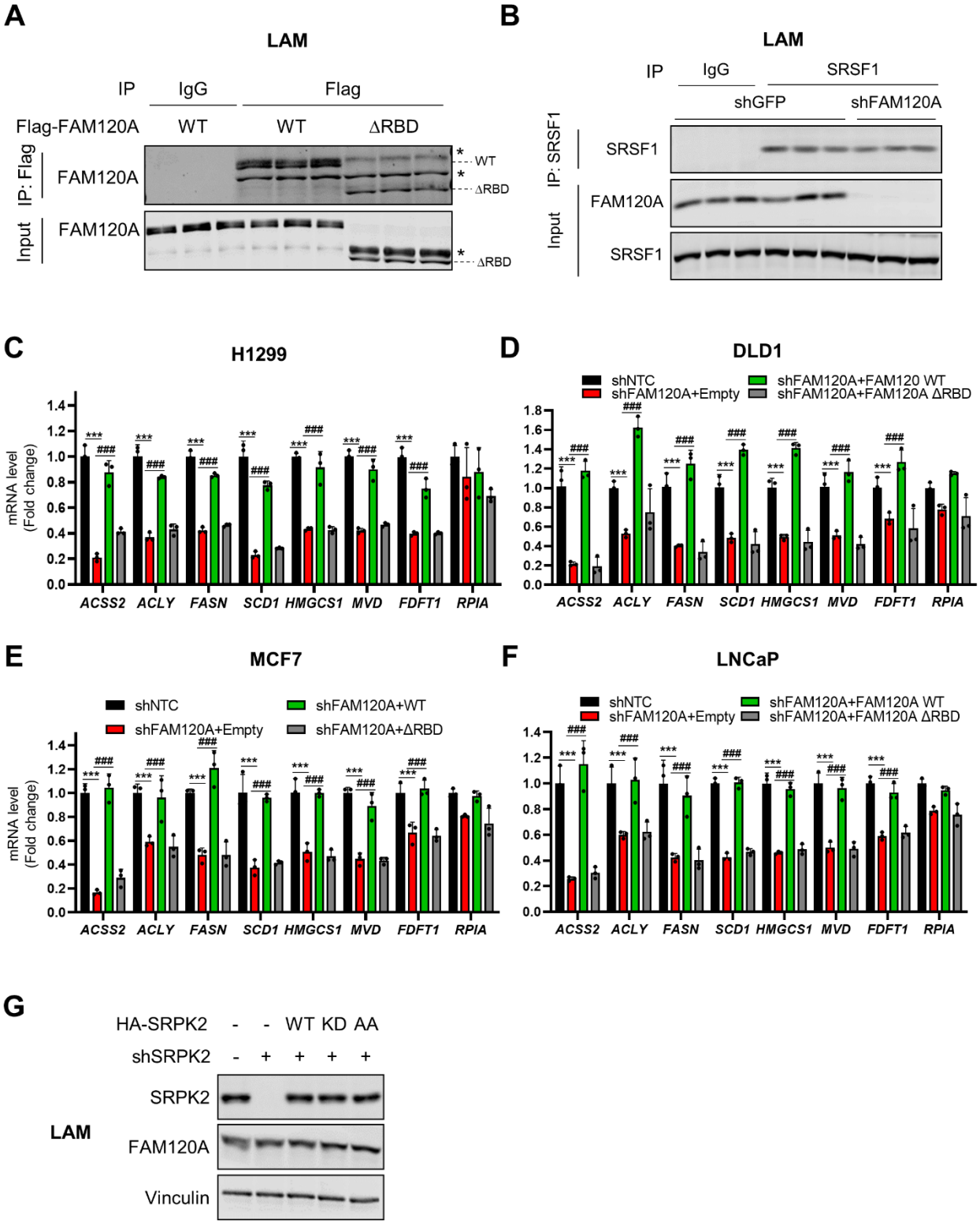
(C) Circular histogram shows the distribution of various splicing events in siFAM120A and siSRSF1analyzed by VAST-TOOLS.

(D) Scheme of identifying the genes that show increased intron retention (IR) and decreased gene expression by both siFAM120A and siSRSF1 compared to control.

