Role of TGF-β1 in age-related macular degeneration

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Transforming growth factor beta (TGF-β) is a protein that controls a variety of cellular functions (ten Dijke et al.,2004). We discovered that TGF-β1 prevents retinal damage induced by amyloid β (Aβ). Aβ is a peptide involved in the pathogenesis of Alzheimer's diseases and age related macular degeneration (AMD). Recently, a specific impairment of TGF-β1 signaling pathway has been demonstrated in Alzheimer's disease (AD) an amyloid-related neurodegenerative disorder, that share similar features with age-related macular degeneration (Luibl et al.,2006; Isas et al.,2010; Fisichella et al.,2016). The aim of this study was to investigate the protective effect of TGF-β1 in an animal model of age-related macular degeneration and to develop a topical formulation of transforming growth factor 1 to assess the ocular pharmacokinetics profile. TGF-β1 has been formulated as encapsulated in small unilamellar vesicles (SUV) in the presence of annexin V. Sprague-Dawley rats were used. Human Aβ1-42 oligomers were prepared and intravitreally injected (10μM) with and without recombinant human TGF-β1 (1ng/1 μl). After 48h, the animals were sacrificed and the eyes removed. The apoptotic markers Bax and Bcl-2 were assessed by Western Blot analyses. Small lipid unilamellar vesicles loaded with TGF-β1 were complemented by annexin V and Ca2+ prior topical administration to albino rabbits. TGF-β1 bioavailability was evaluated in the vitreous at different time points (30', 60', 120', 180', 240') by a commercial ELISA kit, after single topical administration of the new formulation. Ocular tolerability of TGF-β1 formulation was also assessed by a modified Draize's test. Treatment with Aβ oligomers induced a strong increase of Bax protein level (about 4fold; $p<0.01$) and a significant reduction of Bcl2 protein level (about 2fold; $p<0.05$). Co-injection of TGF-β1 triggered a significant reduction of Bax protein induced by Aβ oligomers. These findings suggest that TGF-β1 can prevent retinal damage elicited by Aβ oligomers. Finally, the novel liposomal formulation was able to deliver remarkable levels of TGF-β1 into the back of the eye after topical instillation. Targeting of TGF-β1 signalling pathway may be of value for treatment of AMD.

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