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Mesenchymal stem cells-based therapy for glaucoma through regeneration of the trabecular meshwork

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In open angle glaucoma, dysfunction of the trabecular meshwork (TM) leads to elevated intraocular pressure (IOP) and concomitant optic nerve damage. Consequently, regeneration of the TM cells may represent an effective therapeutic option for many cases of glaucoma. We previously demonstrated the regenerative effects of mesenchymal stem cells conditioned media (MSC-CM) in tissue regeneration in laser damaged TM. This process led to a decrease in IOP in a rat model of glaucoma. This mechanism is depended solely on macrophage recruitment. In this study, we have investigated the mechanism of MSC-CM educated macrophages on tissue regeneration. To better understand the role of macrophages in the TM regeneration process, rats were pretreated with clodronate liposomes resulting in a reduction in the number of macrophages within the damaged TM. This culminated in the

attenuation of the effect of MSC-CM on the IOP. In addition, reintroduction of *in vitro* MSC-CM educated macrophages into macrophage depleted eyes restored the healing effect. Furthermore, to elucidate the mechanistic basis of MSC-CM educated macrophages-mediated decrease in IOP, we injected the supernatant from MSC-CM educated macrophages into glaucomatous eyes. Surprisingly, this resulted in a decrease in the IOP, thus indicating that MSC-CM educated macrophages mediate TM regeneration and a decrease in IOP through paracrine factor secretion. In addition, we have identified one factor which we call RPF1 (Regenerative paracrine factor 1) produced by MSC-CM educated macrophages as a potent mediator of this regenerative effect. This finding provides a novel cellular therapeutic approach for glaucoma treatment.

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