Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Mitochondrial Dysfunction in Diabetic Periodontitis: Mechanisms and Therapeutic Potential

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Abstract: Diabetic periodontitis is a common oral complication of diabetes characterized by progressive destruction of periodontal tissues. Recent evidence suggests that mitochondrial dysfunction plays a crucial role in the pathogenesis and progression of this condition. This review aims to systematically summarize the role and potential mechanisms of mitochondrial dysfunction in diabetic periodontitis. We first explore the relationship between diabetes and mitochondrial dysfunction, then analyze the specific manifestations of mitochondrial dysfunction in diabetic periodontitis, including morphological changes, energy metabolism disorders, increased oxidative stress, and enhanced apoptosis. We further delve into the connections between mitochondrial dysfunction and the pathogenic mechanisms of diabetic periodontitis, such as exacerbated inflammatory responses, decreased tissue repair capacity, and autophagy dysregulation. Finally, we discuss potential therapeutic targets based on mitochondrial function, including antioxidant strategies, mitochondria-targeted drugs, and autophagy regulators. We also propose future research directions, emphasizing the need for in-depth exploration of molecular mechanisms, development of new diagnostic markers and therapeutic strategies, and personalized treatment approaches. This review provides new insights into understanding the pathogenic mechanisms of diabetic periodontitis and offers a theoretical basis for developing targeted prevention and treatment strategies to improve oral health in diabetic patients.

Keywords: diabetic periodontitis, mitochondrial dysfunction, inflammation, therapeutic targets

Introduction

Diabetic periodontitis is a chronic inflammatory disease commonly observed in diabetic patients, characterized by progressive destruction of periodontal tissues.[1] This condition not only affects oral health but may also negatively impact the overall control of diabetes, creating a vicious cycle.[2] Epidemiological studies indicate that diabetic patients have a significantly higher risk of developing periodontitis compared to non-diabetic individuals. Statistics show that approximately 45% of patients with type 2 diabetes suffer from moderate to severe periodontitis, a proportion far exceeding that of the general population.[3]

The clinical manifestations of diabetic periodontitis are typically more severe than those in non-diabetic patients. Common symptoms include gingival bleeding, swelling, deepening of periodontal pockets, and accelerated alveolar bone resorption.[4] Notably, diabetic periodontitis often progresses more rapidly, exhibits more severe tissue destruction, and responds relatively poorly to conventional treatments.[1] These characteristics underscore the necessity of in-depth research into its pathogenic mechanisms to develop more effective prevention and treatment strategies.

The pathological changes of diabetes and their impact on periodontal disease are mainly reflected in the following points: (1) The characteristic of diabetes is chronic hyperglycemia, which has a profound effect on multiple organ systems, including periodontal tissues. Hyperglycemia induces the formation of advanced glycation end products (AGEs), which accumulate in periodontal tissues and bind to their receptors (RAGE).[5] This interaction activates inflammatory pathways, including NF-κB, leading to the overproduction of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[6] (2) Diabetes also impairs the

Received: 18 August 2024
Accepted: 5 November 2024
Published: 10 January 2025

immune system by reducing neutrophil chemotaxis, phagocytosis, and pathogen clearance. This compromised host defense makes individuals with diabetes more susceptible to periodontal infections.[7] (3) Endothelial dysfunction caused by diabetes leads to reduced bioavailability of nitric oxide, thereby impairing vascular tone and reducing blood flow to periodontal tissues. This results in delayed wound healing and reduced oxygen delivery to periodontal tissues, exacerbating tissue damage.[8] (4) Hyperglycemia increases the production of reactive oxygen species (ROS), leading to oxidative stress and further amplifying the inflammatory response. In periodontal tissues, excessive ROS can damage cellular components such as proteins, lipids, and DNA, ultimately causing cell death and exacerbating periodontal destruction.[9,10]

