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Supplementary Table 1. The values of blood glucose and body weight. The 6-month-old diabetic male mice (5-month diabetes duration) and their non-diabetic male littermate control mice were weighed and measured for glucose. * $p<0.05$ vs. non-diabetic WT control. ** <0.0001 vs. non-diabetic WT mice. # $p<0.05$ vs. non-diabetic $PlGF^{-/-}$ mice. $ $p<0.05$ vs. Akita diabetic mice.

Glucose and weight	$PlGF^{+/+}$	Akita.$PlGF^{+/+}$	$PlGF^{-/-}$	Akita.$PlGF^{-/-}$
HbA1c (%)	8.0±3.8	19.0±6.3**	7.5±2.5	19.8±5.4
HbA1c (mmol/mol)	63.5±18.3	183.8±45.0**	58.2±3.3	193.4±35.8$
Body weight (g)	31.1±5.1	26.3±3.9*	28.1±2.7	20.9±0.6#$

Supplementary Table 2. Quantification of acellular capillaries, vascular ECs, and pericytes in trypsin digests. The 6-month-old diabetic male mice (5-month diabetes duration) and their non-diabetic male littermate control mice were used for the preparation of retinal vasculature by trypsin digestion. The samples were numbered, randomized and counted in a masked fashion. EC: endothelial cell. * $p<0.05$ vs. non-diabetic WT mice. $ $p<0.05$ vs. Akita diabetic mice.

Quantification	$PlGF^{+/+}$	Akita.$PlGF^{+/+}$	$PlGF^{-/-}$	Akita.$PlGF^{-/-}$
Acellular capillary/mm^2	14±2	45±9*	19±4	21±4$
EC (cells/mm^2)	324±40	314±29	378±50	294±36
Pericyte (cells/mm^2)	125±23	98±16*	172±30	113±18$
EC/pericyte	2.6±0.2	3.2±0.5*	2.2±0.3	2.6±0.2$

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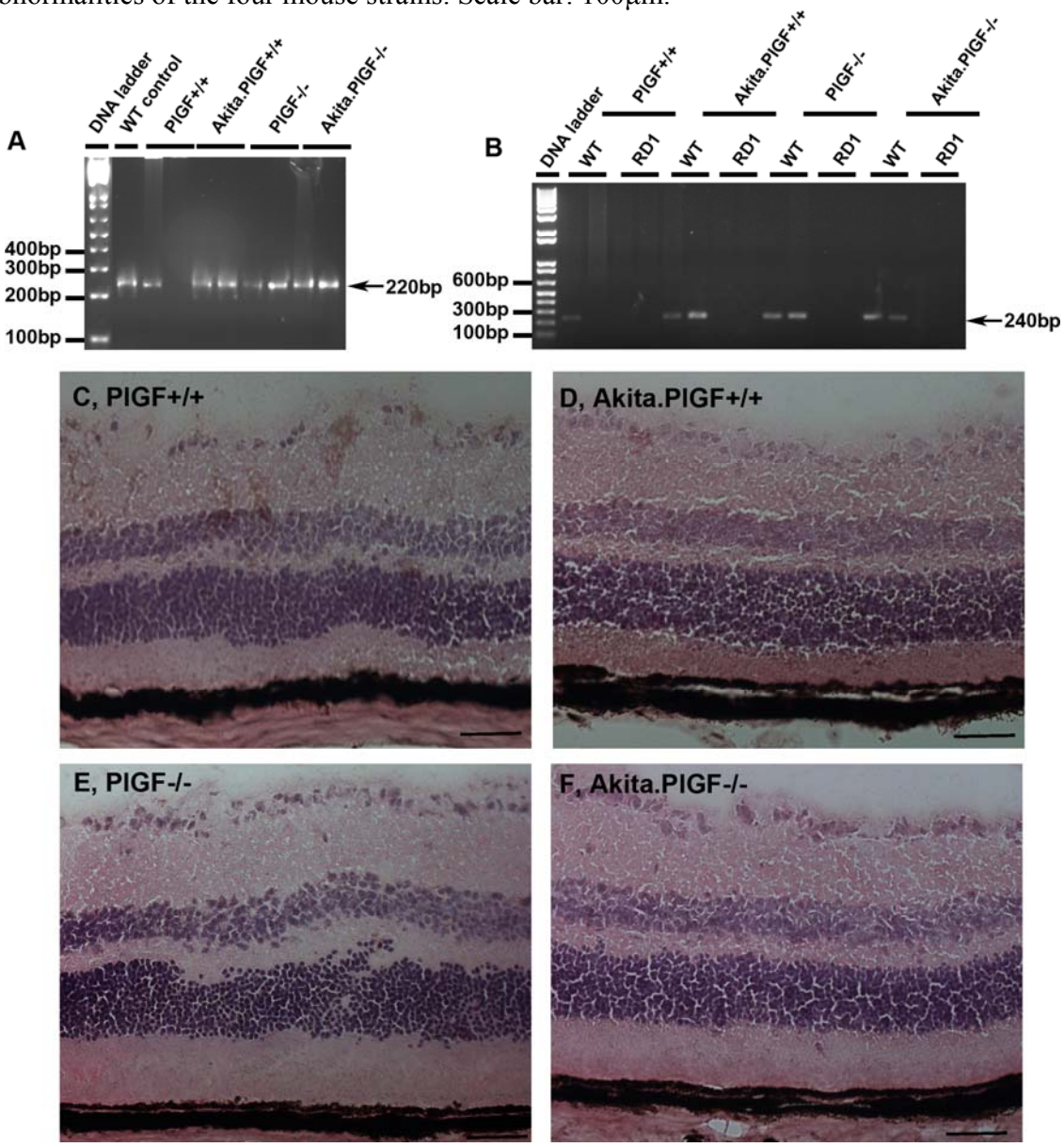
Supplementary Figure 1. Absence of retinal degeneration genes in the four mouse strains in this study. (A) PCR genotyping indicated that RD8 gene is absent. (B) PCR genotyping indicated that RD1 gene is absent. (C) H&E staining indicated that retinas are normal without evidence of retinal degeneration and other abnormalities of the four mouse strains. Scale bar: 100μm.



