Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Research Progress of Mitochondrial Dynamics and Autophagy in Diabetic Complications: New Treatment Strategies

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Abstract: Diabetes has emerged as a critical global health issue, with its associated complications posing a severe threat to patients' quality of life. Current research demonstrates that imbalance in mitochondrial dynamics and autophagic dysregulation play pivotal roles in the pathogenesis of diabetic complications, particularly in diabetic cardiomyopathy, nephropathy, peripheral neuropathy and retinopathy. Strategic modulation of mitochondrial function and autophagic activity represents a promising therapeutic approach for managing diabetic complications. Furthermore, integrating mitochondrial dynamics and autophagy, we have outlined the application prospects of strategies related to diabetic complications, including mitochondrial fission inhibitors, autophagy inducers, and certain compounds extracted from traditional Chinese medicines, and incorporated new breakthroughs in mitochondrial imaging, omics, and artificial intelligence-based therapeutic prediction. This review systematically examines the intricate relationship between diabetic complications and dysregulations in mitochondrial dynamics and autophagic dysfunction, while elucidating the underlying molecular mechanisms, and highlights the significance of mitochondrial dynamics and autophagy in diabetic complications. Imbalances in mitochondrial dynamics—whether abnormal fission or fusion—and autophagic dysregulation do not exist in isolation. A comprehensive understanding of the interplay between diabetic pathophysiology and the mitochondrial-autophagy axis may provide novel research perspectives for therapeutic development. This paper provides a comprehensive review of the literature to clarify the above content, using a narrative review approach. Future investigations should prioritize translational exploration to harness the clinical potential of these mechanistic insights, thereby advancing precision medicine strategies for the management of diabetic complications.

Keywords: diabetic cardiomyopathy, diabetic nephropathy, diabetic peripheral neuropathy, diabetic retinopathy

Introduction

Diabetes is a metabolic disorder, and epidemiological studies indicate that the prevalence of diabetes is increasing annually. By 2045, global projections estimate 783.2 million individuals will live with diabetes.[1] Individuals with diabetes frequently develop macrovascular and microvascular pathologies, which give rise to complications that compromise quality of life and elevate mortality risk. These complications encompass cardiovascular disease, diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy. The core pathological pathway of diabetes mellitus involves absolute insulin deficiency (secondary to autoimmune destruction of pancreatic β-cells) or relative insulin insufficiency (attributed to insulin resistance), which induces impaired glucose uptake, utilization, and storage, thereby leading to chronic hyperglycemia and metabolic disturbances. As the central hub of cellular energy metabolism, mitochondrial dysfunction is closely linked to metabolic diseases. By regulating key processes including glucose oxidation, energy production, and insulin sensitivity, mitochondria are deeply involved in the pathological progression of diabetes, serving as a critical target for elucidating the mechanisms underlying its metabolic derangements. Emerging evidence highlights the critical role of mitochondrial function in the pathogenesis and progression of diabetic complications. Specifically,

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mitochondrial dynamics and autophagy have become central research focuses in elucidating the mechanisms underlying diabetes-associated tissue injury. Currently, there are drug studies targeting mitochondrial dynamics and autophagy, such as mitochondrial fission inhibitors and autophagy inducers.

Mitochondria are dynamic organelles that continuously undergo fusion and fission to adapt to cellular metabolic demands and environmental changes.[2] Mitochondrial fusion is mediated by key regulatory proteins, such as mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 (OPA1).[3,4] During fusion, mitochondria exchange mitochondrial genomic material, proteins, and metabolites, facilitating cellular adaptive responses under stress and optimizing mitochondrial function. In contrast, mitochondrial fission is regulated by dynamin-related protein 1 (DRP1), fission protein 1 (FIS1), and mitochondrial fission factor (MFF).[5] Fission promotes the biogenesis of new mitochondria and the elimination of damaged organelles, thereby safeguarding cellular homeostasis. The equilibrium between mitochondrial fusion and fission is essential for cellular survival and function, whereas disruptions in this balance can induce cell death and pathological conditions.[6]

Mitophagy is a selective form of autophagy responsible for the removal of damaged or redundant mitochondria, thereby maintaining mitochondrial quality and quantity homeostasis within the cell.[7] The molecular mechanisms of mitophagy are broadly categorized into two primary pathways: ubiquitin-dependent and ubiquitin-independent pathways. Among these, the PTEN-induced kinase 1 (PINK1)-Parkin (E3 ubiquitin ligase) pathway represents the best-characterized ubiquitin-dependent signaling cascade in mitophagy.[8] Mitophagy is a highly intricate and finely regulated biological process, and in-depth investigation of its mechanisms may provide new avenues for disease diagnosis and therapeutic interventions.[9]

Accumulating evidence indicates that MFN1, MFN2, and Parkin play key roles in both mitochondrial dynamics and mitophagy, establishing a functional link between these two processes.[10–12] This review focuses on summarizing the roles of mitochondrial dynamics and mitophagy in diabetic complications, elucidating their specific mechanisms, and discussing potential strategies for restoring mitochondrial function to mitigate the impact of diabetic complications. These insights may provide valuable references for further understanding the pathogenesis of diabetic complications and identifying novel therapeutic targets.

