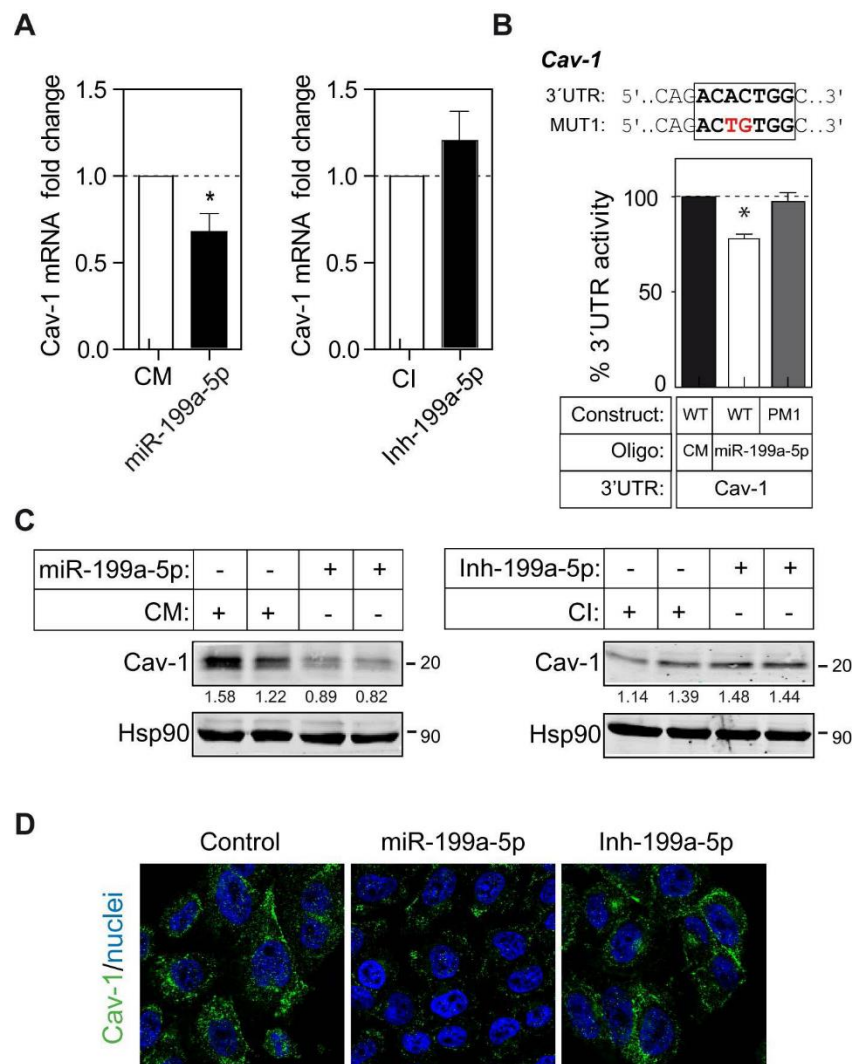
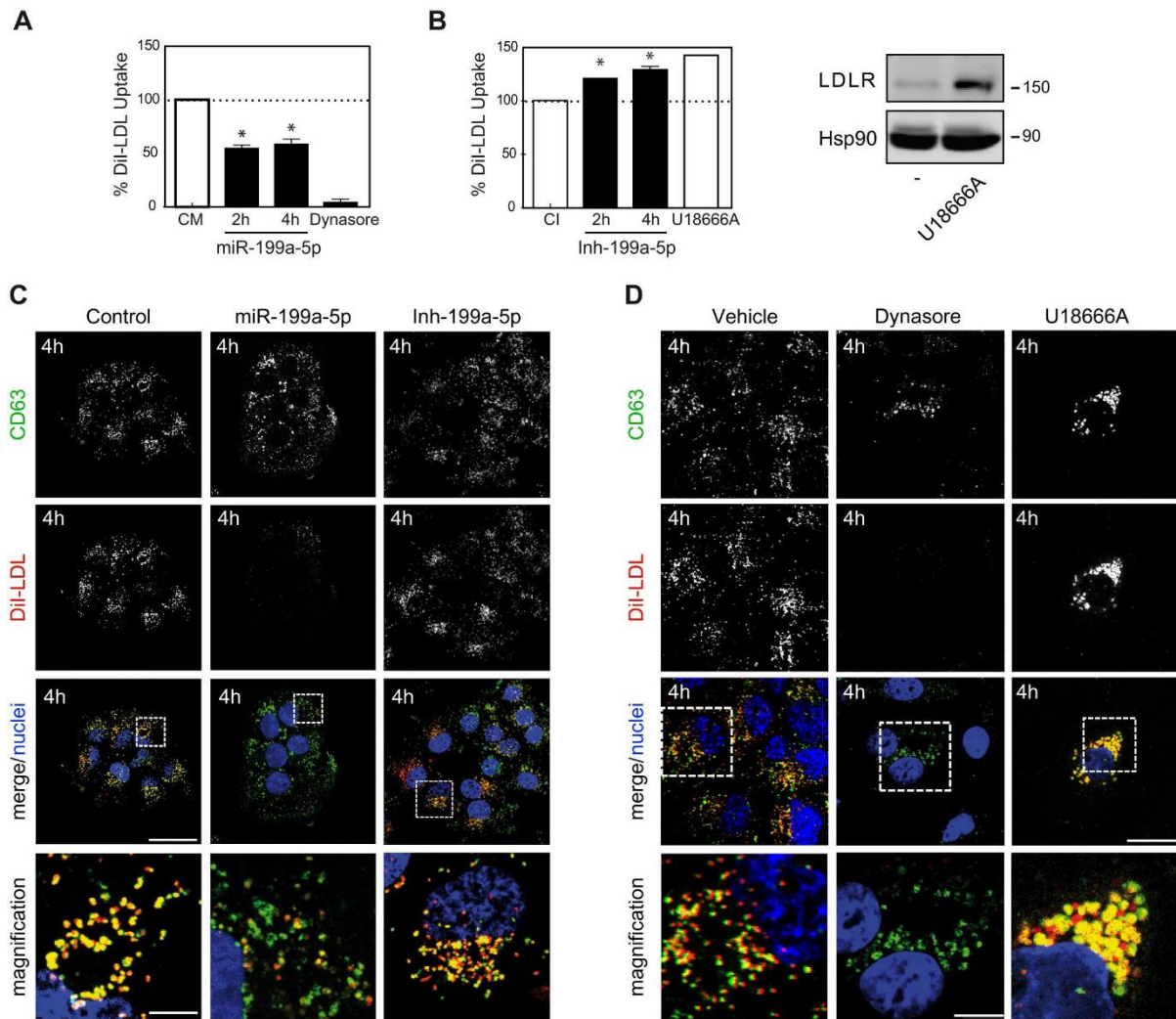


