

Supplemental Table 1.**Supplemental Table 1. Summary of the *in vivo* RPE cell transplantation in monkeys**

Name	Operated eye	Graft RPE cells (human RPE)	Drugs	IHC evaluation	Rejection*	Complications
HM-1	R	Cell suspension	IVTA	6 months	+	None
	L	Cell suspension	IVTA	5 months 1 week	++	None
HM-2	R	Cell suspension	IVTA	3 months 1 week	+	None
	L	Cell suspension	IVTA	3 months	+++	None
HM-3	R	Cell suspension	IVTA	3 months	+	None
HM-4	R	Cell suspension	None	6 months	+	ERM
HM-5	R	Cell suspension	IVTA Systemic CsA	3 months	-	None
HM-6	R	Cell suspension	IVTA + STTA	8 months 1 week	±	None
	L	Cell suspension	IVTA + STTA	4 months 1 week	±	None
HM-7	R	Cell suspension	IVTA + STTA	3 months	±	Macular damage**
HM-8	R	Cell suspension	IVTA	5 months	+	ERM
	L	Cell suspension	IVTA	4 months 2 weeks	+	ERM, endophthalmitis

*Grading of the RPE graft-related immune rejections was as follows: non (-), slight (±), mild (+), moderate (++), and severe (+++). **Macular damage due to operation error (reference 21 in main text). CsA – Cyclosporine A. IVTA; intravitreal triamcinolone acetonide, STTA; sub-Tenon triamcinolone acetonide, ERM; epiretinal membrane.

Supplemental Fig. 1.

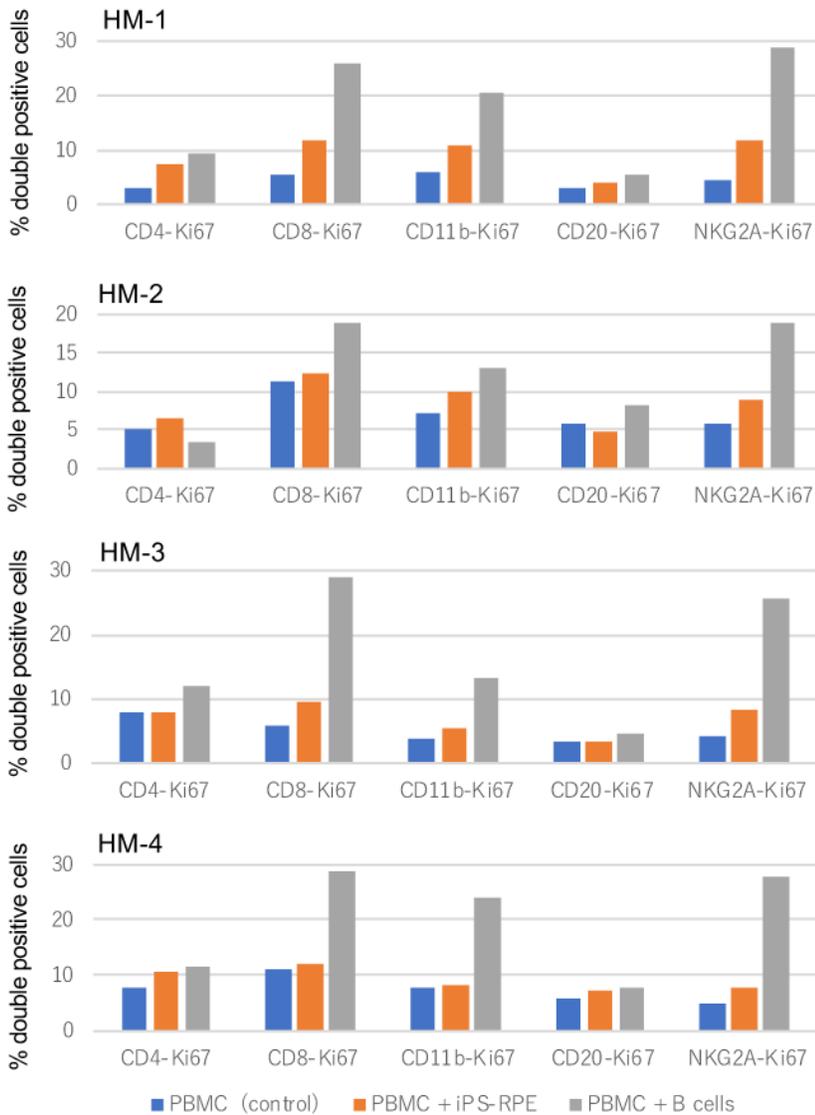


Figure S1. Summary of LGIR *in vitro* assay in monkeys.

