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IL-6 induces lipolysis and mitochondrial dysfunction, but does not affect insulin-mediated glucose transport in 3T3-L1 adipocytes

Chenbo Ji · Xiaohui Chen · Chunlin Gao · Liuhong Jiao · Jianguo Wang · Guangfeng Xu · Hailong Fu · Xirong Guo · Yaping Zhao

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Abstract Interleukin-6 (IL-6) has emerged as an important cytokine involved in the regulation of metabolism. However, the role of IL-6 in the etiology of obesity and insulin resistance is not fully understood. Mitochondria are key organelles of energy metabolism, and there is growing evidence that mitochondrial dysfunction plays a crucial role in the pathogenesis of obesity-associated insulin resistance. In this study, we determined the direct effect of IL-6 on lipolysis in adipocytes, and the effects of IL-6 on mitochondrial function were investigated. We found that cells treated with IL-6 displayed fewer lipids and an elevated glycerol release rate. Further, IL-6 treatment led to decreased mitochondrial membrane potential, decreased cellular ATP production, and increased intracellular ROS levels. The mitochondria in IL-6-treated cells became swollen and hollow with reduced or missing cristae. However, insulin-stimulated glucose transport was unaltered. PGC-1α, NRF1, and mtTFA mRNA levels were markedly increased, and the mitochondrial contents were also increased. Our results demonstrate that IL-6 can exert a direct lipolytic effect and induce mitochondrial dysfunction. However, IL-6 did not affect insulin sensitivity in adipocytes in vitro. We deduce that in these cells, enhanced mitochondrial biogenesis might play a compensatory role in glucose transport.

Keywords IL-6 · Adipocytes · Lipolysis · Mitochondria · Insulin resistance

Chenbo Ji and Xiaohui Chen contributed equally to this work.

C. Ji · X. Guo (✉)
Department of Pediatrics, Nanjing Maternal and Child Health Hospital of Nanjing Medical University,
123 Tianfei Lane,
Nanjing 210004, China
e-mail: xrguo@njmu.edu.cn

C. Ji · X. Chen · X. Guo
Institute of Pediatrics, Nanjing Medical University,
140 Hanzhong Road,
Nanjing 210029, China

C. Gao
Department of Pediatrics, Jinling Hospital,
Nanjing, China

L. Jiao · J. Wang · G. Xu · H. Fu · Y. Zhao (✉)
Department of Clinical Laboratory,
The 82nd Hospital of the People's Liberation Army,
100 Jiankang Road,
Huaian 223001, China
e-mail: zyp82yy@yahoo.com.cn

Introduction

Interleukin (IL)-6 is expressed in immune cells, endothelial cells, and myocytes. Recently, it was shown that IL-6 is also expressed in and released from adipocytes. Indeed, under non-inflammatory conditions, it is thought that 15% to 30% of circulating IL-6 is derived from adipose tissue (Mohamed-Ali et al. 1997; Fried et al. 1998). Some studies have suggested a link between IL-6 and impaired insulin action based on the observation that circulating and adipose tissue IL-6 levels are often increased in patients with obesity and type 2 diabetes; these increased IL-6 levels

correlate with BMI and adiposity (Roytblat et al. 2000; Vozarova et al. 2001; Bastard et al. 2002). In contrast, there is a strong body of literature suggesting that IL-6 does not cause insulin resistance, and may in fact have beneficial effects on the disease in some instances (Carey et al. 2006; Wolsk et al. 2010). IL-6 can enhance both glucose uptake and fat oxidation (Carey et al. 2006; Wolsk et al. 2010). Overexpression of IL-6 in mice leads to hypoglycemia and weight loss, whereas IL-6 knockout mice develop mature-onset obesity (Wallenius et al. 2002; Franckhauser et al. 2008). Thus, the effect of IL-6 on glucose and lipid metabolism is paradoxical, and therefore further studies are warranted.

