PROSPECTS FOR STEM CELL THERAPY TO TREAT TYPE 1 DIABETES MELLITUS

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The discovery of insulin in 1921 was one of the greatest medical breakthroughs in history. Individuals, whose life expectancies were measured in months were now able to prevent fatal ketoacidosis by taking injections of crude "soluble" (later known as regular) insulin. Of course, new problems were soon noted. Hypoglycemia, occasionally life-threatening, was encountered as diabetes mellitus monitoring by urine testing for glycosuria was crude at best during those first years after the discovery of insulin. The insulin itself was often impure and varied in potency from lot to lot. Allergic reactions were common and occasionally anaphylaxis would occur. Even more concerning was the appreciation that these patients often succumbed to chronic vascular complications which either dramatically reduced quality of life or resulted in a fatal cardiovascular event.

The search for new solutions in the treatment of diabetes mellitus is an integral part of the medical development's strategy of the new millennium. Understanding the genetic aspects in the pathogenesis of disease entities, such as type 1 diabetes mellitus, leading to new ways to unlock the biological mechanisms in type 1 diabetes mellitus. An example is the introduction of the stem cells in the treatment of diabetes mellitus.

We conducted a literature review of the stem cells therapy to treat type 1 diabetes mellitus. We have studied the literature data for the last 5 years, the Internet resource Medline.

Since the advent of pluripotent stem cells, (embryonic and induced pluripotent stem cells), applications of such pluripotent stem cells are of prime importance. Indeed, scientists are involved in studying the basic biology of pluripotent stem cells, but equal impetus is there to direct the pluripotent stem cells into multiple lineages for cell therapy applications. Scientists across the globe have been successful, to a certain extent, in obtaining cells of definitive endoderm and also pancreatic β-islets by differentiating human pluripotent stem cells. Pluripotent stem cell differentiation protocols aim at mimicking in vivo embryonic development. As in vivo embryonic development is a complex process and involves interplay of multiple cytokines, the differentiation protocols also involve a stepwise use of multiple cytokines. Indeed the novel markers for pancreas organogenesis serve as the roadmaps to develop new protocols for pancreatic differentiation from pluripotent stem cells. Earliest developed protocols for pancreas differentiation involved "Nesting selection pathway", a pathway common for both neuronal and pancreatic differentiation lead to the generation of cells that were a combination of cells from neuronal lineage. Eventually with the discovery of hierarchy of β-cell transcription factors like Pdx1, Pax4, and Nkx2.2, forced expression of such transcription factors proved successful in converting a pluripotent stem cell into a β-cell. Protocols developed almost half a decade ago to the recent ones rather involve stepwise differentiations involving various cytokines

and could generate as high as 25 % functional insulin-positive cells in vitro. Most advanced protocols for β-islet differentiations from human pluripotent stem cells focused on 3D culture conditions, which reportedly produced 60-65 % functional β-islet cells.

Many authors consider that transplantation of pancreatic islets offers a direct treatment for type 1 diabetes and in some cases, insulin-dependent type 2 diabetes. However, its widespread use is hampered by a shortage of donor organs. Many extant studies have focused on deriving β-cell progenitors from pancreas and pluripotent stem cells. Efforts to generate β-cells in vitro will help elucidate the mechanisms of β-cell formation and thus provide a versatile in vivo system to evaluate the therapeutic potential of these cells to treat diabetes. Various successful experiments using β-cells in animal models have generated extensive interest in using human embryonic stem cells to restore normoglycemia in diabetic patients. While new techniques are continually unveiled, the success of β-cell generation rests upon successful manipulation of culture conditions and the induction of key regulatory genes implicated in pancreas development.

N. Holmes, A. Cooke discussed the nonobese diabetic mouse has provided an important animal model for studying the mechanism and genetics of type 1 diabetes over the past 30 years. Arguably, the bio-breeding rat model may be an even closer phenotypic mimic of the typical human disease. A large number of distinct genetic traits, which influence diabetes development, have been defined through an extraordinary effort, most conspicuously in the mouse model. However, in both NOD and BB models the lack of availability of robust means for experimental genetic manipulation has restricted our understanding of the mechanisms underlying this spontaneous autoimmune disease. Recent developments in the derivation of embryonic stem cells have the potential to transform this picture. We argue here that targeting of NOD strain ES cells can bring much needed certainty to our present understanding of the genetics of type 1 diabetes in the NOD mouse. In addition, ES cells can play important roles in the future, in both the NOD mouse and BB rat models, through the generation of new tools to investigate the mechanisms by which genetic variation acts to promote diabetes.

Thus, one of the most promising treatments for type 1 diabetes is transplantation therapy and the stem cells represent a potential source material for the generation of large amounts of cells needed.