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REVIEW

The Role of Autophagy in the Regulation of Bidirectional Relationships in Diabetic Periodontitis

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Abstract: A bidirectional relationship exists between diabetes and periodontitis. For individuals with diabetes, hyperglycemia can exacerbate periodontal tissue destruction by triggering inflammatory responses, enhancing oxidative stress, and promoting alveolar bone resorption. Meanwhile, as a chronic inflammatory disease, periodontitis involves periodontal pathogens and their secreted virulence factors, which can elicit systemic inflammatory responses. Consequently, this intensifies insulin resistance and elevates blood glucose levels, establishing a vicious cycle. Despite extensive research on the association between diabetes and periodontitis, the precise mechanisms underlying this connection remain a topic of ongoing debate. Autophagy, a crucial defensive mechanism responsible for maintaining cellular homeostasis, plays a vital role in this relationship. Emerging evidence indicates that autophagy influences inflammation in periodontal tissue and blood glucose levels by regulating pathogen clearance, modulating inflammatory and immune responses, maintaining bone metabolism, and fine-tuning autophagic activity. As such, targeting modulation of autophagy represents a promising therapeutic strategy for managing diabetic periodontitis. In this paper, we will provide a review of the mechanisms of autophagy in the bidirectional relationship between diabetes and periodontitis. Elucidating these mechanisms will enhance a more profound comprehension of the intricate relationship between diabetes and periodontitis, provide novel therapeutic strategies for the combined treatment of diabetic periodontitis by regulating the autophagy pathway, and establish a theoretical foundation for the development of effective interventions.

Keywords: autophagy, diabetes, periodontitis, inflammation, microbiota

Introduction

Periodontitis is a chronic infectious disease of the oral cavity. A worldwide epidemiological survey from 2011 to 2020 reported the prevalence of periodontitis in adults to be approximately 62%.[1] The primary clinical manifestations include the destruction of the periodontal supporting tissues, the formation of periodontal pockets, and the loss of attachment and alveolar bone. Ultimately, this can lead to tooth mobility and loss, affecting masticatory function and even the digestive system.[2] Recent studies have demonstrated that periodontitis is associated with several non-communicable chronic systemic diseases, particularly diabetes mellitus.[3] Diabetes mellitus is one of the most common metabolic diseases,[4] with a rising prevalence globally. It is mainly characterized by hyperglycemia, which triggers stress responses and functional disorders in periodontal tissue cells, such as fibroblasts, epithelial cells, periodontal ligament cells, and immunocytes, thereby contributing to the progression of periodontitis.[5,6] The risk of periodontitis in diabetic patients is 2 to 3 times higher than that in the general population, and the inflammatory response and destruction of periodontal tissues are more severe.[7] Meanwhile, periodontitis exacerbates systemic inflammation, damages intracellular insulin signaling pathways, and increases the risk of insulin resistance,[8–10] thus affecting systemic blood glucose control.

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There is a significant bidirectional relationship between periodontitis and diabetes. However, the exact molecular mechanisms and pathways are obscure. Some studies suggest that their interactions are mediated by the interplay of microbiota, inflammation, host immune responses, metabolic disorders, and other factors.[11] These factors work in concert to disrupt intracellular environmental homeostasis, resulting in cell death. Thus, maintaining cellular homeostasis is crucial for periodontal tissue health, especially when confronted with factors such as microbial dysbiosis, abnormal host immune responses, excessive activation of inflammatory factors, advanced glycation end products, oxidative stress, and bone homeostasis imbalance.[12,13]

During these processes, maintaining a balance between cell survival and cell death is essential for tissue homeostasis. Autophagy, as a self-protective cellular mechanism, has been shown to promote cell survival by degrading damaged and aging organelles, misfolded proteins, and invading pathogens.[12,13] It plays an integral role in sustaining the stability of cellular homeostasis and the development of host organisms.[14] Emerging evidence suggests that autophagy may be pivotal in the bidirectional relationship between diabetes and periodontitis by controlling the invasion of pathogens, regulating inflammatory immune responses, balancing bone metabolism, and modulating autophagic levels.

Therefore, further investigation into the regulatory role of autophagy in the bidirectional relationship between diabetes and periodontitis will facilitate the understanding of its intricate mechanisms. This article reviews the mechanisms of autophagy, the bidirectional relationship between diabetes and periodontitis, and related studies on the role of autophagy in the interaction between these conditions. Finally, we summarize potential therapeutic modalities that may modulate autophagy to improve diabetic periodontitis.

Autophagy

Basic Process of Autophagy

Autophagy is a lysosomal degradation pathway responsible for transporting intracellular damaged or aged proteins, organelles, and microorganisms to lysosomes for digestion and degradation.[15] Based on the mechanism by which substrates are delivered to the lysosome, autophagy can be classified into three different types, including macroautophagy, chaperone-mediated autophagy, and microautophagy. Among these, macroautophagy is the most dominant and important form of autophagy.[16,17]

In this review, macroautophagy is referred to as "autophagy" for simplicity. In contrast to other intracellular degradation pathways, the process of autophagy can be categorized into the following four phases: induction, initiation, elongation, and maturation/degradation stages.[18] The core mechanism of autophagy primarily involves the formation of a vesicle with a double-membrane structure called the autophagosome, which engulfs part of the cytoplasm, intracellular proteins, organelles, or microorganisms. Subsequent to this, the mature autophagosomes fuse with the lysosomes to form the autolysosomes, where acidic hydrolases degrade the contents, leading to the inactivation and breakdown of the encapsulated material.[19] The synthesized small molecules, such as amino acids and nucleotides, are efficiently recycled and reused by the cell to meet its needs.[20] Autophagy is involved in a variety of physiological activities, such as the production of amino acids during nutrient deprivation, the quality control of intracellular proteins and organelles, the regulation of selective substrate expression, the degradation of pathogens, and antigen presentation.[12,21–27] It is associated with a range of pathological conditions, including cancer,[28] neurodegeneration,[16] chronic inflammatory diseases,[29] and cardiovascular diseases.[30] In summary, autophagy represents a selective intracellular degradation process that participates in various biological processes, provides energy for cellular repair, and maintains intracellular homeostasis.

