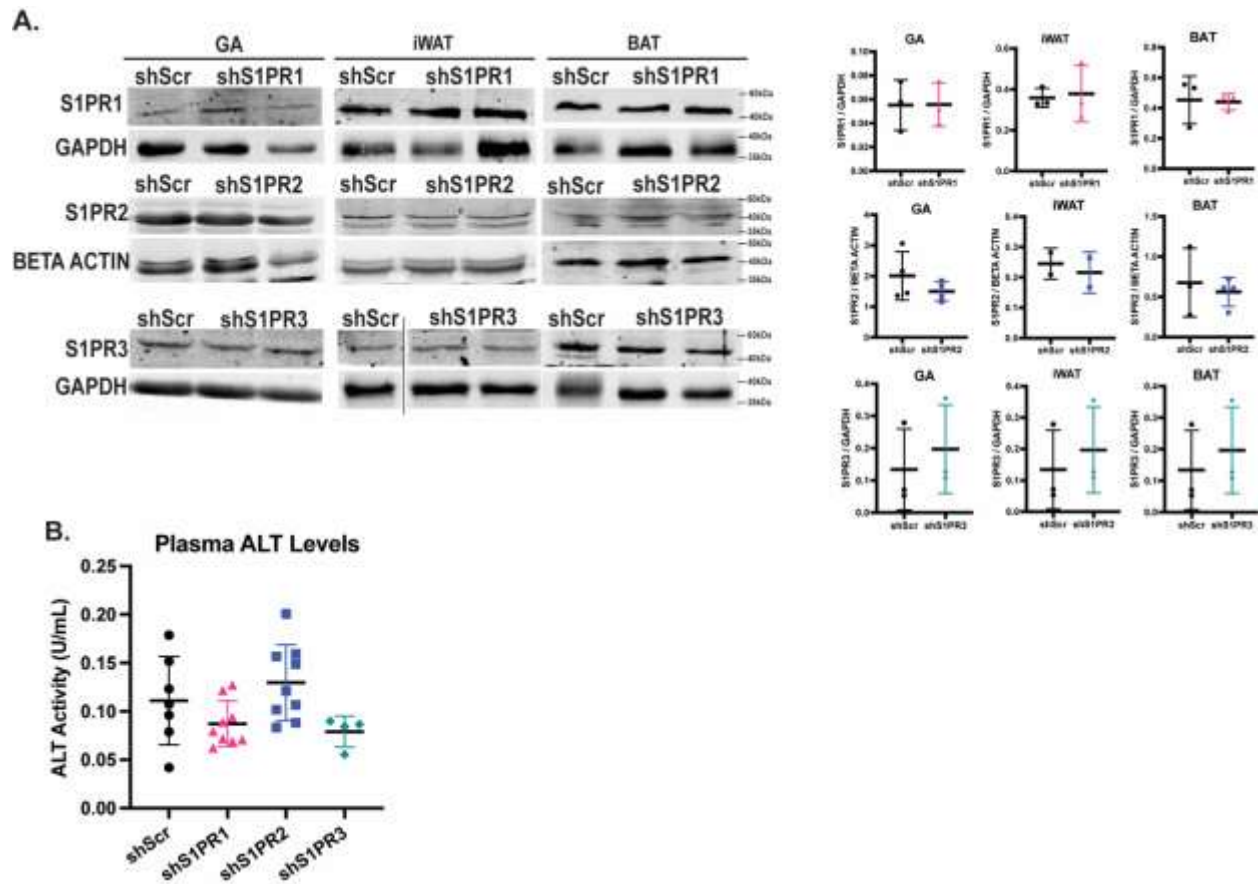
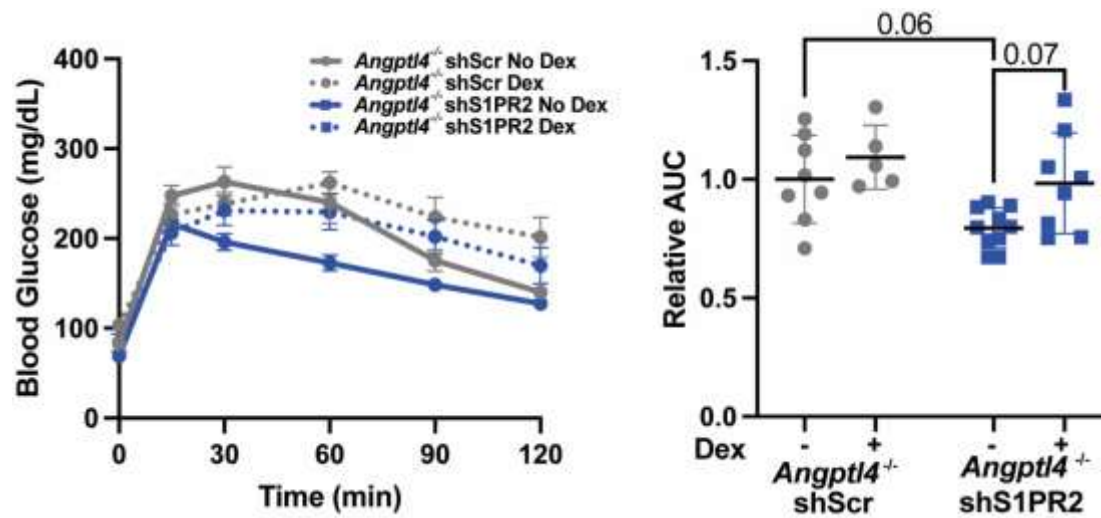


