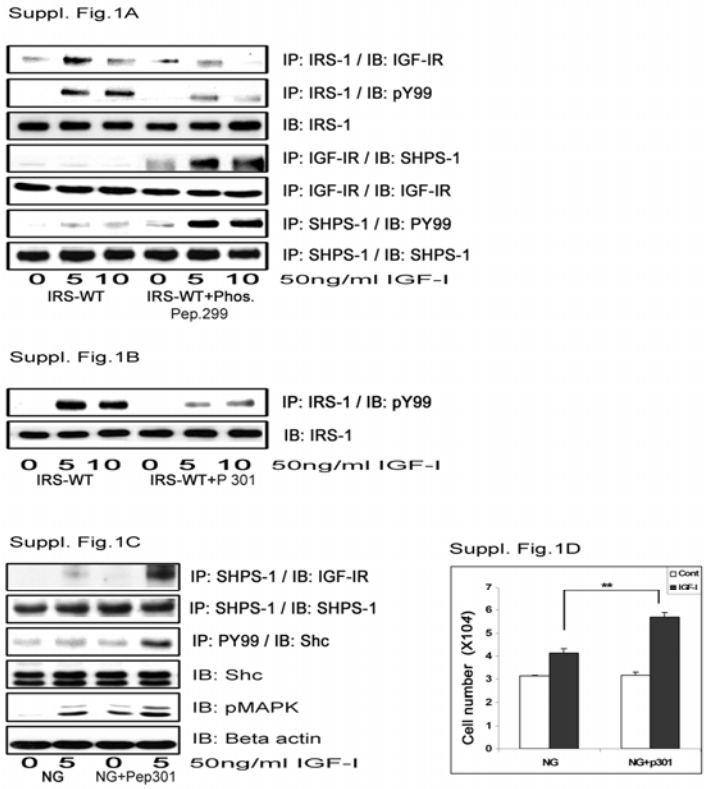
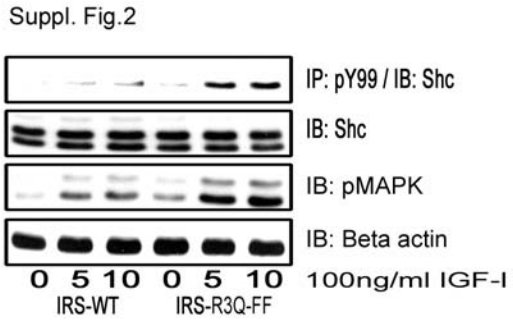
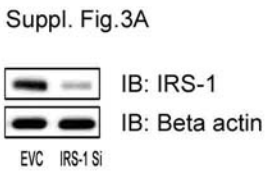


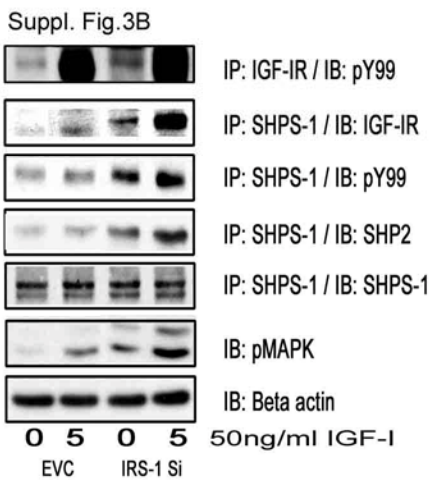
Supplemental Figure 1. **Inhibition of IRS-1 binding to IGF-IR increases association of SHPS-1 with IGF-IR and increases SHPS-1 phosphorylation.**