The Molecular Mechanisms of Autophagy

When cells undergo damage such as oxidative stress, nutrient depletion, lack of growth factors, hypoxia, and infection, autophagy is activated to rapidly degrade old or depleted molecules and recycle new metabolites.[17] The entire process is primarily regulated by the mammalian target of rapamycin complex 1 (mTORC1) and the Beclin 1 complex. Under conditions of nutrient scarcity or cellular stress, signaling pathways suppress mTOR and/or activate AMP-activated protein kinase (AMPK).[31,32] UNC-51-like kinase 1 (ULK1) serves as a bridge connecting upstream nutritional or energy sensors (mTOR and AMPK) with the downstream autophagic machinery. It is indispensable for cellular homeostasis. Its

phosphorylation plays a crucial role in autophagy initiation. The induction of autophagy can be suppressed by phosphorylated ULK1 in a mTORC1-dependent manner or activated by phosphorylated ULK1 in an AMPK-dependent manner.[33] The activated ULK1/2 (ULK1 is the homolog of the yeast Atg1) interacts with the direct homologs of yeast Atg17, such as Atg13, Atg101, and FIP200 (a 200 kDa focal adhesion kinase family interacting protein), to form large protein complexes that assemble near the endoplasmic reticulum membrane, thereby recruiting downstream autophagy-related proteins (ATGs) and initiating autophagosome formation.[34]

ATGs participate in autophagosome formation.[35] To date, over 40 ATGs have been identified, with nearly half being directly implicated in autophagosome formation.[36] These ATGs usually assemble into multi-subunit complexes, which work together in coordinating autophagosome formation.[37,38] The formation of autophagosomes is mainly regulated by three key protein complexes: the ULK1 complex, the PI3KC3 complex (including Beclin 1), and the ATG16L1 complex (including ATG16L1, ATG5, and ATG12).[39]

Upon activation, ULK1 is transported to the endosomal region, where it phosphorylates the Beclin 1 at Ser-14, thus enhancing the activity of VPS34, which contains ATG14L.[40] VPS34 is the only class III phosphatidylinositol 3-kinase (PI3K) in mammals, and its phosphorylation generates phosphatidylinositol 3-phosphate (PtdIns3P).[40] BECN1 facilitates the formation of class III PI3K, phosphorylating phosphatidylinositol and creating "nucleation" signals for the recruitment of other ATGs.[41] Two ubiquitin-like reactions drive the elongation and expansion of phagophore. First, PtdIns3P, in association with its binding protein WIPI2, recruits the ATG16L1 complex, which is formed via ubiquitin-like conjugation. The ubiquitin-like molecules ATG12 and ATG5 are covalently bound through E1-like (ATG7) and E2-like (ATG10) enzymes, forming an oligomeric complex that immediately attaches to the autophagosome.[42] Subsequently, the ATG5-ATG12 conjugate non-covalently binds ATG16L1 to form a large complex, which resides on the outer membrane of the autophagosome and facilitates the lipidation of ATG8/LC3 and the elongation of the phagophore.[43] ATG16L1 also plays a key role in determining the lipidation site of ATG8/LC3 by regulating the targeting of the ATG12-ATG5 conjugate.[44] Meanwhile, in another ubiquitin-like reaction, the microtubule-associated protein light chain 3 (LC3) undergoes covalent modification. ATG4 protease cleaves the C-terminal of ATG8/LC3, yielding the cytosolic form LC3-I. LC3-I then binds with phosphatidylethanolamine (PE) to form LC3-II, a process requiring E1-like and E2-like enzymes (ATG7 and ATG3).[45] LC3 serves as a well-established marker for autophagy. Its two isoforms, LC3-I and LC3-II, coexist in equilibrium. While LC3-I remains in the cytoplasm, LC3-II stably associates with the autophagosomal membrane and participates in the closure of autophagic vesicles and autophagosome formation.[46] ATG4 can dissociate LC3-II from the outer membrane, releasing LC3-I for later use, while LC3-II in the inner membrane system is degraded following autophagosome-lysosome fusion.[47] Finally, the edges of the autophagic vesicle fuse to form the autophagosome, which then fuses with the lysosome containing hydrolytic enzymes with a low pH, forming the autolysosome and degrading its contents[48](Figure 1).

Thus, the entire dynamic process of the autophagosome and lysosome, referred to as the autophagic flux, can be detected by Western blot to measure the levels of autophagy markers or by immunofluorescence to show positive vesicles.[49,50] In addition, autophagosomes can sequester specific soluble proteins, such as the receptor protein SQSTM1/p62,[51] which can bind to LC3 or ubiquitin chains and be enclosed in the autophagosome, ultimately being degraded through lysosomal acidification. Consequently, p62 can serve as a marker for detecting autophagic flux,[52] with a decrease in SQSTM1/p62 levels correlating with an increase in autophagic activity.[53]

Bidirectional Relationship between Periodontitis and Diabetes

Microbial Pathway

Periodontitis is primarily driven by microbial dysbiosis in the subgingival plaque biofilm.[54] Among patients with uncontrolled diabetes and chronic periodontitis, a marked alteration in the subgingival microbiota is observed when compared to non-diabetic counterparts.[55] The dysbiotic microbial profile in periodontitis has been shown to be strongly associated with suboptimal glycemic control in diabetic patients.[10,56] Studies suggest that the complexity and diversity of the oral microbiota in periodontitis can significantly elevate glycosylated hemoglobin (HbA1c) levels, thereby impairing glycemic regulation in individuals with diabetes.[57] On the other hand, inadequate blood glucose control can alter the

