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Review

Mitochondrial Dynamics and Mitochondrial Dysfunction in Diabetes

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The mitochondria are involved in active and dynamic processes, such as mitochondrial biogenesis, fission, fusion and mitophagy to maintain mitochondrial and cellular functions. In obesity and type 2 diabetes, impaired oxidation, reduced mitochondrial contents, lowered rates of oxidative phosphorylation and excessive reactive oxygen species (ROS) production have been reported. Mitochondrial biogenesis is regulated by various transcription factors such as peroxisome proliferator-activated receptor γ coactivator–1α (PGC–1α), peroxisome proliferator-activated receptors (PPARs), estrogen-related receptors (ERRs), and nuclear respiratory factors (NRFs). Mitochondrial fusion is promoted by mitofusin 1 (MFN1), mitofusin 2 (MFN2) and optic atrophy 1 (OPA1), while fission is governed by the recruitment of dynamin-related protein 1 (DRP1) by adaptor proteins such as mitochondrial fission factor (MFF), mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51), and fission 1 (FIS1). Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and PARKIN promote DRP1-dependent mitochondrial fission, and the outer mitochondrial adaptor MiD51 is required in DRP1 recruitment and PARKIN-dependent mitophagy. This review describes the molecular mechanism of mitochondrial dynamics, its abnormality in diabetes and obesity, and pharmaceuticals targeting mitochondrial biogenesis, fission, fusion and mitophagy.

Key words: fusion, fission, oxidative stress, mitochondria, diabetes

Mitochondria efficiently produce cellular ATP and determine the ATP availability in the cell, since they are a major site for the generation of ATP. Mitochondrial dysfunction contributes to the development of age-dependent insulin resistance [1], since mitochondrial capacity has been considered to be a good indicator of insulin sensitivity [2]. In addition to their role as the 'power house' of the cell, mitochondria are involved in the regulation of the energy balance through the induction of mitochondrial biogenesis. Calorie restriction and exercise result in increases in the NAD^+/NADH and AMP/ATP ratios, respectively. Sirtuin (SIRT) 1/3 which requires NAD^+ as the nucleotide is a co-substrate and activates peroxisome proliferator-activated receptor (PPAR) γ coactivator–1 α (PGC–1α) by deacetylation [3]. The increase in the AMP/ATP ratio directly activates AMP-activated kinase (AMPK) and further activates the PGC–1α through phosphorylation [4]. The phosphorylated and deacetylated PGC–1α co-activates nuclear-encoded nuclear genes via transcription factors such as the nuclear translocation of nuclear respiratory factor (NRF) 1/2, estrogen-related receptor (ERR) α,

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β, γ, and PPAR α, β, γ [5]. These transcription factors activate mtDNA transcription, translation and replication, the production of oxidative phosphorylation (OXPHOS) subunits, and tricarboxylic acid (TCA) cycle enzymes and fatty acid oxidation enzymes, which leads to increased mitochondrial biogenesis [5].

In patients with diabetes, hyperglycemia induces intracellular glucose oxidation generating NADH and pyruvate, and enhances the influx of pyruvate into the mitochondria. Pyruvate is oxidized by the TCA cycle to produce NADH and $FADH_2$, which donate electrons that flow through the mitochondrial electron transport chain formed by inner-membrane-associated enzyme complexes. If the electrochemical potential difference is too high under high-glucose conditions, reactive oxygen species (ROS) are demonstrated to be generated at complex I and the interface between ubiquinone and complex III. The inhibitor of complex II, manganese superoxide dismutase (SOD), and uncoupling protein-1 (UCP-1) prevent the high-glucose-induced ROS production in bovine endothelial cells and inhibit the subsequent activation of protein kinase C (PKC), the formation of advanced glycation end-products (AGEs), sorbitol accumulation, and nuclear factor-kappa B (NFκB) activation [6, 7]. However, recently, a new concept in the understanding of diabetic complications, 'mitochondrial hormesis', was presented [8, 9]. In response to excess glucose exposure or nutrient stress, there is a reduction in mitochondrial superoxide, oxidative phosphorylation, and mitochondrial ATP generation in several tissues targeted in diabetes complications [8]. The continuous reduction of mitochondrial function is linked to the overproduction of oxidants from non-mitochondrial sources and the release of proinflammatory and profibrotic cytokines [9]. The series of evidence suggested that the activation of AMPK, SIRT1/3 and PGC-1α increased the mitochondrial capacity for OXPHOS, restoration of physiologic mitochondrial superoxide production, which is beneficial for insulin secretion by pancreatic β cells, insulin sensitivity in skeletal muscle and liver, and prevention of micro- and macro-vascular complications in diabetes [8].

Quality control of the mitochondria is critical for the maintenance of mitochondrial function, and dysfunction of the mitochondria plays critical roles in the development of diabetes and obesity. Mitochondria are reticular organelles that have high plasticity in their dynamic structures and constantly undergo fusion and fission processes; this plasticity is important for the quality control of mitochondria [10]. In this review, abnormalities in the mitochondrial fusion and fission dynamics, mitophagy in diabetes, and the significance of mitochondria as a therapeutic target is highlighted.

