Genetic LAMP2 deficiency accelerates the age-associated formation of basal laminar deposits in the retina

Shoji Notomi[a,b], Kenji Ishihara[a], Nikolaos E. Efstathiou[a], Jong-Jer Lee[a,c], Toshio Hisatomi[b], Takashi Tachibana[b], Eleni K. Konstantinou[a], Takashi Ueta[a], Yusuke Murakami[b], Daniel E. Maidana[a], Yasuhiro Ikeda[b], Shinji Kume[d], Hiroto Terasaki[e], Shozo Sonoda[e], Judith Blanz[f], Lucy Young[a], Taiji Sakamoto[e], Koh-Hei Sonoda[b], Paul Saftig[g], Tatsuro Ishibashi[b], Joan W. Miller[a], Guido Kroemer[h,i,j,k,l,1], and Demetrios G. Vavvas (Δημήτριος Γ. Βάββας)[a,1]

[a]Angiogenesis Laboratory, Ophthalmology Department, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA 02114; [b]Department of Ophthalmology, Kyushu University, Fukuoka 812-8582, Japan; [c]Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan; [d]Department of Medicine, Shiga University of Medical Science, Shiga 520-2192, Japan; [e]Department of Ophthalmology, Kagoshima University, Kagoshima 890-8520, Japan; [f]Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611; [g]Institute of Biochemistry, Kiel University, Kiel D-24098, Germany; [h]Metabolism, Cancer & Immunity Laboratory, INSERM U1138, Centre de Recherche des Cordeliers, Sorbonne Université, Université de Paris, Paris 75006, France; [i]Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, Villejuif 94800, France; [j]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris 75015, France; [k]Suzhou Institute for Systems Medicine, Chinese Academy of Medical Sciences, Suzhou 100050, China; and [l]Department of Women's and Children's Health, Karolinska Institute, Karolinska University Hospital, Stockholm 171 76, Sweden

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The early stages of age-related macular degeneration (AMD) are characterized by the accumulation of basal laminar deposits (BLamDs). The mechanism for BLamDs accumulating between the retinal pigment epithelium (RPE) and its basal lamina remains elusive. Here we examined the role in AMD of lysosome-associated membrane protein-2 (LAMP2), a glycoprotein that plays a critical role in lysosomal biogenesis and maturation of autophagosomes/phagosomes. LAMP2 was preferentially expressed by RPE cells, and its expression declined with age. Deletion of the *Lamp2* gene in mice resulted in age-dependent autofluorescence abnormalities of the fundus, thickening of Bruch's membrane, and the formation of BLamDs, resembling histopathological changes occurring in AMD. Moreover, LAMP2-deficient mice developed molecular signatures similar to those found in human AMD—namely, the accumulation of APOE, APOA1, clusterin, and vitronectin—adjacent to BLamDs. In contrast, collagen 4, laminin, and fibronectin, which are extracellular matrix proteins constituting RPE basal lamina and Bruch's membrane were reduced in *Lamp2* knockout (KO) mice. Mechanistically, retarded phagocytic degradation of photoreceptor outer segments compromised lysosomal degradation and increased exocytosis in LAMP2-deficient RPE cells. The accumulation of BLamDs observed in LAMP2-deficient mice was eventually followed by loss of the RPE and photoreceptors. Finally, we observed loss of LAMP2 expression along with ultramicroscopic features of abnormal phagocytosis and exocytosis in eyes from AMD patients but not from control individuals. Taken together, these results indicate an important role for LAMP2 in RPE function in health and disease, suggesting that LAMP2 reduction may contribute to the formation of BLamDs in AMD.

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Cellular and extracellular debris accumulate in age-associated disorders such as atherosclerosis, Alzheimer disease, and age-related macular degeneration (AMD). AMD is the leading cause of central vision loss in developed countries and exists in 2 forms: the neovascular or "wet" form (~15%) and the non-neovascular or "dry" form (85%) (1, 2). Dry AMD, for which effective treatments are elusive (1), is characterized by a particular form of extracellular debris accumulating with age, the so-called drusen (3, 4). Importantly, large drusen are associated with the risk of developing late AMD—namely, neovascular AMD or geographic atrophy (5). Histopathological examination of AMD specimens has identified material between the retinal pigment epithelium (RPE), a monolayer of cells beneath the neurosensory retina, and the underlying Bruch's membrane (BrM). The debris accumulating beneath the RPE can be classified into 2 categories: basal linear deposits (BLinDs) and basal laminar deposits (BLamDs). BLamDs are the most prevalent histopathologic finding in early AMD (6). However, the mechanism of BLamD generation remains unclear.

One of the major functions of RPE cells is the phagocytosis of photoreceptor outer segments (POSs) that are shed daily from retinal photoreceptor cells. Phagocytic removal of POSs may be involved in a unique age-related change in the RPE, lipofuscin accumulation. The cargo of lipofuscin granules includes the remnants of POSs that are being degraded (7, 8). Although the

Significance

Extracellular tissue debris accumulates with aging and in the most prevalent central-vision-threatening eye disorder, age-related macular degeneration (AMD). In this work, we discovered that lysosome-associated membrane protein-2 (LAMP2), a glycoprotein that plays a critical role in lysosomal biogenesis and maturation of autophagosomes/phagosomes, is preferentially expressed in the outermost, neuroepithelial layer of the retina, the retinal pigment epithelium (RPE), and contributes to the prevention of ultrastructural changes in extracellular basolaminar deposits including lipids and apolipoproteins. LAMP2 thus appears to play an important role in RPE biology, and its apparent decrease with aging and in AMD specimens suggests that its deficiency may accelerate the basolaminar deposit formation and RPE dysfunction seen in these conditions.

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The authors declare no competing interest.

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[1]To whom correspondence may be addressed. Email: kroemer@orange.fr or vavvas@meei.harvard.edu.

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