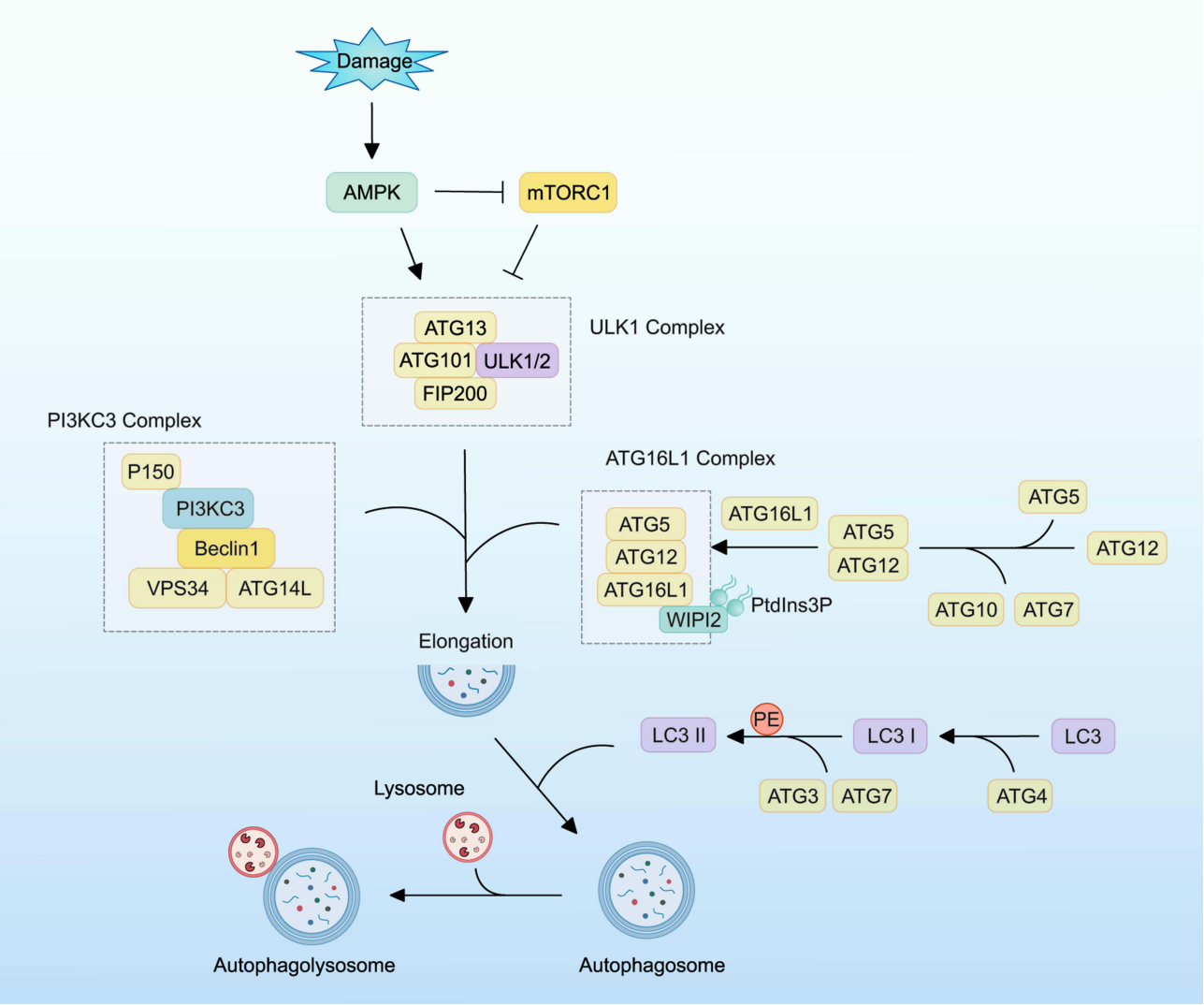

Figure 1 The molecular mechanisms of autophagy. Under conditions of nutrient scarcity or cellular stress, the ULK1 complex, PI3KC3 complex, and ATG16L1 complex are sequentially activated. The ULK1 and PI3KC3 complexes promote the nucleation of free cellular membranes. Two ubiquitin-like reactions drive the elongation and expansion of phagophore to form autophagosomes through the ATG16L1 and LC3-II complexes. Figure 1 was independently designed by the authors using Affinity Designer 2, with all elements created using native software features.

composition of the subgingival microbiota, contributing to the exacerbation of inflammatory processes.[58] Additionally, bacterial infections in dental plaque stimulate the production of lipopolysaccharide (LPS), which acts as a potent inducer of systemic immune responses, resulting in increased levels of pro-inflammatory cytokines and immune cell aggregation. This process exacerbates insulin resistance and glucose intolerance in diabetic models, raising blood glucose concentrations within the context of periodontitis and consequently contributing to the pathogenesis of diabetes.[59]

Inflammatory Factor Pathway

Microbial-induced inflammation in periodontal tissues leads to the activation and overexpression of inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1 β (IL-1β), with particularly pronounced effects observed in the serum of individuals suffering from both periodontitis and diabetes. This dysregulation in the balance between pro-inflammatory and anti-inflammatory cytokines intensifies the serum inflammatory conditions of periodontitis patients.[60] LPS can activate macrophages to secrete pro-inflammatory factors such as IL-1, TNF-α, and prostaglandin E2 (PGE2), which stimulate osteoclasts and promote bone resorption, leading to periodontal tissue destruction.[61] Notably, the significant elevation of TNF-α levels induced by periodontal inflammation is closely

associated with the glycemic marker HbA1c, which, in concert, inhibits insulin secretion and enhances insulin resistance.[62] Furthermore, the sustained mild upregulation of inflammatory factors manifests as a subclinical inflammatory response—microinflammation. Periodontitis can elevate inflammatory cytokines such as IL-6 and IL-1β in the bloodstream through microinflammation, thereby impairing insulin receptor substrate (IRS) phosphorylation, disrupting insulin signaling, and compromising glycemic control.[63,64]

