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Review

Molecular and cellular bases of diabetes: Focus on type 2 diabetes mouse model-TallyHo

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A B S T R A C T

Diabetes is a chronic lifestyle disorder that affects millions of people worldwide. Diabetes is a condition where the body does not produce sufficient insulin or does not use it efficiently. Insulin resistance in diabetes or obesity causes the pancreatic β-cells to increase the insulin output. Diabetes occurs in multiple forms, including type 1, type 2, type 3 and gestational. Type 2 diabetes accounts for ~90–95% of total affected population and is associated with both impaired insulin production by the β-cells of the pancreas and impaired insulin release in response to high blood glucose levels. Diabetes is tightly linked with genetic mutations and genetic and lifestyle activities, including diet and exercise. Recent epidemiological studies established a close link between the diabetes and progression to Alzheimer's disease. This article summarizes various molecular mechanisms involved in the developments of diabetes, including biochemical characteristics, genetic and molecular links with Alzheimer's disease, β-cell function, and factors associated with diabetes. This will help us in the development of novel therapeutic strategies targeting AD in future.

1. Introduction

Diabetes is a heterogeneous metabolic disorder that is characterized by elevated blood glucose due to either insufficient amount of insulin or the body's inability to use the produced insulin efficiently, or both [1]. Diabetes is a chronic condition affecting 8% (24 million) of the US population [2] and associated with an increased risk for mortality as well as morbidity. The prevalence of diabetes (type 1 and type 2) is expected to increase by 54% to > 54.9 million persons between 2015 and 2030 just in the United States [3]. By 1930, the total number of annual deaths from 2015 to 2030 is expected to increase to 385,800 in the United States, with associated annual medical and societal costs expected to reach $622 billion by 2030.

In type 1 of diabetes mellitus (T1DM), autoreactive T cells attack the insulin secreting pancreatic β cells, resulting in no insulin being synthesized in the β-cells. However, in type 2 diabetes Mellitus (T2DM), which accounts for about 90–95% of the total diabetes-affected population, there is not only impaired insulin production by the β-cells of the pancreas but also impaired insulin release in response to high blood glucose levels (a condition termed *hyperglycemia*). This increased glucose level causes insulin resistance in the tissues. The complex interplay of both genetic and life style factors are involved in the pathophysiology of T2D. Both T1DM and T2DM, if not controlled, can result in long-term complications, like defective leptin signalling and damage to the central nervous system. These complications could be the result of a pathogenic process at the mitochondrial level [4]. Studies have shown that mitochondrial dysfunction is linked with T2DM and age-related insulin resistance. Besides diabetes, several other factors also can also affect mitochondrial function, such as genetic factors, oxidative stress, mitochondrial biogenesis, and aging [5].

The purpose of this article is to highlight the determinants of T2DM, including life style, biochemical characteristics, genetic and molecular links with Alzheimer's disease (AD). This article is also focused on a naturally occurring polygenic mouse model for type 2 diabetes – TallyHo mice as a perfect model to uncover the molecular link between T2D and AD.

2. Diabetes overview

Glucose is the major source of energy for the body, especially for the

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brain to maintain its normal functions. Glucose homeostasis is regulated by the hormone insulin. Insulin dysregulation causes diabetes mellitus (DM), and is characterized by elevated blood glucose levels. Elevated blood glucose concentration occurs either due to insufficient amount of insulin or insulin resistance or both. The National Institutes of Health defined has diabetes as "a chronic disease in which the body is unable to regulate blood sugar levels." DM is associated with a wide variety of risk factors, such as: neuropathy, retinopathy, nephropathy, and heart and blood vessel damage. If left untreated, DM can lead to organ failure [6]. The pathology of this disease is complex, involving an autoimmune destruction of pancreatic β-cells, resulting in insufficient insulin and eventually leading to insulin resistance [7]. The resistance to insulin in DM is due to reduced insulin action on the target tissue such as liver, skeletal muscle and adipose tissue. The normal effect of insulin on carbohydrates metabolism is hypoglycemia; on lipids it favors lipogenesis and decreases its break down by favoring cholesterol biosynthesis and on protein it favors protein synthesis by decreasing protein catabolism. Dysregulation of insulin in metabolizing carbohydrates, proteins, and lipid metabolism can trigger hyperglycemic conditions [7].

2.1. Types of diabetes mellitus

Due to metabolic complexity and heterogeneity, it is difficult to classify DM. The most widely accepted classification was proposed by the American Diabetes Foundation (ADA) in 1997. DM is typically classified as type1, type 2, other types and gestational diabetes mellitus (GDM) [7] (Fig. 1). Below is a short overview of different kinds of DM.

2.1.1. Type 1 diabetes mellitus

Only 5%–10% of patients are affected with T1DM, of which 80–90% are children in their adolescence [8,9]. T1DM, sometimes called juvenile DM, involves Autoreactive T-cells and circulating antibodies of the immune system destroy insulin-secreting pancreatic β-cells, leading to lifelong dependency on an external source of insulin. Insulin, isoforms of glutamic acid decarboxylase (GAD), protein tyrosine phosphatase (IA2 and IA2β) and zinc transporter protein (ZnT8A) are the major autoantigens of T1DM [10]. The human leukocyte complex (HLA), especially the *DR* and the *DQ* genes, plays a major role in the manifestation of T1DM [7]. The *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* genes belong to HLA family. The HLA complex helps the immune system distinguish the body's own proteins from those proteins produced by foreign invaders, such as viruses and bacteria.

