

Supplementary methods and figures

Cell transfection

Cells were seeded into 6-well plates and cultured for 24 h until reaching 60%–70% confluence and transfected with LOC100132249 plasmid, SNAIL1 plasmid, or corresponding empty plasmid vector (all procured from RiboBio) with Lipofectamine 3000 Reagent and P3000 Reagent (Thermo Fisher Scientific, USA). The overexpression or knockdown of miR-199a-5p was achieved with miR-199a-5p mimics or miR-199a-5p inhibitor, respectively, with mimics NC and inhibitor NC serving as controls (RiboBio, China). Knockdown of LOC100132249 was conducted with RiboTM Smart Silencer (RiboBio, China), which contained three siRNAs and three antisense oligonucleotides targeting different sequences. Three siRNAs targeting the SNAIL1 gene were designed and synthesized by RiboBio, and the most effective siRNA (si-SNAIL1-1) was verified by RT-qPCR. All cells were harvested 48 h after transfection for subsequent analysis.

RNA extraction and quantitative real-time PCR analysis (RT-qPCR)

Total RNA was extracted from cultured cells, clinical samples, and corresponding exosomes with TRIzol reagent (Life Technologies, Carlsbad, CA, USA) and reverse transcribed into complementary DNA (cDNA). For lncRNA and mRNA, cDNA template was synthesized with a PrimeScript RT reagent Kit (Takara), whereas for miRNA, an miDETECT A Track RT Reagent Kit (RiboBio, China) was used. RT-qPCR of lncRNA, mRNA, and miRNA was performed with a StepOnePlus Real-Time PCR system (Applied Biosystems, San Jose, CA, USA) according to the manufacturer's

1 instructions. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 served as
2 endogenous controls for lncRNA, mRNA, and miRNA, whereas miR-39-3p was
3 applied as an external control. Relative gene expression levels were quantified via the
4 $2^{-\Delta\Delta C_t}$ method. Each well had three replicates, and all assays were performed in
5 triplicate. The Bulge-loop[™] miRNA qRT-PCR Primer Sets (one RT primer and a pair
6 of qPCR primers for each set) specific to miR-199a-5p, miR-39-3p, miR-1296-5p, and
7 U6 were designed by RiboBio Company (Guangzhou, China), and the sequences were
8 covered by a patent (**Supplementary Table S6**).

9 **Western blotting**

10 The protein concentrations of PDR-exo, MH-exo, NG-exo, HG-exo, and cells from
11 each culture group were quantified with a BCA protein assay kit (Thermo Fisher
12 Scientific, USA) according to the instructions. Approximately 30 µg protein was
13 separated via electrophoresis on a 10% sodium dodecyl sulfate-polyacrylamide gel and
14 then transferred to polyvinylidene fluoride membranes (0.22 µm pore size; Millipore,
15 Waltham, MA, USA), which were blocked with 5% skim milk at room temperature for
16 2 h to eliminate non-specific binding. After blocking, membranes were incubated with
17 specific primary antibodies overnight at 4°C. The next day, membranes were washed
18 with Tris-buffered saline Tween-20 three times, then incubated with horseradish
19 peroxidase-conjugated goat anti-rabbit IgG or goat anti-mouse IgG secondary antibody
20 for 1 h at room temperature. All bands were detected with an enhanced
21 chemiluminescent substrate (NCM Biotech Co., Ltd, Newport, RI, USA) with a Tanon
22 5200 Multi instrument (Tanon, Shanghai, China). GAPDH served as the internal

1 reference. The primary antibodies anti-CD9 antibody (1:1,000; 20597-1-AP), anti-
2 CD63 antibody (1:1,000; 25682-1-AP), anti-CD81 antibody (1:1,000; 66866-1-Ig),
3 anti-TSG101 antibody (1:2,000; 28283-1-AP), anti-calnexin antibody (1:2,000; 10427-
4 2-AP), and anti-GAPDH (1:5,000; 60004-1-Ig) antibody were purchased from
5 Proteintech (Rosemont, IL, USA). Anti-SNAI1 antibody (1:1000; ab180714), anti-VE-
6 cadherin antibody (1:1,000; ab33168), anti-CD31 antibody (1:5,000; ab76533), anti-
7 vimentin antibody (1:1,000; ab92547), anti- α -SMA antibody (1:10,000; ab124964),
8 and anti- β -catenin antibody (1:4,000; ab16051) were obtained from Abcam (Fremont,
9 CA, USA).