Mitochondrial Fusion and Fission Dynamics

Once close contact between mitochondria is established, the dynamin-related outer mitochondrial membrane (OMM) proteins mitofusin 1 (MFN1) and mitofusin 2 (MFN2) form homotypic (MFN1-MFN1 and MFN2-MFN2) or heterotypic (MFN1-MFN2) complexes [11]. After tethering, inner mitochondrial membrane (IMM) fusion is mediated by optic atrophy 1 (OPA1) depending on the inner membrane potential [12]. The process of fusion retains the capacity of the mitochondria and maintains genetic and biochemical homogeneity by allowing the dilution of superoxide species and mutated DNA and the repolarization of membranes [13]. Fission, a division process that produces one or more daughter mitochondria, requires cytosolic dynamin-related protein 1 (DRP1). Mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs) function as membrane contact sites between the ER and mitochondria. These ER-mitochondria contact sites have emerged as major players in lipid metabolism, calcium signaling, autophagy and mitochondrial dynamics [14]. The mitochondria constriction and division occur at ER contact sites [15]. Multiple receptors recruit DRP1 to the mitochondria, including four mitochondrially localized adaptor proteins: mitochondrial fission factor (MFF) [16], mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51) [17, 18], and fission 1 (FIS1) [19]. The assembly of DRP1 dimers and oligomers forms a helical structure, and DRP1 hydrolyzes GTP and divides the mitochondria by constriction. So far, no mammalian inner membrane fission machinery has been identified [20] (Fig. 1).

Mitochondrial Biogenesis

The generation of new mitochondria, mitochondrial biogenesis, is distinct from mitochondrial fission, and

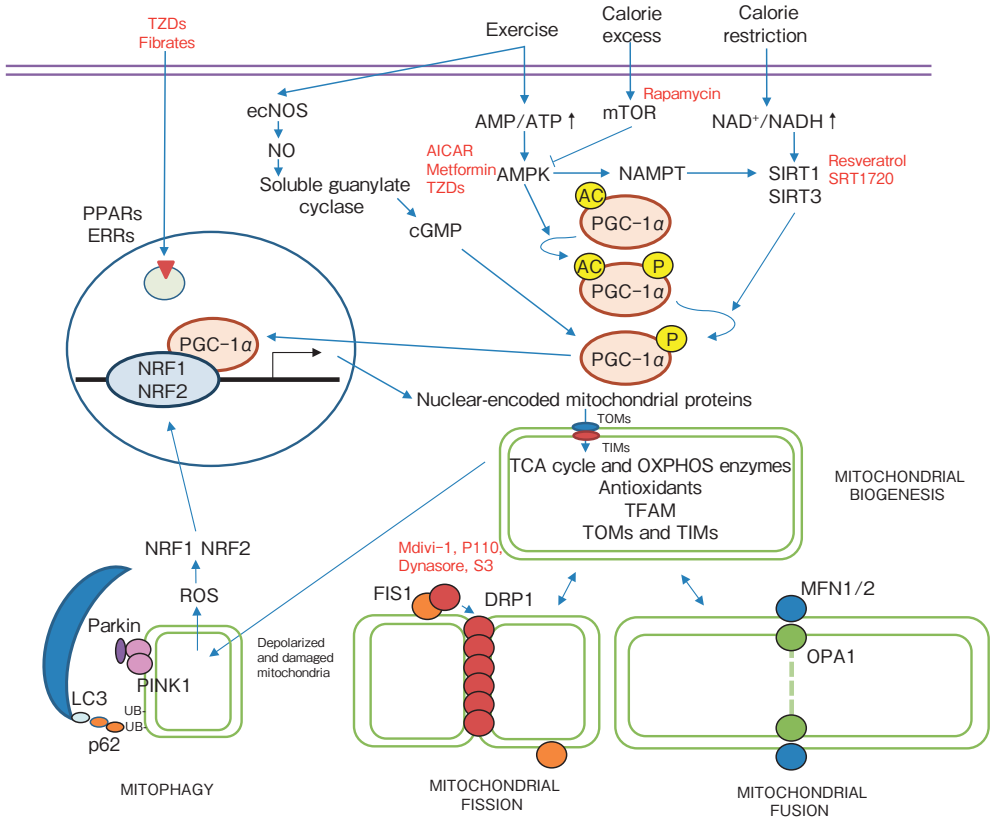

Fig. 1 Mitochondrial biogenesis, fission, fusion, and mitophagy. AICAR (5-aminoimidazole-4-carboxamide riboside), AMPK (AMP-activated kinase), DRP1 (dynamin-related protein 1), ecNOS (nitric oxide synthase 3), ERRs (estrogen-related receptors), FIS1 (fission 1), LC3 (microtubule-associated protein light chain 3α), Mdivi-1 (mitochondrial division inhibitor-1) MFN1, 2 (mitofusin 1, 2), mTOR (mammalian target of rapamycin), NAMPT (nicotinamide phosphoribosyltransferase), NO (nitric oxide), NRF1, 2 (nuclear respiratory factor 1, 2), OPA1 (optic atrophy 1), OXPHOS (oxidative phosphorylation), PGC-1α (proliferator-activated receptor γ coactivator-1α), PINK1 (phosphatase and tensin homolog (PTEN)-induced putative kinase 1), PPARs (peroxisome proliferator-activated receptors, ROS (reactive oxygen species), SIRT1, 3 (sirtuin 1, 3), TCA (tricarboxylic acid), TFAM (mitochondrial transcription factor A), TIMs (translocases of inner mitochondrial membrane), TOMs (translocases of outer mitochondrial membrane), TZDs (thiazolidinediones), UB (ubiquitin).

