Intravitreal triamcinolone acetate promotes rod and cone survival in RP

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Cortical Dysfunction induces retinal microglia activation and photoreceptor cell loss and death. The destruction of photoreceptors by activated microglia suggests that microglia are a promising therapeutic target for the treatment of photoreceptor degenerative diseases. In this study, we aimed to investigate the effect of intravitreal injection of a slow-release corticosteroid (triamcinolone acetate) on retinal microglia activation and photoreceptor survival. We found that the intravitreal injection of triamcinolone acetate (IVTA) inhibits the activation of retinal microglia and promotes photoreceptor survival.
Methods

Wild type (WT) and P23H RHODOPSIN mutant RP pig littermates were followed for retinal apoptosis, expression of cytokines, microglial migration and engulfment of mutant rods at different ages and stages of retinal degeneration. The effects of IVTA injection at these ages and stages was compared. All of the changes (e.g., WT vs. RP and control vs. treated) in ERG, OKR, ONL rows and OS number exceeded statistical significance $\leq 0.05$. 
Results - Rod loss in pig RP does not correlate with apoptosis

Because apoptosis can be triggered by chronic ER stress from misfolded proteins, we followed apoptosis during the time course of rod loss in the pigs. Although low levels of rod apoptosis (blue arrow) were evident regionally in the retina, this apoptosis did not correlate with or account for most rod loss during RP progression.
Programmed cell removal (PrCR) by microglia

The high percentage of mutant rods being phagocytosed by microglia appears to account for most rod loss during disease progression.

(I-K) Expression of IBA1 prior to birth at E105 and after birth at P14 in central, mid-peripheral and peripheral regions of RP pig retinas.

IMMUNOSTAINING SHOWING IBA1+ MICROGLIA
ER protein calreticulin (CALR) is a DAMP - i.e. an “eat me” recognition signal for microglia, induced by ER stress in RP.

Upon ER stress, the ER protein calreticulin (CALR) translocates to the rod cell surface (G), where it serves as a damage-associated molecular pattern [DAMP], “eat me”, recognition signal for microglia. CALR co-localizes on the cell surface with CD73 (P73)(H).
CD47 is an immune checkpoint – i.e. “don’t eat me” recognition signal for microglia, induced by IVTA.

IVTA activates tyrosine receptor kinase B (TrkB) on rod surfaces establishing CD47 (P47) an immune checkpoint, “don’t eat me”, inhibition signal. CD47 is abundantly expressed (G) after IVTA but mostly absent (E) in untreated hosts.
CD47 immune checkpoint, “don’t eat me”, inhibition signal prevents microglial activation

The CD47 immune checkpoint, “don’t eat me”, inhibition signal reduces expression of chemotactic/inflammatory cytokines and microglial programmed cell removal (PrCR). The absence of microglial activation on P30 (J) after IVTA is contrasted with no treatment on P14 (K).
Preservation of rods allows IVTA to maintain cone OS

Representative immunostaining for cone opsin in the central and mid-peripheral retina showing identification of cone OS after IVTA at P65 (B,B’), but no cone OS after sham injection (C,C’).
IVTA maintains expression of glucose-dependent genes in the ONL

Txnip protein and FAS enzyme are important in aerobic glycolysis and OS synthesis. They are induced in IS, along with cone opsin in OS, after IVTA (B,D), but not after sham injection (A,C).
Conclusions

Chronic ER stress resulting from mutant misfolded protein in rods initiates activation of retinal microglia and removal of rods in RP. IVTA, a slow release intravitreal glucocorticoid, inhibits microglia by expression of a checkpoint inhibitor on rods, with surviving rods promoting glucose transport to cones for at least 60 days post-injection. The efficacy of an intravitreal glucocorticoid implant in achieving a similar effect is being studied.