Mitochondrial Dynamics, Mitophagy and Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is a diabetes-related myocardial disorder characterized by cardiac structural and functional alterations independent of other established cardiovascular risk factors. Without intervention, DCM can progress to heart failure, arrhythmias, cardiogenic shock, and sudden cardiac death.[13] In acute heart failure populations, the estimated prevalence of DCM is 1.6%.[14] The pathogenesis of DCM is multifactorial, encompassing hyperglycemia, mitochondrial dysfunction, apoptosis, fibrosis, metabolic disorders, inflammatory responses, and the accumulation of advanced glycation end products (AGEs).[15,16] Hyperglycemia induces oxidative stress, resulting in excessive reactive oxygen species (ROS) production, which impairs mitochondrial function in cardiomyocytes and exacerbates metabolic dysregulation. Elevated oxidative stress directly disrupts mitochondrial dynamics, altering the balance between fusion and fission, which impairs myocardial energy supply and contributes to cardiac dysfunction.[17,18] Mitochondrial dynamics and autophagy constitute the core components of the mitochondrial quality control system, tasked with eliminating damaged mitochondria, regulating mitochondrial morphology, and maintaining cardiac energy homeostasis.[19] Thus, maintaining mitochondrial homeostasis is essential for preserving cardiac metabolic integrity and halting the progression of DCM.

Excessive nutrient consumption disrupts mitochondrial fusion, fission, and autophagy processes in cardiomyocytes, thereby compromising mitochondrial homeostasis and cardiac function.[20] In DCM, diminished mitochondrial fusion capacity, coupled with either excessive or inadequate mitochondrial fission, leads to a deterioration of mitochondrial quality, causing an imbalance in the number and function of mitochondria within cardiomyocytes. Under hyperglycemic conditions, DRP1 orchestrates mitochondrial fission in rat cardiomyocytes, which promotes the overproduction of ROS. Tetracycline has been demonstrated to induce the upregulation of MFN2, thus maintaining mitochondrial function.[21] Similarly, in obese mice with DCM, DRP1 expression is significantly increased, while the levels of MFN1 and MFN2 are substantially decreased.[22] Studies have also demonstrated that prenatal exposure to a high-glucose and high-fat diet

results in shorter and wider mitochondria in neonatal rat cardiomyocytes, which subsequently impairs mitochondrial function.[23] Additionally, post-translational modifications are pivotal in regulating proteins associated with mitochondrial dynamics. Hyperglycemia enhances O-linked N-acetylglucosamine (O-GlcNAc) glycosylation of OPA1, exacerbating mitochondrial dysfunction.[24] DRP1 undergoes O-GlcNAc modification at threonine residues 585 and 586, which elevates the level of its GTP-bound active form. This modification facilitates the translocation of DRP1 from the cytoplasm to the mitochondria, inducing mitochondrial fission and decreasing mitochondrial membrane potential, thus further exacerbating mitochondrial dysfunction in DCM.[25]

Mitophagy exerts a pivotal function in cardiac development and maturation.[26] Impaired mitophagy leads to mitochondrial dysfunction and lipid accumulation, exacerbating the progression of DCM. Accumulating evidence indicates that the loss of Parkin inhibits mitophagy,[27] leading to enhanced lipid accumulation and deteriorated diastolic dysfunction. Conversely, the activation of mitophagy mitigates mitochondrial dysfunction, diminishes lipid accumulation, and improves diastolic function.[28] FUN14 domain-containing protein 1 (FUNDC1) serves as a mitophagy receptor, interacting with microtubule-associated protein 1 light chain 3 (LC3) to initiate mitophagy in mammalian cells. The interaction among FUNDC1, DRP1, and OPA1 contributes to the regulation of mitochondrial fission, fusion, and mitophagy, thus maintaining mitochondrial quality control (Figure 1).[29] Notably, emerging research has demonstrated that downregulating FUNDC1 expression alleviates mitochondrial calcium overload, ultimately improving DCM outcomes.[30] Overall, a more profound understanding of mitochondrial dynamics and mitophagy mechanisms may lay the foundation for more efficacious therapeutic strategies and drug development for DCM in the future (Table 1).

