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Mitochondrial function in vascular endothelial cell in diabetes

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Abstract

Micro- and macrovascular complications are commonly seen in diabetic patients and endothelial dysfunction contributes to the development and progression of the complications. Abnormal functions in endothelial cells lead to the increase in vascular tension and atherosclerosis, followed by systemic hypertension as well as increased incident of ischemia and stroke in diabetic patients. Mitochondria are organelles serving as a source of energy production and as regulators of cell survival (*e.g.*, apoptosis and cell development) and ion homeostasis (*e.g.*, H^+, Ca^{2+}). Endothelial mitochondria are mainly responsible for generation of reactive oxygen species (ROS) and maintaining the Ca^{2+} concentration in the cytosol. There is increasing evidence that mitochondrial morphological and functional changes are implicated in vascular endothelial dysfunction. Enhanced mitochondrial fission and/or attenuated fusion lead to mitochondrial fragmentation and disrupt the endothelial physiological function. Abnormal mitochondrial biogenesis and disturbance of mitochondrial autophagy increase the accumulation of damaged mitochondria, such as irreversibly depolarized or leaky mitochondria, and facilitate cell death. Augmented mitochondrial ROS production and Ca^{2+} overload in mitochondria not only cause the maladaptive effect on the endothelial function, but also are potentially detrimental to cell survival. In this article, we review the physiological and pathophysiological role of mitochondria in endothelial function with special focus on diabetes.

Keywords

fission and fusion; biogenesis; mitophagy; apoptosis; complications

Introduction

Diabetes is a metabolic disorder characterized by glucose intolerance and hyperglycemia due to deficiency of insulin and/or loss of effectiveness to insulin action. There are two main types of diabetes: Type-1 diabetes and Type-2 diabetes. Type-1 diabetes mellitus is mainly caused by autoimmune destruction of the beta cells in the islets of pancreas, where insulin is secreted upon glucose absorption. The patients with Type-1 diabetes exhibit lower or loss of plasma insulin and are characterized by total reliance on exogenous insulin for survival. On the other hand, Type-2 diabetic patients still produce and secrete insulin. However, they develop diabetes because of insufficient production/secretion of insulin and/or improper utilization of insulin (called insulin resistance). Type-1 diabetes usually develops in children or in young adults, whereas Type-2 diabetes mellitus is mainly seen in people over the age of 45 and accounts for nearly 90–95 percent of all diabetes cases. Not surprisingly, the

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prevalence of Type-2 diabetes in children and adolescents is growing worldwide, which correlates with obesity rate in the population (Rosenbloom, 1999; Broomgarden, 2004).

The common complications of diabetes are heart disease, hypertension, stroke, retinopathy, nephropathy, and neuropathy. Heart disease includes coronary artery disease and cardiac myopathy, which are the risk factors of the heart failure, and it is the leading cause of mortality and morbidity in patients with diabetes. Coronary artery disease is the result from narrowing the diameter of small coronary arteries by atherosclerotic lesion and increased coronary arterial tension. Hypertension is the most common complication in diabetic patients and is induced by increased vascular reactivity in the resistant arteries (*e.g.*, mesenteric artery). Stroke and retinopathy are also caused by abnormal vascular reactivity. Endothelial cells serve as a key player in the development of these diseases. Vascular endothelium, which is a monolayer lining the inner surface of the blood vessels, plays an important role in *a*) vascular barrier function, which prevents the migration of inflammatory cells and fluid leakage into vascular media (Rao *et al.*, 2007; Dejana *et al.*, 2009), *b*) regulating vascular tone by releasing vasoconstrictors and vasodilators (Conger, 1994; Esper *et al.*, 2006; Dora, 2010), and *c*) new vascular formation (Carmeliet, 2000; Madeddu, 2005). Endothelial dysfunction is implicated in many cardiovascular diseases including diabetes. It has been shown that in diabetic patients, as well as in diabetic animal models, 1) vascular tension is increased by attenuated endothelium-dependent relaxation and increased release of vasoconstrictors from endothelium cells (Hink *et al.*, 2001; Vinik and Flemmer, 2002; Farhangkhoee *et al.*, 2006; Hermans, 2007), 2), vascular inflammation is augmented via increased endothelial permeability (Zhang *et al.*, 2003; Spinetti *et al.*, 2008) and surface adhesion molecules (Baumgartner-Parzer *et al.*, 1995; Zou *et al.*, 2002; Savoia and Schiffrin, 2007), and 3) endothelial apoptosis is increased, which is a main cause of the blood-retina barrier breakdown (Kern, 2007; Barber *et al.*, 2011) and the decrease in capillary density in the heart (Yoon *et al.*, 2005).

The mitochondria play a critical role in cell survival and death by regulating ATP synthesis through lipid and glucose metabolism, ROS generation, calcium homeostasis, apoptosis stimulation, and aging (McBride *et al.*, 2006; Contreras *et al.*, 2010). Therefore, the abnormal function of mitochondria leads to various cardiovascular diseases (Duchen, 2004; Ballinger, 2005; Davidson and Duchen, 2007). Endothelial cells produce the energy mainly via the anaerobic glycolytic metabolism of glucose but not through the mitochondrial ATP synthesis (Culic *et al.*, 1997; Quintero *et al.*, 2006), it is thusendothelial mitochondria are more like the sensor and initiator of the cell death. In this article, we will review the mitochondrial functions in the vascular endothelial cells and the pathophysiological role of mitochondria in endothelial dysfunction in diabetes mellitus.

Mitochondrial fusion and fission

1) Mitochondrial fusion- and fission-related proteins—Mitochondria are complex organelles that move, fuse, divide, and constantly change their volume/structure upon physiological stimulus and any stress (Frazier *et al.*, 2006; Bereiter-Hahn *et al.*, 2008). The definition of mitochondrial fission is the division of a mitochondrion within a cell to form two or more separate mitochondrial compartments, whereas mitochondrial fusion is merging two or more mitochondria within a cell to form a single compartment. Increased mitochondrial fission and decreased mitochondrial fusion result in the mitochondrial fragmentation (Detmer and Chan, 2007; Knott *et al.*, 2008).

