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Review

Effects of Mitochondrial Dynamics in the Pathophysiology of Obesity

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Abstract

Obesity has become an urgent and serious public health challenge with an overwhelming increase over the decades worldwide. The rate of obese children and adolescents has recently accelerated, especially in China. Obesity is closely related to unbalanced cellular energy metabolism. Mitochondria, as the main organelles of energy metabolism, play an important role in the pathophysiology of obesity. Recent researches have revealed that mitochondrial dynamics with constant fission and fusion, can alter mitochondrial structure, organelle connections, ROS production, neuronal activity, and OXPHOS system as well as adipose tissue thermogenesis, which ultimately lead to obesity. In this review, we will update the latest findings about mitochondrial fission/fusion related GTPase proteins and discuss the effects of mitochondrial dynamics in the pathophysiology of obesity.

Keywords: mitochondrial dynamics; fission; fusion; obesity; Opa1; Drp1; Mfn1; Mfn2

1. Introduction

Obesity has become an urgent and serious public health challenge with an overwhelming increase worldwide over the past 50 years. A total of 1.9 billion and 609 million adults, approximately 39% of the world's population, were estimated to be overweight and obese in 2015 [1,2]. The total number of worldwide obese population has nearly tripled while the number of obese children and adolescents (aged 5 to 19 years) worldwide has risen tenfold since 1975. Over 41 million children under the age of 5 and over 340 million children and adolescents aged 5–19 years old were reported overweight or obese in 2016 [3,4].

Obesity has physical and psychological health impact throughout all stages of life [5]. Obesity itself can cause high blood pressure, high cholesterol, fatty liver disease, increasing the risk of impaired glucose tolerance, insulin resistance, and type 2 diabetes, as well as the metabolic syndrome in childhood [6–9]. Alarmingly, childhood obesity increases the likelihood of adult obesity with an additional increased risk of cardiovascular morbidity and mortality [10–12].

Excessive energy intake and reduced energy consumption contribute to the development of obesity. Obesity is closely related to unbalanced cellular energy metabolism, especially mitochondrial metabolism [13]. Mitochondrial dysfunction is highlighted in the pathophysiology of obesity, including mutation of mitochondrial DNA, reduction in mitochondrial content and/or biogenesis, impaired dynamics (fission/fusion), impaired mitophagy, failure in bioenergetics, reduced enzyme activity, and augmented oxidative stress [14]. It has becoming increasingly well-acknowledged that mitochondria are dynamic organelles. Mitochondrial shapes can be club-shaped, spherical, filamentous and so on. One shape of mitochondria may transform into any other type, by either fusion or division (fission) [15,16]. Recent researches have revealed that mitochondrial dynamics as a conserved mechanism can regulate mitochondrial remodeling with the fission and fusion processes, thus affecting the pathophysiology of metabolic diseases, including obesity and type 2 diabetes [17–19].

This review focuses on the new aspects of mitochondrial dynamics and pathophysiology of obesity. We will summarize the recent findings of mitochondrial dynamic regulatory proteins, and discuss the effects of the unbalanced mitochondrial fission and fusion by reviewing the updated literature on their dysregulations in obesity so as to further understand the pathophysiology of obesity and provide new insights for future treatments.

2. Mitochondrial Fission and Obesity

Mitochondrial dynamics are regulated by a family of GTPase proteins. Dynamin-related protein 1 (Drp1) is the main fission protein that clefts mitochondrial membrane [20]. Besides Drp1, mitochondrial fission 1 protein (Fis1) also regulate the mitochondrial division [21,22]. On the other hand, mitochondrial dynamin like GTPase optic atrophy 1 (Opa1) leads to the mitochondrial fusion of mitochondrial inner membrane [23], while mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) are responsible for the fusion of mitochondrial outer membrane [24]. Membrane-associated

