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11

In utero stem cell transplantation and gene therapy: Recent progress and the potential for clinical application

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Advances in prenatal diagnosis have led to the prenatal management and treatment of a variety of congenital diseases. Although surgical treatment has been successfully applied to specific anatomic defects that place the fetus at a risk of death or life-long disability, the indications for fetal surgical intervention have remained relatively limited. By contrast, prenatal stem cell and gene therapy await clinical application, but they have tremendous potential to treat a broad range of genetic disorders. If there are biological advantages unique to fetal development that favor fetal stem cell or gene therapy over postnatal treatment, prenatal therapy may become the preferred approach to the treatment of any disease that can be prenatally diagnosed and cured by stem cell or gene therapy. Here, we review the field including recent progress toward clinical application and imminent clinical trials for cellular and gene therapy.

Prenatal stem cell therapy

Currently, the most likely and imminent applications of stem cell therapy to the fetus are in utero hematopoietic stem cell transplantation (IUHCT) and in utero mesenchymal stem cell

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transplantation (IUMSCT). Our discussion is confined primarily to IUHCT as a paradigm for all prenatal stem cell therapies. The hematopoietic stem cell (HSC) is a multipotent stem cell that maintains functional hematopoiesis by generation of all hematopoietic lineages throughout fetal and adult life [1]. It is the most extensively characterized stem cell and the only stem cell that has been prospectively isolated to purity. While HSCs derived from embryonic or fetal sources may have many biological advantages, there are significant practical and ethical barriers to utilizing the embryo or fetus as an HSC source [2]. Thus, we believe that the most likely initial application of IUHCT will utilize adult HSC derived from bone marrow (BM) or peripheral blood (PB), and we focus our review on this specific approach.

The rationale for IUHCT

The rationale for IUHCT is based on unique events that occur during normal development, which may facilitate cellular engraftment [3]. The most important event is the induction of fetal tolerance [4]. In the early phase of gestation, the immune system undergoes a process of self-education. This occurs primarily in the fetal thymus and consists of two components: the positive selection of pre-lymphocytes for recognition of "self" major histocompatibility complex antigen (MHC) and a negative selection (deletion) of pre-lymphocytes that have high-affinity recognition of self-antigens in association with self-MHC. This leaves a range of lymphocytes that recognize foreign antigens in association with self-MHC [5,6]. Thus, the introduction of foreign cells prior to completion of this process should result in donor-specific immune tolerance. Current understanding of human immune ontogeny would predict the emergence of effector lymphocytes from the thymus at around 12–14 weeks of gestation, which has historically been considered the theoretical limit of the "window of opportunity" for IUHCT-induced tolerance. However, there is now an abundance of data supporting mechanisms of peripheral tolerance, predominantly via T-regulatory cells that are generated in the thymus and migrate to peripheral tissues to suppress self-reactive T-effector cells that escape thymic deletion. Recent studies on IUHCT [7–9] suggest that similar mechanisms may protect the graft against rejection and the host from graft-versus-host disease (GVHD). This balance of effector/regulatory activity may extend the limits of tolerance induction, but there are no data currently to conclusively define a late limit for clinical IUHCT.

Experimental support for IUHCT

Fleischman and Mintz administered transplacental injection of donor BM cells at E11 into fetal mice with a stem cell deficiency in the absence of c-kit [10]. These early studies were directed toward questions in stem cell biology rather than IUHCT as a therapeutic approach; nevertheless, they established the basic principle that high levels of engraftment could be achieved when a competitive advantage exists for donor cells. In these studies, the degree of erythroid replacement correlated with the degree of underlying anemia, with complete early replacement by donor erythroid cells in lethally anemic homozygous mice. Blazar et al. extended this to lineage deficiency by demonstrating only lymphoid reconstitution (split chimerism) in the mouse severe combined immunodeficiency (SCID) model, which has a T-cell proliferation and survival defect [11,12]. These studies reaffirm the importance of host cell competition, whether at the level of the stem cell, or lineage progenitor in limiting engraftment after IUHCT.

Until relatively recently, the majority of studies of IUHCT in normal animal models including the goat [13,14], dog [15,16], primate [17–20], and mouse [21–24] demonstrated minimal or no detectable engraftment. The exception is the ovine model. Early experiments in the ovine model achieved an allogeneic engraftment level of up to 30% after a single injection of fetal liver-derived donor cells [25]. In general, however, results obtained in the sheep model have not been translated into human clinical application, thus limiting its value as a preclinical model.

With increasing experimental and clinical experiences, it became clear that there were significant barriers to successful engraftment after IUHCT, and that the fetal hematopoietic environment posed very different challenges than those encountered in postnatal BM transplantation [3]. In order to systematically examine the relative importance of these barriers and develop strategies to overcome