In mammals, mitochondrial fusion is regulated by at least three proteins: optic atrophy 1 (OPA1), mitofusin 1 (MFN1), and mitofusin 2 (MFN2) (Cipolat *et al.*, 2004), whereas mitochondrial fission is controlled by dynamin related protein 1 (DRP1/DLP1/DNM1) and fission 1 (FIS1) (Yoon *et al.*, 2003) (Fig. 1). A recent study identified another tail-anchored

mitochondrial outer membrane protein, mitochondrial fission factor (MFF) (Gandre-Babbe and van der Bliek, 2008), and the physiological function of MFF is for the recruitment of DRP1 to the mitochondrial membrane (Otera *et al.*, 2010). Classically, FIS1 was the only one that recruits DRP1 from the cytosol to mitochondria upon the fission reaction (Mozdy *et al.*, 2000; Yoon *et al.*, 2003). OPA1 is located in the inner-mitochondrial membrane, and MFN1 and MFN2 are localized to the outer mitochondrial membrane. During mitochondrial fusion, OPA1 interacts with MFN1 and MFN2 (Cassina *et al.*, 2000; Olichon *et al.*, 2006). These proteins are first found to be related to neuropathy (Delettre *et al.*, 2000; Zuchner *et al.*, 2004; Ferre *et al.*, 2005).

The function of fission/fusion-related proteins is regulated by various regulators, cleavage of the protein, posttranslational modifications, protein-protein interactions, and the lipid environment. GTP hydrolysis is required for fission/fusion-related proteins to be activated (Chan, 2006). DRP1 activity is negatively controlled by cyclic AMP. Phosphorylated DRP1 by cyclic AMP-dependent protein kinase increases the mitochondrial tubular formation, whereas dephosphorylation of DRP1 by calcineurin increases mitochondrial fission (Cribbs and Strack, 2007). OPA1 exhibits both long and short forms for fusion to proceed and the balance of those forms is maintained by constitutive processing. There are two cleavage sites in OPA1, S1 and S2, and YME1L (an intermembrane space AAA protease) cleaves OPA1 at the site of S2 constitutively following mitochondrial import, whereas the loss of mitochondrial membrane potential leads to the cleavage of the S1 site by OMA1 (zinc metalloprotease), which is followed by complete conversion of OPA1 to the short isoform and shutting off mitochondrial fusion (Griparic *et al.*, 2007; Song *et al.*, 2007; Head *et al.*, 2009). Various posttranscriptional modifications of proteins regulate the activity of the fusion and fission machineries. MARCH5, a ubiquitin ligase in the outer membrane, associates with and ubiquitylates MFN1, MFN2, DRP1, and FIS1 (Yonashiro *et al.*, 2006; Park *et al.*, 2010). Although MARCH5 binds to both fission and fusion related proteins, knockdown of MARCH5 induces the mitochondrial elongation via notable accumulation of MFN1 protein (Park *et al.*, 2010). DRP1 is sumoylated by mitochondrial-anchored protein ligase (MAPL, small ubiquitin-like modifier [SUMO] ligase) (Braschi *et al.*, 2009) and desumorylated by sentrin-specific protease 5 (SENP5) (Zunino *et al.*, 2007). Sumoylation of DRP1 stimulates mitochondrial fission (Harder *et al.*, 2004; Zunino *et al.*, 2007; Braschi *et al.*, 2009). We have recently reported that high-glucose treatment leads to *O*-GlcNAcylation of OPA1 and mitochondrial fragmentation, while an inhibition of *O*-GlcNAcylation by overexpression of GlcNAcase decreases the mitochondrial fragmentation induced by high glucose (Makino *et al.*, 2011). S-nitrosylation of DRP1 results in mitochondrial fission (Cho *et al.*, 2009).

An imbalance in the fusion/fission dynamics dramatically changes overall mitochondrial morphology (Bereiter-Hahn and Voth, 1994). Recent evidence from our laboratory, as well as others, has shown that mitochondrial dynamics play important roles in mitochondrial functions, including cell development, apoptosis, ROS generation and functional complementation of mitochondrial DNA (mtDNA) mutations by context mixing (Nakada *et al.*, 2001; Frazier *et al.*, 2006; Makino *et al.*, 2010). Mitochondrial fission is essential for appropriate redistribution of mtDNA during cell division (Scott *et al.*, 2003; Hales, 2004; Taguchi *et al.*, 2007). In addition, damaged mitochondria are removed by mitophagy through mitochondrial fission (Twig *et al.*, 2008a; Twig *et al.*, 2008b). Fusion also influences mitochondrial distribution in neural cells (Chen *et al.*, 2007). Fused mitochondrial networks serve as electrically united systems that transmit the membrane potential generated by the proton pumps of the respiratory chain (Amchenkova *et al.*, 1988; Skulachev, 2001) and also facilitate the propagation of Ca^{2+} wave and energy transfer in the cells (Szabadkai *et al.*, 2004; Jou, 2008). Mitochondrial fusion is dramatically increased when mitochondrial ATP synthesis is enhanced (Tondera *et al.*, 2009). The damaged/depolarized parts of the

mitochondrial membrane are recovered by mitochondrial fusion that facilitates proper mixing of mtDNA and metabolites (Nakada *et al.*, 2001; Twig *et al.*, 2008b).

2) Other factors which induces mitochondrial fragmentation—The endoplasmic reticulum (ER) is an intracellular Ca^{2+} store and releases Ca^{2+} via Ca^{2+} releasing channels upon the stimulation. The mitochondria are located close to the ER to support communication between them such as the transferring lipids, and the exchange of calcium and ATPs (Vance and Shiao, 1996; Mannella *et al.*, 1998; Hayashi *et al.*, 2009; Rizzuto *et al.*, 2009). At the pathological condition, Ca^{2+} release from the ER causes calcium overload in the mitochondria and leads to mitochondrial fragmentation via facilitating the DRP1 translocation to the mitochondrial outer membrane (Breckenridge *et al.*, 2003).