Table 1
Genetic variants associated with T1DM in humans.

Locus	Gene	Chromosome number
CCR5	C-C motif chemokine receptor 5	3
CTLA 4	Cytotoxic T-lymphocyte associated protein	2
FOX P3	Forkhead box P3	X chromosome
HLA-DQA-1	Major histocompatibility complex class II DQ α1	6
HLA-DQB-1	Major histocompatibility complex class II DQ β1	6
HNF1A	HNF homeobox A	12
IL2RA	Interleukin 2 receptor subunit α	10
IL6	Interleukin 6	7
ILS	Insulin	7
OAS 1	2′-5′-oligoadenylate synthetase 1	12
PTPN22	Protein tyrosine phosphatase, non-receptor type 22	1
SUMO4	Small ubiquitin-like modifier 4	6

Table 1 gives an overview of the genetic variants associated with T1DM. Multiple genetic loci are involved with T1DM, including C—C motif chemokine receptor 5, cytotoxic T-lymphocyte associated protein, forkhead box P3, major histocompatibility complex class II DQ alpha 1, major histocompatibility complex class II DQ beta 1, HNF homeobox A, interleukin 2 receptor subunit alpha, Interleukin 6, insulin, 2′-5′-oligoadenylate synthetase 1, protein tyrosine phosphatase, non-receptor type 22 and small ubiquitin-like modifier 4. Genetic variants in these genes located in different chromosomes and are responsible for alterations in insulin synthesis. Environmental factors such as viral infection and stress are also know to implicate in the etiology of diseases [10].

2.1.2. Type 2 diabetes mellitus

Type 2 diabetes mellitus also known as *adult –onset diabetes*, occurs during the later stages of life and comprises 95% of the diabetes-affected population [11,12]. T2DM is characterized by declining insulin production and eventual pancreatic β-cell failure. This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells

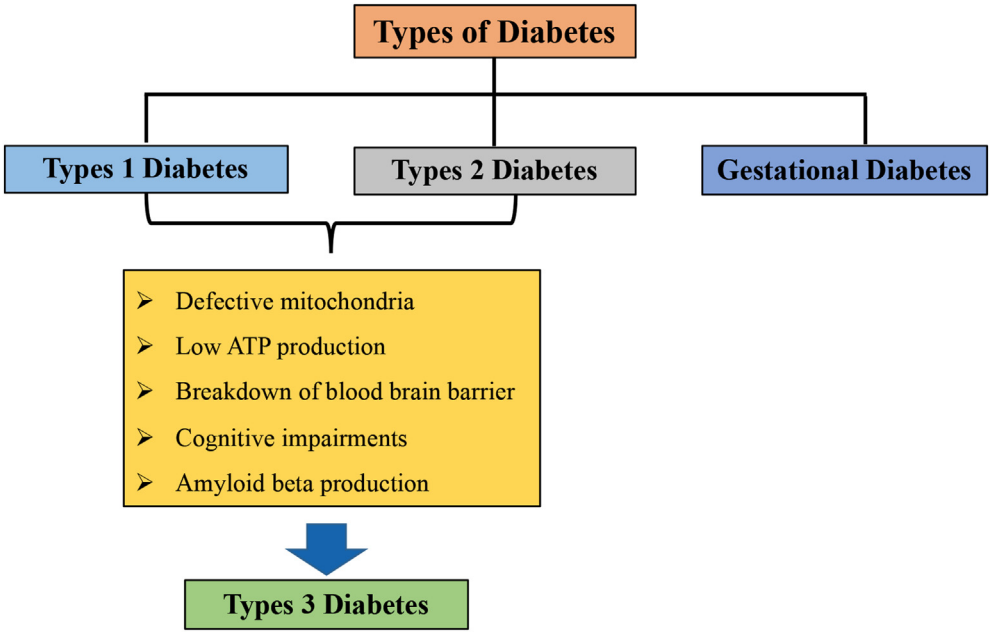

Fig. 1. Types of diabetes and mitochondrial dysfunction.

Table 2
Genetic variants associated with T2DM in humans [15].

Locus	Gene	Chromosome number
PPARG	Peroxisome proliferator-activated receptor gamma	3
IRS1, IRS2	Insulin receptor substrate 1,2	2
KCNJ11	Potassium inwardly-rectifying channel, subfamily J, member 11	11
WFS1	Wolfram syndrome 1	4
HNF1B,	Hepatocyte nuclear factor 1 β	
OTCH2	NOTCH family of proteins	1
THAD 1	Thyroid adenoma associated	2
PROX 1	Prospero homeobox 1	1
GCKR	Glucokinase regulator	2
IGFBP 7	Insulin like growth factor binding protein 7	4
ADCY5	Adenylate cyclase 5	3
CDKAL 1	CDK5 regulatory subunit associated protein 1	6
JAZF 1	Juxtaposed with another zinc finger protein 1	7
KLF14	Kruppel-like factor 14	7
GCK	Glucokinase	7
DGKB/TMEM195	Diacylglycerol kinase β	7
SLC30A8	Zinc transporter 8	8
TP53INP1	Tumor protein p53-inducible nuclear protein 1	8
CDKN2A/B	cyclin dependent kinase inhibitor 2A	9
TLE4	Transducin-like enhancer of split 4	9
TCF7L2	Transcription factor 7-like 2	10
HHEX	Hematopoietically expressed homeobox	10
CAMK1D	Calcium/calmodulin dependent protein kinase	10
KCNQ1	Potassium voltage-gated channel subfamily Q member 1	11
MTNR1B	Melatonin receptor 1B	11
HMGA2	High mobility group AT-hook 2	12
PRC1	Protein regulator of cytokinesis 1	15

[13,14]. T2DM goes undiagnosed for several years resulting in long-term effects because hyperglycaemia develops gradually over the years. The precise causal factors for T2DM is not completely understood.