**Figure S1. Multispecies alignment of miR-199a-5p and miR-199b-5p sequences and miR-199a/b family expression in human tissues.** (A) MiR-199a-5p and miR-199b-5p sequence conservation across species. Red color indicates those nucleotides that have diverged with respect the human sequence. Boxes denote 2-8 seed sequences of each miRNA. (B) qRT-PCR analysis of miR-199b-5p and *DNMI1* expression in selected human tissues. Data are expressed as

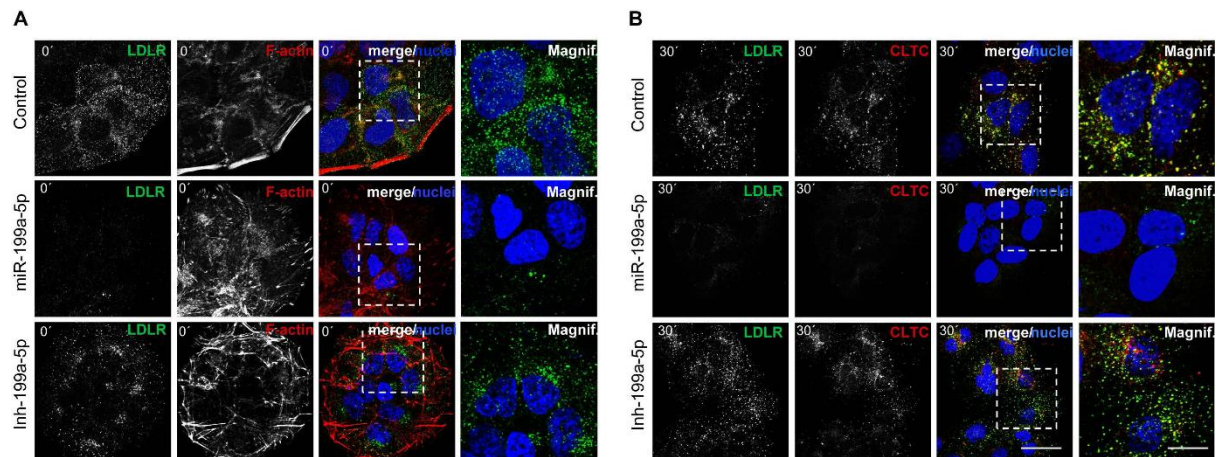
relative to expression in liver and are the mean  $\pm$  SEM and are representative of  $\geq 3$  experiments. **(C)** qRT-PCR analysis of pre-miR-199a-1, pre-miR-199a-2 and pre-miR-199b precursors (Stem loop) in selected human tissues. Data are expressed as relative to expression in liver and are the mean  $\pm$  SEM and are representative of  $\geq 3$  experiments. **(D)** Sequence analysis and conservation of the miR-199a/b-5p binding sites in the 3'UTR of *LDLR*, *CLTC*, *Cav-1*, *Rab5A* and *Rab21*. Grey color indicates nucleotides that have diverged with respect to the human sequence. Boxes and bold letters denote the predicted binding site for each miR-199a/b-5p target.