Mitochondria are energy-producing organelles and the main sites of fat metabolism. Currently, there is growing evidence that mitochondrial dysfunction plays a crucial role in the pathogenesis of obesity-associated insulin resistance (Kim et al. 2008; Bournat and Brown 2010). Several studies have shown impaired mitochondria in myocytes and adipocytes from obese diabetic rodents and patients with obesity (Rong et al. 2007; Wilson-Fritch et al. 2004; Chanseaume et al. 2010), which usually display increased IL-6 levels. Interestingly, it is well known that IL-6 is rapidly released into the circulation following exercise, whereas endurance exercise effectively stimulates mitochondrial biogenesis and increases muscle oxidative capacity (Pedersen and Fischer 2007; Chow et al. 2007). Exercise has been thought to be a key component of comprehensive treatment programs for optimal weight loss and insulin sensitivity. Therefore, it is necessary to clarify the effects of IL-6 on mitochondrial function.

In this study, we observed the effects of IL-6 on lipolysis, mitochondrial function, mitochondrial biogenesis, and mitochondrial contents in differentiated 3T3-L1 adipocytes. We also determined the changes in adipocyte glucose uptake after treatment with IL-6. We show that IL-6 induces lipolysis and mitochondrial dysfunction, but does not affect insulin-stimulated glucose transport in 3T3-L1 adipocytes

Materials and methods

Cell culture and treatment

3T3-L1 cells were cultured and maintained and differentiated by using a previously described method (Student et al. 1980). Briefly, the cells were grown in DMEM/high-glucose medium (Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco) in a 5% CO2 environment. Medium was changed every 2 days. Two days after the cells became confluent, differentiation into adipocytes was initiated as follows: medium was supplemented with 0.5 mmol/L 3-isobuty-1-methylxanthine (MIX; Sigma, St. Louis, MO, USA), 1 μmol/L dexamethasone (Sigma), and 10 μg/mL insulin (Sigma) for 2 days. The medium was then changed and supplemented with insulin only for an additional 2 days. Thereafter, the cells were maintained in DMEM medium containing only 10% FBS.

On the 8th day after induction of differentiation, when more than 90% of the cells showed morphological and biochemical properties of adipocytes, the cells were used for experiments. After overnight incubation in serum-free DMEM, the 3T3-L1 adipocytes were treated with 20 ng/mL IL-6 (Sigma) for 24 h (Sopasakis et al. 2004).

Measurement of lipolysis

Glycerol release into the culture medium was used to assess changes in lipolysis levels (Green et al. 2004). Media were collected and glycerol release was determined using free glycerol reagent (Sigma) in a spectrophotometer (Jingke, Shanghai, China) with the wavelength set at 540 nm.

Oil red O staining

Cells were fixed with 4% formalin in phosphate buffer for 30 min at room temperature. After fixation, cells were stained with 0.6% (w/v) filtered oil red O solution (60% isopropanol, 40% water) for 30 min then counterstained with hematoxylin for 1 min at room temperature. Cells were then washed with water to remove unbound dye, visualized by light microscopy, and photographed.

ATP production

ATP content was measured using a luciferase-based luminescence assay kit (Biyuntian, Nantong, China). The cells were homogenized in ice-cold ATP-releasing buffer. Using an ATP standard, the concentration of ATP was determined using a single-tube luminometer (Turner Biosystems, CA, USA) and was normalized to protein concentration.

Confocal laser microscopy and flow cytometry

MitoTracker, a red mitochondria-specific cationic fluorescent dye (Molecular Probes, Invitrogen, Carlsbad, CA, USA), was used to evaluate mitochondrial membrane

potential. A H2-DCFDA probe (Sigma) was used to estimate intracellular ROS levels. The cells were incubated with 150 nM of MitoTracker and 5 μM of H2-DCFDA for 30 min at 37 °C, washed 3 times with pre-warmed PBS, and then imaged using a confocal laser scanning microscope (excitation at 579 nm and 488 nm, emission at 644 nm and 525 nm, respectively, ×400 magnification). For flow cytometry, the cells were trypsinized and centrifuged at 300 rpm at 4 °C for 5 min, and then resuspended in KRP-HEPES buffer (pH 7.4, with 0.5% BSA). The cells were analyzed with a FACScan flow cytometer using CellQuest software (BD Biosciences, San Jose, CA, USA).

