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Engineered superparamagnetic $Mn_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticles as a heat shock protein induction agent for ocular neuroprotection in glaucoma

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ABSTRACT

Ocular neuroprotection induced by localized heat shock proteins (HSPs) has been paid considerable attention as an efficacious treatment modality for glaucoma. However, the current clinical approaches to induce HSPs in the retinal ganglion cells (RGCs) are limited due to undesirable side effects. Here, we present that the induction of HSPs by local magnetic hyperthermia using engineered superparamagnetic $Mn_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticle agents (EMZF-SPNPAs) with a 5.5 nm mean particle size is promisingly feasible for a physiologically tolerable ocular neuroprotection modality. The sufficiently high specific absorption rate (SAR) (~256.4 W/g in an agar solution) achieved at the biologically safe range of applied AC magnetic field and frequency as well as the superior biocompatibility of EMZF-SPNPA, which were confirmed from both in-vitro and in-vivo animal pilot studies, allowing it to be considered as a potential localized HSPs agent. Furthermore, the successful demonstration of a newly designed infusion technique, which diffuses the EMZF-SPNPAs through the vitreous body to the retina in a rat eye, more strongly verified the promises of this biotechnical approach to the ocular neuroprotection modality in glaucoma clinics.

1. Introduction

Glaucoma is a progressive and incurable optic neuropathy where the optic nerve is damaged with the loss of retinal ganglion cells (RGCs) due to mechanical injuries. This disease has been considered as one of the most fatal diseases responsible for irreversible blindness [1,2]. Ocular hypertension, the increase of intraocular pressure, is a typical symptom and has been widely accepted for the main risk factor to cause the damage of optic nerve and RGCs [1,3]. Accordingly, all of the treatment modalities for glaucoma so far were entirely focused on dropping the intraocular pressure such as by taking a medicine or by doing surgical operation. However, these methods have been found to temporarily cure glaucoma, there has been no efficacious modality to completely treat the glaucoma as well as protect optic nerves from the glaucoma-induced mechanical damages.

The induction of heat shock proteins (HSPs) has been recently considered to be a new powerful modality for the protection of optic nerves, ocular neuroprotection, from glaucoma [4–6]. The HSPs, called by stress proteins, are a group of proteins that exist in all of the living creatures covering bacteria to human beings. They can be induced in living cells by hyperthermia, metabolic stress, or oxygen deprivation [7,8]. In particular, HSPs 70 families in the mammalian central nervous system (CNS) has been known to enhance neuronal tolerance against ischemic insults and confirmed to be effective for neuroprotection against light-induced injuries in a rat retina [9–11]. The first demonstration of the effects of HSPs on the neuroprotection against ischemic and excitotoxic cell death was performed in cultured RGCs (in-vitro) [5]. Since then, the research efforts to apply the induction of HSPs for neuroprotection have been intensively focused on improving the technical effectiveness to the glaucoma clinics. For instance, whole body hyperthermia, intraperitoneal zinc injection, and intraperitoneal geranylgeranylacetone injection methods have been attempted to induce

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