the former involves the complete replication of mitochondrial DNA. Mitochondrial biogenesis is driven by the transcriptional activator of NRF-1, NRF-2, PGC-1α, which is activated by various pathways such as receptor tyrosine kinases, natriuretic peptide receptors and nitric oxide through the generation of cGMP: the activation of AMPK, Akt, SIRT1-mediated acetylation, PPARs, and ERRs [21]. The expressions of nuclear-encoded mitochondrial genes are actively transcribed, and the proteins with mitochondrial target sequences including the enzymes of the TCA cycle and OXPHOS, antioxidant enzymes, and mitochondrial transcription factor A (TFAM) are imported via translocase of the OMM and IMM complexes (TOM and TIM) into the mitochondria. In type 2 diabetes, the expressions of PGC-1α and its targeted genes are reduced, and they are associated with an impaired ability to produce mitochondrial ATP [22] and increased ROS production from the electron transport chain [6]. Thus, the activation of mitochondrial biogenesis by pharmacological activation targeting these molecules seems to be beneficial in the treatment of type 2 diabetes and obesity [23, 24].

Apoptosis and Mitophagy

Upon the induction of apoptosis, the OMM is fragmented by the translocation of DRP1 from the cytosol to the mitochondria, where it is preferentially localized to the site of organelle division [25]. DRP1

further promotes the Bax/Bak-induced cytochrome c release during apoptosis [26]. During mitochondrial fragmentation, apoptotic stimuli such as UV irradiation induced a decrease in cytoplasmic and mitochondrial DRP1 phosphorylation on Ser (637) and enhanced the interaction between DRP1 and MFF, while interaction between DRP1 and MiD51 decreased [27]. Thus, fission proteins are orchestrated to mediate the fission process during apoptosis.

OPA1 is involved in mitochondrial fusion and cristae remodeling, and they are functionally distinct processes; the latter is correlated with apoptotic cytochrome c release, which can be rescued by OPA1 overexpression [28]. Furthermore, the loss of OPA1 or the inhibition of mitochondrial fusion and the subsequent fragmentation of the mitochondrial network triggers cell death [28]. Bax and Bak are required for the physiological fusion of mitochondria from elongated mitochondria via the functional activity of OMM proteins including MFN1 and MFN2, which inhibit cytochrome c release, Bax translocation and the oligomerization induced by apoptotic stimuli [29].

Mitophagy is an organelle-specific process of elimination of damaged and depolarized mitochondria by selective ubiquitination, targeting autophagosomes via ubiquitin and microtubule-associated protein light chain 3α (LC3)-binding adaptor proteins, and the fusion of autophagosomes with lysosomes [30]. Parkin and phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1), which encode a cytosolic E3 ubiquitin-protein ligase and a mitochondrial serine/threonine-protein kinase, account for clinically similar autosomal recessive early-onset forms of Parkinson's disease [31]. PINK1 and Parkin promote DRP1-dependent mitochondrial fission, and the outer mitochondrial adaptor MiD51 is required in DRP1 recruitment and Parkin -dependent mitophagy [32].

Diabetes, Obesity and Mitochondrial Dynamics

The accumulation of damaged or depolarized mitochondria in pancreatic β cells is associated with oxidative stress and the subsequent development of diabetes. Mitochondria in pancreatic β cells are continuously recruited in the fusion and fission processes [33]. In a cultured pancreatic β cell line (INS-1), high levels of glucose- and palmitate-induced mitochondrial fusion arrested and reduced respiratory function [34]. In INS1 cells, mitochondria with fission demonstrated reduced $\Delta\psi$ and decreased levels of the fusion protein OPA1. The inhibition of fission machinery proteins using DRP1 and FIS1 RNAi resulted in decreased mitochondrial autophagy, the accumulation of oxidized mitochondrial proteins, reduced respiration, and impaired insulin secretion, suggesting that selective fission of damaged mitochondria is followed by their removal by autophagy [35]. In another study, the beneficial aspects of fusion and mitochondrial networking were emphasized [36]. INS-1 cells were treated with palmitate and high glucose, and the fragmentation of mitochondria with reduced fusion activities was observed [36]. The application of FIS1 RNAi that shifts the dynamic balance to favor fusion is able to prevent mitochondrial fragmentation, maintain mitochondrial dynamics, and prevent apoptosis [36]. The roles of mitochondrial fusion and fission dynamics in the pancreatic β cells in animal models of diabetes [37] and the influence of insulin therapy [38] have not been fully explored, and more research is required to elucidate the significance of mitochondrial fusion and fission dynamics in the maintenance of pancreatic β cell function.

Obesity, type 2 diabetes, and aging are associated with impaired skeletal muscle oxidation, reduced mitochondrial contents, and lowered rates of OXPHOS [39]. Patients with type 2 diabetes and obesity demonstrated reduced expression of MFN2, which may be related to the reduced function of mitochondria in skeletal muscle [40]. In 17 obese subjects, 12 weeks of exercise improved insulin sensitivity and fat oxidation. Skeletal muscle biopsy demonstrated that decreased phosphorylation of DRP1 at serine 616 and the reduction of DRP1 Ser (616) phosphorylation were negatively correlated with increases in fat oxidation and insulin sensitivity [41]. In this study, there was a trend towards an increase in the expression of both MFN1 and MFN2 [41].