10 **Small RNA sequencing of LOC100132249-overexpressed cells**

11 To determine the miRNA targeted by LOC100132249, we conducted small RNA
12 sequencing of cells transfected with the LOC100132249 plasmid and empty plasmid
13 vector as a control. After 48 h of transfection, 8×10^6 cells from each group were
14 collected and sent for sequencing. Differentially expressed miRNAs were selected
15 according to a fold change > 2 and p-value < 0.05 .

16 **Bioinformatics analysis**

17 A hierarchical clustering analysis was performed to identify the differentially expressed
18 lncRNAs with the R language package. TargetScan, miRDB, miRTarBase, and
19 miRWalk were used to predict targeted genes of the selected miRNAs. A Venn diagram
20 was constructed to obtain the intersection of genes identified by three of the four tools.
21 KOBAS3.0 software was used to annotate the comprehensive functions of the potential

1 targets of lncRNAs with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway
2 analysis. All signaling pathways were analyzed with a threshold of significance defined
3 by a p-value < 0.05.

4 **Dual-luciferase reporter assays**

5 To detect the potential molecular interactions among LOC100132249, miR-199a-5p
6 and SNAIL, we performed luciferase reporter assays. The wild-type (WT) or mutant
7 (Mut) miR-199a-5p binding sites targeting LOC100132249 or SNAIL were separately
8 inserted into luciferase reporter plasmids and cotransfected with miR-199a-5p mimics
9 or mimics NC (all purchased from RiboBio, China) into cells in 24-well culture plates.
10 The relative firefly and Renilla luciferase activities were measured 48 h later with a
11 dual luciferase reporter assay kit (Promega, Madison, WI, USA), and each transfected
12 well was detected in triplicate. Renilla luciferase activity was used as a standardized
13 control.

14 **Immunofluorescence staining**

15 HRVECs transfected with LOC100132249 plasmid or empty vector plasmid were
16 seeded on cover slips in 24-well plates and fixed with 4% paraformaldehyde for 30 min
17 at room temperature. Then cells were washed in PBS three times and permeabilized
18 with 0.5% Triton X-100 at room temperature for 30 min. The cells were then blocked
19 with 5% bovine serum albumin (BSA) and treated with primary antibodies against
20 SNAIL, CD31, VE-cadherin, vimentin, α -SMA, β -catenin, and β -tubulin (all from
21 Abcam, USA) overnight at 4°C. The cells were incubated with Alexa Fluor coupled
22 secondary antibodies for 2 h at room temperature the next day, and DAPI was used to

1 stain cell nuclei. Finally, images were recorded with a fluorescent microscope (Leica
2 THUNDER DMi8; Leica, Nanjing, China).

3 **Hematoxylin and eosin (HE) staining**

4 Eyeballs were immersed in formalin and embedded in paraffin for subsequent
5 sectioning with 4 μm thickness. After dewaxing, the sections were stained with
6 conventional HE stains, then photographed with a light microscope (Olympus, Japan).

7 **Cell proliferation assays**

8 Cell proliferation was assessed with a CellLight EdU Apollo 567 In Vitro Kit (RiboBio,
9 China). Cells at a density of 2×10^4 /well were seeded on 96-well plates and pretreated
10 with different stimuli for 48 h. After incubation with 50 μM EdU medium in complete
11 ECM for 2 h, cells were rinsed with PBS, fixed with 4% PFA at room temperature for
12 30 min and neutralized with 2 mg/mL glycine. Then the cells were washed in PBS twice
13 and permeabilized with 0.5% Triton X-100 for 10 min. After extensive washing in PBS,
14 the cells were stained with Apollo 567 for 30 min and washed in PBS containing 0.5%
15 Triton X-100 three times, and finally incubated with DAPI for visualization under a
16 fluorescent microscope (Leica THUNDER DMi8; Leica, Nanjing, China). The
17 proportion of the red-labeled EdU positive cells was measured and analyzed in ImageJ
18 software.