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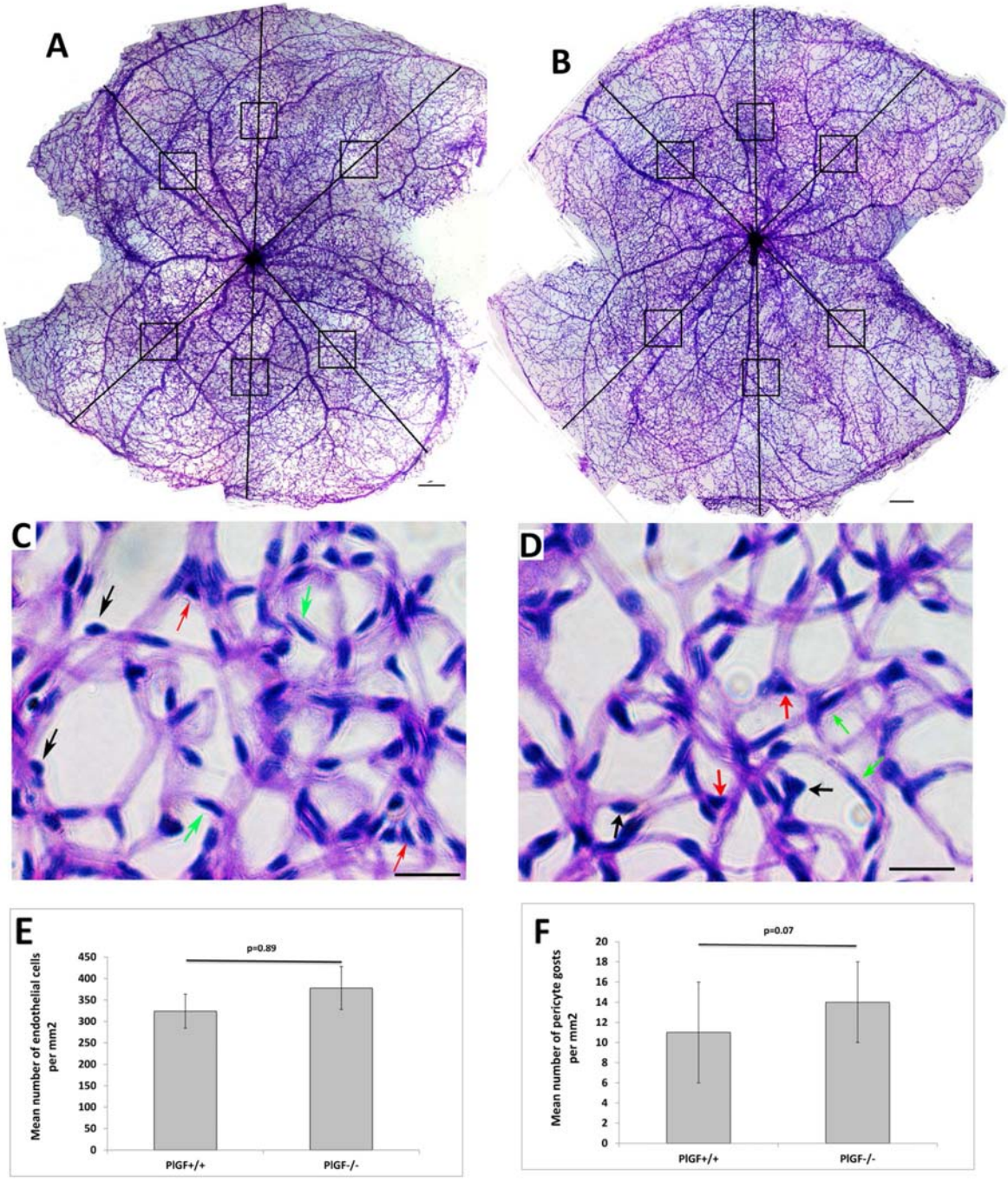
Supplementary Figure 2. There were no differences in vascular cell density and pericyte death in the retinas of non-diabetic $PlGF^{-/-}$ mice and $PlGF^{+/+}$ (WT) mice. Six-month-old $PlGF^{-/-}$ mice and WT mice were used for this analysis. (A&B) Examples of intact retinal vasculatures for $PlGF^{+/+}$ mouse (A) and $PlGF^{-/-}$ mouse (B). Boxes in the mid-zone of retinal blood vessel bed indicated the areas used for quantification of ECs and pericytes. Scale bars: 200μm. (C&D) Higher magnification micrographs show the morphology and position of ECs (black arrows), pericytes (green arrows), and pericyte ghosts (yellow arrows) in the retinal vasculatures of $PlGF^{+/+}$ mouse (C) and $PlGF^{-/-}$ mouse (D). Scale bar: 