We performed LGIR assay with PBMC from healthy monkeys, HM-1, 2, 3, 4 (n=4). PBMC were harvested and stained with anti-CD4, anti-CD8, anti-CD11b, anti-CD20, anti-NKG2A, and anti-Ki-67 antibody for FACS analysis. We then made the individual graph of Ki-67 FACS and evaluated the responses against iPS-RPE cells (e.g., CD4-Ki67 positive indicate proliferation of helper T cells). PBMC without RPE cells was experimental control (blue bars). Allogeneic B cells (B95-8 B cell lines: positive control; gray bars) were also used in this assay.

Supplemental Fig. 2.

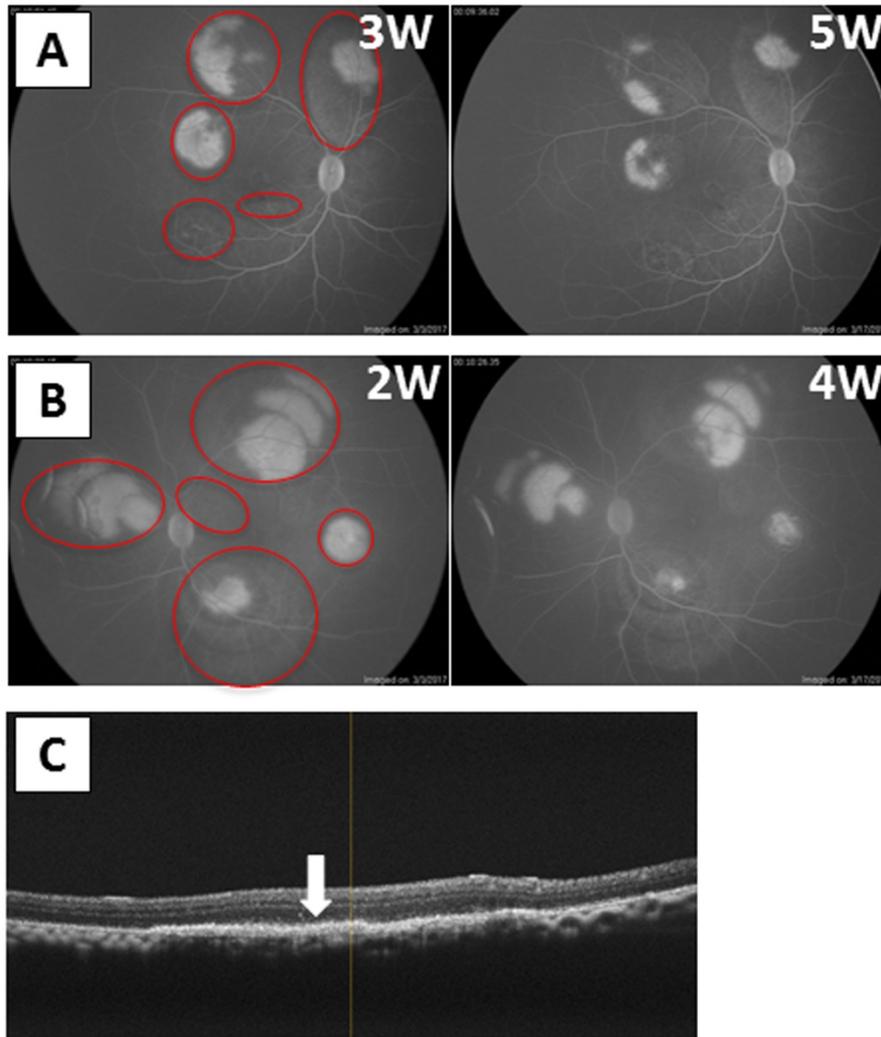


Figure S2. iPSC-RPE cell suspension transplantation displaying inflammatory differences in right and left eyes by fluorescein angiography (FA).

Late phase FA in the right and left eyes of HM-1 after transplantation are shown. Transplanted sites are shown by the red circles. (A) Leakages from the transplanted sites in the right eye gradually decreased. (B) In the nasal and upper area of the left eye, leakages remained for 4 weeks after the surgery. (C) OCT showed the presence of grafted cells (arrow) without any abnormal features.

