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Cover story

Intracellular enzymes of the retinal pigment epithelial cells for controlled drug delivery

Current therapeutic approaches to treat posterior segment diseases of the eye, such as age-related macular degeneration (AMD), utilize monthly intravitreal injections of anti-VEGF agents (antibodies and soluble VEGF receptor trap) to target neovascularization [1]. The therapies have shown promise in slowing the progression of the disease. Chronic intraocular injections, however, are invasive causing a burden to the healthcare providers and patients. Furthermore, the vitreal half-lives of most drugs are in the hours necessitating intravitreal injections at short dosing intervals (a few days) [2]. This is a difficult proposition in the clinical setting. Although controlled drug release systems have been investigated for extending the intravitreal dosing intervals, their clinical translation has been rare [3]. One of the contributing factors is the materials toxicity that often limits clinical applications of new formulations. Ocular toxicity or immunological reactions may be caused by the polymeric materials, their degradation products, and/or carry-over additives from the drug formulation.

Professor Arto Urtti and his research group present an alternative peptide-based delivery system with cleavable linkers for controlled intracellular cargo release [4]. This strategy exploits cleavage by intracellular enzymes of the human retinal pigment epithelial (RPE) cells for the release of drug prototypes. Altering the peptide linker sequences allows adjusting the cargo release rate from fast to slow in the cells. This strategy is useful for intracellular drug delivery in the RPE cells. More importantly, it renders the cells to act as a 'hotspot' that can gradually release a drug to the extracellular space and neighboring cellular drug targets in the retina and choroid. It is a new approach utilizing designed peptide sequences and cellular enzymes as an activator for controlled release of exogenous drug molecules. The study quantitated the released cargo in the RPE cells and to the basolateral side using LC-MS. The quantitation of the cellular cargo release is an improvement over previous studies that have relied on fluorescence and secondary readout-based methods. The peptide linkers are stable in the vitreous suggesting that the drug delivery system is activated only after its cellular entry into the RPE cells.

The work by the Urtti team provides an impetus in exploring alternate drug delivery systems that are based on the drug release in the RPE cells. This approach does not rely on the long-acting depot formulation, but exploits the peptide sequences and endogenous components of the RPE cells for sustained drug release. While this approach is new and provides additional tools for drug delivery scientists to exploit, the long-term drug release needs to be tested and confirmed in animal studies. The peptide-based delivery system has to remain in the intravitreal space because the system will not function effectively if its own half-life is short. The immediate importance of this approach resides in the revival of the enzyme-controlled drug delivery. For treating diseases such as AMD, inter-individual variations in the enzyme activity may not affect the overall efficacy and usefulness of the approach. In addition, the approach may not be limited only to intravitreal delivery, as it, in principle, is applicable for the delivery of any molecules that can be covalently linked to peptides. It is expected that the Urtti group's work is widely adapted as it expands the horizon of the formulation design.

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