Rethinking A2E

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The article "Lack of correlation between the spatial distribution of A2E and lipofuscin fluorescence in the human retinal pigment epithelium," by Ablonczy and colleagues,[1] forces us to re-evaluate 2 decades of dogma, and has potentially profound implications for the role (or lack thereof) of the bisretinoid A2E in human retinal degenerations. Using the elegant new method of imaging mass spectrometry, this manuscript clearly and convincingly shows that, unlike in the mouse retina where A2E and lipofuscin topographies closely correspond, the human retina has significant RPE lipofuscin throughout periphery but an A2E trough in the macula.

Why did we believe that A2E was abundant in the macula in the first place? The original studies identifying A2E used RPE from whole eyecups, in which the macula was perhaps only 10% of the sample. When HPLC and mass spectrometry were used for defined punches of macula and periphery,[2] it was apparent that the two regions might differ starkly in A2E content.

A second widely held belief is that lipofuscin, particularly A2E, is a toxic agent in retinal degenerations such as AMD. The involvement of clinical hyperfluorescence attributable to lipofuscin and, by inference, A2E in human retinal disease had been questioned by publications showing that the hyperfluorescence surrounding the geographic atrophy of AMD only poorly predicted RPE death,[3] and was explained by stacked cells rather than high intracellular lipofuscin content.[4] Thanks to Ablonczy et al., it is now particularly difficult to blame A2E specifically for macular insult if A2E is scarcely present.[1] The rationale for several drugs that target A2E formation for macular diseases, currently in clinical and preclinical trials, rests on increasingly doubtful bases.

We need to find the missing macular fluorophore. Once we unlearn what we thought was true, the work begins anew.

References

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