Supplemental Fig. 3.

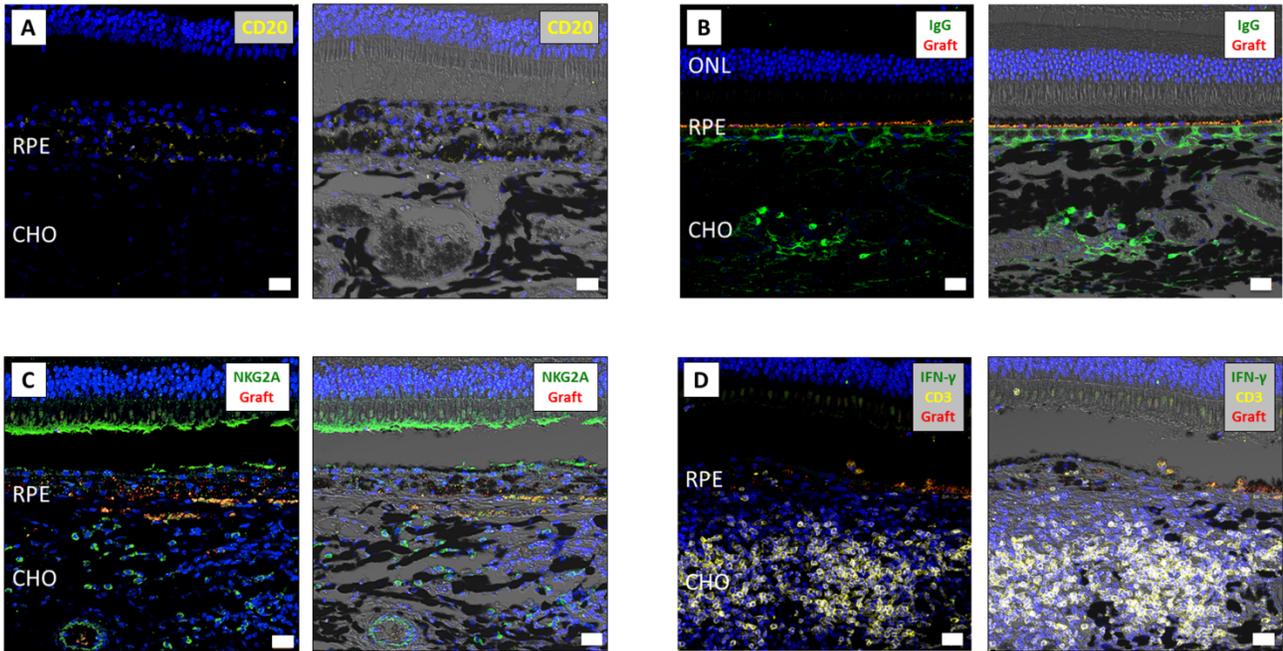


Figure S3. Representative IHC images of inflammatory immune cells in iPSC-RPE cell suspension transplantation.

(A) CD20⁺ cells (B cells: Yellow) were observed around the grafts in the transplanted sites. (B) PKH positive graft cells extended in the subretinal space (Red: around host RPE layer). IgG deposits (Green) was also observed around the graft and in the choroid. (C) NKG2A positive NK cells (Green) were observed around the graft and in the choroid. (D) A lot of T cell infiltrates with IFN- γ (perhaps Th1 type T cell) was observed in the choroid.

Supplemental Fig. 4.

