Intravitreal triamcinolone acetate promotes rod and cone survival in Retinitis Pigmentosa

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Purpose:

An unfolded protein response (UPR) initiated in response to ER stress, such as mutant rhodopsin (RHO), can lead to loss of rod photoreceptors and Retinitis Pigmentosa (RP). Cones are dependent upon rods for glucose transport, for assembly of outer segments (OS). Retinal microglia phagocytosis initiates the demise of rods. We investigated the possibility of pharmacologically inhibiting the activation of microglia by the intravitreal injection of a slow-release corticosteroid (triamcinolone acetate) [IVTA].

Methods:

Wild type (WT) and P23H RHO mutant RP pig littermates were followed for retinal apoptosis, expression of cytokines, microglial migration and engulfment of mutant rods, and effects of IVTA injection at different ages and stages of retinal degeneration. Based on standard deviations derived from our previous extensive studies in WT and RP animals, we calculated three samples would be sufficient to detect a 30% change with a confidence of 0.95 in each of these measurements. All of the changes (e.g., WT vs. RP and control vs. treated) in ERG, OKR, ONL rows and OS number exceeded 30%. Each experiment was repeated at least three times.

Results:

Rod loss in pig RP does not correlate with apoptosis suggesting that rod removal is occurring primarily by a non-apoptotic mechanism. Programmed cell removal (PrCR) by microglia is responsible for most rod loss resulting the expression of multiple retinal chemotactic and microglial activating cytokines. Upon ER stress, the ER protein calreticulin (CALR) translocates to the rod cell surface, where it serves as a damage-associated molecular pattern [DAMP], “eat me”, recognition signal for microglia. IVTA activates tyrosine receptor kinase B (TrkB) on rods establishing a CD47 immune checkpoint, “don’t eat me”, recognition signal inhibiting expression of chemotactic/inflammatory cytokines and microglial PrCR. IVTA-mediated rod survival is able to maintain cone glucose transport and OS synthesis for at least 60 days post-injection.

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.