T2DM is a polygenic disorder that develops due to a complex interaction between multiple genes and environmental factors. T2DM is largely associated with aging. Lifestyle conditions, including physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol, are reported to play an important role in the development of T2DM.

Genetic factors are also known to increase the risk of developing T2DM substantially. Persons with T1DM and with T2DM have genetic predisposition. However, the genetic predisposition of T1DM is stronger than that in T2DM. The risk for developing T2DM is not in area or organ, but appears to be the result of the interaction of multiple genes scattered all across the genome [15].

Table 2 gives an overview of genetic variants that are associated with T2DM.

Recently, genes discovered to be significantly associated with developing T2DM include *TCF7L2*, *PPARG*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2,and *TCF7L2* (transcription factor 7-like 2) regulates proglucagon gene expression and thus the production of glucagon-like peptide-1 [16].

Researchers have recently found that *Astyanax mexicanus* (Blind Cave Tetra), a fish that lives in the dark caves of Mexico, can survive without food for several months. This fish leads a long and healthy life. To ward off food scarcity, this fish has features that create symptoms like large blood sugar swing. It also was found to have fatty liver, which resembles diabetes-linked fatty liver disease in humans. However, in this fish, these changes are adaptations, not a disease. Tabin and his colleagues (2017) identified that this cave fish showed insulin resistance at cellular and biochemical levels. Genetic analysis revealed that the cave fish have unique mutations in the insulin receptor gene that help them gain body weight, a physical characteristic that helps them control their levels of blood glucose, fatty liver, and insulin resistance. Researchers are now trying to understand how the fish is able to tackle these issues, which can be a potential solution to diseases like diabetes and obesity [17]. Mutations in insulin receptor gene in humans cause T2DM. Physiological relevance of mutation in insulin receptor gene needs be investigated.

2.1.3. Type 3 diabetes

Recent studies have established links between systemic metabolic dysfunction, such as diabetes, and neurocognitive impairment, including dementia, obesity, insulin resistance, diabetes, and metabolic syndrome [18]. Brains of patients with Alzheimer's disease (AD) showed reduced expression of insulin and neuronal insulin receptors, as compared with those of age-matched controls. This event gradually leads to a breakdown of the entire insulin-signalling pathway, which manifests insulin resistance [21]. Studies have shown the links between derangements of carbohydrates, proteins, lipids, proteins and brain dysfunction, and cognitive impairment [18]. T3D can be defined as neuroendocrine disorder that represents the progression of T2DM to AD [22]. These include insulin growth factor signalling, acetylcholine esterase activity, inflammatory responses, ApoE4A allele on synaptic plasticity, and vascular dysregulation of brain capillaries.

2.2. Gestational diabetes mellitus

During pregnancy, gestational diabetes in the mothers is linked to hyperglycemia in the fetus. Hyperglycaemia in pregnant women increases the risk of adverse maternal, fetal, and neonatal outcomes. Gestational diabetes is characterized by carbohydrate intolerance during pregnancy [1]. A glucose challenge test is done between 22 and 24 weeks of pregnancy by giving an oral glucose load of 50 g of glucose. If the 2-h post-glucose value is > 140 mg/dL, the test is positive. The oral glucose tolerance test (OGTT) confirms or excludes a diagnosis of GDM. Some obstetricians prefer to do an OGTT without a screening test with 75 g of glucose. In these cases, three blood samples are drawn, fasting, 1 h and 2-h post-glucose load. Women with GDM are at increased risk for subsequent development of frank diabetes. GDM is associated with an increased incidence of neonatal mortality. Maternal hyperglycemia causes the fetus to secrete more insulin, causing stimulation of foetal growth and increased birth weight. After birth, the women should be re-assessed [19,20]. Once an individual is diagnosed as pre-diabetic, education and other interventions may prevent diabetes and other types of diabetes.

2.3. Other types of type 2 diabetes

Other kinds of type 2 diabetes include monogenic diabetes and mitochondrial diabetes. Monogenic diabetes is due to a genetic defect in a single gene in pancreatic β cells, which results in β-cell not functioning well or a reduction in the number of β cells. Conventionally, monogenic diabetes is classified according to the age of onset as neonatal diabetes before the age of six months or Maturity Onset Diabetes of the Young (MODY) before the age of 25 years [7].

Mitochondrial diabetes occurs due to a point mutation in the mitochondrial DNA associated with deafness and maternal transmission of the mutant DNA can result in maternally-inherited diabetes [8].