Mitochondria, serving as the "power plants" of cells, play a crucial role in maintaining normal cellular functions.[11] These organelles are not only responsible for energy production but also participate in various important cellular processes, including calcium ion balance regulation, ROS generation and elimination, and apoptosis regulation.[12] The basic structure of mitochondria includes the outer membrane, inner membrane, intermembrane space and matrix.[13] In terms of energy metabolism, mitochondria synthesize ATP through the tricarboxylic acid cycle and electron transport chain, providing energy for cells. Additionally, mitochondria play important roles in cellular signal transduction, including the transmission of stress response signals and sensing of metabolic states.[14] In recent years, researchers have increasingly recognized the complex communication between mitochondria and cell nucleus, which is crucial for maintaining cellular homeostasis.[15]

Mitochondrial dysfunction has been confirmed to be closely associated with various chronic diseases, including neurodegenerative diseases, cardiovascular diseases, and metabolic syndrome.[16,17] In the context of diabetes, persistent hyperglycemic conditions can lead to significant alterations in mitochondrial function, including mitochondrial DNA (mtDNA) damage, energy metabolism disorders, and increased oxidative stress.[18] These changes may play important roles in the occurrence and development of diabetic complications, including diabetic periodontitis.[19]

In recent years, significant advances have been made in mitochondrial biology research, particularly in the areas of mitochondrial dynamics (fusion and fission), quality control mechanisms, and mitochondria-targeted therapeutic strategies.[20,21] This new knowledge provides fresh perspectives for understanding the pathophysiological processes of diabetic periodontitis, while also indicating directions for developing innovative treatment methods.

This review aims to systematically summarize the role and potential mechanisms of mitochondrial dysfunction in diabetic periodontitis. We will first explore the relationship between diabetes and mitochondrial dysfunction, then analyze the specific manifestations of mitochondrial dysfunction in diabetic periodontitis in detail. Next, we will delve into the connections between mitochondrial dysfunction and the pathogenic mechanisms of diabetic periodontitis, including exacerbated inflammatory responses, increased apoptosis, and decreased tissue repair capacity. Finally, we will discuss potential therapeutic targets based on mitochondrial function and propose future research directions. Through this review, we hope not only to provide new insights into understanding the pathogenic mechanisms of diabetic periodontitis but also to provide a theoretical basis for developing targeted prevention and treatment strategies, ultimately improving the oral health and quality of life for diabetic patients.

Diabetes and Mitochondrial Dysfunction

Diabetes is a common metabolic disorder characterized by chronic hyperglycemia.[22] In recent years, accumulating evidence suggests that mitochondrial dysfunction plays a crucial role in the pathogenesis and progression of diabetes.[23–25] This dysfunction not only affects insulin secretion from pancreatic β-cells but also influences insulin sensitivity in peripheral tissues, thereby exacerbating the pathological process of diabetes.

Mitochondrial Metabolic Dysfunction

Persistent hyperglycemia exerts multiple adverse effects on intracellular mitochondria. Firstly, high glucose levels lead to over-activation of the mitochondrial electron transport chain, increasing the production of ROS. Excess ROS not only directly damage mtDNA, proteins, and lipids but also trigger a series of inflammatory responses, further exacerbating cellular damage.[26] Secondly, hyperglycemia affects mitochondrial energy metabolism function. Studies have found that in diabetic conditions, mitochondrial oxidative phosphorylation efficiency decreases, resulting in reduced ATP

production. This energy metabolic disorder may be caused by decreased activity of electron transport chain complexes and impaired mitochondrial inner membrane integrity caused by hyperglycemia.[27,28] Additionally, hyperglycemia interferes with mitochondrial calcium ion balance. Mitochondria are important intracellular calcium ion storage organelles, and calcium ion balance is crucial for maintaining mitochondrial function.[23] Under diabetic conditions, mitochondrial calcium overload is common, which may lead to mitochondrial membrane potential collapse and trigger cell apoptosis.[29]

Diabetes-Related MtDNA Damage

MtDNA is more susceptible to oxidative stress damage than nuclear DNA due to its unique structure and repair mechanisms.[30] In diabetic patients, researchers have found significantly increased rates of mtDNA mutations and deletions.[31] These damages may originate from hyperglycemia-induced oxidative stress and the accumulation of AGEs.[32]

mtDNA damage directly affects the synthesis of mitochondrial proteins, leading to respiratory chain dysfunction and forming a vicious cycle.[33] For example, a study on patients with type 2 diabetes found a significant decrease in mtDNA copy number in peripheral blood, which negatively correlated with patients' blood glucose levels.[34] Furthermore, mtDNA damage may exacerbate systemic inflammatory responses by activating inflammatory signaling pathways, such as the NLRP3 inflammasome, which plays an important role in the development of diabetic complications.[35]