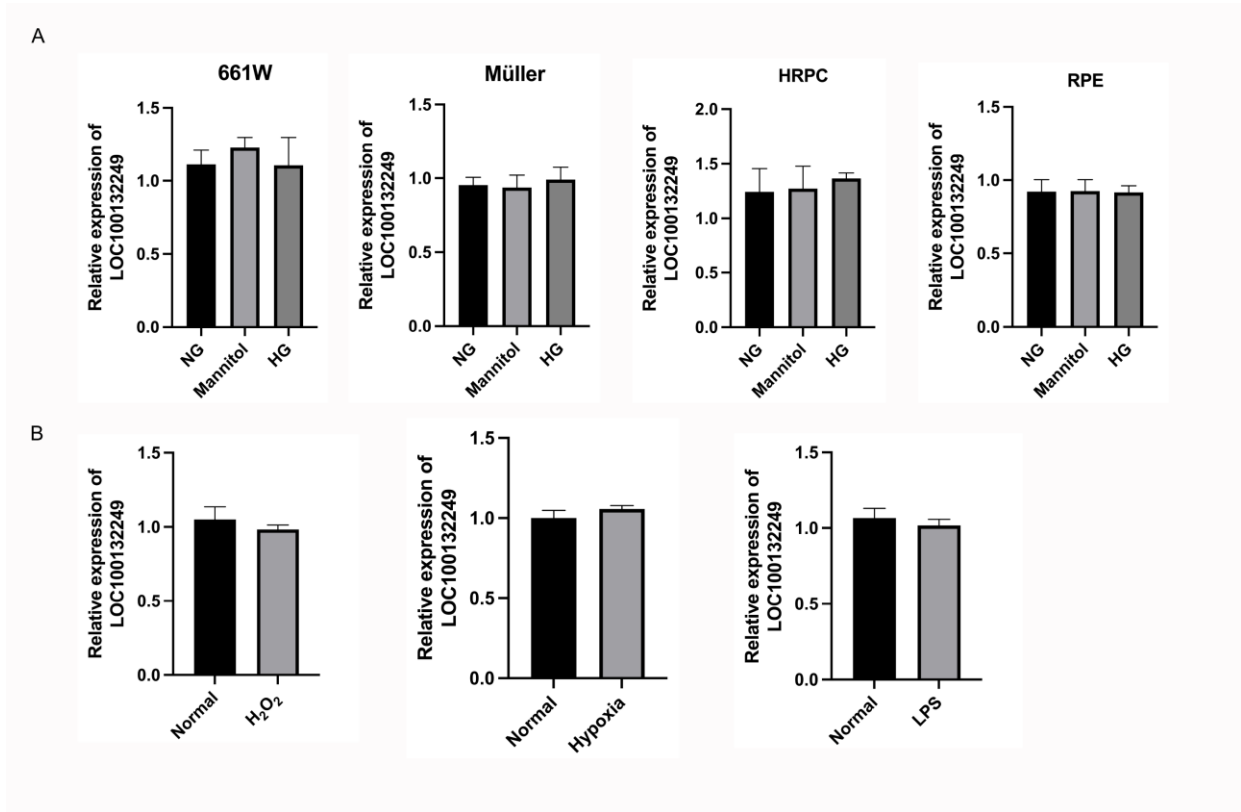
19 **Transwell migration assays**

20 To investigate cell migration ability, we conducted Transwell assays. Cells were first
21 pretreated with corresponding exosomes or transfected with plasmids or siRNAs for 48
22 h. A total of 3×10^4 cells were resuspended in 200 μL serum-free medium and seeded

