Understanding RPE Lipofuscin

In the recent paper by Allingham et al., fundus autofluorescence (AF) was studied in relation to progression of geographic atrophy (GA) in age-related macular degeneration (AMD), a subject of intense ongoing interest. The primary conclusion was that rim area focal hyperautofluorescence (RAFH) was positively correlated with GA progression rate ($r = 0.49$, $P < 0.001$), consistent with Bearelly et al. The purpose of this joint letter is further clarification of related important issues. The relationship between AF and GA progression is complex, and the authors correctly noted that there are multiple proposed etiologies of AF in the context of GA. Correlation of clinical imaging with histopathologic findings and mechanistic insights from studies of animal models has the potential to shed new light on both the mechanism and implications of AF secondary to dry AMD. To this point, the question of correlation of increased AF in the rim area of GA with future GA growth is really two distinct questions, one global and one local. First, is the total area of AF in the rim area correlated with total GA area progression? Second, do the local areas of AF in the rim area correlate spatially with GA progression in those same areas? The answer to the first question, as demonstrated in the paper under discussion and Bearelly et al. is yes. However, the answer to the second question, as was demonstrated by one of us (RTS) in Hwang et al., is no. Indeed, as also pointed out in Allingham et al., while AF has not been shown to predict the location of future GA growth, morphologic features identifiable on spectral domain optical coherence tomography possess a significant advantage over AF in doing so.

Why is this distinction important? The prevailing theory behind the association of AF and GA is that increasing accumulation of lipofuscin, the source of fundus AF, within RPE is toxic and results in RPE cell death and possibly other manifestations of dry AMD. Thus, lipofuscin toxicity in this theory would be expected to cause local effects, and one would expect areas of increased lipofuscin as shown by AF to be at higher risk for conversion to GA. However, the conclusions of Hwang et al. do not support the concept that regions of high AF are destined to become GA. On the other hand, the global association between AF and GA studied in Allingham et al. does not require toxicity but simply confirms that the metric of total RAFH is a good predictor of total disease progression, by whatever mechanism.

The methodology for reaching these conclusions is therefore also important. A technical point concerns the image analysis algorithms used in Allingham et al. versus the one used in Hwang et al. The present paper states, "[T]he algorithm used by Hwang et al. uses a single threshold across the entire image to define RAFH, whereas ours uses a combination of a global threshold and a local area intensity measurement." While it is technically correct that the algorithm in Hwang et al. uses a single threshold, it also compensates for local AF intensity variation, but by a different method. It is based on AF background leveling, with a background model for each image built from quadratic polynomials constructed and blended in 12 zones of the macula. It is only after subtraction of the background model that uniform thresholds are applied, which can be considered as a local thresholding technique. A head-to-head comparison is needed to assess the effectiveness of each of these two techniques.

Perhaps now is a good time to reevaluate these questions about lipofuscin and GA with more high-quality data. The global relationship between RAFH and GA seems established from the present paper and others. As noted in Allingham et al., "There are multiple proposed mechanisms of hyperautofluorescence at GA lesion border." Replication of the findings of Hwang et al. in a larger dataset would have interesting mechanistic implications and would be a good place to start.

R. Theodore Smith
Sina Farsiu
Michael Allingham

1Department of Ophthalmology, NYU Langone Medical Center, New York, New York, United States; 2Department of Biomedical Engineering, Duke University, Durham, North Carolina, United States; and the 3Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina, United States.

E-mail: roland.smith@nyumc.org

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