2.4. Role of pancreatic β-cells in diabetes mellitus

The human body is equipped with a highly sophisticated network of

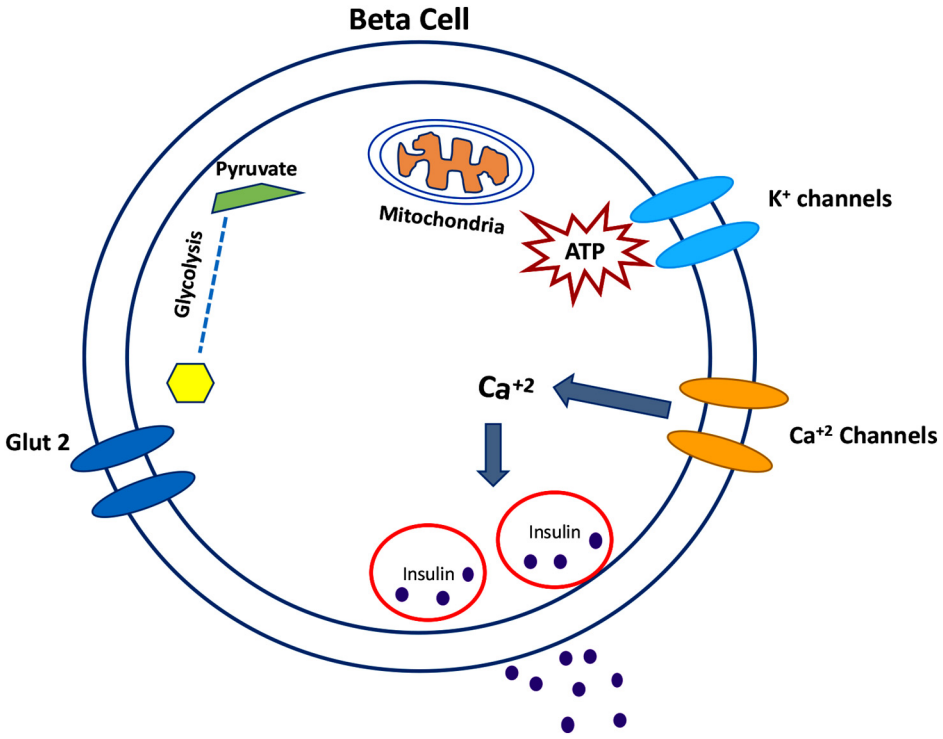

Fig. 2. Model representing glucose-stimulated insulin secretion in pancreatic βcells. Glucose enters the cell via the GLUT transporter, where glucose is phosphorylated by glucokinase. Lycolysis occurs, yielding pyruvate which then preferentially enters the mitochondria, resulting in ATP generation. ATP is then transferred to the cytosol, raising the ATP/ADP ratio. This causes the closure of ATP sensitive potassium channels and subsequent depolarization of the cell membrane. This opens voltage-dependent Ca^{2+} channels, increasing cytosolic Ca^{2+} concentrations, which trigger insulin exocytosis [21].

hormones and neuropeptides that are released mainly from the brain, pancreas, liver, intestine, adipose tissue,and muscle tissue, keeping glucose levels in the blood under check [21]. The pancreas is a key player and acts as a glucose sensor within this network; the task of the β-cell is to adjust the amount of insulin that is released into the blood to regulate glucose levels. In this process, mitochondria play a central role [22] (Fig. 2). The clinical presentations of T1DM and T2DM are associated with a decrease in the pancreatic β-cell function and a decrease in the mass of β-cell [23].

Studies have shown that apoptosis along with necrosis is responsible for pancreatic β-cell death and in the development of diabetes [24]. According to this "accelerator hypothesis," both T1DM and T2DM are basically the same disorder distinguished by the rate of destruction of pancreatic β-cells and the accelerators that cause β-cell loss. These accelerators include a high intrinsic rate of apoptosis, insulin resistance, and autoimmunity. These accelerators operate in various degrees in individuals in order to maintain body metabolism [25]. It is hypothesised that the accelerators are interconnected and together they mediate the destruction of pancreatic β-cells. It is believed that insulin resistance increases apoptosis through pro-inflammatory mediators, which is then followed by the release of βcell antigens and the commencement of an autoimmune attack on the pancreatic βcells in genetically vulnerable individuals [25–27].

2.5. Blood glucose regulation by pancreatic β cells

Increased glucose in the blood stimulates pancreatic β-cells to sense the increase in glucose level and then to secrete insulin in an amount that is essential [28]. This was observed in studies of diabetes in rats, where pancreatic islets increased glucose or methyl succinate a mitochondrial substrate induced the insulin secretion [34]. Rising glucose levels in the blood follows its concentration gradient by diffusion with the help of specific transporters. Glucose then undergoes phosphorylation, thereby initiating glycolysis. Subsequently, mitochondrial metabolism generates ATP, which promotes the closure of ATP-sensitive K + channels, resulting in the depolarization of the plasma membrane. This leads to an influx of Ca^{2+} through voltage-gated Ca^{2+} channels and an increase in cytosolic Ca^{2+}. This increase triggers insulin exocytosis. T2D arises when the β cells fail to sense the increase in glucose, which leads to faulty regulation of the appropriate amount of insulin in the blood [29]. The insulin that is secreted acts on insulin-sensitive tissues, such as those in the liver, skeletal muscles, and adipose tissues, and mediates the uptake of glucose, amino acids, and fatty acids. In turn, these insulin-sensitive tissues, through a feedback mechanism, sends information about the need for insulin to be released into the blood, to the pancreatic β-cells. Insulin resistance in diabetes or obesity causes the pancreatic β-cells to increase the insulin output. However, if pancreatic β cells are incapable of this task, blood glucose levels increase, causing hyperglycaemic conditions.