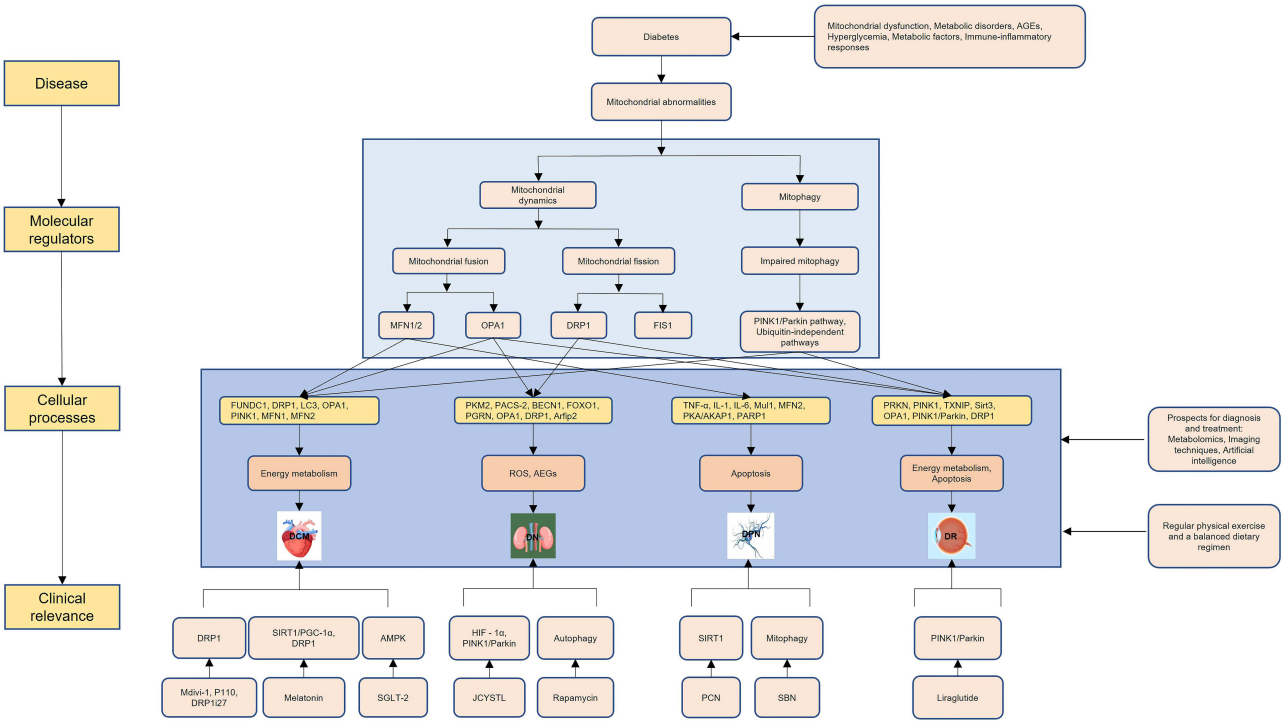

Figure 1 The role and mechanism of mitochondrial dynamics and autophagy in diabetic complications, as well as related potential therapeutic targets.
Abbreviations: MFN1, mitofusin 1; MFN2, mitofusin 2; OPA1, optic atrophy 1; DRP1, dynamin-related protein 1; FIS1, fission protein 1; MFF, mitochondrial fission factor; PINK1, PTEN-induced kinase 1; DCM, diabetic cardiomyopathy; AGEs, advanced glycation end products; ROS, reactive oxygen species; O-GlcNAc, O-linked N-acetylglucosamine; FUNDC1, FUN14 domain-containing protein 1; LC3, light chain 3; DN, diabetic nephropathy; CKD, chronic kidney disease; PKM2, pyruvate kinase M2; PACS-2, phosphofurin acidic cluster sorting protein 2; MAM, mitochondrial-associated membrane; FOXO1, fork head box protein O1; PGRN, progranulin; mtDNA, mitochondrial DNA; DPN, diabetic peripheral neuropathy; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; IL-6, interleukin-6; Mul1, mitochondrial ubiquitin ligase 1; ER, endoplasmic reticulum; DR, diabetic retinopathy; NGR1, notoginsenoside R1; TXNIP, thioredoxin-interacting protein; Sirt3, sirtuin 3; LRP6, low density lipoprotein receptor - related protein 6; SGLT-2, sodium-glucose cotransporter-2; TCM, traditional Chinese medicine; TLN, tangluoning; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; KD, ketogenic diet; Arfip2, ADP-Ribosylation Factor-Interacting Protein 2; PARP1, poly (ADP-ribose) polymerase 1; SGLT-2, sodium-glucose cotransporter-2; HIF-1α, Hypoxia-inducible factor-1α; JCYSTL, Jin-Chan-Yi-Shen Tong-Luo formula; SBN, Silybin; PCN, Piceatannol.

Table 1 Comparison of the Roles of Key Molecules Regulating Mitochondrial Function in Diabetes-Related Complications

Classification	Molecule	DCM	DN	DPN	DR
Mitochondrial fusion	MFN2	Downregulation exacerbates myocardial mitochondrial dysfunction, whereas upregulation improves function.[21]	–	Deficiency impairs mitochondrial transport in neuronal axons, while excessive activation induces excessive mitochondrial fusion.[31]	Downregulation exacerbates retinal mitochondrial damage, while overexpression protects mitochondrial function.[32]
	OPA1	Hyperglycemia induces its abnormal modification, exacerbating myocardial mitochondrial dysfunction and participating in the regulation of mitochondrial dynamics.[24]	Its expression is regulated by PKM2, maintaining mitochondrial stability.[33]	–	Downregulation leads to retinal mitochondrial swelling and increased fission, exacerbating capillary injury.[34]
Mitochondrial fission	DRP1	Mediates hyperglycemia-induced myocardial mitochondrial fission, promotes ROS production, and exacerbates dysfunction.[25]	Inhibition of its activity reduces podocyte injury and proteinuria, and ameliorates renal damage.[35]	Excessive activation leads to excessive mitochondrial fission, disrupting neuronal energy metabolism.[36]	Increased levels promote mitochondrial fission, trigger retinal endothelial cell apoptosis, and exacerbate vascular dysfunction.[37]
	TXNIP	-	-	-	TXNIP promotes mitochondrial fission.[38]
Mitochondrial autophagy	PINK1/ Parkin	-	Activation enhances autophagy, alleviates podocyte injury, improves renal function.[39]	Inhibition of this pathway by PARP1 weakens autophagy, exacerbates neural injury, and its activation protects neurons.[40]	Activation enhances autophagy and alleviates retinal injury; aberrant pathway function exacerbates the damage.[41]
	FUNDC1	It participates in the regulation of myocardial mitochondrial dynamics and mitophagy, maintaining quality control.[29]			
	Arfip2	-	Deficiency exacerbates podocyte injury and proteinuria by inhibiting autophagy.[42]	-	-
	PARP1	-	-	It inhibits neuronal autophagy, exacerbating neural injury; its inhibitor can ameliorate the symptoms.[40]	-
	Sirtuin3	-	-	-	Sirtuin3 activates mitophagy and protects retinal cells.[43]