Mitochondria constantly generate ROS via the electron transport chain reaction. At the physiological condition, majority of molecular oxygen is converted to water and less than 5% of the oxygen is incompletely reduced to O_2^-. Massive ROS production in the mitochondria is implicated in various cardiovascular diseases (Griendling and FitzGerald, 2003; Sugamura and Keaney, 2011), whereas ROS leads to the mitochondrial fragmentation in many cell types like rat cardiac myocytes (Yu *et al.*, 2008; Fan *et al.*, 2010), and mouse coronary endothelial cells (Makino *et al.*, 2010). These data imply that mitochondrial fragmentation is enhanced by excess ROS production in pathophysiological condition.

3) Mitochondrial morphological change in endothelial cells in diabetes—There is increasing evidence showing that mitochondrial morphology is sensitive to the metabolic properties. The exposure of high glucose to endothelial cells *ex vivo* increases mitochondrial fragmentation (Makino *et al.*, 2010; Trudeau *et al.*, 2010; Shenouda *et al.*, 2011). We demonstrate that mouse coronary endothelial cells isolated form Type-1 diabetic mice exhibit more fragmented mitochondrial structure and lower DRP1 protein expression levels than endothelial cells from control mice (Makino *et al.*, 2010). The study examining the mitochondrial morphology using venous endothelial cells isolated from patients with Type-2 diabetes shows that FIS1 protein expression level and mitochondrial fragmentation are significantly increased in endothelial cells from diabetic patients compared with cells from control patients (Shenouda *et al.*, 2011). Interestingly, mitochondria in retina endothelial cells are more elongated in the diabetic rat compared to the control rat; although MFN2 protein expression level is significantly decreased and DRP1 expression level is increased in diabetes, implying that the mitochondrial morphological change might be regulated by not fission-fusion related proteins in this case (Zhong and Kowluru, 2011).

4) Altered mitochondrial morphology in other cell types in diabetes—The exposure of free fatty acid to the C2C12 muscle cells augments mitochondrial fragmentation via increased DRP1 and FIS1 protein expression levels andmitochondrial in skeletal muscles in obesity and Type-2 diabetic mice are more fragmented (Jheng *et al.*, 2012). In Type-2 diabetic patients, MFN2 protein expression level is decreased in skeletal muscle compared with control patients (Zorzano *et al.*, 2009). High glucose treatment increases mitochondrial fragmentation (Yu *et al.*, 2008; Makino *et al.*, 2011) via decreased OPA1 protein expression in the neonatal cardiac myocyte (Makino *et al.*, 2011). High glucose or high insulin treatment increases the protein expression of DRP1 and enhances mitochondrial fragmentation in adult dorsal root ganglion neurons, suggesting that mitochondrial morphological change might contribute to the neuropathy in Type 2 diabetes (Vincent *et al.*, 2010). *Ex vivo* high glucose treatment leads to mitochondrial fragmentation in β-cell via increase in DRP1 protein expression (Men *et al.*, 2009). Mitochondria in β-cell from Type-2 diabetic rat exhibit more fragmented structure than that in control (Dlaskova *et al.*, 2010). Mitochondrial fission- and fusion-related proteins are cloned during the last decade and we

expect to see more functional roles of these proteins in diabetic complications in the next decade.

Mitochondrial biogenesis

1) Proteins related with mitochondrial biogenesis—The cells undergo mitochondrial biogenesis process in response to varied physiological stimulus and tissue- or signal-specific modification of mitochondrial gene expression and function. Mitochondrial biogenesis is a complex process that involves the synthesis, import, and incorporation of proteins and lipids to the existing mitochondrial reticulum, as well as replication of the mtDNA (Lopez-Lluch *et al.*, 2008). Upon the stimulation of mitochondrial biogenesis, mitochondrial genes in the nucleus and in mitochondria will be transcribed. Majority of genes required for mitochondrial biogenesis and function are in the nucleus, and the few genes crucial for oxidative phosphorylation, are on the mitochondrial gene. The peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is the nucleus genome-encoded protein and a transcriptional coactivator of nuclear respiratory factor (NRF)-1, GA-binding protein (GABP) (also known as NRF-2), and peroxisome proliferator-activated receptors (PPARs) (Puigserver *et al.*, 1998; Wu *et al.*, 1999; Duncan *et al.*, 2007). The activation of NRF-1 and 2 by PGC-1α leads to the expression of mitochondrial transporters, mitochondrial ribosomal proteins, oxidative phosphorylation components, and mitochondrial transcription factor (TFAM) (Feige and Auwerx, 2007; Scarpulla, 2008). PPARs regulate a broad set of genes which are required for lipid homeostasis and glucose and lipid oxidation (Djouadi *et al.*, 1998; Burkart *et al.*, 2007; Yang and Li, 2007).

PGC-1α activity is regulated by various kinds of posttranslational modifications. Phosphorylation is required for the activation of PGC-1α and its phosphorylation is regulated by AMP-activated protein kinase (Jager *et al.*, 2007), mitogen-activated protein kinase p38 (Knutti *et al.*, 2001; Akimoto *et al.*, 2005), and glycogen synthase kinase-3 (GSK-3) (Anderson *et al.*, 2008), acetylation by Sirtuin 1 (SIRT1) (Rodgers *et al.*, 2005; Gerhart-Hines *et al.*, 2007), and arginine methylation by protein arginine N-methyltransferase1 (PRMT1) (Teyssier *et al.*, 2005). In the muscle cells, the increase in cytosolic Ca^{2+} leads to PGC-1α activation through Ca^{2+}/calmodulin-dependent kinases and p38 activation (Ojuka *et al.*, 2003; Wright *et al.*, 2007). Nitric oxide (NO) increases PGC-1α expression via cyclic GMP dependent pathway (Nisoli *et al.*, 2003). On the other hand, PGC-1α is negatively regulated via deacetylation by GCN5 (Lerin *et al.*, 2006) and ubiquitination by SCF^{cdc4} (Olson *et al.*, 2008). 2) Mitochondrial biogenesis in endothelial cells in diabetes

Since the energy in endothelial cells is mainly generated by glycolytic metabolism instead of via mitochondrial ATP synthesis, mitochondrial biogenesis is not as critical as in muscle cells or in adipocytes. It is, however, important to maintain the good quality and quantity of mitochondria in endothelial cells for cell survival. mtDNA copy number, PGC-1α and NRF-1 protein expression in nuclear extract, PGC-1α activity, and TFAM protein expression level in mitochondria are commonly used to determine the mitochondrial biogenesis. Hyperglycemia significantly decreases PGC-1α protein expression in retinal endothelial cells (Zheng *et al.*, 2010). Santos *et al.* (2011) demonstrate that retinal mtDNA copy number is decreased in Type-1 diabetic mice and the mitochondrial number is lowered in retina in diabetic patient, and in retinal endothelial cells treated with high glucose.

