Fetal cell/tissue therapy in adult disease: a new horizon in regenerative medicine

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Summary

Fetal tissue is the richest source of primordial stem cells and has several properties that make it particularly useful for transplantation. It is superior to adult (mature) tissue in certain respects. First, fetal cells are capable of proliferating faster and more often than mature, fully differentiated cells. This means that these donor cells are able to quickly reverse the lost function of the host. In addition, these fetal cells can often differentiate in response to the environmental cues around them. This is because of their location – they can grow, elongate, migrate, and establish functional connections with other cells around them in the host. It has been found that fetal tissue is not easily rejected by the recipient due to the low levels of histocompatibility antigens in the fetal tissue. At the same time, angiogenic and trophic factors are at high levels, enhancing their ability to grow once they are transplanted. Since early fetal hematopoietic tissue lacks lymphocytes, graft vs host reactions are minimized. Fetal cells tend to survive excision, dissection, and grafting better because they generally do not have long extensions or strong intercellular connections. Finally, fetal tissue can survive at lower oxygen levels than mature cells. This would make them more resistant to the ischemic conditions found during transplantation or in vitro situations.

Studies on fetal cell/tissue transplant have been encouraging. Fetal tissue can be used in different indications, for instance, fetal liver transplants may be used in combating aplastic anemia, placental umbilical cord whole blood transfusion can serve as an emergency alternative to adult whole blood transfusion, fetal adrenal transplant has been tried in combating intractable pain in arthritis, and fetal thymic transplant in combating leucopenia in non-Hodgkin's lymhoma and other immunodeficiency conditions like DiGeorge Syndrome, only to name a few. Fetal brain tissue transplant has also been done in a heterotopic site and the proliferation of the tissue has been observed. Neurotransplantation with fetal tissue in Parkinsonism shows positive results in some globally accepted studies.

There are futuristic potential uses of fetal tissue in bioengineering through coating/seedling of fetal tissue on implants, stents and other artificial surgical life-saving devices to improve their functioning, and it may also extend the life of these costly gadgets. By properly using pre-HLA fetal tissue seedling in orthopedic, thoracic and also neurosurgical appliances, there could be a reduction of long-term irritation sequelae of the implant and the host interphase, and thus, a better device, i.e., a more biofriendly interphase could be developed. This may help in the reduction of pseudomembrane formation, loss of patency and other resultant TH2 reactions of the host system.

Key words: Stem cell-rich human fetal tissue transplant; Host integration; GVH; Regenerative medicine; Fetal cell therapy.

Introduction

One of the most important medical advances in the field of the treatment of intractable disease has come from stem cell or clone research (nuclear transplant). Nuclear transplant has more abusive potential and more ethical controversy is attached to it. Stem cell research offers enormous potential for the treatment of both malignant and nonmalignant disorders, due to its surprising plasticity and versatility. Stem cells derived from adults can be detected in astroglial cells of the central nervous system, skeletal muscles, osteoblasts, liver, cardiomyocytes, vascular endothelial cells, etc. Astonishing new findings are being made every day. Stem cells have the potential to treat cancer, bone marrow failure syndrome, hemoglobinopathies, inborn errors of metabolism, immunodeficiencies and many more disease conditions. New developments include stem cell treatment for strokes, metabolic disease, muscular dystrophy and cartilage disease. There is a possibility that patients suffering from an entire list of human diseases and miseries may benefit from these new developments.

The question may be raised as to whether adult stem cells can be a substitute for fetal or embryonal stem cells. In an open letter to President George W. Bush, 80 scientists including several Nobel laureates sent an appeal to the President: "Current evidences suggest that adult stem cells have markedly restricted differentia-

tion potential … than fetal or embryonal stem cells" [1]. The U.S National Institute of Health also issued a policy statement in the year 2001 in which it asserted that, "There is considerable evidence that adult stem cells may have limited potential compared to pleuripotent stem cells derived from embryos or fetal tissue" [2].

Fetal tissue is the richest source of tissue specific and non-specific primordial stem cells whose enormous regeneration capacity and the possible role in the reversal of Hayflick's limit of replicative senescence has not been evaluated properly so far in medicine and biology, even though stem cell therapy has been found to have a positive impact in its regeneration ability involving bone, blood, liver tissue, brain damage, disorders of the eye, spinal cord, stroke, kidney disease, muscle disease, heart disease, diabetes, cardiovascular disease, etc.

