論　文　要　旨

Toxic effects of extracellular histones and their neutralization by vitreous in retinal detachment

川野　浩輝

Histones are DNA-binding proteins and are involved in chromatin remodeling and regulation of gene expression. Histones can be released after tissue injuries, and the extracellular histones cause cellular damage and organ dysfunction. Regardless of their clinical significance, the role and relevance of histones in ocular diseases are unknown. We studied the role of histones in eyes with retinal detachment (RD). Vitreous samples were collected during vitrectomy, and the concentration of histone H3 was measured by enzyme-linked immunosorbent assay. The location of the histones and related molecules was examined in a rat RD model. The release of histones and their effects on rat retinal progenitor cells R28 and ARPE-19 were evaluated in vitro. In addition, the protective role of the vitreous body against histones was tested. The intravitreal concentration of histones was higher in eyes with RD (mean, 30.9±9.8 ng/ml) than in control eyes (below the limit of detection, $P<0.05$). In the rat RD model, histone H3 was observed on the outer side of the detached retina and was associated with photoreceptor death. Histone H3 was released from cultured R28 by oxidative stress. Histones at a concentration 10 μg/ml induced the production of interleukin-8 in ARPE-19 cells (2.5-fold increase, $P<0.05$) that was mediated through the ERK1/2- and p38 MAPK-dependent pathways and Toll-like receptor 4. Histones were toxic to cells at concentrations of ≥20 μg/ml. Vitreous body or hyaluronan decreased toxicity of histones by inhibiting diffusion of histones. These results indicate that histones are released from retinas with RD and may modulate the subretinal microenvironment by functioning as damage-associated molecular pattern molecules, thereby inducing

proinflammatory cytokines or cell toxicity. In addition, the important role of the vitreous body and hyaluronan in protecting the retina from these toxic effects is suggested.

（Laboratory Investigation, advance online publication, March 10, 2014）