Diabetes type 1 immunology mechanism

Basic Mechanism An autoimmune disease occurs when the body produces an abnormal immune response against self antigens. It is caused by failure of the tolerance processes to protect the host from the action of self reactive lymphocytes. An organ-specific autoimmune disease involves gradual damage to cellular structures and is replaced by the compensating connective tissue which depletes the function of the gland/organ. Type 1 diabetes (TD1), is an organ specific autoimmune disease characterize by distraction of the B cells located at the islets of langerham in pancreas resulting in a limited secretion of hormone.

T1D sufferer’ s immune cells such as anti body T cell and CD8 killer cells mistakenly attacks the B cell as a foreign invader. This mechanism is a results of a delayed hypersensitive response to excessive immune reaction meditated by antigen-activated T lymphocytes, including CD4+ and CD8+ T cytotoxic cell . Mediated hypersensitivity reactions may induced by either environmental and self-antigens. Inappropriate activation these cell mediated cell can be directed against self antigens or exogenous antigens which may cause chronic inflammation in a the islets of pancreas in type 1 diabetes (Lopez 2009, pp. 3). Development of the disease involves both genetic and environmental factors. During development of T1D three major auto-antigens (aAgs), insulin, glutamic acid decarboxylase (GAD) and islet associated antigen (IA-2) are known to be targeted by the human immune system . TD1 is the most common amongst childhood but may manifest at any age. The first factor is the Genetic predisposition in humans, links a strong bond that contribute to disease susceptibility to type 1 diabetes Timmins (2006 pp. 189).

Major histocompatibility complex 11 are localize in chromosome 6; in the human leucocyte antigen (HLA) , (which encodes structures responsible for antigen presentation) is associated with the development of type 1 Diabetes. The second factor link to developing type 1 diabetes is the environmental factor that may trigger or accelerate the development of autoimmune disease. A study shown Timmins (2006) conducted in mice revealed understanding that virus cells have the ability to induce mediated cell damaging target organs directly or via secretion of inflammatory cytokines that specifically harm beta cells.

The relationship of T cell mediated destruction of the beta cell in both mice and human suggests the auto aggressive T cell presence upon the distruption of Beta cell secretion. In humans, a sample gathered from an Autopsy of a recently died T1D patient also provide an insight mechanism of tyoe 1 diabetes as it showed a large infiltration of macrophages and lymphocytes with a high proportion of CD8+ cells in pancreas. Pathogenesis and Progression Originate precursor of type 1diabetes originates from both and genetic and environmental factors.

In the islets of langerham, of pancreas lies the chromosome 6 HLA class 11; of which abnormal expression of this gene may cause an auto reactive Tcell and CD 8 killer cell activation. In response to this event is the destruction of Beta cell. Upon the islets of langerham cells, the presence of autoantibodies insulin (IAAs), the 65-kDa isoform of GAD (autoantibody to GAD , and the protein tyrosine phosphatase–related molecules IA can be found. These specialized autoantibodies can be use for the traces of clinical type 1 diabetes (Lopez 2009, pp. 43).

The illustrated image below (fig. 1. 2) is the visual representation of B cell reduced production as the development of type 1 diabetes progress influenced by both genetic and environmental factors. fig. 1. 2 shows the faith of insulin with the reduction of B cell mass. (Baker et al. 2001, p. 3. 58-221-229). Diagnosis and Clinical Symptoms Genetic (HCL) chromosome 6 and environment (virus, toxic) Abnormal reaction on T lymphocytes destruction of beta cells by CDK 8 (IAA and GAD) autoantibody Little or no insulin production igh blood glucose level Hyperglycaemic prolonged type 1 diabetes Fig. 2. 1 illustrates the simple pathway of acquiring type 1 diabetes in an individual Image of Fig. 1. 2 shows the classical steps in direct development of type 1 diabetes. The symptomatic characteristics of the diseases becomes more prominent as it worsen very quickly overtime. These symptoms includes: * Hunger * Fatigue * Frequent urination * Dramatic weight loss * Blurred vision * Nausea As the disease continues to progress, complication in the organs and other parts of the body may severely damage.