Why and how the fetus survives in utero, violating the laws of classical transplantation immunology, remains a mystery. There is no direct contact between the mother and the growing fetus, except at the extra-embryonic placental site, where the growing fetus expresses HLA-C, HLA-E and HLA-G [3]. Therefore, maternal allorecognition, mediated through progesterone and interleukin dependent natural killer (NK) cells ($CD56^{bright}$), can be assumed to exist and this NK cell number progressively decreases from mid-gestation to term. It has been further observed that in order to survive the hostile maternal environment, the feto-placental unit adjusts itself as an allograft and follows the path of the older innate immune system, taking advantage of its hypo-antigenicity and the tacit support of non-cytopathic blocking antibodies of the mother, as an additional guard. To achieve its multiple goals of growth, maturation and non-recognition by the host system and simultaneously, to prepare its own immune system to grow and to differentiate between itself and non-self identities, the fetal cells and their stromal support which constitute the fetal tissue, selectively participate with the growing immune system in the up-regulation and the down-regulation of the antigenic expression of the cell/tissue, and in the process acquire many specialized characteristics including immortality.

Potential use of some immortal cells in tissue or cellular regeneration biology

Cells in the human system can be classified under two basic groups, mortal cell line (most of the cells in our body), and immortal cells, i.e., cancer cells and certain specialized fetal cells, for instance, stem cells. In case of mortal cells, with each cell division the telomeric end diminishes in size until it reaches an irreducible stage when there is cellular senescence which stimulates apoptosis (programmed cell death). In case of immortal cells like stem cells or cancer cells, there is no reduction in size of the telomeric end with each cell division due to the presence of reverse transcriptase which restores the size of the telomeric end after each cell division.

Stem cells are unique, undifferentiated cells which can divide and renew themselves for long periods of time and can even respond to demands and change their characteristics according to their milieu. Thus, they have all the potential to become the source of repair for damaged or diseased tissue.

Stem cell research actually started after the first description of stem cells by Stevens, Martin and Evans [4]. The existence of the concept of some form of stem cells began among scientists working on the problem of bone marrow repopulation after ionizing radiation [5]. Today, stem cells can be obtained from embryonal sources (inner cell mass stage of development), fetal sources (fetal organs like the liver, etc.), neonatal sources (placenta and cord blood after the birth of a baby) or from mature adult sources. A discarded human placenta after the birth of a baby contains enough placental cord blood stem cells to supply the total stem cell demand of a 40 kg individual.

These undifferentiated cells have the ability to reproduce rapidly at a rate much higher than that of other cells and can specialize according to the environment into various tissues subtypes. With maturation embryonal stem cells lose their totipotency gradually but the pleuripotency remains, for example, human mesenchymal stem cells are pleuripotent cells that are able to differentiate along different pathways including osteogenic, adipogenic and chondrogenic pathways. These mesenchymal stem cells play an important role in tissue regeneration and their frequency in fetal tissue is much higher than in adult tissue. After the completion of organogenesis, the ability of most tissues to withstand damage due to illness or injury depends on tissue-specific stem cells present in various organs.

After transplantation stem cells can survive engraft, specialize under regulatory control of the host, and even participate in the repair of damaged cells and restore their function. Moreover, embryonic stem cells

can reach any damaged site through migration, establish intracellular links, and liberate specific cytokines under proper and adequate stimulation. For example, embryonic ectoderm derived nerve cells may be used to treat Parkinson's disease or spinal cord injuries. Embryonic entodermal derived insulin-producing cells might be used to treat diabetes and mesodermal stem cell derivatives might be used for the treatment of leukemia or heart disease.

