AB012. Retinopathy in a mouse model for Zellweger spectrum disorder

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Background: Zellweger spectrum disorder (ZSD) is an autosomal recessive disease caused by mutations in any one of 13 PEX genes whose protein products are required for peroxisome assembly. Retinopathy leading to blindness is one of the major untreatable handicaps faced by patients with ZSD but is not well characterized, and the requirement for peroxisomes in retinal health is unknown. To address this and to inform future therapeutic studies, we examined the progression of retinopathy in our murine model for the common PEX1-G843D allele.

Methods: Retinal electrophysiology (ffERG) and histology were performed in a cohort of Pex1-G844D (equivalent to human G843D) mice from 2 to 32 wks. Visual acuity was assessed using optokinetics. The levels of PEX1-G843D protein, its binding partner Pex6, and its putative ligand Pex5 (the peroxisome enzyme receptor) in the retina were determined by immunoblotting. Peroxisome biochemical metabolites in the whole eye and retina were measured using LC/MSMS. Retinal immunohistochemistry was used to visualize various cell types.

Results: Cone ffERG response in the mutants remained residual (5% that of control) regardless of age. Maximal rod-mediated responses (50–70% of control) was reached at 4–6 wks, and then progressively decreased with age. B-waves were affected more severely than a-waves, while high frequency ERG components (oscillatory potentials) are better preserved than low frequency components (a- and b-waves). Visual evoked potential was diminished at 32 weeks. Assessment of visual acuity using optokinetics showed low visual reflexes by 11–13 weeks of age. We found normal amounts of Pex1-G844D, Pex6, and Pex5 protein in retina, suggesting that the mutated protein is not degraded. Measurement of peroxisome metabolites showed elevated very long chain fatty acids (VLCFA) and decreased plasmalogens in the whole eye, indicative of peroxisome dysfunction. In the retina, VLCFAs were not elevated, and only C22:6 (docosahexaenoic acid) was decreased of the plasmalogens measured. There were normal amounts and localization of Pex1-G844D and Pex6, as well as normal staining of rod cells, amacrine cells, horizontal cells, Müller cells, and synaptic layers. Cone cell and bipolar cell nuclei were preserved while their cell bodies extending to the OSL and OPL, or OPL to IPL, respectively, were absent. Staining for Glial fibrillary acidic protein (GFAP) was present in mutant retinas, which could indicate photoreceptor degeneration, increased oxidative stress, and/or Müller cell de-differentiation. Peroxisomes were recently shown to cluster at the base of the OSL, which is continuously regenerated due to light exposure, and is likely to require several peroxisome-dependent processes. To examine a functional link between light exposure and visual impairment, we performed dark adaptation from 2–4 or 4–6 wks. However, there was no improvement in ERG responses in our mutant mice.

Conclusions: In summary, we have shown that Pex1-G844D mice have poor functional vision and develop a progressive cone-rod retinal dystrophy. Thus far, cellular changes are found only in the cone cells and bipolar cells, which lack the necessary physical connections to receive and transfer light-induced signals. We determined that the mechanism(s) underlying the abnormal ERG response is not influenced by light exposure. This murine natural history study allows us to pinpoint ages and accurate clinical endpoints for therapeutic interventions. It will also guide us in future studies of human retinal degeneration in ZSD.

Keywords: Zellweger spectrum disorder (ZSD); peroxisome disorder; PEX1

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