International Journal of Dentistry, Diabetes, Endocrinology and Oral Hygiene, 5(1) pp,32-45, 2023
Print ISSN: ISSN 2631-567X
Online ISSN: ISSN 2631-5688
Website: https://www.eajournals.org/
Publication of the European Centre for Research Training and Development-UK

Role of Genome Model of Living-things in Type 1 Diabetes Mellitus and Pathogenic Mutation

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doi: https://doi.org/10.37745/ijddeoh.18/vol5n13245 Published November 15 2023

Citation: Eriso F. (2023) Role of Genome Model of Living-things in Type 1 Diabetes Mellitus and Pathogenic Mutation, *International Journal of Dentistry, Diabetes, Endocrinology and Oral Hygiene*, 5(1) pp,32-45

ABSTRACT: *The word "diabetes" was from the Greek word meaning "a siphon" because people with diabetes "passed water like a siphon" whereas in Greek "mellitus" means "sweet like honey", reflecting the sweet smell and taste of the patient's urine due to the high level of glucose in it. Pancreatic beta (β) cells are destroyed by T cells of immune system, causing the start of* ***type 1 diabetes mellitus****,* ***insulin-dependent diabetes mellitus****, or* ***juvenile-onset diabetes mellitus****. The key objective of this paper is to clarify or impart, i.e., make known the real scientific truth about the fact that why and how the immune system specifically destroys insulin-producing β cells in the pancreas while exempting other adjacent hormone-producing cells including alpha (α), delta (δ), and epsilon (ε) cells which secrete glucagon, somatostatin, and ghrelin hormones respectively. Type 1 diabetes mellitus is caused by occurrence of pathogenic mutation in the human genome found inside insulin-producing β cells. When a type 1 diabetes mellitus (T1DM) patient is treated by transplantation of pancreatic islets donated from a nondiabetic cadaver, there is a possibility or a challenge of graft rejection. The best optional method of treating T1DM patients, affected by pathogenic mutation, is applying the* ***gene knock out*** *and* ***gene knock in*** *method by identifying the gene or cluster of genes with interdependent functions affected & its/their function/s in the human genome's sequence inside (β) cells of the patient. The scientific report of this study is one of the fruits of* ***Genome Model of Living-things*** *which has massively and drastically revolutionized the whole world of both pure and applied biological sciences in favor of better life of all human races on this planet, Earth. Application of* ***gene knock out*** *and* ***gene knock in*** *method of treatment against T1DM is as possible as natural* ***insertions*** *of transposons* ***(jumping genes)*** *on DNA molecules. This is an exceptionally jubilant scientific victory for care provider health professionals and their clients (T1DM patients) including researcher scientists of biological sciences.*

KEY WORDS: Insulin, β-cell, Immune response, T cells, Type 1 diabetes mellitus, MHC, Pathogenic mutation

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INTRODUCTION

Pancreatic beta (β) cells are destroyed by T cells of immune system, causing the start of **type 1 diabetes mellitus (T1DM**), **insulin-dependent diabetes mellitus,** or **juvenile-onset diabetes mellitus**. The word "diabetes" is from the Greek **word meaning** "a siphon" because people with diabetes "passed water like a siphon" whereas in Greek " mellitus" **means** "sweet like honey", reflecting the sweet smell and taste of the patient's urine due to the high level of glucose in it. To develop a successful approach to protect (β) cells, we must understand how and why T cells are directed to specifically destroy insulin-producing β cells in the pancreas while sparing/exempting other adjacent different hormone-producing cells including alpha (α), delta (δ), and epsilon (ε) cells [1-7]. Whether Human Type 1 Diabetes Mellitus results from a defect of the immune system, target pancreatic islet-β-cells dysfunction, or both **has remained unknown for centuries** as an open issue **until the appearance of this paper** [2]. Type 1 diabetes mellitus is the result of an autoimmune reaction that develops against pancreatic β-cells. There are two types of diabetes mellitus:- type 1 diabetes mellitus, and type 2 diabetes mellitus. Type 1 diabetes mellitus, also called Insulin Dependent Diabetes Mellitus (IDDM) or juvenile diabetes mellitus, which is characterized by the selective destruction of the insulin-secreting pancreatic β cells by the autoreactive immune cells. Therefore, T1DM is characterized by the absolute deficiency of insulin, and patients require injection of exogenous insulin for survival, which renders the blood glucose unable to be regulated at a perfect level. A majority of T1DM are believed to be triggered by infections such as viral infection. Also less commonly, other environmental factors such as stress and certain chemical or drug exposure appeared to be triggers for T1DM. As the major effector cells for β-cell destruction, T cells and T-cell-mediated adaptive immunity are considered to be the main factor for T1DM.

The key objective of this paper is to clarify or impart, i.e.,make known the real scientific truth about the fact that why and how the immune system specifically destroys insulin-producing β cells in the pancreas while exempting other adjacent hormone-producing cells including α, δ, and ε cells which secrete glucagon, somatostatin, and ghrelin hormones respectively.