PPARγ activator, thiazolidinedione (TZD), is approved for use in Type-2 diabetic patients to improve insulin sensitivity by several mechanisms, including increased uptake and metabolism of free fatty acids in adipose tissue (Saltiel and Olefsky, 1996; Spiegelman, 1998; Kalaitzidis *et al.*, 2009). Recent reports demonstrate that TZD induces mitochondrial biogenesis via the activation of PGC-1α in human umbilical vein endothelial cells (Fujisawa

et al., 2009) and other cell types (see next paragraph). PGC-1α is the coactivator of PPARγ and the activation of PPARγ by TZD induces PGC-1α expression. Further studies are required to identify the role of TZD on mitochondrial biogenesis and the regulatory mechanisms of the positive feedback by PPARγ activation in endothelial cells.

3) Mitochondrial biogenesis in other cell types in diabetes—mtDNA copy number and mRNA expression of PGC-1α and TFAM are significantly decreased in aorta from Type-2 diabetic mice compared with the control (Csiszar *et al.*, 2009). Lowered mtDNA copy number is observed in skeletal muscle from the patient with Type-2 diabetes (Hsieh *et al.*, 2011) and muscles from Type-2 diabetic rats compared with the control (Shen *et al.*, 2008). On the other hand, it has been reported that there is increased mitochondrial area, mitochondrial number and mtDNA in the heart of Type-1 diabetic mice, but the function of mitochondrial is attenuated (Shen *et al.*, 2004).

PGC-1α is induced by TZD in white and brown adipocyte cells (Wilson-Fritch *et al.*, 2004; Hondares *et al.*, 2006), and neuronal cells (Miglio *et al.*, 2009). The adipose tissue obtained from the patient with Type-2 diabetes exhibits lower mitochondrial number and TFAM mRNA expression level compared with the control; and TZD treatment restores the mitochondrial abnormality (Bogacka *et al.*, 2005; Hakansson *et al.*, 2011). Mitochondrial biogenesis is significantly attenuated in adipose tissue from Type-2 diabetic mice compared with the control, whereas TZD increases PGC-1α mRNA expression and restores the mitochondrial biogenesis in diabetic mice (Rong *et al.*, 2007). PGC-1β also serves as a key regulator in energy metabolism by promoting mitochondrial biogenesis. There is increasing evidence showing that TZD enhances mitochondrial biogenesis by increase in PGC-1β expression, but not PGC-1α, in adipocyte cells (Deng *et al.*, 2011; Pardo *et al.*, 2011) and osteocytes (Wei *et al.*, 2010).

Mitochondrial autophagy/mitophagy

1) Molecular mechanisms of mitophagy—Autophagy is cellular degradation system through their encapsulation by a double membrane structure called as an autophagosome (Kelekar, 2005). There are two types of autophagy, non-selective autophagy and cargo-specific autophagy. At the low level of energy demand or at the starvation condition, cells undergo non-selective autophagy to supply/re-use the metabolic component and energy by degradation of their organelles, whereas the cargo-specific autophagy could be initiated independent from the nutrient level (Kundu and Thompson, 2005; Komatsu and Ichimura, 2010; Rabinowitz and White, 2010). The selective elimination of mitochondria is called mitophagy (Lemasters, 2005). The purpose of mitophagy is primarily 1) to maintain the mitochondrial integrity in the cells and 2) to eliminate the damaged mitochondria (Narendra *et al.*, 2008; Twig *et al.*, 2008a). The excess amount of mitochondria at the low energy demand is the source of excessive ROS. The damaged mitochondria release various apoptosis-promoting factors and lead to further damage of neighboring mitochondria and entire cell (Crompton *et al.*, 1999). Therefore, mitophagy is the well-designed cytoprotective pathway.

Depolarized mitochondrial membrane is the hallmark of damaged mitochondria and sustains the mitochondrial fission status (Song *et al.*, 2007; Twig *et al.*, 2008a). Mitochondrial fusion is the physiological function to fuse the damaged membrane with intact membrane and minimize the damage. Damaged mitochondria that failed to be fused will be the target of the mitophagy. The PTEN-induced putative kinase protein 1 (PINK1) is a voltage-sensitive kinase and it will be accumulated on the outer membrane in the mitochondrial upon the membrane depolarization (Narendra *et al.*, 2008; Jin *et al.*, 2010; Matsuda *et al.*, 2010). The accumulation of PINK1 facilitates the recruitment of Parkin, an E3 ubiquitin ligase, to the

mitochondrial surface (Sha *et al.*, 2010; Vives-Bauza *et al.*, 2010). Ubiquitinated mitochondrial proteins by Parkin interact with the autophagy adaptor p62, and subsequently lead to the autophagosomal degradation of the mitochondria (Geisler *et al.*, 2010; Okatsu *et al.*, 2010) (Fig. 2). Another protein which regulates mitophagy in mammalian cells is NIX (Kanki, 2010), although detailed mechanism is not clear.

Extensive damage by sustained membrane depolarization facilitates the opening of the mitochondrial permeability transition pore (mPTP), increases mitochondrial membrane permeability and releases of pro-apoptotic molecules, and results in cell apoptosis. This will be described in the following section (4. Mitochondria-induced cell apoptosis).

