

Proceedings of German Society for Stem Cell Research (PGSSCR)

Human embryonic stem cells elicit an immune regulatory phenotype by upregulating CTLA-4 and IL-10 expression in T cells

Ajjikuttira P^a, Wong SC^b, Penzkofer S^{a*}, Ying JY^a, Kadereit S^{a*}

^aInstitute of Bioengineering and Nanotechnology

^bCenter for Molecular Medicine, Singapore

*University Konstanz, Germany

Published on 16 May 2007

Introduction:

Human embryonic stem cells (hESC) hold great promise for regenerative medicine. Presumably, however, they would be rejected by the immune system of the recipient, as hESC would be transplanted into an allogeneic setting. Surprisingly, previous reports had shown reduced immune reactivity against hESC, with reduced proliferation and reduced cytotoxicity. Underlying cellular immune mechanisms are however not well defined. Interestingly, the inhibitory effect was shown to be soluble factor-independent, as fixation of hESC did not abrogate this inhibitory effect.

Materials and Methods:

We used well established *in vitro* human co-culture systems to investigate mechanisms underlying the immune-modulatory effect of hESC. Fixed hESC were incubated with human peripheral blood mononuclear cells (PBMC) stimulated with allo- and xenoantigens, as well as with strong T cell receptor (TCR) stimulation in presence of co-stimulation. The latter stimulation provides a

strong antigen-independent activation of T cells. We assessed proliferation, apoptosis, presence of regulatory T cells and expression of immune modulators CTLA-4 and IL-10.

Results:

We found that the presence of hESC could reduce specifically T-cell proliferation against allogeneic and xenogeneic antigens, as well as against the much stronger antibody-mediated TCR activation. Reduced T-cell proliferation in presence of hESC was neither due to an increase in apoptosis, nor to an increase in FoxP3+ regulatory T cells. Rather, we showed that T cell stimulation in the presence of hESC resulted in an increase in the proportion of surface CTLA-4 expressing T cell. CTLA-4 is a major inhibitor of T cell proliferation. Concomitantly, we also found an increase in IL-10 secreting T cells. IL-10, a major regulator of inflammation, inhibits T-cell proliferation and plays a role in tolerance induction after hematopoietic stem cell transplantation. Moreover, IL-10 has also been shown to be an effector of CTLA-4-mediated immune regulation.

Conclusion:

Our results thus strongly suggest that the reducing effect of hESC on T-cell proliferation is mediated through upregulation of these two potent immune-regulatory molecules. Moreover, this effect was mediated by membrane-associated molecules on the hESC, as only fixed cells were used. It will be now interesting to characterize such molecules and to specifically address whether their presence would be maintained throughout terminal differentiation of hESC, as for transplantation no undifferentiated hESC would be transplanted.

JSRM
www.pubstemcell.com