REVIEW

Autoreactive $CD8^+$ T cells are confirmed to be critical for T1DM pathogenesis in patients. Other than $CD8^+$ T cells, self-antigen specific $CD4^+$ T cells can also promote the production of antibodies against β cells by B lymphocytes. Therefore, most T1DM related studies have been focused on adaptive immunity, while the role of innate immunity is overshadowed. Recently, accumulating evidence indicates that innate immunity also plays an essential role in the initiation and progression of T1DM. For example, in addition to T cells, innate immune cells such as dendritic cells (DCs), macrophages, and natural killer cells (NK cells) are highly enriched in the insulitis lesion during diabetogenic process [4].

When encountering antigens derived from the host, the immune system in a normal individual is able to recognize them as self and decide not to respond. Dysfunction of the immune system is believed to cause various immune disorders such as immunodeficiency and autoimmune diseases. Host immune system including innate and adaptive immune system relies on the innate recognition to make the decision to respond or not to respond to a particular antigen.

Recent findings suggest that innate immune cells play an essential role in the initiation of β-cell-specific autoimmune response. Innate immune cells such as DCs, macrophages, and NK cells are found in a large number in the autoimmune diabetic pancreas in addition to lymphocytes. Furthermore, DCs and macrophages are the major population of infiltrating immune cells during the initial phase of autoimmune insulitis. Their presence at the pancreas precedes the infiltration of T and B lymphocytes. In addition to the early stage of autoimmunity, accumulation of innate immune cells is also observed during the later β-cell destructive insulitis process. There, the entry of macrophages and DCs is considered as the initial sign of autoimmunity in T1DM pathogenesis and Viral infection, as an environmental perturbant, is believed to be the most common trigger for T1DM development [4].

Innate immune response, as one of the two pillars of the immune system and mediator of adaptive immune response, plays an essential role in pathogenesis of T1DM. Pattern recognition receptors expressed on the innate immune cells sense the conserved pathogen specific molecules or alarmins released by host cells to initiate an immune response. In the normal condition, self antigens can be distinguished from foreign antigens and do not provoke an immune response. However, under certain circumstances, self antigens released from damaged host cells could be processed and presented to autoreactive T cells with the presence of pattern recognition receptor (PRR) signaling. For the case of type 1 diabetes mellitus, defective clearance of apoptotic β cells during neonate β cells mass turnover by phagocytes results in the accumulation of apoptotic β cells in the pancreas, which then undergo a secondary necrosis along with the release of β-cell-derived autoantigens and danger signals. Danger signals subsequently activate PRRs and promote self antigen presentation by APCs. Furthermore, PRR signals also induce maturation and migration of APCs, which facilitate both innate and adaptive immune response to mediate the destruction of β cells. The effect of current therapeutic approaches for T1DM is unsatisfied. A variety of severe complications developed in the relatively large proportion of T1DM patients. Therefore, a clear understanding of the recognition of β-cell antigens and the initiation of autoreactive immune response against β cells is essential to the development of better effective therapeutic approaches for this devastating disorder [4-6].

Upon islet infiltration, the $CD4^+$ T cells activate cytotoxic $CD8^+$ T cells bound to matching peptides presented on MHC I on the β cells. Finally, the $CD8^+$ T cells destroy the β cells by several effector mechanisms, including Fas, perforin and granzyme B [7].

Type 2 Diabetes Mellitus, Insulin-Independent Diabetes Mellitus, or **adult-onset diabetes mellitus** is characterized by its insulin resistance [8]. The good news is that the level of insulin resistance can be lowered and the level of insulin sensitivity can be raised by modifying life style

choices, particularly doing exercise (physical activity) and eating fibrous food such as vegetables and fruits [8].

Diabetes Insipidus: The term "Insipidus" comes from the **word** "insipid," **meaning** tasteless, referring to the fact that the diabetes insipidus patient's urine is not sweet like honey unlike that of a diabetes mellitus patient. Diabetes insipidus is a condition where the body loses too much fluid through urination, causing a significant risk of dangerous dehydration as well as range of other illnesses and conditions. It is a rare disorder affecting the regulation of body fluid levels [9]. People with diabetes insipidus produce excessive amounts of urine, resulting in frequent urination and thrist. However, the underlying cause of these two symptoms differs from **types 1 and 2 diabetes mellitus**. Diabetes insipidus has two main forms:

►Nephrogenic diabetes insipidus, and
►Central or neurogenic diabetes insipidus.