Notes: The symbol "-" indicates content not shown in the manuscript[a].
Abbreviations: MFN1, mitofusin 1; MFN2, mitofusin 2; OPA1, optic atrophy 1; DRP1, dynamin-related protein 1; PINK1, PTEN-induced kinase 1; DCM, diabetic cardiomyopathy; ROS, reactive oxygen species; FUNDC1, FUN14 domain-containing protein 1; DN, diabetic nephropathy; PKM2, pyruvate kinase M2; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; TXNIP, thioredoxin-interacting protein; Sirt3, sirtuin 3; PARP1, poly (ADP-ribose) polymerase 1; Arfip2, ADP-Ribosylation Factor-Interacting Protein 2.

Mitochondrial Dynamics, Mitophagy and Diabetic Nephropathy

Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes and a leading cause of chronic kidney disease (CKD) and end-stage renal disease, affecting approximately 700 million people worldwide.[44] The pathogenesis of DN is multifactorial, encompassing metabolic derangements, hemodynamic changes, immune-inflammatory responses, cellular and molecular mechanisms, and genetic susceptibility.[45,46] Under hyperglycemic conditions, excessive generation of ROS and the accumulation of AGEs induce cellular dysfunction and renal cell injury.[46] Moreover, diabetes is frequently associated with hypertension, which exacerbates glomerular hyperfiltration, leading to glomerular hypertrophy, tubulointerstitial fibrosis, ultimately impairing renal function.[46]

Mitochondrial fission is intricately linked to the pathogenesis of DN. In diabetic mice, podocyte-specific deletion of DRP1 diminishes proteinuria, attenuates mesangial matrix expansion, and maintains podocyte morphology. Evidence from both in vivo and in vitro models indicates that DRP1 inhibition enhances mitochondrial adaptability in podocytes,

mitigates excessive mitochondrial fission, and retards DN progression, thereby improving renal injury in diabetic mice.[47] Pyruvate kinase M2 (PKM2) is a key regulator of podocyte development and promotes OPA1 expression to maintain mitochondrial stability (Figure 1).[33,48] Additionally, the overexpression of phosphofurin acidic cluster sorting protein 2 (PACS-2) has been shown to inhibit DRP1 mitochondrial recruitment, reducing high glucose-induced mitochondrial hyperfission. This restoration of mitochondrial-associated membrane (MAM) integrity enhances mitophagy, as demonstrated in the renal tubules of diabetic mice and in PACS-2-overexpressing HK-2 cells. These changes are closely associated with alterations in mitochondrial dynamics and mitophagy-related proteins, including DRP1 and Beclin-1.[35,49]

Preclinical evidence demonstrates that suppressing mitophagy in podocytes drives the progression of DN.[50] The progression of DN is associated with a gradual decline in Parkin expression in renal tubular epithelial cells of diabetic patients, whereas Parkin overexpression has been found to alleviate inflammation and improve renal function in STZ-induced diabetic mice.[51] In both Arfip2-knockout human podocytes and Arfip2-knockout combined with STZ-induced diabetic mouse models, Arfip2 deficiency exacerbates autophagic dysfunction in mice, leading to podocyte foot process effacement, histopathological changes, and early albuminuria, while in human podocytes, it disrupts ATG9A trafficking and the PINK1/Parkin pathway, resulting in impaired mitochondrial fission and reduced mitophagy; thus, Arfip2 may represent a novel regulator of podocyte autophagy and mitochondrial homeostasis.[42] Fork head box protein O1 (FOXO1) transcriptionally activates PINK1, leading to the upregulation of Parkin expression and the initiation of mitophagy. Activation of FOXO1 has been shown to mitigate diabetes-induced podocyte injury in renal tubules and protect kidney function. Additionally, progranulin (PGRN), a secretory glycoprotein precursor, enhances mitophagy by promoting PINK1 and Parkin expression, thereby slowing the progression of DN. Moreover, DN patients display reduced mitochondrial DNA (mtDNA) content, leading to impaired energy metabolism and metabolic inflexibility, which further exacerbates mitochondrial dysfunction and renal pathology.[52] MtDNA mutations compromise mitophagy efficiency, as mitochondria with mtDNA mutations can evade mitophagic clearance.[53] The cooperative interaction among FOXO1, Arfip2, PGRN, PINK1, and Parkin is essential for preserving podocyte integrity and represents a promising molecular target for DN therapy (Table 1).[39,54,55]

Elucidating the mechanisms of mitochondrial dynamics and mitophagy, along with identifying key molecular targets, could pave the way for innovative therapeutic strategies in the management of DN.