Adult tissue also contains stem cells, which remain in a quiescent phase. Adult stem cells have been discovered in the adult liver [6], brain [7] pancreas [8], etc. With fascinating new developments in the field of stem cell research, not a single branch of medicine can escape from the neo-regenerative clinical implications of stem cell research, i.e., repair of the heart after a heart attack, or for palliation from neurodegenerative disease conditions, etc. and even in cases of multiple sclerosis or lupus erythematosus, stem cell therapy may be useful. Recent stem cell researchers have suggested that diabetes in mice could be reversed [9], blood cells may be made from muscle cells, bone marrow stem cell can be converted to brain cells [10], or in case of liver failure, stem cells can help in the formation of new liver tissue. In muscular dystrophy or acute leukemia or even atherosclerosis, stem cell technologies can extend life and relieve the suffering of patients and can even reverse replicative senescence (Hayflick's effect) [11], which has immediate implications for geriatric patients with multiple organ failure or dysfunction.

Fetal tissue transplant uses all sources of fetal tissue collection, i.e., ectopic pregnancy, still birth, spontaneous abortion, etc., but the reliability, quality and safety of these sources have to be examined thoroughly before using fetal tissue. In cases of any suspicious abnormality in growth/maturation due to intrinsic (genetic) defects or extrinsic causes, for instance, toxoplasma, rubella, cytomegalovirus, herpes simplex, etc., which may have actually triggered an abortion process, the specimen should be discarded immediately. Only induced abortion cases after proper screening should be used for fetal tissue transplantation. In our laboratory, fetal tissue is collected from consenting mothers admitted for hysterotomy or ligation [12-20].

Use of fetal tissue in basic research

Scientists use fetal tissue for numerous purposes, i.e., for basic research in human genetics as well as in the development of new drugs and vaccines. Fetal cell cultures have special characteristics – they can allow reproduction of human viruses so that experimentation on the diagnosis of diseases and production of vaccines may be undertaken. In 1930, fetal cell cultures were first used in patients suffering from diabetes. The importance of the healing and curative potential of fetal tissue has been recognized since then. In 1950, fetal kidney cells were used to help develop polio vaccine and subsequently, it was also used to develop rubella vaccine and for the prenatal diagnosis of genetic diseases. Fetal cells have, moreover, been used to study (1) how smoking affects the fetus by examining the carcinogenicity of tobacco on fetal cells, (2) the mechanisms of viral infections, and (3) inherited diseases.

Fetal cell/tissue transplant in neurodegenerative conditions

There are billions of nerve cells in the human brain. In neuro-degenerative diseases like Parkinson's disease or Huntington's disease, selective loss of some 500,000 cells in critical regions of the brain can cause devastating symptoms with varying degrees of rigidity/tremor/dyskinesia, to name a few. Neuro-degeneration in these patients continues from years to decades, leading to conditions like lack of movement (Parkinsonism) or excessive movement (Huntington's disease). Neuroscientists are currently engaged in research on finding ways to replace the neurotransmitters in the brain through pharmacological means, for instance, through the use of L-Dopa, Bromocriptine, monoamino-oxidase inhibitors, etc. However, with time, the drugs progressively lose their efficacy. As standard pharmacological therapies become ineffective through prolonged use, alternative strategies are attempted at centers of excellence, by CT-guided stereotactic placement of dopaminergic cells from the patient's own adrenal medulla, from genetically engineered cells, or from fetal mid-brain tissue sources. Intense research work is currently being directed towards drugs that may block nerve cell death and also towards novel cell-based therapies, e.g., stem cells from embryonal sources or fetal sources. Numerous animal experimentations over the last decade have provided evidence that implanted fetal neurons can replace dead host neurons by forming effective synapses with host neurons, and can synthesize necessary neurotransmitters. In this way, dopaminergic cells collected from fetal sources (adrenal medulla or substantia niagra) can grow in the Parkinson's patient's brain and if even a minute quan-

tity, i.e., one tenth of a million of the total number of nerve cells, grows in the host's brain, movement disorders show a marked improvement. Apart from Parkinson's disease, other indications of fetal tissue use include Alzheimer's disease, stroke, spinal cord injury, motor neuron disease and muscular dystrophy, only to mention a few [21].

We have transplanted fetal brain tissue (1 g of cortical tissue 1 cm from the frontal opercula) in a heterotopic site, i.e., the axilla, in 12 patients suffering from varying degrees of Parkinsonism. These patients were evaluated at pre- and one month post- transplantation by the Unified Parkinsonism Rating scale (0-108), and 83.2% of the cases showed a mild to moderate improvement from the pre-transplant state within one month [18]. We have conducted similar experimentation with fetal adrenal tissue transplants to combat pain and inflammation in advanced rheumatoid arthritis, and these too, have shown unique positive results [19].