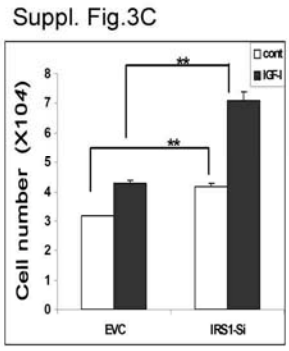
A, Confluent cultures expressing IRS1-WT serum starved overnight and then incubated with or without cell permeable peptide 299 containing a phosphorylated tyrosine using a concentration of 20μg/ml for 2 hr. IGF-I was added for either 5 or 10 min. Cell lysates were immunoprecipitated with anti-IRS-1 and immunoblotted for IGF-IR (upper panel) or pY99 (second panel). The blots were stripped and re-probed for IRS-1 (third panel). Cell lysates from the same experiments were immunoprecipitated with anti-IGF-IR antibody and immunoblotted with anti-SHPS-1 antibody (fourth panel). The blots were stripped and re-probed with anti-IGF-IR antibody (fifth panel). Cell lysates were immunoprecipated with anti-SHPS-1 antibody and immunoblotted for phospho-tyrosine (sixth panel) then they were stripped and re-probed with anti-SHPS-1 antibody (last panel). ***B,*** In addition cell lysates from the same and similar experiments (as explained in Fig.4A and B) were immunoprecipitated with anti-IRS-1 and immunoblotted for pY99 (top panel). Cell lysates were also immunoblotted directly for IRS-1(lower panel). ***C,*** Cell lysates from the same and similar experiments as previously explained (Fig.4C) were immunoprecipitated with anti-SHPS-1 and immunoblotted for IGF-IR (top panel). The blots were stripped and re-probed with anti-SHPS-1 antibody (second panel). Additionally the cell lysates were immunoprecipitated with anti-pY99 antibody and immunoblotted for Shc (third panel). Equal amounts of protein from same cell lysates were immunoblotted directly for Shc (fourth panel), phospho-MAPK (fifth panel) and beta-actin (last panel). ***D,*** VSMCs were plated ($3x10^4$) in DMEM-NG with 2% FBS. 2 hrs prior to exposure to IGF-I (100ng/ml) along with 0.2% platelet poor plasma cells were either incubated with or without peptide 301 (5 μg/ml). The peptide was added at same concentration every 12 hrs and forty-eight hours after IGF-I stimulation, cell number was determined. **, $p < 0.01$ when the change in number of cells proliferating in response to IGF-I compared between cells with or without peptide exposure. Error bars represent mean $\pm$ S.E.



Supplemental Figure 2. **Inhibition of IRS-1 binding to both IGF-IR and SHP-2 restores phosphorylation of Shc and MAPK in response to IGF-I.**
Near confluent cultures of IRS-WT and IRS-R3Q-FF cells were serum starved and then exposed to IGF-I for the indicated time periods. The cell lysates were immunoprecipitated with pY99 antibody and immunoblotted for p52Shc (top panel). Ten micrograms of protein from the same cell lysates was immunoblotted directly using anti-Shc (second panel), anti-phospho-MAPK (third panel) or anti-beta actin antibody (bottom panel).







Supplemental Figure. 3 **Silencing IRS-1 increases basal IGF-IR and SHPS-1 phosphorylation and IGF-IR/SHPS-1 association.**
A, Confluent VSMCs expressing an empty vector control (EVC) or IRS-1 shRNA maintained in DMEM-NG were serum starved for 16-18 hrs in DMEM-NG and analyzed for IRS-1 protein expression (Top panel). The blots were stripped and reprobed for beta-actin. ***B,*** Confluent EVC and IRS-1Si cell cultures were serum starved for 16 hrs and IGF-I was added for 5 min. Cell lysates were immunoprecipitated with anti-SHPS-1 antibody and then immunoblotted for IGF-IR (first panel), or pY99 (second panel) or SHP-2 (third panel) or SHPS-1 (fourth panel). Lysates containing ten micrograms of protein from the same experiment were directly immunoblotted for pMAPK (fifth panel) or beta-actin (bottom panel). ***C,*** EVC and IRS-1 Si cells were plated ($3x10^4$) in DMEM-HG with 2% FBS prior to exposure to IGF-I (50ng/ml) in DMEM-NG with 0.2% platelet poor plasma. Forty-eight hours after the addition of IGF-I cell number was determined.