Electron microscopy

The cells were collected after trypsin digestion, washed with fresh PBS, and fixed in 2.5% glutaraldehyde/4% paraformaldehyde in the same buffer. The cells were then washed with 0.1 M cacodylate buffer, post-fixed with 1% osmium tetroxide/1.5% potassium ferrocyanide for 1 h, stained with 1% aqueous uranyl acetate for 30 min, and then dehydrated through a graded series of ethanol to 100%. The samples were then infiltrated and embedded in TAAB Epon (Marivac Canada Inc., St. Laurent, Canada). Ultrathin sections (60 nm) were cut on a Reichert Ultracut-S microtome, placed onto copper grids, stained with uranyl acetate and lead citrate, and examined using a transmission electron microscope (JEOL JEM-1010, Tokyo, Japan) at an accelerating voltage of 80 kV (×50,000 magnification).

Glucose uptake

2-Deoxy-D-[^{3}H] glucose (Amersham Biosciences, Piscataway, NJ, USA) uptake was assayed as previously described with some modifications (Ceddia et al. 2005). Briefly, prior to the assay, the cells were deprived of serum for 4 h. The cells were then incubated in KRP-HEPES buffer (pH 7.4, 0.1% BSA) in the presence or absence of 100 nmol/L insulin for 30 min at 37 °C. Subsequently, 2-deoxy-D-[^{3}H]glucose was added to a final concentration of 1 μCi/mL. The reaction was terminated by 3 washes of ice-cold phosphate-buffered saline (PBS) supplemented with 10 mmol/L D-glucose. The cells were solubilized in 1 mol/L NaOH, and aliquots of the cell lysate were transferred to scintillation vials for radioactivity counting. The remainder of the lysate was used to measure the protein content with a bicinchoninic acid (BCA) protein assay kit (Pierce, Rockford, IL, USA). Radioactivity measurements were normalized to protein concentration.

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR)

Total RNA was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and quantified spectrophotometrically at 260 nm. cDNAwas synthesized from 1 μg of total RNA using an AMV Reverse Transcriptase Kit (Promega A3500; Promega, Madison, WI, USA) according to the manufacturer's instructions. Real-time qPCR was performed using the SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) in an Applied Biosystems 7300 Sequence Detection System (ABI 7300 SDS; Foster City, CA, USA). β-Actin was used as a reference for the comparative CT method to determine the relative changes in the samples. Sequences of the primers for each gene are shown in Table 1.

Real-time qPCR for mtDNA

Relative amounts of mtDNA were determined by real-time qPCR, and 2 primer sets were used for PCR analysis. Amplification of a 110-bp long fragment within the *CYTB* gene was used to quantify mtDNA. The PCR product was previously cloned into a pMD-T18 plasmid and was verified by DNA sequencing. Plasmid standards of known copy number were used to generate a log-linear standard curve, from which the CYTB copy number of the samples could be determined by real-time qPCR. Real-time qPCR was performed using an Applied Biosystems 7300 Sequence Detection System. A 291-bp region of the 28S rRNA gene was used to normalize the results. A standard curve of the plasmid containing the 28S fragment was used to determine the copy number of the samples. The ratio of mtDNA to nuclear DNA reflects the number of mitochondria per cell. The sequence of the primers and Taqman probes (Shenggong, Shanghai, China) are shown in Table 1.

Statistical analysis

Each experiment was performed at least 3 times. All values are presented as the means ± standard deviation (SD). Statistical analyses were performed using the Student's *t*-test. A P value <0.05 was considered statistically significant.