The autophagy induced by starvation (non-selective autophagy) is mediated by mammalian target of rapamycin (mTOR)/AMP-activated protein kinase (AMPK) pathway. At the high nutrient, mTOR phosphorylates UNC-51-like kinase (ULK) that has inhibitory effects on the kinase activity of ULK. Starvation increases AMPK activation, which promotes mTOR inhibition and activates ULK, and subsequently leads to autophagy (Lee *et al.*, 2010; Egan *et al.*, 2011; Kim *et al.*, 2011). It has to be noted that AMPK increases SIRT1 activity, which deacetylates PGC-1, and results in mitochondrial biogenesis as described above (2. Mitochondrial biogenesis). Therefore, mitochondrial autophagy and biogenesis are coordinately regulated.

There are other factors which possibly regulate the autophagy, including ROS and Bcl2. During autophagic process, autophagy-regulating protein (ATG) 8 conjugates to the autophagosomal membrane through an ubiquitin-like conjugation system. ATG4 negatively regulates ATG8 function by cleavage of ATG8, which releases ATG8 from the autophagosomal membrane and inhibits autophagy (Kaminskyy and Zhivotovsky, 2012). ATG4is redox sensitive and oxidation of ATG4 inhibits the cleavage activity of ATG4 and stabilizes the ATG8-mediated autophagosomal expansion (Scherz-Shouval *et al.*, 2007). Beclin1, the mammalian ortholog of yeast ATG6, was identified as a Bcl-2-interacting protein (Kabeya *et al.*, 2000) and it induces the formation of autophagosomes and promotes autophagy (Sinha and Levine, 2008). Anti-apoptotic protein Bcl-2 binds to Beclin1 and inhibits autophagy (Pattingre *et al.*, 2005; Kang *et al.*, 2011).

2) Mitophagy in diabetes—Interestingly, there is no report which demonstrates the change in mitochondrial autophagy/mitophagy in endothelial cells in diabetes. The exposure of oxidized LDL (ox-LDL) leads to autophagic pathway in HUVECs and HMECs (Zhang *et al.*, 2010; Muller *et al.*, 2011). High-glucose treatment augments autophagy in H9c2 cardiomyoblasts via increase in Beclin1 and LC3 protein expression level (Younce *et al.*, 2010). Cardiac myocytes in Type-1 diabetic mice exhibits decreased autophagy determined by the number of autophagic vacuoles number in the cells (Xie *et al.*, 2011), whereas skeletal muscles from Type-2 diabetic rat show increased autophagy assessed by the protein expression level of LC3 and Beclin1 (Yan *et al.*, 2011). Mitochondrial autophagy is increased in pancreatic cell of Type-2 diabetic mice (Lo *et al.*, 2010) and in adipose tissue in Type-2 diabetic patients (Ost *et al.*, 2010). The reason for these inconsistent results might be due to the differences of the diabetic model, tissues used for the experiments, and methods to determine the mitochondrial autophagy.

Mitochondria-induced cell apoptosis

Mitochondria serve as the key organelles which maintain the cell function via generating ATP, regulating cellular Ca^{2+} homeostasis and heme biosynthesis, whereas mitochondria also determine the cell fate, as well as terminate the cell life, through several mitochondria-induced cell apoptosis pathways. In this section, we discuss the cell apoptosis pathway

induced by mitochondria (*e.g.*, regulation of Bcl-2 protein family, mitochondrial ROS generation and mitochondrial Ca^{2+} overload).

1) Mitochondria-mediated apoptosis—There are two main apoptotic pathways: the extrinsic pathway and intrinsic pathway (Fig. 3). The extrinsic pathway is initiated by the binding of the ligands to the cell surface-specific receptors, called “death receptors”, whereas the intrinsic pathway is initiated by mitochondria. Both pathways are overlap at the point of mitochondrial outer membrane permeabilization (MOMP). MOMP is triggered by the formation of pores in the outer mitochondrial membrane (OMM) and the Bcl-2 protein family regulates the pore formation. Bcl-2 protein families can be classified into four groups based on their functions: 1) effectors whose oligomerization creates pores [Bax and Bak], 2) inhibitors of Bax and Bak [Bcl-2, Mcl1 and BclxL], 3) activators of Bax and Bak [Bid and Bim], and 4) sensitizers which antagonize antiapoptotic Bcl-2 like proteins [Bad, Bik, Noxa and Bmf]. The extrinsic pathway involves formation of a death-inducing signal complex (DISC) in the plasma membrane. DISCs contain multiple adaptor proteins that recruit and promote the activation of initiator procaspases, including procaspase 8. Activated caspase 8 induces cell apoptosis through two pathways; 1) direct cleavage of procaspase 3 followed by the cleavage of a variety of substrates and the cell apoptosis, 2) truncation of Bid to tBid, which leads to Bax/Bak oligomers, creates pores in OMM, and releases proapoptotic peptides such as cytochrome *c* (Liu *et al.*, 1996), apoptosis inducing factor(AIF) (Susin *et al.*, 1999), endonuclease G (EndoG) (Li *et al.*, 2001), Smac/Diablo (Du *et al.*, 2000), Omi/HtrA2 (Hedge *et al.*, 2002). These molecules activate both caspase dependent and independent cell death pathways (Donovan and Cotter, 2004).

The intrinsic pathway involves both MOMP and the opening of the mPTP. The mPTP is a transmembrane channel formed between the inner and outer mitochondrial membranes and composed of voltage-dependent anion channel (VDAC) in OMM, adenine nucleotide translocator (ANT) in the inner mitochondrial membrane, and cyclophilin D in the mitochondrial matrix (Crompton *et al.*, 1999; Halestrap and Pasdois, 2009). VDAC is a bidirectional transporter and permeable to solutes of up to 5 kDa. At the physiological condition, VDAC serves as a shuttle of respiratory chain substrates such as ATP. On the other hand, ANT is impermeable under normal conditions. During apoptosis, excess Ca^{2+} influx triggers the increase of ANT conductivity, followed by an inward flux of protons and ions through ANT. The increase in matrix osmolality leads to water influx, mitochondrial swelling, and apoptogenic protein release from the mitochondrial storage to the cytosol though the mPTP opening, BAX/BAK-VDAC channel, and or ruptured OMM (Ott *et al.*, 2002; Tsujimoto and Shimizu, 2002; Baines, 2011). It has been reported that the opening of mPTP is regulated by Bcl-2 and pH change in inner mitochondrial membrane (Matsuyama and Reed, 2000).