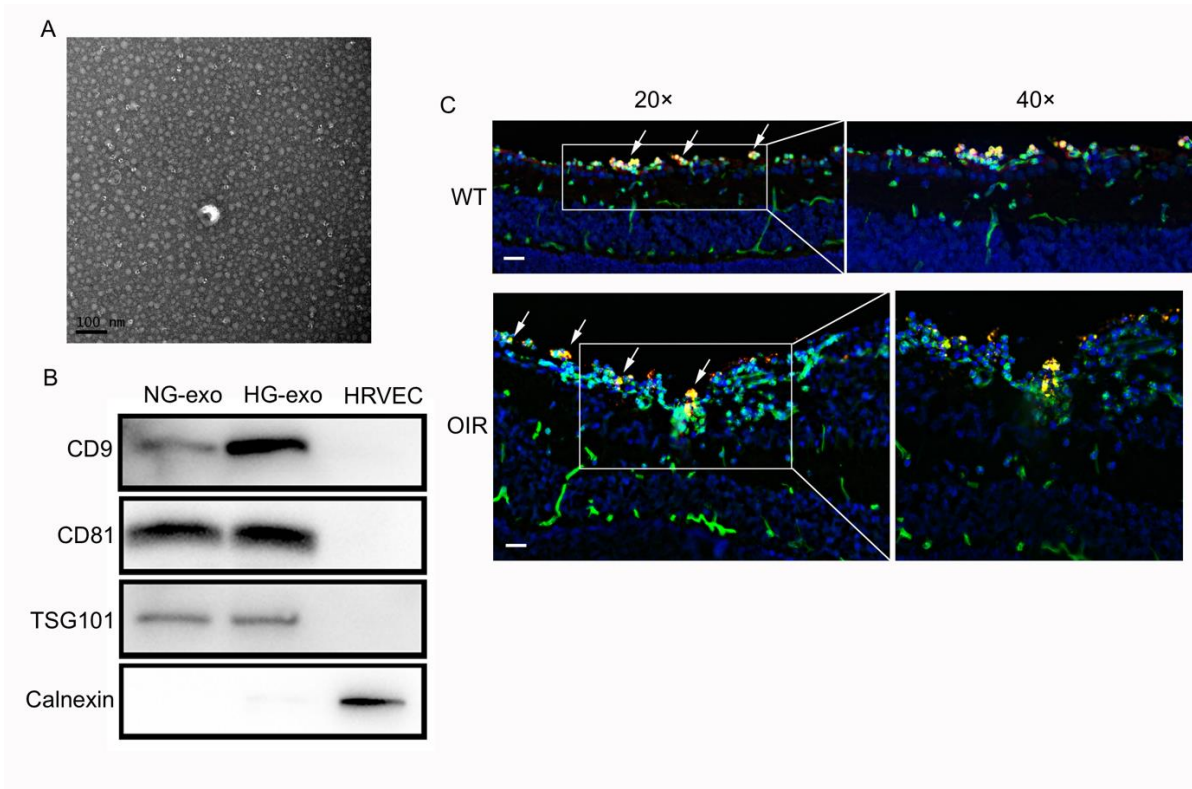
1 into the upper compartments of Corning Transwell units (8.0 μm pore size; Corning,
2 NY, USA), which were placed in 24-well plates. Meanwhile, 600 μL conventional
3 medium supplemented with 20% FBS was added to the lower chamber as a
4 chemoattractant. After 24 h of culture, cells were gently wiped from the inner-
5 membrane surface with a cotton swab, and the outside penetrating cells were fixed with
6 4% PFA, then dyed with Crystal Violet solution (Beyotime, Shanghai, China) for 20
7 min. Representative images were taken with a light microscope (Olympus Corporation,
8 Tokyo, Japan). Three randomly selected fields were counted per insert, and all
9 experiments were repeated independently in triplicate.

