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Role of Inflammatory Mechanisms in Pathogenesis of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by progressive β-cell dysfunctioning and insulin resistance. This article reviews recent literature with special focus on inflammatory mechanisms that provoke the pathogenesis of T2DM. We have focused on the recent advances in progression of T2DM including various inflammatory mechanisms that might induce inflammation, insulin resistance, decrease insulin secretion from pancreatic islets and dysfunctioning of β-cells. Here we have also summarized the role of various pro-inflammatory mediators involved in inflammatory mechanisms, which may further alter the normal structure of β-cells by inducing pancreatic islet's apoptosis. In conclusion, it is suggested that the role of inflammation in pathogenesis of T2DM is crucial and cannot be neglected. Moreover, the insight of inflammatory responses in T2DM may provide a new gateway for the better treatment of diabetes mellitus. J. Cell. Biochem. 114: 525–531, 2013.

KEY WORDS: PRO-INFLAMMATORY CYTOKINES; OXIDATIVE STRESS; HYPERGLYCEMIA; DYSLIPIDEMIA; INTERLEUKIN-1 RECEPTOR ANTAGONIST

T2DM is one of the complicated and most prevalent type of diabetes [Yang et al., 2010a]. A large number of proposals and hypothesis have been developed to describe the mechanisms, which are usually involved in the propagation of T2DM [Shoelson et al., 2006; Donath et al., 2009]. Obesity, aging, β-cell dysfunction, tissue lipid accumulation, oxidative stress, endoplasmic reticulum stress (ER-stress) in β-cells, tissue inflammation, and physical inactivity are the most commonly known factors linked to insulin resistance which progress T2DM. Interestingly, other than these determinants, recently autoimmune participants causing inflammation have been also considered playing their role in insulin resistance by affecting β-cells of pancreatic islets [Brooks-Worrell et al., 2011; Goldfine et al., 2011]. Insulin resistance persists the entire period of T2DM from early stage of pre-diabetes to later stage of overt T2DM. In order to compensate insulin resistance, pancreatic islets increase their cell mass and insulin secretion but when these pancreatic islets become unable to compensate insulin resistance, insulin deficiency occurs in peripheral tissues, which may lead to the development of T2DM. Once T2DM occurs, it imparts long-term consequences which may include atherosclerosis, neuropathy, retinopathy, and nephropathy [Donath and Shoelson, 2011].

Even though, as mentioned earlier there are many pathogenic factors involved in T2DM, it is quite difficult to estimate that which type of mechanism is involved in different tissues, nevertheless, it is still noteworthy that all of these cellular stress mechanisms are considered to overlap each other and provoke inflammation in pancreatic tissues [Donath et al., 2008; Hotamisligil and Erbay, 2008; Ehses et al., 2009a].

Insulin, the hormone of pancreatic β cells secreted in response to blood glucose level also participates in regulating metabolism, cell growth, and differentiation via acting on cell-surface receptors. T2DM is simply characterized by uneven insulin secretion and its related effects [Robertson et al., 2004; Prentki and Nolan, 2006]. In terms of pathogenesis, glucolipotoxicity can be stated as one of an essential determinant of T2DM. In general, glucolipotoxicity is a common term used in combination for glucotoxicity and lipotoxicity as both are known to progress simultaneously [Poitout and Robertson, 2002]. Glucotoxicity refers to constantly elevated levels of blood glucose (hyperglycemia) that impact damaging effects on normal functioning of β-cells and finally decreases insulin secretion. Similarly, levels of lipids (lipotoxicity) specifically, FFAs have been also known to regulate insulin secretion,