Mitochondrial Dynamics, Mitophagy and Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, typically manifesting as symmetrical pain and sensory abnormalities in the lower limbs. The pathogenesis of DPN is closely associated with hyperglycemia, dyslipidemia, and insulin resistance.[56] Hyperglycemia-induced metabolic disorders lead to elevated ROS levels, resulting in oxidative stress that damages neuronal cell membranes and intracellular molecules, ultimately causing neuronal injury.[57] Moreover, hyperglycemia triggers an inflammatory response, increasing the levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). This inflammatory milieu exacerbates neuronal dysfunction and promotes apoptotic cell death, further deteriorating neural integrity in DPN.[58]

Mitochondria play a crucial role in the pathophysiology of DPN. Mitochondrial dysfunction in DPN is characterized by excessive ROS production, calcium homeostasis imbalance, decreased mitochondrial membrane potential, ATP depletion, and subsequent impairments in axonal transport or increased apoptotic factors.[59] These diabetes-induced structural and functional mitochondrial alterations directly compromise neuronal energy metabolism and metabolic equilibrium, thereby exacerbating neuronal dysfunction in DPN.[60] Mitochondrial dynamics are essential for synaptic function, and the loss of MFN2 impairs axonal mitochondrial transport, disrupting energy supply to neurons and exacerbating metabolic deficits.[31] Furthermore, mitochondrial dynamics are closely linked to the PKA/AKAP1 signaling pathway. PKA-mediated phosphorylation regulates mitochondrial morphology by modulating DRP1, a process crucial for maintaining neuronal structure and function. Excessive phosphorylation of DRP1 leads to excessive mitochondrial fission, leading to compromised energy metabolism and neuronal structural instability.[36,61] Given these findings, targeting mitochondrial dynamics may represent a promising therapeutic strategy for DPN (Table 1).

Moreover, mitochondrial dysfunction augments neuronal energy demands, thereby exacerbating synaptic impairment and neurological dysfunction. Within this pathological context, mitophagy functions as a selective quality-control mechanism, critically mitigating neuronal injury and promoting neuronal survival. Neurons require a continuous supply of energy to maintain synaptic transmission and long-distance axonal transport. Insufficient autophagosome load leads to the release of large amounts of ROS from damaged mitochondria, resulting in DNA fragmentation and protein misfolding. However, persistent hyperglycemia may cause the autophagosome load to exceed the normal threshold, leading to reduced autophagic efficiency and accumulation of autophagosomes.[62,63] Mitochondrial ubiquitin ligase 1 (Mul1) suppresses Parkin-mediated mitophagy in mature neurons by maintaining the contact sites between the endoplasmic reticulum (ER) and mitochondria. Experimental evidence indicates that Mul1 deficiency upregulates MFN2 activity, inducing excessive mitochondrial fusion, and functions as an antagonist of ER-mitochondrial tethering, thereby decreasing ER-mitochondrial interactions. The diminished ER-mitochondria contact results in increased cytosolic calcium ion concentration, which activates calcineurin, subsequently triggering DRP1-dependent mitochondrial fission and mitophagy.[64] Studies have shown that in db/db mouse models, poly(ADP-ribose) polymerase 1 (PARP1) induces peripheral nerve injury by inhibiting mitophagy in dorsal root ganglion neurons, whereas administration of PARP1 inhibitors ameliorates such nerve injury symptoms.[40] Chronic dysregulation of calcium homeostasis may impair the balance between mitochondrial fission and fusion, resulting in decreased autophagic efficiency. Sustained hypercalcemia in neurons can inhibit mitochondrial mobility and impede the docking of autophagosomes with lysosomes.[65] Furthermore, mitophagy facilitates the removal of excessive ROS and damaged mitochondria, thereby reducing oxidative stress, protecting neurons from damage, and extending their lifespan.[66] Thus, modulating the interplay between MFN2, DRP1, and Parkin not only optimizes mitochondrial dynamics but also fine-tunes mitophagy, additionally, targeting such mechanisms as mitochondrial autophagic flux and calcium dynamics may represent a novel therapeutic strategy for DPN. (Figure 1).

Mitochondrial Dynamics, Mitophagy and Diabetic Retinopathy

Diabetic retinopathy (DR) is a common microvascular complication of diabetes, characterized by chronic and progressive retinal microvascular leakage and occlusion, leading to a series of fundus pathologies that result in visual impairment and even blindness. According to statistical data from 2020, approximately 1.07 million individuals worldwide have experienced blindness due to DR, while about 3.28 million have suffered from vision impairment caused by this condition.[67] The pathogenesis of DR is multifactorial, encompassing hyperglycemia-driven metabolic derangements, inflammatory cascades, mitochondrial dysfunction, microvascular anomalies, pathological neovascularization, and neurodegenerative processes.[68]