20 μm. (E & F) Quantification showed there were no a statistically significant difference in vascular EC density (C) or pericyte ghosts (D) between the two non-diabetic mice.



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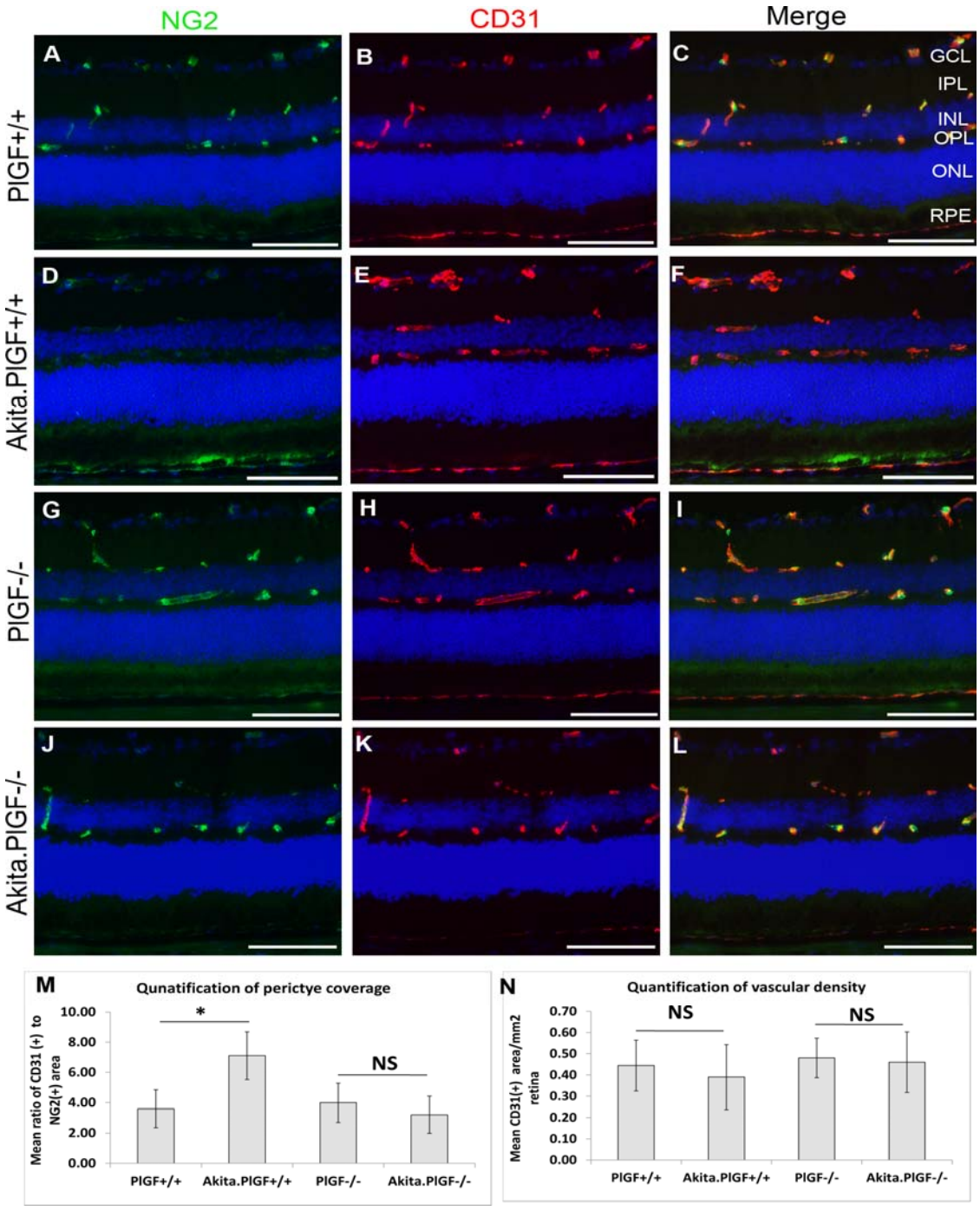
Supplementary Figure 3. Prevention of pericyte coverage loss in the retinas of Akita.PlGF$^{-/-}$ mice. The 6-month old diabetic mice (about 5-month diabetes duration) and non-diabetic mice were used for this analysis. (A-L) Representative immunofluorescence images of PlGF$^{+/+}$ mice (A-C), Akita.PlGF$^{+/+}$ mice (D-F), PlGF$^{-/-}$ mice (G-I), and Akita.PlGF$^{-/-}$ mice (J-L). (M&N) The quantification of ratio of CD31(+) vascular area to NG2 (+) vascular area (M) and CD31-immunopositive (+) vascular area (N). * $p<0.05$ versus PlGF$^{+/+}$ mice. NS: non significant. GCL: ganglion cell layer; IPL: inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; RPE: retinal pigment epithelium. Scale bar: 100μm.