Use of fetal tissue in immunodeficiency conditions

In congenital immunodeficiency (DiGeorge syndrome, which is a rare birth defect where the baby is born without a working thymus and parathyroid along with increased susceptibility to infections, hypocalcemia and congenital heart defects), fetal thymus transplant can have a positive impact on the overall immune reconstitution [22].

In other cases of acquired immunodeficiency, leucopenia may be corrected with fetal thymus transplantation. We reported a case of a non Hodgkin's lymphoma, Ann Arbor Stage IV, who developed leucopenia during chemotherapy, but dramatically improved with fetal thymus transplantation [15]. Attempts have also been made to reconstitute the immune system by fetal liver (8-13 weeks old; the risk of graft vs host reaction is more if it is a 20 weeks or older fetus) transplant in severe immunodeficiency conditions. Additionally, a fetal thymus transplant on the same patient from the same donor may help even further [23].

Fetal tissue privileges in transplantation biology

Transplantation biologists are also concentrating on fetal tissue research. The potential to cure experimentally induced diabetes mellitus in animals through the syngenic transplantation of fetal pancreas has been documented [24].

Fetal tissue has the potential to revolutionize the science of transplantation, since it grows more quickly than adult tissue and is far less specialized, which means easy adaptability to foreign tissue. In the future, it will be no surprise to transplantation biologists if fetal cell/tissue transplant gradually replaces adult tissue/organ transplant. This is because of the intrinsic advantages of fetal tissue for better integration, growth and differentiation due to its higher telomer content and its lack of proper HLA expression and hence, less graft *vs.* host reaction.

Our experience since 1999 with umbilical cord whole blood transfusion as an emergency alternative to adult whole blood transfusion, suggests that the procedure is absolutely safe and effective [13, 14, 17, 20]. We have also transplanted fetal heart, lung, pancreas and liver tissue in a heterotopic site and there was no immunological or inflammatory reaction in these HLA and sex-randomized fetal tissue transplant cases [16]. Fetal liver transplantation has been attempted in aplastic anaemia for immune reconstitution and also in acute mylegenous leukemia since 1987 [25].

Animal experiments have shown that transplanted fetal liver cells are capable of restoring hematopoiesis and immunity in lethally irradiated rodents. Experiments in dogs have demonstrated that non histocompatible antigen-mismatched fetal liver grafts can restore T and B-cell function in irradiated dogs [26].

Fetal cells have the additional ability to produce trophic substances that not only increase their own ability to survive and grow but can also promote regeneration of damaged tissue. Angiogenic factors from the fetal tissue can promote blood vessel formation and nerve growth factor released from fetal neuroblasts can assist fetal tissue regeneration [27].

Hence, with the use of fetal tissue for transplants, the role of immunosuppressive drugs would be minimized, and the possibility of long-term potential complications of the induction of malignancy and other disease conditions could be reduced, leaving aside the problem of procurement of organs and the present day prohibitive cost of organ transplantation surgery.

According to one report from the United States, there is a progressive and increased disparity between the demand and supply of the organs needed for patients awaiting organ transplantation. While the number of patients awaiting transplant increases at approximately 15% per year the number of cadaver donors increases

by only 1-3% [28]. Whether fetal tissue/cellular transplant has the potential for filling the existing gap of demand and supply, is a matter under intense scientific study.

Potential use of fetal cell/tissue in bio-engineering

The principle of cell transplantation in bionic devices as a replacement of diseased or failing tissue functions of an organ may have many potential fields of application. Hypoantigenic fetal tissue has the possibility of making a perfect non-irritant, i.e., a biofriendly interphase in case of different synthetic/metallic grafts used in medicine and surgery. Another approach could be seedling with embryonal stem cells over a metallic graft. Since embryonal stem cells do not express Class II HLA molecules apart from the lack of dendritic cells responsible for allorecognition and immune response [29], the implant is made more immunofriendly, and less implant/host interphase reaction is expected as a result.