Results

IL-6 increased lipolysis in 3T3-L1 adipocytes

To assess the possibility that IL-6 increases lipolysis in adipocytes, glycerol accumulation in culture medium was measured. Fully differentiated 3T3-L1 adipocytes were incubated with IL-6 for 24 h. The results show

Table 1 Oligonucleotide sequences for primer/probe sets used in qPCR

Gene.	Forward prime r(5′-3′)	Reverse primer(5′-3′)	Probe
Cyt B	TTTTATCTGCATCTGA GTTTAATCCTGT	CCACTTCATCTTACCATTTATTATCGC	AGCAATCGTTCACCT CCTCTTCCTCCAC
28 s	GGCGGCCAAGCGTTCATAG	AGGCGTTCAGTCATAATCCCACAG	TGGTAGCTTCGCCCC ATTGGCTCCT
PGC-1α	CGGAAATCATATCCAACCAG	TGAGGACCGCTAGCAAGTTTG	
NRF1	TGGTCCAGAGAGTGCTTGTG	TTCCTGGGAAGGGAGAAGAT	
mtTFA	GGAATGTGGAGCGTGCTAAAA	TGCTGGAAAAACACTTCGGAATA	
β-actin	CCTGAGGCTCTTTTCCAGCC	TAGAGGTCTTTACGGATGTCAACGT	

that the cells displayed significantly fewer lipids as judged by the reduced level of oil red O staining (Fig. 1a), and the rate of glycerol release was significantly elevated (Fig. 1b).

IL-6 decreased cellular ATP production and mitochondrial membrane potential in 3T3-L1 adipocytes

Mitochondria are intracellular organelles that generate ATP through the process of oxidative phosphorylation (OXPHOS). To probe for the effect of IL-6 on mitochondrial function, we determined total cellular ATP production in IL-6-treated and control (untreated) adipocytes. As shown in Fig. 2a, cellular ATP production in adipocytes incubated with IL-6 was markedly lower than in the control cells. Mitochondrial membrane potential is fundamental for the conversion of ADP to ATP via ATP synthase. Consistent with the decreased ATP content in adipocytes treated with IL-6, we found that mitochondrial membrane potential was also greatly decreased (Fig. 2b).

IL-6 increased intracellular ROS levels in 3T3-L1 adipocytes

Intracellular ROS, a byproduct of the electron transport chain, is mainly produced in the mitochondria. We next examined ROS levels in IL-6-treated and control adipocytes. As shown in Fig. 3, IL-6 dramatically increased ROS levels in 3T3-L1 adipocytes.

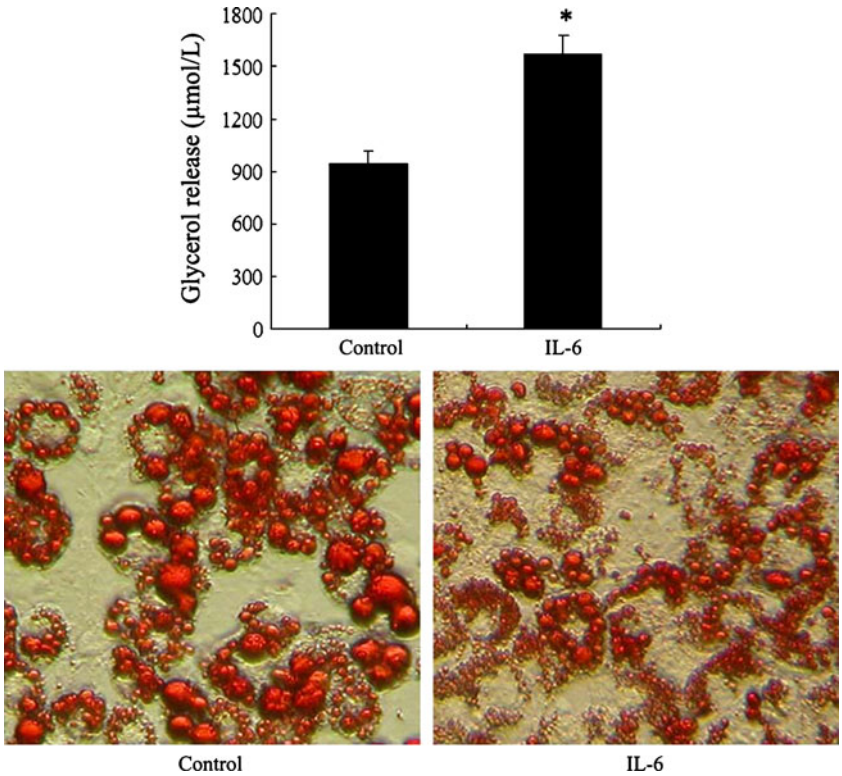

Fig. 1 Effect of IL-6 on lipolysis. Fully differentiated 3T3-L1 adipocytes were incubated in serum-free DMEM overnight then treated with 20 ng/mL IL-6 for 24 h. Media were collected to measure glycerol release. Data are presented as the mean ± SD (n=6). *, P<0.001 compared to the control cells. Cells were stained with oil red O solution, visualized by light microscopy, and photographed

