American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Involvement of Oxidative Stress in Type 1 Diabetes

Widad Sobhi[1,2]* and Abdelhalim Khenchouche[1]

[1]*Faculty of Nature and Life Sciences, Ferhat Abbas Setif 1 University, Algeria*

[2]*National Research Center in Biotechnology, Algeria*

***Corresponding author:** Widad Sobhi, Faculty of Nature and Life Sciences, Laboratory of Applied Biochemistry, Ferhat Abbas Setif 1 University, National Research Center in Biotechnology CRBT, Algeria.

To Cite This Article: *Widad Sobhi, Involvement of Oxidative Stress in Type 1 Diabetes. Am J Biomed Sci & Res. 2020 - 6(6). AJBSR.MS.ID.001100. DOI:* 10.34297/AJBSR.2020.06.001100.

Received: December 31, 2019 ; **Published:** January 17, 2020

Abstract

Type 1 diabetes mellitus (T1D) is a chronic T-cell mediated autoimmune disease that progressively destroys β-cells in Langerhans islets. T1D develops mainly in children and adolescents. Genetic, immunological and environmental factors are implicated in the mechanisms of β cell death leading to absolute insulin deficiency. ER stress, is also implied in the β cell apoptosis. However, oxidative stress, widely studied for its role in the complications of diabetes, can be pointed out as a most significant factor in the pathogenesis history of T1D. In this review, we present the part of each cited factor in the β cell death with particular attention to the various arguments in favor of the role of early oxidative stress in the development of T1D.

Keywords: Type 1 Diabetes; T1D; β Cell; Oxidative Stress; Apoptosis

Introduction

Diabetes is one of the most prevalent diseases in the world. According to the WHO, diabetes currently affects more than 422 million people worldwide and more than 1.6 million deaths [1]. In its two major forms, type 2 and type 1 diabetes cause many complications and worsen patients' health. If the causes of type 2 diabetes are more or less clear and obvious, those who cause type 1 diabetes (T1D) are not yet, despite scientific progress. T1D represents about 10% of the total number of diabetics. If it is characterized essentially by a high level of glucose in the blood, a common peculiarity with type 2 diabetes (T2D), it differs from the first in its patho-physiology and etiology. T1D is classically described as an autoimmune disease-specific for β-cells in pancreatic islets. This definition is supported by a large number of experimental and clinical scientific studies advocating the involvement of the immune system and leading to the development of type 1diabetes. The diagnosis, which is based on hyperglycemia, shows the presence of several types of antibodies [2]. The destruction of β cells is a final step in a cascade of very complex events involving factors related to immunity, genetics and the environment. Oxidative stress is another source of factors that would be involved in the physiopathology of T1D. Oxidative stress can be endogenous or exogenous. In both cases, the consequences on the survival of β cells are more and more mentioned [3, 4].

Role of Immunity

The clinical manifestations of T1D in humans are always a late event, preceded by a silent subclinical phase that lasts for several months or even years. The biological analyses show the presence of various types of antibodies (anti-insulin Ac, anti-GAD Ab, anti-IA2 Ab, anti-ZnT8...) indicating the destruction of β cells. The presence of these antibodies characterizes an ultimate stage of a cascade of very complex events of autoimmunity. However, brilliant studies conducted by Simoni and his collaborators (2011) show the important role of the innate immunity that precedes autoimmune reactions and therefore opens up other fields of investigation. Innate immunity is the first step whose consequences lead to the installation of β-cell-specific autoimmunity because it offers the initial inflammatory site in the action of TCD8 lymphocytes by pDC dendritic cells. Studies conducted on 2-3-week-old NOD mice show the presence of innate immunity cells: neutrophils, B-1 lymphocytes and dendritic cells [5,6]. The role of pDCs in T1D is related to the

production of an IFNα cytokine. This cytokine will contribute to the activation of auto reactive CD4 and CD8 T cells in the first phase. In the second phase (Effector phase), activation of pDC leads to production by these cells an immunosuppressive enzyme [7]. pDCs can present antigens derived from β cells, the necessary step for the activation of self-reactive T cells.