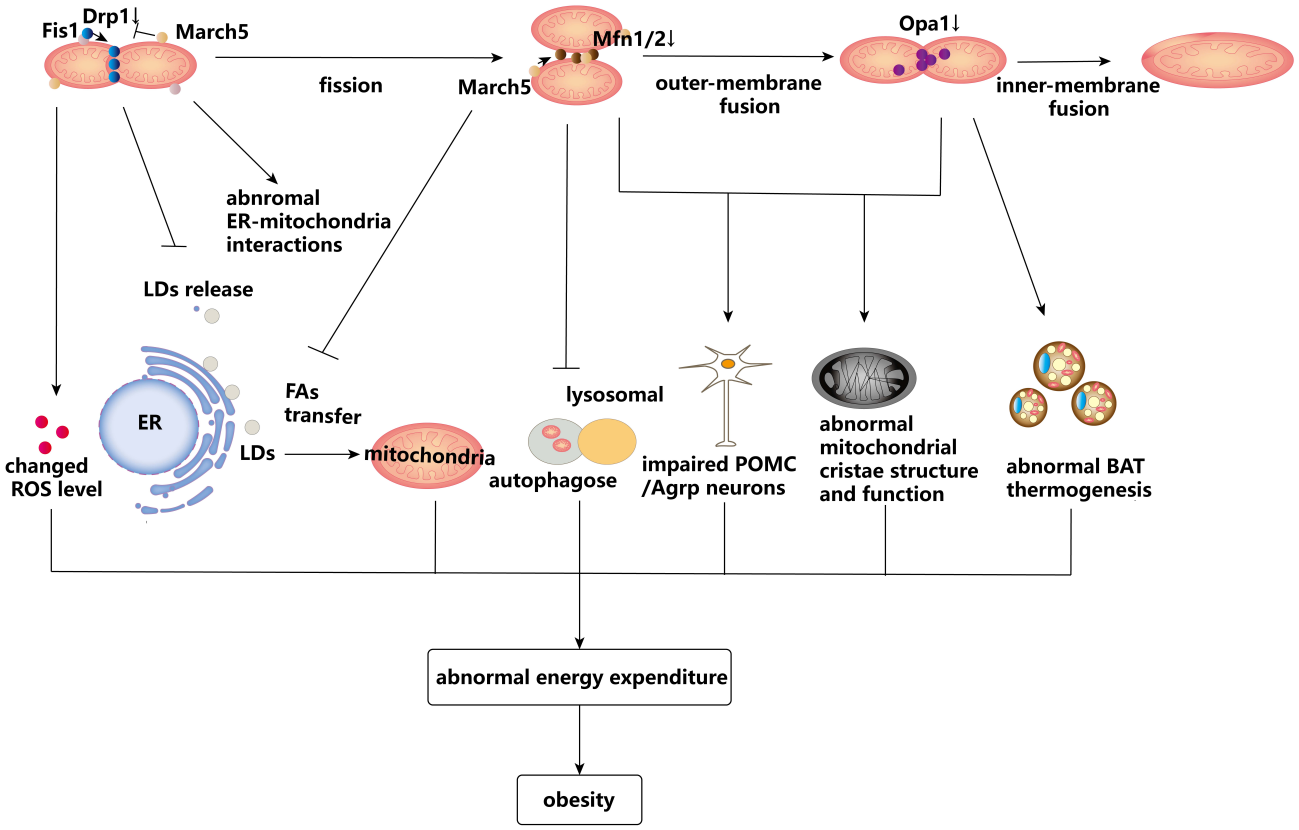

Fig. 1. Mitochondrial dynamics and organelle/cell interactions on obesity.

RING-CH-type finger 5 (March5) is a newly discovered mitochondrial fusion regulatory protein [25]. Mitochondrial dynamic related GTPase proteins and the main functions are listed in Table 1. Fig. 1 presents the interactions between mitochondrial fission/fusion and regulations between organelle/cell in the pathophysiology of obesity (Fig. 1).

2.1 Main Mitochondrial Fission Protein: Drp1

Drp1 is the main mitochondrial fission protein that is responsible for the cleavage of mitochondrial inner and outer membranes in mammals. Mutations in the GTPase domain can specifically cause alterations in the mitochondrial morphology and mitochondrial collapse [26]. Drp1 is proved to participate in the mitochondrial fission in mammalian cells as well as in C. elegans [27,28]. Drp1 alone has the ability to constrict and sever cell membranes. Cutting requires the membrane binding, self-assembly and GTPase activity of Drp1, which plays the dominant role in the division of mitochondria and peroxisome [20]. Drp1 also plays a role in mitochondrial cristae remodeling mediated by the endoplasmic reticulum (ER) Ca^{2+} inflow and Drp1 recruitment to mitochondria [29].

The mitochondrial fission function of Drp1 is related to protein molecular modification and interactions. Norepinephrine (NE) mediated phosphorylation of Drp1 Ser-600 mediates the mitochondrial division and induces the mitochondrial uncoupling in brown adipose tissue (BAT), which results in increased heat production and energy expenditure. The mitochondrial division in BAT may be a novel potential therapeutic target to treat obesity [30]. In contrast, the hyperphosphorylation of Drp1 Ser-637 enhances the mitochondrial respiration by increasing mitochondrial fusion and lengthening mitochondria. Hyperphosphorylation of Drp1 Ser-637 also leads to increased mitochondrial proton gradient energy transfer, which increases the oxidative metabolism and prevented high-fat diet (HFD)-induced obesity [31]. Adipose tissue-specific DNA methyltransferase 1 (*DNMT1*) knockout blocks the interaction between enhancers and DRP1 by influencing DNA methylation, thereby inhibiting mitochondrial fission and leading to adipocyte hypertrophy and impaired expansion of adipocyte precursors. Loss of DNMT1 can lead to the damage of adipocyte β-oxidation, reduced membrane potential and mtDNA, and result in obesity in mice [32].

Induced by apoptosis, Drp1 is transferred to mitochondria and preferentially locates at potential sites of division [33]. Endoplasmic reticulum is reported to play a central role in Drp1 aggregation on mitochondria fission. Drp1 oligomerization can be transferred from ER to mitochondria or peroxisome by the communication between the ER and mitochondria [34]. Formin-like protein Inf2 mediates the Drp1 polymerization of ER, leading to the increased ER-mitochondrial contact. The increased endoplasmic reticulum calcium inflow to mitochondria causes the mitochon-

Table 1. Mitochondrial dynamic related GTPase proteins.

Fission/fusion protein		Change	Model	Organ/tissue	The main mechanisms	Influence on obesity
fission	Drp1	Ser-600 phosphorylation	mice	BAT	increased thermogenesis	protective
		Ser-637 hyperphosphorylation	mice	skeletal muscle	increased oxidative metabolism	protective
		transcription inhibition	mice	WAT	damaged adipocyte β-oxidative	accelerative
		tissue specific ablation	mice	adipose tissue	failure of LDs release	accelerative
		tissue specific ablation	mice	liver	increased expression of FGF21	protective
		tissue specific ablation	mice	muscle tissue	reduced the phosphorylation of P38	protective
	Fis1	reduced level due to maternal obesity during pregnancy	mice	whole body	reduced energy metabolism	accelerative
		reduced expression	mice	adipocytes	reduced TG content	protective
fusion	Opa1	abnormal Oma1-Opa1 system	mice	BAT	abnormal thermogenesis	accelerative
		IL-1R-MyD88-IRAK2-PHB/OPA1 pathway	mice	adipose tissue	reduced β-oxidation	accelerative
		tissue specific downregulated expression	mice	BAT	abnormal mitochondrial cristae structure	protective
		tissue specific gene inactivation	mice	POMC neurons	decreased lipolysis of WAT	accelerative
		tissue specific gene deletion	mice	muscle tissue	increased secretion of FGF21	protective
	Mfn1/2	MFN2 p.R707W mutant	human	whole body	inhibition of leptin expression	accelerative
		MFN1/2 tissue specific gene deletion	mice	Agrp neurons	impaired electrical activity of neurons	protective
		MFN2 tissue specific gene deletion	mice	POMC neurons	loss of mitochondria-ER contact	accelerative
		increased Mfn1/2 expression induced by PGC-1α and HO-1	mice	adipose tissue	increased thermogenesis	protective
		Mfn2 cell specific dysfunction	Human/ mice	Hela/muscle cell	repressed nuclear-encoded subunits of OXPHOS complexes	accelerative
		Mfn2 tissue specific reduced expression	mice	adipose tissue	reduced fatty acid transfer	accelerative
		cell MFN2 knockout	human	Hela/muscle cell	inhibit autophagic-lysosomal fusion	accelerative
	March5	cell specific knockout	mice	adipocytes	increased lipid uptake and synthesis	protective