Mitochondrial Dynamics Abnormalities

Mitochondria are highly dynamic organelles, their morphology and function finely regulated by fusion and fission processes.[36] This dynamic balance is crucial for maintaining the integrity and function of the mitochondrial network. However, under diabetic conditions, this balance is often disrupted.[37] Studies have found that hyperglycemic environments promote the activation of mitochondrial fission proteins (such as Drp1) while inhibiting the expression of fusion proteins (such as Mfn1, Mfn2, and OPA1).[38,39] This imbalance leads to fragmentation of the mitochondrial network, affecting mitochondrial function and cellular metabolic state. For instance, in a diabetic nephropathy model, researchers observed significant fragmentation of mitochondria in glomerular podocytes, accompanied by mitochondrial dysfunction and increased cell apoptosis.[40,41]

Manifestations of Mitochondrial Dysfunction in Diabetic Periodontitis

Diabetic periodontitis is a common oral complication of diabetes, with a complex pathogenesis involving multiple cellular and molecular level alterations.[17] In recent years, increasing research has focused on the crucial role of mitochondrial dysfunction in diabetic periodontitis.[42] This dysfunction not only affects the metabolic state of periodontal tissues but also participates in the regulation of inflammatory responses and tissue damage processes (Figure 1).[43]

Morphological Changes of Mitochondria in Periodontal Tissues

Significant morphological changes in mitochondria have been observed in the periodontal tissues of patients with diabetic periodontitis.[44] Electron microscopy studies have shown that compared with healthy controls, mitochondria in gingival fibroblasts and periodontal ligament cells of diabetic patients exhibit characteristics of swelling, disorganized cristae structure, and even fragmentation.[45] These morphological changes are generally considered to be visual manifestations of mitochondrial dysfunction.[46] A study on experimental diabetic rats found that as diabetes progressed, the number of mitochondria decreased while their volume increased.[47] This change may reflect the attempt of mitochondria to compensate for functional decline by increasing volume, ultimately leading to the destruction of the mitochondrial network. Furthermore, a significant decrease in mtDNA copy number was observed in the diabetes.[48] The reduction in mtDNA copy number is typically closely associated with mitochondrial dysfunction and may lead to decreased mitochondrial protein synthesis and reduced energy production efficiency.[49]

Mitochondrial Energy Metabolic Disorders

Mitochondria are the center of cellular energy metabolism, and their dysfunction directly affects cellular energy supply.[50] Energy metabolic disorders not only affect normal cellular function but may also trigger adaptive responses. For instance, studies have

