論文の内容の要旨

論文題目　Simvastatin ameliorates epithelial-to-mesenchymal transition (EMT) by suppressing uterine sensitization-associated gene-1 (USAG-1) in mouse tubulointerstitial fibrosis model

和訳　シンバスタチンはマウス尿細管間質線維化モデルにおいて USAG-1 を抑制することで EMT を改善する～シンバスタチンによる腎線維化抑制のメカニズム～

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Uterine sensitization-associated gene-1 (USAG-1), a bone morphogenetic protein-7 (BMP-7) antagonist, is assumed to promote renal fibrosis because BMP-7 has anti-fibrotic effect by counteracting transforming growth factor-β1 (TGF-β1) induced epithelial-to-mesenchymal transition. We evaluated whether simvastatin (SIM), a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, attenuates renal fibrosis by modulating USAG-1. C57/BL6 mice fed a 0.2% adenine-containing diet for 4 weeks developed renal dysfunction accompanied with severe tubulointerstitial fibrosis. Subsequent SIM treatment (50 mg/kg/day) for 2 weeks significantly suppressed fibrosis progression and α-smooth muscle actin (α-SMA) expression in the kidney. SIM reduced USAG-1 expression and increased BMP-7 signaling without affecting BMP-7 expression in the kidney. Because USAG-1 is expressed in renal distal tubular epithelial cells, we conducted *in vitro* experiments using Madin–Darby Canine Kidney (MDCK) cells. MDCK cells incubated with TGF-β1 showed increased expression of USAG-1; SIM significantly reduced USAG-1 expression. Gene knock-down experiments using MDCK cells suggested that homeobox protein Hox-A13 (HOXA13) functions as a

suppressor of the USAG-1 gene and that SIM decreased USAG-1 expression by increasing HOXA13. The data from our study demonstrate that HOXA13–USAG-1 axis contributes to the renal anti-fibrotic effect of simvastatin, and this axis will be a therapeutic target for preventing renal fibrosis.