Causes of both types of diabetes insipidus are linked to a hormone called vasopressin but occur in different ways. Vasopressin promotes water retention in the kidneys. Central diabetes insipidus is caused by reduced or absent levels of vasopressin whereas nephrogenic diabetes insipidus can be inherited or acquired and affects the response of the kidneys to vasopressin [9]. In short, diabetes insipidus is a rare disorder that occurs when a person's kidneys pass an abnormally large volume of urine that is insipid(meaning dilute & odorless).
Diabetes insipidus and diabetes mellitus (type 1 & 2 diabetes mellitus) are unrelated, although both conditions cause frequent urination and constant thirst [9]. Diabetes mellitus causes high blood glucose, or blood sugar, resulting from the body's inability to use blood glucose for energy. People with diabetes insipidus have normal blood glucose levels; however, their kidneys cannot balance fluid in the body.

Scientific evidences about the fact that Type 1 Diabetes Mellitus is caused by pathogenic mutation

Scientific evidences about the fact that **Type 1 Diabetes Mellitus** is caused by becoming foreign/nonself of the **genome** inside the pancreatic β-cells of islets due to pathogenic mutation as it does in other human body cells to cause diseases such as cancer. The scientific evidences forwarded about the fact that the genome of pancreatic β-cells has become foreign to the body of the patient where the very cause can be either due to **pathogenic mutation**, or **viral infection** include**:**

1. Type 1 diabetes mellitus (T1DM) is a T-cell-mediated autoimmune disease caused by the **change/mutation in the genome** of pancreatic β-cells, whereas Type 2 Diabetes Mellitus (T2DM) is the result of peripheral cell resistance to endogenous insulin. The best evidence supporting immune system involvement in T1DM are the studies reporting: lymphocytic infiltrate in the islets of people with T1DM,
2. Lymphocytic infiltrate in donated & transplanted cadaveric islets of T1DM,

3. Islet-specific antibody production in individuals with T1DM,
4. Identical twin studies in which the twin with T1DM rejected islet transplants from their non-diabetic twin [1].
5. Analyses of pancreas sections harvested from individuals with T1DM have shown fulminant immune infiltration within individual islets, confirming/corroborating a key role for $CD4^+$ T and $CD8^+$ T cells in β cell destruction [1]. This is in sharp contrast to pancreas sections from individuals with T2DM, who, despite having high levels of systemic inflammatory markers, do not have similar T cell infiltration within pancreatic islets [1].
6. Virtually all individuals who develop T1DM before the age of 5 years produce insulin-specific antibodies, suggesting an important role for peptides derived from insulin molecule in disease pathogenesis [1].

7. Islet autoantibodies are differential diagnosis marker for T1DM versus T2DM and arise from autoreactive B cell and autoreactive $CD4^+$ T cell interactions. Human leukocyte antigens (HLAs) class II alleles DR4, DQ8, and DQ2 confer the highest genomic risk for T1DM in human patients. This strong HLA II allele association with T1DM suggests that HLA II-restricted $CD4^+$ T cells play a key role in disease pathogenesis. $CD4^+$ T cells can provide "help" to B cells and stimulate antibody production as noted above, as well as promote responses by effector $CD8^+$ T cells, and stimulate islet-resident macrophages [1]. With this in mind, autoreactive $CD4^+$ T cells in response to the non-self antigen resulted from the pathogenic mutation/change in the **genome** of pancreatic **β-cells** represents an active area of research and clinical interest for therapies. $CD4^+$ T cell targets are **peptides** that are produced by the directives of the nonself genome and restricted to MHC II which will display them on the external surfaces of β-cells. In human T1DM, the available evidence from studies of individual islets from the Network for Pancreatic Organ Donors with T1DM suggests that β cell destruction is mediated in large part through direct $CD8^+$ T cell contact with β cells and $CD4^+$ T cell-mediated polarization (activation) of M1 macrophages [1]. Autoreactive $CD8^+$ T cells are activated through interaction with peptides presented by MHC class I on β-cells and can mediate every β cell death in a contact-dependent manner through perforin and granzyme molecules [1].

8. Studies confirmed that insulitis happens only in the islets containing β cells, indicating that the autoimmune reaction in T1DM is driven by β-cell-derived antigens/peptides [4]. This type of attack to pancreatic β-cells is accurately similar to the attack directed to a virus-infected cell or a cancered cell by immune cells in bodies of humans [10].

DISCUSSION

Any kind of living-thing, any kind of living cell or any kind of biological molecule is synthesized by its specific type of genome (i.e., by the coded directives/information or plan that is determined by the sequence of nucleotides/nitrogenous bases in its genome). Because of this determinant effect of sequence of the nucleotides, **whole genome sequencing** is of critical importance.