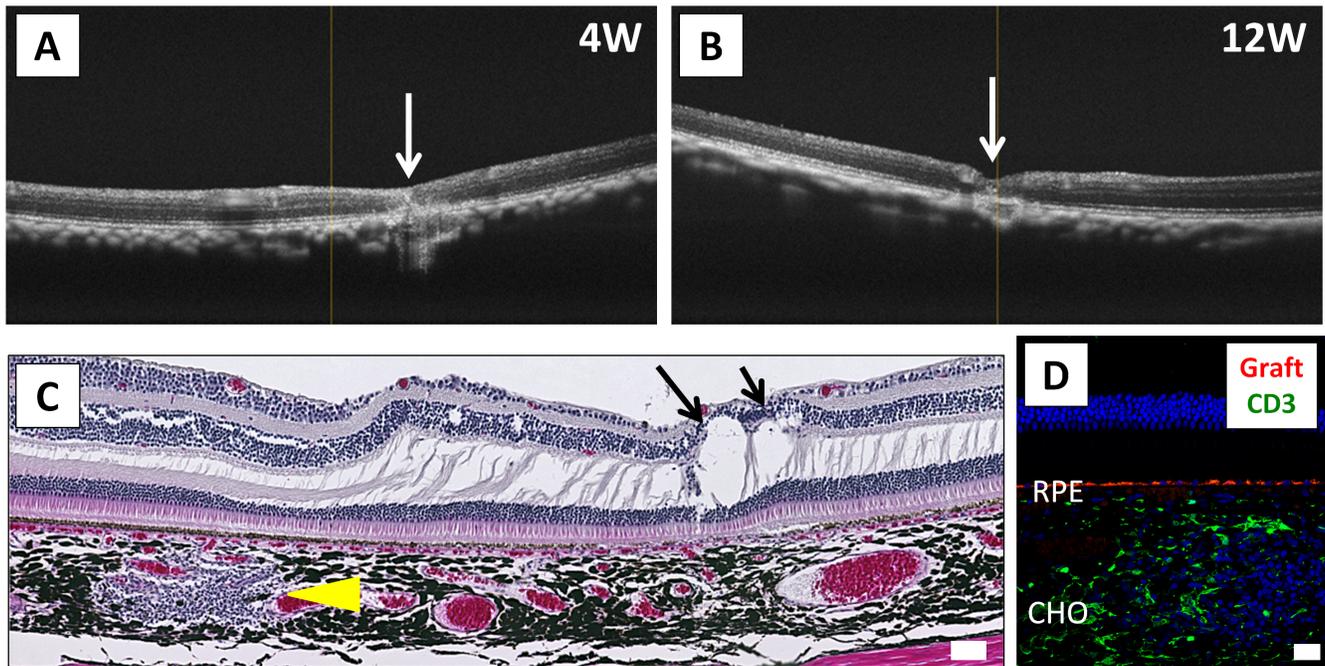
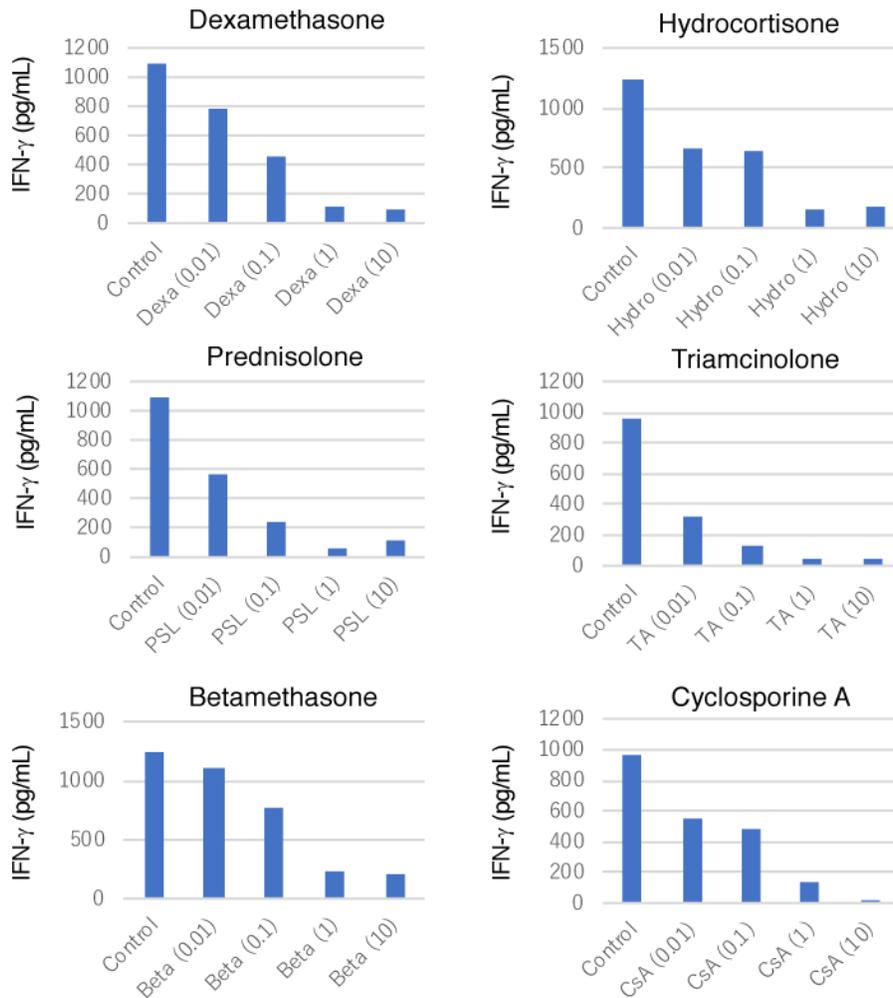