2.6. Various factors involved in the destruction of pancreatic β-cells

2.6.1. Glucotoxicity and lipotoxicity

Pancreatic β-cells are extremely sensitive to blood glucose levels. Chronic exposure to abnormally elevated levels of blood glucose is known to have adverse effects on insulin synthesis, insulin release, and cell survival, leading to hyperglycaemia (Fig. 3). Pancreatic β-cells can exist in various reversible states, like desensitisation: A temporary state of cellular refractoriness to glucose stimulation or exhaustion: depletion of insulin stores reversible with cell rest. Upon glucose normalization, β-cells recover from these states and improve their insulin secretion. Glucotoxicity brings about an irreversible change to the cellular components of insulin secretion [36].

Glucotoxicity refers to the structural and functional damage in the β-cells and target tissues of insulin, caused by chronic hyperglycemia. These changes cause a lower hormonal secretion and insulin resistance. Lipotoxicity refers to the damage caused by persistently high free fatty acid levels. Glucotoxicity and lipotoxicity are reported to impair β-cell function through multiple pathways. In general, excess glucose metabolism in the β cell tend to over-produce reactive oxygen species (ROS). However, these β-cells have fewer antioxidant enzymes, such as SOD, glutathione, and catalase, making β-cells susceptible to oxidative stress [30], which in turn increases the protein kinase inhibitor, decreases the ATP-to-ADP ratio, decreases the calcium influx resulting in apoptosis, and decreases insulin sensitivity and insulin secretion [31].

ROS is produced from several sources, such as the electron transport

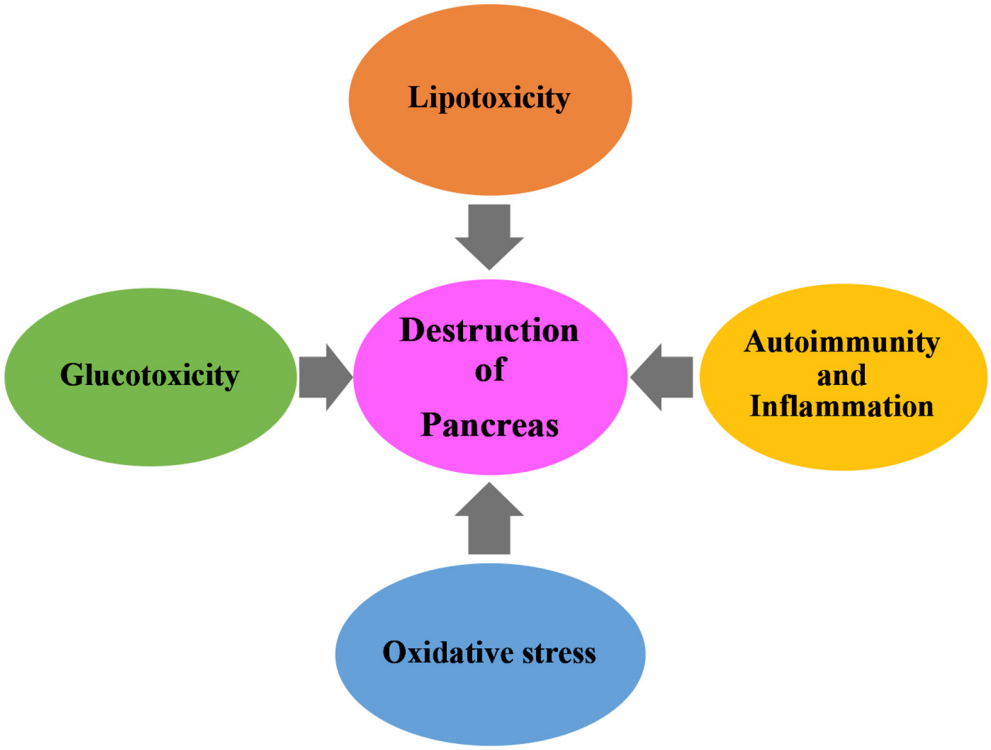

Fig. 3. Summary of factors that are responsible for the destruction of pancreatic β-cells.

chain (ETC) in mitochondria, non-enzymatic glycosylation, and membrane bound NADPH oxidase [32]. The ETC is an important source of ROS. Under diabetic conditions, the ETC is activated, which leads to increased production of ROS. In diabetic animals, non-enzymatic glycation results in various products, such as the glycosylated hemoglobin, albumin, and lens crystalline. These changes eventually leads to advanced glycosylation end products (AGEs) and ROS. NADPH oxidase is also an important source of ROS. NADPH oxidase is activated by various stimuli, such as AGEs, insulin, and angiotensin II, all of which are possibly induced under diabetic conditions [32].

Studies of islets isolated from pancreas of subjects with T2DM showed increased markers of oxidative stress, and these markers correlated with the degree of glucose-stimulated insulin secretion impairment [33]. In addition to the pancreas, the liver and skeletal muscles play an important role in glucose metabolism. Magnetic resonance spectroscopy studies using human subjects showed that delicate changes in mitochondrial function could play a role in the pathogenesis of type 2 diabetes.

