Understanding RPE Lipofuscin

In the Research Highlight article titled “Rethinking A2E,” Smith et al.1 offer interpretations of the recent paper by Ablonczy et al.,2 titled “Lack of Correlation Between the Spatial Distribution of A2E and Lipofuscin Fluorescence in the Human Retinal Pigment Epithelium.” Readers will benefit from further discussion.

Although not acknowledged by Smith et al.,1 RPE lipofuscin consists of multiple fluorescent components, only one of which is A2E. While the excitation maxima of the published lipofuscin fluorophores varies from approximately 440 to 510 nm, they have similar emission maxima (~600 nm) that also match that of fundus autofluorescence (AF).3–5 Thus, the terms lipofuscin and A2E are not synonymous.

Smith et al.1 revisited the 2006 study wherein he and colleagues tested RPE lipofuscin, (measured as increased fundus AF in the immediate surround of geographic atrophy [GA]) as a forerunner of GA progression.6 They concluded that single pixels exhibiting higher AF did not have a greater probability of converting to GA and, thus, that increased AF is not a factor driving the enlargement of GA. Nonetheless, current fundus AF images do not have sufficient spatial resolution to allow single pixel values to inform disease progression.7 Besides, Curcio and colleagues8 recently attributed hyperautofluorescence in the junctional zone of GA, at least in some cases, to abnormal overlap of RPE cells. This is a scenario previously proposed.9 Since disease-related changes are already present cannot be predictive of impending GA progression, the presence of vertically superimposed RPE cells at the edge of GA is not instructive of the role of lipofuscin in AMD nor of its value as a therapeutic target.

Abca4−/− mice, on the other hand, being burdened with increased A2E,10,11 are informative of the impact of RPE lipofuscin on the retina. These mice exhibit increased expression of proteins of the complement system, excessive complement activation, downregulation of complement inhibitory proteins, and Bruch’s membrane thickening due to basal laminar deposits.12 In albino Abca4−/− mice, loss of photoreceptor cells is accelerated.5,13 Similar abnormalities are associated with enhanced deposition of the lipofuscin fluorophores A2E and all-trans-retinal dimer in RPE of RdB8−/−/Abca4−/− mice.13,15 These findings indicate a link between RPE lipofuscin, on the one hand, and complement dysregulation and Bruch’s membrane changes on the other.

And, of course, in recessive Stargardt disease, augmented RPE lipofuscin deposition precedes RPE atrophy and vision loss.16

Other known RPE lipofuscin fluorophores5,14 are of no less interest than A2E as they share key structural features. Like A2E, other bisretinoid lipofuscin fluorophores are subject to photooxidation and photodegradation with all-trans-retinal dimer being even more prone to oxidation than A2E.15,17 The process of photodegradation is not benign as it leads to the release of aldehyde-bearing molecular fragments that can be damaging.18 Some of these fragments are small dicarboxyls that are known to react with and damage protein provoking the formation of advanced glycation end products (AGE).19 Advanced glycation end products incite inflammatory processes and given their presence in drusen,20,21 reflect a link between RPE bisretinoid lipofuscin and the formation of sub-RPE deposits. In in vitro models, A2E and all-trans-retinal dimer incite complement activation.22

Grey and colleagues23 observed that oxidized A2E does not accumulate with age. This finding would not be surprising, if the oxidized species were degrading into damaging, small molecular fragments, as shown.18 Indeed, lower levels of A2E in the macula may be a consequence of greater lipofuscin photodegradation in central RPE with the latter explaining, at least in part, the propensity of the macula for disease.

Interpretations of fundus autofluorescence are complex. While fundus AF generally signals the RPE, under some conditions intensified AF may be a read-out of amplified lipofuscin formation in impaired photoreceptor cells. Examples of this are the rapid onset of elevated fundus AF that colocalizes with scotomas associated with acute macular neuroretinopathy,24 the hyperautofluorescent rings observed in fundus AF images of RP patients,25 and the intense autofluorescence emanating from photoreceptor cell rosettes in a mouse model of experimental retinal detachment.26 Increased fundus AF associated with photoreceptor cell dysfunction after RPE atrophy or loss may explain why Smith and colleagues27 observed that areas of AF images exhibiting decreased or absent AF indicative of RPE atrophy can subsequently exhibit increased AF.

Relatively lower levels of A2E in the macula could be intriguing in other ways. For instance, such a finding could indicate that local conditions in photoreceptor cells influence the species of bisretinoid generated in human photoreceptors. As precedent for this line of thinking, note that the lipofuscin fluorophore all-trans-retinal dimer is more abundant in RdB8−/− mice than in Abca4−/− mice, while the reverse is true for A2E.14 Smith et al.,1 express the importance of finding the missing fluorophore. Given the relatively long-wavelength spectral characteristics of lipofuscin, the most likely candidate fluorophores would be other bisretinoids or related molecules. Other contenders, such as retinaldehyde, flavoproteins, AGE-modified proteins or heme, do not have the spatial and/or spectral features consistent with a substantial contribution to fundus AF.5,28,29

While the view that RPE lipofuscin is a primary factor in initiating AMD is not proven, evidence indicating that lipofuscin is a participant in the etiology of AMD should not be ignored. Instead, efforts could be made to understand the possible intersection of RPE lipofuscin-related events with other factors, including age-related lipid accumulation in Bruch’s membrane.

Janet R. Sparrow1
John E. Dowling2
Dean Bok3

1Departments of Ophthalmology and Pathology and Cell Biology, Columbia University, New York, New York; 2Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts; and 3Jules Stein Eye Institute, University of California at Los Angeles, Los Angeles, California. E-mail: jrs88@columbia.edu

References


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