(E) Heatmap of z-scores for intron retention ratios calculated using IRFinderS. 408 intron loci were found to exhibit significant intron retention in siFAM120A and siSRSF1 compared to control including the introns of *de novo* lipid synthesis enzymes (gene names listed on the right side of the heatmap).

(F) Pathway analysis of genes from (D) that show IR-increase and gene expression decrease in both siFAM120A and siSRSF1 (N = 186).

Supplemental Figure S3 (Related to Figure 4)



Supplemental Figure S3. Additional immunoblot and qPCR analysis of cells overexpressing or knocked down with *FAM120A* (Related to Figure 4).

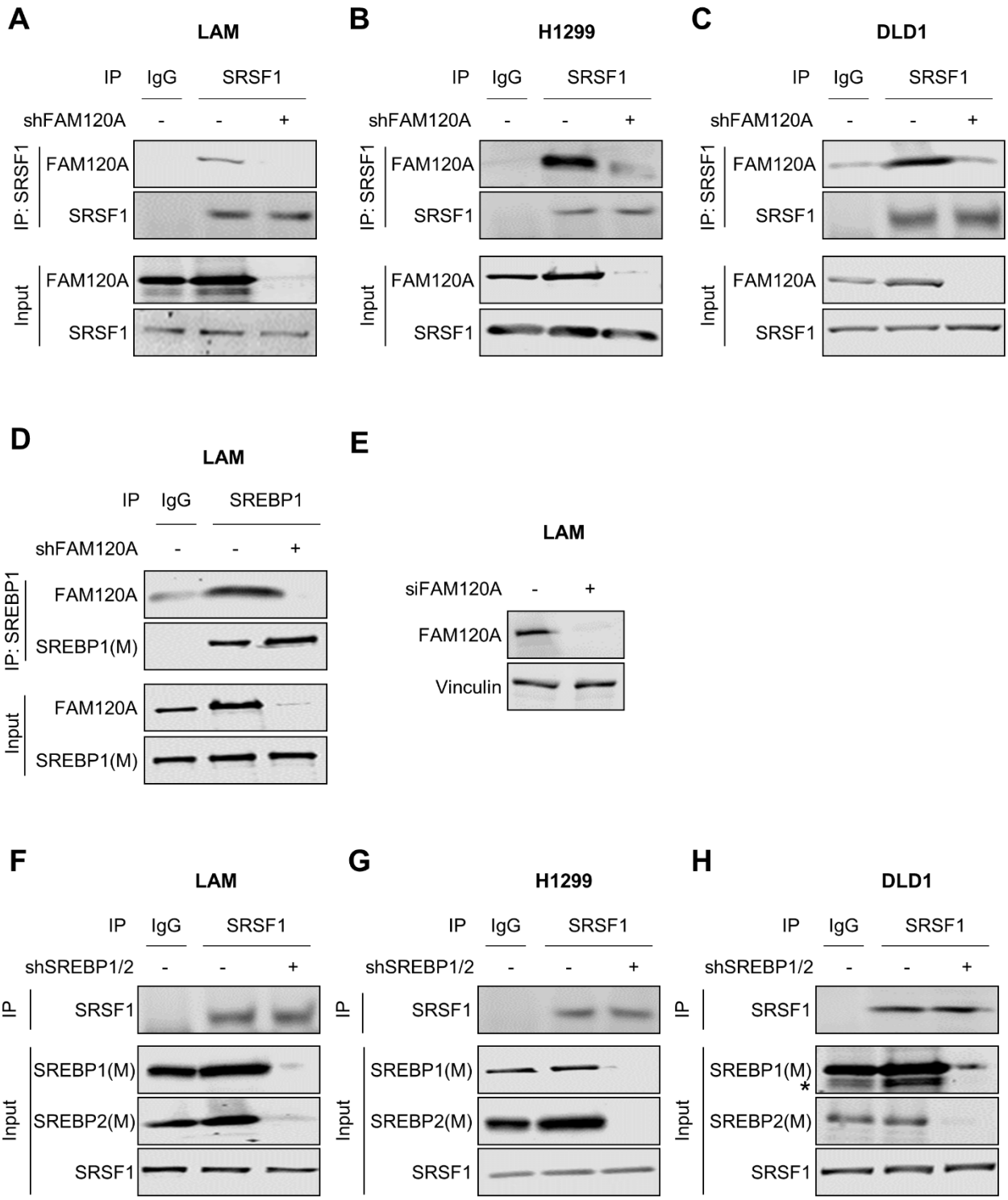
(A) Immunoblot analysis of RIP products from LAM cells expressing Flag-FAM120A WT or ΔRBD. 1% of total cell lysate was loaded as an input. Asterisks indicate non-specific bands.

