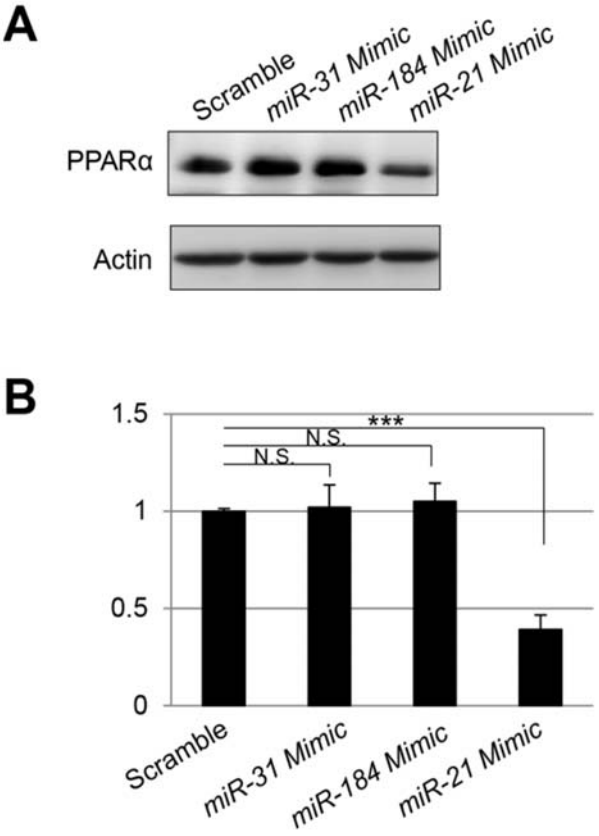
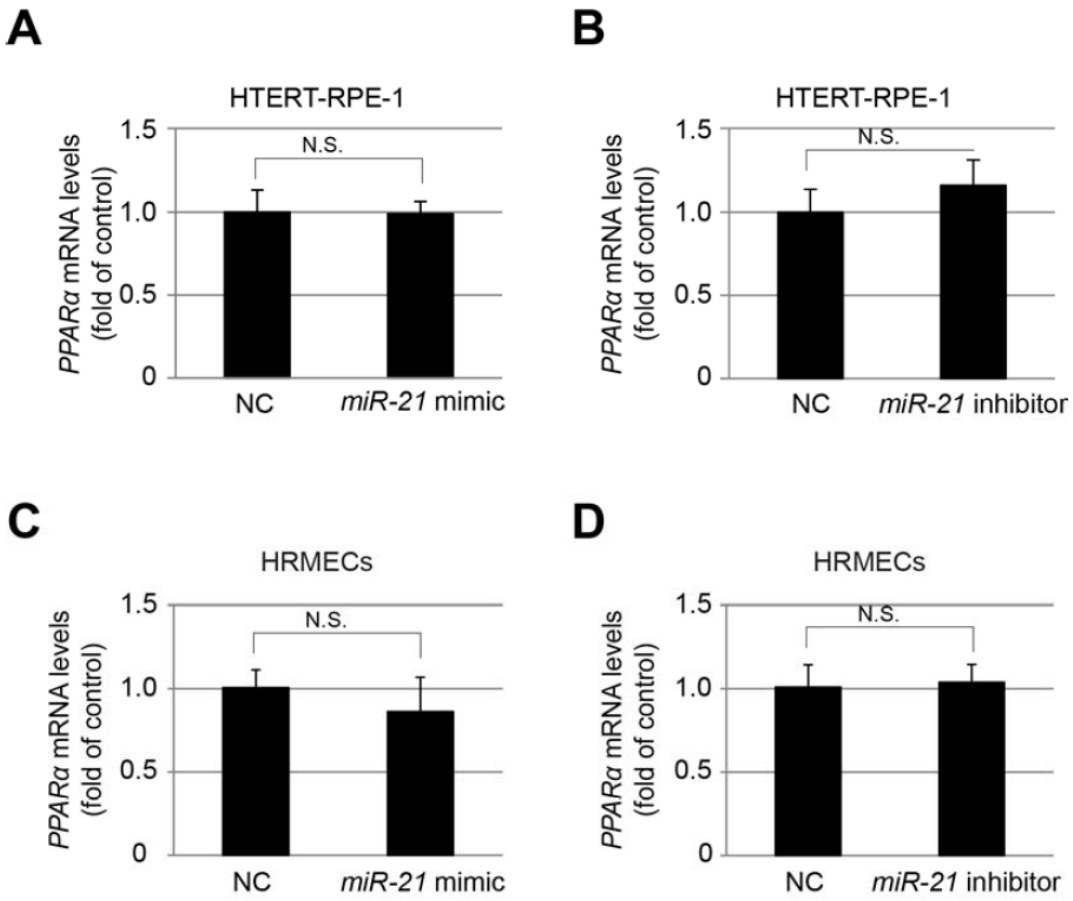
SUPPLEMENTARY DATA

**Supplementary Figure 1.** Specificity of PPARα regulation by *miR-21*. *MiR-184* mimic, *miR-31* mimic and *miR-21* mimic were separately transfected into HRMECs, and (**A**) protein levels of PPARα were measured by Western blot analysis and (**B**) semi-quantified by densitometry (data are representative of 3 independent experiments. N.S., non-significant).



