The ROYAL COLLEGE of OPHTHALMOLOGISTS

COMMENT

A newly anticipated role for Laptm4b in retinal outer segment development

Brianna Rodriguez[1], Maribel Vazquez[1] and Li Cai[1]✉

Eye (2022) 36:1342–1343; https://doi.org/10.1038/s41433-022-01996-6

Retinal degeneration is caused by a group of progressive neurological disorders that may arise from genetic mutations and environmental/pathological damage, leading to visual impairment or visual loss. Common retinal degenerative diseases in adults include age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, and retinitis pigmentosa. The prevalence of these diseases ranges from millions to hundreds of millions [1–4] and is projected to increase with aging global population.

Current treatments for retinal degeneration include cell transplantation, drug delivery, and gene therapy [5–7]. Gene therapy has produced transformational knowledge in retinal treatments by examining the transient expression of different types of enzymes, transcription factors, and genes that mediate retinal development and function. These factors are currently highly examined as potential therapeutics for retinal repair and regeneration. Moreover, genetic engineering is an emerging research field, in which direct manipulation of one or more genes can be used to determine their function or role. For example, gene knockdown is often utilized to determine the role of a certain gene by observing how the function or development of the retina is altered through the loss-of-function of the gene.

Our lab recently developed a computational pipeline [8] was used to identify functional genes significant to development, as well as expression patterns of a variety of genes in the retina. Many of these genes that showed peak expression levels were novel in regard to their function in the retina, including Lysosomal-associated Transmembrane 4-Beta (*Laptm4b*), *Pde8b*, and *Nr1h4*. To further confirm a functional role of *Laptm4b* during retinal development, immunohistochemistry was employed to detect its expression in the developing mouse retina at postnatal day 14 (P14). Immunofluorescence staining revealed that the expression of *Laptm4b* was concentrated in the mouse outer segment (OS) of the retina, whose development reaches peak levels around P14 [9], and overlaps with the staining pattern of the known OS marker, Rhodopsin. This suggests that *Laptm4b* function may be important, specifically, for the development of the OS of the retina.

Laptm4b belongs to a membrane spanning lysosomal LAPTM family of proteins [10, 11] and has been implicated in a number of functions and roles within the human body. Some of these roles/functions include membrane composition [12], exosome transport [13], tumor development [11, 14, 15], sphingolipid regulation [12, 13], and autophagy [10, 14, 15]. Previous findings regarding *Laptm4b* include: (1) affecting the subcellular distribution of cytotoxic drugs [10], (2) regulating epidermal growth factor receptor signaling by acting on its lysosomal sorting, degradation, and autophagy initiation [10, 14, 15], (3) being a novel oncogene that promotes tumorigenesis and may be a biomarker for several cancers [11, 14, 15], (4) being a determinant of glycosphingolipid profile and membrane properties of small extracellular vesicles for cellular transport and waste removal [12], and (5) association with molecules within the sphingolipid network for exosome release, such as ceramide (Cer) [12, 15].

While *Laptm4b* has been studied in many research areas, such as exosome release and cancer research, its functional role in the retina has been yet to be examined. Sphingolipids have been recently associated with many retinal degenerative diseases including AMD and glaucoma, and recent findings have linked *Laptm4b* to sphingolipids. Autophagy has also been implicated in retinal development and associated with *Laptm4b*. These findings have led to the belief that *Laptm4b* may be involved in the retina during the developmental stages.

Building a connection between the role(s) of *Laptm4b* on retinal development will provide novel findings regarding OS development, as well as retinal degeneration. This newfound link may contribute to the efforts toward developing treatments and/or cures for vision loss and blindness caused by retinal degenerative diseases.

REFERENCES

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:e106–16.
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121:2081–90.
3. Iannaccone A, Berdia J. Retinitis pigmentosa: national organization for rare diseases. 2021. https://rarediseases.org/rare-diseases/retinitis-pigmentosa/.
4. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology. 2021;128:1580–91.
5. Kim HM, Woo SJ. Ocular drug delivery to the retina: current innovations and future perspectives. Pharmaceutics. 2021;13:108.
6. MacLaren RE, Bennett J, Schwartz SD. Gene therapy and stem cell transplantation in retinal disease: the new frontier. Ophthalmology. 2016;123:S98–S106.
7. Mut SR, Vazquez M. Commentary: organ cultures for retinal diseases. Front Neurosci. 2021;15:714094.

[1]Department of Biomedical Engineering Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA. ✉email: lcai@soe.rutgers.edu

Received: 28 November 2021 Revised: 3 February 2022 Accepted: 16 February 2022
Published online: 25 February 2022

8. Colon A, Hirday R, Patel A, Poddar A, Tuberty-Vaughan E, Fu T, et al. A computational pipeline for functional gene discovery. Sci Rep. 2021;11:23522. https://doi.org/10.1038/s41598-021-03041-0.
9. Kim J-W, Yang H-J, Oel Adam P, Brooks Matthew J, Jia L, Plachetzki David C, et al. Recruitment of rod photoreceptors from short-wavelength-sensitive cones during the evolution of nocturnal vision in mammals. Developmental Cell. 2016;37:520–32.
10. Blom T, Li S, Dichlberger A, Bäck N, Kim YA, Loizides-Mangold U, et al. LAPTM4B facilitates late endosomal ceramide export to control cell death pathways. Nat Chem Biol. 2015;11:799–806.
11. Wang F, Wu H, Zhang S, Lu J, Lu Y, Zhan P, et al. LAPTM4B facilitates tumor growth and induces autophagy in hepatocellular carcinoma. Cancer Manag Res. 2019;11:2485–97.
12. Dichlberger A, Zhou K, Bäck N, Nyholm T, Backman A, Mattjus P, et al. LAPTM4B controls the sphingolipid and ether lipid signature of small extracellular vesicles. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866:158855.
13. Yuyama K, Sun H, Mikami D, Mioka T, Mukai K, Igarashi Y. Lysosomal-associated transmembrane protein 4B regulates ceramide-induced exosome release. FASEB J. 2020;34:16022–33.
14. Meng Y, Wang L, Chen D, Chang Y, Zhang M, Xu JJ, et al. LAPTM4B: an oncogene in various solid tumors and its functions. Oncogene. 2016;35:6359–65.
15. Chu C, Niu X, Ou X, Hu C. LAPTM4B knockdown increases the radiosensitivity of EGFR-overexpressing radioresistant nasopharyngeal cancer cells by inhibiting autophagy. Onco Targets Ther. 2019;12:5661–77.

AUTHOR CONTRIBUTIONS

LC and BR conceptualized the idea. MV contributed to the preparation of the paper. BR wrote the paper. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work was supported by funding from the National Institutes of Health under award number EY031439-02 (LC and MV).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Li Cai.