(B) Immunoblot analysis of RIP products of LAM cells stably expressing shRNAs targeting *FAM120A* or control. 1% of total cell lysate was loaded as an input.

(C-F) QPCR analysis of H1299 (C), DLD1 (D), MCF7 (E), and LNCaP (F) cells stably expressing shNTC or shFAM120A with FAM120A WT or ΔRBD. Cells were serum starved overnight before analysis. N = 3. Data are represented as mean ± SD. $^{***}p < 0.001$ and $^{\#\#\#}p < 0.001$.

(G) Immunoblot analysis of LAM cells stably expressing HA-SRPK2 (WT (wild type), KD (kinase dead, SRPK2-K110M), or AA (non-phosphorylatable, SRPK2-S394A/S397A)). Endogenous *SRPK2* was knocked down by shRNA targeting 3'UTR of *SRPK2*. Cells were serum-starved overnight.

Supplemental Figure S4 (Related to Figure 5)



Supplemental Figure S4. Immunoblot analysis of ChIP samples prepared from cells knocked down with *FAM120A or SREBP1/2* (Related to Figure 5).

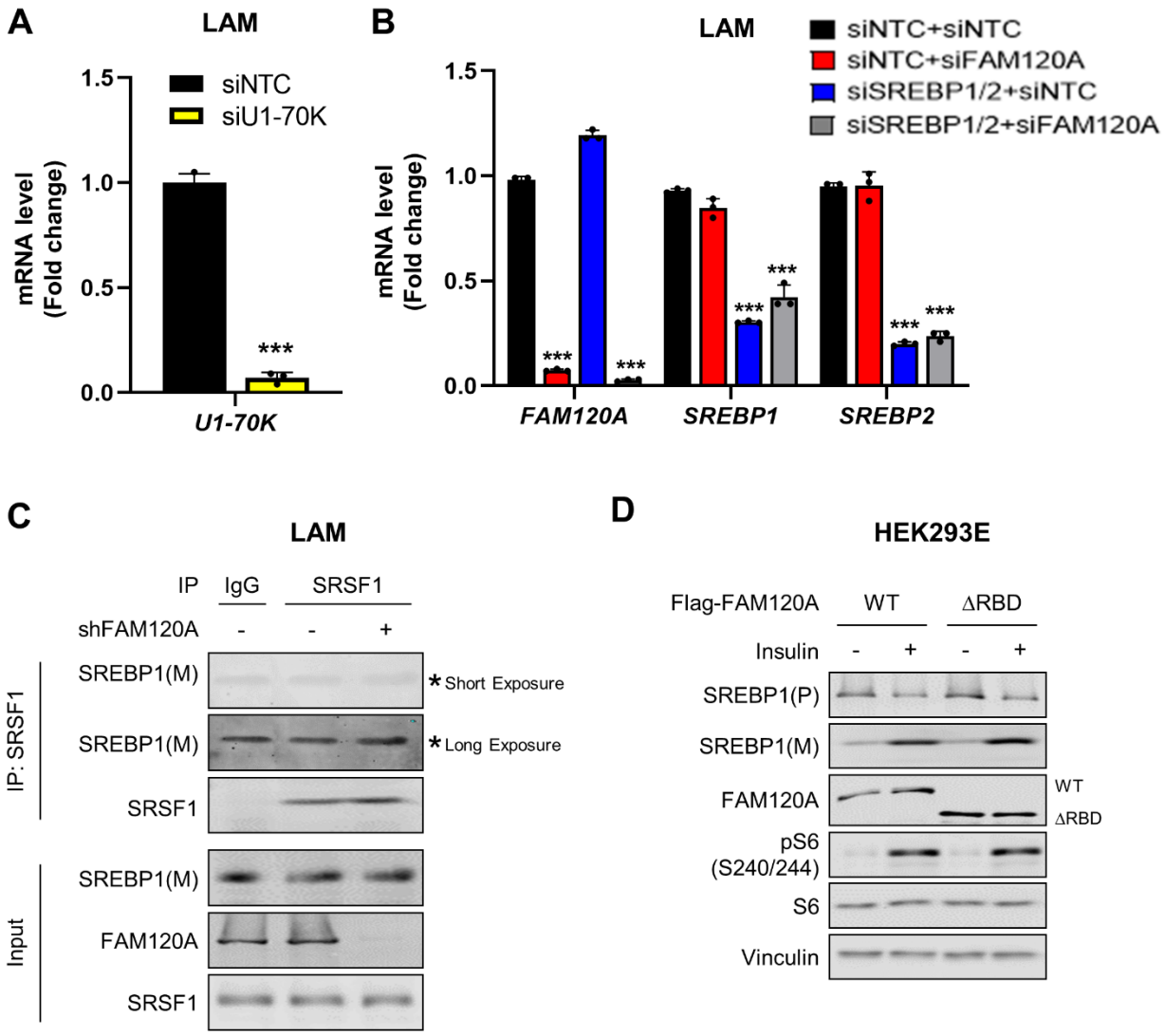
(A-C) Immunoblot analysis of ChIP products from LAM (A), H1299 (B), and DLD1 (C) cells stably expressing shNTC or shFAM120A. IP was performed with IgG or anti-SRSF1 antibodies.