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however, chronically increased plasma levels of FFAs may also lead to β-cell dysfunctioning [van Raalte and Diamant, 2011]. This glucolipotoxicity in turn may cause ER-stress within pancreatic islets [Cnop et al., 2008]. ER is well recognized for the synthesis of majority of proteins including pro-insulin in pancreatic β-cells, which is produced in excess during chronically elevated glucose level exerting extra stress on ER. If ER homeostasis for the production of protein is not regained, ER-stress might end up with cell apoptosis [Eizirik et al., 2008]. Moreover, hyperglycemia might also promote the generation of reactive oxygen species (ROS) inducing oxidative stress in β-cells, these cells are already known to be susceptible to oxidative stress because of having modest levels of antioxidants enzymes [Poitout and Robertson, 2008; Akash et al., 2011]. In diabetes mellitus, mitochondria has been reported to be the principle origin for oxidative stress which develop and progress T2DM as chronic hyperglycemia alters the activity of mitochondrial electron transfer chain (involving complex I–IV) causing generation of mROS [Lambert and Brand, 2004]. This oxidative stress results in the production and release of pro-inflammatory mediators (cytokines and chemokines), which have been known for their involvement in causing β-cell dysfunctioning leading to insulin resistance and inflammation attributing to T2DM (Fig. 1). Further in this article we will discuss the recent knowledge regarding the role of inflammatory mechanisms in T2DM.

MECHANISMS OF INFLAMMATORY RESPONSES AND INFLAMMATORY MEDIATORS IN T2DM

Many studies have been conducted in order to develop the relationship between various inflammatory mediators and T2DM, and have found abnormally high levels of various cytokines, plasminogen activator inhibitor, chemokines, acute phase proteins (such as CRP) in type 2 diabetic patients [Spranger et al., 2003; Herder et al., 2009] concluding that high circulating levels of IL-1β, IL-6, and CRP can be the main predictive indicators for progression of T2DM [Pradhan et al., 2001; Spranger et al., 2003]. These high levels of numerous cytokines and CRPs may induce the activation of innate immune system in type 2 diabetic patients due to overnutrition; however, these inflammatory mediators do not clearly reveal the magnitude of inflammation in different peripheral tissues. The term overnutrition is a frequent overconsumption of nutrients relative to the amounts required for normal growth and development of the body to the point that it becomes dangerous for health. All compounds that are necessary for normal body functions and development including minerals, vitamins, fats, carbohydrates, and proteins are termed as nutrients. It is the main inducer of inflammatory mediators and CRPs, moreover, the circulating levels of these mediators are considered to vary from individual to individual and tissues to tissues [Donath and Shoelson, 2011]. In patients with T2DM, augmented circulating levels of various pro-inflammatory cytokines and chemokines along with overt tissue inflammation have been detected [Maedler et al., 2004; Ehses et al., 2007]. Consequently, one may not predict the degree and extent of inflammation in specific tissue by only observing the circulating levels of these pro-inflammatory mediators.

It has been clear from the above-mentioned facts that inflammation plays a crucial role in the dissemination of T2DM. Thereby, T2DM may be stated as a chronic form of auto-inflammatory disease producing IL-1β from β-cells of pancreatic islets; which eradicates β-cells themselves [Maedler et al., 2002; Dinarello, 2010] leading to β-cell dysfunction (Fig. 2). Following are the potential inflammatory responses that play their pivotal role in inflammatory mechanism for pathogenesis of T2DM.

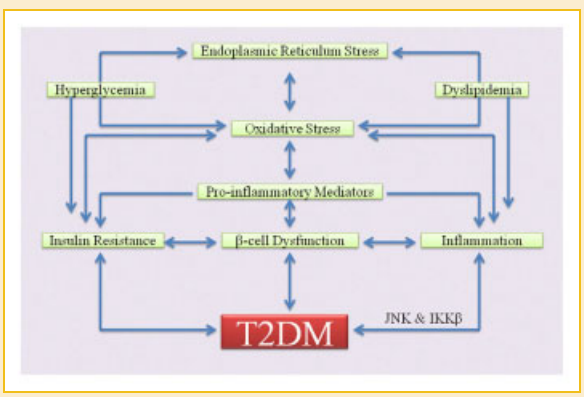

Fig. 1. Various pathogenic factors that extend beyond each other and participate in the pathogenesis of T2DM. Hyperglycemia and dyslipidemia decisively provoke oxidative stress and endoplasmic reticulum stress (ER stress). Oxidative and ER stress may also potentiate the effects of each other. Once oxidative stress is produced, it induces the generation of various pro-inflammatory mediators. These pro-inflammatory mediators may further cause inflammation in pancreatic islets and peripheral tissues. Due to inflammation, insulin resistance is developed in peripheral tissues. Inflammation in pancreatic islets impairs normal functions of β-cells that ultimately leads to cell death. Hence, T2DM occurs.

