**SI Materials and Methods**

**Reagents.** Control and Rictor shRNA packed in lentiviral particles were purchased from Santa Cruz (Santa Cruz, CA). U937 cells infected with control or Rictor shRNA lentivirus were selected and maintained in RPMI containing 10% FBS and 2 \( \mu \text{g/mL} \) puromycin. Phospho-specific antibodies against AKT, p70 S6K, rpS6, 4E-BP1 and antibodies against AKT, rpS6 protein and Pras40 were from Cell Signaling (Beverly, MA). Antibodies against p70 S6K, Hsp90 and tubulin were from Santa Cruz (Santa Cruz, CA). An anti-Rictor antibody was from Bethyl Labs (Montgomery, TX). Total GAPDH and phospho-specific antibody against PRAS40 were from Millipore (Billerica, MA). An anti-mouse ISG15 antibody has been described previously (1). An antibody against human ISG15 antibody was a gift from Dr. Ernest Borden (Taussig Cancer Centre, Cleveland Clinic, Cleveland, OH). An anti-ISG54 antibody was obtained from Abcam (Cambridge, MA). Recombinant human IFN-\( \alpha \) was from Hoffmann La Roche, and mouse IFN-\( \alpha \) was from Wellcome Research laboratories. Mouse IFN\( \beta \) was from Biogen Idec (Cambridge, MA). Insulin was purchased from Sigma (St Louis, MO). The ISRE-luciferase construct included the wild type ISG15 ISRE (TCGGGAAAGGGAA-ACCGAAACTGAAGCC) cloned via cohesive ends into the BamHI site of the pZkLuc vector (2), and was provided by Dr. Richard Pine (Public Health Research Institute, Newark, NJ).

**Real time PCR.** Real time PCR was carried out using custom made ISG15 and GAPDH primers and SYBR green mix (Applied Biosystems). The primers sequences were as follows: Isg15 forward primer 5'-TGA CTG TGA GAG CAA GCA GC3', ISG15 reverse primer 5'CCC CAG CAT CTT CAC CTT TA3', Gapdh forward primer 5'CGT CCC GTA GAC AAA ATG GT3', Gapdh reverse primer 5'TTG ATG GCA ACA ATC TTC AC3.' GAPDH was used for normalization. SYBR Green PCR amplifications were carried out using an Applied Biosystem 7500 thermocycler (Applied Biosystems). The reactions were carried out in a 96-well plate in a 20 \( \mu \)L reaction volume containing 1X SYBR Green Master Mix (Applied Biosystems) and 0.2 \( \mu \)M each of forward and reverse primer concentration.


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**Fig. S1.** Immortalized mLST8\(+/-\) or mLST8\(-/-\) murine embryonic fibroblasts (MEFs) were treated with mouse IFN-\( \alpha \) for the indicated times. Equal protein amounts were subjected to immunoblot analysis with anti–phospho-Ser473-AKT (A), anti–phospho-Thr389 p70S6K (B), or anti–phospho-Ser235/236 rpS6 (C) antibodies. The blots in respective upper panels were stripped and reprobed with anti-AKT (A, Lower), anti-p70S6K (B, Lower), and anti-rpS6 (C, Lower) antibodies.
Fig. S2. Immortalized Sin1<sup>+/−</sup> or Sin1<sup>−/−</sup> MEFs were treated with mouse IFN-α for the indicated times. Equal protein amounts were subjected to immunoblot analysis with an anti–phospho-Thr246 Pras40 antibody (A, Upper). The same blot was then stripped and reprobed with anti-Pras40 antibody (A, Lower). mLST8<sup>+/−</sup> or mLST8<sup>−/−</sup> MEFs were treated with mouse IFN-β for indicated times. Equal protein amounts were subjected to immunoblot analysis with an anti–phospho-Thr246 Pras40 antibody (B, Upper). Equal amounts of lysates from the same experiment were analyzed separately by SDS/PAGE and immunoblotted with anti-Pras40 antibody (B, Lower).

Fig. S3. The signals for phospho-Thr389 p70S6K and total p70S6K from three independent experiments, including the one shown in Fig. 3A, were quantified by densitometry. The ratio of intensity of phospho-p70 S6K to total p70 S6K was calculated, and the data are expressed as means of ratios ± SE for each experimental condition.
Fig. S4. (A–D) Immortalized Rictor+/+ or Rictor−/− MEFs were starved overnight in DMEM containing 0.5% FBS, followed by treatment with IFN-α, insulin, or serum. Equal amounts of protein were subjected to SDS/PAGE and processed for immunoblot analysis with anti–phospho-Thr389 p70S6K (A) or anti–phospho-Ser235/236-rpS6 (B) antibody. The blots in respective upper panels were stripped and reprobed with antibody against total p70S6K (A, Lower) or rpS6 (B, Lower). Lysates from the same experiment were analyzed separately, resolving the proteins by SDS/PAGE and then by immunoblot analysis with an anti-phospho-Ser473AKT (C) or anti-phospho-Thr246 Pras40 antibody (D). The blots in respective upper panels were stripped and reprobed with anti-AKT (C, Lower) or anti-Pras40 (D, Lower) antibodies as shown.