drial division [35,36]. ER stress leads to diverse mitochondrial outcomes. Ablation of adipose tissue specific *DRP1* leads to the failure of ER lipid droplets (LDs) release and shape change. Abnormal lipid droplets shape and accumulation during ER stress can further lead to mitochondrial dysfunction, lipolysis disorders, reduced thermogenesis, and finally defective systemic lipid metabolism [37]. In contrast, the deletion of hepatic *DRP1* gene induces ER stress, and promotes the expression of fibroblast growth factor 21 (*FGF21*) in liver [38]. Increased expression of *FGF21* and ER stress can lead to the increased energy expenditure in mice, thus playing a protective role in HFD-induced obesity [38–40]. Currently strong evidence shows that CerS6-derived sphingolipids promote Drp1-mediated mitochondrial fragmentation in obesity [41]. Ablation of CerS6 in a mouse model of HFD-induced insulin resistance facilitates a successful reversal of the fragmentation of hepatic mitochondrial network, rescues the insulin-sensitive phenotype and prevented HFD-induced obesity [42].

Reactive oxygen species (ROS) is considered as the mediator of mitochondrial fission in endothelial cells [43]. ER stress leads to the increased ROS production in adipocytes and decrease the catalase synthesis, thus affecting the lipid metabolism [44]. Besides, ROS acts as signal molecules to activate P38, a member of mitogen activated kinase-like protein (MAPK) family [45]. Obesity can increase the phosphorylation of P38 in the skeletal muscle, which is reversed by reduced mitochondrial fission due to *DRP1* ablation [46]. Therefore, increased *DRP1* expression increases the ROS level by inducing cell division, forming a vicious cycle that eventually leads to abnormal cell metabolism.

2.2 Other Protein that Regulates Mitochondrial Fission: Fis1

The dynamin-related GTPase Fis1 locates in the outer membrane of mitochondria and also induces the mitochondrial division [22,47]. Fis1 recruits Drp1 from the cytoplasm to participate in the mitochondrial division, resulting in increased mitochondrial fragmentation and changed mitochondrial shape [48,49]. Researches show that increased mitochondrial fission proteins Drp1 and Fis1 with decreased fission protein Mfn2 can lead to impaired mitochondrial function and oxidative stress [50]. Maternal obesity during pregnancy can reduce the expression of Fis1, Opa1, Mfn1, Mfn2 in offspring, resulting in reduced energy

metabolism and fat utilization. Studies reveal that alteration of regulatory mitochondrial factors in offspring may lead to the impaired mitochondrial health and increased susceptibility to obesity later in life [51]. After mitochondrial fusion induced by silencing mitochondrial fission proteins including Fis1 and Drp1 in adipocytes, the content of triacylglycerol (TG) in adipocytes was reduced. It was speculated that the mitochondrial fusion may be more efficient in carrying out pyruvate dehydrogenation, oxidative phosphorylation and lipid metabolism [52]. A novel selective peptide inhibitor, P110, is reported to inhibits the Drp1/Fis1 interaction and production of ROS in cultured neurons. Thus, P110 is helpful with treatment of obesity [53].

3. Mitochondrial Fusion and Obesity

3.1 Main Mitochondrial Inner Membrane Fusion Protein: Opa1

As a component of the mitochondrial network, the dynamin-related protein Opa1, encoded by nuclear gene *OPA1*, plays a role in the mitochondrial aggregation and stabilization of inner membrane [54–57]. Opa1 is located in the inner membrane of mitochondria and coordinates the mitochondrial cristae, which is essential in the mitochondrial respiratory chain and oxidative metabolism [58–61]. Different isoforms of Opa1 play different roles. They can restore the cristae structure, mtDNA abundance and energy efficiency. The complete recovery of mitochondrial dynamic network requires the interaction of different Opa1 isoforms [62]. *OPA1* gene inactivation leads to dramatic alterations in mitochondrial network, in which mitochondrial fragments are scattered, and the mitochondrial cristae is broken and disorganized [63].

Mitochondrial protease OMA1 zinc metallopeptidase (Oma1) can inactivate Opa1 under stress and inhibit mitochondrial fusion [64]. It has been proved that β-oxidation in the brown adipose tissue requires both Oma1 and Opa1 in mice. Oma1 deficient mice gradually gain weight with hepatic steatosis. Therefore, abnormal Oma1-Opa1 system may change the thermogenesis and metabolism of BAT, thus causing obesity [65]. Besides, Opa1 stabilizes respiratory chain supercomplexes (RSCs) to regulate the mitochondrial membrane potential to maintain the mitochondrial activity [66]. Mitochondrial proteins prohibitins (PHBs) act as scaffolds for mitochondrial inner membrane by forming multimeric ring complexes [67]. The latest research shows that interaction between the PHBs and Opa1 impairs the formation of mitochondrial RSCs and subsequently inhibits oxidative phosphorylation, and fatty acid β-oxidation (FAO), through unconventional interleukin-1 receptor (IL-1R)–MyD88 innate immune signal transduction adaptor (MyD88)–interleukin-1 receptor associated kinase 2 (IRAK2)–PHB/Opa1 pathway. Therefore, interleukin-1 (IL-1) induced chronic inflammation in obesity can reprogram the mitochondrial metabolism in adipocytes to exacerbate obesity [68].