Recently, the role of MAMs has been highlighted in calcium, lipid, and metabolite exchange, although the ER and mitochondria play distinct cellular roles. Obesity leads to a marked reorganization of MAMs resulting in mitochondrial calcium overload, reduced respiratory function, and augmented oxidative stress [42]. In contrast, Disrupting the integrity of MAMs by knocking out cyclophilin D leads to hepatic insulin resistance through the disruption of inter-organelle

Ca^{2+} transfer, ER stress, mitochondrial dysfunction, lipid accumulation, the activation of c-Jun N-terminal kinase and PKCε [43]. Although MAMs are new therapeutic targets for treating insulin resistance in the liver under obese states [44], the target molecules for pharmaceutical intervention and the relation between MAMs and the fusion/fission dynamics of mitochondria need to be explored in future studies.

Pharmaceuticals Targeting Mitochondrial Biogenesis

Various physiological conditions with increased energy demand and decreased energy supply, such as acute stress and starvation, favor mitochondrial elongation with respiration coupled with ATP synthesis, while conditions with decreased energy demand and increased supply are associated with mitochondrial fragmentation with decreased coupling [45]. Although life style modification is the most fundamental therapy in patients with obesity and type 2 diabetes, pharmacological interventions targeting mitochondrial quality controls, including mitochondrial biogenesis and fusion and fission dynamics, are a promising area in the development of pharmaceuticals.

Various pharmacological activators of mitochondrial biogenesis such as AMPK activators, SIRT1 activators, nuclear receptor agonists, and cGMP modulators are beneficial for the treatment of obesity, type 2 diabetes, and vascular complications [5, 21]. Metformin is most commonly used in patients with type 2 diabetes; it was found to activate AMPK in skeletal muscle in rodents [46] and humans [46], and long-term administration of metformin was seen to increase the activity of PGC-1α [4]. In addition, metformin activates AMPK in human umbilical vein endothelial cells and reduces hyperglycemia-induced mitochondrial ROS production and mitochondrial biogenesis [47]. 5-aminoimidazole-4-carboxamide riboside (AICAR) acts as an AMP analogue and stimulates the oxidative metabolism as an exercise mimetic and also stimulates mitochondrial biogenesis [48]. However, AICAR demonstrates significant toxicity, as it can cause bradycardia and hypoglycemia [49].

Sirtuins are a family of protein deacetylase, and they are linked to mitochondrial biogenesis and mitochondrial function [21]. SIRT1 requires the oxidized coenzyme NAD^+ and it deacetylates PGC-1α, coactivates various nuclear-encoded mitochondrial genes via the activation of transcription factors such as NRFs and PPARs [5]. Resveratrol, a SIRT1 activator, has been shown to enhance mitochondrial biogenesis and to be beneficial in ameliorating glycemic control and insulin resistance [50]. The therapeutic potential of resveratrol is limited by its lower bioavailability, and so synthetic small molecules such as SRT1720 were developed [51]. SRT1720 expands both the mean and maximum life spans of mice fed a high-fat diet and is associated with reduced liver steatosis, increased insulin sensitivity, and normalization of markers for inflammation and apoptosis [52].

Various nuclear receptor agonists targeting ERRs and PPARs have been evaluated for their potency to regulate mitochondrial biogenesis and metabolism [21]. Estrogen 17β-estradiol (E2) is involved in mitochondrial functions such as ATP production, the generation of membrane potential, and mitochondrial biogenesis [53]. However, the clinical application of estrogens is limited by their gynecological and tumor-promoting effects. The development of a glucagon-like peptide-1-estrogen conjugate improved energy, glucose and lipid metabolism without the side effects of estrogen such as reproductive toxicity and oncogenicity [54]. Pan-PPAR (α, δ, and γ) agonist bezafibrate was known to stimulate fatty acid oxidation and peroxisome proliferation, and it also regulates mitochondrial function via PPARs and PGC-1α. Bezafibrate simulates PGC-1α expression, respiratory capacity, OXPHOS function, and mitochondrial DNA replication and biogenesis [55, 56]. PPARγ agonists such as rosiglitazone and pioglitazone are used for patients with type 2 diabetes to regulate mitochondrial biogenesis and oxidative mechanisms [57].

Pharmaceuticals Targeting Mitochondrial Fusion and Fission

Recently, the interest in the development of mitochondria-related drugs has been directed to mitochondrial dynamics such as mitochondrial fusion, fission, and mitophagy [23]. Mitochondrial division inhibitor-1 (mdivi-1) inhibits mitochondrial fragmentation by selectively inhibiting the assembly and GTPase activity of DRP1 in yeast and mammalian cells [58]. Smaller and shorter mitochondria and increased mitochondrial fission machinery were observed in the

skeletal muscle of mice with genetic obesity and in those with diet-induced obesity, and the inhibition of mitochondrial fission improved the muscle insulin signaling and systemic insulin sensitivity [59]. Although short-term and acute inhibition of the fission process is beneficial, long-term inhibition may inhibit cell proliferation and bioenergics in smooth muscle cells [60] and induce cancer-cell death [61, 62].

P110, a peptide inhibitor, reduces the enzyme activity of DRP1 and the interaction between DRP1 and FIS1 and inhibits aberrant mitochondrial fission [63]. P110 was found to be neuroprotective due to its ability to inhibit mitochondrial fission and ROS production and to the subsequent improvement in the mitochondrial membrane potential and mitochondrial integrity [63]. P110 is beneficial in neuronal diseases with mitochondrial dysfunction such as Parkinson's disease [63, 64] and in brain ischemia and reperfusion injuries [65].

