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OXIDATIVE STRESS-INDUCED EPIGENETIC REGULATIONS IN DIABETES AND DIABETES-RELATED COMPLICATIONS

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Abstract

Oxidative stress-induced epigenetic modifications play a crucial role in the pathogenesis of diabetes and its related complications. Characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defense, oxidative stress significantly contributes to cellular damage and dysfunction, thereby exacerbating conditions such as type 2 diabetes mellitus (T2DM). Elevated glucose levels in diabetes lead to increased ROS, activating various signaling pathways that result in harmful epigenetic changes, including DNA methylation and histone modifications. These alterations impact gene expression by influencing transcription factors and chromatin structure, promoting insulin resistance and the progression of diabetic complications such as neuropathy, retinopathy, and nephropathy. Key findings indicate that specific histone modifications, like H3K4me1 and H3K9me2, are associated with diabetes progression, while decreased levels of histone acetylation correlate with disease exacerbation. This review thoroughly explores these oxidative stress-induced epigenetic mechanisms, providing insights into the molecular underpinnings of diabetes and highlighting potential therapeutic targets for managing the disease and its complications.

KEYWORDS: Reactive Oxygen Species; Oxidative Stress; Diabetes; Diabetic Complications; Epigenetics

Introduction

Oxidative stress occurs when reactive oxygen species (ROS) production exceeds the body's antioxidant capacity, leading to cellular damage [1]. This imbalance can result from environmental stressors, xenobiotics, or insufficient antioxidant defenses [2]. Oxidative stress affects various organ systems, particularly the lungs, brain, eyes, circulatory, and reproductive systems [3]. It is associated with numerous age-related diseases, including cardiovascular disorders, diabetes, and neurodegenerative conditions [4, 5]. Biomarkers such as malondialdehyde, carbonylated proteins, and DNA damage indicators are used to assess oxidative injury [2]. Antioxidants, both endogenous (e.g., glutathione) and exogenous (e.g., vitamins, flavonoids), play a crucial role in combating oxidative stress [1]. Therapeutic strategies involving synthetic antioxidants like nitrone-based compounds are being explored to mitigate oxidative stress and its associated health impacts [2].

Diabetes mellitus is a chronic metabolic condition, arising either from the pancreas's inability to produce sufficient insulin or from defects in insulin action on peripheral tissues, leading to persistent hyperglycemia. This prolonged elevation in blood sugar levels is a hallmark of diabetes and can cause significant damage to various organs over time. In 2019, 48% of all diabetes-related deaths occurred in individuals aged 70 years or younger [6]. In recent decades, there has been a substantial rise in diabetes prevalence across nearly all regions globally, with 415 million people now living with the condition. Type 2 diabetes mellitus (T2DM) accounts for more than 75% of all cases worldwide and is linked to modifiable risk factors such as obesity, poor dietary habits, a sedentary lifestyle, alcohol consumption, and smoking [7, 8]. This growing burden of diabetes presents significant public health challenges, increasing the risk of complications such as cardiovascular disease, kidney failure, and blindness while placing considerable strain on healthcare systems worldwide [9, 10].

Oxidative stress plays a crucial role in the development of diabetic complications, particularly affecting endothelial cells [11]. It activates various cellular signaling pathways and transcription factors, including PKC, JNK, MAPK, FOXO, and NF-κB [11, 12]. Diabetes exacerbates oxidative stress, leading to epigenetic modifications that influence gene transcription [13]. These modifications include DNA methylation, protein and lipid nitration, and microRNA modulation [13]. In diabetic retinopathy, NADPH oxidase 2 (Nox2) activation precedes mitochondrial damage, with Rac1 playing a key role [14]. Epigenetic regulation of Rac1 involves complex interactions between DNA methylation and hydroxymethylation

enzymes, ultimately allowing NF-κB binding and Rac1 activation [14]. Understanding these oxidative stress-induced epigenetic changes is crucial for elucidating the pathogenesis of diabetic complications and developing potential therapeutic strategies. The objective of this review is to examine the role of oxidative stress in driving epigenetic modifications in diabetes and its related complications. By analyzing current findings, this review aims to provide a comprehensive understanding of how oxidative stress influences epigenetic regulation and contributes to the progression of diabetes and its complications.

