

Expanded View Figures

Figure EV1. The chelation-dependent thalassemia patients show retinal degeneration and functional improvement by taking AKG.

- A–H SD-OCT of the four thalassemia patients with a history of taking DFO showed interruption of the ellipsoid zone (Case I; Gelman *et al*, 2014), decreased photoreceptor nuclear layer, and thinning of the retinal layers (Cases II–IV). Focal thickening and bumps of RPE were also noted in Case I. Granular hyper-reflective deposits within the RPE (yellow arrows) can be seen in all four cases. An intraretinal degenerative cyst (Case IV) and multiple areas of choroidal hyper-transmission were also noted in Cases II–IV.
- I The fERG examination on Case IV with continuous supplementation of AKG for 18 months (2 g/day). Repeated fERG examination (lower panel) on both eyes showed increased amplitudes in light-adapted single-flash cone and 30 Hz flicker responses compared with the amplitude prior to taking AKG (upper panel). The exact numbers of the peak value are indicated inside the panel boxes. Y-Axis: microvolts; X-Axis: milliseconds.

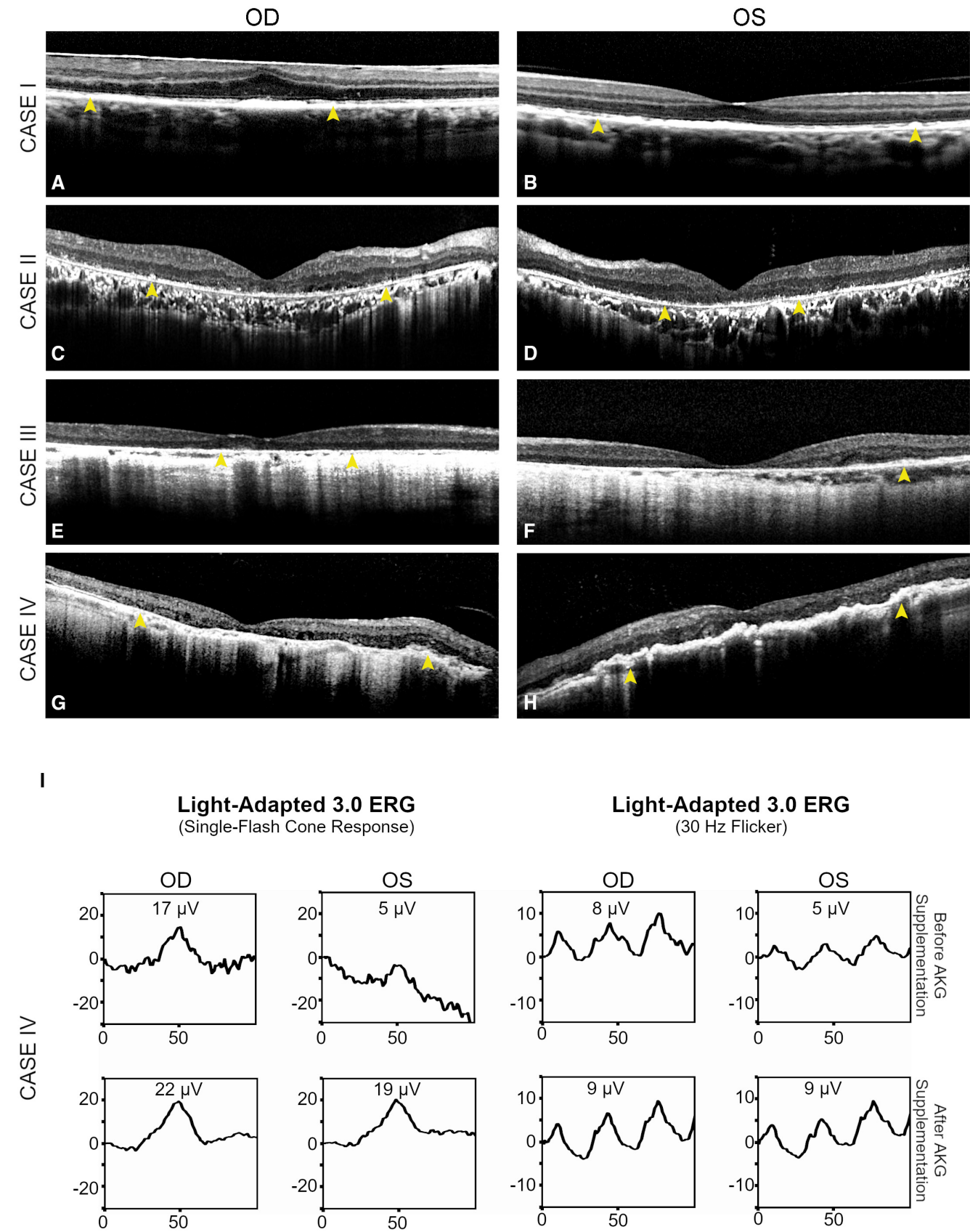


Figure EV1.

Figure EV2. The toxic effects of DFO in the outer retina/RPE area.

- A, B SD-OCT was performed on DFO-treated mouse eyes to display potential changes to RPE and retina, respectively. Yellow arrows denote hyper-reflective signal and outer retinal lesion in SW-AF and SD-OCT, respectively (A); and hypo-reflective signal and lesions located in the photoreceptor outer segment/RPE microvilli area (B). Yellow lines in the near-infrared images indicate the sections scanned by SD-OCT.
- C, D Cell death was examined by TUNEL assay in the retinas collected from the mice with DFO treatment for five months.
- E, F Cone photoreceptors were stained by Arrestin 3 in retinal flat mounts from the mice with DFO treatment for five months.

Data information: (C–F) The images were captured at 10× magnification and stitched together. Scale bar: 1 mm.