Immune Pathway in Periodontal Tissues

Diabetes can alter the host's immune response to periodontal microbiota, thereby exacerbating periodontal inflammation. Meanwhile, periodontitis-associated pathogens dysregulate immune cell function, increase the release of inflammatory factors, and further drive the progression of inflammation. Neutrophils are abundant in diabetic periodontitis. High glucose conditions lead to dysfunction in neutrophil recruitment, chemotaxis, and phagocytosis, thereby compromising the host's ability to eliminate pathogenic microorganisms and disrupting immune homeostasis in response to infection.[65] In addition, neutrophil aggregation, in conjunction with hyperglycemia, induces oxidative stress in periodontal tissue cells, with levels significantly correlating with the severity of inflammation.[66,67]

Alveolar Bone Remodeling Pathway

In diabetic patients, high blood glucose causes periodontal tissues to be in a pro-oxidative state. Hyperglycemia has been demonstrated to attenuate the activity of the oxidation-sensitive nuclear transcription factor κB (NF-κB) through antioxidant mechanisms, thus modulating RANKL-induced osteoclastogenesis and leading to aberrant bone remodeling.[68] Additionally, comparative investigations have demonstrated significantly elevated concentrations of AGEs in the gingival crevicular fluid of individuals with diabetes-associated chronic periodontitis relative to non-periodontitis diabetic counterparts,[69] which is significantly correlated with the severity of periodontitis.[70] The interaction between AGEs and their receptor (RAGE) elicits inflammatory cascades and oxidative stress,[71] promoting cell autophagy and apoptosis. This further exacerbates bone tissue destruction[72](Figure 2).

To sum up, diabetes exacerbates periodontal tissue deterioration by directly or indirectly amplifying host inflammatory and immune responses via periodontal dysbiosis and AGEs-RAGE signaling, consequently inducing oxidative stress, upregulating pro-inflammatory cytokines, and facilitating osteoclast differentiation. Conversely, periodontitis affects glucose control in diabetes by diminishing insulin production and exacerbating insulin resistance. The pro-inflammatory mediators secreted by periodontal pathogens and inflammation-associated immune cells contribute to the degradation of periodontal soft and hard tissues, further aggravating insulin resistance under hyperglycemic conditions.

Role of Autophagy in the Bidirectional Relationship between Diabetes and Periodontitis

Autophagy's Impact on Periodontal Pathogens in Diabetic Periodontitis

Periodontitis is an inflammatory disease of the periodontal tissues caused by microbial dysbiosis between the normal oral microbiota and periodontal pathogens. Among the key etiological agents, Porphyromonas gingivalis (P. gingivalis), a Gram-negative anaerobic bacterium, is recognized as a keystone pathogen,[73] playing a critical role in the initiation and progression of the disease.[74] P. gingivalis colonizes the subgingival periodontal pocket and secretes a variety of virulence factors, such as LPS, gingipains, and fimbriae. These virulence factors not only enable immune evasion and trigger host immune-inflammatory responses[75] but also enter the bloodstream, leading to further destruction of periodontal tissues and damage to distant organs. Consequently, periodontitis is closely associated with several systemic diseases, such as diabetes, cardiovascular diseases, and cancer.[59,76]

Hyperglycemia results from insulin resistance or impaired insulin secretion. Research indicates that elevated blood glucose levels in diabetic patients' gingival crevicular fluid affect the growth of subgingival microbiota.[77] In the early stages of diabetes, hyperglycemia facilitates the colonization of P. gingivalis.[78]

Autophagy plays a dual role in bacterial infections, functioning both as a host defense mechanism against microbial invasion and as a survival strategy exploited by certain pathogens to evade immune recognition and clearance.[79]

