論文の内容の要旨

論文題目　**Studies on the mechanism of liver fibrosis induced by Oncostatin M**

（オンコスタチンＭによるマウス肝線維化促進機構の解析）

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Oncostatin M (OSM) is a member of IL-6 family cytokines with pleiotropic functions. A previous study showed that OSM contributed to liver regeneration after acute liver injury, partly by regulating the remodeling of extracellular matrix. However, the role of OSM in chronically injured liver accompanying fibrosis is unknown. The current studies show that OSM is continuously expressed during fibrogenesis and responsible for the promotion of fibrosis. OSM-deficient mouse exhibited significant reduction of fibrosis in chronically injured liver compared to wild-type mouse. Conversely, continuous expression of OSM in normal liver by hydrodynamic tail vein injection of OSM cDNA was sufficient to induce remarkable fibrosis with the up-regulation of

several fibrogenic genes. Importantly, no sign of hepatic injury was observed in this case, suggesting that OSM-induced fibrosis was not caused by inflammation or hepatic damage but the fibrogenic property of OSM. The OSM receptor was predominantly expressed on hepatic stellate cells (HSCs) and liver macrophages (LMs). OSM directly up-regulated the expression of tissue inhibitor of metalloproteinase-1 gene in HSC *in vitro*, whereas it promoted that of collagen gene via the activation of LMs. In chronically injured liver, infiltrating bone marrow-derived macrophages were more responsive to OSM for the induction of fibrosis-related genes than liver resident macrophages. In conclusion, OSM is a powerful fibrogenic factor and its persistent expression in chronic liver diseases can be a risk factor for liver fibrosis. OSM is a possible therapeutic target for liver fibrosis.