10 **Matrigel tube formation of HRVECs**

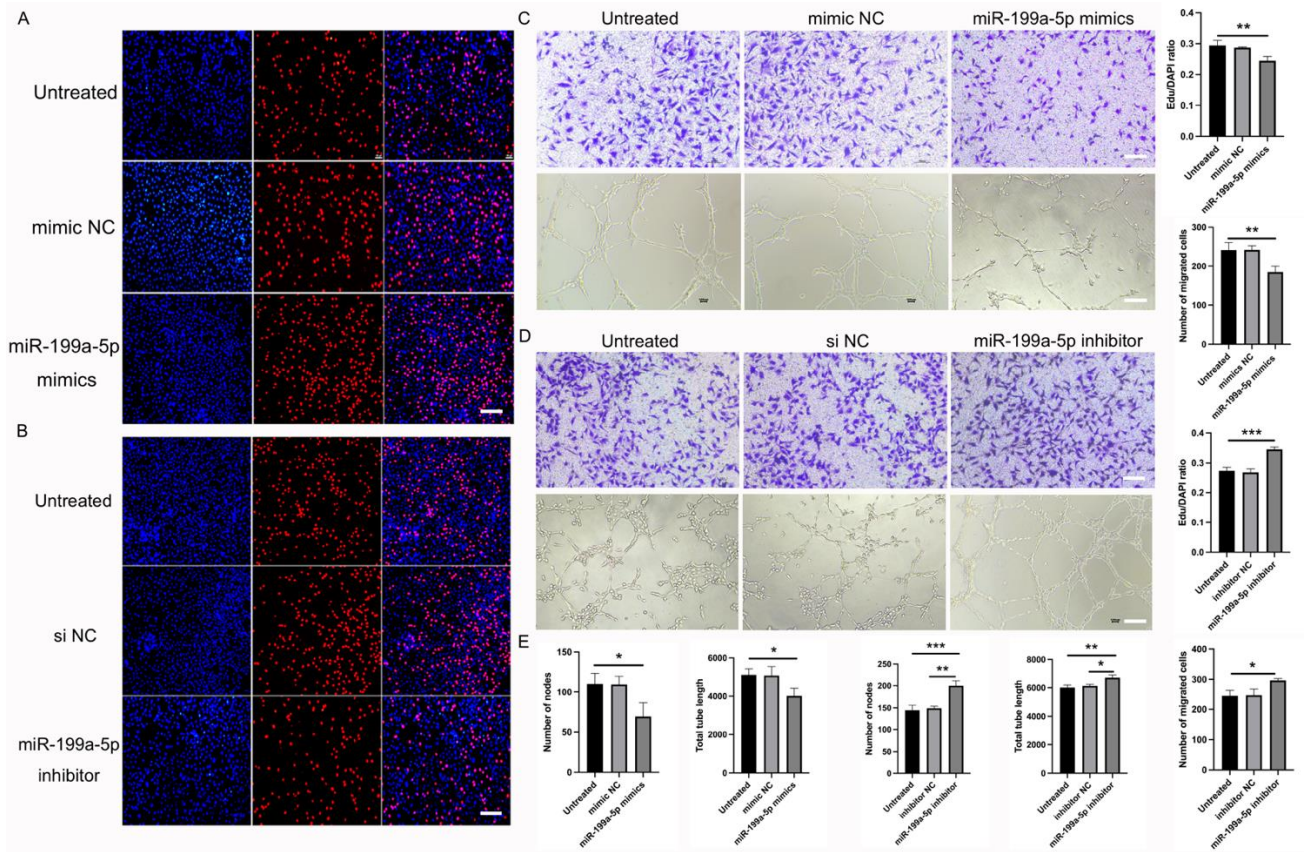
11 Briefly, endotheliocytes (2×10^4 cells/well) that had been treated with the indicated
12 stimuli for 48 h were seeded in 96-well plates that were precoated with 50 μL Matrigel
13 Basement Membrane Matrix (356234; BD Biosciences, San Jose, CA, USA) in
14 advance and incubated at 37°C for 6 to 8 h. The formation of tube-like structures was
15 photographed under an inverse phase contrast light microscope (Olympus, Japan) in at
16 least three different fields. The total tube length of cell cords and node numbers of the
17 enclosed lumen structures were quantified in ImageJ software.



