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Mesenchymal Stromal cells: Heroes or non-combatants?

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Graft versus Host disease (GvHD) is a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation. In the absence of any perfect pharmacological treatment recent attention has focused on cell therapies to treat GvHD. Regulatory T cells (Tregs) are strongly immune suppressive and inhibit GvHD in mice ¹ and men, but there are concerns that within the inflammatory environment of GvHD they may differentiate towards an inflammatory effector T cell phenotype ². Mesenchymal stromal cells (MSC), on the other hand, do not differentiate into inflammatory cells; they enhance stem cell engraftment in mouse models ³, and inhibit T cell proliferation in *in vitro* cell culture ⁴ and also across MHC barriers⁵. Moreover, in *in vivo* mouse models, MSC infusion prolong skin graft survival ⁶. Supported by clinical observations, the potential of MSC to inhibit the alloimmune responses associated with GvHD has created immense excitement in the field of transplantation. Unfortunately, murine GvHD experiments with mouse MSC have produced conflicting results; some showing prevention, ⁷ and others, no prevention of GvHD ⁸. It is worth noting that murine MSC differ from their human counterparts ⁹ raising the concern that mouse models are unreliable indicators of MSC function in man.

In this issue of *Cytotherapy*, Bruck *et al* ¹⁰ found that human MSC failed to prevent human T cell-induced xenogeneic GvHD in mice. The significance of this study lies in the fact that human cells were used. The authors used two well-established models of xenogeneic GvHD in humanized mice. To prevent GvHD, MSC were administered repeatedly using weekly i.p and i.v infusions. MSC treatment delayed GvHD occurrence but was incapable of preventing T cell engraftment long term in both lymphoid and target GvHD organs. Mice were initially protected but later succumbed to GvHD-related mortality. Moreover, no significant difference in Treg numbers or presence were noted following MSC infusion. Interestingly, a single mouse that survived until day 60 post MSC infusion developed chronic GvHD. Thus while the *in vitro* results shown by Bruck *et al* are consistent with previous *in vitro* observations, *in vivo* MSC did not improve survival. Taking into consideration previous work from the same group showing that xenogeneic GvHD could be treated with Tregs or mTOR inhibition ¹¹, the results dampen enthusiasm for using MSC to treat human GvHD. The findings are puzzling when considered alongside the positive clinical results showing that MSC enhance engraftment ¹², cure patients with steroid-refractory GvHD ¹³ and prevent GvHD when co-infused with hematopoietic stem cells¹⁴. However, data on long term outcomes of MSC treatment. (including chronic GvHD) is scanty. The murine experiments should be interpreted as a warning that while MSC infusion can have immediate benefit, they may not confer long-term protection for patients with GvHD.

Although secretory factors may be important in MSC function, their transient engraftment renders them less attractive as a cell product for long term therapy.

The field is certainly confused. On balance, both bench and bedside data suggest that MSC have potential for treating GvHD. However, before we can fully exploit the beneficial properties of MSC, both clinical and laboratory approaches await a better understanding of the basic biology and function of MSC. Identification of specific factors responsible for MSC function could point the way to cell engineering to provide appropriate molecular interventions¹⁵

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