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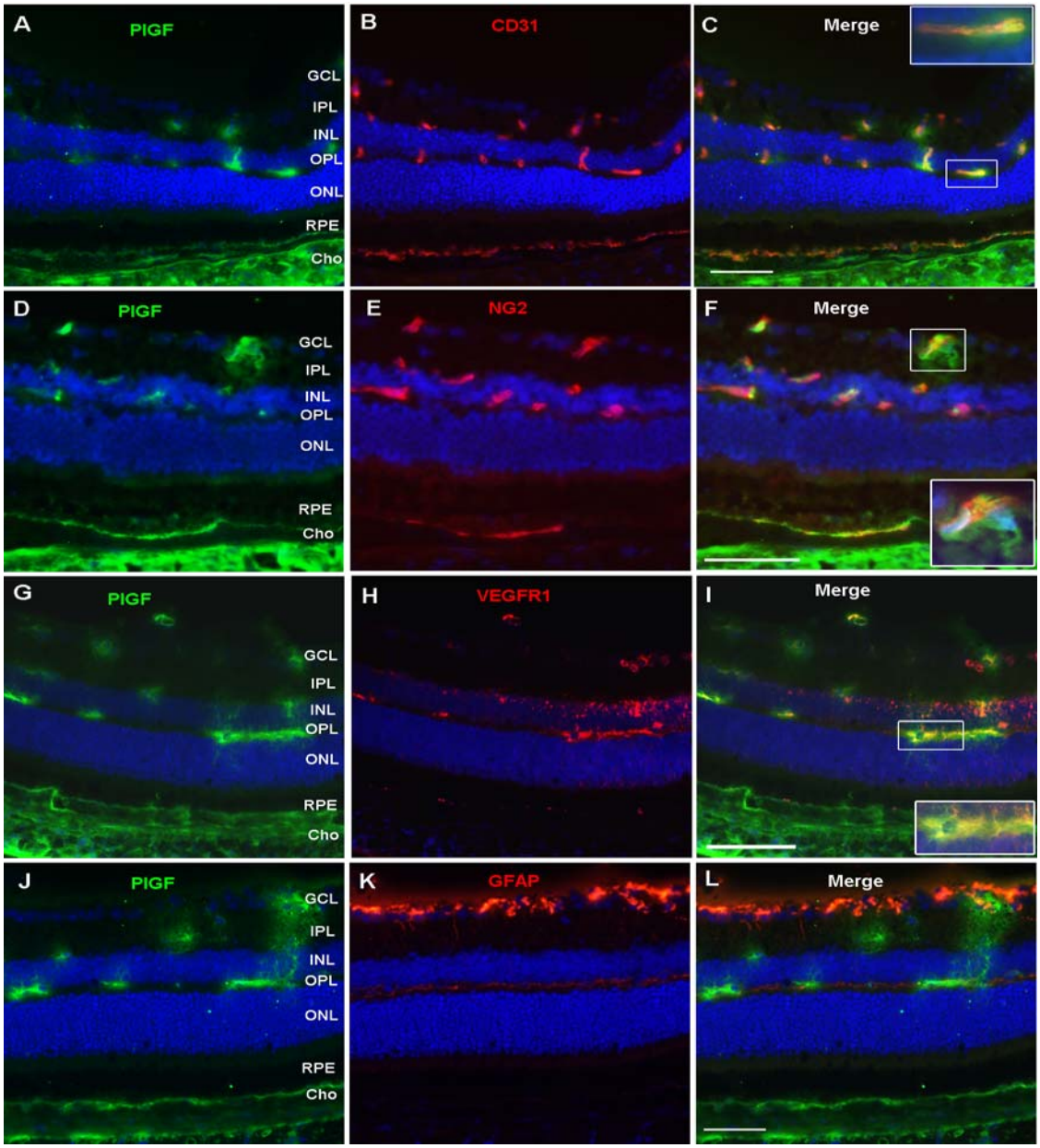
Supplementary Figure 4. Colocalization of PlGF, and VEGFR1, NG2, or CD31 in the retinas of diabetic mice. Cryosections from 3 months old Akita diabetic mice (about 2-month diabetes duration) were used for double labeling of PlGF(A,D,G,J) and CD31 (B), or NG2 (C), or VEGFR1 (H), or GFAP (K). PlGF co-localized with CD31 (C), NG2 (F) and VEGFR1 (I), but not with GFAP (L). Note that GFAP protein is known to increase in astrocytes and Müller cells in diabetic retina, but our IF staining showed GFAP was present only in astrocytes; this might be due to the differences in species and diabetes duration. CD31: cluster of differentiation 31; NG2: pericytes/glia maker; VEGFR1: vascular endothelial growth factor receptor 1; GFAP: gilial fibrillary acidic protein. GCL: ganglion cell layer; IPL: inner plexiform layer; inl: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; RPE: retinal pigment epithilum. Cho: choroid. Scale bar: 50μm.



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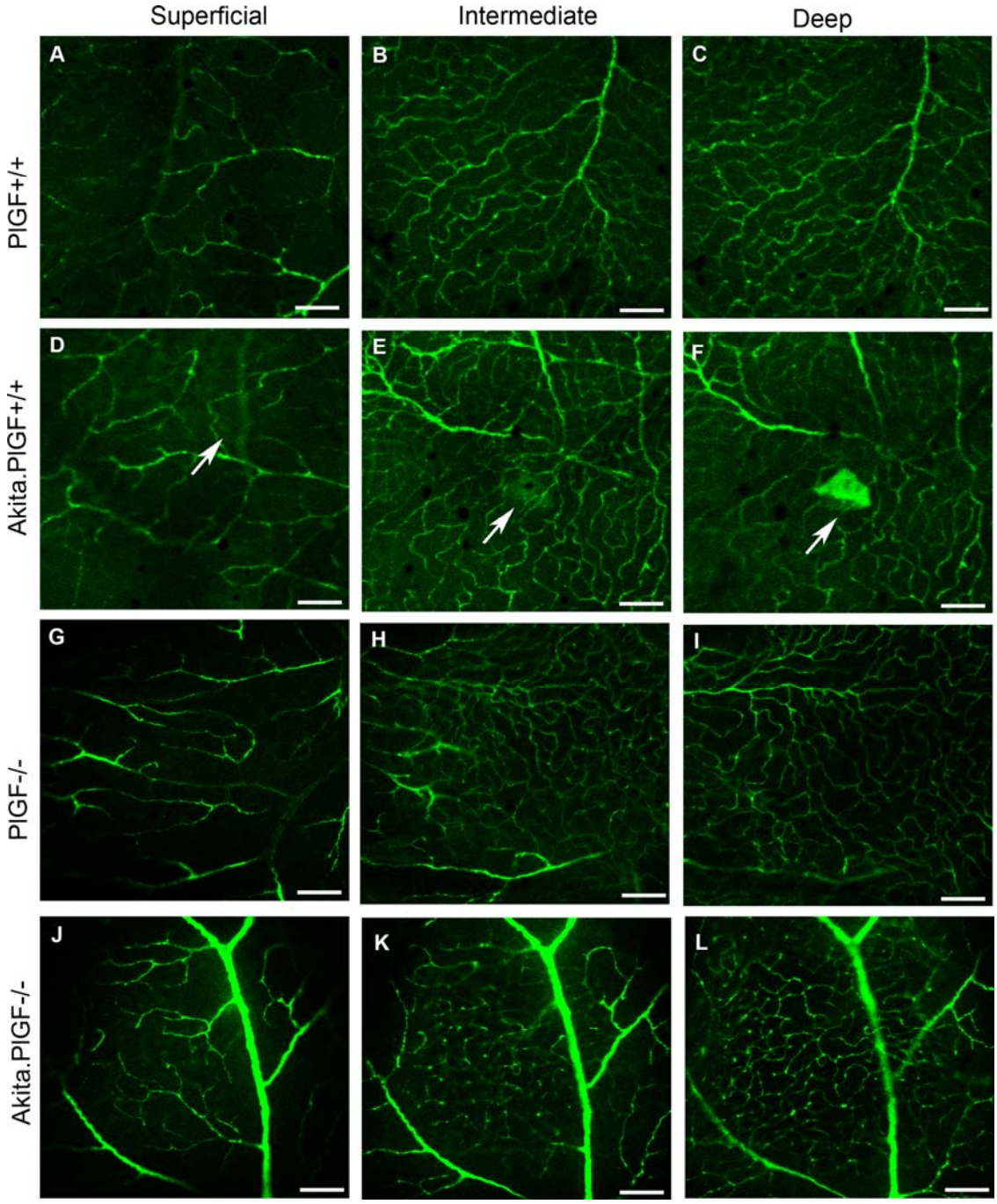
Supplementary Figure 5. Prevention of vascular leakage in the retinas of Akita.PlGF$^{-/-}$ mice. Six-month-old diabetic mice (about 5-month diabetes duration) and age-matched non-diabetic control mice were subjected to transcardial perfusion with FITC-dextran (70kDa). Retinal flatmounts were examined with scanning laser confocal microscopy. (A-C) Non-diabetic PlGF$^{+/+}$ mice. (D-F) Akita.PlGF$^{+/+}$ diabetic mice. (G-H) non-diabetic PlGF$^{-/-}$ mice. (J-L) Akita.PlGF$^{-/-}$ diabetic mice. Scable bar: 50μm. Arrows indicate the leakage sites.