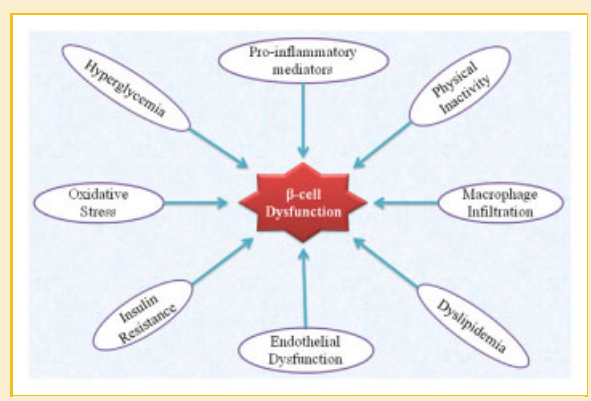

Fig. 2. Mechanism of β-cell dysfunction. Multiple risk factors are involved in induction of β-cell dysfunction. These include optimal glucolipotoxicity (hyperglycemia and dyslipidemia), which can impact the development of insulin resistance, oxidative stress and/or endothelial cells dysfunction, as well as the activation of pro-inflammatory mediators and macrophage infiltration. Collectively, these factors may lead to β-cell dysfunction due to which impairment of insulin secretion occurs that may provoke the onset of T2DM.

REDUCED OXYGENATION

It also known as hypoxia and occurs when oxygen supply is limited. To overcome this, a compensatory phenomenon known as angiogenesis is stimulated through the secretion of numerous angiogenic factors in order to compensate the required amount of oxygen in rapidly growing tissues (e.g., cancerous tissues) [Carmeliet, 2005]. Similar type of phenomenon has also been observed in animal models of obesity [Hosogai et al., 2007; Yin et al., 2009] and in human adipose tissues that may cause tissue dysfunction [Pasarica et al., 2010]. Hypoxia may also stimulate the induction of various pro-inflammatory genes in macrophages. Macrophages accumulate at the site of hypoxia and endow a link between rapidly growing adipose tissues and commencement of inflammation [Burke et al., 2003]. Moreover, hypoxia has been also known for initiating ER-stress in pancreatic islets most probably by influencing the ER redox potential and decreasing the concentration of ATP which results in β-cell death [Tu and Weissman, 2004].

TRANSCRIPTIONAL PATHWAYS

There are many metabolic pathways that cause insulin resistance in peripheral tissues. They provoke inflammation and stress-induced kinases such as IκB kinase-β (IKKβ) and JUN N-terminal kinase (JNK). These kinases are known to efficiently participate in pathogenesis of diabetes (Fig. 1) [Shoelson et al., 2006]. IKKβ may potentiate the activation of nuclear factor-κB (NF-κB), which in turn induces pro-inflammatory cytokines (TNF-α and IL-1β) in liver and adipose tissues. These cytokines result in insulin resistance in peripheral tissues [Arkan et al., 2005]. However, JNK potentiates activating transcription factor-2 (ATF2) and ELK1. Although, the role of JNK stimulated transcription factors is not known [Solinas and Karin, 2010] but some experimental studies have provided ample evidences that JNK plays its crucial role in inflammatory responses for pathogenesis of T2DM.

TNF-α and IL-1β, which are produced by the activation of NF-κB are also known to stimulate both NF-κB and JNK in response to feed-forward mechanism through the involvement of their particular receptors [Donath and Shoelson, 2011]. Other then NF-κB and JNK pathways, FFAs and advanced glycation end-products may promote insulin resistance and overt T2DM by the activation of toll like receptors (TLRs) and receptors for advanced glycation end-products (RAGE) [Shi et al., 2006]. These extracellular stimuli bind these cell surface receptors by activating intracellular pathways that unite on both JNK and NF-κB. Activation of these pathways takes place in liver and adipose tissues and upregulates the production of TNF-α, IL-1β, and IL-6 [Sabio et al., 2008]. Hyperglycemia and over production of IL-1β in β-cells of pancreatic islets also activate NF-κB. Blockade of NF-κB activation by naturally occurring anti-inflammatory cytokine interleukin-1 receptor antagonist (IL-1Ra) protects β-cells from various deleterious effects [Eldor et al., 2006; Akash et al., 2012a]. Since, these NF-κB and JNK pathways are activated in many tissues and play crucial role in tissue inflammation, blocking the activity of these pathways may stop the prevalence of inflammation.