Dynasore is a dynamin GTPase inhibitor of endocytic pathways that is known to prevent the division or formation of dynamin-dependent endocytic vesicles. Pretreatment with dynasore prevented ischemia/reperfusion-induced elevation of diastolic pressure in the left ventricular end in Langendorff-perfused mouse hearts [66]. Dynasore protects against cardiac lusitropy and limits cell damage through a mechanism that maintains mitochondrial morphology and intracellular ATP in stressed cells [66].

A diterpenoid derivative, 15-oxospiramilactone (S3), is an inhibitor of mitochondria-associated deubiquitinase USP30 and increases non-degradative ubiquitination of MFN1 and MFN2, which promote mitochondrial fusion activity [67]. S3 is also known as an inhibitor of Wnt/β-catenin signaling, and it inhibits the tumorigenesis of colon cancer cells [68].

Although abnormalities in mitochondrial fusion and fission dynamics in obesity and type 2 diabetes were observed in previous studies, it remained unexplored whether therapeutic interventions using mdivi-1, P110, dynasore, and S3 were truly beneficial or not. We generated AP2-promotor-driven Timm44 transgenic mice and fed them high-fat, high-sucrose (HFHS) chow. Timm44 anchors mitochondrial heat-shock protein 70 (mtHsp70) to the translocase of the inner mitochondrial membrane 23 (TIM23) complex and facilitates the import of mitochondria-targeted preproteins into the mitochondrial matrix dependent on the inner membrane potential and ATP hydrolysis in the ATPase domain of mtHsp70 [69]. The adipocyte size in Timm44 Tg mice was reduced, and mitochondrial fusion associated with decreased expression of fission genes, such as Dnm1l and Fis1, was observed in Timm44 Tg mice fed HFHS chow [69].

Pharmaceuticals Targeting Mitophagy

Pharmacological approaches to enhancing or blocking the specific targeting of injured mitochondria, mitophagy, are attractive strategies in the treatment of diabetic vascular complications such as myocardial infarction [70] and diabetic nephropathy [71]. The mitochondria-localized BNIP3 interacts with the autophagosome-localized LC3, suggesting that BNIP3, similar to BNIP3L (NIX), functions as a LC3-binding receptor in mitochondria [72]. Drugs that interfere with the binding of the LC3-interacting region of BNIP3 could be used to block the specific degradation of mitochondria, which may help prevent excessive cardiac atrophy following mechanical loading [70]. BNIP3 may also be targeted to enhance mitophagy and recovery following myocardial ischemia and reperfusion injuries [70]. The specific activation of Parkin/PINK1-mediated mitophagy may be beneficial in myocardial ischemia with fewer off-target effects [70].

The impairment of autophagy/mitophagy is a feature of diabetic nephropathy, and various compounds which inhibit the autophagy/mitophagy process have been identified, such as sirolimus (rapamycin), a mammalian target of rapamycin (mTOR) complex inhibitor [71]. Rapamycin protects against renal hypertrophy [73], glomerulosclerosis and proteinuria [74, 75], and mesangial expansion in rodent models [75, 76]. The beneficial effects of the specific activation of mitophagy by the BNIP3 or Parkin/PINK1 pathways in diabetic nephropathy have not yet been reported.

Conclusion

Mitochondrial biogenesis and the fusion process are impaired in diabetes and obesity, and they are promising pharmaceutical targets. For the stimulation of mitochondrial biogenesis, thiazolidinediones, fibrates, metformin, SRT1720, and rapamycin are good candidates. The inhibition of the fission process by Mdivi-1, P110, dynasore, and S3 is beneficial to shift the

mitochondria to fusion states, and it represents a future therapeutic strategy for the treatment of diabetes and obesity.