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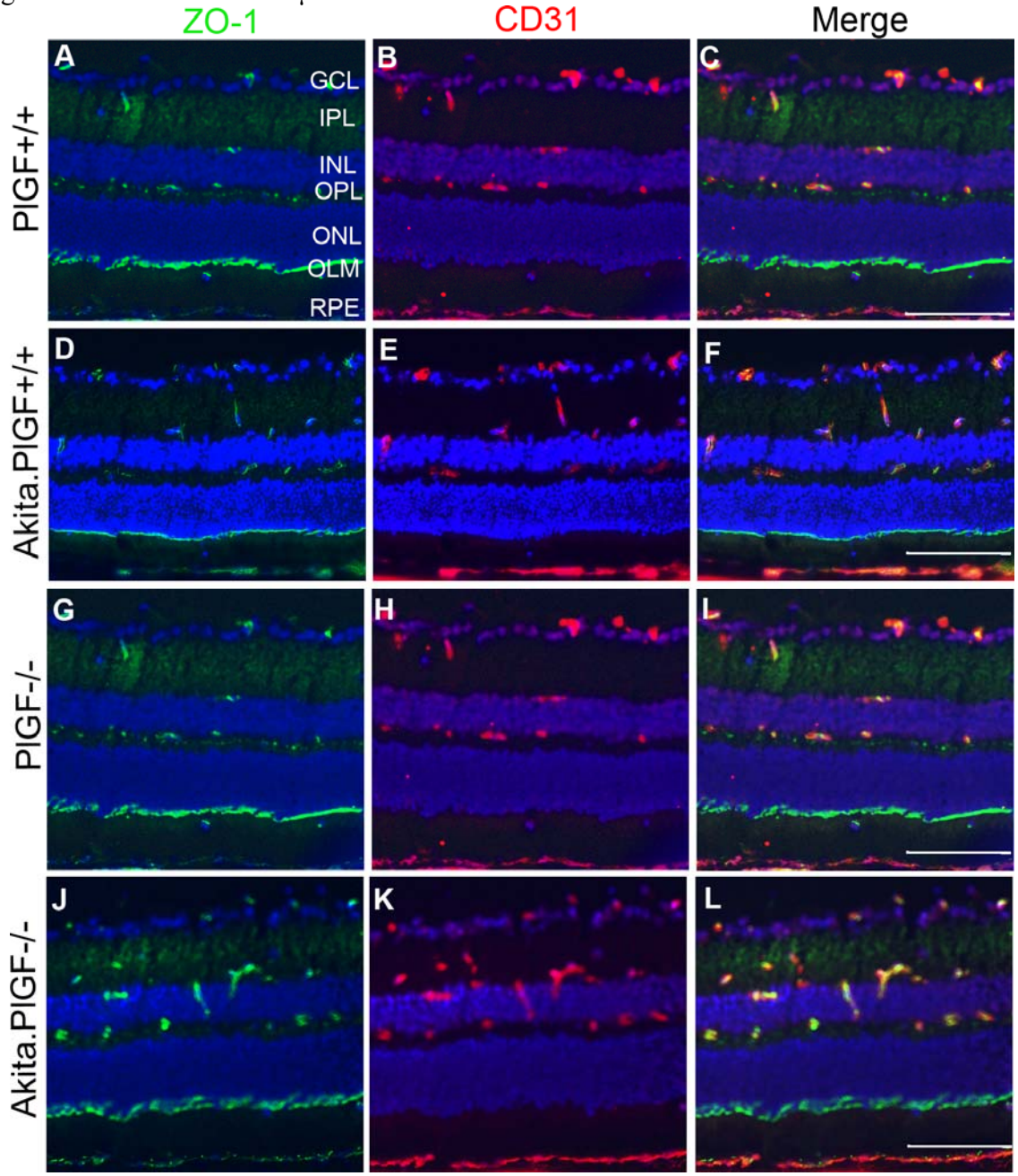
Supplementary Figure 6. Prevention of tight junction zonula occludens (ZO)-1 protein degradation in the retinas of Akita.PlGF$^{-/-}$ mice. Double immune labeling of ZO-1 and CD31/PECAM1 was performed on six-month-old diabetic PlGF$^{+/+}$ and PlGF$^{-/-}$ mice (5-month diabetes duration) and respective non-diabetic control mice. (A-C) Non-diabetic PlGF$^{+/+}$ mice. (D-F) Akita.PlGF$^{+/+}$ diabetic mice. (G-H) non-diabetic PlGF-/- mice. (J-L) Akita.PlGF$^{-/-}$ diabetic mice. Note that the immunoreactivity of ZO-1 is decreased in the inner retina and near OLM of Akita.PlGF$^{+/+}$ diabetic mice, compared with the non-diabetic PlGF$^{+/+}$ mice. GCL: ganglion cell layer; IPL: inner plexiform layer; inl: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; RPE: retinal pigment epithelium. OLM: outer limiting membrane. Scale bar: 50μm.



