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HLA-independent transplantation of human mesenchymal stem cells from bone marrow and adipose tissue for regeneration of bone

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Mesenchymal stem cells (MSC) are an attractive cell population for the regeneration of bone tissue. Some of the potential sources from which these cells can be isolated are bone marrow aspirates and adipose tissue. MSC from bone marrow are negative for immunologically relevant surface markers such as MHC-II and inhibit the proliferation of allogenic T cells *in vitro*. With due consideration for these observations, MSC from bone marrow must be described as immunologically privileged or even immunomodulating cells and could potentially be available for an allogeneic cell therapy.

Before and after osteogenic induction the influence of MSC on the proliferative behaviour of resting and activated allogeneic lymphocytes was studied as a measure of the elicited immune response (mixed lymphocyte culture). At the same points the expression of immunologically relevant surface markers (e.g. MHC-I, MHC-II, CD40, CD40L) was measured and correlations between the different sets of results were sought. In subsequent *in vivo* experiments, MSC from bone marrow and fat tissue seeded on mineralized collagen sponges have been transplanted in a xenogenic mouse model (heterotopic subcutaneous transplantation). Engraftment of MSC has been investigated using in situ hybridisation of human specific Alu-repeats. The pattern of surface antigen expression of mesenchymal stem cells isolated from bone marrow is largely the same as that of stem cells isolated from adipose tissue. Analogous to bone marrow derived cells, undifferentiated cells isolated from adipose tissue lack expression of MHC-II, this being a characteristic that is not lost in the course of the osteogenic differentiation process. With reference to their influence on allogenic lymphocytes, independently of their origin, MSC have analogous immunological features. In co-culture with allogeneic lymphocytes, both cell types fail to lead to any significant stimulation, and they both retain these characteristics during the differentiation process. In co-culture with activated lymphocyte cultures MSC from bone marrow and adipose tissue inhibit proliferation before and after differentiation. 4 and 8 weeks after xenogenic transplantation, engraftment of both cell types could be demonstrated using in situ hybridisation. On a histological level, no relevant immune response against transplanted xenogenic cells could be detected.

Our results confirm that MSC are immune modulating cells. These properties are retained even with osteogenic induction *in vitro* and seem to be characteristic for both MSC from bone marrow and cells isolated from adipose tissue. With regard to the engraftment of MSC after xenogenic transplantation, our results suggest that HLA-unmatched transplantation of human mesenchymal cells from bone marrow and from adipose tissue would be possible, for example in the context of tissue engineering. Nevertheless, for this purpose the ability for adaequat tissue specific matrix synthesis compared to autologous MSC needs to be further investigated.