Mice With Cholesterol in Bruch's Membrane: Have We Arrived?

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The earliest discovered and majority druse component by volume is lipid. Further, aging, the largest risk factor for age-related macular degeneration (AMD), features a marked lipidization of human Bruch's membrane (BrM). Both phenomena are attributed to esterified cholesterol (EC)-rich lipoprotein particles containing apolipoproteins B and E. These form a hydrophobic barrier between outer retinal cells and choriocapillaris and pool to form soft drusen and basal linear deposit in AMD macula. Gene expression and secretion studies implicate the retinal pigment epithelium as a lipoprotein secretor. With evidence from epidemiology and genetics, these findings prompted the atherosclerosis-inspired response-to-retention theory of AMD lesion biogenesis.¹

Fujihara, Cano, and Handa² tested this hypothesis by analyzing chorioretinal cellular and tissue expression and deposition of apoB100 lipoproteins in mice systemically deficient in endogenous apoB48. Notably, these investigators used specific filipin histochemistry to demonstrate EC, electron microscopy of tissues postfixed optimally for extracellular lipid, and metabolic labeling to confirm apolipoprotein synthesis. Although EC and solid electron-dense particles localized to BrM, the absence of extracellular deposits led the authors to conclude that secretion alone is insufficient to produce drusen and that other factors are required, even in older animals.

Although mice lack maculas and get criticized for minimally replicating AMD pathology, they are nevertheless excellent experimental systems. The laser-injury model of choroidal neovascularization differed importantly from human AMD yet was essential for translating VEGF inhibitors to the clinic³ while VEGF biology was independently explored. ApoB100 mice now join apoE^{-/-4} and apoB100, LDLR^{-/-5} mice as commercially available strains exhibiting BrM EC, with apoB100 the best characterized to date. Fujihara et al. should be lauded for evincing EC in the right place without complex animal husbandry, thus achieving molecular and anatomical accuracy if not physical drusen. While mechanisms of BrM lipoprotein source, composition, and retention require future research, apoB100 mice will be attractive for investigating the removal of BrM lipids for atrophic AMD.⁶

Acknowledgments

Supported by National Institutes of Health Grant EY06109 (CAC) and unrestricted funds to the Department of Ophthalmology from Research to Prevent Blindness, Inc., and EyeSight Foundation of Alabama.

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