Any stent in the body, be it in the prostate, pancreas, common bile duct or coronary artery, can possibly be made much more biofriendly through a fetal pre-HLA endothetial cell lining and this can also lead to a minimization of progressive platelet and other cellular interaction/*vis a vis* erosion; and it can also help to extend the life/patency of these stents. In cardiovascular surgery, clinical endothelial cell lining with polytetrafluoroethylene graft has a long clinical experience. It has been observed that a synthetic prosthesis is equal or better than a saphenous vein graft with regard to patency in all positions and at different stages of clinical diseases [30, 31]. The replacement of arteries with purely synthetic vascular prostheses often leads to failure in low turbulence situations or small diameter vascular flow situations, due to progressive increased thrombogenicity of the internal graft surface. In order to increase the long-term patency, the concept of endothelial cell seedling was mooted and it was found to be a better and more biocompatible vascular substitute. The performance may improve further if it is a 1- or 2-stage harvested culture of autologous or non autologous cells, and the impact is found to be clinically superior in certain studies. However, the non autologous cells also express HLA. Hence, long-term rejection can not be avoided, unless of course radiation priming or anticancer drug lining is applied. Pre-HLA fetal tissue seedling could be a rational alternative in such situations.

In orthopedic surgery, total hip/knee/shoulder replacement devices if allowed to be covered with pre-HLA fetal cells can also help extend the life of the implant by the biofriendly interphase formation which can minimize the lining tissue and inert tissue interphase interactions and thus prevent TH_2 cellular responses by fibroblast proliferation and other tissue specific degranulation/degradation attempts by the host tissue. There is an interesting article by Stocum [32] on regeneration biology and engineering strategies for tissue restoration which is worth reading.

Future direction and unresolved problems

There have been attempts at developing alternatives to fetal tissue transplant. Costly high tech alternatives to the use of human fetal tissue are also available for immunodeficieny disorders (e.g., bone marrow transplant) and in diabetes mellitus (e.g., adult islet cell transplantation). In neuronal transplantation, cell culture with the support of growth factors, which can help convert some paraneuronal cells to neuronal cells, may have the potential to be a second approach. Xenotransplantation with advanced immunosuppressive therapy is a possible third approach. The fourth, and a budding high-tech approach, is the use of genetically engineered cell lines by the insertion of oncogenes capable of both proliferating and producing specific substances, *viz*, neurotransmitters.

Although the initial trial reports of stem cell transplants have been encouraging, little attention has so far been paid to the problem of the eventual increase in immunogenecity of the transplanted stem cell/fetal cell/tissue, through proliferation and differentiation in the host system. For example, *human embryonal cells express HLA Class I but not Class II molecules and they lack dendritic cells. There is a possibility that the progressive expression of these molecules will increase with time through differentiation in vitro to embryoid bodies, and in vivo to terratomas. Hence, in order to thwart the long-term potential complications of immunogenicity and eventual cellular rejection, other approaches should be considered: (1) therapeutic cloning or nuclear transfer, (2) genotyped stem cell banking, (3) attempted genetic modification to create a universal donor type of stem cell, (4) use of nonspecific advanced immunosuppressive drugs, (5) hematopoietic chimerism of the recipient or other immunomodulation approaches [33]. If, in the long-run, cellular*

rejection does take place, then the possibility is that the clinical advantages we get with the fetal tissue transplant may be due to the impact of trophic hormones and cytokines associated with the growing fetal tissue on the host system. These are some of the issues to be examined and solved in the future.

Ethics

Lastly, one important question may be raised, i.e., the ethical issue of fetal tissue transplant. There is, of course, a fine line that is chalked between being ethical and being corrupt. State/country regulations must be effective in order to ensure that a woman is never coerced into having an abortion, so that the medical scientist can have the extra tissue needed for a procedure. Fortunately, technology today has enabled the storage and preservation of fetal tissue for a significant period of time. Supply and demand can therefore coincide.

The use of fetal tissue will raise certain value-loaded questions in society about life, death and parenthood. It is undoubtedly a very complex issue, but if simple rationality prevails, one will fail to understand why the discarded fetus going to a pink box/incinerator, should not be used in a worthy potential life-saving endeavor, thoroughly screened and in front of the eagle eye of an ethical committee and senior medical experts, who will justify the procedure with objectivity, provided the woman having the abortion gives her proper informed consent.

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