A P347L Rhodopsin Transgenic Rabbit Model of Retinitis Pigmentosa

Purpose: The transgenic P347L rabbit model of autosomal dominant retinitis pigmentosa (RP) represents a new and valuable tool in the exploration of RP fulfilling a convenient large eye need. Our goal was to assess the dependence of retinal remodeling on cone survival in the Tg P347L rabbit model of autosomal dominant RP.

Methods: 3 Tg P347L rabbits (3, 4, 10 months) were euthanized via intraperitoneal urethane, eyes enucleated and retinas incubated in vitro for excitation mapping with 1-amino-4-guanidobutane (AGB). Retinas were incubated 10 min at 35 deg C in oxygenated Ames-Hepes medium + 5 mM AGB with/without iGluR agonists (KA 50 μM, NMDA 1 mM), followed by fixation, embedding in epoxy resins and serial sectioning at 200 nm. Retinal neurons were classified by computational molecular phenotyping and electroretinography was performed to assess the state of rod loss prior to tissue harvest.

Results: As in human retina, progressive rod-specific degeneration in the Tg P347L rabbit leads to complete loss of rods (and rod signaling) and extensive survival of extremely deconstructed cones that prevent onset of gross remodeling, preserving iGluR-coupled signaling to horizontal and bipolar cells. Also similar to human retina, surviving bipolar cells show evidence of neurite sprouting and potential reprogramming by up-regulation of iGluR expression.

Conclusions: The Tg P347L rabbit model mimics human disease, including cone-mediated preservation of bipolar cell signaling and triggering of remodeling and thus represents superior model for cell biological, progenitor cell transplantation and prosthetic studies.

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Summary: The P347L rabbit mimics the autosomal dominant focal, cone sparing RP found in human, the rd116v mouse and P470S porcine models. Rods survive up to 3 months and cones survive up to 10 months, but rod bipolar cells lose rod contacts and make ectopic cone contacts, expressing iGluRs, effectively switching phenotype from ON to OFF. By 10 months, no expression of opsin can be found in cones with their presence prevents gross retinal remodeling. The P347L rabbit model will allow the continued exploration of axonogenesis, neoutogenesis and retinal remodeling. Additionally, the large eye allows for a more convenient model for cell transplantation, surgical interventions and exploration of bionic prosthetic studies. To the best of our knowledge, this is the first transgenic rabbit model of retinal degeneration. Like other retinal degenerative diseases, the speed of retinal degeneration is dependent on the expression level of the transgene.