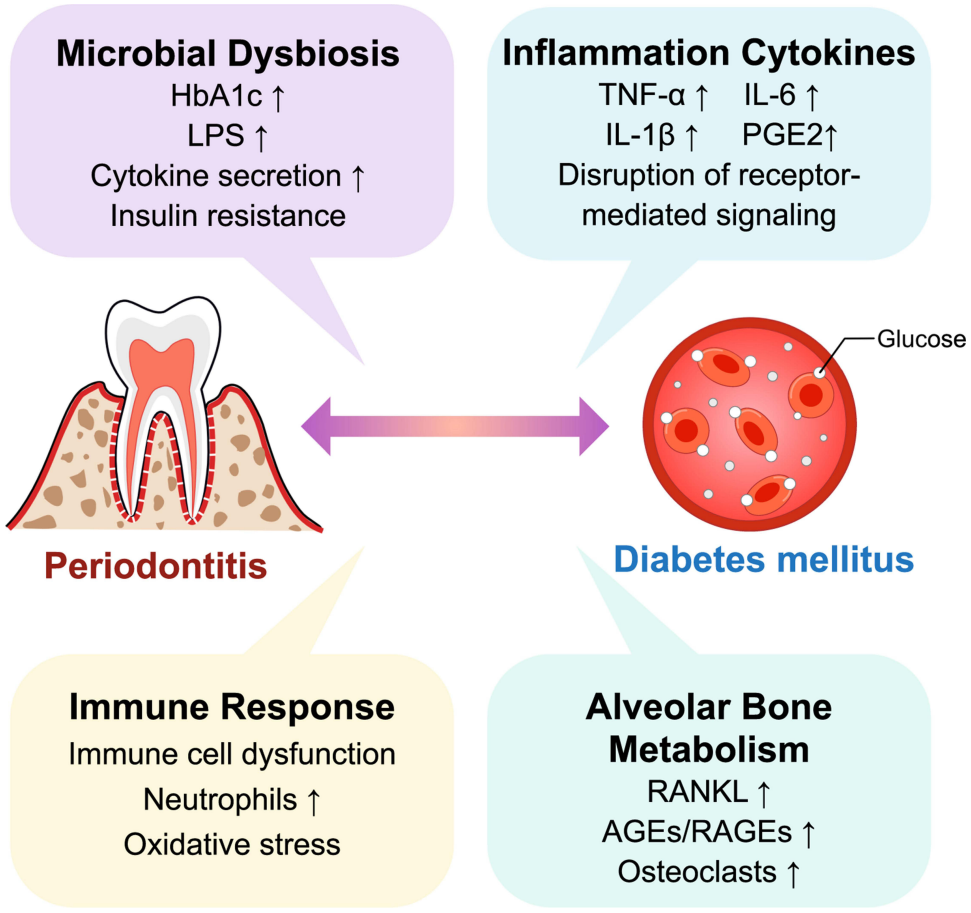

Figure 2 Bidirectional relationship between periodontitis and diabetes. Dysbiosis of the microbiota, increased secretion of pro-inflammatory cytokines, overactive immune responses, and alveolar bone metabolic disorders are linked to the vicious cycle between periodontitis and diabetes. The upward black arrow represents the trend of increasing. Figure 2 was independently designed by the authors using Affinity Designer 2, with all elements created using native software features.

Evidence suggests that P. gingivalis is negatively regulated by the PI3K/Akt/mTOR pathway, promoting autophagy in human gingival fibroblasts (HGFs) to mitigate bacterial invasion.[80] Meanwhile, P. gingivalis activates autophagy in human dental pulp fibroblasts (HDPFs) by upregulating Beclin1, ATG12, and autophagy markers. P. gingivalis can also evade immune surveillance via the PI3K/Akt/mTOR pathway, exacerbating the inflammatory response.[81] Furthermore, upon internalization into human gingival epithelial cells (GECs), P. gingivalis survives and replicates. By targeting the DC-SIGN receptor on dendritic cells (DCs) with its Mfa1 fimbriae, P. gingivalis activates the Akt/mTOR signaling pathway to suppress dendritic cell autophagy,[82] facilitating its intracellular survival and dissemination.[83]

In the context of diabetes, hyperglycemia affects the periodontal tissue's response to pathogens and disrupts the autophagic-lysosomal pathway (ALP). Research has demonstrated that high glucose levels in diabetic patients block the ALP in GECs by downregulating the ATP6VOC gene and reducing lysosomal acidification. This disruption facilitates intracellular bacterial persistence and proliferation while inducing the overexpression of pro-inflammatory cytokines IL-1β and IL-18, thereby exacerbating periodontal inflammation[84](Figure 3). Additionally, hyperglycemia inhibits P. gingivalis-induced autophagy in THP-1 macrophages, an acute monocytic leukemia-derived cell line, further amplifying the inflammatory response.[85] These findings underscore the intricate and context-dependent role of autophagy in the pathogenesis of periodontal disease under diabetic conditions, which is influenced by both host cell type and bacterial species. The precise impact of autophagy in diabetic periodontitis—whether protective or deleterious—warrants further investigation.

Therefore, elucidating the mechanistic interplay between autophagy, diabetes-associated periodontitis, and periodontal pathogens is crucial for advancing novel therapeutic strategies aimed at mitigating disease progression.