Cardiolipin (CL), located in the inner membrane of mitochondria, is also important for the mitochondrial cristae stability. It has been reported that mitochondrial lipids, especially CL, play a major role in regulating the mitochondrial cristae shape and dynamics under PH changes [69,70]. It has been discovered that carbohydrate response element-binding protein (ChREBP) KO mice are resistant to obesity, and recent research has found that is due to the combined influence of decreased CL synthesis and downregulated expression of Opa1 in brown adipose tissue (BAT). All of these two changes can cause abnormal mitochondrial cristae structure in BAT of ChREBP KO mice to display an anti-obese phenotype [71].

The stability of the mitochondrial cristae in different tissues also ultimately affects obesity. Recently it has been proved that adequate mitochondrial fusion and fission in neurons is important for metabolic regulation. In proopiomelanocortin (POMC) neurons, *OPA1* gene inactivation leads to dramatic alterations in mitochondrial cristae topology, mitochondrial Ca^{2+} processing, decreased lipolysis of WAT, and ultimately leading to obesity [72]. Besides, in muscle tissue, *OPA1* deletion can cause non-lethal impaired electron transport chain and adenosine triphosphate (ATP) production due to the disrupted mitochondrial cristae structure. Activation of ER stress due to the *OPA1* ablation may induce the secretion of FGF21 to reverse diet-induced obesity and insulin resistance [73].

3.2 Main Mitochondrial Outer Membrane Fusion Protein: Mfn1 and Mfn2

The mitofusins (Mfn1 and Mfn2) lead to the mitochondrial fusion and regulate the mitochondrial cristae structure [74]. Both homomorphic and heteromorphic complexes work together to promote the mitochondrial outer membrane fusion in mammals [24,75–77]. By influencing mitochondrial fusion, Mfn1 and Mfn2 regulate obesity-related metabolic changes such as reduced glucose oxidation, mitochondrial membrane potential, cellular respiration, and lipid toxicity [78,79]. Enhanced mitochondrial fusion is beneficial to the mitochondrial biogenesis and lipid metabolism, which is impaired in obesity [78,80,81]. What's more, decreased transcription of *MFN2* gene is reported in obese humans, and the expression of MFN2 is negatively correlated with body mass index (BMI) [82]. Mutations in *MFN2* (p.R104W, p.R707W) are found in obese patients [83,84]. Broken mitochondrial networks and mitochondrial dysfunction with *MFN2* mutations are speculated to cause inhibition of leptin expression and increase adipocyte proliferation and survival [85]. Moreover, selective deletion of *MFN1* and *MFN2* in mice impairs the mitochondrial fusion (both mitochondrial size and shape) in agouti-related protein (Agrp) neurons, resulting in impaired electrical activity of Agrp neurons, with increased resistance to fat gain and reduced weight gain in mice during high-fat diet [86]. Moreover, specific ablation of *MFN2*

in POMC neurons in the hypothalamus leads to loss of mitochondrial endoplasmic reticulum contact, resulting in endoplasmic reticulum stress, leptin resistance, hyperphagia, and reduced energy expenditure, which eventually lead to severe obesity [87].

The expression of mitochondrial fusion genes *MFN1* and *MFN2* is regulated by peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) through synergistic activation of estrogen-associated receptor α [88–90]. PGC-1α promotes the transcription of *MFN1* in mice, resulting in increased mitochondrial biogenesis and autophagy flux, which are impaired in obesity [91]. Moreover, PGC-1α can increase the level of heme oxygenase-1 (HO-1) to enhance the expression of *MFN1* and *MFN2*, and then play a role in increasing the heat production, regulating the adipocyte differentiation, and improving the metabolic homeostasis [92,93]. While decreased expression of PGC-1α and abnormal mitochondrial metabolism caused by mitochondrial dynamics disruption may promote lipid accumulation in cells [94]. Besides, leptin plays a role in inhibiting liver lipid deposition and improving hyperglycemia and hyperlipemia by increasing mitochondrial fusion-related transcription factors peroxisome proliferator-activated receptor α (PPARα), PGC-1α to up-regulate Mfn1 and Mfn2 [95].

In addition, Mfn2 dysfunction represses nuclear-encoded subunits of oxidative phosphorylation (OXPHOS) complexes I, II, III and V, thereby inhibiting pyruvate, glucose, and fatty acid oxidation and reducing mitochondrial membrane potential [81]. Mfn2 can also affect energy metabolism by regulating the interaction between lipid droplets and mitochondria [96]. Contact between activated mitochondria and lipid droplets will promote the transfer of fatty acids from lipid droplets to mitochondria for β-oxidation. Reduced Mfn2 expression levels in adipocytes may lead to reduced fatty acid transfer, thereby inhibiting fatty acid oxidation and facilitating fat storage [97]. *MFN2* knockout can inhibit autophagose-lysosomal fusion, resulting in impaired autophagy degradation. Thus, mitochondrial respiration, ATP production, and cellular glycolysis are reduced, which affect the cellular biosynthesis and obesity [30,98,99]. A flavonoid compound derived from natural products named Vitexin is helpful in obesity treatment. Vitexin promotes the expression of Mfn2 and inhibits the expression of Drp1, thereby increasing mitochondrial membrane potential and alleviating the mitochondrial dysfunction [100].

3.3 Novel Regulating Proteins: March5

Human membrane-associated RING-CH(March)-V/March5 is a novel mitochondrial outer membrane transmembrane protein. March5 plays a promoter role in the mitochondrial fusion [25]. March5 can bind Mfn2 to promote the formation of long tubular mitochondria and mitochondrial networks. It can also promote the ubiquitination of Drp1 to inhibit the mitochondrial division. March5 is regulated by peroxisome proliferator-activated receptor-γ (PPARγ) during adipogenesis. Knockout of MARCH5 leads to an increase in cellular glycolysis and basal mitochondrial respiration, as well as an increase in lipid uptake and synthesis [101].

4. Conclusion and Perspective

In general, mitochondrial fission and fusion can affect the pathophysiology of obesity in several ways: (a) the connection between organelles, (b) protein molecular modification, (c) neuronal activity, (d) mitochondrial cristae stability and OXPHOS system function, (e) adipose tissue thermogenesis.

