（第３号様式）

学　位　論　文　要　旨

氏　　名　裴　作為

論　文　名　オステオポンチン欠損はアポリポタンパク質Ｅ欠損マウスにおける高コレステロール血症の腎障害を軽減する

学位論文要旨

書き方
（和文 2,000 字又は英文 800 語以内）
（日本人の大学院生は，和文で記載）
（標準書式：日本工業規格Ａ４，11 ポイント，１行 42 字，１ページ 40 行）

Background

Hypercholesterolemia is a well-established risk factor for kidney injury, which can lead to chronic kidney disease (CKD). Apolipoprotein E knockout ($ApoE^{-/-}$) mice are considered a well-accepted model of hypercholesterolemia. In $apoE^{-/-}$ mice, dyslipidemia-related kidney injury is associated with marked pathological alterations, including lipid deposition in the glomerulus, mesangial expansion, and increased extracellular matrix (ECM) area. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a receptor for oxidized low-density lipoprotein (ox-LDL). LOX-1 binds to multiple ligands, has diverse physiological functions, and plays a critical role in signal transduction. It may be a key factor in the development of hypertension, diabetes mellitus, and hyperlipidemia. Osteopontin (OPN) is a secreted glycoprotein that is found in many organs; bone and kidney show the greatest OPN content. OPN is thought to play a role in the renal damage associated with inflammatory glomerulonephritis, obstructive uropathy, and tubule interstitial disease. One of our recent studies showed that OPN deficiency protects against aldosterone-induced inflammation, oxidative stress, and interstitial fibrosis in the kidney.

氏名　裴　作為

Aim

The aim of the study was to evaluate the effects of OPN on hypercholesterolemia-induced renal dysfunction.

Methods

We used two hypercholesterolemia models: apolipoprotein E knockout ($ApoE^{-/-}$) mice and ApoE / OPN knockout ($ApoE^{-/-}/OPN^{-/-}$) mice. Eight-week-old mice were divided into 4 groups: $ApoE^{-/-}$ mice fed a normal diet (ND) or high cholesterol diet (HD), and $ApoE^{-/-}/OPN^{-/-}$ mice fed ND or HD for 4 weeks. Blood samples were obtained from the inferior vena cava and collected in serum tubes and stored at -80°C until used. Coronal sections of the kidneys were fixed in 10％ formalin and then embedded in paraffin for histological evaluation. Primary mesangial cells were lysed for isolation of mRNA and protein and evaluation of LOX-1 expression by quantitative RT-PCR and western blotting.

Results

After 4 weeks, there were no differences in serum total cholesterol and low-density lipoprotein (LDL) cholesterol between $ApoE^{-/-}/OPN^{-/-}$ HD mice and $ApoE^{-/-}$HD mice. Periodic acid-Schiff (PAS) and oil red O staining revealed excessive lipid deposition in the glomeruli of $ApoE^{-/-}$HD mice. In contrast, lipid deposition was suppressed in $ApoE^{-/-}/OPN^{-/-}$ HD mice. $ApoE^{-/-}/OPN^{-/-}$ mice showed markedly reduced collagen typeIV accumulation in glomeruli compared with $ApoE^{-/-}$ mice consuming HD by immunostaining. LOX-1 expression was significantly lower in the glomeruli of $ApoE^{-/-}/OPN^{-/-}$HD mice than in $ApoE^{-/-}$ HD mice. Pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 genes were upregulated in $ApoE^{-/-}$ HD mice; however this up-regulation was attenuated in $ApoE^{-/-}/OPN^{-/-}$HD mice. In an in vitro study, primary mesangial cells were incubated with recombinant mouse OPN (rmOPN). RmOPN induced LOX-1 mRNA and protein expression in primary mesangial cells. Pre-treatment with an ERK inhibitor (PD98059) suppressed the LOX-1gene expression induced by rmOPN.

Conclusion

These results indicate that OPN contributes to kidney and glomerular damage in hypercholesterole -mia and suggest that inhibition of OPN may provide a potential therapeutic target for the prevention of hypercholesterolemia.

キーワード（３～５）	OPN; LOX-1; hypercholesterolemia; mesangial cell