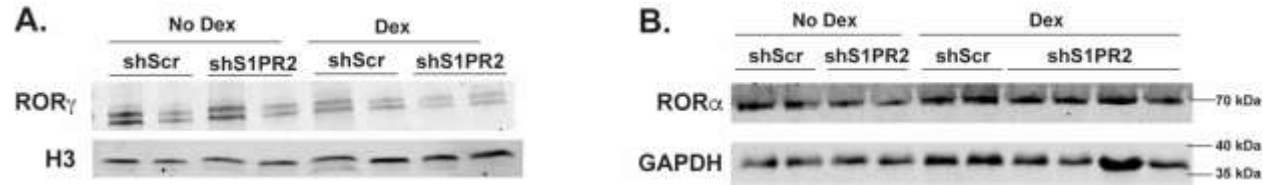
Supplementary Figures



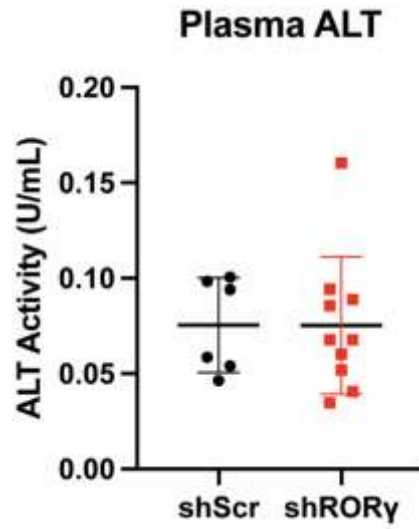
Supplementary Figure 1: Hepatic S1PR1, S1PR2, and S1PR3 knockdown is specific to liver and does not cause liver injury. (A) Western blots of S1PR1, S1PR2, and S1PR3 in AAV8-shScr (black circles), AAV8-shS1PR1 (magenta triangles), AAV8-shS1PR2 (blue squares), and AAV8-shS1PR3 (teal diamonds) gastrocnemius muscle (GA), inguinal white adipose tissue (iWAT), and brown adipose tissue (BAT). Images are from the same blot. Expression is normalized to BETA ACTIN and GAPDH using ImageJ, $n=2-4$. * $p<0.05$ using student's t test with Welch's correction. (B) Plasma alanine transaminase (ALT) levels in AAV8-shScr, AAV8-shS1PR1, AAV8-shS1PR2, and AAV8-shS1PR3 mice, $n=4-9$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$ using a Welch's ANOVA. Error bars represent standard deviation.



Supplementary Figure 2: S1PR2 signaling participation of Dex induced glucose intolerance requires ANGPTL4. (A) IPGTT and Relative Area Under the Curve of *Angptl4*^{-/-} mice treated AAV8-shScr No Dex (solid gray circles), with Dex (dashed gray circles), or AAV8-shS1PR2 No Dex (solid blue squares), with Dex (dashed blue squares) after 16 hr fast, n=5-8, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 using a two way ANOVA with a Benjamini and Hochberg FDR correction, The error bars represent standard deviation and SEM for tolerance test.



Supplementary Figure 3: Hepatic S1PR2 knockdown reduces ROR γ protein levels, but not ROR α . (A) Western blot of nuclear levels of ROR γ in AAV8-shScr and AAV8-shS1PR2 mice livers treated with or without Dex. (B) Western blot of ROR α in AAV8-shScr and AAV8-shS1PR2 mice livers treated with or without Dex.



Supplementary Figure 4: Hepatic ROR γ knockdown does not induce liver injury. Plasma alanine transaminase (ALT) levels in AAV8-shScr (black circles) and AAV8-shROR γ (red squares), n=6-9, using student's *t* test with Welch's correction. Error bars represent standard deviation