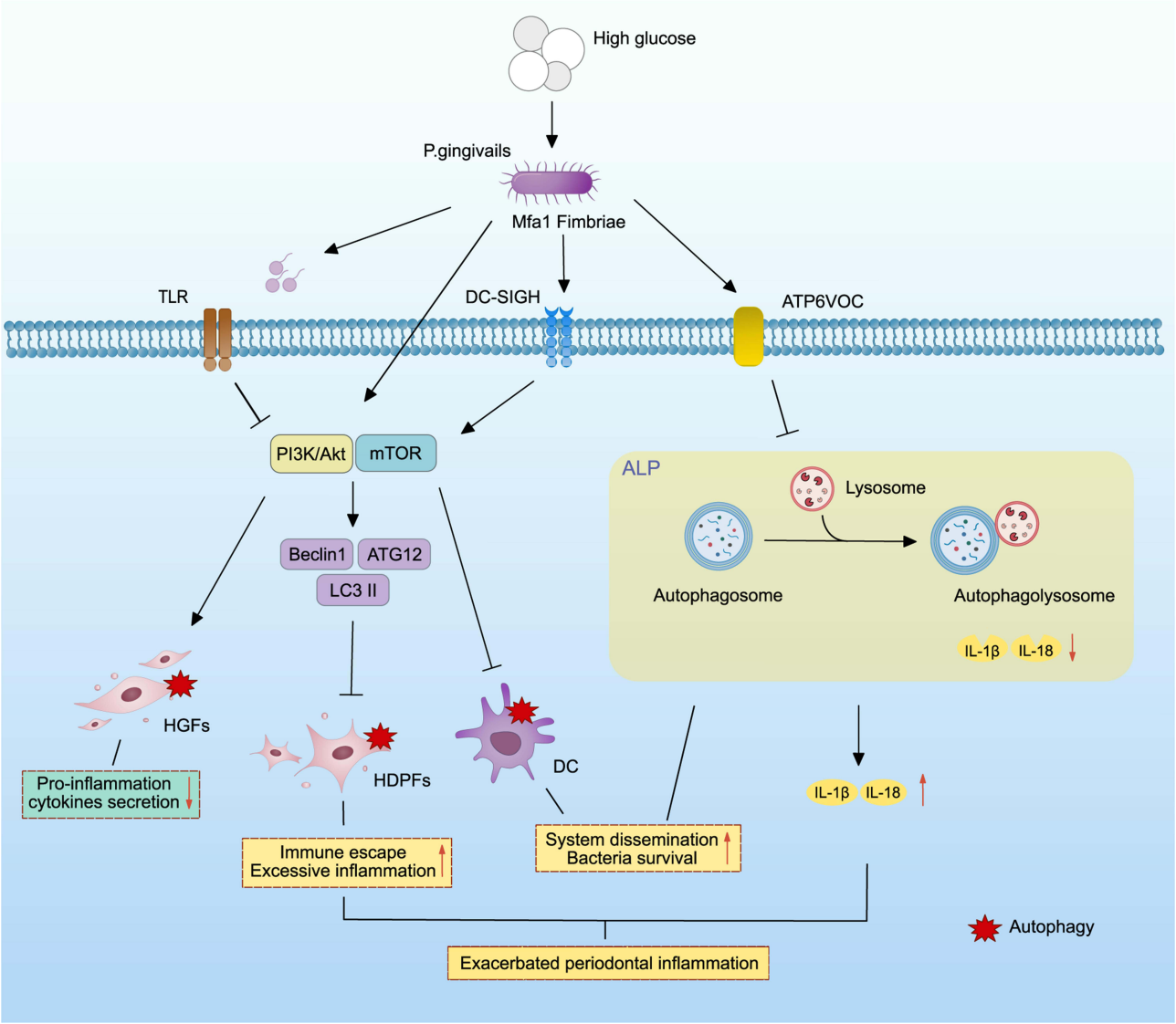

Figure 3 Dual Role of Autophagy in Periodontal Tissue under Periodontal Pathogen Infection and Diabetes Environment. On the one hand, (P) gingivalis is negatively regulated by PI3K/Akt/mTOR, which activates autophagy in HGFs to block pathogen invasion. On the other hand, it can modulate autophagy in HDPFs by regulating Beclin1, ATG12, and autophagy markers to evade immune surveillance, causing excessive inflammation. Additionally, after invading human GECs, (P) gingivalis binds to the DC-SIGN receptor on DCs via its Mfa1 fimbriae, activating the Akt/mTOR signaling pathway to suppress dendritic cell autophagy, promoting survival and spread of the bacteria within the cells. In the diabetic environment, hyperglycemia blocks the ALP through the ATP6VOC gene, facilitating bacterial survival and proliferation and intensifying periodontal inflammation. Red upward arrows denote upregulation, whereas red downward arrows indicate downregulation. Figure 3 was independently designed by the authors using Affinity Designer 2, with all elements created using native software features.

Autophagy's Impact on Immunocytes in Diabetic Periodontitis

Autophagy is a fundamental defense mechanism in the innate immune system, playing a crucial role in combating invading microorganisms. In the context of diabetic periodontitis, autophagy not only contributes to the innate immune response but also regulates the function of adaptive immune cells. Upon infection, THP-1-derived macrophages sense alterations in the tissue microenvironment and participate in pathogen clearance.[86] Moreover, macrophages can regulate the inflammatory response of non-phagocytic cells (such as GECs) by releasing vesicles.[87] Exosomes (Exos) are extracellular microvesicles abundant in bioactive molecules, such as proteins and nucleic acids. Exos play an essential role in intercellular communication, immune responses, and cell migration.[88] Studies have shown that Exos derived from bone marrow-derived macrophages (BMDMs) carrying miR-381-3p inhibit autophagy in GECs through the transcription factor NR5A2, thus exacerbating periodontal inflammation in diabetes.[89] Similarly, hyperglycemia impairs macrophage

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autophagy, leading to the accumulation of IL-1 and reactive oxygen species (ROS), triggering inflammasome activation, and worsening periodontitis.[90]

Autophagy has recently been recognized as a pivotal factor in macrophage polarization. Macrophages can adopt two distinct phenotypes (M1 and M2) in response to local environmental changes.[91] M1 macrophages promote inflammation in the initial inflammatory phase, while M2 macrophages suppress inflammation and aid tissue repair at later stages.[92] Increased autophagy can induce the polarization of macrophages to the M1 phenotype, which contributes to the development of diabetic periodontitis. AGEs activate the autophagy-regulating factor IRF8, inducing M1 polarization and autophagic activity, which in turn affects inflammatory resolution and tissue repair mechanisms.[93] Thus, regulating autophagic activity and specifically targeting the ROS-inflammasome pathway, as well as exploring macrophage polarization in diabetes, could provide novel therapeutic insights for reversing the diabetic periodontitis environment.

Neutrophils, the most abundant immunocytes in the blood, also rely on autophagy for their defense mechanisms at various stages, including the regulation of phagocytosis and oxidative burst.[94] Hyperglycemia-mediated activation of NADPH oxidase leads to a heightened production of ROS. In normal neutrophils, ROS contributes to pathogen elimination through phagocytosis and induction of neutrophil extracellular traps (NETs). However, under conditions of diabetic periodontitis, hyperglycemia interacts directly with AGE-RAGE, inducing oxidative stress and activating NADPH oxidase. This, in turn, triggers autophagy. The resultant accumulation of excess ROS leads to the overproduction of NETs and impairs neutrophils' phagocytic capacity.[95] Additionally, in vivo studies have demonstrated increased levels of neutrophil apoptosis and ROS in diabetic rats, which may be attributable to the excessive activation of mTOR signaling pathways that suppress autophagy, ultimately contributing to cellular death.[96] Therefore, delving into innate immune responses in periodontal disease can promote the identification of therapeutic targets and the development of related drugs for diabetic periodontitis.