B-1a lymphocytes were also detected in the pancreas of NOD mice. It appears that these cells are essential for the recruitment of T cells into the pancreas by influencing the expression of adhesion molecules, including VCAMs that allow the entry of lymphocytes into the pancreas [8]. Macrophages present in insulitis have an APC function and produce pro-inflammatory cytokines (ie TNF-α and IL-1β) that promote the expression of apoptosis-inducing receptors (ie Fas) on β-cells [9]. Although their role is not yet well understood, neutrophils are also observed in NOD mice of 2-3 weeks. The iNKT cells producing IL17 are present in the pancreas of the NOD mice where they express IL. This interleukin can induce the production of nitric oxide (NO) and thus cause the death of β cells. It can also bind to its membrane receptor on the surface of β cells and induce the release of chemokines by them [5]. Among the chemokines are CXCL10, which leads to the recruitment of immune cells and the destruction of β cells [10,11]. B1 lymphocytes recruited into the islets. They produce anti-DNA IgG antibodies that will complex with DNA and induce neutrophil activation. These produce the antimicrobial peptide CRAMP. The multimolecular complex, composed of anti-DNA IgG and CRAMP, activates pDCs by TLR9 and induces the production of type 1 IFN that will induce the activation of the adaptive immune system and the generation of a strong auto-reactive response by CD8 + T cells [12]. The mechanism of β-cell destruction by CD8 + T cells involves Fas/Fas-L interaction, granzyme/perforin production, and pro-inflammatory cytokine production. Once all β cells are destroyed, CD8 T cells leave the pancreas [6]. In T1D, genetic factors can modulate the autoimmune potential by controlling the generation and expansion of self-reactive T cells. The INS insulin gene is involved in these reactions. The tandem nucleotide repeat (VNTR) variables located 596 bp upstream of the INS insulin gene promoter site can regulate the transcription of insulin messenger RNA into the pancreas and thymus [13]. Class I VNTR predisposition alleles induce high expression of mRNA in the pancreas and at low levels in the thymus [14,15] leading to less effective elimination (positive selection) of anti-insulin T cells and their presence in larger amounts in the circulation and triggered an autoimmune T1D response.

Role of Genetic

In addition to the role of the immune system, there is also evidence that a genetic predisposition exposes some people to this disease [16]. The different family studies of T1D, show that 6 to 10% of patients have a family history of diabetes in the first degree, the prevalence is of the order of 0.3% [17]. Homozygous twins have a concordance rate for T1D of about 40% [18]. The risk of T1DM progression is due to specific HLA DR / DQ alleles. The human leukocyte antigen (HLA) -DRB1, HLA-DR3 genes have shown a stronger association with the disease [20] as is the case for example for the combinations DRB1 * 03-DQB1 * 0201 (DR3 / DQ2) or DRB1 * 04-DQB1 * 0302 (DR4 / DQ8). Also, the HLA DQB1 * 0602 allele is associated with dominant protection against T1D in several populations [19]. The three sets of HLA-B-DR3 haplotypes, mainly B58-DR3, B50-DR3, and B8-DR3, showed modulated (variable) susceptibility for T1D worldwide [20]. Other studies have revealed that other genes outside the MHC are also associated with T1D, such as genes involved in inflammation and autoimmunity [21] and more recently, BTNL2 [22]. The miRNA studies also show that they can also be used as markers for T1D. Samandari et al. (2017) show, for example, that 6 mi-RNAs appear to be associated with DT1. hsa-miR-197-3p is linked to 6 genes: TUSC2, CD82: related to cancers. NSUN5 encodes a methyltransferase. BMF and PMAIP1 are involved in apoptosis while MTFD1 is involved in vitamin metabolism (Samandari et al., 2017). The micro-RNAs miR-146a and miR-155 can provide information on the residual beta cells and kinetics of the evolution of T1D [23].

