Dysregulated ABCA1 increases risk for pathogenesis of normal tension glaucoma

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Glaucoma is the first leading cause of blindness in Japan. An elevated intraocular pressure (IOP) has long been considered to directly damage retinal ganglion cells (RGCs) thereby causing blindness. However, a growing body of evidences has shown that glaucoma is affected by many risk factors other than IOP. Recent genome wide association studies (GWAS) have identified that single nucleotide polymorphism (SNP) of gene encoding ATP-binding cassette transporter A1 (*ABCA1*) is the highest risk for glaucoma. Here, we report that deficiency of astrocytic ABCA1 causes pathogenesis of glaucoma. We found that conventional ABCA1 knockout (KO) mice show an increase in the number of apoptotic RGCs at middle-age (12 months old). Deficiency of ABCA did not cause IOP elevation. Expression level for *Abca1* mRNA was significantly higher in optic nerve head through optic nerve, where astrocytes are highly accumulated. Magnetic cell separation has revealed that *Abca1* was highly enriched in astrocyte and Müller cell fraction. To clarify the role of astrocytic ABCA1, we generated astrocyte-specific ABCA1 knockout (cKO) mice. The cKO mice had no IOP elevation. The number of apoptotic RGCs was increased in middle-aged cKO mice. The middle-aged cKO mice also showed impaired visual functions. Taken together, our data showed that (1) ABCA1 has no impact on IOP; (2) loss-of-function of ABCA1 is involved in glaucoma; and (3) ABCA1 in glial cells contributes to pathogenesis of normal tension glaucoma.