In one study, Petersen, et al. (2003) found that, in comparison to young control subjects, healthy, lean elderly subjects showed high insulin resistance, high levels of triglycerides, lower mitochondrial oxidative capacity, and lower mitochondrial ATP levels in liver and skeletal muscles [34]. This finding supports the hypothesis that mitochondrial fatty acid oxidation has a role in insulin resistance. Defective mitochondrial fatty acid oxidation can eventually lead to an increase in intracellular fatty acid metabolites, such as acyl -CoA and diacylglycerol, which are known to eventually disrupt insulin signalling [35].

Studies have also shown that the binding of two transcription factors – PDX-1 (pancreatic and duodenal homeobox-1) [36] and MafA to insulin promoter – was markedly reduced in diabetic conditions. When pancreatic islets were exposed to free fatty acids, ROS was induced, leading to the reduction of insulin secretion and β-cell dysfunction. This reduced insulin suggests that lipotoxicity is also involved in β-cell dysfunction [37,38]. When isolated rat islets where exposed to ROS, the JNK(c-Jun N-terminal kinases) pathway was activated and PDX-1 was translocated from the nuclei to cytoplasm, indicating a change in the binding of PDX-1 to the insulin promoter. Adenoviral overexpression of dominant-negative type JNK1 (DN-JNK) protected insulin gene expression. DN-JNK overexpression inhibited the ROS-induced PDX-1 translocation, suggesting that activation of the JNK pathway is involved in PDX-1 translocation by ROS. Suppression of the JNK pathway can protect cells from ROS [39].

Taken together, it is likely that ROS is closely associated with the development of diabetes mellitus. Recent clinical trials with antioxidants, such as vitamin *C*, *N*-acetyl-L-cysteine, and vitamin E, have shown that antioxidants have little effect, if any, on the progression of diabetes. Hence there is a need for a stronger antioxidant such as SS31 that is targeted to the mitochondria that would exert more beneficial effects on the development of T2DM.

2.6.2. Autoimmunity and inflammation

It is very well established that TIDM is caused by an autoimmune destruction of pancreatic β-cells [26]. Studies have reported the presence of certain autoimmune markers in T2DM subjects [40,41] (Fig. 3). In T1DM and T2DM, there is an infiltration of immune cells of pancreatic β-cells and increased cytokine production. Islets are very susceptible to stress [42,43]. Pancreatic β-cell inflammation in T2DM is due to chronic metabolic stress conditions, such as lipotoxicity and glucotoxicity, which are known to trigger inflammatory responses in pancreatic βcells where there is an increased production of chemokines and cytokines [44]. IL-1β is the key cytokine that regulates other pro-inflammatory cytokines and chemokines, such as the tumor necrosis factor α (TNF α), the chemokine (C-X-C motif) ligand (CXCL) 1, the monocyte chemotactic protein (MCP)-1, and macrophage inflammatory protein (MIP) α [44]. IL-1β is known bring about apoptosis and β-cell impairment. The secretion of chemokines and cytokines attract the local macrophages and trigger an inflammation and autoimmune responses [45].

Islet autoimmune processes occur in both types of DM, although differences exist: the cell-mediated autoimmune disease in T1DM is triggered by environmental factors, and T2DM results from chronic

inflammatory responses associated with obesity and metabolic stressors [46].

2.6.3. Oxidative stress

β-cell glucose toxicity occurs when they are exposed to high concentrations of glucose (Fig. 3). Chronic hyperglycemia is the major cause of impaired insulin biosynthesis, its secretion, and ROS production. These events subsequently bring about pancreatic β-cell apoptosis. Studies have shown that under diabetic conditions, expressions of ROS markers 8-hydroxy–deoxyguanosine (8-OHdG), 4-hydroxy-2 and 3-nonenal (4-HNE) were increased in islets. Pancreatic β cells are vulnerable to ROS due to the relatively low expression of antioxidant enzymes. Therefore, it is likely that ROS is involved in cell deterioration under diabetic conditions [30]. Studies have also shown that the binding of the transcription factors PDX-1 (pancreatic and duodenal homeobox-1) [36] and MafA to insulin promoter was markedly reduced in diabetic conditions.

When pancreatic islets were exposed to free fatty acids, ROS was induced, which led to the reduction of insulin secretion and a reduction of cell dysfunction, suggesting that lipotoxicity is also involved in β-cell dysfunction [37,38].When isolated rat islets where exposed to ROS, the JNK(c-Jun N-terminal kinases) pathway was activated, and PDX-1 was translocated from the nuclei to cytoplasm and hence a change in the binding of PDX-1 to the insulin promoter. Adenoviral overexpression of dominant-negative type JNK1 (DN-JNK) protected insulin gene expression. DN-JNK overexpression inhibited the ROS-induced PDX-1 translocation, suggesting that activation of the JNK pathway is involved in PDX-1 translocation by ROS. Suppression of the JNK pathway can protect cells from ROS [39].

Taken together, it is likely that ROS are closely associated with the development of type 2 diabetes. Present clinical trials with antioxidants such as vitamin *C*, *N*-acetyl-L-cysteine, vitamin E have shown to have little effect, if any, in the progression of diabetes. Hence there is a need for a stronger antioxidant that is targeted to the mitochondria that would exert more beneficial effects on the development of T2D.