Figure S4. iPSC-RPE cell suspensions extended in the subretinal space of the transplanted monkey's eye.

(A) The arrow in the OCT image indicates the transplantation site. (B) The thickness of the host retina (arrow) decreased over time. (C) H&E section at 12 weeks after transplantation demonstrated cystoid retinal edema (arrows), and a mass of inflammatory cells in the choroid (arrowhead). Scale bar, 50 μ m. (D) PKH-stained graft RPE cells were detected in the subretinal space, and CD3-positive T cells were observed in the choroid. Scale bar, 20 μ m.

Supplemental Fig. 5.**Figure S5. A range of concentrations for each drug in *in vitro* preliminary assay.**

In preliminary experiments, we tested a range of concentrations for each drug before the Drug-LGIR assay. For this, we evaluated the suppression of the activities of monkey lymphocytes in PBMC (5×10^5 /well in 96-well round plate) under 4 concentrations of each drug (0.01, 0.1, 1 and 10 $\mu\text{g/mL}$). After culturing PBMC for 5 days in the presence of the drug at each concentration, we evaluated IFN- γ levels in the supernatants. All drugs greatly suppressed the activities of lymphocytes (production of IFN- γ cytokines) at the concentration around 1 or 10 $\mu\text{g/mL}$. Therefore, we used the concentration of 1 $\mu\text{g/mL}$ for all drugs in the following experiments.

Supplemental Fig. 6.

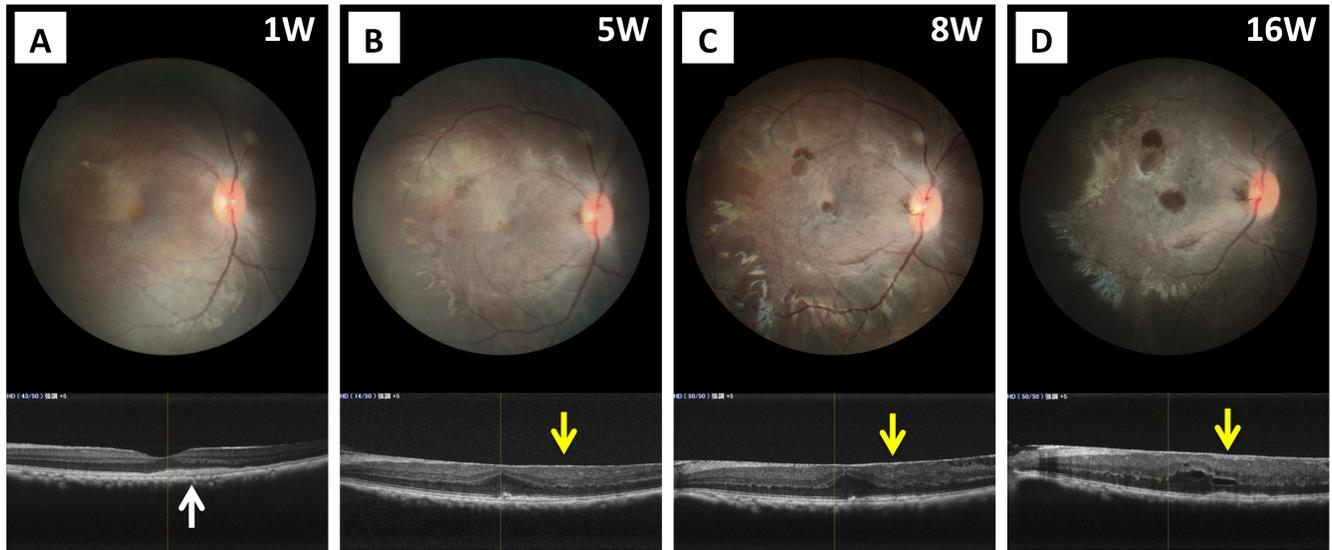


Figure S6. Surgical complications seen after the iPSC-RPE cell suspension transplantation; Epiretinal membrane.