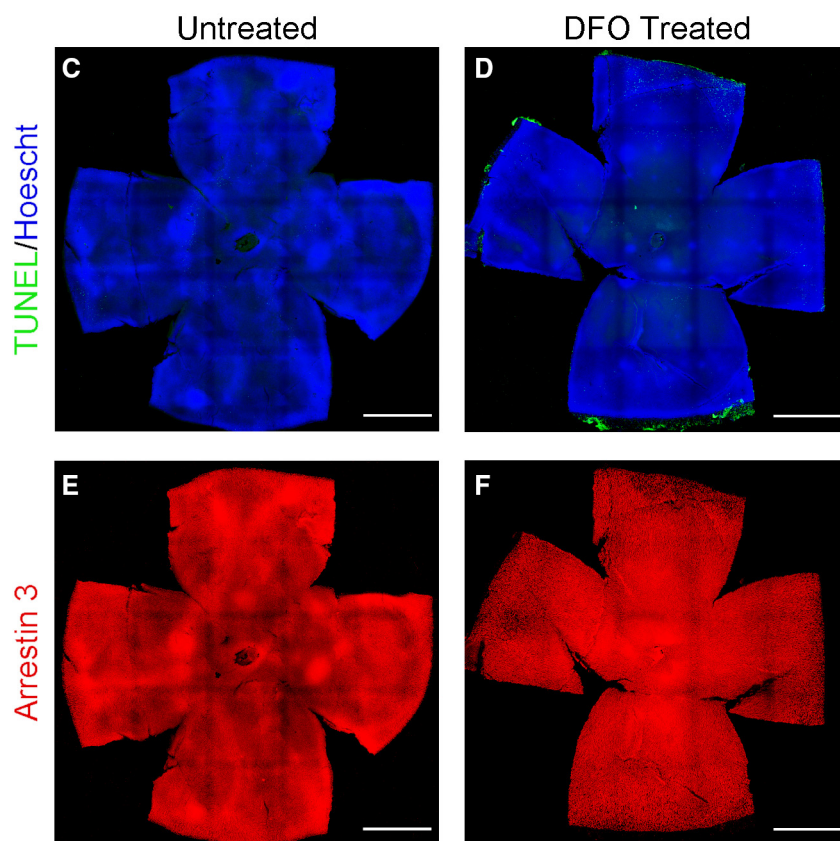
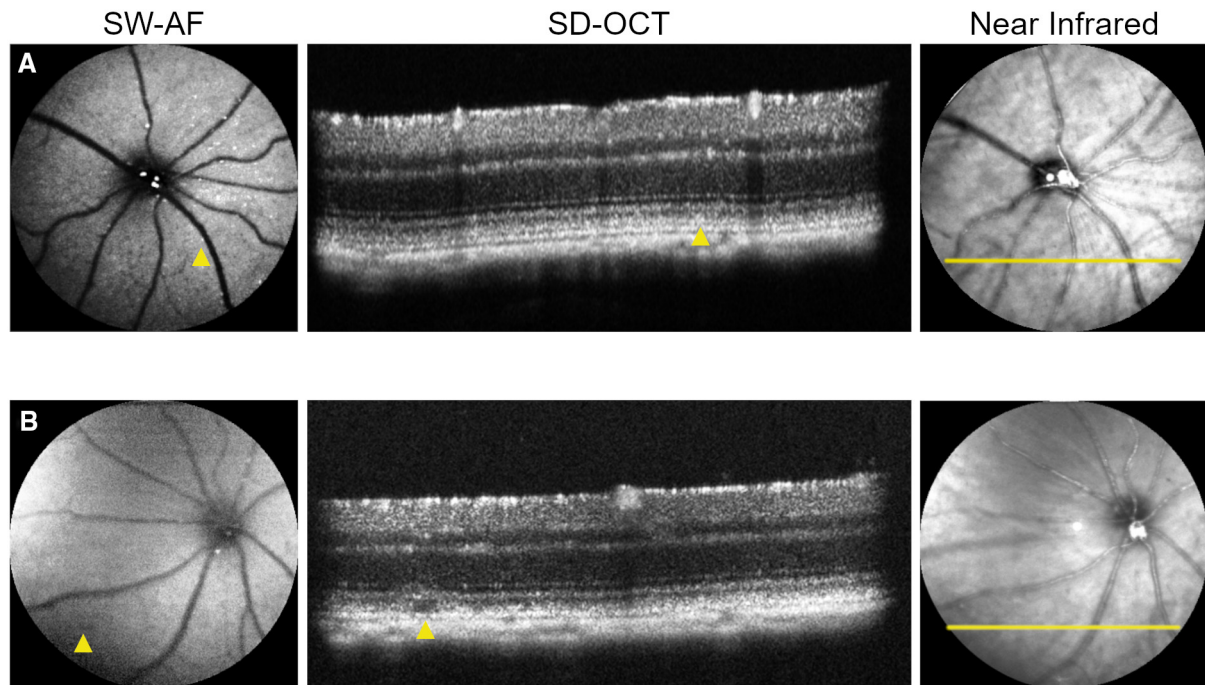


Figure EV2.