2) Mitochondrial O_2^- generation and apoptosis—Mitochondria continuously generate superoxide anion (O_2^-) through reduction of molecular oxygen by the electron transport chain to produce superoxide. The electron transport chain (ETC) is composed of four multiple subunit complexes; complex I (NADH-ubiquinone oxidoreductase), II (succinate-dehydrogenease), III (ubiquinol-cytochrome *c* oxidoreductase), and IV (cytochrome *c* oxidase), and the main function is to oxidize NADH and $FADH_2$ to NAD^+ and FAD^+, that will be used in the tricarboxylic acid cycle (TCA cycle) to generate ATPs. The protons transported across the membrane in the ETC will serve as a motive force in complex V to synthesize ATPs. O_2^- is primarily generated at complexes I and III; complex I releases O_2^- predominately into the matrix, while complex III releases O_2^- to both sides of the mitochondrial inner membrane (Han *et al.*, 2001; Muller *et al.*, 2004; Lenaz *et al.*, 2006). O_2^- is dismutated to hydrogen peroxide by CuZn-superoxide dismutase (SOD, in the inter-membrane space and cytosol) and Mn-SOD (in the matrix) (Faraci and Didon, 2004), and

subsequently reduced to water by catalase (in the cytosol) and glutathione peroxidase (in mitochondria and cytosol) (Chance *et al.*, 1979; Phung *et al.*, 1994). Majority of O_2^- is reduced to water and very few O_2^- is leaked out from the ETC in normal cells, whereas excess O_2^- production in mitochondria is implicated in the pathogenesis of cardiovascular diseases (Li and Shah, 2004; Ballinger, 2005).

mtDNA is more sensitive than genomic DNA to ROS-induced damage, as it is not protected by histones and its repair capabilities are limited (Wei and Lee, 2002). Damaged mtDNA promotes outer membrane permeabilization and the release of cytochrome c, AIF, or Smac/Diablo from mitochondria to the cytosol and leads to cell apoptosis (Ryter *et al.*, 2007). ROS also stimulates the extrinsic or intrinsic apoptotic signaling via activation of JNK (Dhanasekaran and Reddy, 2008). The translocation of activated JNK to nuclear initiates activator protein 1-mediated expression of proapoptotic factors, such as TNFα, FasL, and Bak (Fan *et al.*, 2001), while the translocation to mitochondria promotes to release cytochrome *c* (Kharbanda *et al.*, 2000). Furthermore, the interaction of ROS with NO regulates the cell apoptotic pathway (Cassina *et al.*, 2000; Jang and Han, 2006; Nakagawa *et al.*, 2007; Wang *et al.*, 2008). 3) Mitochondrial Ca^{2+} homeostasis and apoptosis

There are several Ca^{2+}-sensitive intramitochondrial enzymes that regulate physiological cell functions (*e.g.*, pyruvate dehydrogenase phosphate phosphatase, NAD^+-isocitrate dehydrogenase) (McCormack and Denton, 1984). It is thus important to maintain appropriate level of Ca^{2+} in the mitochondrial for their routine work, while Ca^{2+} overload in mitochondria causes the maladaptive effect on mitochondrial function, as well as cell function, and it is implicated in variety of different disease processing (Esper *et al.*, 2006; Halestrap and Pasdois, 2009). Mitochondrial Ca^{2+} overload leads to an opening of mPTP and it is followed by cell apoptosis and necrosis (see details in the section 4.1.). Excess mitochondrial $[Ca^{2+}]$ causes an increase in mitochondrial O_2^- via several mechanisms including by stimulation of the ETC to increase electron leak, by facilitating cytochrome *c* dislocation and by enhancing NO• generation which blocks complex IV and causes electron leak from complex III (Peng and Jou, 2010), and subsequently leads tomitochondria-mediated cell apoptosis (see details in the section 4.2.). Ca^{2+} overload in mitochondrial decreases mitochondrial membrane potential, which leads to mitochondrial fission. The fragmented/damaged mitochondria will be the target of the mitophagy, but too much fission will lead to more caspase release and cause cell apoptosis (Jeong and Seol, 2008; Suen *et al.*, 2008; Liesa *et al.*, 2009; Jahani-Asl *et al.*, 2010; Westermann, 2011).

Where is the source of Ca^{2+} which accumulates in mitochondria? Mitochondria increase their $[Ca^{2+}]$ in response to elevated cytosolic $[Ca^{2+}]$ (Szabadkai *et al.*, 2001; Pitter *et al.*, 2002), and this Ca^{2+} transfer might be required for the physiological mitochondrial function such as ATP synthesis. There is increasing evidence showing that Ca^{2+} released from the ER is the main source of mitochondrial Ca^{2+} overload in pathophysiological condition (reviewed in Contreras *et al.*, 2010; de Brito and Scorrano, 2010; Patergnani *et al.*, 2011). Mitochondrial Ca^{2+} uptake is achieved by VDAC in the OMM and mitochondrial Ca^{2+} uniporter (MCU) in the IMM. VDAC is a channel permeable to both anions and cations, and the selectivity of the channel depends on the mitochondrial membrane potential; low potential is more preferable to anion transfer and high potential to cation. It has been demonstrated that VDAC is more permeable to Ca^{2+} in the closed states of the channel, and thus VDAC closure is a proapoptotic signal (Rostovtseva *et al.*, 2005; Tan and Colombini, 2007). MCU is the highly selective ion channel and Ca^{2+} uptake by MCU is also driven by the membrane potential (Gunter and Gunter, 1994). It has been shown that Ca^{2+} has a biphasic effect on the MCU activity. Before reaching a certain level, cytosolic Ca^{2+} inactivates the uniporter and prevents further Ca^{2+} uptake. This mechanism allows the mitochondrial Ca^{2+} oscillation, but it prevents an excessive mitochondrial Ca^{2+}

accumulation. Above the certain range of $[Ca^{2+}]_{cyt}$, Ca^{2+} activates MCU by the Ca^{2+}-dependent calmodulin activation (Moreau *et al.*, 2006).

