[1679] Hematopoietic Origin of Hepatic Stellate Cell. Session Type: Poster Session, Board #807-I

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Hepatic stellate cells are believed to play a key role in the development of liver fibrosis. They undergo a gradual transition from a quiescent, fat-storing phenotype to an activated myofibroblast-like phenotype and then produce high amount of extracellular matrix such as collagen by liver injury. They express mesenchymal markers such as vimentin and desmin, or neural/ neuroectodermal markers such as glial fibrillary acidic protein (GFAP). Based on the characteristic phenotype, the embryonic origin of stellate cells is thought to be the septum transversum mesenchyme or neural crest. However, their origin in the adult liver is still unknown. Recently, several studies have reported that crude bone marrow (BM) cells can give rise to hepatic stellate cells. However, since adult BM cells are thought to contain hematopoietic stem cells and mesenchymal stem cells, it is important to clarify which type of stem cells is the true source of hepatic stellate cells. We hypothesized that hepatic stellate cells are derived from hematopoietic stem cells. To test this hypothesis, we generated chimeric mice by transplantation of singe enhanced green fluorescent protein (EGFP)-marked hematopoietic stem cells (Lin^- $Sca\text{-}1^+$ $c\text{-}kit^+$ $CD34^-$ cells) into lethally irradiated nontransgenic mice and examined the histology of liver tissues obtained from chimeric mice with carbon tetrahydrochloride (CCl_4)-induced injury. Following 12 weeks treatment of CCl_4, hepatic nodules and bridging fibrosis developed in all livers. We detected $EGFP^+$ cells in the liver and some of them contained intracytoplasmic lipid droplets, which were proved by oil red O staining. Immunohistochemical analysis demonstrated that 60% of $EGFP^+$ cells were negative for leukocyte common antigen (CD45); however, they expressed vimentin, GFAP and ADAMTS-13, which is a circulating zinc metalloproteinase synthesized in hepatic stellate cells. Moreover, nonparenchymal cell populations were isolated from the livers of chimeric mice with CCl_4 treatment and were incubated on noncoated glass slides for 3 days. $EGFP^+$ cells were also positive for type I collagen. These phenotypes are consistent with those of hepatic stellate cells. Our findings suggest that hematopoietic stem cells contribute to the generation of hepatic stellate cells upon liver injury.

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