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Review Article

Stem Cell therapy in Pediatric Endocrine Disorders

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ABSTRACT

In the last decade stem cell therapy has emerged as a promising treatment modality in treatment of number of diseases including autoimmune disorders. A number of studies have shown that stem cells exhibit significant immunomodulatory properties which could be utilized in successful treatment of autoimmune diseases particularly type 1 diabetes and autoimmune thyroid disease seen in children. Human and animal studies have demonstrated that stem cells have the ability to differentiate into insulin producing beta cells, which could provide an excellent treatment strategy for subjects with type 1 diabetes. Stem cells could also decrease the need for immunosuppression in these patients, which is associated with significant long-term side effects. Evidence also shows that stem cells can be successfully differentiated into endodermally derived cell lines such as thyroid follicular cells which may be potentially used therapeutically in autoimmune thyroid disease i.e. Grave's disease and Hashimoto's thyroiditis. Other areas of interest for stem cell oriented management protocols are being explored in Parkinson's disease, Crohn's disease, leukemia, multiple sclerosis and Systemic Lupus Erythematosus (SLE).

Introduction

In the last decade, stem cell therapy has emerged as a promising treatment modality in the treatment of autoimmune diseases. Stem cells are primitive undifferentiated cells capable of self-renewal and differentiation into to virtually any tissue or organ [1]. They demonstrate infinite regenerative capacity additionally to the ability relocate and differentiate where needed. There are three categories of stem cells namely embryonic stem cells (ESCs), cord blood (CB) stem cells, and adult stem cells (ASCs) [2]. Embryonic stem cells originate in, and are derived from the inner cell mass of the human blastocyst and have latent differentiation capacity for endodermal, mesodermal, and ectodermal cell line origins. Cord blood stem cells are derived from umbilical cord hematological tissue and differentiate into adipogenic, osteogenic, chondrogenic, bone marrow tissues and hematological cell types [3-5]. Adult stem cells are undifferentiated cells found among differentiated cells in a tissue or organ and exhibit the property of trans-differentiation or plasticity. Through isolation and culturing procedures combined with targeted manipulation, such cells can be used to replace diseased, damaged, or dead terminally differentiated cells inherently incapable of self-reorganization, restructuring and self-regenerative capacities. Studies both vitro and vivo exhibit results indicating stem cell ability to exert observable immunomodulatory effects [3, 4, 6, 7]. Evidence demonstrates that mesenchymal stem cells (MSCs) have the ability to regulate T-cell function by promoting regulatory dendritic cell (DC) generation. MSCs also modulate alteration of dendritic cell cytokine profiles by effecting augmented secretion of regulatory cytokine chemical messengers such as IL-10 and by causing a decrease in production of inflammatory cytokines such as Interferon gamma, IL-12 and Tumor Necrosis Factor alpha resulting in an anti-inflammatory or tolerant dendritic cell phenotype [8, 9]. These immunomodulatory effects have sparked interest in stem cells for treatment of autoimmune disorders and a number of clinical trials are underway in this area. MSCs have been employed with some success in treatment of type 1 diabetes, Parkinson's disease, autoimmune thyroid disorders, graft versus host disease (GVHD), Crohn's disease, multiple sclerosis, and in systemic lupus erythematosus [10-13]. Application in leukemia or chemotherapy

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and infusion of post-infarct myocardial tissue has also been explored. MSCs have additionally been used for cell therapy and gene therapy [14, 15]. Uncomplicated harvesting procedures from bone marrow aspirate and proclivity for cell line expansion in culture makes them potentially useful for cell and gene therapy [15]. This review will focus on role of stem cell therapy in type 1 diabetes and autoimmune thyroid disorders.

Stem cell therapy in type 1 DM:

Type 1 diabetes (also known as insulin dependent or juvenile diabetes) is an autoimmune disorder caused by caused by immune mediated destruction of pancreaticbeta (β) cells in islets of Langerhans resulting in impaired insulin secretion [16]. Type 1 diabetes incidence is increasing on a global scale and is associated with significant clinical morbidity. In the United States, more than 15,000 – 40,000 children are diagnosed with Type 1 diabetes annually (www.jdrf.org). A European study, which evaluated demographics from 17 countries confirmed 29,311 new cases of type 1 diabetes annually and this number is projected to double by 2020 [17]. Onset of autoimmune diabetes is preceded by infiltration of pancreatic islets by immune cells and a break in self-antigen tolerance allowing activation of auto-reactive T cells against β-cells. This pathogenic process progresses insidiously over a variable time period, becoming clinically evident when the mass of Langerhans islets destroyed results in hypo-secretion of insulin. Without sufficient beta cells the patient becomes insulin dependent and requires exogenous insulin for survival. These patientsare at risk for a number of complications including diabetic ketoacidosis, shock and hyperglycemic hyperosmolar syndrome [18]. In type 1 DM, although insulin replacement increases survival,it provides only temporary management and is not curative. Such therapy does not prevent a multitude of long-term complications, which affect multiple body systems [19]. Other forms of intervention attempt to reverse the disease process if early diagnosis is established, using immunosuppression with agents such as anti-CD3 agents [20]. Immunosuppression provides some clinical benefit in terms of sparing islet reserve, however it is associated with significant long term toxicities and complications. Moreover, differentiated beta cells cannot be expanded efficiently in vitro [21]. Some promising results have already been obtained throughapplication of embryonic stem cells of both rodent and human origin [22,23,24]. Hisanagaet al. demonstrated an induction method of murine bone marrow derived mesenchymal cells allowing differentiation in to insulin secreting cells using conophylline and betacellulin-delta 4 [25]. This study observed that mouse bone marrow derived mesenchymal cells expressed insulin when cultured for 60 days in a medium of 10% fetal calf serum and 25mM glucose [25]. In another study published by Chen LB et al. in the World Journal of Gastroenterology it was shown that rat mesenchymal cells could be differentiated in to pancreatic beta cells and ultimately produce new insulin, which may play an important role in treatment of type 1 diabetes [26]. The findings are consistent with the study by Wu Xh et al. who observed reversal of hyperglycemia after portal vein transplantation of islet like cells derived from bone marrow mesenchymal stem cells in diabetic rats [27]. Human studies in this area are still in elementary stages with in vivo studies lacking. According to Yuhua L et al. human bone marrow mesenchymal stem cells transfected with human insulin genes secrete insulin and this provides a new strategy to address beta cells shortage. This may develop into therapy for patients with type 1 diabetes [28]. Oh Sh et al. in their study showed that adult bone marrow derived cells,if cultured under defined conditions can be induced to Trans-differentiate into insulin producing cells in vitro [29]. This finding is supported by Moriscot C et al. in which it was demonstrated that in vitro human bone marrow derived stem cells can differentiate into insulin expressing cells [30]. A variety of other studies support these findings [31,32]. Several other studies show genetically modified human mesenchymal cells could be differentiated into insulin producing cells in vitro [33,34].