Role of the Environment

Studies on genetic susceptibility confirm its role in T1D. However, arguments in favor of environmental conditions are raised. Studies have also revealed that approximately 60% of children who develop T1D develop the first antibodies in the first two years of life [24,25], which means that of the environment may be involved most likely early in the patients' lives. Thus, the role of viral infections (enteroviruses) [26,27] and early feeding [28] have been pointed for many years. Vitamin D deficiency and obesity are also highlighted [29,30]. Also, the methylation of certain genes such as the TNFα gene has been detected in children newly diagnosed with T1D [31]. The methylation of the INS1 and INS2 genes NOD mice islets and in humans has been raised [32]. However, disparate and unconfirmed opinions of many doctors indicate that the rates of this pathology are increasing considerably, and that the role of the environment could be strongly involved.

Oxidative Stress

Oxidants are mainly reactive oxygen and nitrogen species (ROS and NOS) produced during natural processes. They play many important physiological roles in healthy cells. They are produced during several reactions: glucose oxidation, non-enzymatic proteins glycation, and proteins glycated degradation [33]. Through its activity, the mitochondrion is at the heart of oxidative stress. ROS are produced there by the different enzymes of the respiratory chain. The mitochondria produce approximately 90% of cellular ROS [34]. The rest of the ROS are produced in other cellular compartments including the ER and the peroxisome. The availability of enzymatic and non-enzymatic antioxidants protects the body against toxic effects of ROS and NOS.

Oxidative stress is the state of the body in which a prooxidant / antioxidant balance is disordered. The unsteadiness or disorder is generated when an increasing rate and/or a decreasing of antioxidants levels are observed. Free radicals are reactive oxygen species (ROS) such as OH., O^{-}_{2}., ... and reactive species of nitrogen (NOS) like NO. and NO_2.. ROS and NOS include other non-radical species like H_2O_2, $ONOO^-$, $^1O_2$ and HOCl which are harmful to the organisms.

Oxidative Stress and Inflammation

Inflammation is the physiological response of the vascularized tissues following an attack causing impairment of tissue integrity. The causes are variable, of endogenous or exogenous origin [35]. Inflammation is a defense mechanism of the body against various aggressors. It is acute or chronic. The mechanisms used in both cases are complex and lead to the production of pro-inflammatory cytokines, ROS and NOS [36]. Acute inflammation is rapid and self-limiting. It is part of the innate immunity that protects the organism from different microorganisms. It is organized in several stages: vascular phase, cell phase and resolution phase [37]. The recruitment of immune system cells such as neutrophils contributes to the production in the site of inflammation of free radicals derived from ROS and NOS and proteases [38]. The resolution of inflammation is a spontaneous phenomenon and characterized by the recruitment of anti-inflammatory mediators such as IL-10, TGFβ and glucocorticoids. Monocytes are also involved and allow the elimination of cellular debris [39]. The elimination of the chemical mediators used in the first two stages will also be eliminated. Expression of CD195 on the surface of apoptotic human polynuclear cells allows them to sequester pro-inflammatory cytokines [40]. CD195 expression is inhibited by pro-inflammatory stimuli, including tumor necrosis factor, leading to chronic inflammation. Monocytes are also involved and allow the elimination of cellular debris [39]. The elimination of the chemical mediators used in the first two stages will also be eliminated. Expression of CD195 on the surface of apoptotic human polynuclear cells allows them to sequester pro-inflammatory cytokines [40]. CD195 expression is inhibited by pro-inflammatory stimuli, including tumor necrosis factor, leading to chronic inflammation.

Endoplasmique Reticulum Stress in β Cell

B cells are cells characterized by their ability to produce and secrete a high amount of insulin. The synthesis of this peptide is modulated by the level of blood glucose. To cope with high blood sugar levels, β cells synthesize more insulin. Adequate refolding of insulin is crucial. RE stress generated by the accumulation of misfolded insulin leads to apoptosis of β cells and the development of diabetes [41,42]