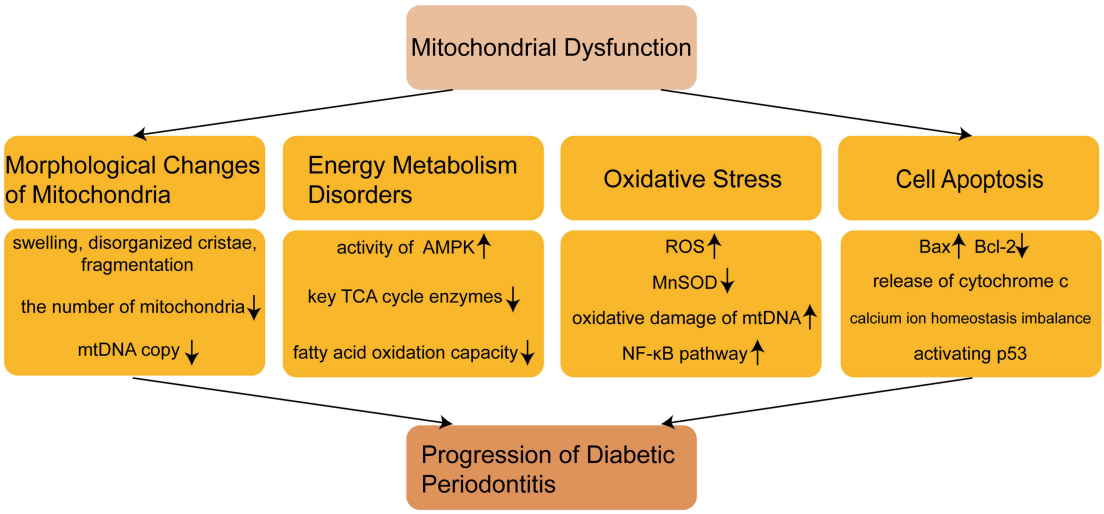

Figure 1 The main manifestations of mitochondrial dysfunction in diabetic periodontitis.

found increased activity of AMP-activated protein kinase (AMPK) in the periodontal tissues of patients with diabetic.[51] AMPK is a cellular energy sensor, and its increased activity may be a compensatory response to mitochondrial dysfunction.[52] The tricarboxylic acid (TCA) cycle, a central pathway in mitochondrial energy metabolism, exhibits significant perturbations in diabetic periodontitis. A metabolomic analysis of gingival tissues from patients with diabetic periodontitis revealed substantial alterations in TCA cycle-associated metabolites.[53] Notably, elevated levels of citrate and α-ketoglutarate were observed, concurrent with decreased succinate concentrations. These metabolic shifts suggest inhibition of key enzymes of TCA cycle, potentially compromising energy metabolism efficiency.[54] The etiology of these metabolic disruptions is postulated to be linked to persistent hyperglycemia-induced enzyme glycation and oxidative stress.[55] Moreover, fatty acid β-oxidation, another crucial mitochondrial energy pathway, is similarly impaired in diabetic periodontitis. Under hyperglycemic conditions, periodontal tissue cells demonstrate reduced fatty acid oxidation capacity.[56] These alterations may precipitate intracellular lipid accumulation, potentially exacerbating mitochondrial dysfunction and inflammatory responses.[57] Such metabolic dysregulation underscores the complex interplay between diabetes and periodontal pathology, highlighting potential therapeutic targets for intervention.

Increased Mitochondria-Related Oxidative Stress

Oxidative stress is a key factor in the pathogenesis of diabetic periodontitis, and mitochondria are the main source of ROS in cells.[58] In diabetic periodontitis, mitochondrial dysfunction leads to increased ROS production, while the antioxidant defense system is impaired, ultimately resulting in exacerbated oxidative stress.[54] Studies have found that in the gingival tissues of patients with diabetic periodontitis, the activity of mitochondrial superoxide dismutase (MnSOD) is significantly reduced, while lipid peroxidation levels are elevated.[59] This disruption of the oxidative-antioxidative balance not only directly damages cellular components but may also activate inflammatory signaling pathways, such as the NF-κB pathway, further exacerbating the inflammatory response.[60] Moreover, the increase in mitochondria-derived ROS may lead to oxidative damage of mtDNA.[61] A study on diabetic mice showed significantly elevated levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA oxidative damage, in periodontal tissues.[62] Damage to mtDNA may further exacerbate mitochondrial dysfunction, forming a vicious cycle.[63]

Increased Mitochondria-Mediated Cell Apoptosis

Mitochondria play a central role in regulating the apoptosis process.[64] In diabetes, researchers have observed a significant increase in apoptosis in periodontal tissue cells, which may be closely related to mitochondrial dysfunction.[65] Specifically, in the periodontal tissue of rats with diabetes, the expression of pro-apoptotic protein Bax is increased, while the expression of anti-apoptotic protein Bcl-2 is decreased.[66] These changes lead to increased mitochondrial membrane permeability, promoting the release of cytochrome c, which in turn activates downstream caspase cascades, ultimately resulting in cell apoptosis.[67]

Furthermore, mitochondrial dysfunction may promote cell apoptosis through other mechanisms. For example, mitochondrial calcium ion homeostasis imbalance may activate calcium-dependent proteases, triggering the apoptosis process.[29] Additionally, the increase in mitochondria-derived ROS may directly damage DNA, activating p53-mediated apoptotic pathways.[68]

Mitochondrial Dysfunction and Pathogenic Mechanisms of Diabetic Periodontitis

Mitochondrial dysfunction plays a central role in the pathogenic mechanisms of diabetic periodontitis, influencing disease progression through multiple pathways.[69] These mechanisms interact to form a complex network, ultimately leading to periodontal tissue destruction and functional loss. A thorough understanding of these mechanisms is crucial for developing new prevention and treatment strategies (Figure 2).