2. The Role of Oxidative Stress in Diabetes and Diabetic Complications

In recent years, oxidative stress has gained considerable attention for its significant impact on human health, especially its link to diabetes. It occurs when there is an imbalance between the generation of reactive oxygen species (ROS) and the body's capacity to neutralize them through its antioxidant defense system [15-17]. This imbalance triggers a cascade of harmful effects within the body, as the excessive buildup of ROS can damage key cellular components such as proteins, lipids, and DNA. This damage leads to cellular dysfunction and disrupts normal physiological processes. As a result, inflammation is triggered, and the function of essential cellular structures is impaired, contributing to the onset and progression of several diseases, including diabetes [18] (Figure 1).

Oxidative stress plays a crucial role in the progression of diabetes and its complications [19]. Hyperglycemia leads to overproduction of reactive oxygen species (ROS), suppressing antioxidant defenses and activating pathways implicated in diabetic complications [20]. This oxidative stress contributes to neuropathy, retinopathy, nephropathy, and vasculopathy in diabetes [20, 21]. The exact mechanisms are not fully understood but involve impaired vascular function and endogenous antioxidant defense systems [21, 22]. Antioxidant therapy has shown promise in managing diabetes and its complications [22]. Common antioxidants include vitamins A, C, and E, glutathione, and enzymes like superoxide dismutase and catalase [23-26].

It is well established that impaired insulin secretion by β-cells is a key factor in all forms of diabetes mellitus. Given the role of β-cells in regulating insulin release, it is evident that mitochondria, and consequently mitochondrial ROS production, play a crucial role in β-cell function and the development of type 2 diabetes (T2D). Furthermore, several features of β-cells render them particularly vulnerable to oxidative stress. Firstly, β-cells are highly metabolically active but possess weaker antioxidant defenses compared to other cells and

tissues [27-29]. Secondly, glucose serves as the primary carbon source in β-cells, with approximately 80% being oxidized, which is a significantly higher percentage compared to other cell types [30]. Additionally, β-cells display low levels of lactate dehydrogenase, leading to the majority of pyruvate being metabolized through the TCA cycle in the mitochondria to generate ATP [31].