2.7. Mitochondrial dysfunction in diabetes

Mitochondrial dysfunction and oxidative stress have been extensively reported in diabetic patients and diabetic mouse models [47–59]. Recent studies have indicated abnormal mitochondrial dynamics along with overproduction of ROS in diabetic patients [47,48]. T2DM results from a combination of reduced tissue sensitivity to insulin and inadequate insulin secretion. It usually develops in adults and is thought to result from a complex interaction between obesity, physical inactivity, diet and genes [49]. A recent study done on diabetic and obese patients established the impaired glucose and lipid homeostasis in skeletal muscle [50]. Increased fat mass leads to several factors that inhibit insulin action including decreased glucose transporter type 4 (GLUT4), increased free fatty acids and other circulating molecules [51,52]. Due to decreased insulin response in sensitive tissues, excess glucose accumulates leading to chronic hyperglycaemia [49].

Recent studies established that IR and T2DM have been associated with mitochondrial dysfunction [53]. Reduced mitochondrial respiration, ATP production and mitochondrial density and mRNA have been reported in the insulin resistance and type 2 diabetic patients [54–59]. Also, overproduction of ROS has been linked with the pathogenesis of IR [60]. A short-term high calorie diet resulted in increased markers for oxidative stress and a transient increase in OXPHOS enzyme protein expression. mtDNA is more predominantly susceptible to oxidative damage induced by excess of ROS during OXPHOS process in mitochondria of brain [61]. In both obesity and T2DM, It is evident from the previous studies that mitochondrial biogenesis is reduced in the condition of diabetes and obesity [50,62,63]. Mitochondrial dysfunction inhibits insulin signalling pathway through the overproduction of ROS and interfering with oxidation of acetyl CoA, consequently resulting in increased lipid and diacylglycerol [5,60,64,65]. Disturbed mitochondrial biogenesis may be a reason for decreased number and oxidative capacity in diabetic condition. PGC-1α also regulates the process of mitochondrial biogenesis [66,67]. Furthermore, mitochondrial dysfunction seems to play a key role in the pathophysiology of IR and T2DM and may be considered as a target for therapeutic measures in metabolic diseases. Accumulation of amyloid beta in the brain tissue and pancreatic cells may shows a common connection between diabetes and AD and thereby showing a possible mechanisms between involved between them [68]. Islet amyloid polypeptide (IAPP) has been recognised as the key component of the pancreatic amyloid of T2DM. It is evident from the previous studies that there is an excess of pancreatic amyloid in the transgenic mice which leads to the beta cell dysfunction and T2DM. In animal studies, inducing insulin resistance is known to promote the deposition of amyloid in brain and pancreatic islet cells. An increased amount of neurofibrillary tangles and amyloid plaques in the hippocampus have been found on autopsy in patients with diabetes [69].

2.8. Are Tally-Ho mice represents human type 2 diabetes?

Tally-Ho mice mimics many characteristics of human non-insulin dependent type 2 diabetes mellitus (NIDDM). It was developed in the Jackson laboratory from the progeny of diabetic males [70]. Male Tally-Ho mice can develop hyperglycaemia, hyperinsulinemia, hyperlipidaemia, moderate obesity, and enlargement of the islets of Langerhans. However, the phenotype is < 100% penetrant. In this model, the onset of hyperglycaemia begins between 10 and 14 weeks of age. Female Tally-Ho mice display moderate hyperinsulinemia, hyperlipidaemia, and obesity, but do not manifest overt diabetes (i.e. hyperglycaemia).

The identification of susceptibility loci contributing to the hyperglycemia trait was studied in TallyHo mice [71] using male backcross 1 offspring obtained from a cross between (Normal B6 Female Diabetic TH Male)F1 Female and Diabetic TH Male or CAST/Ei 3 TH)F1 and TH mice. This genome wide scan identified three diabetes-related quantitative trait loci (QTLs), Tanidd1, 2 and 3. Mutations in the major

Table 3
Genetic variants associated with T2DM in Tally-HO mice [86].

Locus	Gene	Notes	Chromosome number
Tabw2	Tally-HO associated body weight 2	This allele confers increased body weight and increased plasma glucose compared to C57BL/6 J.	6
TabW	Tally-HO associated body weight	This allele confers decreased body weight compared to C57BL/6 J.	7
Tafat	Tally-HO associated mesenteric fat pad weight	This allele confers decreased adiposity compared to CAST/Ei and C57BL/6 J.	4
Tanidd1	Tally-HO associated non-insulin dependent diabetes mellitus 1	This allele confers susceptibility to hyperglycemia compared to CAST/Ei and C57BL/6.	19
Tanidd 2	Tally-HO associated non-insulin dependent diabetes mellitus 2	This allele confers susceptibility to hyperglycemia compared to C57BL/6.	13
Tanidd 3	TallyHo associated non-insulin dependent diabetes mellitus 3	This allele confers susceptibility to hyperglycemia compared to CAST/Ei.	16

QTL, Tanidd1 (TallyHo-associated NIDDM) located on Chromosome 19, are primarily responsible for hyperglycemia in TallyHo mice.

