Hydrogel nanoparticles for targeting retinal tissue

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Statement of Purpose: Blindness is often associated with retinal diseases, including retinal detachment, retinal dysplasia, retinal neovascularization, retinopathy, vitreoretinopathy,…etc. Since the eye is naturally isolated from the systemic circulation, it is difficult to deliver the drug to the posterior portion of the eyes. Thus, there is intense research effort on the development of drug delivery devices for targeting posterior eye tissues, such as retinal cells. Among all delivery alternatives for treating posterior eye diseases, intravitreous injection is the most effective methods in delivering drugs to retinal tissues. Unfortunately, intravitreal injection is often associated with many severe complications, such as retinal detachment, hemorrhage, endophthalmitis, and infection. Intravitreal administration often requires repeat injections and they are not always well tolerated by the patient. In addition, drugs injected directly into the vitreous are rapidly eliminated. Thus, there is an urgent need in the development of intravitreal sustained-release devices. Because our recent studies have uncovered that hydrogel nanoparticles have excellent tissue compatibility (Weng et al., 2005; Hu et al., 2005) and good drug release and tissue targeting properties, a series of hydrogel nanoparticles with different characteristics have been tested for their affinity to retinal tissues using an animal implantation model.

Methods: Thermal responsive poly-N-isopropylacryl-amide (PNIPAM) hydrogel has been studied intensively for controlled drug delivery. Thus, PNIPAM nanoparticles were used in this investigation. In the beginning of this investigation, two different building blocks of N-isopropylacrylamide-derivative micro-particles and nanoparticles were synthesized using an emulsion polymerization method. The size of PNIPAM nanoparticles and micropartricles tested in this study were around 100 nanometer and 4 micrometer diameters, respectively. Amine-rich PNIPAM nanoparticles were also produced by cross-linking the particles in the presence of allylamine. Some of these particles were labeled with FITC prior to implantation. The diffusibility and biocompatibility of the particles are determined in mice. As an animal implantation model, 2 µl of FITC-labeled PAIPAM particles was injected into intravitral space of Balb/C mice. Following implantation for different periods of time (4, 12 hours, 1, 3, and 7 days), mice were sacrificed and the eyes were recovered for analyses. To assess the nanoparticles migration, the eyes were fixed for frozen section and tissue frozen sections were observed under fluorescence microscope. To test the particles' biocompatibility, some of the tissue sections were subjected to H&E and immunohistochemical staining for inflammatory cells.

Results / Discussion: Both microparticles and nanoparticles of PNIPAM did not prompt prominent foreign body reactions assessed by the recruitment of CD11b positive cells. Shortly after implantation, microparticles were found to aggregate inside and failed to disperse in the intravitreous cavity. Microparticle implants then migrated toward ciliary body. On the other hand, there is lesser aggregation found on nanoparticles. We also found that PNIPAM nanoparticles failed to disperse and to accumulate in retinal tissue (Figure 1a). We have then expanded our investigation to include PAIPAM particles with amine group ($-NH_3$). Rather surprisingly, we find that amine-rich PAIPAM nanoparticles evenly penetrated into retinal tissue 4 hours following administration. The distribution of all PAIPAM nanoparticles was almost resided in the intravitreal space. Amine-rich PAIPAM nanoparticles were also found to be well tolerated in the intravitreal space.

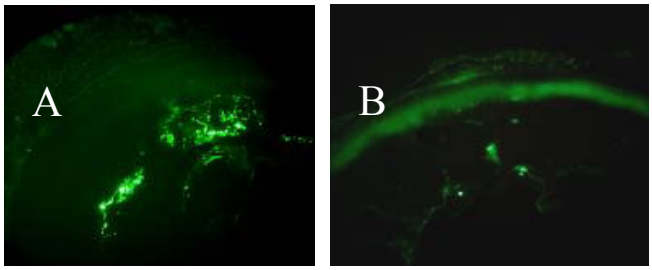

Figure 1. PAIPAM nanoparticles distributions in the posterior chambers of eyes were investigated following 4 hour intravitreal injection in mice eyes. (A). Untreated nanoparticles aggregated and failed to disperse in the vitreous fluid. (B). Amine-rich nanoparticles evenly penetrated into retinal tissue.

Conclusions: This investigation has uncovered that amine-rich PAIPAM nanoparticles is potentially useful as a retina targeting drug delivery system for treating vitreoretinal diseases such as retinopathy and endophthalmitis

References:

Hu, Z, et al. Macromolecular Symposia 2005,227:275-284.
Weng H, et al. J Biomater Sci Polym Ed. 2004,15:1167-1180.