This may include poor blood circulation in the legs and feet that may potentially lead to lower leg amputation. The significant increased likelihood of heart disease and stroke may also develop due to high blood pressure and high glucose level in the blood. Other risk factors may also include kidney damage, nerve damage and even death Todd (2009). Finding Type 1 Diabetes Patients with type 1 diabetes mellitus (T1DM) require extreme amount of insulin for survival and should be identified as soon as possible to avoid high morbidity due to late insulin treatment.

There are many diagnostic types on identifying the disease on an individual. Some of these method are as follows: * Fasting Plasma Glucose. The fasting plasma glucose (FPG) test is the standard test for diagnosing diabetes. It is a simple blood test taken after 8 hours of fasting. Normal level lies in the range of 5. 5 (mmol/L) or below. Pre- and diabetic lies in the range of (7. 0 mmol/L) or higher. * Glucose Tolerance Test. The oral glucose tolerance test (OGTT) is complex than the FPG and may mis diagnose diabetes in people who do not have it.

It is a method of drinking a special glucose solution and a blood test may gather after 2 hours. Normal range lies in the amount of 140 mg/dL or below whilst pre and diabetic positives lies in the 200 mg/dL or higher. * Autoantibody Test as type 1 diabetes is characterized by the presence of antibodies that attack the islet cells, These antibodies are referred to as autoantibodies because they attack the body's own cells . Blood tests for these autoantibodies differentiate between type 1 and type 2 diabetes.

Identified autoantibodies are insulin (IAAs), the 65-kDa isoform of GAD (autoantibody to GAD [GADA]), and the protein tyrosine phosphatase–related molecules IA-2 (autoantibody to IA-2 [IA-2A]). Autoantibodies do not exclusively develop before age 2 years, but children who develop autoantibodies later have a slower progression to multiple antibodies and type 1 diabetes. Children who progress to type 1 diabetes have IAAs of high affinity and also develop GADAs concomitantly or soon after the first IAA response.

Once islet autoantibodies appear, they usually persist, although significant fluctuations in antibody titer can be observed during the pre-diabetic phase.

Of the three islet autoantibodies discussed, IAAs are reported to be the least persistent. High amount of these autoantibodies identified reflects the immune response of the pancreatic islets in regards to destruction of Beta cell (Lopez 2009, pp. 43). Treatment : Current treatment Insulin replacement is generally the main option in maintaining a normal level in an individual with a type 1 diabetes.

The method includes a series of injection usually 2 to 3 times of daily . insulin has to enter the blood stream to become effective . the timing of absorption varies on the individual . Injecting it to the abdominal wall works the fastest to control glycaemia between meals and and injections of prandial insulin before each meal to control meal relates hyperglycemia. Regular human insulin should be administered 30 to 45 minutes before meals because of slow absorption or action (30-60 minutes) that does not match normal insulin release .

The onset of NPH insulin is approximately 2 to 4 hours, peak action is between 4 and 10 hours, and duration of action is between 12 and 18 hours (Lopez 2009, pp. 43). Future treatment: Use of Animal Research (Clinical trial of Rabbits for a Hematopoietic Stem cell Study) Recent studies have shown from Stem Cell Engineering Laboratory of Yunnan Province, Kunming General Hospital Osaka in 2012, (Baker et al. 2012, pp. 672-689) elaborates that autologous hematopoietic stem cell transplantation (HSCT) injection in the pancreatic islets is a promising new approach for the treatment of type 1 diabetes .

The aim of this study is to induce medication-free remission by correcting the immunotolerance and preservation of Beta cell function . Hematopoietic

stem cells (HSCs) are multipotent stem cells originate in the bone marrow. They are multiple capable of self-renewal and differentiation properties. Differentiation of these cells can proliferate into lineages of blood cells, such as monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes and even T and B cells. More interestingly, HSCs also have the ability to enhance and re-educate the immune system (Baker et al. 2012, pp. 72-689). The efficacy of the study introduced to 35 common healthy rabbits of both sexes, with a body weight of 2. 3? ±? 0. 3? kg. After 30 days of normal feeding, weight and blood glucose levels were determined for each animal . Rabbits Rabbits with blood glucose levels of 4. 6? ±? 0. 7? mmol/L were selected. The rabbits were randomly divided into two groups: a normal control group. After four weeks of transplantation, results were gathered. Blood was collected via the marginal ear vein, and blood glucose, plasma insulin and plasma C-peptide levels were determined weekly Todd (2009) .