Exacerbation of Inflammatory Responses

Mitochondrial dysfunction is a significant factor contributing to the exacerbation of inflammatory responses in diabetic periodontitis.[54] Firstly, excessive production of mitochondria-derived ROS can activate various inflammatory signaling pathways, such as NF-κB and the NLRP3 inflammasome.[70] A study on diabetic rat periodontal tissues found that ROS increase due to mitochondrial dysfunction positively correlated with NF-κB activation, subsequently promoting the expression of inflammatory factors IL-1β, TNF-α, and IL-6.[71]

Secondly, the release of mtDNA can act as damage-associated molecular patterns (DAMPs), triggering innate immune responses.[72] In the gingival tissues of patients with chronic periodontitis, researchers detected significantly elevated levels of circulating mtDNA, which positively correlated with inflammatory marker levels.[73] This mtDNA release may be caused by impaired mitochondrial membrane integrity. Furthermore, mitochondrial dysfunction may regulate inflammatory

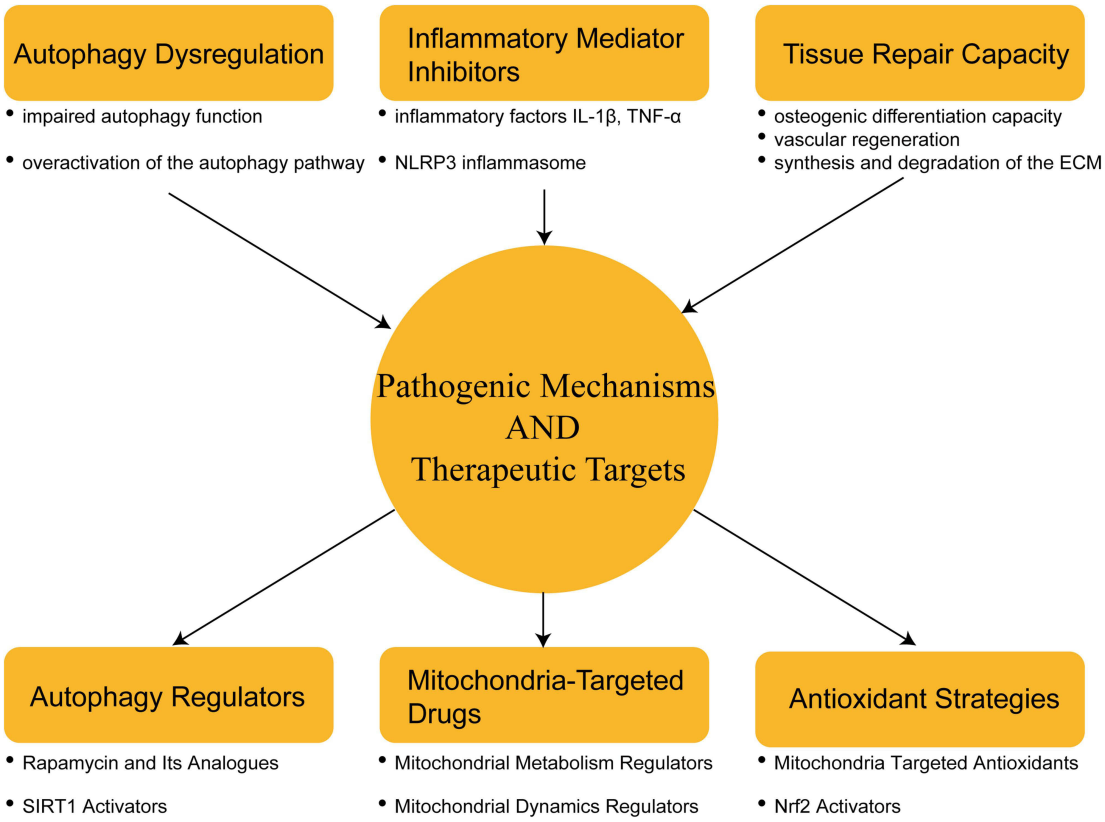

Figure 2 Pathogenic Mechanisms and Potential Therapeutic Targets for Mitochondrial Dysfunction in Diabetic Periodontitis.