4) Mitochondria-induced endothelial cell apoptosis in diabetes— Pathophysiological changes of metabolic parameters in diabetes are related with or lead to the increase in endothelial apoptosis (Nakagami *et al.*, 2005; Piconi *et al.*, 2006; Leduc *et al.*, 2010; van den Oever *et al.*, 2010; Barber *et al.*, 2011). As described above, cell apoptosis could be induced in a mitochondria-dependent or mitochondria-independent manner, and the mitochondria-dependent cell apoptosis is modulated by mitochondrial functional and morphological changes including the increase in mitochondrial ROS formation, mitochondrial fission, mitochondrial Ca^{2+} overload, and the opening of mPTP. In addition, these mitochondrial pathophysiological changes interact and regulate each other. Although the initiation of mitochondria-mediated apoptosis could be varied and complex, it seems to be one common downstream, which is the opening of mPTP and the release of the proapoptotic factors from mitochondrial to the cytosol. In diabetes, increased mitochondrial O_2^- is well documented in endothelial cells (Nishikawa and Araki, 2007; Di Lisa *et al.*, 2009; Giacco and Brownlee, 2010; Cheng *et al.*, 2011). Hyperglycemia leads to increased BAX expression (Meng *et al.*, 2008; Yang *et al.*, 2008; Guan *et al.*, 2011), mitochondrial Ca^{2+} overload (Paltauf-Doburzynska *et al.*, 2004), opening of mPTP in endothelial cells (Detaille *et al.*, 2005; Huang *et al.*, 2010) and releasing the proapoptotic proteins from the mitochondria (Kowluru and Abbas, 2003; Detaille *et al.*, 2005; Kowluru, 2005; Leal *et al.*, 2009; Li *et al.*, 2009; Trudeau *et al.*, 2010; Chong *et al.*, 2011; Li *et al.*, 2011), and subsequently increases endothelial apoptosis. Type-2 diabetic mellitus is usually accompanied by hyperlipidemia and ox-LDL accumulation (Shimada *et al.*, 2004). Increased ox-LDL also induces mitochondria-mediated apoptosis in endothelial cells (Zhang *et al.*, 2003; Chen *et al.*, 2004; Vindis *et al.*, 2005; Takabe *et al.*, 2010; Chang *et al.*, 2011). These data suggest that the changes of metabolic parameter in diabetes lead to endothelial cell apoptosis via mitochondrial dysfunction that may regulate the vascular permeability and capillary density as well as the vascular tone in diabetes.

5) Mitochondria-mediated apoptosis in other cell types in diabetes—Although there are many reports describing the mitochondria-mediated cell apoptosis in diabetes (reviewed in Duchen, 2004; Allen *et al.*, 2005; Joza *et al.*, 2009 Szabadkai and Duchen, 2009), it is limited number of reports in which the actual assessment of the mPTP activity is carried out. Most prominent cell types which were examined for mPTP opening in diabetes are the cardiac myocyte. Cardiac myocytes isolated from diabetic patients (Anderson *et al.*, 2010) and diabetic animal models (Oliveira, 2005; Bhamra *et al.*, 2008; Williamson *et al.*, 2010; Lumini-Oliveira *et al.*, 2011) exhibit augmented mPTP activity compared with the control. On the other hand, the increase in proapoptotic protein in the cytosol has been demonstrated in many cell types in diabetes, which is the downstream cascade of the mPTP opening (reviewed in (Adeghate, 2004; Duchen, 2004).

Apoptosis plays an important role in biological processes and various pathophysiological events. An alteration of mitochondrial function is heavily involved in the death pathway, which results in the cardiovascular dysfunction in many diseases. The molecular mechanisms of mitochondria-mediated cell apoptosis has been extensively studied during past 10 years and it greatly helps understanding the cell fate determined by mitochondria in diabetes.

Conclusion

Mitochondria are small organelles in the cytosol and have been known as an ATP producing organelle. During past decades, their role has been expanded not only in the physiological

cell function, but also in the development and progression of many diseases including in diabetes. Main function of mitochondrial morphological changes is to ensure proper inheritance and distribution of mitochondria and to maintain them in a healthy state. Mitochondrial autophagy takes care of damaged mitochondria to minimize the maladaptive effect on cell functions and mitochondrial biogenesis keeps energy supply to the cell demands. Any abnormal alteration in these steps affects cell fate and tissue functions.

Endothelial dysfunction is the key risk factor of complications seen in diabetes, and here we demonstrate that mitochondrial dysfunction in endothelial cells represent a crucial step in the development of endothelial dysfunction. There are still many things to be examined to define mitochondrial pathophysiological role in endothelial function in diabetes, such as the relation between mitochondrial autophagy and endothelial dysfunction in diabetes and the contribution of mitochondrial abnormality to decreased quantity and quality of circulating endothelial progenitor cells in diabetes. Mitochondrial morphological and functional alteration in endothelial cells will remain an exciting field of diabetic research in another decade.