CYTOKINES

The most promising part among multifactorial pathophysiologies for dissemination of T2DM is played by numerous pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. These cytokines released from adipose tissues induce inflammation not only in the corresponding tissue but also in the β-cells of pancreatic islets and ultimately leads to insulin resistance [Zhao et al., 2006; Tilg and Moschen, 2008; Ehses et al., 2009a]. Initially, it was anticipated that mechanism of inflammation in β-cells of pancreas originates by β-cells apoptosis induced by hyperglycemia [Donath et al., 1999]. Later on, this proposed mechanism was observed by Maedler et al. [2003] in which they found that elevated levels of glucose stimulates pro-apoptotic receptor FAS on β-cells and may induce the production of IL-1β. Instead to glucose-induced stimulation of IL-1β, expression of IL-1β in pancreatic islets is also regulated by FFAs that stimulate the secretion and production of IL-1β and IL-1 dependent pro-inflammatory cytokines [Böni-Schnetzler et al., 2008, 2009]. Once, IL-1β is induced by either glucose and/or FFAs, it regulates its secretion and production in pancreatic islets by autostimulation [Akash et al., 2012a]. This autostimulation of IL-1β may be prevented by blocking the activity of NF-κB and/or reducing the signaling of IL-1RI for IL-1β with IL-1Ra. Thereby, the stimulation of IL-1β due to glucose and/or FFAs may be prevented by blocking the signaling of IL-1RI [Böni-Schnetzler et al., 2008]. Moreover, stimulation of β-cells to produce IL-1β, also increases the nitric oxide production leading to reduction in mitochondrial ATP concentration which can cause β-cell dysfunction and reduced insulin secretion [Arafat et al., 2007; Yang et al., 2010b].

Other than IL-1β, TNF-α also plays an essential role by creating a linkage among insulin resistance, obesity, and inflammation [Tilg and Moschen, 2008]. To be precise, TNF-α has been recognized as a key factor linking inflammation and insulin resistance. It modulates the activities of IKKβ/NF-κB and JNK pathways regulating insulin resistance [Tilg and Moschen, 2008]. Overproduction of TNF-α in adipose tissues causes insulin resistance in peripheral tissues by the induction of inflammation and β-cell death in pancreatic islets [Rosenvinge et al., 2007].

The role of IL-6 in T2DM is considered to be complex and controversial, however, various experimental studies have confirmed that IL-6 induces insulin resistance in peripheral tissues [Fève and Bastard, 2009; Akash et al., 2012a], apoptosis in pancreatic islets together with other inflammatory cytokines [Pradhan et al., 2001; Akash et al., 2012a] and stimulates the inhibition of cytokine's signaling proteins [Pradhan et al., 2001]. Due to these deleterious effects, IL-6 is considered as an independent risk factor and acts as predictor and pathogenic marker for insulin resistance and progression of T2DM [Tilg and Moschen, 2008].

Pro-inflammatory cytokines may potentiate the inflammatory mechanisms in peripheral tissues as well as in pancreatic islets, IL-1Ra is the only naturally occurring anti-inflammatory cytokine that exterminate these mechanisms by neutralizing the actions of pro-inflammatory cytokines [Akash et al., 2012b]. IL-1Ra is highly expressed in endocrine pancreas of normal individuals. Its expression level is decreased in type-II diabetic patients that increase the ability of IL-1β to exert its deleterious effects on pancreatic islets [Maedler et al., 2004].