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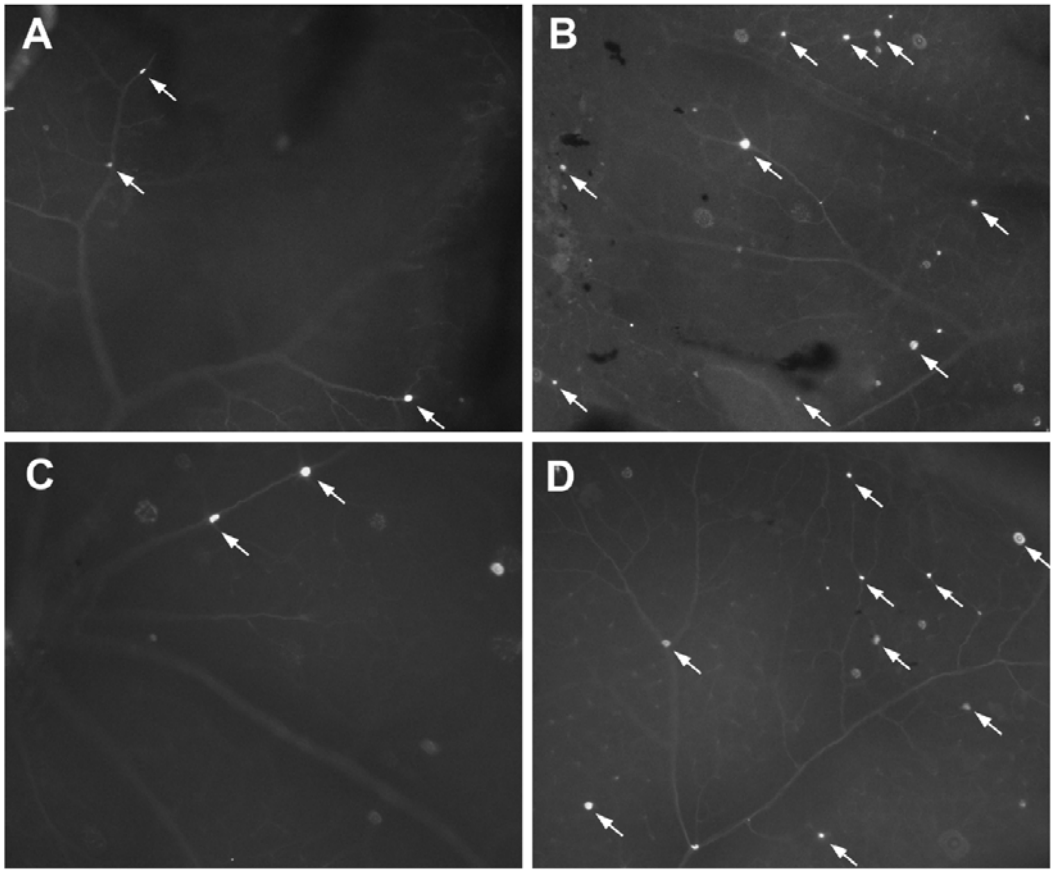
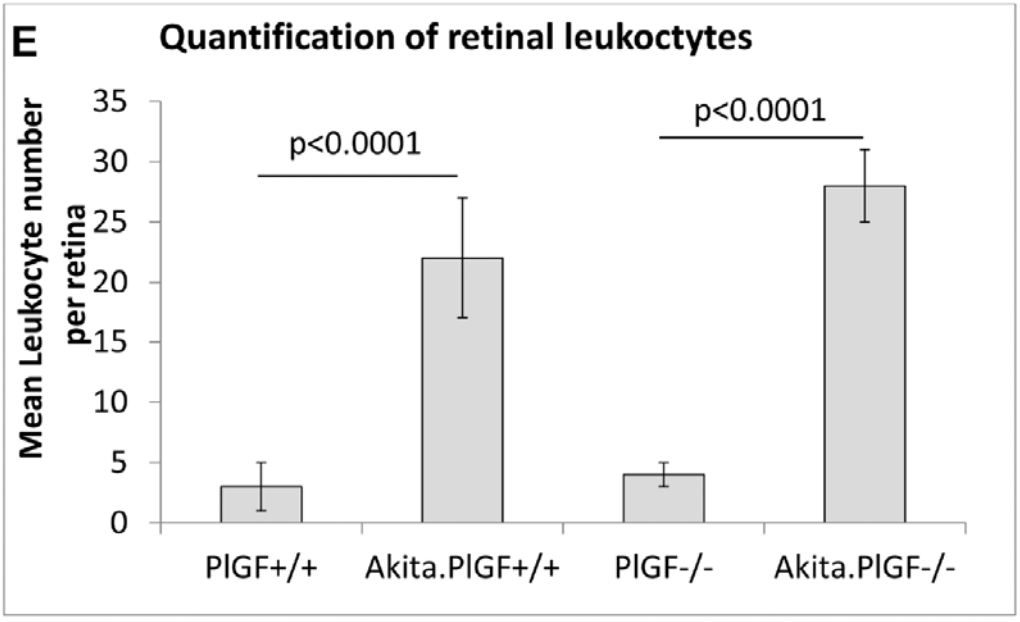
Supplementary Figure 7. Increased retinal leukostasis in both Akita.PlGF$^{+/+}$ mice and Akita.PlGF$^{-/-}$ mice. Leukostasis was assessed on the 6-month-old diabetic mice (about 5-month diabetes duration) and their non-diabetic control mice were used. (A-D) Example of retinal leukostasis for PlGF$^{+/+}$ (A), Akita.PlGF$^{+/+}$(B), PlGF$^{-/-}$ (C), Akita.PlGF$^{-/-}$ (D). (E) Quantification of retinal leukocyte number. The results were averaged for six mice.





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