(様式 5)

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学位（博士）論文要旨

(Doctoral thesis abstract)

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論 文 題 目 (Title)	眼疾患の新規治療薬開発に向けた基盤研究：緑内障モデルの病態研究と角膜上皮の恒常性に関わる microRNA の同定

論文要旨 (2000 字程度)
(Abstract(400 words))
※欧文・和文どちらでもよい。但し、和文の場合は英訳を付すこと。
(in English or in Japanese)

The exploratory studies were conducted to develop and characterize the experimental glaucoma model and to identify microRNAs associate with homeostasis of corneal epithelium.

Glaucoma is a chronic optic neuropathy which causes death of retinal ganglion cell (RGC). One of the major risk factors is elevation of intraocular pressure (IOP), but the mechanisms of glaucomatous optic neuropathy has not been fully understood. Animal glaucoma model are essential to elucidate the mechanisms underlying glaucoma and to develop new glaucoma drugs. In this study, a new rat glaucoma model were developed by injection of conjunctival fibroblasts into the anterior chamber. IOP elevation was initiated from the 3rd day after cell injection and sustained until the 28th day. The number of RGCs significantly decreased by 37.5% on the 28th day, correlating with IOP value in eyes with IOP lower than 50 mmHg. In this group, optic nerve head cupping and retinal thinning were displayed from the 3rd day and the 7th day, respectively. Glial activation in the retina started to be observed on the 7th day and it was obvious on the 14th day. Apoptotic signaling in the retina were also observed on the 14th day. Then, glial activation and apoptotic signaling were attenuated on the 28th day. These results suggest that this model mimicked the glaucoma features on all disease stages. This model may contribute to the investigation of pathogenic mechanisms of glaucoma.

Corneal epithelial defect affects patient's quality of life. However, few drugs have been developed for promoting corneal wound healing. microRNA (miRNA) is small noncoding RNA that negatively regulate gene expression. miRNAs exist within cells

and in body fluids, and extracellular miRNAs associate with the surrounding tissues. Therefore, miRNAs in tear are predicted to regulate corneal epithelial cell function. However, information on the miRNA expression profile of tear is limited and the functions of tear miRNAs for corneal epithelial cells are still unknown. In this study, microarray and qPCR analyses showed that miR-184 and miR-203 were expressed significantly more highly in monkey tear than in serum. Of these two miRNAs, transfection of a miR-203 mimic significantly reduced the viability of human corneal epithelial (HCE-T) cells, while a miR-203 inhibitor significantly increased this viability. miR-203 mimic and inhibitor changed the expression level of insulin-like growth factor-binding protein 5 (IGFBP5) mRNA in HCE-T cells. Moreover, silencing of IGFBP5 resulted in decreasing the cell viability of HCE-T cells. IGFBP5 gene had two putative target sites of miR-203 in their 3'-UTR, and a dual luciferase reporter assay demonstrated that IGFBP5 is a direct target gene for miR-203. This study suggested that miR-203 control the viability of corneal epithelial cells by regulating IGFBP5 expression, and the inhibition of miR-203 may has potential therapeutic role for corneal epithelial wound healing.

（英訳）※和文要旨の場合(400 words)