https://doi.org/10.2147/JIR.S492041

responses by influencing the metabolic reprogramming of immune cells.[74] For instance, under diabetic conditions, impaired mitochondrial oxidative phosphorylation in macrophages leads to a preference for glycolytic metabolism, which is associated with a pro-inflammatory phenotype.[75] An in vitro study demonstrated that targeted improvement of macrophage mitochondrial function could significantly alleviate high glucose-induced inflammatory responses.[76]

Decreased Periodontal Tissue Repair Capacity

Mitochondrial dysfunction also affects the repair capacity of periodontal tissues, playing a crucial role in the sustained progression of diabetic periodontitis.[77] Firstly, mitochondrial dysfunction impacts the self-renewal and differentiation abilities of periodontal ligament stem cells (PDLSCs).[78] A study found that PDLSCs derived from diabetic patients exhibited significant mitochondrial dysfunction, including decreased mitochondrial membrane potential and reduced ATP production, which was closely related to their diminished osteogenic differentiation capacity.[79] Secondly, mitochondrial dysfunction affects the balance between synthesis and degradation of the extracellular matrix (ECM).[80] This imbalance ultimately results in excessive ECM degradation and reduced periodontal tissue support capacity.[81] Additionally, mitochondrial dysfunction interferes with the blood supply to periodontal tissues by affecting vascular endothelial cell function.[82] Studies have shown that mitochondrial dysfunction in vascular endothelial cells under hyperglycemic conditions leads to decreased expression of angiogenic factors (such as VEGF), ultimately affecting vascular regeneration during tissue repair processes.[83]

Autophagy Dysregulation

Autophagy is an important mechanism for cellular stress response, with mitophagy being a key process for clearing damaged mitochondria.[84] In diabetic periodontitis, there is a complex interaction between mitochondrial dysfunction and autophagy dysregulation.[85] On one hand, persistent mitochondrial dysfunction can lead to overactivation of the autophagy pathway, potentially resulting in autophagic cell death.[86] In the periodontal tissues of diabetic rats, researchers observed significantly increased expression of autophagy markers LC3-II and p62, which positively correlated with the degree of tissue damage.[87] On the other hand, long-term hyperglycemic environments may lead to impaired autophagy function, especially in the mitophagy process.[88] This decline in autophagy function results in the accumulation of damaged mitochondria, further exacerbating oxidative stress and inflammatory responses.[89] An in vitro study showed that pharmacological activation of PINK1/Parkin-mediated mitophagy could significantly improve mitochondrial function and cell viability in periodontal ligament cells under high glucose conditions.[90]

Potential Therapeutic Targets for Mitochondrial Dysfunction in Diabetic Periodontitis

As our understanding of the role of mitochondrial dysfunction in diabetic periodontitis deepens, mitochondria-targeted therapeutic strategies have gradually become a research hotspot. These strategies primarily focus on reducing oxidative stress, improving mitochondrial energy metabolism, regulating mitochondrial dynamics, and promoting mitochondrial biogenesis.[56,91]

Antioxidant Strategies

Given the crucial role of oxidative stress in diabetic periodontitis, mitochondria-targeted antioxidant strategies have become an important therapeutic direction.[92]

Mitochondria-Targeted Antioxidants

Traditional antioxidants have shown limited efficacy in treating diabetic periodontitis, partly due to their difficulty in effectively entering mitochondria.[93] Consequently, researchers have developed a series of mitochondria-targeted antioxidants, such as MitoQ, SkQ1, and SS-31.[94] These compounds can specifically accumulate in mitochondria, effectively scavenging excess ROS.[95]

Nrf2 Activators

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor regulating the expression of antioxidant genes.[96] In diabetic periodontitis, Nrf2 activity is often suppressed.[97] Therefore, activating Nrf2 has become a potential therapeutic strategy.