(D) Immunoblot analysis of ChIP products from LAM stably expressing shNTC or shFAM120A. IP was performed with IgG or anti-SREBP1 antibodies.

(E) Immunoblot analysis of LAM cells transfected with siRNAs targeting *FAM120A* or control.

(F-H) Immunoblot analysis of ChIP products from LAM (F), H1299 (G), and DLD1 (H) cells stably expressing shNTC or shSREBP1/2. IP was performed with IgG or anti-SRSF1 antibodies.

Supplemental Figure S5 (Related to Figure 6)



Supplemental Figure S5. Immunoblot and qPCR analysis of cells overexpressing or knocked down with *FAM120A or SREBP1/2* (Related to Figure 6).

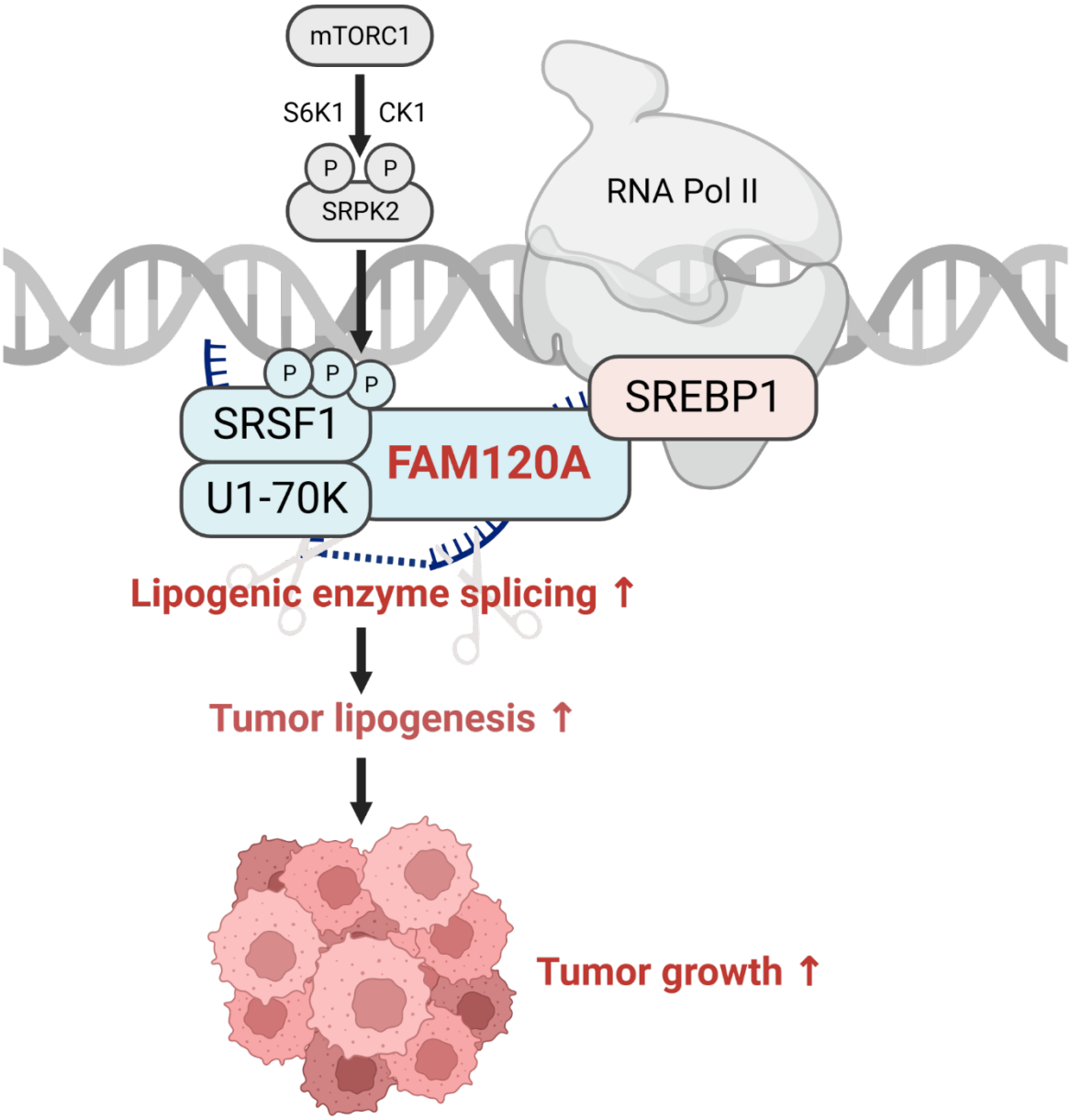
(A) QPCR analysis of LAM cells transfected with siRNAs targeting *U1-70K* or control. Cells were serum-starved overnight before analysis. N = 3.