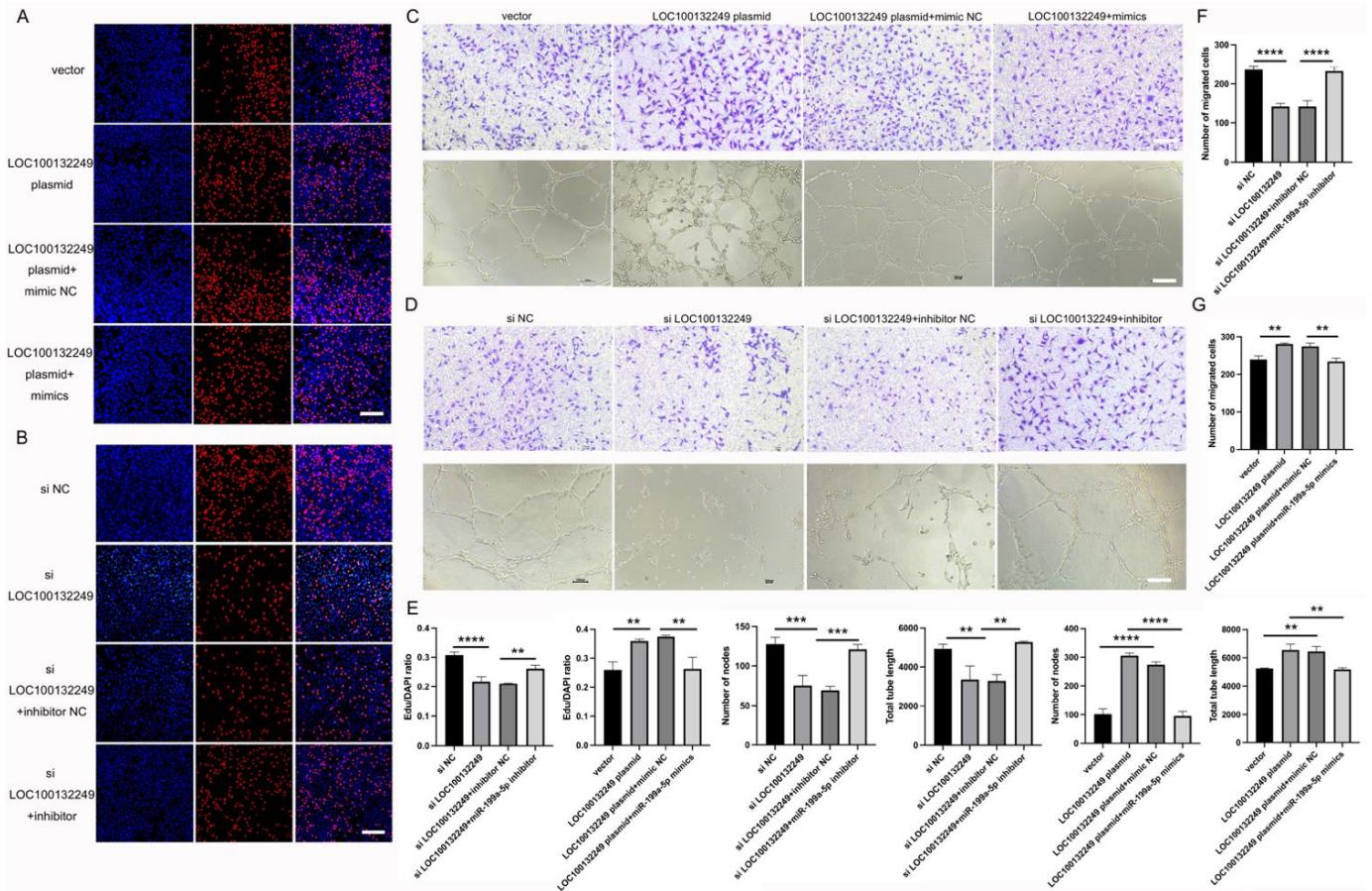
Supplementary Figure 1. Expression levels of LOC100132249 in different retinal cells and under different diabetic stresses. (A) RT-qPCR quantification of LOC100132249 in several retinal cells (661W, Müller, pericytes, and retinal pigment cells). **(B)** Expression level of LOC100132249 in HRVECs under oxidative stress (H₂O₂), an inflammatory stimulus (LPS), and hypoxia mimicking diabetic stress in vitro.