The term that can accurately serve as the synonym to the term **living-thing** is a **genomic-thing** whereas the term **nongenomic-thing** is the synonym to a **nonliving-thing**; otherwise, the term living-thing will be in problem, becoming useless because what we call nonliving-things are also living-things as **matter is neither created nor destroyed** [11-13]. Without these interpretive and equvalent meanings of the terms the student children or learners can be vulnerable to confusion and ambiguity in the processes of learning both pure & applied biological sciences. In fact, we biologists were absolutely wrong not only because we had been unable to define what a living-thing was, but also we were not correct in classifying/categorizing things into living-things and nonliving-things for more than 20.19 centuries until the emergence of **Genome Model of Living-things**. This is so because, as it is mentioned above, what we have been categorizing nonliving-things are also living-things as matter is neither created nor destroyed. At present, a living-thing is defined through **Genome Model of Living-things** and this achievement in turn has enabled the investigator to generate real/actual interpretive meanings to a **living-thing** and a **nonliving-thing** luxuriously [10-13]!!

The differences among **genomes** of living-things result in differences among the biological molecules, biological viruses, living cells, or multicellular living-things they synthesize/build at the level of:

►biological molecules,
►biological viruses
►cells
►tissues,
►**identical twins**,
►**distinctive individuality** (among individuals of the same species),
►**genus**,
►**family**,
►**order**,
►**class**,
►**phylum**, and
►**kingdom**.

From nearly no difference at **identical twins** and **distinctive individuality** (among individuals that belong to the same species) levels respectively to the **complex** differences at the level of **kingdom** of living-things, the complexity of differences among **genomes** increases downwards in the direction from **identical twins** to **kingdom**.

Selfness or foreignness (nonselfness) of:
●a biological molecule,
●a cell,
●a tissue, or
●an organ

that has been transplanted or introduced from one person into another and recognized by immune cells of a recipient is determined only by the extent/degree of selfness or foreignness of the donor's **genome** which synthesized/built the biological molecule, cell, tissue, or organ donated. The **genomes** of identical twins are identical to each other where the biological molecules, cells, tissues, or organs synthesized by each of them are also identical to those of the other and are not responded to by immune cells of the recipient as foreign if transplanted between these identical twins. The **genome** of an **isograft** (i.e.,the graft between identical twins) is more similar to the **genome** of a recipient than that of an **allograft** (i.e., the graft between two different individuals that belong to the same species). In the same comparative approach, the **genome** of an allograft is more similar to the **genome** of a recipient than that of a **xenograft** (the graft between two different individuals where each of them belongs to a different species). Every individual living-thing of all species, from a virus to that of multicellular largest plants and animals, is synthesized (built) by its **genome** using its nutritive substances as raw materials in its compatible environment [11, 12]. As the degree of foreignness, dissimilarity, or nonselfness between the **genome** of the host (recipient) and that of the donor's (invader pathogen's) **genome** increases, the **immunogenicity** of the donor's antigen also increases as far as the immune system of the host (recipient) is in an effective functional state and if evasive factors or parasitophorous vacuoles do not exist to equip the antigen (pathogen or a transplanted graft) against the immune response of the host (recipient). This is the reason for why histocompatibility in transplantation, among all the grafts the autograft and isograft are mostly accepted and others such as allograft & xenograft are rejected by the immune system of recipient (client). Autoimmunity is defined as a mistaken recognition of self-proteins or entities as foreign. It has been believed that autoimmunity leads to the generation of an immune response against "self" cells or tissues and generates a reaction against them.

The immune response of autoimmunity is not a mistaken recognition of self-proteins or entities as foreign. In fact, autoimmunity is accurate, perfect, or 100% correct in recognizing proteins on the external surface of selfcells as foreign because these proteins/peptides are the translations or expressions of the genes found in the genome of the cell that is affected by pathogenic mutation. The **genome** affected by pathogenic mutation inside the β-cell is foreign to the body of the patient. Therefore, the proteins/peptides produced by the coded directives of this foreign **genome** & displayed by MHC on the external surface of β-cells, are foreign (nonself). As the result of this spectacular truth, the β-cells that bear foreign peptides on their external surfaces are destroyed by immune response of the T1DM patient in the same way that virus-infected cells & cancered cells are destroyed by the immune responses of the patients [10]. Pathogenic mutation can occur on anyone gene of a genome, causing several types of genomic disorders/diseases such as **cancer** and **type 1 diabetes mellitus** depending on the type of function of the gene or cluster of genes with interdependent functions that can be affected by the pathogenic mutation [10]. It is potentially possible that pathogenic mutation can occur in any one of the 20,000 to 25,000 genes of the human genome estimated by the Genome Project; the occurrence of this results in a corresponding