Whole-organ pancreatic transplant or pancreatic islet cell transplants are others form of intervention being explored with some success. Studies have demonstrated restoration of glycol-metabolic control and C- peptide secretion with beta cell replacement thus slowing the progression of diabetic complications [35,36, 37]. To prevent the body from rejecting the transplanted pancreatic tissue, indefinite immunosuppressive therapy is required. Such management makes patients susceptible to a host of other infections and diseases. Another drawback is the limited and irregular supply of cadaveric donor tissue[38, 39]. It has been proposed that stem cell implantation, adequately differentiated may produce physiologically active islet cells. This method could be employed to produce a continuous supply of new islet cells replacing those being destroyed by autoimmune pathology. The physiological insulin secretory capacity may at least mitigate disease severity.

Stem Cell therapy in autoimmune thyroid disorders:

Autoimmune thyroid disease is the most common autoimmune condition, affecting approximately 2% of the female population and 0.2% of the male population [40]. It is the most common cause of acquired thyroid dysfunction in children. A female to male ratio of 2:1 has been documented [41]. Hashimoto's thyroiditis and Grave's Disease are the two most common autoimmune thyroid disorders seen in the pediatric age group. Both of these disorders are characterized by production of thyroid autoantibodies and lymphocytic infiltration.

Hashimoto's thyroiditis (also known as autoimmune thyroiditis or lymphocytic thyroiditis) is a hypothyroid disorder characterized by the presence of thyroid peroxidase (TPO) antibodies, thyroglobulin antibodies and diffuse lymphocytic infiltration of the thyroid gland, which are responsible for the hypothyroidism. Patients with Hashimoto's usually present with goiter and disease should be suspected even in the absence of clinical features of thyroid dysfunction.

Graves' disease (GD), also known as Basedow's disease or diffuse toxic goiter is a hyperthyroid disorder noted by presence of

thyroid stimulating antibodies (also known as thyroid stimulating immunoglobulins or TSI) which contribute to hyperthyroid clinical presentation. Primary autoimmune thyroid disease may coexist with other systemic autoimmune diseases like SLE. Current treatment involvesthyroid replacement therapy in Hashimoto's disease, andemployment of anti-thyroid drug modalities in Graves' disease.Immunosuppressive or immunomodulatory medications may be added if necessary.

Stem cell research provides a new approach, intending to alter the behavior of autoimmune cells, in efforts to arrest the pathogenic mechanism, thus offering a promising strategy in management of autoimmune thyroid disorders. Adult stem cells have been detected in human thyroid gland. In a study by Thomas et al.,the expression of Oct-4(a stem cell marker in cultures isolated from human goiters) was detected [42]. They also detected other endodermal markers such as GATA-4 and HNF4 alpha [42]. In another study by Camaselle-Teijeiro et al. it reported that cell nests of human thyroid origin appear to have stem cell properties like self-renewal and the ability to differentiate in to more than one cell type. Arufe et al. in 2006 demonstrated that enriched, appropriately supported embryonic stem cells could be differentiated into thyroid follicle like clusters with the support of Matrigel in a serum free medium supplemented with TSH [44]. In a study by D'Amour at al. they showed that activin A, a member of the TGFβ family caneffectively induce differentiation of human embryonic stem cells into endodermal cells. Further, they demonstrated that transplantation of these stem cell derived endodermal cells into the renal capsule caused differentiation into more mature cells of endodermal organs [45]. Several other studies [46, 47, 48] have confirmed the ability of human embryonic stem cells to generate endodermal derived cells. Since thyroid follicular cells arise from endoderm, similar strategies may be employed to generate them from human embryonic stem cells. This could provide a novel strategy in management of autoimmune thyroid disorders. In order to attempt stem cell replacement, certain requirements must be met.First, precursor stem cells capable of differentiating into thyroid cells in vitro must be identified. These cells must be capable of synthesizing thyroid hormones. The proliferative capacity has to be tightly regulated to avoid hyperthyroidism. These new cells must evade the body's immune mechanism [49].

Conclusion:

Stem cell therapy provides promising treatment options for diseases like type 1 diabetes, Parkinson's disease and thyroid disorders. In the future, stem cells could potentially help in development of novel approaches for treating children with thyroid dysfunction. Stem cell-based therapies offer many exciting possibilities for the development of novel treatments, and perhaps even cures, for autoimmune diseases like autoimmune type 1 diabetes

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