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Chronic accumulations of complement-expressing microglia/macrophages accompany the progressive expansion of the retinal lesion in an animal model of atrophic AMD

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Abstract



Purpose : Dysregulation of the complement system is a key factor in the pathogenesis of all forms of age-related macular degeneration (AMD). In geographic atrophy, complement activation has been linked to the progressive expansion of the macular lesion via genome-wide association studies, although how this process occurs is unclear. Using a rat model of photooxidative stress and inflammation, we explore the role of microglia/macrophages in propagating complement activation within expanding lesions over a 2-month period, as chronicled via Optical Coherence Tomography (OCT).

Methods : Adult SD rats were exposed to 1000 lux bright light for 24 hours (LD). Following light exposure, OCT images were captured at 0, 3, 7, 14 and 56 days following LD (n=4), to map histological changes of the outer nuclear layer (ONL) and retinal integrity. For other animals, eyes and retinas were collected at each of the aforementioned time points, and assayed for expression and localisation of complement genes (qPCR and in situ hybridisation), and deposition of the complement activation product C3d (immunohistochemistry).

Results : Following LD, OCT revealed a significant thinning of the ONL which culminated in a substantial lesion in the superior retina by 7 days. This lesion slowly expanded over the ensuing post-exposure period, and reached maximal thinning at 56 days ($P < 0.05$). In correlation, the expression of all complement genes assessed (C1s, C2, C3, C4a, CFB, CFD, SERPING1, CFH and CFI) was persistently up-regulated throughout the LD time course. Some, including C1s, C3 and C4a, remained up-regulated even after 56 days post-exposure ($P < 0.05$). Using in situ hybridization, C1s and C3 mRNA were found to co-localise with subretinal microglia/macrophages, which were present at the edges of the expanding lesion up to 56 days after LD and were in close proximity to C3d deposits at the lesion edges.

Conclusions : Our findings suggest that complement activation at the edges of atrophic lesions is promoted by the recruitment of subretinal microglia/macrophages, and that this may facilitate its chronic expansion over time. Consequently, the modulation of microglial activation and recruitment may be a useful therapeutic avenue to curtail deleterious complement activation and slow the progression of atrophic AMD.

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