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Cover Story

Nanoparticle diffusion in the bovine vitreous

Numerous ocular diseases may benefit from the development of effective nanoparticle- and microparticle-based ocular drug delivery systems [1] and gene therapy systems [2]. Drug delivery by intravitreal injection currently plays an important role in effective treatment of ocular diseases, including those that affect the posterior segment of the eye, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME) and glaucoma. Intravitreal injection of anti-vascular epithelial growth factor (anti-VEGF) medications is now commonly used to treat neovascular AMD, DR and DME. However, the relatively short intraocular half-life of unencapsulated drugs delivered by intravitreal injection requires repeated injections over an extended period of time. Even once a month injection is still too frequent for most elderly patients. Such frequent injections are not only a burden on the patients, their families, and the healthcare system, but also a cause of injection-related complications in rare cases [3]. Drug-loaded particles with prolonged intraocular retention capable of providing sustained and/or targeted delivery for months after intravitreal injection may help to reduce the frequency of administration, enhance drug effectiveness, and increase patient compliance. Intravitreal injection also represents an attractive strategy for gene delivery to the back of the eye, compared to more complicated subretinal injections. Understanding the diffusion properties of various particulate drug delivery systems in the vitreous is important for rationale design of nano/micro formulations.

Despite the promise of intravitreal injection for treating diseases at the back of the eye, relatively little was previously known about the vitreous environment through which drugs and therapeutic nanoparticles must travel to reach their target. The vitreous is composed of a delicate mesh network of gel-forming collagen fibrils and hyaluronan molecules, and is susceptible to liquefaction upon removal from the eye. In this issue, members of the Center for Nanomedicine at Johns Hopkins, led by Professors Justin Hanes, Elia Duh, Peter McDonnell and Richard Cone, present a novel approach to preserving the structure of bovine vitreous that allows measurements of nanoparticle diffusion in, and determination of the micro-rheology of, this material [3]. They applied polystyrene (PS) nanoparticles of different sizes (84–1,190 nm) and surface chemistries (carboxylated, PS-COOH; amine-modified, PS-NH_2; and PEGylated, PS-PEG) to minimally perturbed bovine vitreous, and followed the motions of the particles using multiple particle tracking [4]. They found that particle mobility was a complex function of not only size and surface chemistry, but also particle concentration. Negatively-charged PS-COOH nanoparticles as large as 227 nm diffused rapidly within vitreous, but aggregated at concentrations exceeding 0.1% w/v. Positively-charged PS-NH_2 nanoparticles aggregated within the vitreous and did not diffuse rapidly. Finally, neutrally-charged, PEG-coated, PS-PEG nanoparticles with minimal adhesive interactions with the vitreous gel diffused rapidly if they were smaller than 800 nm, but PS-PEG particles of 1,190 nm in diameter were immobilized owing to steric obstruction from the vitreous mesh. By further analyzing the motions of PS-PEG nanoparticles, the team determined that the average mesh size of fresh bovine vitreous was ~550 nm, with some pore sizes up to 1 μm or larger.

The range of pore sizes in the vitreous gel gives rise to its length scale-dependent rheology: objects 1,190 nm in size experienced the bovine vitreous as a viscoelastic solid barrier independent of particle surface chemistry, while objects smaller than 794 nm, and that avoided aggregation or adhesion to the vitreous mesh, experienced the vitreous as a low viscosity viscoelastic liquid that is readily permeated. Understanding the architecture and rheological behavior of the vitreous gel, as experienced by nano-sized particles, has important implications for the use of nanoparticle-based systems for various applications in the eye. For example, based on their results, the team formulated biodegradable drug and gene carriers composed of either a 230 nm poly(lactic-*co*-glycolic acid)-based core coated with poly(vinyl alcohol) or 350 nm × 11 nm rod-shaped, highly-compacted $CK_{30}PEG_{10k}$/DNA nanoparticle with PEG coating. Both of these formulations diffused rapidly within vitreous, and could be useful for targeted delivery to the retina. The authors also proposed that biodegradable particles with diameters larger than ~1.2 μm may be used for long-term delivery of therapeutics (e.g., anti-VEGF agents for wet-AMD and DME), since particles in this size range are expected to be retained in vitreous for longer durations.

The study by Professor Hanes and his colleagues is highly important, as it advances our understanding of the dynamics of nanoparticle transport in vitreous and provides the basis for further development of intravitreal drug and gene delivery platforms to treat diseases of the eye. Some formulations may have to diffuse freely in vitreous to achieve their intended goal, while some may require slow or no diffusion for long-term, e.g., 6–12 months, drug delivery. The information described in the article by the members of the Center for Nanomedicine at Johns Hopkins provides a great starting point for further study on the impact of particle size on the efficacy of various particulate formulations.

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