Mitochondrial dynamics provides new approaches to treatment of obesity. Several candidates are under study in animal and *in vitro* models based on mitochondrial fusion/fission theory, such as P110 and Vitexin. These inhibitors may be helpful for the treatment of diseases with unbalanced mitochondrial dynamics including obesity.

Abbreviations

Drp1, Dynamin-related protein 1; Fis1, mitochondrial fission 1 protein; Opa1, optic atrophy 1; Mfn1, mitofusin 1; Mfn2, mitofusin 2; March5, membrane-associated RING-CH-type finger; ROS, reactive oxygen species; ER, endoplasmic reticulum; LDs, lipid droplets; FAs, fatty acids; POMC, proopiomelanocortin; Agrp, agouti-related protein; BAT, brown adipose tissue.

Author Contributions

JF and JW contributed to the conception of this manuscript. XL drafted the manuscript. JW contributed to manuscript writing and revision for intellectual content. JW, GD and NZ conducted the literature search critically. WW and KH provided constructive discussions and contributed to paper review. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019; 92: 6–10.

[2] Blüher M. Obesity: global epidemiology and pathogenesis. Nature Reviews. Endocrinology. 2019; 15: 288–298.

[3] Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017; 390: 2627–2642.

[4] Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, *et al*. The obesity transition: stages of the global epidemic. The Lancet Diabetes & Endocrinology. 2019; 7: 231–240.

[5] Morales Camacho WJ, Molina Díaz JM, Plata Ortiz S, Plata Ortiz JE, Morales Camacho MA, Calderón BP. Childhood obesity: Aetiology, comorbidities, and treatment. Diabetes/Metabolism Research and Reviews. 2019; 35: e3203.

[6] Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and risk of the adult metabolic syndrome: a systematic review. International Journal of Obesity. 2012; 36: 1–11.

[7] Bacha F, Gidding SS. Cardiac Abnormalities in Youth with Obesity and Type 2 Diabetes. Current Diabetes Reports. 2016; 16: 62.

[8] Pollock NK. Childhood obesity, bone development, and cardiometabolic risk factors. Molecular and Cellular Endocrinology. 2015; 410: 52–63.

[9] Africa JA, Newton KP, Schwimmer JB. Lifestyle Interventions Including Nutrition, Exercise, and Supplements for Nonalcoholic Fatty Liver Disease in Children. Digestive Diseases and Sciences. 2016; 61: 1375–1386.

[10] Litwin SE. Childhood obesity and adulthood cardiovascular disease: quantifying the lifetime cumulative burden of cardiovascular risk factors. Journal of the American College of Cardiology. 2014; 64: 1588–1590.

[11] Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. a follow-up of the Harvard Growth Study of 1922 to 1935. The New England Journal of Medicine. 1992; 327: 1350–1355.

[12] Kelsey MM, Zaepfel A, Bjornstad P, Nadeau KJ. Age-related consequences of childhood obesity. Gerontology. 2014; 60: 222–228.

[13] Prasun P. Mitochondrial dysfunction in metabolic syndrome. Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease. 2020; 1866: 165838.

[14] Das M, Sauceda C, Webster NJG. Mitochondrial Dysfunction in Obesity and Reproduction. Endocrinology. 2021; 162

[15] Lewis MR, Lewis WH. Mitochondria in tissue culture. Science. 1914; 39: 330–333.

[16] Lewis WH. Giant centrospheres in degenerating mesenchyme cells of tissue cultures. The Journal of Experimental Medicine. 1920; 31: 275–292.

[17] Archer SL. Mitochondrial dynamics–mitochondrial fission and fusion in human diseases. The New England Journal of Medicine. 2013; 369: 2236–2251.

[18] Dahlmans D, Houzelle A, Schrauwen P, Hoeks J. Mitochondrial dynamics, quality control and miRNA regulation in skeletal muscle: implications for obesity and related metabolic disease. Clinical Science. 2016; 130: 843–852.

[19] Dai W, Jiang L. Dysregulated Mitochondrial Dynamics and Metabolism in Obesity, Diabetes, and Cancer. Frontiers in Endocrinology. 2019; 10: 570.

[20] Kamerkar SC, Kraus F, Sharpe AJ, Pucadyil TJ, Ryan MT. Dynamin-related protein 1 has membrane constricting and severing abilities sufficient for mitochondrial and peroxisomal fission. Nature Communications. 2018; 9: 5239.

[21] Otsuga D, Keegan BR, Brisch E, Thatcher JW, Hermann GJ, Bleazard W, *et al*. The dynamin-related GTPase, Dnm1p, controls mitochondrial morphology in yeast. The Journal of Cell Biology. 1998; 143: 333–349.

[22] Losón OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Molecular Biology of the Cell. 2013; 24: 659–667.

[23] Misaka T, Murate M, Fujimoto K, Kubo Y. The dynamin-related mouse mitochondrial GTPase OPA1 alters the structure of the mitochondrial inner membrane when exogenously introduced into COS-7 cells. Neuroscience Research. 2006; 55: 123–133.

[24] Eura Y, Ishihara N, Yokota S, Mihara K. Two mitofusin proteins, mammalian homologues of FZO, with distinct functions are both required for mitochondrial fusion. Journal of Biochemistry. 2003; 134: 333–344.

[25] Nakamura N, Kimura Y, Tokuda M, Honda S, Hirose S. MARCH-V is a novel mitofusin 2- and Drp1-binding protein able to change mitochondrial morphology. EMBO Reports. 2006; 7: 1019–1022.

[26] Smirnova E, Shurland DL, Ryazantsev SN, van der Bliek AM. A human dynamin-related protein controls the distribution of mitochondria. The Journal of Cell Biology. 1998; 143: 351–358.

[27] Labrousse AM, Zappaterra MD, Rube DA, van der Bliek AM. C. elegans dynamin-related protein DRP-1 controls severing of the mitochondrial outer membrane. Molecular Cell. 1999; 4: 815–826.