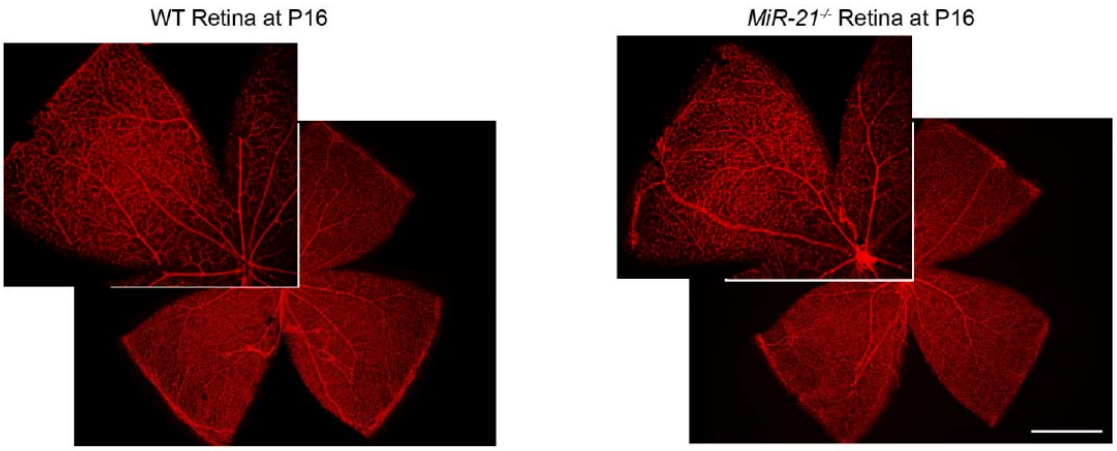
SUPPLEMENTARY DATA

**Supplementary Figure 2**. ***MiR-21* does not destabilize the *PPARα* mRNA**. **(A)** *MiR-21* mimic, **(B)** *miR-21* inhibitor and their respective controls were separately transfected into hTERT-RPE-1 cells, and levels of the *PPARα* mRNA were measured by qPCR. **(C-D)** Similarly, **(C)** *miR-21* mimic and **(D)** *miR-21* inhibitor were transfected into HRMECs, and levels of the *PPARα* mRNA were measured by qPCR (data are representative of 3 independent experiments. N.S., non-significant).



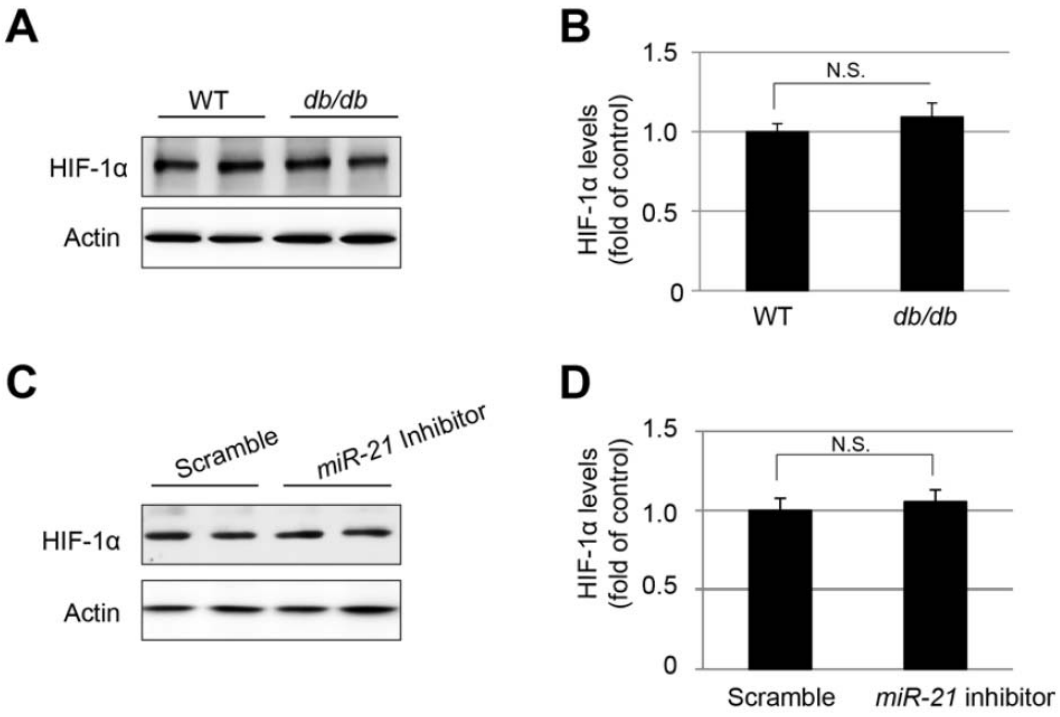
SUPPLEMENTARY DATA

**Supplementary Figure 3. Lack of vascular defects in *miR-21*$^{-/-}$ mice at P16**. Flat-mounted retinas of WT and *miR-21*$^{-/-}$ mice at age of P16 were stained with isolectin B4 (red). The retinal vessels in *miR-21*$^{-/-}$ mice were similar to those in WT mice (n=10). Scar bar: 1000μM.