**Figure S2. MiR-199a-5p regulates Cav-1 expression in HeLa cells** (A) qRT-PCR analysis of Cav-1 expression in HeLa transfected with CM and miR-199a-5p mimic, or CI and inh-199a-5p. (B) Western blot analysis of Cav-1 expression in HeLa cells transfected with CM and miR-199a-5p mimic, or CI and inh-199a-5p. Representative confocal images of Cav-1 immunostaining in HeLa cells transfected with CM, miR-199a-5p mimic and inh-199a-5p are shown. (C) Luciferase reporter activity in COS7 cells transfected with CM or miR-199a-5p mimic and Cav-1 3'UTR containing or not the indicated PM as shown in the upper sequences. \*,  $p \leq 0.05$ . In panel B, Hsp90 was used a loading control. Quantification of the band densitometry analysis is shown at the bottom of the blot images. In panel A, data is expressed as mean  $\pm$  SEM and representative of  $\geq 3$  experiments in triplicate. \*,  $p \leq 0.05$ . In panel C, data is expressed as mean percentage of the 3'UTR activity of CM  $\pm$  SEM and is representative of  $\geq 3$  experiments in triplicate. \*,  $p \leq 0.05$ .



**Figure S3. miR-199a-5p regulate Dil-LDL uptake and effect of Dynasore and U18666A in LDL uptake in Huh7 cells.** (A) Flow cytometry analysis of Dil-LDL uptake in Huh7 cells transfected with CM or miR-199a-5p mimic and incubated with 30  $\mu$ g/ml Dil-LDL for 2 h and 4 h at 37°C. (B) Left panel; Flow cytometry analysis of Dil-LDL in Huh7 cells transfected with CI and inh-199a-5p. Pre-treatment with Dynasore (8 h) and U18666A (8 h) was used as a negative and positive control of LDLR internalization respectively. Data are expressed as percentage of the control (cells transfected with CM or CI). Mean $\pm$ S.E.M. of three experiments. \*,  $p \leq 0.05$ . (B) Right panel; Western blot of LDLR and Hsp90 in Huh7 cells treated with vehicle or U18666A for 8 h. (C and D) Representative confocal immunofluorescence images of Huh7 cells treated as indicated and subjected to 4 h Dil-LDL uptake at 37°C, fixed and stained for the lysosomal marker, CD63, and TOPRO for the nuclei. Scale bar, 10 $\mu$ m. Magnification insets are shown, Scale bar, 2.5 $\mu$ m.



**Figure S4. LDLR internalization is inhibited in Huh7 cells transfected with miR-199a-5p. (A)** Confocal microscopy immunofluorescence showing Huh7 cells transfected with non-targeting control-miR (CM), miR-199a-5p or Inh-199a-5p and incubated with anti-LDLR antibody for 60 min at 4°C before fixing and then staining with anti-mouse Alexa 488 for LDLR antibody. To visualize the F-actin fibers and nuclei, phalloidin-red and DAPI were used respectively. **(B)** Huh7 cells treated as in (A) were then allowed to internalize antibody complexes for 30 min at 37°C, acid stripped, PFA fixed, and then staining for CLTC (red), LDLR (green) and DAPI (blue). Scale bar, 10 μm. Representative images are shown. Magnification insets show details in the right panel. Scale bar, 5μm.