genomic disease/disorder.
Scientific evidence number 4 reported that:
"Identical twin studies in which the twin with T1DM rejected islet transplants from their nondiabetic twin". The reason for why the islet transplant from the nondiabetic identical twin was rejected by his/her recipient diabetic identical twin was due to:
-the adaptive immunity that had already been sensitized/activated by the nonself autointracellular pathogenic genome (created by pathogenic mutation) inside the β-cells which had been destroyed by the activated immune response in the patient. In this diabetic twin, if the same β-cells having the same autointracellular pathogenic genome is transplanted or grafted to the diabetic twin, even more powerful secondary immune response will destroy or reject the transplant or graft donated from the nondiabetic identical twin, because the memory cells are ready to fight off if the same antigen is encountered again in the body of the diabetic identical twin. The islet transplant (isograft) which was believed to be from nondiabetic identical twin was not actually nondiabetic [14, 15]. Although the concordant onset of T1DM was not clinically manifested, the islet transplant (isograft) from the identical twin who externally looked like nondiabetic did have β-cells which concordantly contained **mutated pathogenic genome**/ **autointracellular pathogenic genome** (i.e., **diabetic genome** that makes the person T1DM patient, caused by pathogenic mutation) against which very powerful secondary immune response was waiting in the body of the recipient diabetic identical twin. As the result, the isograft transplanted was rejected. This is so because the process in the disease of T1DM is slow; some of the immune and metabolic changes can occur many months, even years, before the onset of clinical diabetes. In other words, the actual altered or pathogenically mutated metabolic expression/translation, of gene/cluster of genes altered, into altered proteins that are recognized foreign by the immune system of the patient can occur many months, even several years before the visible symptomatic onset/clinical manifestation of T1DM patient[10]. This is the reason for why "Identical twin studies in which the twin with T1DM rejected islet transplants from their nondiabetic twin". One of the mutagenic agents can be some insertions of transposons which jump from a DNA molecule onto another DNA molecule and are known as "jumping genes".

When a T1DM patient is treated by transplantation of pancreatic islets donated from a nondiabetic cadaver, there is a possibility or a challenge of graft rejection. The best method of treating T1DM patients, affected by pathogenic mutation, is to focus on **gene knock out** and **gene knock in** method by identifying the gene or cluster of genes with interdependent functions affected & its/their function/s in the genome's sequence found inside β-cells of pancreatic islets in the patient. This is an exceptionally jubilant scientific victory for care provider health professionals and their clients (T1DM patients). This method is nonproblematic, being possible as it is for **transposons** known as **jumping genes.**

Table 1: Immune responses to pathogenic mutations and viral genome infections in the body of humans are exactly in the same way.

Name of infection/invasion	**Pathogen in the host cell and action of immune response**	**Cause of the disease; name of the disease in red**
viral infection/invasion	Exogenous intracellular pathogenic genome entered from a virus and immune response kills/destroys the viral genome-infected cell.	eg, Infection with a rabies virus; **rabies**
pathogenic mutation of a gene/cluster of genes in a genome	Endogenous intracellular pathogenic genome, or autointracellular pathogenic genome; eg., a cancerous genome and immune response kills/destroys the cancered cell.	Pathogenic mutation of growth regulating genes in the genome inside a cell; **cancer**
pathogenic mutation of a gene/cluster of genes in a genome	Endogenous intracellular pathogenic genome, or autointracellular pathogenic genome; eg, type 1 mutated diabetogenic or diabetogenous genome and immune response kills/destroys the diabetized β cell.	Pathogenic mutation of a gene/cluster of genes in the genome inside β-cells; **T1DM**

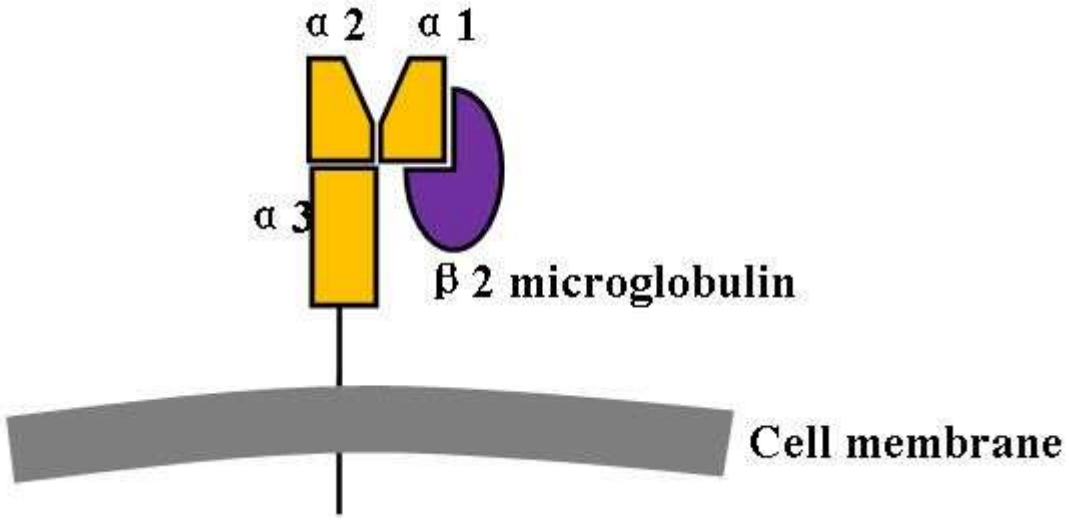

Figure 1. Molecular Structure of MHC Class I: MHC class I protein is composed of two chains: α chain and β2 microglobulin. The α chain consists of a transmembrane region and three extracellular domains: α1, α2, and α3. MHC class I molecule is expressed on the membrane of all nucleated cells.