Autophagy's Impact on Alveolar Bone Metabolism in Diabetic Periodontitis

Alveolar bone resorption is one of the clinical manifestations of periodontitis. Diabetes disrupts the dynamic balance between osteoblasts and osteoclasts. This imbalance results in pathological resorption of alveolar bone.[97] Emerging evidence has demonstrated the role of autophagy in regulating bone metabolism, particularly in the context of periodontal disease.[98] In a diabetic context, high glucose levels inhibit osteoclast autophagy through the AMPK/mTOR/ULK1 pathway, diminishing the autophagy activity of osteoclasts and impairing their differentiation and function.[99] Another study found that a novel adiponectin receptor agonist, AdipoAI, at low doses, enhances osteoclast autophagy, inhibiting osteoclast formation and alleviating the severity of diabetic periodontitis.[100] Therefore, regulating autophagy in osteoclasts may serve as a promising therapeutic strategy to reduce alveolar bone resorption in diabetic periodontitis.

In the early stages of osteoblast differentiation into mature osteocytes, inhibition of autophagy leads to abnormal osteocyte morphology and significant bone loss.[101] Conversely, enhancing osteoblast autophagy has been shown to mitigate bone resorption under related inflammatory conditions, such as apical periodontitis.[102] However, excessive autophagy may lead to adverse outcomes. Reduced insulin sensitivity and hyperglycemia have been implicated in the upregulation of osteoblast autophagy, which initially offers cellular protection during stress responses and promotes osteoblast maturation. However, sustained excessive autophagy may trigger osteoblast differentiation into non-mineralized osteocytes, reducing bone formation and leading to bone metabolism disorders.[103] Another study found that 1α,25-dihydroxyvitamin D3 can inhibit diabetes-induced excessive autophagy of osteoblasts via the PI3K/Akt/FoxO1 signaling pathway, enhancing osteoblast differentiation and proliferation and attenuating bone resorption[104] (Figure 4). These findings suggest that regulating osteoblast autophagy may be an effective strategy for promoting alveolar bone repair in diabetic periodontitis patients.

Periodontal ligament stem cells are multipotent stem cells derived from the periodontal ligament, characterized by their self-renewal capacity. They can differentiate into various cell types, such as osteoblasts, periodontal ligament cells, and fibroblasts. These stem cells play a critical role in the repair and regeneration of periodontal tissue damage.[105] Early-stage autophagy is associated with enhanced osteogenic differentiation of periodontal ligament stem cells. However, this effect appears to diminish at later stages, possibly due to the suppression of autophagic activity. Evidence suggests that hyperglycemic conditions impair the activity of periodontal ligament stem cells. In contrast, enhancing autophagy can