[28] Smirnova E, Griparic L, Shurland DL, van der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Molecular Biology of the Cell. 2001; 12: 2245–2256.

[29] Germain M, Mathai JP, McBride HM, Shore GC. Endoplasmic reticulum BIK initiates DRP1-regulated remodelling of mitochondrial cristae during apoptosis. The EMBO Journal. 2005; 24: 1546–1556.

[30] Wikstrom JD, Mahdaviani K, Liesa M, Sereda SB, Si Y, Las G, *et al*. Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure. The EMBO Journal. 2014; 33: 418–436.

[31] Pfluger PT, Kabra DG, Aichler M, Schriever SC, Pfuhlmann K, García VC, *et al*. Calcineurin Links Mitochondrial Elongation with Energy Metabolism. Cell Metabolism. 2015; 22: 838–850.

[32] Park YJ, Lee S, Lim S, Nahmgoong H, Ji Y, Huh JY, *et al*. DNMT1 maintains metabolic fitness of adipocytes through acting as an epigenetic safeguard of mitochondrial dynamics. Proceedings of the National Academy of Sciences. 2021; 118: e2021073118.

[33] Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F, *et al*. The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Developmental Cell. 2001; 1: 515–525.

[34] Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK. ER tubules mark sites of mitochondrial division. Science. 2011; 334: 358–362.

[35] Ji W, Chakrabarti R, Fan X, Schoenfeld L, Strack S, Higgs HN. Receptor-mediated Drp1 oligomerization on endoplasmic reticulum. The Journal of Cell Biology. 2017; 216: 4123–4139.

[36] Steffen J, Koehler CM. ER-mitochondria contacts: Actin dynamics at the ER control mitochondrial fission via calcium release. The Journal of Cell Biology. 2018; 217: 15–17.
[37] Li X, Yang L, Mao Z, Pan X, Zhao Y, Gu X, *et al*. Novel role of dynamin-related-protein 1 in dynamics of ER-lipid droplets in adipose tissue. The FASEB Journal. 2020; 34: 8265–8282.
[38] Wang L, Ishihara T, Ibayashi Y, Tatsushima K, Setoyama D, Hanada Y, *et al*. Disruption of mitochondrial fission in the liver protects mice from diet-induced obesity and metabolic deterioration. Diabetologia. 2015; 58: 2371–2380.
[39] Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, *et al*. FGF-21 as a novel metabolic regulator. The Journal of Clinical Investigation. 2005; 115: 1627–1635.
[40] Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, *et al*. Fibroblast Growth Factor 21 Corrects Obesity in Mice. Endocrinology. 2008; 149: 6018–6027.
[41] Roszczyc-Owsiejczuk K, Zabielski P. Sphingolipids as a Culprit of Mitochondrial Dysfunction in Insulin Resistance and Type 2 Diabetes. Frontiers in Endocrinology. 2021; 12: 635175.
[42] Hammerschmidt P, Ostkotte D, Nolte H, Gerl MJ, Jais A, Brunner HL, *et al*. CerS6-Derived Sphingolipids Interact with Mff and Promote Mitochondrial Fragmentation in Obesity. Cell. 2019; 177: 1536–1552.e23.
[43] Makino A, Scott BT, Dillmann WH. Mitochondrial fragmentation and superoxide anion production in coronary endothelial cells from a mouse model of type 1 diabetes. Diabetologia. 2010; 53: 1783–1794.
[44] Jackisch L, Murphy AM, Kumar S, Randeva H, Tripathi G, McTernan PG. Tunicamycin-Induced Endoplasmic Reticulum Stress Mediates Mitochondrial Dysfunction in Human Adipocytes. The Journal of Clinical Endocrinology & Metabolism. 2020; 105: 2905–2918.
[45] Maddux BA, See W, Lawrence JC, Jr., Goldfine AL, Goldfine ID, Evans JL. Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by mircomolar concentrations of alpha-lipoic acid. Diabetes. 2001; 50: 404–410.
[46] Jheng H, Tsai P, Guo S, Kuo L, Chang C, Su I, *et al*. Mitochondrial Fission Contributes to Mitochondrial Dysfunction and Insulin Resistance in Skeletal Muscle. Molecular and Cellular Biology. 2012; 32: 309–319.
[47] James DI, Parone PA, Mattenberger Y, Martinou J. HFis1, a novel component of the mammalian mitochondrial fission machinery. The Journal of Biological Chemistry. 2003; 278: 36373–36379.
[48] Yoon Y, Krueger EW, Oswald BJ, McNiven MA. The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1. Molecular and Cellular Biology. 2003; 23: 5409–5420.
[49] Stojanovski D, Koutsopoulos OS, Okamoto K, Ryan MT. Levels of human Fis1 at the mitochondrial outer membrane regulate mitochondrial morphology. Journal of Cell Science. 2004; 117: 1201–1210.