CHEMOKINES

Adipocytes secrete various chemokines that recruit monocytes and macrophages. It has been demonstrated that the adipose tissues in obese individuals secrete more chemokines as compared to non-obese individuals [Kanda et al., 2006; Tilg and Moschen, 2008]. There are various types of chemokines such as CCL2 (MCP1), CCL3 (MIP-1α), CCL6, CCL7, CCL8, and CCL9. These chemokines are released from adipose tissues, pancreatic islets [Ehses et al., 2007; Böni-Schnetzler et al., 2009; Akash et al., 2012a], and endothelial cells [Shanmugam et al., 2003; Ehses et al., 2007]. Increased production of these chemokines has also been confirmed in various diabetic animals [Böni-Schnetzler et al., 2009; Ehses et al., 2009ab]. Some experimental studies have observed that these chemokines play their role in the pathogenesis of T2DM along with pro-inflammatory cytokines however, the precise mechanism of these chemokines still remains to be elucidated [Dedon and Tannenbaum, 2004; Ehses et al., 2009a].

ADIPOCYTOKINES

Leptin and adiponectin are well known as adipocytokines and are usually produced from adipocytes. These adipocytokines exert their immunomodulatory effects in T2DM. Due to the structural similarity of leptin with other pro-inflammatory cytokines, it is also considered as pro-inflammatory cytokine [Otero et al., 2005]. Leptin induces apoptosis in pancreatic islets via induction of IL-1β secretion and suppression of IL-1Ra [Ehses et al., 2009b], which impairs insulin secretion from β-cells [Zhao et al., 2006]. Leptin does not play its role in obesity-induced inflammation [Donath and Shoelson, 2011]. The role of adiponectin in T2DM is totally opposite to that of leptin. It exerts its anti-inflammatory effects on endothelial cells through inhibition of TNF-α induced adhesion-molecule expression and NF-κB, and activation of IL-1Ra [Wolf et al., 2004] whereas in obese animals, it diminishes the levels of glucose by improving insulin sensitivity.

FACTORS THAT POTENTIATE TISSUE INFLAMMATION IN T2DM

Although, many pathogenic responses may be involved in inducing insulin resistance due to inflammation and blocking of insulin secretion from β-cells, however, hyperglycemia, dyslipidemia, and oxidative stress [Akash et al., 2012a] are considered to be directly involved in tissue specific inflammation. Here in following paragraphs, we have tried to describe that how these phenomena can potentiate tissue specific inflammation.

HYPERGLYCEMIA

Hyperglycemia refers to the constantly elevated levels of blood glucose that imparts its damaging effects on normal functioning of β-cells finally decreasing insulin secretion. Augmented level of glucose in plasma is a primary motive for pathogenesis of T2DM. High levels of glucose are very toxic to β-cells [Weir and Bonner-Weir, 2004]; once, it enters into the β-cells of pancreatic islets along FFAs [Dinarello, 2011], it induces the stimulation of various pro-inflammatory mediators such as IL-1β, TNF-α, IL-6, and various other IL-1 dependent cytokines and chemokines [Maedler et al., 2004; Böni-Schnetzler et al., 2008, 2009; Ehses et al., 2010; Akash et al., 2012a]. As these pro-inflammatory mediators are provoked, they might cause tissue specific inflammation.

DYSLIPIDEMIA

The term dyslipidemia is used when circulating levels of various lipids are changed accordingly in response to insulin resistance and overnutrition. The effect of change in concentration of lipids on β-cells depends on specific lipid profile. Some saturated fatty acids (palmitate) may act as pro-apoptotic for β-cells whereas; mono-saturated fatty acids (oleates) protect β-cells from harmful effects of saturated fatty acids and glucose [Maedler et al., 2003]. As the insulin resistance in peripheral tissues increases, the circulating levels of FFAs are also increased [Reaven et al., 1988]. Once circulating levels of FFAs are augmented, they subsequently migrate to β-cells of pancreatic islets where they cause the disruption of β-cells by inducing the secretion of IL-1β [Maedler et al., 2003]. Like fatty acids, lipoproteins may also exert their effects on the survival and normal functioning of β-cells. Very low density lipoproteins (VLDL) and low density lipoproteins (LDL) are very harmful and behave as pro-apoptotics for β-cells like saturated fatty acids whereas, the role of high density lipoprotein (HDL) is to protect the β-cells from harmful effects of other lipoproteins, saturated fatty acids and glucose [Roehrich et al., 2003].