(B) QPCR analysis of LAM cells transfected with siRNAs targeting *FAM120A, SREBP1/2,* or control. Cells were serum-starved overnight before analysis. N = 3.

(C) Co-IP analysis of LAM cells stably expressing shRNAs targeting *FAM120A* or control. Immunoprecipitation was performed with IgG or anti-SRSF1 antibodies. 1% of total cell lysate was loaded as an input. Asterisks indicate non-specific binding of SREBP1 to IgG.

(D) Immunoblot analysis of HEK293E cells expressing Flag-FAM120A WT or ΔRBD. Cells were serum starved overnight followed by insulin (100 nM) stimulation for 4 hr. SREBP1(P), precursor SREBP1; SREBP1(M), cleaved and matured SREBP1.
Data are represented as mean ± SD. ***$p < 0.001$.

Supplemental Figure S6 (Related to all Figures)

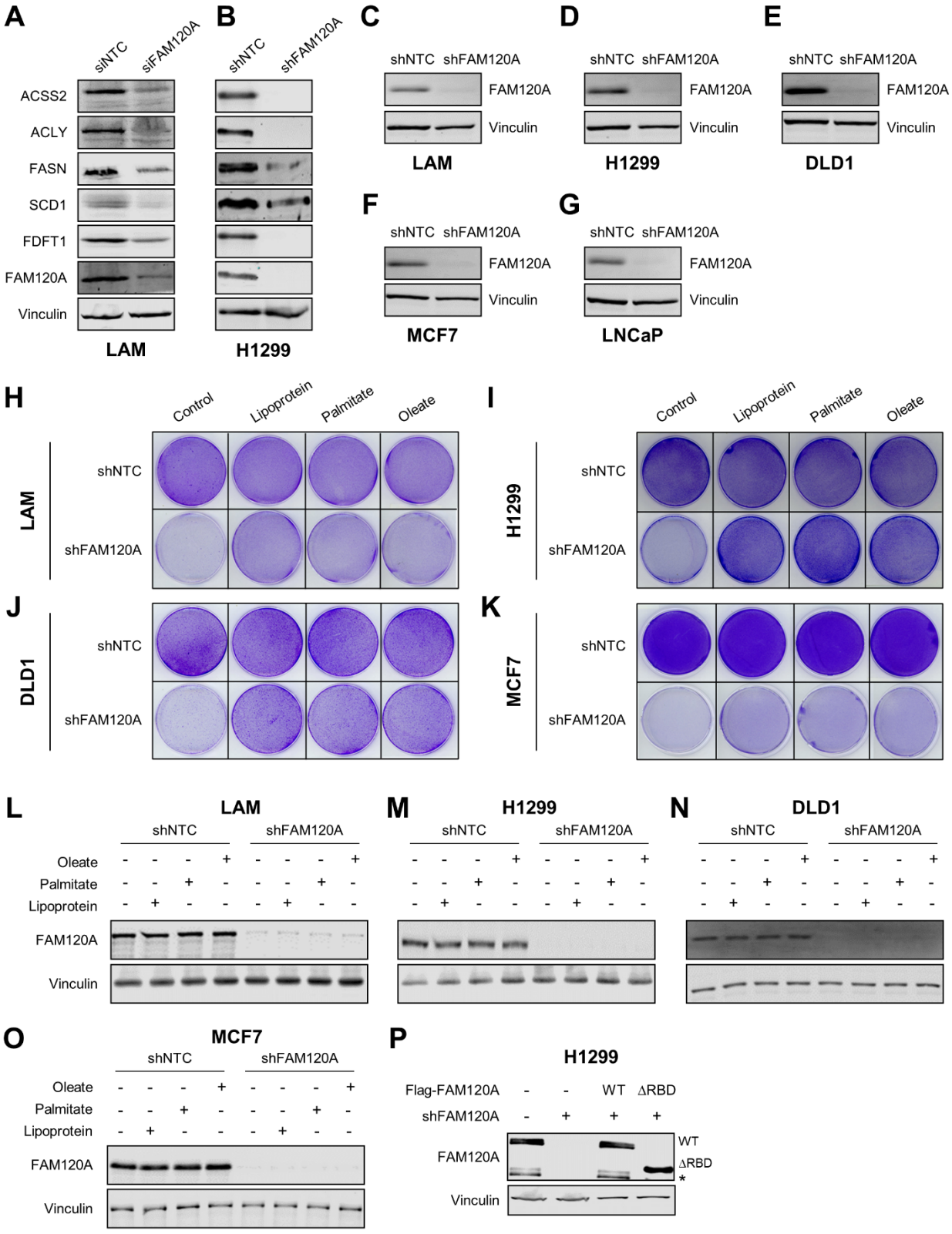


Supplemental Figure S6. mTORC1 promotes *de novo* lipogenesis through FAM120A (Related to all Figures).

Through phosphorylation of SRSF1, mTORC1-SRPK2 induces the interaction of FAM120A with RNA splicing factors SRSF1 and U1-70K. FAM120A also interacts with a transcription factor SREBP1 and RNA pol II to promote efficient splicing of lipogenic transcripts through SRSF1 and