Hyperglycemia-induced inflammatory responses augment vascular permeability and retinal blood flow, ultimately culminating in apoptosis. Under hyperglycemic conditions, excessive generation of ROS inflicts damage on mitochondrial DNA, resulting in mitochondrial dysfunction and retinal impairment. Retinal ischemia and hypoxia exacerbate capillary endothelial cell injury, ultimately promoting neovascularization.[69,70] In diabetic mice, the retinal expression of OPA1 is markedly decreased, resulting in mitochondrial swelling and localized constriction, thus facilitating mitochondrial fission. This phenomenon is associated with partial mitochondrial damage in the retinal capillaries of diabetic mice.[34] In both in vivo and in vitro models of DR, overexpression of MFN2 in retinal endothelial cells has been demonstrated to safeguard against hyperglycemia-induced structural and functional mitochondrial damage, enhance mitochondrial DNA integrity and transcription, and mitigate the hyperglycemia-induced elevation in capillary cell apoptosis.[32] In DR, the levels of MFN2 protein are decreased, whereas the levels of DRP1 are increased,[37] resulting in augmented mitochondrial fission and compromised fusion. Excessive mitochondrial fragmentation initiates endothelial cell apoptosis, further exacerbating retinal vascular dysfunction.

Under high-glucose conditions, Parkin accumulates within the mitochondria of retinal cells, thereby inducing mitophagy. However, in the diabetic retina of db/db mice, the mitophagosome-to-mitochondria ratio is reduced, accompanied by increased oxidative stress, which may be mediated by alterations in mitophagy-related proteins such as PRKN and PINK1.[71] Notably, notoginsenoside R1 (NGR1) has been demonstrated to augment PINK1-Parkin–dependent mitophagy, thereby alleviating retinal cell damage.[41] Müller cells, which are the predominant type

of glial cells in the retina, play a crucial role in maintaining retinal function and homeostasis.[72] Neurovascular coupling represents a core mechanism that sustains normal neural function—particularly visual function—by regulating vascular activity to match the metabolic demands of neurons in the retina and brain. When retinal neuronal activity increases, insufficient vascular dilation leads to inadequate blood flow and oxygen supply, triggering local hypoxia and damaging mitochondria in retinal neurons and glial cells such as Müller cells. This not only exacerbates energy metabolism disorders but also impairs the regulatory capacity of neurovascular coupling.[73,74] Mitochondria are key regulators of neurovascular coupling. Under diabetic conditions, mitochondrial dysfunction induces abnormal signal transmission between neurons and vascular endothelial cells: excessive production of mitochondrial ROS inhibits the bioavailability of nitric oxide, impairs vasodilation, and aggravates retinal ischemia and hypoxia. Additionally, mitochondrial damage activates inflammatory pathways, promotes macrophage polarization, and further disrupts the blood-retinal barrier. The interplay between inflammation and mitochondrial dysfunction accelerates the progression of DR.[75–77] Hyperglycemia induces an upregulation of thioredoxin-interacting protein (TXNIP) levels, promotes mitochondrial fission, and enhances autophagic flux in Müller cells. Silencing of TXNIP decreases both mitochondrial fission and autophagy in these cells,[78] indicating that targeting TXNIP may represent a potential therapeutic strategy for diabetes and its associated complications, including DR (Figure 1).[38,43] Moreover, the mitochondrial deacetylase Sirtuin 3 (Sirt3) is capable of activating mitophagy via the FOXO3a/PINK1-Parkin pathway, thereby safeguarding retinal pigment epithelial cells.[79] The interaction between mitochondrial dynamics and autophagy exerts a significantly influence on retinal cell fate and overall health and function of the retina. The dynamic balance between these processes is essential for maintaining cellular homeostasis. Modulating the PINK1/Parkin pathway or inhibiting mitochondrial fission proteins, including DRP1, can effectively alleviate retinal cell damage and preserve visual function, presenting novel therapeutic approaches for DR. As research progresses, these insights could offer valuable guidance for the development of pharmacological interventions aimed at treating DR (Table 1).

Application Prospects of Mitochondrial-Related Intervention Strategies in Diabetic Complications

Mitochondria represent one of the most crucial organelles for maintaining cellular homeostasis. The interaction between mitochondrial dynamics and autophagy is fundamental for preserving organ function and regulating physiological processes. A more profound comprehension of these mechanisms may expedite the development of novel therapeutic strategies. Mitochondrial fission inhibitors, including Mdivi-1,[80] P110, and DRP1i27,[81] decrease DRP1 levels, inhibit mitochondrial fragmentation, and enhance mitochondrial fusion. Mdivi-1, a quinazolinone derivative, has been demonstrated to attenuate the activation of DRP1 signaling in vivo studies of end-stage DCM in mice (Figure 1). Specifically, Mdivi-1 alleviates autophagy inhibition and fatty acid metabolism dysregulation resulting from low density lipoprotein receptor - related protein 6 (LRP6) deficiency, ultimately ameliorating cardiac dysfunction.[82] Melatonin improves mitochondrial function and cardiac function by inhibiting SIRT1/PGC-1α-dependent mitochondrial fission, which reduces the expression level of Drp1, thereby suppressing mitochondrial remodeling and oxidative stress, decreasing cardiomyocyte apoptosis.[83] Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated the ability to prevent mitochondrial swelling, enhance mitochondrial repair and regeneration, and ameliorate mitochondrial dysfunction by inhibiting aberrant mitochondrial fission via the AMPK signaling pathway.[84] Moreover, autophagy inducers including rapamycin have been proposed to alleviate diabetes-associated renal injury by promoting autophagic activation.[48] As a deacetylase 1 activator, silybin (SBN) can ameliorate high glucose -induced sciatic nerve injury and oxidative damage in mouse neuroblastoma cells (N2A) and STZ-induced Sprague-Dawley rats, and exerts neuroprotective effects by enhancing mitophagy.[85] Liraglutide prevents DR by inhibiting the PINK1/Parkin pathway, thereby reducing mitophagy.[86]