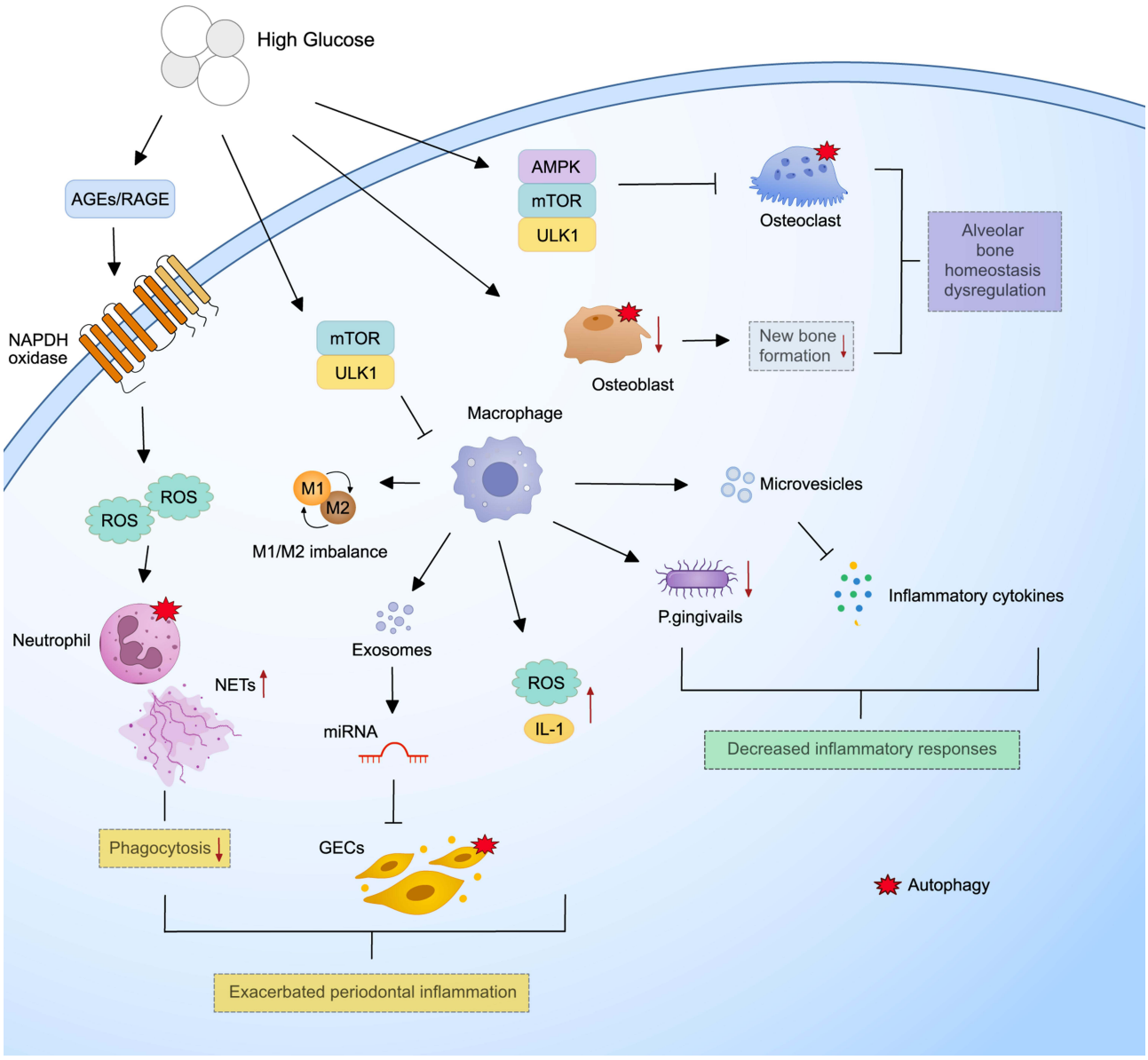

Figure 4 Dual Effects of Autophagy on Immune Response and Alveolar Bone Metabolism in a Diabetic Environment. Hyperglycemia influences neutrophil and macrophage autophagy through NADPH oxidase and mTOR/ULK1 signaling pathways, which either exacerbate or alleviate periodontal inflammation. The diabetic environment disrupts the balance between osteoblasts and osteoclasts, activating autophagy to regulate alveolar bone metabolism and leading to bone metabolic disorders. Red upward arrows denote increasing, whereas red downward arrows indicate reducing. Figure 4 was independently designed by the authors using Affinity Designer 2, with all elements created using native software features.

preserve their activity, protect their osteogenic differentiation ability, and partially reverse the damage to periodontal tissues in high-glucose conditions.[106] These findings highlight the essential role of autophagy in alveolar bone metabolism in diabetic periodontitis. Modulating autophagy to maintain alveolar bone homeostasis may represent a promising therapeutic strategy for diabetic periodontitis treatment.

Autophagy as a Therapeutic Target in Diabetic Periodontitis

The management of diabetic periodontitis presents several therapeutic challenges, including insufficient alveolar bone formation, secondary bone resorption, and recurrent infections.[77] Autophagy, as a potential therapeutic target for diabetic periodontitis, has significant clinical research implications. Below is a summary of recent studies on potential drugs that regulate autophagy, providing insights into the prevention and treatment of diabetic periodontitis.

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Polyphenol-mediated redox-active hydrogels can reverse the inflammatory environment caused by hyperglycemia, enhancing tissue regeneration in periodontitis. The synergistic effect of these hydrogels with hydrogen sulfide-bioelectrical coupling amplifies autophagy in periodontal ligament stem cells and regulates macrophage polarization, promoting alveolar bone formation in diabetic periodontitis.[107] Artemisunate (ART), a derivative of artemisinin, has been shown to exert immunomodulatory, anti-inflammatory, hypoglycemic, and anti-osteoclastic effects. Furthermore, in vivo research reveals that ART intervention can modulate the periodontal microbiome, downregulate the expression of inflammatory cytokines in periodontal tissues, and attenuate alveolar bone loss in rats with diabetic periodontitis by promoting autophagy and suppressing inflammatory responses, thereby facilitating bone remodeling.[108]

Metformin, a first-line therapeutic agent for type 2 diabetes, has been shown to mitigate oxidative stress-induced cellular senescence and partially restore the osteogenic potential of human periodontal ligament stem cells through the activation of autophagy.[109] Similarly, calcitriol (1α,25-dihydroxy vitamin D3), the active form of vitamin D, plays a protective role in immune regulation, bone metabolism, and inflammation. Calcitriol has been proven to enhance autophagy in GECs, thereby attenuating periodontal inflammation in type 2 diabetic rat models.[110] Additionally, hyperglycemia exacerbates P. gingivalis-induced inflammatory responses through autophagy inhibition. Vanillylacetone can activate autophagy to alleviate inflammation, making it a potential therapeutic agent for P. gingivalis-induced periodontal inflammation in diabetic patients.[85]

In summary, research on targeting autophagy in the treatment of diabetic periodontitis remains in its early stages. The regulation of autophagy through biomaterials or drugs holds promising research prospects, which can represent an effective approach to tissue regeneration and immune repair in diabetes-related inflammatory diseases.

Conclusion

Periodontitis has been recognized as the sixth major complication of diabetes. Both the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) list diabetes as a risk factor for periodontal disease progression. The bidirectional interplay between periodontitis and diabetes exacerbates disease severity through mechanisms involving microorganisms, inflammatory cytokines, host immune responses, and AGEs. This interplay leads to a disrupted intracellular environment and decreased capacity for external regulation. Therefore, regulating this bidirectional relationship is of paramount clinical significance.

Existing in vivo and in vitro studies have demonstrated that autophagy plays a protective role in diabetes-related inflammatory diseases, showing immense potential in preventing and alleviating tissue inflammation. As a fundamental cellular homeostatic mechanism, autophagy exhibits dual functionality in the pathogenesis of diabetic periodontitis. First, it can clear periodontal pathogens, regulate host immune responses, suppress inflammation, reduce alveolar bone resorption, and promote periodontal tissue regeneration and repair, thus serving a protective function. Second, pathogens can exploit autophagy to evade immune surveillance. Meanwhile, excessive autophagy may induce programmed cell death and disrupt bone metabolism, thereby contributing to disease pathogenesis.

The molecular mechanisms governing autophagic regulation in diabetic periodontitis necessitate further elucidation. Targeting autophagic activity may emerge as a novel prevention and treatment strategy, improving the treatment outcomes for diabetic periodontitis patients.

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.

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Disclosure

The authors declare that they have no competing interests in this work.

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