OXIDATIVE STRESS

The role of oxidative stress in pathogenesis of T2DM [Prasad et al., 2009] is well recognized. It may cause tissue damage that accompanies chronic hyperglycemia. Several factors induce oxidative stress (Fig. 3) that may demolish the structural and

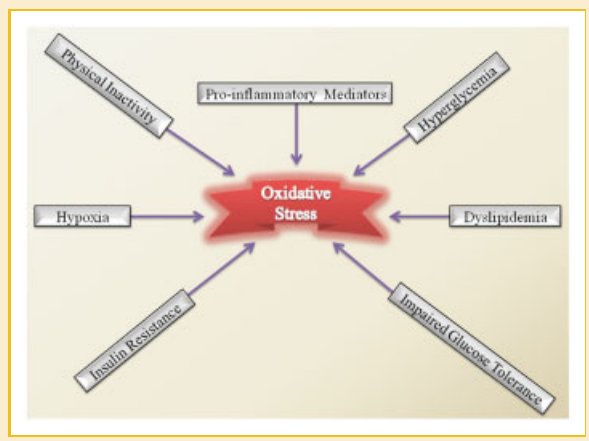

Fig. 3. Schematic representation of production of oxidative stress in individuals with T2DM. Multiple risk factors are decisively involved to provoke oxidative stress. The optimal factors include pro-inflammatory mediators, insulin resistance, and glucolipotoxicity (hyperglycemia and dislipidemia) whereas; physical inactivity, impaired glucose tolerance, and hypoxia are account for partial optimal factors. Once oxidative stress is generated, it may cause further insulin resistance and activation of pro-inflammatory mediators that lead to onset of T2DM.

functional integrity of β-cells of pancreatic islets. Oxidative stress may also potentiate the generation of ROS along with other pro-inflammatory cytokines and chemokines around the β-cells [Akash et al., 2012a] that disrupts the blood flow into the β-cells and abolishes its function [Dedon and Tannenbaum, 2004; Ehses et al., 2007]. As anti-oxidative enzymes (Cu/Zn superoxide dismutase, Mn superoxide dismutase, catalase, and glutathione peroxidase) are not sufficiently present in β-cells, these cells are highly vulnerable to oxidative stress [Akash et al., 2011]. In addition to β-cells destruction (Fig. 2), oxidative stress may also potentiate inflammation (Fig. 1) and insulin resistance [Evans et al., 2002; Evans et al., 2003; Akash et al., 2012a] in peripheral tissues along with generation of ROS in endothelial cells by abolishing their normal functions [Hayden and Sowers, 2007].

In general, many responses may be involved in the inflammatory mechanism for pathogenesis of T2DM. These responses may be either common or tissue specific. For example, in pancreatic islets, inflammation is mainly induced by over expression of nutrients (hyperglycemia and dyslipidemia) that may lead to activation of IL-1β and IL-1 dependent cytokines and chemokines. While in adipose tissues, excessive storage of fat may initiate inflammation in these tissues and other peripheral tissues. These responses may also potentiate the activation of some transcriptional pathways such as NF-κB, JNK, and IKKβ that might stimulate the secretion of pro-inflammatory cytokines and chemokines leading to the recruitment of immune cells infiltration.

CONCLUSION

In conclusion, prevalence of T2DM has been raised to an alarming state. In T2DM, metabolic abnormalities such as glucolipotoxicity, oxidative stress, and insulin resistance provoke tissue specific inflammation that plays crucial role in pathogenesis of T2DM. Consequently, there is a need for such therapeutic modalities to be applied on diabetic patients that have the ability to abate these inflammatory responses. Various anti-inflammatory therapeutic interventions have been studied to prevent these inflammatory mechanisms. These anti-inflammatory approaches include the blockade of binding of IL-1β directly to IL-1RI with either IL-1Ra or antibodies and/or inhibition of NF-κB pathway. To be precise, the inflammatory mechanisms involved in pathogenesis of T2DM implicates this disease to be an auto-inflammatory syndrome, thereby, it is suggested that better understanding of such mechanisms may help identify new therapeutic targets for the treatment of β-cell dysfunctioning and insulin resistance. In future, the elucidation of inflammatory responses responsible for causing insulin resistance may provide an opportunity for the development of immune-modulating and anti-inflammatory agents.

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