UPR Response: The presence of stress in the ER triggers the unfolded protein response (UPR) [43]. It is a set of mechanisms whose objective is to decrease the number of proteins accumulated in the ER. UPR slows the synthesis of new proteins of the secretion pathway, increases the synthesis of proteins involved in the folding of neo-synthesized proteins such as chaperones and foldases, and triggers the degradation of irreversibly misfolded proteins by the proteasome [44]. If all the actions fail, the UPR can then tip the cells into the apoptosis pathways [45]. UPR actions are provided by three ER membrane proteins: PERK, ATF6, and IRE1 bound and held in their inactive state by GRP78. GRP78/BiP is a major chaperone protein implied for protein quality control of the ER [46]. When misfolded proteins accumulate in the ER, GRP78 binds misfolded proteins, thereby releasing the protein sensors of ER stress and allowing for the activation of the cytoprotective UPR [44,47]. PERK autophosphorylates in trans, activates eIF2α. Phosphorylation of eiF2α activates the translation of the transcription factor ATF4 (activating transcription factor 4). ATF6 translocates to the Golgi apparatus and is cleaved to yield a transcription factor that up-regulates the expression of molecular chaperones to aid in the folding of accumulated proteins in the ER. IRE1 autophosphorylates in trans and splices XBP-1 mRNA. The spliced mRNA encodes a transcription factor that up-regulates the expression of additional molecular chaperones and UPR proteins to relieve ER stress. If ER stress is too great or prolonged, the UPR induces expression of pro-apoptotic proteins such as CHOP (CEBP homologous protein) [48,49,74,75,79].

IRE1 has also been shown to form a trimeric complex with TRAF-2 (TNF receptor-associated factor) [50] and ASK-1 (apoptosis signal-regulating kinase 1) and activate the JNK pathway (from Jun N-terminal kinase), which leads to apoptosis [51,52]. Also, pro-apoptotic proteins Bax (Bcl-2 – associated X protein) and Bak (Bcl-2 homologous antagonist killer) in persistent ER stress, undergo a conformational change and cause the exit of Ca^{+}_{2} in the cytosol [53,79] the abnormally increased Ca^{+}_{2} concentration in the cytosol leads to several events which, activation of caspase-12, directly involved in cell apoptosis [36,75].

β Cell, Oxidative Stress and Inflammation

In T1D, the role of oxidative stress can be observed at two levels of the disease: First, oxidative stress is mainly involved in the various classic complications of diabetes. Many mechanisms have been elucidated to identify biological markers: lipid oxidation markers such as MDA, Isoprostanes and hydroperoxide lipids [33] and markers of protein peroxidation. Glucose reacts easily with the free amino groups of proteins to form Amadori products. These are relatively unstable and degrade into advanced glycation products (AGEs) or Maillard products [55]. In the presence of transition metals (such as iron), glycated proteins can give an electron to molecular oxygen, leading to oxygen free radicals [56].

Several cellular studies have shown that under oxidative stress conditions, insulin signaling is altered by several mechanisms including induction of IRS serine/threonine phosphorylation, disruption of cellular redistribution of insulin signaling components,

decreased GLUT4 gene transcription, and impaired mitochondrial activity [57] leading to insulin resistance [58].

ROS and oxidative stress also lead to the activation of multiple serine/threonine kinase signaling cascades [59]. The serine / threonine kinases involved in insulin signaling (PKC, PKB, mTOR and GSK-3) can be directly activated by ROS [59,60] or indirectly, by inducing a number of stress-sensitive signaling pathways, such as NF-*k*B, JNK / SAPK and p38 MAPK [59-61]. These activated kinases can act on several potential targets of the insulin signaling pathway, including the insulin receptor and the IRS protein family. For IRS-1 and IRS-2, an increase in serine phosphorylation decreases the extent of tyrosine phosphorylation [59]. As a result, the association and activity of the downstream signaling molecules are decreased, resulting in PI3K quenching and reduction of IGU (insulin-dependent glucose uptake) thereby decreasing glucose uptake and associated decrease in ROS production [62].

On another level, it is interesting to point out that if chronic hyperglycemia is at the origin of oxidative stress, this could also be at the origin of T1D by a phenomenon of apoptosis of pancreatic beta cells [77]. Oxidative stress would be involved in the early stages of the disease. According to some studies, a state of oxidative stress could explain the disorders of insulin secretion and the death of β cells [59]. Studies have shown that oxidative stress is one of the factors involved in this process, without defining with certainty the roles of the studied molecules in the death of β cells. [63], For example, describe the role of NADPH oxidase in the secretion of insulin by β-cells in the presence of hyperglycemia.