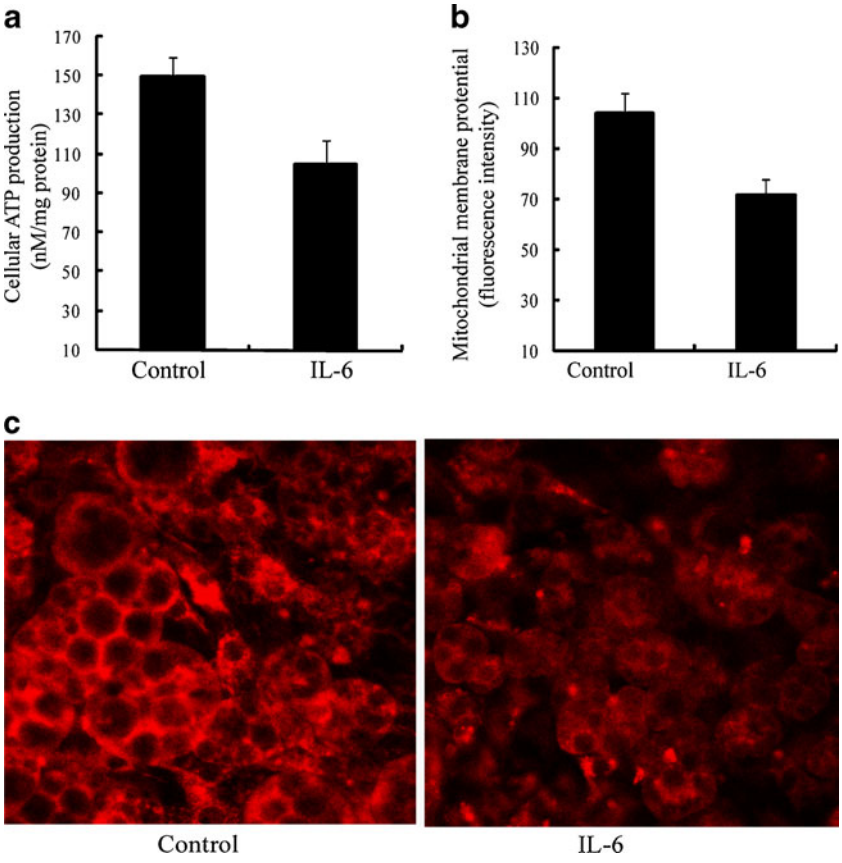

Fig. 2 Effect of IL-6 on cellular ATP production and mitochondrial membrane potential in 3T3-L1 adipocytes. Cellular ATP production was measured using a luciferase-based luminescence assay and normalized to protein concentration (n=6) (**a**). *, P<0.001 compared to the control cells. IL-6-treated adipocytes and control cells were stained with MitoTracker Red, analyzed using a FACScan flow cytometer (n=6) (**b**), and then imaged using a confocal laser-scanning microscope (×400 magnification) (**c**). *, P<0.001 compared to the control cells

