

Titel	Hematopoietic stem and progenitor cells and potentials for application in fetal cell replacement therapy
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Fetal cell replacement therapy or in utero hematopoietic cell transplantation (IUHCT) is proposed as a non-myeloablative alternative to bone marrow transplantation (BMT) for a number of inborn immunologic, hematologic and metabolic disorders. IUHCT represents the method through which variable amounts of natural or genetically modified hematopoietic cells can be transferred to the fetal recipient in hope of correcting the disorder and preventing postnatal permanent organ damage. Although proof-of-principle has been achieved by successful correction of X linked severe combined immune deficiency (X-SCID), in the majority of target diseases treated with IUHCT engraftment was insufficient for clinical benefit. Thus, the therapeutical promise of IUHCT remains unfulfilled and many challenges stand. In the present thesis we investigate the optimal cell population for IUHCT by first identifying a novel commitment/differentiation step of hematopoietic stem cells (HSCs) in adult murine hematopoiesis and then evaluating the therapeutical potential of the lymphoid primed multipotent progenitors (LMPPs) for immune reconstitution in a model of fetal X-SCID transplantation. We find that LMPPs generate rapid and sustained lymphoid reconstitution with polyclonal T cells, but that HSCs are most likely required for long term engraftment. We also find that the fetal microenvironment is apparently more receptive to donor HSCs (but also LMPPs) as it allows higher levels of chimerism after IUHCT than after BMT in neonatal or adult age. In the last part we investigate in adult and fetal animal models the proposed plasticity of HSCs, a feature that holds promise for clinical BMT (or IUHCT) to non-hematopoietic disorders. We find that HSCs plasticity is a result of heterotypic cell fusion, probably induced by inflammation/injury in the target tissue. We also show that heterotypic cell fusion is not a physiological frequently occurring event during development and we demonstrate that not only myeloid, but also lymphoid cells are efficient fusogenic partners to non-hematopoietic tissues.