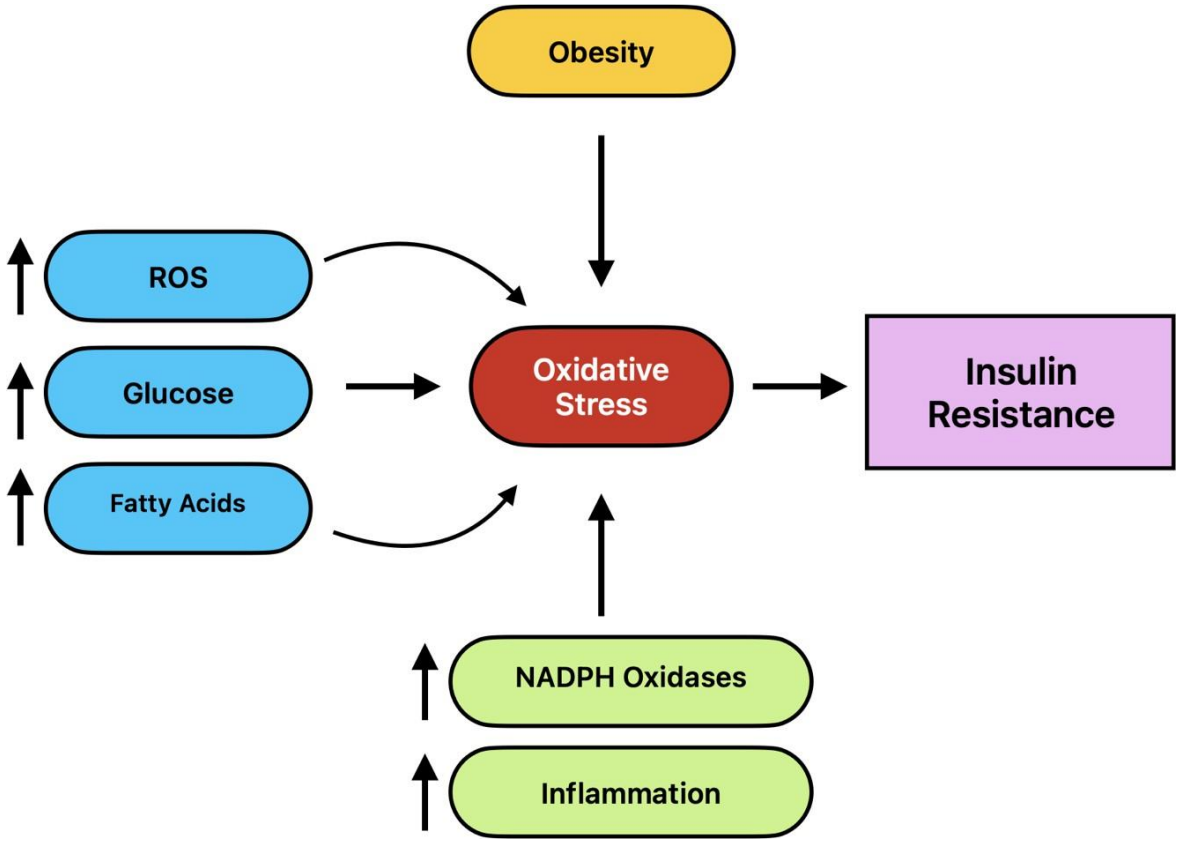

Figure 1: Illustrates a flowchart linking obesity to oxidative stress and insulin resistance. It shows that factors like ROS, glucose, and fatty acids contribute to oxidative stress, which then leads to inflammation and insulin resistance. NADPH oxidases are identified as a mechanism related to oxidative stress.

The primary contributor to oxidative stress is the increase in blood glucose levels. Once glucose enters the cells, it is oxidized either through the pentose phosphate pathway, which generates biosynthetic molecules and NADPH, or via the glycolytic pathway [32]. Significantly, as glucose concentration rises, the enzyme hexokinase becomes saturated and is unable to catalyze

the conversion of glucose to glucose-6-phosphate (G-6-P). As a result, glucose is transformed into sorbitol through the action of aldose reductase, which is then further converted to fructose by sorbitol dehydrogenase (SDH). This pathway consumes excess NADPH, which is required by glutathione peroxidase (GPx) to produce glutathione (GSH) [33]. Therefore, the inhibition of antioxidant enzymes in this pathway further exacerbates oxidative stress. Additionally, under hyperglycemic conditions, sorbitol dehydrogenase (SDH) is upregulated, resulting in increased production of fructose. This fructose is subsequently converted into the triose phosphates glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone-3-phosphate (DHA-3-P), ultimately leading to the activation of protein kinase C (PKC) and the promotion of oxidative stress [34].

3. Oxidative Stress in Diabetes: Epigenetic Implications

Epigenetic modifications, which alter gene expression without changing the DNA sequence, mediate dynamic processes of transcriptional activation or inhibition. These modifications occur through mechanisms such as DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting, which collectively influence the interactions between RNA polymerases or transcription factors and specific regions of target DNA [35, 36]. Abnormal epigenetic modifications in cells are closely linked to oxidative stress. The key enzymes responsible for DNA methylation and histone acetylation or methylation are inherently sensitive to redox changes. For instance, DNA methyltransferases (DNMTs) are a type of redox-sensitive enzyme [37]. Oxidative stress can increase DNA methylation levels by promoting the deprotonation of the cytosine molecule and facilitating the reaction between DNA and the positively charged intermediate S-adenosyl-l-methionine (SAM) [38].

DNA methylation, recognized as the most stable and extensively studied epigenetic mechanism, serves as the primary regulator of transcription. To explore the connection between hyperglycemic memory and DNA methylation, Chen et al. (2016) examined patients with type 1 diabetes mellitus (T1DM) from the DCCT and EDIC studies. They identified twelve uniquely annotated differentially methylated loci that showed a significant association with hyperglycemia and were closely related to diabetic complications [39]. In another study, Park et al. (2014) isolated foot fibroblasts from diabetic patients, both with and without ulcers, as well as from nondiabetic individuals without foot ulcers. They cultured foot fibroblasts from diabetic patients for four passages under normoglycemic conditions and utilized global and genome-wide DNA methylation profiles to detect changes in DNA methylation. Their findings

demonstrated that DNA methylation and metabolic memory were linked to adverse wound healing outcomes in patients with diabetic foot ulcers [40].