(A) Grafted cells (white arrows) were detected in the subretinal space. (B) Epiretinal membrane (yellow arrows) was seen at 5 weeks (5W). (C) The thickness of the membrane increased over time up to 8W. (D) Retinal edema (arrowhead) can also be seen along with increases in the membrane at 16W.

Supplemental Fig. 7.

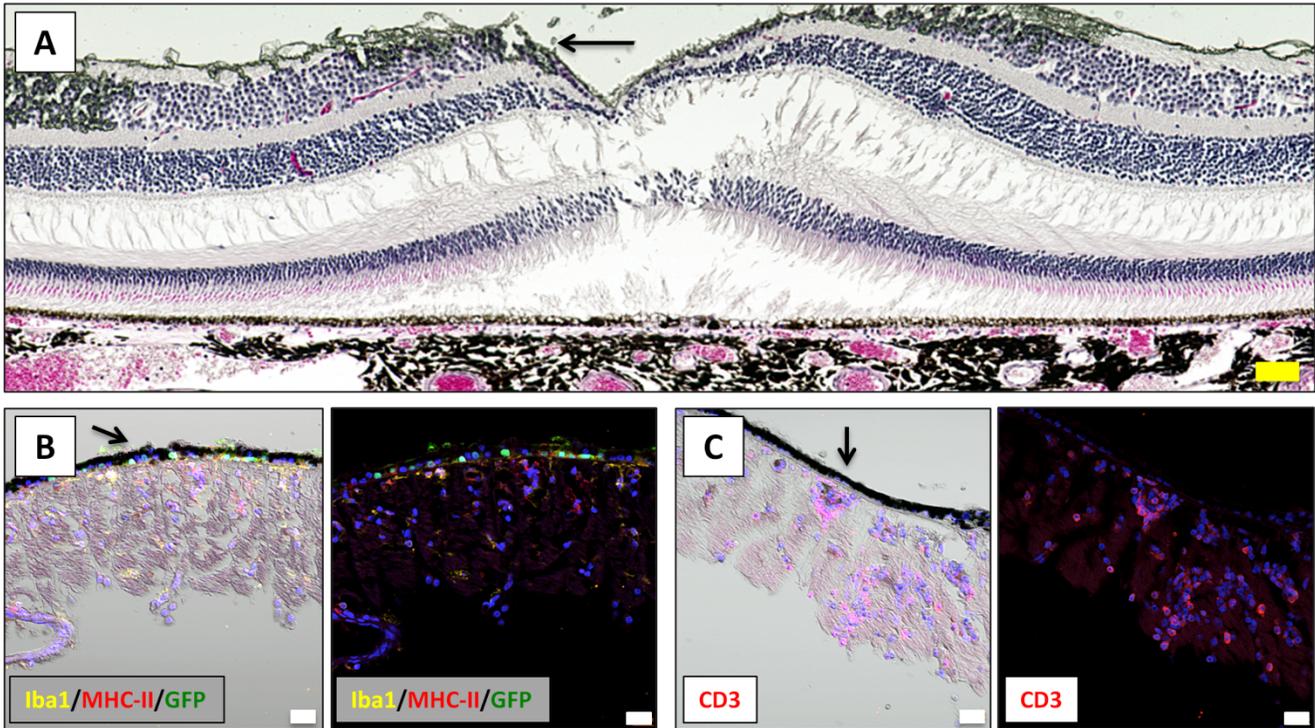


Figure S7. Surgical complication in iPSC-RPE cell suspension transplantation; epiretinal membrane (ERM) together with inflammatory cells in IHC.

(A) H&E stained section demonstrated the macular area and the overlying ERM (arrow). Scale bar: 50 μm . (B) In IHC, ERM (arrow) included GFP labeled graft RPE cells. MHC class II⁺ / Iba1⁺ cells (antigen-presenting cells) were also detected in the ERM tissues. Scale bars: 20 μm . (C) Many CD3⁺ cells (T cells) were also detected in the ERM. Scale bars: 20 μm .