U1-70K. The spliced lipogenic gene transcripts produce lipogenic enzymes to induce lipid synthesis and tumor growth.

Supplemental Figure S7 (Related to Figure 7)



Supplemental Figure S7. Additional immunoblot analysis and cell growth analysis images of cells knocked down with or overexpressing *FAM120A* (Related to Figure 7).

(A) Immunoblot analysis of LAM cells transfected with siRNAs targeting *FAM120A* or control.

(B-G) Immunoblot analysis of H1299 (B, D), LAM (C), DLD1 (E), MCF7 (F), and LNCaP (G) cells stably expressing shRNAs targeting *FAM120A* or control.

(H-K) Crystal violet staining of LAM (H), H1299 (I), DLD1 (J), and MCF7 (K) cells stably expressing shRNAs targeting *FAM120A* or control. Cells were grown in lipoprotein-deficient serum (LPDS)-containing media supplemented with lipoprotein (25 μg/ml), palmitate-albumin (10 μM, palmitate), oleate-albumin (50 μM, oleate), or fatty acid-free albumin (25 μM, control).

(L-O) Immunoblot analysis of LAM (L), H1299 (M), DLD1 (N), and MCF7 (O) cells stably expressing shRNAs targeting *FAM120A* or control. Cells were treated as described in (H-K).

(P) Immunoblot analysis of xenograft H1299 tumors stably expressing shNTC or shFAM120A with FAM120A WT or ΔRBD. Asterisk indicates a non-specific band.