Upon the investigation, one rabbit developed an air embolism and was killed. The appearance, size and textures of each animal's pancreas were examined. Results shows that injection of induced cells to the experimental group; it lowered the blood sugar levels and there were an increase in plasma insulin C peptide level in compare to animals treated with non induced HCT injections. Histopathological examination of the pancreases from the experimental group with induced stem cells showed that they contained healthier beta cell islets in the pancreases than of the non-induced group.

These results suggest Todd (2009) that transplanted HSCT induced cells can direct their way to islets to repair and improve pancreatic islet functioning.

Mechanism of the multipotent stem provide an answer to autoimmune destruction of T cell. It do so by peripherally self reactivate the T cells and reverse the autoimmune response by shifting the balance of immune tolerance via altering cytokine and Beta cell antigen humoral responses. This method not only solves the problem of limited cell sources, but also addresses the question of transplant rejection.

Therefore, the data suggest that multipotent stem cells might provide a promising answer for regenerating islet beta cells and the treatment of type 1 diabetes. Further more, studies are still needed to support the long-term effects and safety of HSCT, (Tsui et al. 2007) as it hasn’t yet clinically tested in human beings. In conclusion, the use of rabbit as a subject enabled a larger size pancreatic organ to examine and provide a closer physiology ethical access to humans for investigating the efficacy of HSCT stem cells.

This experiment provides a very promising result yet a lesser accomodability in regards with financial aspect and continuing into human trials. References : Adam D Timmis 2001, " Diabetes", British Medical Bulletin, vol. 59, no. 1, pp. 159. Baker, R. L. , Mallevaey, T. , Gapin, L. & Haskins, K. 2012, " T cells interact with T cells via CD40-CD154 to promote autoimmunity in type 1 diabetes", European journal of immunology, vol. 42, no. 3, pp. 672-689. Cure for Type 1 Diabetes 2012, , APN Newspapers Pty Ltd, Gladstone, Qld. Fox, C. , Kilvert, A. amp; Sonsken, P. 2008, Type 1 Diabetes, Ebsco Publishing, Ipswich Gan, M. J. , Albanese-O'Neill, A. ; Haller, M. J. 2012, " Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research", Current problems in pediatric and adolescent health care, vol. 42, no. 10, pp. 269-291. Kolb, H. 1999, " Pathophysiology of type 1 diabetes

mellitus", EXPERIMENTAL AND CLINICAL ENDOCRINOLOGY ; DIABETES, vol. 107, pp. S88-S88. Lopez, J. C. 2010, " Protecting the pancreas. (AUTOIMMUNITY)(type 1 diabetes)(Brief article)", Nature Medicine, vol. 6, no. 1, pp. 43. Orban, T. , Eisenbarth, G. , Sosenko, J. M. , Cuthbertson, D. , Krischer, J. P. , Skyler, Diabetes Prevention Trial Type 1 Stu ; Diabetes Prevention Trial-Type 1 Study Group 2009, " Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial-Type 1", Diabetes care, vol. 32, no. 12, pp. 2269-2274. Todd, J. A. 2009, " Stem cells and a cure for type 1 diabetes? ", Proceedings of the National Academy of Sciences of the United States of America, vol. 106, no. 37, pp. 15523-15524. Todd, J. 990, " GENETIC-CONTROL OF AUTOIMMUNITY IN TYPE-1 DIABETES", IMMUNOLOGY TODAY, vol. 11, no. 4, pp. 122-129. Tsui, H. , Razavi, R. , Chan, Y. , Yantha, J. ; Dosch, H. 2007, "'Sensing' autoimmunity in type 1 diabetes", Trends in molecular medicine, vol. 13, no. 10, pp. 405-413. Immunology assignment Type 1 Diabetes (Juvenille) Rbm 3720 Marifer Rafael Sammy Sakkal 3822692 13/5/13