[50] Lionetti L, Mollica MP, Donizzetti I, Gifuni G, Sica R, Pignalosa A, *et al*. High-lard and high-fish-oil diets differ in their effects on function and dynamic behaviour of rat hepatic mitochondria. PLoS ONE. 2014; 9: e92753.
[51] Borengasser SJ, Faske J, Kang P, Blackburn ML, Badger TM, Shankar K. In utero exposure to prepregnancy maternal obesity and postweaning high-fat diet impair regulators of mitochondrial dynamics in rat placenta and offspring. Physiological Genomics. 2014; 46: 841–850.
[52] Kita T, Nishida H, Shibata H, Niimi S, Higuti T, Arakaki N. Possible Role of Mitochondrial Remodelling on Cellular Triacylglycerol Accumulation. Journal of Biochemistry. 2009; 146: 787–796.
[53] Qi X, Qvit N, Su YC, Mochly-Rosen D. A novel Drp1 inhibitor diminishes aberrant mitochondrial fission and neurotoxicity. Journal of Cell Science. 2013; 126: 789–802.
[54] Eiberg H, Kjer B, Kjer P, Rosenberg T. Dominant optic atrophy (OPA1) mapped to chromosome 3q region. i. Linkage analysis. Human Molecular Genetics. 1994; 3: 977–980.
[55] Pelloquin L, Belenguer P, Menon Y, Ducommun B. Identification of a Fission Yeast Dynamin-Related Protein Involved in Mitochondrial DNA Maintenance. Biochemical and Biophysical Research Communications. 1998; 251: 720–726.
[56] Delettre C, Lenaers G, Griffoin JM, Gigarel N, Lorenzo C, Belenguer P, *et al*. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nature Genetics. 2000; 26: 207–210.
[57] Alexander C, Votruba M, Pesch UE, Thiselton DL, Mayer S, Moore A, *et al*. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nature Genetics. 2000; 26: 211–215.
[58] Chen H, Chomyn A, Chan DC. Disruption of fusion results in mitochondrial heterogeneity and dysfunction. The Journal of Biological Chemistry. 2005; 280: 26185–26192.
[59] Cipolat S, Martins de Brito O, Dal Zilio B, Scorrano L. OPA1 requires mitofusin 1 to promote mitochondrial fusion. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 15927–15932.
[60] Song Z, Chen H, Fiket M, Alexander C, Chan DC. OPA1 processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Yme1L. The Journal of Cell Biology. 2007; 178: 749–755.
[61] Olichon A, Emorine LJ, Descoins E, Pelloquin L, Brichese L, Gas N, *et al*. The human dynamin-related protein OPA1 is anchored to the mitochondrial inner membrane facing the intermembrane space. FEBS Letters. 2002; 523: 171–176.
[62] Del Dotto V, Mishra P, Vidoni S, Fogazza M, Maresca A, Caporali L, *et al*. OPA1 Isoforms in the Hierarchical Organization of Mitochondrial Functions. Cell Reports. 2017; 19: 2557–2571.
[63] Griparic L, van der Wel NN, Orozco IJ, Peters PJ, van der Bliek AM. Loss of the intermembrane space protein Mgm1/OPA1 induces swelling and localized constrictions along the lengths of mitochondria. The Journal of Biological Chemistry. 2004; 279: 18792–18798.
[64] Head B, Griparic L, Amiri M, Gandre-Babbe S, van der Bliek AM. Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells. The Journal of Cell Biology. 2009; 187: 959–966.
[65] Quirós PM, Ramsay AJ, López-Otín C. New roles for OMA1 metalloprotease. Adipocyte. 2013; 2: 7–11.
[66] Rosselin M, Santo-Domingo J, Bermont F, Giacomello M, Demaurex N. L-OPA1 regulates mitoflash biogenesis independently from membrane fusion. EMBO Reports. 2017; 18: 451–463.
[67] Jian C, Xu F, Hou T, Sun T, Li J, Cheng H, *et al*. Deficiency of PHB complex impairs respiratory supercomplex formation and activates mitochondrial flashes. Journal of Cell Science. 2017; 130: 2620–2630.
[68] Zhou H, Wang H, Yu M, Schugar RC, Qian W, Tang F, *et al*. IL-1 induces mitochondrial translocation of IRAK2 to suppress oxidative metabolism in adipocytes. Nature Immunology. 2020; 21: 1219–1231.
[69] Khalifat N, Puff N, Bonneau S, Fournier J, Angelova MI. Membrane deformation under local pH gradient: mimicking mitochondrial cristae dynamics. Biophysical Journal. 2008; 95: 4924–4933.
[70] Khalifat N, Fournier J, Angelova MI, Puff N. Lipid packing variations induced by pH in cardiolipin-containing bilayers: the driving force for the cristae-like shape instability. Biochimica Et