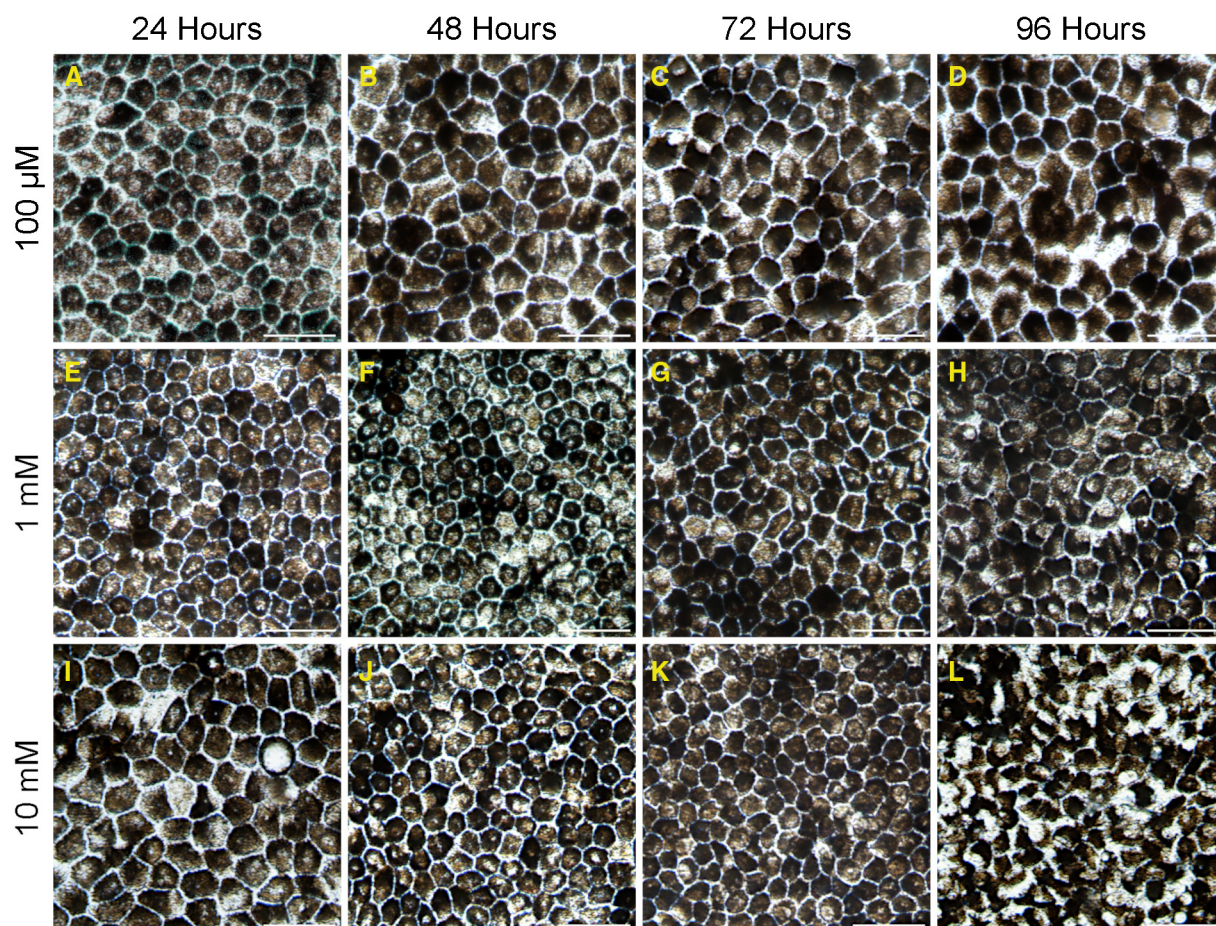


Figure EV3. Examination of the toxicity gradient of DFO in iRPE cells.

A–D The iRPE cells were treated with DFO for different time points at 100 μ M.

E–H The iRPE cells were treated with DFO for different time points at 1 mM.

I–L The iRPE cells were treated with DFO for different time points at 10 mM.

Data information: The toxic effect was monitored by light microscopy over a course of time for up to 96-h until the disruption of cell integrity distinctly appeared. Scale bar: 20 μ m.

Source data are available online for this figure.

Figure EV4. Measurement of HIF α and its target genes in response to DFO in iRPE cells.

A–E The HIF α -regulated transcripts were determined by qPCR with iRPE cells subject to DFO treatment for 48-h. The cDNA transcript extracted from the untreated iRPE was included as the control. The level of each transcript was normalized to *ACTB*. (A) Measurement of the HIF1 α and HIF2 α transcripts. The statistics are analyzed by one-way ANOVA with the Tukey test. The results are presented as mean $\pm$ S.E.M., $n = 4$ iRPE lines for each group. (B) Measurement of cell-survival-related transcripts regulated by HIF α . (C) Measurement of apoptosis-related transcript regulated by HIF α . (D) Measurement of glycolysis-related transcript regulated by HIF α . (E) Measurement of iron-transport-related transcript regulated by HIF α .

F RPE lysate from the one-year-old mice subject to 10-month DFO treatment with or without concomitant supplementation of AKG was used for immunoblotting against HIF1 α . The RPE harvested from the age-matched untreated mice was included as the control. HIF1 α (degraded) was predicted to be 40–80 kDa. Actin was used as the loading control.

Data information: (B–E) The statistics are analyzed by ratio paired Student's *t*-test. The results are presented as mean $\pm$ S.E.M., $n = 4$ iRPE lines for each group.