Histones are well-conserved, positively charged alkaline proteins that include core histones (H2A, H2B, H3, and H4) and linker histones (H1 and H5) [41]. The four core histones share similar structures characterized by a conserved central motif domain and an unstructured amino-terminal tail. The fundamental structural units of chromatin, known as nucleosomes, are composed of DNA wrapped around a histone protein octamer, which consists of an H3-H4 tetramer and two H2A-H2B dimers [42]. Post-translational modifications (PTMs) of histones are the primary means of regulating chromatin structure. These modifications typically occur on amino acid residues such as lysine, arginine, serine, tyrosine, and threonine, ultimately impacting transcriptional activity [43]. Histone acetylation is a process in which histone acetyltransferases (HATs) add an acetyl group to the lysine residues of core histones. Typically, histone acetylation is abundant at the promoters and enhancers of actively transcribed genes, while it is reduced in repressed genomic regions. Since acetylation can neutralize the negative charge of DNA, it facilitates easier access for transcription factors (TFs) and their coactivators to chromatin. Consequently, the acetylation of lysine residues on histones is generally linked to transcriptionally active genes [44].

Filgueiras et al. (2017) showed that the mRNA and protein levels of STAT1/MyD88 remained elevated for at least six days in macrophages derived from diabetic mice. This upregulation could be reduced by using the histone acetyltransferase (HAT) inhibitor anacardic acid [45]. Additionally, in the skeletal muscle tissue of diabetic mice, the sustained increase in Ped/Pea-15 expression was associated with histone H3 lysine 4 monomethylation (H3K4me1), but not with histone H3 lysine 27 acetylation (H3K27Ac). The elevated levels of H3K4me1 remained consistent even after re-exposure to a medium containing 5 mM glucose. In contrast, there was a rapid decline in acetylation at lysine 27 on histone H3, along with a decrease in p300 recruitment at Ped/Pea-15 [46].

Chronic insulin resistance (IR) can lead to the development of type 2 diabetes mellitus (T2DM), representing a long-standing pathological condition. Extensive studies on histone modifications associated with insulin resistance have been conducted, encompassing hepatic insulin resistance, T2DM, and obesity [47]. For instance, the progression of type 2 diabetes mellitus (T2DM) is characterized by elevated levels of H3K4me1 and H3K9me2, alongside decreased levels of H3K9 acetylation (H3K9ac) and H3K23 acetylation (H3K23ac) [48]. In a

study, global proteomic analysis identified 15 histone modifications that were differentially abundant in mice subjected to a high-fat diet (HFD) [49]. HDAC8 has been linked to the promotion of insulin resistance (IR) in non-alcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC). In mice induced with a high-fat diet (HFD) that were glucose-tolerant, approximately 5,000 regions of H3K27 acetylation (H3K27ac) enrichment were found to be significantly altered. Numerous genes have been reported to exhibit altered expression levels, contributing to the pathogenesis of type 2 diabetes mellitus (T2DM) [50].

Thus, epigenetic modifications play a critical role in the pathogenesis of diabetes and its associated oxidative stress (ROS). Various mechanisms, including DNA methylation and histone modifications, influence gene expression without altering the underlying DNA sequence. Elevated blood glucose levels can lead to abnormal epigenetic changes, such as increased DNA methylation and alterations in histone acetylation, which are linked to insulin resistance and the progression of type 2 diabetes mellitus (T2DM). Studies have shown that key enzymes involved in these processes are sensitive to oxidative stress, thereby creating a feedback loop that exacerbates metabolic dysfunction. For instance, the persistent activation of certain histone modifications and the recruitment of specific transcription factors in response to hyperglycemia contribute to inflammatory pathways and cellular dysfunction, ultimately impacting the progression of diabetes and its complications. Thus, understanding these epigenetic changes provides insights into the molecular mechanisms underlying diabetes and highlights potential areas for therapeutic intervention.

4. Summary

This review highlights the critical role of oxidative stress-induced epigenetic modifications in the development and progression of diabetes and its complications. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses, leading to cellular damage that significantly impacts various organ systems. In the context of diabetes, particularly type 2 diabetes mellitus (T2DM), elevated glucose levels exacerbate oxidative stress, resulting in harmful epigenetic changes, such as altered DNA methylation and histone modifications. These modifications influence gene expression, contributing to insulin resistance and the onset of complications like neuropathy, retinopathy, and nephropathy. The review emphasizes the relationship between specific histone modifications and diabetes progression, indicating that decreased histone acetylation is linked to disease exacerbation. Overall, the exploration of oxidative stress-induced epigenetic changes provides valuable

insights into the underlying mechanisms of diabetes, suggesting potential therapeutic targets for better management of the disease and its associated complications.

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