Research has found that some natural compounds such as curcumin and resveratrol can improve diabetic periodontitis by activating the Nrf2 pathway.[98] For example, a clinical trial showed that oral curcumin supplementation could significantly reduce gingival inflammation index and periodontal pocket depth in diabetic patients.[99]

Mitochondria-Targeted Drugs

In addition to antioxidant strategies, drugs directly improving mitochondrial function have also shown therapeutic potential.[100]

Mitochondrial Metabolism Regulators

Mitochondrial energy metabolism disorder is an important feature of diabetic periodontitis.[101] Thus, regulating mitochondrial metabolism has become a potential therapeutic target. Metformin, a widely used antidiabetic drug, has recently been found to improve mitochondrial function.[102] It has been shown that metformin improved mitochondrial function by activating the AMPK pathway, thereby alleviating inflammatory responses.[103] Another potential metabolic regulator is pyrroloquinoline quinone (PQQ), which can promote mitochondrial biogenesis.[104]

Mitochondrial Dynamics Regulators

Given the role of mitochondrial dynamics abnormalities in diabetic periodontitis, regulating mitochondrial fusion and fission processes has become a new therapeutic direction.[92] For example, the mitochondrial fission inhibitor Mdivi-1 induces mitochondrial fragmentation induced by P. gingivalis infection, increased the mtROS levels, and decreased the MMP and ATP concentration in vascular endothelial cells.[105] On the other hand, promoting mitochondrial fusion may also have therapeutic effects. Research has found that overexpression of the mitochondrial fusion protein Mfn2 can improve mitochondrial function and inflammatory status in the periodontal tissues of diabetic mice.[106]

Autophagy Regulators

Considering the important role of autophagy in maintaining mitochondrial function, regulating the autophagy process has also become a potential therapeutic strategy.[107]

Rapamycin and Its Analogues

Rapamycin is a classic autophagy activator that promotes autophagy by inhibiting the mTOR pathway.[108] Research has found that low-dose rapamycin can improve the periodontal condition of diabetic mice, which may be related to its role in promoting mitophagy and clearing damaged mitochondria.[109,110]

SIRT1 Activators

SIRT1 is an important metabolic sensor involved in regulating autophagy and mitochondrial function.[111] Based on existing studies, it is hypothesized that SIRT1 activators such as resveratrol may alleviate symptoms of diabetic periodontitis by promoting autophagy and improving mitochondrial function.[112,113]

Conclusions and Future Directions

This review highlights the pivotal role of mitochondrial dysfunction in diabetic periodontitis. Mitochondrial impairment induced by diabetes, including DNA damage, disrupted energy metabolism, increased oxidative stress, and abnormal dynamics, not only compromises periodontal tissue function but also triggers inflammatory cascades, accelerating tissue destruction. We have identified several promising therapeutic strategies targeting mitochondrial function, such as antioxidants, metabolism regulators, and autophagy modulators. These approaches offer new possibilities for managing

diabetic periodontitis. However, further research is needed to validate these treatments in clinical settings and to explore personalized approaches based on mitochondrial status.

In summary, understanding mitochondrial dysfunction in diabetic periodontitis provides valuable insights into the mechanisms of diseases. Future research endeavors should prioritize the translation of basic scientific findings into clinical practice, the development of more efficacious and well-tolerated mitochondria-targeted therapeutic modalities, and the exploration of potential links between mitochondrial dysfunction and other diabetic complications. These efforts aim to formulate more comprehensive and integrated treatment strategies for individuals with diabetes mellitus and its associated periodontal manifestations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Young and Middle-Aged Scientific Research Fund of Wannan medical college (WYRCQD2023028), Anhui Province Engineering Research Center for dental materials and application (Grant No: 2024AMCD06), Program for Excellent Sci-tech innovation Teams of Universities in Anhui Province (Grant No: 2023AH010073).

Disclosure

The authors declare that they have no competing interest.

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