References

1. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW and Shulman GI: Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science (2003) 300: 1140–1142.
2. Bruce CR, Anderson MJ, Carey AL, Newman DG, Bonen A, Kriketos AD, Cooney GJ and Hawley JA: Muscle oxidative capacity is a better predictor of insulin sensitivity than lipid status. The J Clin Endocrinol Metab (2003) 88: 5444–5451.
3. Gurd BJ: Deacetylation of PGC–1alpha by SIRT1: importance for skeletal muscle function and exercise-induced mitochondrial biogenesis. Appl physiol Nutr Metab (2011) 36: 589–597.
4. Jager S, Handschin C, St-Pierre J and Spiegelman BM: AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC–1alpha. Proc Natl Acad Sci USA (2007) 104: 12017–12022.
5. Suliman HB and Piantadosi CA: Mitochondrial Quality Control as a Therapeutic Target. Pharmacological reviews (2016) 68: 20–48.
6. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I and Brownlee M: Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature (2000) 404: 787–790.
7. Kiritoshi S, Nishikawa T, Sonoda K, Kukidome D, Senokuchi T, Matsuo T, Matsumura T, Tokunaga H, Brownlee M and Araki E: Reactive oxygen species from mitochondria induce cyclooxygenase–2 gene expression in human mesangial cells:potential role in diabetic nephropathy. Diabetes (2003) 52: 2570–2577.
8. Sharma K: Mitochondrial hormesis and diabetic complications. Diabetes (2015) 64: 663–672.
9. Dugan LL, You YH, Ali SS, Diamond-Stanic M, Miyamoto S, DeCleves AE, Andreyev A, Quach T, Ly S, Shekhtman G, Nguyen W, Chepetan A, Le TP, Wang L, Xu M, Paik KP, Fogo A, Viollet B, Murphy A, Brosius F, Naviaux RK and Sharma K: AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. J Clin Invest (2013) 123: 4888–4899.
10. Ni HM, Williams JA and Ding WX: Mitochondrial dynamics and mitochondrial quality control. Redox Biol (2015) 4: 6–13.
11. Koshiba T, Detmer SA, Kaiser JT, Chen H, McCaffery JM and Chan DC: Structural basis of mitochondrial tethering by mitofusin complexes. Science (2004) 305: 858–862.
12. Song Z, Ghochani M, McCaffery JM, Frey TG and Chan DC: Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. Mol Biol Cell (2009) 20: 3525–3532.
13. Chan DC: Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev Genet (2012) 46: 265–287.
14. Krols M, van Isterdael G, Asselbergh B, Kremer A, Lippens S, Timmerman V and Janssens S: Mitochondria-associated membranes as hubs for neurodegeneration. Acta Neuropathol (2016) 131: 505–523.
15. Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J and Voeltz GK: ER tubules mark sites of mitochondrial division. Science (2011) 334: 358–362.
16. Gandre-Babbe S and van der Bliek AM: The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell (2008) 19: 2402–2412.
17. Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE and Ryan MT: MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO reports (2011) 12: 565–573.
18. Loson OC, Song Z, Chen H and Chan DC: Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol Biol Cell (2013) 24: 659–667.
19. Serasinghe MN, Seneviratne AM, Smrcka AV and Yoon Y: Identification and characterization of unique proline-rich peptides binding to the mitochondrial fission protein hFis1. J Biol Chem (2010) 285: 620–630.
20. Pernas L and Scorrano L: Mito-Morphosis: Mitochondrial Fusion, Fission, and Cristae Remodeling as Key Mediators of Cellular Function. Annu Rev Physiol (2015) 78: 505–531.
21. Whitaker RM, Corum D, Beeson CC and Schnellmann RG: Mitochondrial Biogenesis as a Pharmacological Target: A New Approach to Acute and Chronic Diseases. Annu Rev Pharmacol toxicol (2016) 56: 229–249.
22. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D and Groop LC: PGC–1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet (2003) 34: 267–273.
23. Jheng HF, Huang SH, Kuo HM, Hughes MW and Tsai YS: Molecular insight and pharmacological approaches targeting mitochondrial dynamics in skeletal muscle during obesity. Ann NY Acad Sci (2015) 1350: 82–94.
24. Valero T: Mitochondrial biogenesis: pharmacological approaches. Curr Pharm Des (2014) 20: 5507–5509.
25. Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F, Smith CL and Youle RJ: The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Dev Cell (2001) 1: 515–525.
26. Clerc P, Ge SX, Hwang H, Waddell J, Roelofs BA, Karbowski M, Sesaki H and Polster BM: Drp1 is dispensable for apoptotic cytochrome c release in primed MCF10A and fibroblast cells but affects Bcl–2 antagonist-induced respiratory changes. Br J Pharmacol (2014) 171: 1988–1999.
27. Zhang Z, Liu L, Wu S and Xing D: Drp1, Mff, Fis1, and MiD51 are coordinated to mediate mitochondrial fission during UV irradiation-induced apoptosis. FASEB J (2016) 30: 466–476.
28. Alavi MV and Fuhrmann N: Dominant optic atrophy, OPA1, and mitochondrial quality control: understanding mitochondrial network dynamics. Mol Neurodegener (2013) 8: 32.
29. Sugioka R, Shimizu S and Tsujimoto Y: Fzo1, a protein involved in mitochondrial fusion, inhibits apoptosis. J Biol Chem (2004) 279: 52726–52734.
30. Ashrafi G and Schwarz TL: The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ (2013) 20: 31–42.
31. Corti O, Lesage S and Brice A: What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev (2011) 91: 1161–1218.
32. Buhlman L, Damiano M, Bertolin G, Ferrando-Miguel R, Lombes A, Brice A and Corti O: Functional interplay between Parkin and Drp1 in mitochondrial fission and clearance. Biochim Biophys Acta (2014) 1843: 2012–2026.
33. Stiles L and Shirihai OS: Mitochondrial dynamics and morphology in beta-cells. Best Pract Res Clin Endocrinol Metab (2012) 26: 725–738.
34. Cerqueira FM, Chausse B, Baranovski BM, Liesa M, Lewis EC, Shirihai OS and Kowaltowski AJ: Diluted Sera From Calorie Restricted Animals Promote Mitochondrial Beta-Cell Adaptations and Protect Against Glucolipotoxicity. FEBS J (2016) 822–833.
35. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, Alroy J, Wu M, Py BF, Yuan J, Deeney JT, Corkey BE and Shirihai OS: Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J (2008) 27: 433–446.
36. Molina AJ, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, Walzer G, Twig G, Katz S, Corkey BE and Shirihai OS: Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. Diabetes (2009) 58: 2303–2315.
37. Gao Y, Li F, Zhang A, Wang L, Tong W and Liu B: Evaluation of mitochondrial divisions in mouse with type–2 diabetes and effect of glucose-oxidase on mouse islet cells RIN-m5F. Cell Biol Int (2014) 38: 368–373.
38. Santos RX, Correia SC, Alves MG, Oliveira PF, Cardoso S, Carvalho C, Duarte AI, Santos MS and Moreira PI: Insulin therapy modulates mitochondrial dynamics and biogenesis, autophagy and tau protein phosphorylation in the brain of type 1 diabetic rats. Biochim Physis Acta (2014) 1842: 1154–1166.
39. Civitarese AE and Ravussin E: Mitochondrial energetics and insulin resistance. Endocrinology (2008) 149: 950–954.
40. Zorzano A, Liesa M and Palacin M: Mitochondrial dynamics as a bridge between mitochondrial dysfunction and insulin resistance. Arch Physiol Biochem (2009) 115: 1–12.
41. Fealy CE, Mulya A, Lai N and Kirwan JP: Exercise training decreases activation of the mitochondrial fission protein dynamin-related protein–1 in insulin-resistant human skeletal muscle. J Appl Physiol (1985) (2014) 117: 239–245.
42. Arruda AP, Pers BM, Parlakgul G, Guney E, Inouye K and Hotamisligil GS: Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. Nat Med (2014)