* $P < 0.05$; ** $P < 0.01$. Round dots: untreated iRPE; square dots: DFO-treated iRPE.

Source data are available online for this figure.

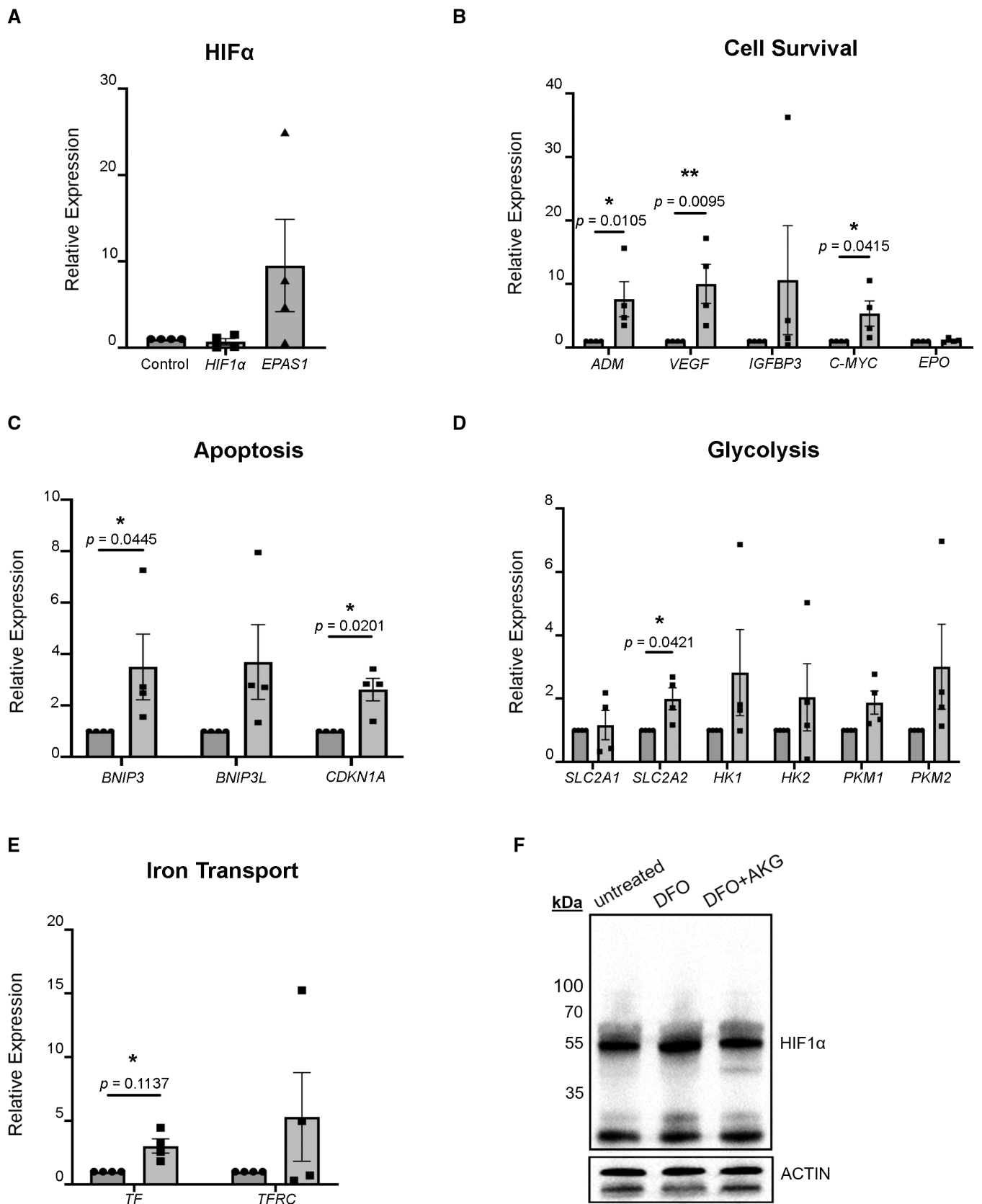


Figure EV4.