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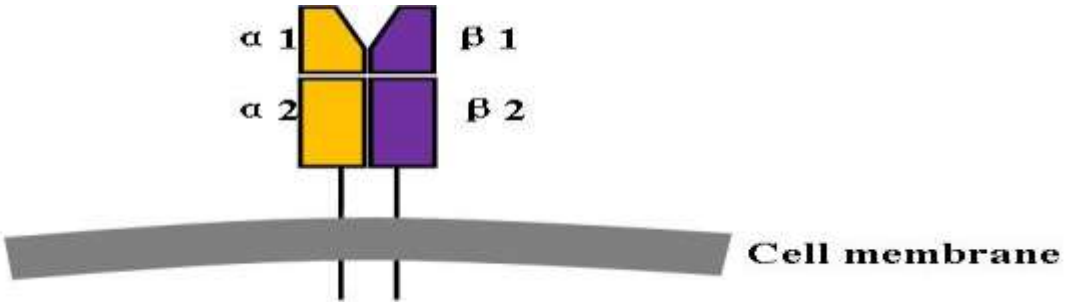

Figure 2. Molecular Structure of MHC Class II: MHC class II molecule has an immunoglobulin-like structure. It consists of one α chain and one β chain. Each chain contains a transmembrane region and two extracellular domains (α1 and α2 in α chain; β1 and β2 in β chain). MHC class II protein is expressed on the membrane of APCs (Antigen Presenting Cells) and is responsible for presenting extracellular antigens.