20: 1427–1435.
43. Rieusset J, Fauconnier J, Paillard M, Belaidi E, Tubbs E, Chauvin MA, Durand A, Bravard A, Teixeira G, Bartosch B, Michelet M, Theurey P, Vial G, Demion M, Blond E, Zoulim F, Gomez L, Vidal H, Lacampagne A and Ovize M: Disruption of calcium transfer from ER to mitochondria links alterations of mitochondria-associated ER membrane integrity to hepatic insulin resistance. Diabetologia (2015) 59: 614–623.
44. Tubbs E, Theurey P, Vial G, Bendridi N, Bravard A, Chauvin MA, Ji-Cao J, Zoulim F, Bartosch B, Ovize M, Vidal H and Rieusset J: Mitochondria-associated endoplasmic reticulum membrane (MAM) integrity is required for insulin signaling and is implicated in hepatic insulin resistance. Diabetes (2014) 63: 3279–3294.
45. Liesa M and Shirihai OS: Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab (2013) 17: 491–506.
46. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ and Moller DE: Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest (2001) 108: 1167–1174.
47. Kukidome D, Nishikawa T, Sonoda K, Imoto K, Fujisawa K, Yano M, Motoshima H, Taguchi T, Matsumura T and Araki E: Activation of AMP-activated protein kinase reduces hyperglycemia-induced mitochondrial reactive oxygen species production and promotes mitochondrial biogenesis in human umbilical vein endothelial cells. Diabetes (2006) 55: 120–127.
48. Canto C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, Elliott PJ, Puigserver P and Auwerx J: AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity. Nature (2009) 458: 1056–1060.
49. Young LH, Li J, Baron SJ and Russell RR: AMP-activated protein kinase: a key stress signaling pathway in the heart. Trends Cardiovasc Med (2005) 15: 110–118.
50. Brasnyo P, Molnar GA, Mohas M, Marko L, Laczy B, Cseh J, Mikolas E, Szijarto IA, Merei A, Halmai R, Meszaros LG, Sumegi B and Wittmann I: Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr (2011) 106: 383–389.
51. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB, Vu CB, Bemis JE, Xie R, Disch JS, Ng PY, Nunes JJ, Lynch AV, Yang H, Galonek H, Israelian K, Choy W, Iffland A, Lavu S, Medvedik O, Sinclair DA, Olefsky JM, Jirousek MR, Elliott PJ and Westphal CH: Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature (2007) 450: 712–716.
52. Minor RK, Baur JA, Gomes AP, Ward TM, Csiszar A, Mercken EM, Abdelmohsen K, Shin YK, Canto C, Scheibye-Knudsen M, Krawczyk M, Irusta PM, Martin-Montalvo A, Hubbard BP, Zhang Y, Lehrmann E, White AA, Price NL, Swindell WR, Pearson KJ, Becker KG, Bohr VA, Gorospe M, Egan JM, Talan MI, Auwerx J, Westphal CH, Ellis JL, Ungvari Z, Vlasuk GP, Elliott PJ, Sinclair DA and de Cabo R: SRT1720 improves survival and healthspan of obese mice. Sci Rep (2011) 1: 70.
53. Duckles SP, Krause DN, Stirone C and Procaccio V: Estrogen and mitochondria: a new paradigm for vascular protection? Mol Interv (2006) 6: 26–35.
54. Finan B, Yang B, Ottaway N, Stemmer K, Muller TD, Yi CX, Habegger K, Schriever SC, Garcia-Caceres C, Kabra DG, Hembree J, Holland J, Raver C, Seeley RJ, Hans W, Irmler M, Beckers J, de Angelis MH, Tiano JP, Mauvais-Jarvis F, Perez-Tilve D, Pfluger P, Zhang L, Gelfanov V, DiMarchi RD and Tschop MH: Targeted estrogen delivery reverses the metabolic syndrome. Nat Med (2012) 18: 1847–1856.
55. Srivastava S, Diaz F, Iommarini L, Aure K, Lombes A and Moraes CT: PGC-1alpha/beta induced expression partially compensates for respiratory chain defects in cells from patients with mitochondrial disorders. Hum Mol Genet (2009) 18: 1805–1812.
56. Viscomi C, Bottani E, Civiletto G, Cerutti R, Moggio M, Fagiolari G, Schon EA, Lamperti C and Zeviani M: In vivo correction of COX deficiency by activation of the AMPK/PGC-1alpha axis. Cell Metab (2011) 14: 80–90.
57. Pardo R, Enguix N, Lasheras J, Feliu JE, Kralli A and Villena JA: Rosiglitazone-induced mitochondrial biogenesis in white adipose tissue is independent of peroxisome proliferator-activated receptor gamma coactivator-1alpha. PloS one (2011) 6: e26989.
