Abstract

Purpose: The complement cascade is associated with pathogenesis of retinal dystrophies including age-related macular degeneration (AMD) although the cellular events that initiate the cascade remains unclear. In this study, we aimed to determine the functional significance of C3 derived from local/retinal sources and systemically-derived C3, and compared the findings with C3 localized in human donor eyes.

Methods: Photo-oxidative damage was used for a focal lesion in rat and mouse retinas, according to published protocols (Rutar et al., 2011; Natoli et al., 2016). The effect of C3 inhibition on the focal retinal degeneration was studied using C3	extsuperscript{-/-} mice, and intravitreal C3-specific siRNA in wildtype mice to locally deplete C3, and intraperitoneally administered cobra venom factor CVF to deplete C3 systemically. Animals were assessed for using electroretinogram(ERG), immunohistochemistry, in situ hybridisation, and qRT-PCR. Human retinas were assessed using in vivo immunohistochemistry and whole tissue hybridisation using C3.
**Results**: Human retinas from AMD patients with atrophic lesions showed C3 mRNA expressed by retinal monocytes within lesions and at the lesions edge, in the subretinal space, optic nerve head and inner retina. In focal lesions of photo-oxidative damaged rodent retina, complement gene expression increased significantly (P=0.0244), with strong immunoreactivity to C3d in retinal lesions in cells that co-localized the monocytes. C3⁻/⁻ retinas had significantly reduced photoreceptor cell death post damage (P=0.0014), a better preserved photoreceptor layer and improved retinal function compared to wildtypes (P=0.005). Local C3 inhibition using siRNA showed significantly reduced C3 gene expression in retinas post damage (P=0.034), accompanied by reduced C3 deposits in the outer retina, thicker photoreceptor layer and higher ERG responses compared to negative-siRNA controls (P=0.036). Systemic complement depletion by CVF had no effect on complement gene expression and did not mitigate the effects of photooxidative damage on retinal morphology or function (P=0.43).

**Conclusions**: Local C3 deposition by retinal monocytes, not systemic complement contributes to the progression of retinal degeneration. This study emphasises that targeting local complement specifically on retinal monocytes population could be a potential approach to slow down the progression of retinal dystrophy.

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