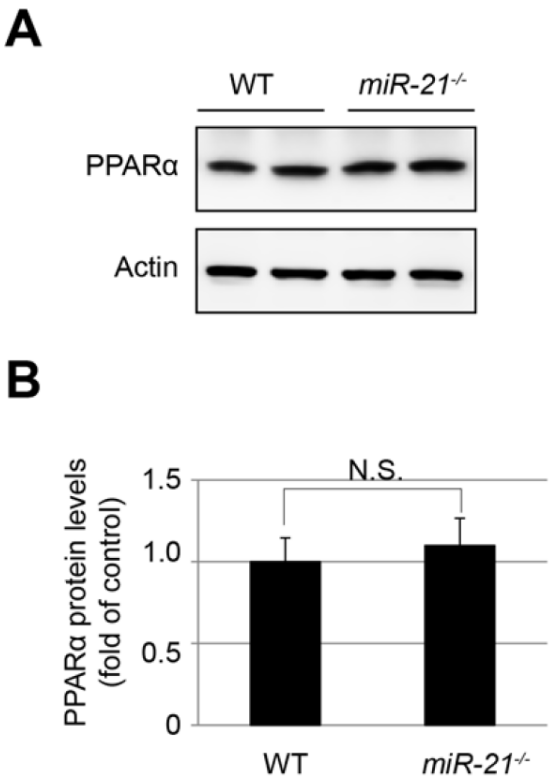
SUPPLEMENTARY DATA

**Supplementary Figure 4. No change of retinal HIF-1α levels in *db/db* mice or *db/db* mice injected with *miR-21* inhibitor. (A)** Protein levels of HIF-1α were measured in the retina of 6 moth-old *db/db* mice and age- and genetic matched WT controls by Western blot analysis. (**B**) Levels of HIF-1α were quantified by densitometry (n=5, N.S.= non-significant). (**C**) Protein levels of HIF-1α were measured in the retina of *db/db* mice injected with nanoparticles containing *miR-21* inhibitor or scramble miRNA (control). (**D**) Levels of HIF-1α were quantified by densitometry (n=8, N.S.= non-significant)



SUPPLEMENTARY DATA

**Supplementary Figure 5. Unchanged PPARα levels in *miR-21*$^{-/-}$ mice under normal condition. (A)** Retinal levels of PPARα were measured in WT and *miR-21*$^{-/-}$ mice by Western blot analysis. (**B**) Levels of PPARα were quantified by densitometry (n=6, N.S., non-significant).



SUPPLEMENTARY DATA

**Supplementary Table 1. Up-regulated miRNAs in the miRNA microarray (*db/db* vs. WT)**

| Name | Fold of changes | Target 3' UTR of *PPARα* mRNA (human) | Target 3' UTR of *PPARα* mRNA (mouse) | Conserved sites in targeting both human and mouse *PPARα* mRNAs | Levels of changes can be verified by qRT-PCR |
|---|---|---|---|---|---|
| *mmu-miR-184* | 3.17 | YES | NO | -- | |
| *mmu-miR-31* | 1.99 | YES | NO | -- | |
| *mmu-miR-379* | 1.72 | YES | NO | -- | |
| *mmu-miR-322* | 1.64 | NO | NO | -- | |
| *mmu-miR-132* | 1.39 | YES | NO | -- | |
| *mmu-miR-376b** | 1.34 | YES | YES | NO | |
| *mmu-miR-342-3p* | 1.33 | NO | YES | -- | |
| *mmu-miR-483* | 1.30 | YES | NO | -- | |
| *mmu-miR-15b* | 1.26 | NO | NO | -- | |
| *mmu-miR-195* | 1.23 | NO | NO | -- | |
| *mmu-miR-9** | 1.22 | YES | NO | -- | |
| *mmu-let-7g* | 1.22 | NO | NO | -- | |
| *mmu-miR-26a* | 1.23 | YES | NO | -- | |
| *mmu-miR-146b* | 1.20 | NO | NO | -- | |
| *mmu-miR-384-5p* | 1.14 | NO | NO | -- | |
| *mmu-miR-361* | 1.12 | NO | YES | -- | |
| *mmu-miR-128* | 1.12 | YES | YES | YES | NO |
| *mmu-miR-183** | 1.10 | NO | NO | -- | |
| ***mmu-miR-21*** | **1.07** | **YES** | **YES** | **YES** | **YES** |
| *mmu-miR-1839-5p* | 1.06 | NO | NO | -- | |
| *mmu-miR-151-5p* | 1.05 | NO | NO | -- | |