Table 3 gives an overview of the genetic variants associated with T2DM in Tally-Ho mouse models. Another strong link between genetic variants and plasma glucose levels was found on Chr 13, designated as Tanidd2. The mice homozygous for TH alleles carrying Tanidd1 and Tanidd2 had elevated plasma glucose levels compared to heterozygous mice. Further, the gene-gene interactions of Tanidd1 with a locus on Chr18, and Tanidd2 with a locus on Chr 16, leads to hyperglycemia in TallyHo mice. Only Tally-Ho males become hyperglycaemic although variability exists between litters whereas Tally-Ho females exhibit normal glucose tolerance. Tally-Ho males exhibit impaired glucose tolerance by 8 weeks of age. At 4 weeks of age, Tally-Ho mice of both sexes are hypercholesteraemic, compared to C57BL/6 J control mice. Tally-Ho males exhibit a higher triglyceride level than Tally-Ho females beginning at 6 weeks; blood glucose levels remained elevated (> 600 mg/dl) until at least 16 weeks of age. These Tally-Ho mice showed increased body weight, compared to C57BL/6 J mice.

At 4 weeks of age, Tally-Ho males are significantly heavier than are C57BL/6 J (000664) controls and have more adipose as they age [72,73]. Obesity in Tally-Ho mice is associated with obesity the TH-associated body weight 2 (Tabw2) on mouse chromosome 6 [72]. Both Tally-Ho males and females develop early pancreatic islet hyperplasia and hypertrophy, but only Tally-Ho males develop pathologic islet changes, including β-cell degranulation, some vacuolization, and variable islet atrophy with scattered apoptotic cells and fibrotic changes [72]. The TallyHo mice at prediabetes stages demonstrated glucose intolerance induced by leptin-mediated inhibition of insulin secretion [74].

At the time of weaning, both male and female Tally-Ho mice were reported to have increased body weight, plasma insulin levels, and plasma leptin levels. Elevated insulin levels suggest that the pancreas was trying to overcome peripheral insulin resistance [54], while elevated plasma leptin levels were positively associated with adiposity. Hence, both obesity and reduced insulin sensitivity may be key features for diabetes in Tally-Ho mice [54].

It has been reported that the soleus muscle in Tally-Ho male mice showed reduced basal and insulin-stimulated 2-DG uptake when compared to control mice, again indicating that insulin resistance is the primary defect in Tally-Ho mice [70]. This mouse model recapitulates many of the metabolic abnormalities observed in human T2D and will be a valuable tool for identifying underlying molecular defects in humans.

3. Clinical significance

Treatment for persons diagnosed with diabetes can be divided into 2 broad categories: 1) non-pharmacological treatments and 2) pharmacological treatments. Non-pharmacological treatment aims at improving mitochondrial function and lowering free radicals through caloric restriction and physical exercise [75]. Physical exercise promotes weight loss and prevents obesity. Exercise improves the body's metabolic state, increasing blood circulation throughout the body, resulting in a reduction in the risk of heart disease and stroke [19]. Exercise can improve glucose uptake through skeletal muscles [19]. In a study of 5000 diabetic patients over a 4-year period, researchers reported that intensive life style changes brought about a mean weight loss of 4.5 kg in the patients in comparison to patients without regular exercise. Weight loss was directly correlated with reductions in the HbA1c fraction (by 0.3–1%), triglyceride concentrations, and systolic and diastolic blood pressure, as well as with a rise in the HDL cholesterol level [76,77]. Based on the study of 5000 diabetic patients, the American Diabetes Association recommends a minimum of 30 min of moderate to intensive physical exercise for at least 5 days a week.

Pharmacological treatment involves the oral administration of anti-hyperglycemic drugs. Metformin has been the preferred treatment for diabetes [78]. Metformin reduces mortality and has positive effects on the body mass index, weight loss, and lipid concentration of persons with diabetes [78].

Alpha-glucosidase inhibitors are another class of antidiabetic drugs that include acarbose, miglitol, and voglibose [79]. They delay carbohydrate absorption and digestion, resulting in a reduction in postprandial hyperglycaemia [67]. Acarbose has been in use for about 20 years and delays the onset of diabetes in patients with compromised glucose tolerance [75,80]. Another group of anti-diabetic drugs is glitazones, which include troglitazone, rosiglitazone, and pioglitazone. They are known to increase hepatic and peripheral insulin sensitivity and to preserveinsulin secretion [81]. Thiazolidindione (TZD) ameliorates hyperglycaemia by reducing lipotoxicity via the mobilization of fat cells out of liver cells, fat cells, and muscles [70].

Insulin therapy is a pharmacological treatment for T2DM. This treatment has proved to be beneficial in terms of recovery and maintenance of β-cell function [82], by allowing cells to rest and recover from hyperglycaemic stress [83]. Insulin therapy is also reported to protect pancreatic β-cells from insulitis, inflammatory responses, and subsequent T cell responses [84].

In addition to non-pharmacological treatments and pharmacological treatments, other therapeutic options include intensive lifestyle intervention and gastric bariatric surgery (especially the Roux-en-Y gastric bypass method), which aim to decrease of body weight and to improve β-cell function.

Yet another approach is the transplantation of pancreatic islets to diabetic patients from healthy subjects, which has been found to increase the insulin-secreting cell masses [85].

4. Conclusions

This article provides insights on the heterogeneity of diabetes and the pivotal role of β-cell dysfunction. It indicates the main factors that influence β-cell function altering the natural course of the disease. The paper also highlights TallyHo strain as a naturally occurring polygenic mouse model for type 2 diabetes and obesity. Clinical considerations are made regarding the therapeutic options which impact on various factors and mechanisms that contribute to the progressive loss of β-cell function and mass. Genetic and molecular studies of TallyHo mice may provide new insights and information about late-onset T2D similar to human condition.

Transparency document

The Transparency document associated this article can be found, in online version.

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