The overproduction of ROS-producing enzymes such as SOD, CAT [64], NADPH oxidase, notably NOX1 and NOX2 isoforms and XO / XDH [57,65,66] or CRP [67], accompanied by the decrease in GSH seem to be involved in the pathogenesis of β cells. Several fundamental transcription factors for the cell are the targets of ROS / NOS among which the Nuclear Factor-KB (NF-*k*B) and the Activator Protein-1 (AP-1) [68]. Inhibition of those factors by ROS or NOS conduce β cell to the apoptosis pathways. The question that remains is: What is the relationship between oxidative stress and ER stress? the answer is certainly not yet elucidated but some information are reported by few studies : i)As we explained above, ii) the ER stress activates UPR which induces expression of pro-apoptotic proteins such as CHOP [49], iii) the calcium influx from the ER, during ER stress, into cytosol than into mitochondria increase the release of cytochrome C and in the consequent triggering ROS production [76] and caspase-mediated cleavage of the IRE1 within its cytoplasmic linker region generates a stable IRE1fragment comprising the ER-lumenal domain and transmembrane segment (LDTM). LDTM exerts negative feedback over apoptotic signaling by inhibiting recruitment of the key pro-apoptotic protein BAX to mitochondria [69].

Morever, it has been reported in an old publication that inhibition of CHOP-mediated apoptosis merely delays, but does not halt, β cell loss and disease onset [70]. These data suggest that apoptosis may not be the only mechanism by which ER stress causes β cell death and diabetes. Paradoxically, [49] indicate that IRE1α kinase/endoribonuclease (RNase) triggers apoptosis and suggest that inhibition of IRE1α using small molecules can spare ER stressed β-cells from death [71-73].

β Cell Death

Apoptosis is the death of β cells following the activation of caspases by exogenous or endogenous signals. The principal pathways of apoptosis are the FasL/Fas, perforin/granzyme, IL-1β, TNF and INFγ pathways triggered mainly by exogenous signals released by the cells of the immune system [3,8]. Mitochondria are at the heart of these events because the mitochondrial stress generated by the activity of mitochondrial enzymes (SOD, CAT , NADPH oxidase, Cytochrome c oxidase ..) or under the influence of several signals leads to the release of cytochrome C which can activate the caspase events [3]. The signals can also be endogenous. Because of its important protein synthesis and secretion activity, β cells undergo oxidative stress in the Endoplasmic Reticulum (ER) [4]. Errors in synthesis and refolding cause the accumulation of damaged and misfolded proteins and activate proteasomes in the secretory route [78]. Other mechanisms for activating apoptosis are underway study.

Finally, the study of the phenomenon of β-cell apoptosis is always associated with the presence of T1D, i.e. in the presence of autoimmunity and a confirmed genetic predisposition. This is the case of studies on animal models predisposed genetically for the development of T1D, such as NOD mice, or on cell lines derived from these animals. The impact of the environment in these cases would be very limited and the interpretation of the results will always favor the impact of the immune system. Healthy animal studies or healthy β-cell lines could be used to study the role of the real environment in T1D.

Conclusion

Despite the high number of studies conducted on T1D and the role of different physiological components and pathological failures, there is still no clear explanation of the pathology. This is also the case of many autoimmune diseases. A careful reading of all of those studies points to the conclusion that T1D isn't just an autoimmune disease as it's commonly described. It's also complicated and multifactorial. The interaction between the genetic background and the triggering environment is certainly essential for the development of autoimmunity and the death of insulin-producing cells. The loss of capital in β cells leads to the clinical manifestation of diabetes. Subsequently, oxidative stress, maintained by chronic hyperglycemia, promotes the development of various complications. However, the endogenous oxidative stress due to cellular activity or caused by exogenous factors and the related ER stress must be studied simultaneously to shed more light on its impacts on β-cell

dysfunction and in the early innate inflammation. The role of β cells and their microenvironment should be incriminated in understanding the pathophysiological history of the disease.

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