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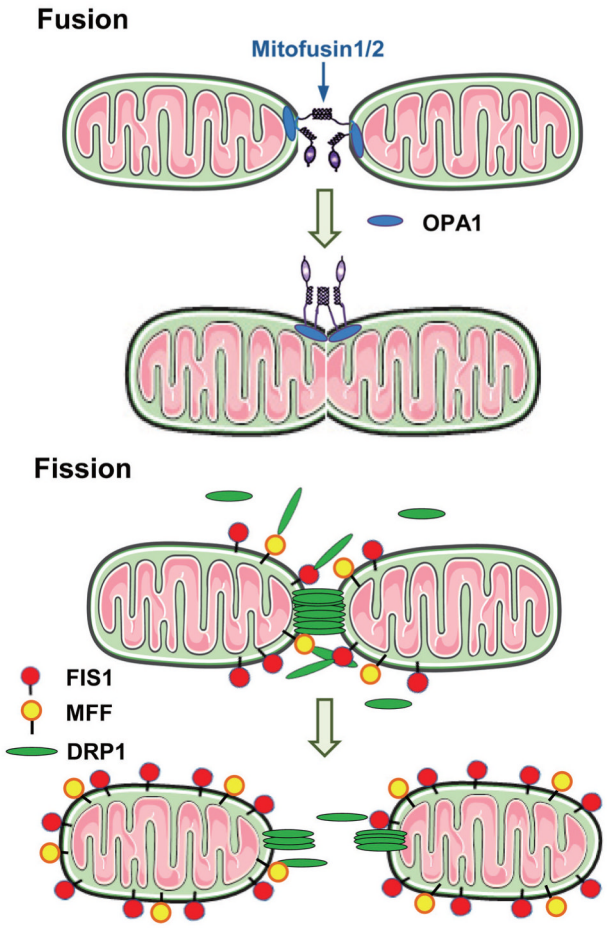

Fig. 1.

Mitochondrial fusion and fission. Mitochondrial fusion is regulated by optic atrophy 1 (OPA1), mitofusin 1 (MFN1), and mitofusin 2 (MFN2), whereas mitochondrial fission is controlled by dynamin related protein 1 (DRP1/DLP1/DNM1), fission1 (FIS1), and mitochondrial fission factor (MFF). OPA1 is located in the inner-mitochondrial membrane, and MFN1 and MFN2 are localized to the outer mitochondrial membrane. During mitochondrial fusion, OPA1 interacts with MFN1 and MFN2. FIS1 and MFF recruit DRP1 from the cytosol to mitochondria upon the fission reaction.

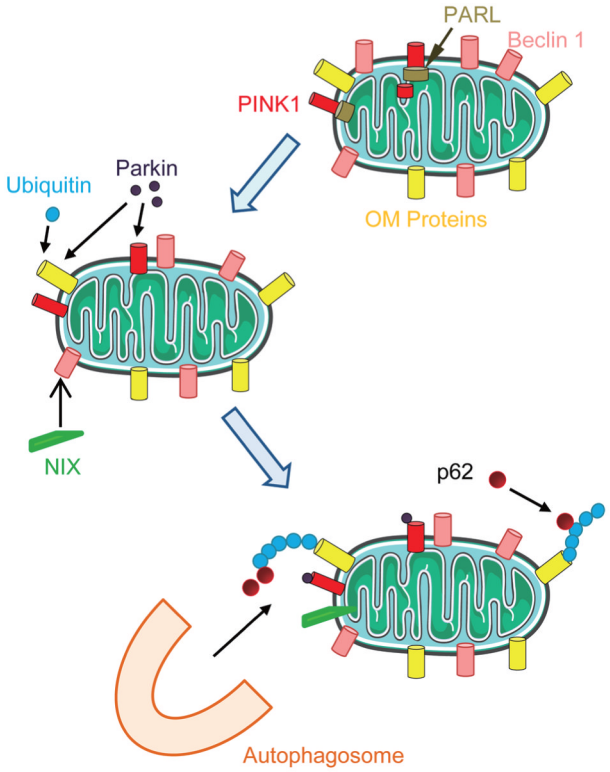

Fig. 2.

Mitohpagy. At the healthy condition, the Pten-induced novel kinase 1 (PINK1) is degraded by presenilins-associated rhomboid-like protein (PARL). Upon mitochondrial damage or loss of mitochondrial membrane potential, PINK1 accumulates on the outer mitochondrial membrane (OMM) without degradation and recruits Perkin from the cytosol to the OMM. Perkin ubiquitylates OM proteins and these ubiquitylated proteins are recognized by the adaptor protein p62 and are targeted by autophagosomes and eventually are degraded in lysosomes.

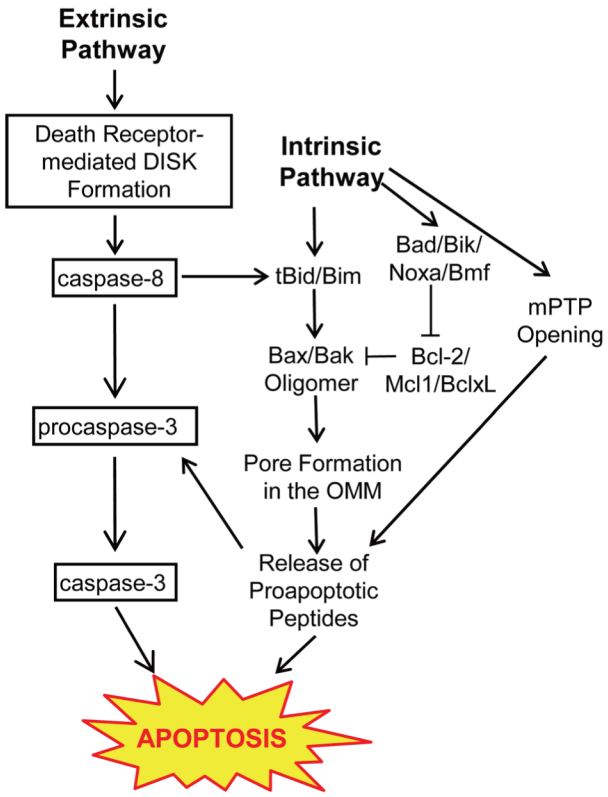

Fig. 3.

Extrinsic Pathway. The binding of the death ligands to the death receptors forms a death-inducing signal complex (DISK). Procaspase 8 is autoactivated at the DISK and converted to the active form, caspase 8. Caspase 8 leads to cell apoptosis via caspase 3 activation and by truncation of Bid to tBid. IntrinsicPathway. Intrinsic pathway is activated by intracellular stimuli (e.g., ROS) and involves the formation of the pore in the OMM (Bax/Bak oligomer) and the opening of the mitochondrial permeability transition pore (mPTP). These pores release proapoptotic peptides and induce cell apoptosis.