Research Announcement

(Pro)renin receptor is associated with angiogenic activity in proliferative diabetic retinopathy

Atsuhiro Kanda$^{1,2}$, Kousuke Noda$^{1,2}$, Wataru Saito$^2$ and Susumu Ishida$^{1,2}$*

$^1$Laboratory of Ocular Cell Biology and Visual Science, $^2$Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Research background:
The renin-angiotensin system (RAS) plays a potential role in the development of end-organ damage, and tissue RAS activation has been suggested as a risk factor for diabetic retinopathy (DR). We have recently shown the significant involvement of (pro)renin receptor [(P)RR] with retinal inflammation in a rodent model of early diabetes. We herein aim to elucidate (P)RR-associated pathogenesis of fibrovascular proliferation, the late-stage angiogenic complication in human DR.

Experimental results:
Vitreous fluids from 23 eyes with proliferative DR (PDR) and 16 controls with non-diabetic, idiopathic macular diseases (macular hole and epiretinal membrane) were collected and protein levels of soluble (P)RR were measured by ELISA (Enzyme-Linked ImmunoSorbent Assay), and immunofluorescence was performed to assess localization of (P)RR and related molecules in fibrovascular tissues from PDR eyes.

(P)RR immunoreactivity was detected in neovascular endothelial cells, co-localized with prorenin, phosphorylated extracellular signal-regulated kinase (ERK) and vascular endothelial growth factor (VEGF). Prorenin application to human retinal microvascular endothelial
cells significantly upregulated mRNA expression of VEGF, especially the VEGF165 isoform, which was abolished by (P)RR or ERK signaling blockade. Proteases known for the cleavage of (P)RR including furin were positive in endothelial cells in fibrovascular tissues. Protein levels of soluble (P)RR in the vitreous fluids were higher in PDR eyes than in non-diabetic control eyes, and were significantly correlated with vitreous VEGF levels and the vascular density of fibrovascular tissues.

Significance:
Our data using human samples provide the first evidence that (P)RR is associated with angiogenic activity in PDR, and suggest the validity of (P)RR as a molecular target for the treatment of PDR.

For Enquiries:
Susumu Ishida, M.D., Ph.D.
Phone : +81-11-706-5944, Fax : +81-11-706-5948
E-mail: ishidasu@med.hokudai.ac.jp