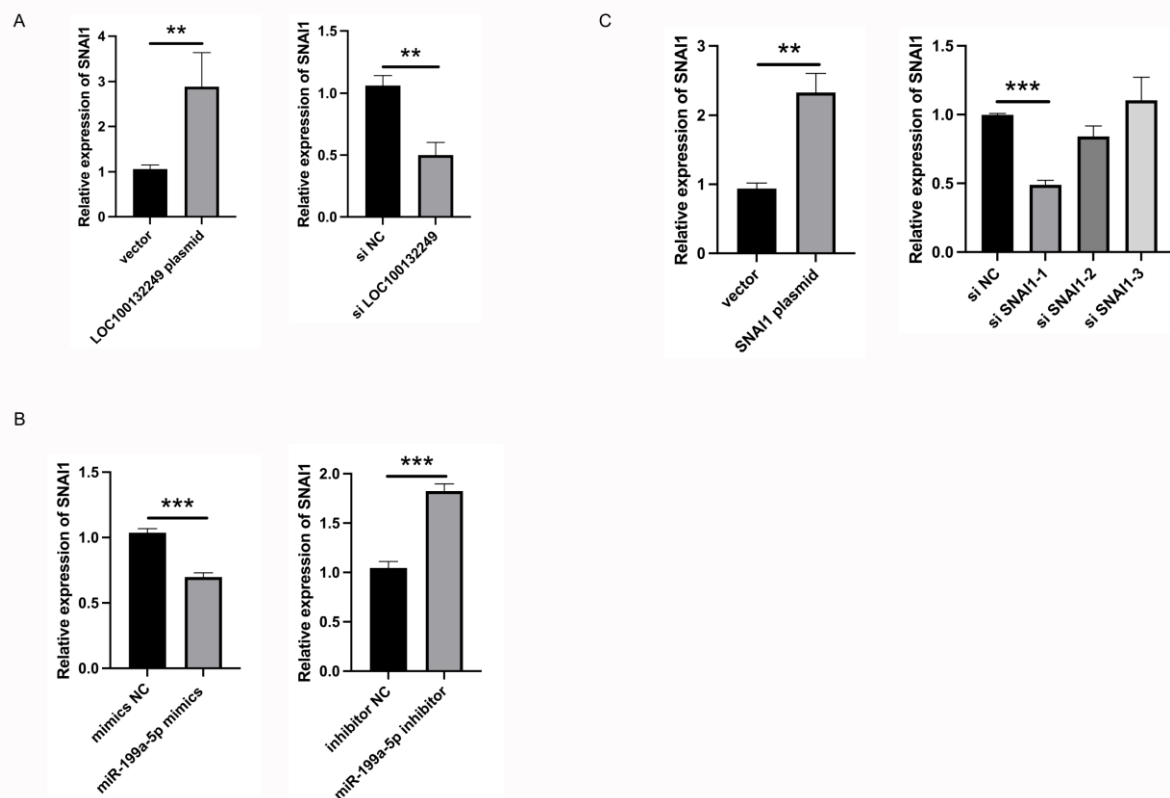
Supplementary Figure 2. Characterization of NG-exo and HG-exo and internalization of exosomes *in vivo*. (A) Identification of exosomes by TEM. Scale bar=100 nm. (B) Western blot analysis of specific exosomal surface markers. (C) Uptake of PKH26-labeled exosomes in WT and OIR mice retinas. Red represents PKH26 labeled exosomes and green represents CD31. The arrows were used to point out the internalization of exosomes by endothelial cells. Scale bar=50 μ m.



Supplementary Figure 3. Effects of miR-199a-5p on HRVECs. (A) Proliferation ability of HRVECs treated with miR-199a-5p mimics. Scale bar=100 μ m. (B) Proliferation ability of HRVECs treated with miR-199a-5p inhibitor. Scale bar=100 μ m. (C) Migration and tube formation ability of HRVECs treated with miR-199a-5p mimics. Scale bar=100 μ m. (D) Migration and tube formation ability of HRVECs treated with miR-199a-5p inhibitor. Scale bar=100 μ m. (E) Quantification of EdU positive cells, migrated cells, number of nodes, and total tube length. * p <0.05; ** p <0.01; *** p <0.001. Error bars denote mean \pm SD.



2 **Supplementary Figure 4. LOC100132249 promotes angiogenesis via inhibiting miR-199a-5p in**
3 **HRVECs. (A)** EdU assays of HRVECs co-transfected with LOC100132249 plasmid and miR-199a-
4 5p mimics. Scale bar=100 μ m. **(B)** EdU assays of HRVECs co-transfected with si LOC100132249
5 and miR-199a-5p inhibitor. Scale bar=100 μ m. **(C)** Transwell assays and tube formation assays of
6 HRVECs co-transfected with LOC100132249 plasmid and miR-199a-5p mimics. Scale bar=100 μ m.
7 **(D)** Transwell assays and tube formation assays of HRVECs co-transfected with si LOC100132249
8 and miR-199a-5p inhibitor. Scale bar=100 μ m. **(E)** Quantification of EdU positive cells, number of
9 nodes, and total tube length in HRVECs co-transfected with LOC100132249 plasmid and miR-199a-
10 5p mimics, or si LOC100132249 and miR-199a-5p inhibitor. **(F)** Quantification of migrated cells
11 after si LOC100132249 and miR-199a-5p inhibitor co-transfection. **(G)** Quantification of migrated
12 cells after LOC100132249 plasmid and miR-199a-5p mimics co-transfection. **p<0.01; ***p<0.001;
13 ****p<0.0001. Error bars denote mean \pm SD.



Supplementary Figure 5. The regulatory roles of LOC100132249, miR-199a-5p, and SNAI1. (A) Expression level of SNAI1 after LOC100132249 overexpressing or interfering. **(B)** Expression level of SNAI1 after miR-199a-5p overexpressing or interfering. **(C)** RT-qPCR verification of the transfection efficiency of SNAI1 plasmid or si SNAI1. ** $p < 0.01$; *** $p < 0.001$. Error bars denote mean \pm SD.

