Therapeutic Effects of Autologous Bone Marrow Cells on Cirrhotic Liver: CD11b+Gr1+ bone marrow cells ameliorate liver fibrosis by producing interleukin-10

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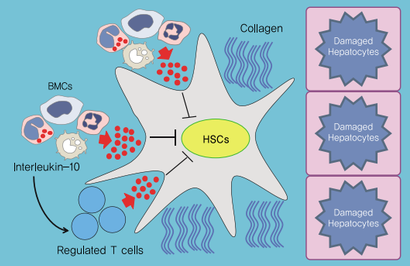


Figure 1. *Anti-fibrotic Roles of BMCs*

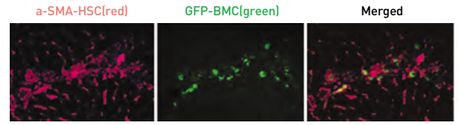
In 2033, viral hepatitis-mediated liver cirrhosis is overcome worldwide, while chronic alcohol consumption or westernized, diet, intake-mediated alcoholic and non-alcoholic liver cirrhosis are sharply increasing in all ages. In this case, all patients with a cirrhotic liver can easily recover by autologous bone marrow cell therapy, which is leading to a huge decrease of social and economic expenses in patients and many foreign patients and people will visit Korea for their therapy and medical tours.

This study demonstrated the beneficial effects of autologous bone marrow cells on patients with liver cirrhosis, which is a representative result of translational research performed at the Graduate School of Medical Science and Engineering, KAIST. In addition, the autologous bone marrow cell infusion therapy will contribute to people's health and welfare and also has huge benefits for social and economic expenses.

Events associated with hepatic fibrosis/cirrhosis are well characterized, notably the excessive production of collagen fibers by activated HSCs. Liver cirrhosis is one of the major causes of morbidity and mortality worldwide but unfortunately there has been no therapeutics except liver transplantation. However, the patients who want to have a liver transplantation have been in trouble with fewer donors, high expenses and side-effects. Contrarily, autologous BMC therapy has many benefits, such as no side-effects, easily obtainable from patients and lowered cost. However, underlying mechanisms are unknown. Thus, the beneficial effects of autologous BMC on patients with liver cirrhosis should be clarified.

Here, we analyzed the early impact of BMC infusion and identified the subsets of BMCs showing antifibrotic effects in mice with carbon tetrachloride-induced liver fibrosis. An interaction between BMCs and activated HSCs was investigated using an *in vitro* co-culturing system. Within 24 hours, infused BMCs were in close contact with activated HSCs, which was associated with reduced liver fibrosis, enhanced hepatic expression of IL-10, and expanded regulatory T cells in the liver at 24 hours after BMC infusion. In contrast, IL-10-deficient BMCs failed to reproduce these effects in fibrotic livers. Intriguingly, in isolated cells, $CD11b^{+}Gr1^{+}$ BMCs expressed more IL-10 after co-culturing with activated HSCs, leading to suppressed expression of collagen and α-smooth muscle actin in HSCs.

Similar to murine data, human BMCs expressed more IL-10 after co-culturing with human HSCs and serum IL-10 levels were significantly elevated in patients with liver cirrhosis after autologous BMC infusion. Surprisingly, 10 of 15 patients after autologous BMC infusion showed improvements. These data reinforce IL-10 as a potential factor in the early response to BMC infusion therapy for treatment of hepatic fibrosis in mice as well as humans.
°°In conclusion, activated HSCs increase IL-10 expression in BMCs, which in turn ameliorated liver fibrosis and expanded hepatic regulatory T cells. Our findings could enhance the design of BMC therapy for liver fibrosis.



Interaction between infused BMC and activated HSCs

Figure 2. Interaction between infused BMC and activated HSCs

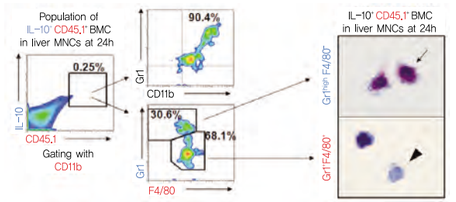


Figure 3. IL-10 Production of $CD11b^{+}Gr1^{+}$ BMC

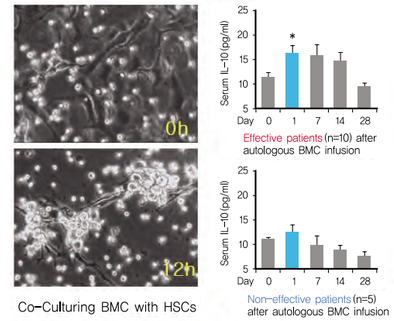


Figure 4. *In vitro* Exp and Serum IL-10 in Patients

⊙ Research Funding

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⊙ Research results

- Nomination of Top 5 on Medical Research Studies performed among 2012 in Korea.
- International Award (7th ISALPD/C) and Blue Ribbon Lecture Award of KSMCB
- Jeong et al., CD11b+Gr1+ bone marrow cells ameliorate liver fibrosis by producing interleukin-10 in mice. Hepatology. 2012, 56(5):1902-12.
- International invitation of lectures (USA, Japan), Domestic invitation of lectures (3 times)