We have previously developed a mouse model of insulin-resistant diabetes by targeted inactivation of the insulin receptor gene. During studies of gene expression in livers of insulin receptor-deficient mice, we identified a novel cDNA, which we have termed sirm (Son of Insulin Receptor Mutant mice). sirm is largely, albeit not exclusively, expressed in insulin-responsive tissues. Insulin is a potent modulator of sirm expression, and sirm mRNA levels correlate with tissue sensitivity to insulin. The product of the sirm gene is a serine/threonine-rich protein with several proline-rich motifs and an NPNY motif, conforming to the consensus sequence recognized by the phosphotyrosine binding domains of insulin receptor substrate and Shc proteins. However, Sirm bears no extended homologies with other known proteins. Based on the sequences of the proline-rich domains, we sought to determine whether Sirm binds to the SH3 domains of FYN and Grb-2. We demonstrate here that Sirm binds to FYN and Grb-2 in 3T3-L1 adipocytes and that insulin treatment results in the dissociation of the Sirm.FYN and Sirm.Grb-2 complexes. We also show that Sirm is a substrate for the kinase activity of FYN in vitro. Based on the patterns of expression of sirm, its regulation by insulin, and the interactions with molecules in the insulin signaling pathway, we surmise that Sirm plays a role in modulating tissue sensitivity to insulin.