Modeling the Progression of Diabetic Retinopathy Using the BXD79 Mouse Strain

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Diabetic retinopathy (DR) is a microvascular disease associated with diabetes mellitus (DM) complications.

- Alterations in blood flow, vasodilation, & blood sugar can negatively affect the vasculature & neurons of the retina, resulting in blindness.
- Animal models elicit a better understanding of the development, genetics, & mechanisms of multiple retinal degenerative diseases seen in humans.
- Despite the complex etiology making DR difficult to model in animals, a spontaneous model of DR—the BXD79 mouse—has been uncovered.
- This model displays naturally occurring phenotypes of hyperglycemia, obesity, vascular leakage, cataracts, & retinal degeneration.
- This ongoing study seeks to investigate the etiology and pathology of DR in the BXD79 model.

The BXD79 strain was found from an AMD genetic study; however, observed to be different in phenotype.

Single nucleotide polymorphism analysis (SNPs) reveals 9 predicted deleterious SNPs linked to many AMD & DR genes. More specifically the genes involved in angiogenesis, Vegfa, Kdr, & Flt1.

BXD79 & C57B/6J (wildtype) mice underwent genetic testing (SNPs), reveals 9 predicted deleterious SNPs. The BXD79 strain was found from an AMD genetic study; however, observed to be different in phenotype.

- Excessive sugar along with other DR-related phenotypes loosen tight junctions of the inner retinal vascular endothelium leading to vascular leakage & edema, respectively.
- Functional test results (Fig. A & B) suggest a progressive reduction in retinal function. A disruption of retinal & vascular integrity (Fig. C & D) from 9 to 18 months.
- IHC reveal minimal mislocalization of innervator segment proteins, thus appearing normal (Fig. E). However, a loss of ganglion cell bodies & dendrites (Fig. F), showing of the inner plexiform layer (Fig. H), and upregulation of KDRI (Fig. I & J).
- The combination of genetic mutations contributing to neurodegeneration & ganglion cell layer death can likely be linked to Vegfa and Vegf receptors (Rt) and KDR.

- The BXD79 strain was found from an AMD genetic study; however, observed to be different in phenotype.

Support

ERG

OKN

Wildtype

BXD79

IHC

Wildtype

BXD79

Results/Discussion

Fig. A. Electroretinograms (ERGs) of wildtype (WT) & BXD79 from ages 6-18 months assessing retinal function. Data reveals dysfunction starting around 9 months in BXD79.

Fig. B. Optokinetic nystagmography (OKN) of WT & BXD79 ages 6-18 months accessing visual acuity & contrast sensitivity. Data reveals loss of function starting at 9 months, persisting to 18 months in BXD79.

Fig. C-D. C) Fluorescent angiography (FA) of WT & BXD79 (6-18 months) examining the vasculature of the retina. Vascular abnormalities & leakage are seen in BXD79 around 9 months. D) Optical coherence tomography (OCT) of WT & BXD79 (6-18 months) assessing the retinal layers reveals retinal thickening around 12 months.

Fig. E-J. Fluorescent immunohistochemistry (IHC) of WT & BXD79 at 18 months examining the localization of proteins in the retina. Data depicts fairly normal photoreceptors (E); however, ganglion cell body & dendritic loss (F), increased retinal stress with the upregulation of GFAP (G), retinal thinning (H), & upregulation of KDR (I-J) can also be observed. Scale bars = 20 μm.