



Supplementary information, Fig. S1. Famsin is a released N-terminal fragment of Gm11437.

a siRNA library screening for single-pass transmembrane proteins (sTMPs), located on the plasma membrane, that modulate the activity of *G6pc-Luc* in HepG2 cells. The four candidate genes were further analyzed by transwell assay, which was used to test whether overexpressed genes in HEK293T modulate *G6pc-Luc* in primary hepatocytes via protein secretion. **b** Correlation between the two replicates of the primary screen, using a siRNA library targeting 941 sTMP-encoding genes. Results are shown as fold change (on a \log_2 scale) of *G6pc-Luc* activity in siRNA knockdown cells relative to cells transfected with non-targeting siRNA. Spearman's rank correlation coefficient ($r = 0.96$) between the two replicates is shown. The results for knockdown of *AKT1* and *INSR* (negative regulators, blue), *FOXO1* and *CRTC2* (positive regulators, green), and *CD80*, *EPHB2*, *INSRR* and *C17ORF78* (red) are shown. **c** Effect of overexpression of *C17ORF78*, *C17ORF78/AA* (K177A, R178A), famsin (aa 1-178 of *C17ORF78*), *CD80*, *EPHB2* or *INSRR* in HEK293T cells on the activity of *G6pc-Luc*, as measured by transwell assay in mouse primary hepatocytes. Data are shown as mean \pm s.e.m. Comparison of different groups was carried out using one-way ANOVA followed by Tukey's test. *** $p < 0.001$. NS, no statistical significance. $n = 6$. **d** Immunoblots showing the expression of *C17ORF78*, *C17ORF78/AA*, Famsin, *CD80*, *EPHB2* or *INSRR* in HEK293T cells after 48-hr transfection. **e** Alignment of human *C17ORF78* and mouse *Gm11437*. The predicted transmembrane domain (TM) is surrounded by a blue box. The furin cleavage site in *Gm11437* is indicated by a red arrow. **f** Effect of overexpression of *Gm11437*, *Gm11437/AA* (K190A, R191A) or famsin (1-191 aa of *Gm11437*) in HEK293T cells on the activity of *G6pc-Luc* in

mouse primary hepatocytes by transwell assay. Data are shown as mean \pm s.e.m. Comparison of different groups was carried out using one-way ANOVA followed by Tukey's test. *** $p < 0.001$. NS, no statistical significance. n = 6. **g** Immunoblots showing the expression of Gm11437, Gm11437/AA or famsin in HEK293T cells after 48-hr transfection. The blue arrowheads indicate full-length Gm11437-FLAG and the red arrowheads indicate famsin. **h** Schematic showing the purification procedure for famsin released from Sf9 cells after cleavage of Gm11437. **i** A representative chromatogram from size exclusion chromatography of famsin. microAU, micro-ultraviolet absorbance at 280 nm. **j** Silver staining and immunoblot showing purified famsin separated by SDS-PAGE. Deglyco, deglycosylation. **k** Schematic showing the *in vitro* digestion and identification of purified famsin from Sf9 cell medium by LC-MS/MS. **l** Amino acid sequence of famsin identified by mass spectrometry.