OPEN

Citation: Cell Death and Disease (2013) 4, e849; doi:10.1038/cddis.2013.373

www.nature.com/cddis

News and Commentary

Bringing back the help: autologous bone marrow infusion restores CD4$^+$ T cells in AIDS patients with chronic liver disease

AB Rabson[*,1]

Cell Death and Disease (2013) **4,** e849; doi:10.1038/cddis.2013.373; published online 10 October 2013

In a recent *Cell Death and Disease* article, Liu *et al.*[1] reported a striking observation that portal vein infusion of autologous bone marrow (ABM) in four AIDS patients with severe liver cirrhosis resulted not only in significant clinical improvement of liver function but also a sustained enhancement of CD4$^+$ T-cell levels, as shown schematically in Figure 1. These results raise the important possibility that ABM infusion, in context of concurrent liver disease, can result in CD4$^+$ T-cell reconstitution in AIDS patients. This provocative study, although performed on only a few patients, raises a number of fascinating questions, both mechanistic and therapeutic.

In the absence of liver transplantation, the traditional treatment of late-stage, cirrhotic liver disease has generally involved symptomatic therapies to avert life-threatening complications, such as severe portal hypertension and hepatic encephalopathy. More recently, reversibility of hepatic fibrosis has been demonstrated following antiviral therapy in virally induced cirrhosis.[2] Other studies have focused on directing regeneration of functional hepatocytes, and cellular therapies of chronic liver disease have begun to be tested.[3] In human clinical trials, ABM infusion in late-stage cirrhotic patients resulted in marked improvements in hepatic function,[4] similar to those seen in the patients studied by Liu *et al.*[1] here, and splenectomy similarly markedly enhanced the effects of ABM infusion.[5] ABM infusion was effective in both virally and non-virally caused cirrhosis, suggesting that antiviral activity is not the responsible mechanism. The mechanisms responsible remain largely unknown; however, animal studies suggest that infused bone marrow (BM) cells make matrix metalloproteinases that can remodel and remove fibrous tissue.[6] One major difference between this study and the previous studies was the direct infusion of ABM into the portal vein; However, both intrahepatic artery and portal vein infusions of BM cells have been used by other groups.[6] A critical question is which cells in the infused BM contribute to the response. Although it was initially hypothesized that hematopoietic stem cells (HSCs) had a critical role, more recent work suggests that mesenchymal stem cells (MSCs)[6,7] may be the key cellular element, potentially through their anti-inflammatory and wound healing properties. MSC production of cytokines has been postulated to be the major effector of MSC immune and tissue modulatory functions,[8] and recent studies implicating increased G-CSF and IL-1β in the healing liver, post ABM infusion[9] are consistent with this hypothesis. Specific studies of the effects of BM-derived MSCs on liver fibrosis will help to answer this question.

The most striking aspect of the Liu *et al.*[1] paper was the persistent increase in CD4$^+$ T cells following ABM infusion in these AIDS patients with cirrhosis. Stable reconstitution of CD4$^+$ T-cell number and function, with complete suppression of viral replication and elimination of viral reservoirs, has been the 'holy grail' of AIDS therapy.[10] Such CD4$^+$ T-cell restoration would require HSCs capable of generating new CD4$^+$ T cells that can resist future HIV infection. These could come from endogenous HSCs or from cellular therapies, such as HSC transplantation.[11] In fact, the only documented 'cure' of HIV infection remains in the German AIDS patient who underwent BM transplantation (BMT) from a CCR5 Δ32 homozygous donor (with decreased binding to R5-tropic HIV strains) as treatment for acute leukemia.[12] HIV viral loads in this patient have remained undetectable even in the absence of antiretroviral therapy. These results have prompted more systematic efforts to develop CCR5-mutated HSCs as a more broadly available HIV therapy, either as banked, naturally mutated umbilical cord blood HSCs[13] or as genetically modified autologous HSCs.[14] Recent studies suggest that BMT from CCR5-wild-type, allogeneic donors may have a beneficial, perhaps even 'curative' effect as well, potentially through a graft-versus-HIV effect, supplying an efficient anti-HIV T-cell response.[15] Autologous BMT (ABMT) represents an alternative approach, which would not have the graft-versus-HIV effect but would be less toxic. ABMT is becoming more common in AIDS patients with malignancies;[16] however, in these settings, is accompanied by chemotherapy that has marked inhibitory effects on the host-immune response.

A careful investigation of the mechanism of CD4$^+$ T-cell increase is now required. Questions abound at multiple levels: Are the increased numbers of CD4$^+$ T cells functional, and have these patients regained 'meaningful' T-cell help?[11] *Ex vivo* assays of T-cell function could provide some indication of this. An even more basic question is whether *de novo* production of CD4$^+$ T cells following ABM infusion is

[1]Child Health Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
*Corresponding author: AB Rabson, Child Health Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, 89 French St, New Brunswick, NJ 08901, USA. Tel: +1 732 235 9523; Fax: +1 732 235 9523; E-mail:rabsonab@rwjms.rutgers.edu