Biophysica Acta (BBA) - Biomembranes. 2011; 1808: 2724–2733.
[71] Sakiyama H, Li L, Kuwahara-Otani S, Nakagawa T, Eguchi H, Yoshihara D, *et al*. A lack of ChREBP inhibits mitochondrial cristae formation in brown adipose tissue. Molecular and Cellular Biochemistry. 2021; 476: 3577–3590.
[72] Gómez-Valadés AG, Pozo M, Varela L, Boudjadja MB, Ramírez S, Chivite I, *et al*. Mitochondrial cristae-remodeling protein OPA1 in POMC neurons couples Ca2+ homeostasis with adipose tissue lipolysis. Cell Metabolism. 2021; 33: 1820–1835.e9.
[73] Pereira RO, Tadinada SM, Zasadny FM, Oliveira KJ, Pires KMP, Olvera A, *et al*. OPA1 deficiency promotes secretion of FGF21 from muscle that prevents obesity and insulin resistance. The EMBO Journal. 2017; 36: 2126–2145.
[74] Santel A, Fuller MT. Control of mitochondrial morphology by a human mitofusin. Journal of Cell Science. 2001; 114: 867–874.
[75] Legros F, Lombès A, Frachon P, Rojo M. Mitochondrial Fusion in Human Cells is Efficient, Requires the Inner Membrane Potential, and is Mediated by Mitofusins. Molecular Biology of the Cell. 2002; 13: 4343–4354.
[76] Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. The Journal of Cell Biology. 2003; 160: 189–200.
[77] Santel A, Frank S, Gaume B, Herrler M, Youle RJ, Fuller MT. Mitofusin-1 protein is a generally expressed mediator of mitochondrial fusion in mammalian cells. Journal of Cell Science. 2003; 116: 2763–2774.
[78] Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J, *et al*. Mitofusin-2 Determines Mitochondrial Network Architecture and Mitochondrial Metabolism. A novel regulatory mechanism altered in obesity. Journal of Biological Chemistry. 2003; 278: 17190–17197.
[79] Xue R, Yu X, Zhao M, Xu M, Wu Q, Cui Y, *et al*. Pyridostigmine alleviates cardiac dysfunction via improving mitochondrial cristae shape in a mouse model of metabolic syndrome. Free Radical Biology and Medicine. 2019; 134: 119–132.
[80] Guillet V, Gueguen N, Cartoni R, Chevrollier A, Desquiret V, Angebault C, *et al*. Bioenergetic defect associated with mKATP channel opening in a mouse model carrying a mitofusin 2 mutation. FASEB Journal. 2011; 25: 1618–1627.
[81] Pich S, Bach D, Briones P, Liesa M, Camps M, Testar X, *et al*. The Charcot-Marie-Tooth type 2a gene product, Mfn2, upregulates fuel oxidation through expression of OXPHOS system. Human Molecular Genetics. 2005; 14: 1405–1415.
[82] Bach D, Naon D, Pich S, Soriano FX, Vega N, Rieusset J, *et al*. Expression of Mfn2, the Charcot-Marie-Tooth Neuropathy Type 2a Gene, in Human Skeletal Muscle: effects of type 2 diabetes, obesity, weight loss, and the regulatory role of tumor necrosis factor alpha and interleukin-6. Diabetes. 2005; 54: 2685–2693.
[83] Genari AB, Borghetti VHS, Gouvêa SP, Bueno KC, dos Santos PL, dos Santos AC, *et al*. Characterizing the phenotypic manifestations of MFN2 R104W mutation in Charcot-Marie-Tooth type 2. Neuromuscular Disorders. 2011; 21: 428–432.
[84] Sawyer SL, Cheuk-Him Ng A, Innes AM, Wagner JD, Dyment DA, Tetreault M, *et al*. Homozygous mutations inMFN2cause multiple symmetric lipomatosis associated with neuropathy. Human Molecular Genetics. 2015; 24: 5109–5114.
[85] Rocha N, Bulger DA, Frontini A, Titheradge H, Gribsholt SB, Knox R, *et al*. Human biallelic MFN2 mutations induce mitochondrial dysfunction, upper body adipose hyperplasia, and suppression of leptin expression. ELife. 2017; 6: e23813.
[86] Dietrich MO, Liu Z, Horvath TL. Mitochondrial dynamics controlled by mitofusins regulate Agrp neuronal activity and diet-induced obesity. Cell. 2013; 155: 188–199.
[87] Schneeberger M, Dietrich MO, Sebastián D, Imbernón M, Castaño C, Garcia A, *et al*. Mitofusin 2 in POMC neurons connects ER stress with leptin resistance and energy imbalance. Cell. 2013; 155: 172–187.
[88] Soriano FX, Liesa M, Bach D, Chan DC, Palacín M, Zorzano A. Evidence for a mitochondrial regulatory pathway defined by peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, estrogen-related receptor-alpha, and mitofusin 2. Diabetes. 2006; 55: 1783–1791.
[89] Martin OJ, Lai L, Soundarapandian MM, Leone TC, Zorzano A, Keller MP, *et al*. A role for peroxisome proliferator-activated receptor γ coactivator-1 in the control of mitochondrial dynamics during postnatal cardiac growth. Circulation Research. 2014; 114: 626–636.
[90] Elezaby A, Sverdlov AL, Tu VH, Soni K, Luptak I, Qin F, *et al*. Mitochondrial remodeling in mice with cardiomyocyte-specific lipid overload. Journal of Molecular and Cellular Cardiology. 2015; 79: 275–283.
[91] Greene NP, Lee DE, Brown JL, Rosa ME, Brown LA, Perry RA, *et al*. Mitochondrial quality control, promoted by PGC-1α, is dysregulated by Western diet-induced obesity and partially restored by moderate physical activity in mice. Physiological Reports. 2015; 3: e12470.
[92] Hull TD, Boddu R, Guo L, Tisher CC, Traylor AM, Patel B, *et al*. Heme oxygenase-1 regulates mitochondrial quality control in the heart. JCI Insight. 2016; 1: e85817.
[93] Singh SP, Schragenheim J, Cao J, Falck JR, Abraham NG, Bellner L. PGC-1 alpha regulates HO-1 expression, mitochondrial dynamics and biogenesis: Role of epoxyeicosatrienoic acid. Prostaglandins & other Lipid Mediators. 2016; 125: 8–18.
[94] Zhao L, Zou X, Feng Z, Luo C, Liu J, Li H, *et al*. Evidence for association of mitochondrial metabolism alteration with lipid accumulation in aging rats. Experimental Gerontology. 2014; 56: 3–12.
[95] Hsu W, Lee B, Pan T. Leptin-induced mitochondrial fusion mediates hepatic lipid accumulation. International Journal of Obesity. 2015; 39: 1750–1756.
[96] Boutant M, Kulkarni SS, Joffraud M, Ratajczak J, Valera-Alberni M, Combe R, *et al*. Mfn2 is critical for brown adipose tissue thermogenic function. The EMBO Journal. 2017; 36: 1543–1558.
[97] Mancini G, Pirruccio K, Yang X, Blüher M, Rodeheffer M, Horvath TL. Mitofusin 2 in Mature Adipocytes Controls Adiposity and Body Weight. Cell Reports. 2019; 26: 2849–2858.e4.
[98] Yu J, Zhang S, Cui L, Wang W, Na H, Zhu X, *et al*. Lipid droplet remodeling and interaction with mitochondria in mouse brown adipose tissue during cold treatment. Biochimica Et Biophysica Acta. 2015; 1853: 918–928.
[99] Ding Y, Gao H, Zhao L, Wang X, Zheng M. Mitofusin 2-deficiency suppresses cell proliferation through disturbance of autophagy. PLoS ONE. 2015; 10: e0121328.
[100] Yang H, Xue W, Ding C, Wang C, Xu B, Chen S, *et al*. Vitexin Mitigates Myocardial Ischemia/Reperfusion Injury in Rats by Regulating Mitochondrial Dysfunction via Epac1-Rap1 Signaling. Oxidative Medicine and Cellular Longevity. 2021; 2021: 1–17.
[101] Bond ST, Moody SC, Liu Y, Civelek M, Villanueva CJ, Gregorevic P, *et al*. The E3 ligase MARCH5 is a PPARγ target gene that regulates mitochondria and metabolism in adipocytes. American Journal of Physiology-Endocrinology and Metabolism. 2019; 316: E293–E304.