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Cover Story

Thermo-responsive polypeptides and micromechanical machines for sustained delivery to the posterior eye

Diseases affecting the posterior segment of the eye, which includes the retina, are among the major causes for impaired vision or blindness [1]. Effective drug delivery has been challenging owing to the unique anatomical and physiological barriers of the eye [2,3]. Intravitreal injections are used clinically to deliver drugs to the retina; however, it remains a challenge to achieve a therapeutic efficacy for weeks or longer by a single injection. In addition to poor patient compliance, more frequent intravitreal administration leads to retinal detachment, endophthalmitis, hemorrhages, and increased intraocular pressure. Therefore, sustained delivery systems that prolong drug retention over extended periods are necessary to minimize complications.

In this issue, a new strategy has been developed for sustained peptide delivery to the retina by Professor MacKay and his coworkers using elastin-like polypeptides (ELPs). The paper by the MacKay group presents a biodegradable polymeric system relevant to the treatment of age-related macular degeneration (AMD) [4]. The therapeutic cargo is a 20-amino acid peptide derived from residues 73-92 of human αB crystalline, which displays cytoprotective and chaperone functions similar to the full-length protein [5]. To retain this peptide longer in the vitreous body, it was fused to an ELP containing a self-assembly motif $(Val\text{-}Pro\text{-}Gly\text{-}Ile\text{-}Gly)_{48}$ [6]. ELPs are protein-polymers derived from human tropoelastin that can be generated through genetic engineering. Recombinant biosynthesis offers high fidelity control of molecular weight, sequence, and monodispersity. Most importantly, thermo-responsive ELPs can be tailored to self-assemble coacervates at 37 °C without compromising the activity of fusion peptides. Thus, when a pharmacologically active peptide fragment from αB crystalline (cry) is fused to an appropriate ELP (to form crySI), it forms a long-lived deposit in the vitreous chamber. Using a mouse model relevant to AMD, the MacKay team tested the protective potential of the polymer fusion crySI compared to the free peptide. The *in vivo* study shows that a single intravitreal injection of crySI rescues the retina from oxidative stress-induced injury, whereas the free peptide does not. Pharmacokinetic studies confirm the increased retention for the fusion peptide compared to the free peptide. While the free peptide was undetectable within 3 days, crySI stayed in the vitreous chamber at protective levels for at least 2 weeks. This study is the first *in vivo* proof-of-concept for the use of ELPs to modulate cytoprotective peptides for treating eye diseases via intravitreal administration, which may lead to possible treatments for AMD or other diseases of the retina. This study suggests that additional models of retinal protection relevant to AMD need to be explored, additional pharmacological peptide cargo may be identified, and the pharmacokinetic effects of intra-ocular ELPs need to be scaled to larger animals through preclinical studies.

In this same issue, another paper by Wang et al. explores the development of novel systems for sustained intravitreal drug delivery. More specifically, they developed a micropump for on-demand vascular endothelial growth factor-targeted drug delivery, which can be precisely controlled by an external magnetic field [7]. Although the performance of this implant in a disease model has not been established, it has the potential for long-term implantable drug delivery in human eyes or other organs without the need for a power supply.

As the elderly population increases, effective treatments of chronic diseases, such as AMD, Parkinson's disease, and Alzheimer's disease, are urgently needed. The two studies highlighted in this issue demonstrate new platforms for sustained drug delivery to the retina using either biodegradable or micro engineered mechanical materials. These two approaches improving patient safety and compliance are not limited to intravitreal delivery, as they are rather universal in sustained drug delivery. While the approach may be experimental and invasive for now, further improvement in technologies in biodegradable polymers and microfabrication will undoubtedly lead to clinically useful long-term drug delivery systems. It is critical that all of us free ourselves from the existing dogma and be willing to explore novel concepts as the two studies described here have done.

References

[1] W.H. Organization, Global Data on Visual Impairments 2010, World Health Organization, Geneva, 2012.
[2] C.M.L. Lau, Y. Yu, G. Jahamir, Y. Chau, Controlled release technology for anti-angiogenesis treatment of posterior eye diseases: current status and challenges, Adv. Drug Deliv. Rev. 126 (2018) 145–161.
[3] K. Peynshaert, J. Devoldere, S.C. De Smedt, K. Remaut, *In vitro* and *ex vivo* models to study drug delivery barriers in the posterior segment of the eye, Adv. Drug Deliv. Rev. 126 (2018) 44–57.
[4] P.G. Sreekumar, Z. Li, W. Wang, C. Spee, D.R. Hinton, R. Kannan, J.A. MacKay, Intravitreal αB crystallin fused to elastin-like polypeptide provides neuroprotection in a mouse model of age-related macular degeneration, J. Control. Release 283 (2018) 94–104.
[5] J. Bhattacharyya, E. Padmanabha Udupa, J. Wang, K.K. Sharma, Mini-αB-crystallin: a functional element of αB-crystallin with chaperone-like activity, Biochemistry 45 (2006) 3069–3076.
[6] W. Wang, P.G. Sreekumar, V. Valluripalli, P. Shi, J. Wang, Y.-A. Lin, H. Cui, R. Kannan, D.R. Hinton, J.A. MacKay, Protein polymer nanoparticles engineered as chaperones protect against apoptosis in human retinal pigment epithelial cells, J. Control. Release 191 (2014) 4–14.
[7] C. Wang, S.-J. Seo, J.-S. Kim, S.-H. Lee, J.-K. Jeon, J.-W. Kim, K.-H. Kim, J.-K. Kim, J. Park, Intravitreal implantable magnetic micropump for on-demand VEGFR-targeted drug delivery, J. Control. Release 283 (2018) 105–112.

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