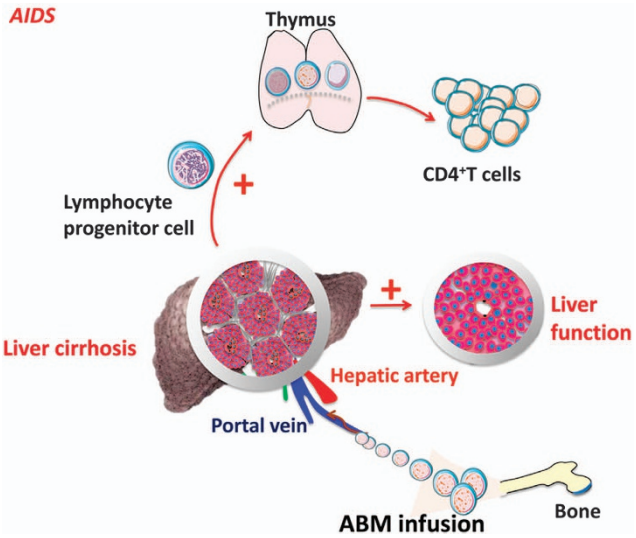

Figure 1 Schematic representation of the results of Liu *et al.*[1] showing that intrahepatic infusion of ABM resulted in enhanced liver function and sustained $CD4^+$ cell increases in patients with liver cirrhosis and AIDS

responsible for the observed increase? This question is answerable by analysis of TRECs (T-cell receptor excision circles found in recently produced T cells), which can confirm production and release of new T cells into the periphery.[17] Alternatively, does ABM infusion lead to increased half-life of existing $CD4^+$ T cells? This is unlikely based on studies of T-cell kinetics with highly active antiretroviral therapies (HAART) alone.[11] Past studies have tested the effects of infusion of autologous $CD8^+$ T cells in HIV patients with some therapeutic effect;[18] however, this is unlikely to explain the increase in $CD4^+$ T cells. Does the coupling of HAART with ABM infusion lead to a more significant effect, allowing the infused hematopoietic cells to persist and to generate new $CD4^+$ T cells? Does the route of infusion (portal vein) have an unexpected role in supporting $CD4^+$ T-cell production and viability?

As with the restoration of liver function in these patients, it will be critical to define the cells in the ABM that are responsible for increased $CD4^+$ T cells. Is this a direct reconstitution of the $CD4^+$ T-cell compartment by progeny of infused HSCs? There was no attempt to purge the BM cells of HIV^+ cells. Would purging of HIV-infected cells through *ex vivo* manipulation potentially enhance efficacy or is it irrelevant? Do MSCs have a role by virtue of their profound immunomodulatory activity? Although some types of MSCs have been shown to be infectable by HIV,[19] there has been little study of the effect of either resting or cytokine-activated MSCs on HIV infection. It is interesting that increases in $CD4^+$, $CD25^+$ T cells have also been observed following ABM infusions undertaken for the treatment of autoimmune disorders, suggesting induction of an as yet unknown regulatory network enhancing $CD4^+$ T-cell production.[20]

Clearly, it is essential that these studies of $CD4^+$ T-cell reconstitution be replicated in larger, controlled patient cohorts, including patients with and without liver disease, to more clearly define the general applicability of ABM infusion in the presence of highly effective antiretroviral therapies. Careful analysis of T-cell function, anti-HIV immune responses and viral load are also essential in future studies. The relatively low, initial $CD4^+$ levels in these patients, even though proviral loads were controlled by HAART, raises the important question of whether similar increases would be observed in patients who have had more significant stable increases in $CD4^+$ T cells from antiretroviral treatment alone. Issues regarding route of administration of BM cells also need to be addressed. This study by Liu *et al.*[1] clearly offers a novel window into the critical goal of true reconstitution of immune response in patients with AIDS, and as such is provocative and noteworthy.

Conflict of Interest

The author declares no conflict of interest.

1. Liu B *et al. Cell Death Disease* 2013; **4**: e739.
2. Schuppan D, Kim YO. *J Clin Invest* 2013; **123**: 1887–1901.
3. Kallis YN, Alison MR, Forbes SJ. *Gut* 2007; **56**: 716–724.
4. Terai S *et al. Stem Cells* 2006; **24**: 2292–2298.
5. Iwamoto T *et al. J Gastroenterol* 2012; **47**: 300–312.
6. Terai S *et al. J Gastroenterol* 2012; **47**: 491–497.
7. Amer ME *et al. Eur J Gastroenterol Hepatol* 2011; **23**: 936–941.
8. Ren G *et al. Stem Cells Translat Med* 2012; **1**: 51–58.
9. Mizunaga Y *et al. Cell Transplant* 2012; **21**: 2363–2375.
10. Durand CM, Flexner C. *Clin Pharmacol Ther* 2013; **93**: 382–384.
11. Scadden DT. *J Hematother Stem Cell Res* 2002; **11**: 759–764.
12. Hutter G *et al. New Engl J Med* 2009; **360**: 692–698.
13. Petz L. *Stem Cells Translat Med* 2013; **2**: 635–637.
14. Li L *et al. Mol Ther* 2013; **21**: 1259–1269.
15. Henrich TJ *et al. Program and abstracts of the XIX International AIDS Conference; July 22-27*, 2012; Washington, DC, USA, Abstract THAA0101.
16. Krishnan A. *Curr Opin HIV AIDS* 2009; **4**: 11–15.
17. Douek DC *et al. Nature* 1998; **396**: 690–695.
18. Ho M *et al. Blood* 1993; **81**: 2093–2101.
19. Gibellini D *et al. Retrovirology* 2011; **8**: 40.
20. Roord ST *et al. Blood* 2008; **111**: 5233–5241.