restriction. TCR recognizes the residues on the peptide and residues from

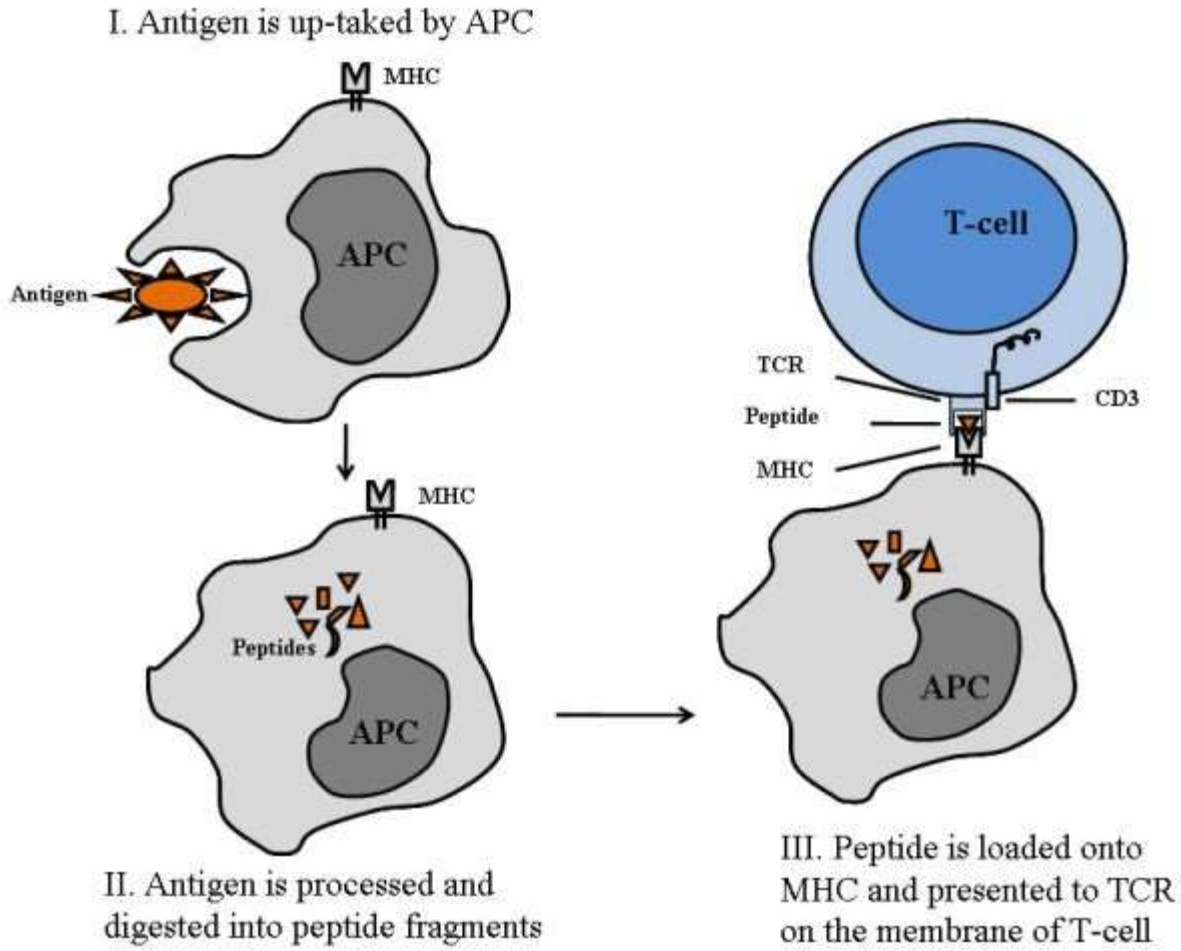

Figure 3: Recognition of p-MHC by TCR: T cell cannot detect an antigen by itself. It can only recognize antigens presented by MHC on Antigen Presenting Cells (APCs). APC uptakes foreign antigens (eg., proteins) and digests them into small peptides which are loaded onto the cleft of MHC molecules and then presented to T cell Receptor (TCR). Once they bind to p-MHC, TCR signal is transduced into T-cell via intracellular domain of associated CD3. T-cell is then activated and reacts to the invaders with corresponding antigen to clear them [4].

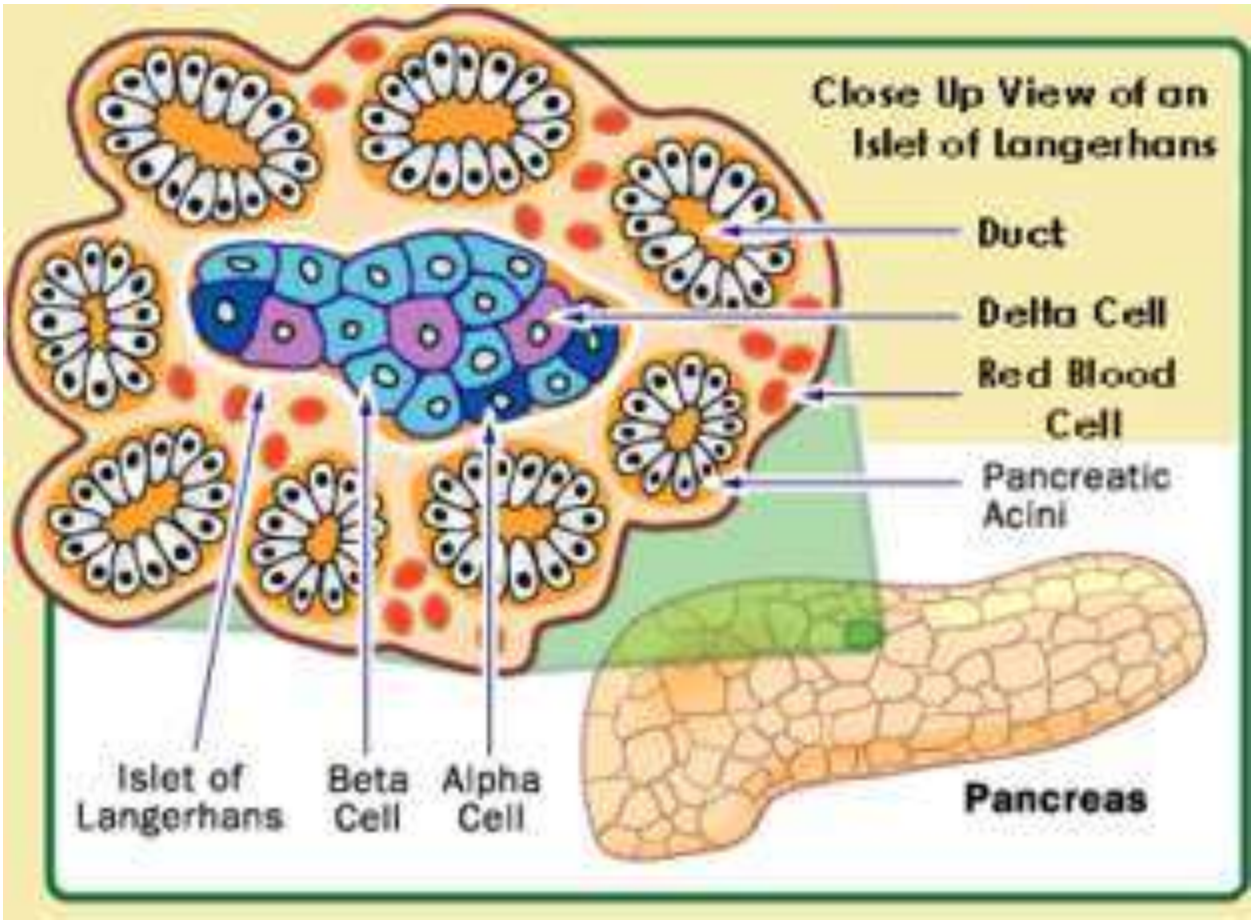

Figure 4: Types of cells in an islet of Langerhans and other pancreatic cells.