58. Cassidy-Stone A, Chipuk JE, Ingerman E, Song C, Yoo C, Kuwana T, Kurth MJ, Shaw JT, Hinshaw JE, Green DR and Nunnari J: Chemical inhibition of the mitochondrial division dynamin reveals its role in Bax/Bak-dependent mitochondrial outer membrane permeabilization. Develop Cell (2008) 14: 193–204.
59. Jheng HF, Tsai PJ, Guo SM, Kuo LH, Chang CS, Su IJ, Chang CR and Tsai YS: Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol Cell Biol (2012) 32: 309–319.
60. Salabei JK and Hill BG: Mitochondrial fission induced by platelet-derived growth factor regulates vascular smooth muscle cell bioenergetics and cell proliferation. Redox Biol (2013) 1: 542–551.
61. Wang J, Hansen K, Edwards R, Van Houten B and Qian W: Mitochondrial division inhibitor 1 (mdivi-1) enhances death receptor-mediated apoptosis in human ovarian cancer cells. Biochem Biophys Res Commun (2015) 456: 7–12.
62. Wang J, Li J, Santana-Santos L, Shuda M, Sobol RW, Van Houten B and Qian W: A novel strategy for targeted killing of tumor cells: Induction of multipolar acentrosomal mitotic spindles with a quinazolinone derivative mdivi-1. Mol Oncol (2015) 9: 488–502.
63. Qi X, Qvit N, Su YC and Mochly-Rosen D: A novel Drp1 inhibitor diminishes aberrant mitochondrial fission and neurotoxicity. J Cell Sci (2013) 126: 789–802.
64. Su YC and Qi X: Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. Hum Mol Genet (2013) 22: 4545–4561.
65. Guo X, Sesaki H and Qi X: Drp1 stabilizes p53 on the mitochondria to trigger necrosis under oxidative stress conditions in vitro and in vivo. Biochem J (2014) 461: 137–146.
66. Gao D, Zhang L, Dhillon R, Hong TT, Shaw RM and Zhu J: Dynasore protects mitochondria and improves cardiac lusitropy in Langendorff perfused mouse heart. PloS one (2013) 8: e60967.
67. Yue W, Chen Z, Liu H, Yan C, Chen M, Feng D, Yan C, Wu H, Du L, Wang Y, Liu J, Huang X, Xia L, Liu L, Wang X, Jin H, Wang J, Song Z, Hao X and Chen Q: A small natural molecule promotes mitochondrial fusion through inhibition of the deubiquitinase USP30. Cell Res (2014) 24: 482–496.
68. Wang W, Liu H, Wang S, Hao X and Li L: A diterpenoid derivative 15-oxospiramilactone inhibits Wnt/beta-catenin signaling and colon cancer cell tumorigenesis. Cell Res (2011) 21: 730–740.
69. Wang Y, Katayama A, Terami T, Han X, Nunoue T, Zhang D, Teshigawara S, Eguchi J, Nakatsuka A, Murakami K, Ogawa D, Furuta Y, Makino H and Wada J: Translocase of inner mitochondrial membrane 44 alters the mitochondrial fusion and fission dynamics and protects from type 2 diabetes. Metabolism (2015) 64: 677–688.
70. Jimenez RE, Kubli DA and Gustafsson AB: Autophagy and mitophagy in the myocardium: therapeutic potential and concerns. Br J Pharmacol (2014) 171: 1907–1916.
71. Higgins GC and Coughlan MT: Mitochondrial dysfunction and mitophagy: the beginning and end to diabetic nephropathy? Br J Pharmacol (2014) 171: 1917–1942.
72. Shi RY, Zhu SH, Li V, Gibson SB, Xu XS and Kong JM: BNIP3 interacting with LC3 triggers excessive mitophagy in delayed neuronal death in stroke. CNS Neurosci Ther (2014) 20: 1045–1055.
73. Sakaguchi M, Isono M, Isshiki K, Sugimoto T, Koya D and Kashiwagi A: Inhibition of mTOR signaling with rapamycin attenuates renal hypertrophy in the early diabetic mice. Biochem Biophys Res Commun (2006) 340: 296–301.
74. Hartleben B, Godel M, Meyer-Schwesinger C, Liu S, Ulrich T, Kobler S, Wiech T, Grahammer F, Arnold SJ, Lindenmeyer MT, Cohen CD, Pavenstadt H, Kerjaschki D, Mizushima N, Shaw AS, Walz G and Huber TB: Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. J Clin Invest (2010) 120: 1084–1096.
75. Mori H, Inoki K, Masutani K, Wakabayashi Y, Komai K, Nakagawa R, Guan KL and Yoshimura A: The mTOR pathway is highly activated in diabetic nephropathy and rapamycin has a strong therapeutic potential. Biochem Biophys Res Commun (2009) 384: 471–475.
76. Yang Y, Wang J, Qin L, Shou Z, Zhao J, Wang H, Chen Y and Chen J: Rapamycin prevents early steps of the development of diabetic nephropathy in rats. Am J Nephrol (2007) 27: 495–502.