Certain bioactive compounds derived from traditional Chinese medicine (TCM), including punicalagin and paeonol, have been demonstrated to attenuate oxidative stress by modulating mitochondrial fusion, thereby ameliorating DCM.[87] Moreover, ginseng and its bioactive extracts exhibit protective effects against DCM by improving mitochondrial dysfunction.[88] Berberine, a quaternary ammonium alkaloid extracted from Coptis chinensis (Huanglian) and Phellodendron amurense (Huangbai), enhances mitochondrial energy homeostasis by activating the peroxisome

proliferator-activated receptor gamma coactivator-1α (PGC-1α) signaling pathway.[89] Furthermore, berberine has been demonstrated to mitigate high-glucose-induced mitochondrial fission and fusion imbalance, as well as impairments in mitotic progression. It exerts protective effects against cardiomyocyte damage by promoting AMPK-dependent mitophagy activation, leading to reduced mitochondrial abundance and cellular injury.[90] In high glucose/hypoxia-induced HK-2 cells and unilateral nephrectomy combined with STZ-induced diabetic kidney disease rat models, Jin-Chan-Yi-Shen Tong-Luo formula (JCYSTL) protects renal tubules against mitochondrial dysfunction and apoptosis by stabilizing HIF-1α to activate PINK1/Parkin-mediated mitophagy.[91] Tangluoning (TLN), a TCM formulation, has been studied for its efficacy in preventing and treating DPN. In DPN rat models, TLN enhances mitochondrial function by inhibiting DRP1 expression and phosphorylation, thereby suppressing mitochondrial fission and upregulating fusion proteins MFN1, MFN2, and OPA1.[92] Piceatannol (PCN), a SIRT1 activator, exerts neuroprotective effects by promoting mitobiogenesis and mitophagy through the SIRT1-PGC-1α-NRF2-TFAM and SIRT1-PINK1-Parkin axes.[93] TCM offers significant promise in modulating mitochondrial function and autophagy, presenting novel therapeutic strategies for diabetic complications. TCM-based interventions targeting the PINK1/Parkin-mediated mitophagy pathway may exert neuroprotective effects in DN. Furthermore, the regulation of mitochondrial dynamics proteins, including MFN1, MFN2, and DRP1, may help restore mitochondrial homeostasis, presenting novel therapeutic insights for managing diabetes-related complications.[94]

The ketogenic diet (KD) is a therapeutic dietary approach that influences mitochondrial dynamics by modulating the AMPK/mTOR signaling pathway.[95] Regular physical exercise and a balanced dietary regimen can reduce excessive apoptosis, promote cellular health, and enhance mitochondrial function and autophagy (Table 2).[96,97]

Table 2 Summary of Bioactive Compounds Targeting Mitochondrial Dynamics and Autophagy

Classification	Bioactive Compounds/ Intervention Methods	Action Target	Advances in Research	Research Phase
Synthetic drugs	Mdivi-1	DRP1	Inhibits DRP1 and improves cardiac function in mouse models of DCM	Preclinical research phase
	P110	DRP1	Reduces DRP1 expression and suppresses mitochondrial fragmentation.	Preclinical research phase
	DRP1i27	DRP1	Reduces DRP1 expression and suppresses mitochondrial fragmentation.	Preclinical research phase
	Melatonin	SIRT1/PGC-1α pathway, DRP1	Enhances cardiac function and diminishes cardiomyocyte apoptosis.	Marketed (expanded to cardiac protection)
	Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	AMPK pathway	Improves mitochondrial function and prevents mitochondrial swelling.	Marketed (for example, dapagliflozin)
	Rapamycin	Autophagy-related pathways	Induces autophagic activation and alleviates diabetes-associated renal injury.	Marketed (expanded to renal injury)
	Liraglutide	PINK1/Parkin pathway	Prevents diabetic retinopathy (DR).	Marketed (for diabetes treatment)
	Berberine	PGC-1α pathway, AMPK	Protects cardiomyocytes and regulates mitochondrial energy homeostasis.	Marketed (expanded to cardiomyocyte protection)

(*Continued*)

Table 2 (Continued).

