

Development and Evaluation of Liposome-Encapsulated Ripasudil for Enhanced Therapeutic Efficacy in Proliferative Vitreoretinal Diseases

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(増殖性硝子体網膜疾患の治療薬としてのリパスジル封入リポソームの開発)

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論 文 内 容 の 要 旨

Proliferative vitreoretinal diseases, such as proliferative vitreoretinopathy (PVR) and neovascular age-related macular degeneration (nAMD), pose substantial challenges in their advanced stages owing to the development of retinal fibrous membranes. Current therapeutic modalities, including surgical interventions for PVR and anti-vascular endothelial growth factor therapy for nAMD, cannot effectively manage intraocular fibrosis associated with epithelial-to-mesenchymal transition (EMT) in retinal pigment epithelium (RPE) cells. Through drug screening, we identified ripasudil, a Rho-kinase inhibitor, as a remarkable suppressor of RPE-EMT. However, the short vitreal half-lives of small-molecule drugs, coupled with the limited stability of ripasudil in the ocular environment, impede its application in vitreoretinal diseases. Considering the advances in nanotechnology-assisted improvement in drug stability and cellular uptake as well as controlled release, we aimed to enhance the efficacy of ripasudil through liposome encapsulation. In our comprehensive in vivo and in vitro analyses, liposome-encapsulated ripasudil (Lipo-Ripa) demonstrated a substantial reduction in subretinal fibrosis in an advanced AMD model and more effective inhibition of PVR progression in rabbits than that induced by ripasudil alone. Pharmacokinetic studies revealed that Lipo-Ripa exhibited improved retention capacity in the vitreous and retina, alongside reduced permeability through the RPE barrier and increased cellular uptake. These characteristics resulted in a sustained elevation of drug concentration within the ocular tissues over time. Our findings suggest that liposomal encapsulation of ripasudil supports enhanced bioavailability and effectiveness of the drug, presenting a promising innovative therapeutic approach for the treatment of proliferative vitreoretinopathy.