

# Mini-Chaperones for Early AMD

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This issue of IOVS presents a novel strategy to develop treatment for nonexudative age-related macular degeneration (dry AMD) that derives from the natural, protective response of RPE cells to cellular stress. Oxidative stress is implicated in AMD pathogenesis and results in the upregulation of small heat shock proteins that act as molecular chaperones to prevent cellular apoptosis and minimize misfolded peptide reactivity. The  $\alpha$ -crystallin family of heat shock proteins is associated with drusen formation and dry AMD. Proteomic analysis shows  $\alpha$ B-crystallin to be a major protein constituent of AMD-associated drusen<sup>1</sup> and  $\alpha$ B-crystallin is overexpressed specifically in RPE cells localized over drusen.<sup>2</sup> Furthermore, RPE cell culture “disease in dish” models of drusen formation show upregulation of  $\alpha$ B-crystallin expression by stress with associated protection from apoptosis. Although crystallins have multiple actions that protect against the onset and progression of AMD, their use as pharmacologic agents has been limited by a lack of entry into cells, necessitating high concentrations of exogenously applied protein for effect.

Sreekumar and colleagues<sup>3</sup> have now harnessed the natural protective effect of crystallin chaperone proteins as potential pharmacologic agents by using small crystallin peptides that enter and appropriately affect RPE cells. The authors identified specific crystallin peptides that both readily enter fetal RPE cells via sodium-coupled transporters and then protect these cultures from oxidative stress-induced, caspase-mediated apoptosis. These effects of crystallin mini-chaperone peptides were enhanced using nanoparticle encapsulation to increase entry into RPE cells and obtain dosing levels reasonable for a dry AMD drug candidate. This important article introduces crystallin mini-chaperone peptides as a promising new approach toward the development of an effective therapy for early AMD.

## References

1. Crabb J, Miyagi M, Gu X, et al. Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2002;99:14682–14687.
2. De S, Rabin D, Salero E, Lederman P, Temple S, Stern J. Human retinal pigment epithelium cell changes and expression of alphaB-crystallin: a biomarker for retinal pigment epithelium cell change in age-related macular degeneration. *Arch Ophthalmol*. 2007;125:641–645.
3. Sreekumar PG, Clothe P, Sharma KK, et al. Antiapoptotic properties of  $\alpha$ -crystallin-derived peptide chaperones and characterization of their uptake transporters in human RPE cells. *Invest Ophthalmol Vis Sci*. 2013;54:2787–2798.