Classification	Bioactive Compounds/ Intervention Methods	Action Target	Advances in Research	Research Phase
TCM	Piceatannol (PCN)	SIRT1 and its downstream related axes	Exerts neuroprotective effects.	-
	Silybin (SBN)	Deacetylase 1, autophagy - related	Attenuates high glucose-induced sciatic nerve injury.	Marketed (expanded to neuroprotection)
	Punicalagin	Mitochondrial fusion - related molecules	Improves DCM	-
	Paeonol	Mitochondrial fusion - related molecules	Improves DCM	-
	Ginseng and its bioactive extracts	Mitochondrial function - related molecules	Exerts protective effects against DCM.	-
	Jin-Chan-Yi-Shen Tong-Luo formula (JCYSTL)	HIF-1α, PINK1/ Parkin pathway	Protects renal tubules in diabetic kidney disease.	Preclinical research phase
Dietary/ lifestyle	The ketogenic diet (KD)	AMPK/mTOR pathway	Regulate the mitochondrial dynamics by modulating the AMPK/mTOR signaling pathway.	-
	Regular physical exercise		Reduce excessive apoptosis, promote cell health, enhance mitochondrial function and autophagy.	-
	Balanced dietary regimen		Reduce excessive apoptosis, promote cell health, enhance mitochondrial function and autophagy.	-

Notes: The symbol "-" indicates that we cannot yet determine the details specifically. [a.]

Abbreviations: MFN1, mitofusin 1; MFN2, mitofusin 2; OPA1, optic atrophy 1; DRP1, dynamin-related protein 1; PINK1, PTEN-induced kinase 1; DCM, diabetic cardiomyopathy; FUNDC1, FUN14 domain-containing protein 1; LC3, light chain 3; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; TXNIP, thioredoxin-interacting protein; Sirt3, sirtuin 3; SGLT-2, sodium-glucose cotransporter-2; TCM, traditional Chinese medicine; TLN, tangluoning; KD, ketogenic diet; JCYSTL, Jin - Chan - Yi - Shen Tong - Luo formula; SBN, Silybin; PCN, Piceatannol; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; HIF-1α, Hypoxia-inducible factor-1α.

Diagnostic Monitoring and Precision Medicine Technologies for Diabetes Mellitus and Mitochondrial Dysfunction

Accurate diagnosis of diabetes mellitus and monitoring of mitochondrial dysfunction are crucial for formulating effective management and intervention strategies. Mitochondrial dysfunction can be diagnosed and identified through metabolomics, proteomics analyses, and imaging techniques, while artificial intelligence has also shown great potential in processing diabetes-related multi-omics data, including genomics, proteomics, and metabolomics.

Metabolomics analysis can characterize metabolic pathways and identify disease-related biomarkers by comprehensively detecting small-molecule metabolites in biological samples such as blood, urine, and tissues. This analysis can reveal systemic metabolic abnormalities and mitochondrial dysfunction, facilitating early disease detection and intervention. Among them, targeted metabolomics and flux analysis techniques can deeply dissect the mechanisms underlying mitochondrial metabolism and energy homeostasis, providing support for the development of personalized therapeutic approaches based on individual metabolic characteristics.[98,99]

Imaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), and near-infrared spectroscopy (NIRS) provide non-invasive diagnostic approaches for evaluating mitochondrial dysfunction in diabetes mellitus by visualizing in vivo mitochondrial function and tissue metabolism. Specifically, PET imaging uses radiolabeled tracers like [^{18}F] fluorodeoxyglucose (FDG) and [^{11}C] acetate to assess glucose uptake and oxidative metabolism in tissues, thereby facilitating in-depth understanding of mitochondrial function and energy metabolic status in diabetic tissues. MRI techniques, including magnetic resonance spectroscopy and diffusion-weighted imaging, can quantify tissue metabolites and water diffusion properties, providing information related to mitochondrial function and tissue microstructure.[100,101]

Data-driven precision medicine provides innovative approaches for the prediction and management of type 2 diabetes mellitus (T2DM). With the advancement of big data and artificial intelligence technologies, the medical field can more accurately identify and predict T2DM risks. By integrating multi-dimensional data including genomics, metabolomics, lifestyle, and environment, artificial intelligence can not only analyze an individual's genetic susceptibility and potential metabolic disorders but also comprehensively and dynamically monitor patients' health status, thereby enabling early warning and personalized treatment of the disease.[102]

Conclusion

Mitochondrial dynamics and autophagy play critical roles in the pathogenesis and progression of diabetic complications. Mitochondrial dynamic imbalance, characterized by aberrant mitochondrial fusion and fission, results in diminished bioenergetic capacity, excessive ROS generation, and compromised mitophagy. These pathological changes are closely associated with the development of chronic diabetic complications, and their regulatory processes are complex and sophisticated, involving interactions among multiple signaling pathways and key molecules. However, due to the unclear regulatory mechanisms of these molecules, it is difficult to precisely target specific targets in mitochondrial dynamics and autophagy in practice, and single interventions fail to achieve satisfactory therapeutic efficacy, thus requiring the combined application of multiple approaches. With the rapid advancement of science and technology, combining omics technologies, artificial intelligence-based prediction, and novel imaging methods in the future is expected to improve diabetic complications through mitochondrial-targeted therapy. This review synthesizes the roles and molecular mechanisms of mitochondrial dynamics and autophagy in diabetic complications (Figure 1). Despite significant progress in recent studies, several unresolved issues remain, including unclear cross-talk between regulatory pathways, undefined epigenetic regulatory mechanisms, lack of systematic investigation into cell-type-specific differences, and insufficient research on the impacts of environmental and genetic factors. Future investigations should further clarify the precise regulatory mechanisms of mitochondrial dynamics and autophagy, while exploring their therapeutic potential for diabetic complications.

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Disclosure

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