Abstract: 77

**Soft Drusen in Rhesus Macaques as a Translational Model for Early Age-related Macular Degeneration**

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**Purpose:**

Development of treatments for early or intermediate age-related macular degeneration (AMD) has been limited by the lack of an animal model, as most laboratory species do not possess a macula. Nonhuman primates are the only mammals to have a true macula and spontaneously develop drusen with age. Here, we characterize the long-term evolution and structure of soft drusen in rhesus macaques using multimodal retinal imaging over 2 years, followed by histologic and ultrastructural analyses.

**Methods:**

Multimodal imaging including fundus photography, spectral domain-optical coherence tomography (SD-OCT), and quantitative fundus autofluorescence (qAF) were used to characterize and track individual drusen lesions in 20 aged rhesus macaques (mean age 23.3 ± 2.7 years) over 2 years, followed by histologic analysis and transmission electron microscopy (TEM).

**Results:**

Drusen volume increased significantly over the 2 years (P = 0.009), with a mean increase of 0.012 mm³ (42%) at year 1 and 0.025 mm³ (86%) at year 2, comparable to drusen volume changes in human AMD. Although most drusen gradually increased in size (25.9%) or remained stable (27.9%), a portion spontaneously regressed (9.8%) or completely collapsed (10.7%) over 2 years, with 25.6% appearing de novo, consistent with the dynamic drusen remodeling seen in humans. Eyes with soft drusen exhibited lower qAF levels than age-matched controls, but many individual lesions were hyperautofluorescent. Interestingly, none of the animals exhibited choroidal neovascularization (CNV) or geographic atrophy (GA). Histologic analyses showed that soft drusen exhibit hypertrophy and dysmorphia of overlying retinal pigment epithelium (RPE), as seen in early and intermediate AMD, but do not exhibit RPE atrophy, RPE migration, or photoreceptor degeneration characteristic of GA or nascent GA. Ultrastructure of soft drusen showed abundant lipid particles within Bruch’s membrane and AMD-related basal linear deposits (BlinD) resembling those in human drusen.

**Conclusions:**

Soft drusen in rhesus macaques demonstrate progression, dynamic remodeling, and anatomic structure similar to human drusen, but do not exhibit CNV or GA, providing a unique translational animal model for testing early AMD therapies. Comparison of imaging, histology, and ultrastructural features of drusen between macaques and humans provides insight into drusen biogenesis and the pathogenesis of AMD.