CONCLUSION

Genome model of living-things kills **lies**, leaving **liars** intact, alive and safe.

Pancreatic β-cells in islets of Langerhans are destroyed by T cells/cellular immune response because of pathogenic mutation in the genome inside β-cells, resulting in

T1DM. In the immune system, T cells attack invaders inside the cells (attack intracellular pathogens); here, the diabetogenous genome is an endogenous foreign invader/pathogen inside β-cells . As the result, β-cells are destroyed by T cells. In other words, **diabetized cells** & **cancered cells** are destroyed by T cells of the immune system because **dibetogenous genome** & **cancerous genome** are autointracellular pathogens like the **viral genome** in a viral genome-infected host cell.

Application of **gene knock out** and **gene knock in** method of treatment against T1DM is as possible as natural **insertions** of transposons (**jumping genes)** on DNA molecules. This is an exceptionally jubilant scientific victory for care provider health professionals and their clients (T1DM patients) including researcher scientists of biological sciences.

Any professional in both **pure** and **applied** (medical & agricultural) biological sciences who has not internalized the concepts and principles of **Genome Model of Living-things** is a **naked beater around the bush**, working unconsciously by trial and error in the field of his/her specialization!!

In the body of humans, viral genome-infected cells, cancered cells, and diabetized cells are destroyed by T cells in spectacularly similar ways; therefore, pancreatic β-cells must be examined for viral infection before confirming that the person suspected for diabetes is a T1DM patient.

It is declared that this article has worked out/interpreted the secrets of **how** and **why** T cells destroy β-cells in the pancreas for the **first time** in the entire world.

Acknowledgement

I am deeply grateful to the scientists acknowledged in the text and list of references of this paper for their providing me with confidential data that can be counterchecked, for their correctness, with observable facts in the natural environment as well as with truths in modern textbooks, reputable journals, and Internet. This is so because science cannot develop without science.

REFERENCES

[1]. Burrack AL, Martinov T, Fife BT. T cell-mediated β-cell destruction: autoimmunity and alloimmunity in the context of type 1 diabetes. Front Endocrinol, 2017; **8:** 343.

[2]. Faideau B, Larger E, Lepault F, Carel JC, Boitard C. Role of β-cells in type 1 diabetes pathogenesis. Diabetes, 2005; 54(suppl.2): S87-S96. https://doi.org/10.2337/diabetes.54.suppl 2.S87

[3]. Marrack P, Kappler JW. Do MHC II-presented neoantigens drive type 1 diabetes and other autoimmune diseases? Cold Spring Harb Perspect Med, 2012; 2(9): a007765. Doi: **10.1101/cshperspect.a007765**

[4]. Zhong J, Xu JF, Yang P, Liang Y, Wang CY. Innate immunity in the recognition of β-cell antigens in type 1 diabetes. Nov. 25th 2011. DOI: **10.5772/22264**

[5]. Mauvais FX, Diana J, Endert PV. Beta cell antigens in type 1 diabetes: triggers in pathogenesis and therapeutic targets. F1000 Res, 2016; **5:** Doi: 10.12688/f1000research.7411.1

[6]. Wan X, Unanue E R. Antigen recognition in autoimmune diabetes: a novel pathway underlying disease initiation. Precision Clin Med, 2018; 1(3): 102-110. **https://doi.org/10.1093/pcmedi/pby015**

[7]. Storling J, Overgaard AJ, Brorsson CA, Piva F, Bang-Berthelsen CH, Nerup J, Pociot F. Do post-translational beta cell protein modifications trigger type 1 diabetes? Diabetologia, 2013; **56(11):** 2347-2354.

[8]. Colberg SR. Increasing insulin sensitivity. Nutrition and Exercise, 2015.

[9]. Felman A. What is to know about diabetes insipidus? Med News Today, 2018; 2-17.

[10]. Feleke E. Immune responses against autointracellular pathogenic genomes or cancered cells. Int J Dev Res, 2018; **08(07):** 21489-21496.

[11]. Feleke E. Genome model of living-things, definition of a living-thing, and the position of biological viruses among living-things. Int J Curr Res, 2017; 9(07): 53764-53778.

[12]. Feleke E. Dynamic and detailed genome model of living-things. Int J Dev Res, 2018; 08(08): 22138-22152.

[13]. Feleke E. Biological viruses are certainly living-things and switching off genomic metabolism. European J Biol Med Sci Res, 2018; 6(5): 19-41.

[14]. Lo SSS, Hawa M, Beer SF, Pyke DA, Leslie RDG. Altered islet beta-cell function before the onset of type 1 (insulin-dependent) diabetes mellitus. Diabetologia, 1992; **35:** 277-282.

[15]. Jerram ST, Leslie RD. The genetic architecture of type 1 diabetes. Genes (Basel), 2017; **8(8):** 209.