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12

The case for intrauterine stem cell transplantation

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The clinical burden imposed by the collective group of monogenic disorders demands novel therapies that are effective at achieving phenotypic cure early in the disease process before the development of permanent organ damage. This is important for lethal diseases and also for non-perinatally lethal conditions that are characterised by severe disability with little prospect of postnatal cure. Where postnatal treatments are limited to palliative options, intrauterine stem-cell therapies may offer the potential to arrest pathogenesis in the early undamaged fetus. Intrauterine stem-cell transplantation has been attempted for a variety of diseases, but has only been successful in immune deficiency states in the presence of a competitive advantage for donor cells. This disappointing clinical record requires preclinical investigations into strategies that improve donor cell engraftment, including optimising the donor cell source and manipulating the microenvironment to facilitate homing. This chapter aims to outline the current challenges of intrauterine stem-cell therapy.

Introduction

As with intrauterine gene therapy (reviewed by Mattar et al. in this issue of *Best Practice and Research Clinical Obstetrics and Gynaecology*), the objective of intrauterine stem-cell therapy (IUSCT) is to remedy a monogenic disease in the fetus through delivery of functioning stem cells that engraft in the host and, through normal proliferation, return the missing protein to normal levels. Allogeneic or

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autologous stem cells can be used as donor cells, although the latter must undergo genetic manipulation to be suitable for transplantation. The justifications for IUSCT are similar to the rationale used in intrauterine gene therapy, where a disease is selected for treatment that is either perinatally lethal or where early onset pathology and a lack of adequate postnatal therapy results in permanent severe morbidity. Additionally, the selected disease must be amenable to phenotype rescue with stem-cell transplantation in a postnatal recipient. This chapter aims to outline the justifications for IUSCT, candidate diseases, autologous and allogeneic strategies, and discuss briefly the clinical obstacles to surmount before human application.

Applicability of stem-cell therapy to monogenic disease

Certain monogenic diseases have been selected for haemopoietic stem cell therapy (HSCT) in adults or children. Such diseases have in common a primary pathology (e.g. failure of erythropoiesis) that is often accompanied by progressive secondary organ damage (e.g. cardiomyopathy), availability of palliative rather than curative treatments, treatment-related complications that add to the disease burden, and are often lethal if sub-optimally treated.

Haemopoietic stem-cell transplantation is the most extensively investigated form of stem-cell therapy and is potentially applicable to several monogenic disorders *in utero* (Table 1). Some diseases are treatable and potentially curable with postnatal HSCT, such as the haemoglobinopathies[1] and severe primary immunodeficiencies.[2] Haemopoietic stem-cell transplantation may potentially arrest neurological deterioration in demyelinating or lysosomal enzyme-deficiency syndromes.[3,4] Recent evidence indicates that allogeneic HSCT, with or without co-transplanted mesenchymal stem cells, can lead to significant biochemical and phenotype improvements in women with recessive

Table 1
Clinical attempts at intrauterine stem-cell therapy for monogenic diseases.

Disease	Authors	Specific disorders	Donor cells	Outcomes
Haemoglobinopathies	Hayward et al., 1998[88] Westgren et al., 1996[89]	Alpha-thalassaemia	Paternal bone marrow; liver	Microchimerism observed, but transfusion-dependent
	Westgren et al., 1996[89] Touraine, 1991[90] Touraine et al. 2004[91]	Beta-thalassaemia	Parental and sibling bone marrow or peripheral blood progenitor cells; autologous fetal cells	Variable engraftment; no phenotype rescue and surviving recipients remained transfusion-dependent
	Westgren et al., 1996[89]	Sickle cell disease	Fetal liver cells	Transfusion dependent
Primary immune deficiency syndromes	Touraine et al., 1989[61] Wengler et al., 1996[58] Flake et al., 1996[60] Westgren et al., 2002[59] Touraine et al., 2004[91]	Bare lymphocyte syndrome Severe combined immunodeficiency Chronic granulomatous disease	Fetal liver cells and parental bone marrow cells	Survivors with bare lymphocyte syndrome and severe combined immunodeficiency showed engraftment and good outcomes; fetuses with chronic granulomatous disease showed no engraftment.
Musculoskeletal disease	Le Blanc et al., 2005[86] Chan (unpublished data)	Osteogenesis imperfecta	Fetal mesenchymal stem cells	Chimerism with improvement in growth and reduction in fracture incidence
Inborn metabolic diseases	Flake and Zanjani 1997[92] Leung et al., 1999[93] Bambach et al., 1997[94]	Globoid cell leukodystrophy Hurler syndrome MPS I Niemann-pick disease Metachromatic dystrophy	Fetal liver and parental bone marrow cells	Overall no engraftment reported and poor outcomes