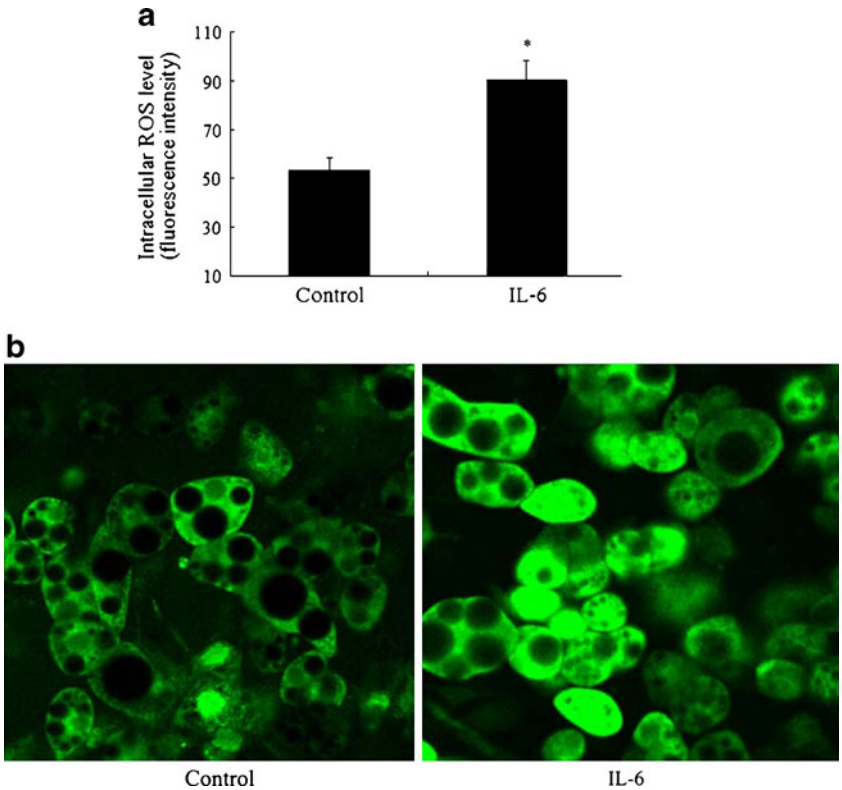

Fig. 3 Effect of IL-6 on intracellular ROS levels in 3T3-L1 adipocytes. ROS levels were determined by detection of a H2-DCFDA probe using a FACScan flow cytometer (n=6) (**a**) and a confocal laser-scanning microscope (×400 magnification) (**b**). *, P<0.001 compared to the control cells

IL-6 caused abnormal mitochondrial morphology in 3T3-L1 adipocytes

We further observed the morphology of mitochondria in IL-6-treated adipocytes using electron microscopy. As shown in Fig. 4, mitochondria in adipocytes incubated with IL-6 appeared swollen and hollow with reduced and missing cristae.

Effects of IL-6 on glucose transport in 3T3-L1 adipocytes

Effects of IL-6 on glucose transport were assessed by measuring 2-Deoxy-D-[^{3}H] glucose uptake rate in adipocytes. The results show that basal glucose uptake in IL-6-treated adipocytes was increased compared to that in untreated control cells. However, IL-6 did not affect insulin-stimulated glucose uptake in adipocytes (Fig. 5).

Effect of IL-6 on mitochondrial biogenesis in 3T3-L1 adipocytes

It is known that most mitochondrial proteins are encoded by the nuclear genome, and that the translated proteins are transported into the mitochondria. Substantial evidence indicates that extracellular stimuli induce mitochondrial biogenesis by increasing gene expression of peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1), nuclear respiratory factor-1 (NRF-1), and mitochondrial transcription factor A (mtTFA) (Spiegelman 2007). In order to determine the effect of IL-6 treatment on mitochondrial biogenesis in adipocytes, we assessed PGC-1α, NRF1, and mtTFA mRNA expression. As shown in Fig. 6a, the levels of PGC-1α, NRF1, and mtTFA mRNA were considerably increased in IL-6-treated adipocytes.

Effect of IL-6 on mitochondrial content in 3T3-L1 adipocytes

To confirm whether the augmented mitochondrial biogenesis causes changes in mitochondrial content within IL-6-treated adipocytes, we measured mitochondrial and genomic DNA in IL-6-treated and control adipocytes using real-time qPCR. Cytochrome b was used as a marker for mtDNA and 18S was used as a marker for nuclear DNA. As expected, the mtDNA copy number in IL-6-treated adipocytes was significantly increased compared to the control cells (Fig. 6b).

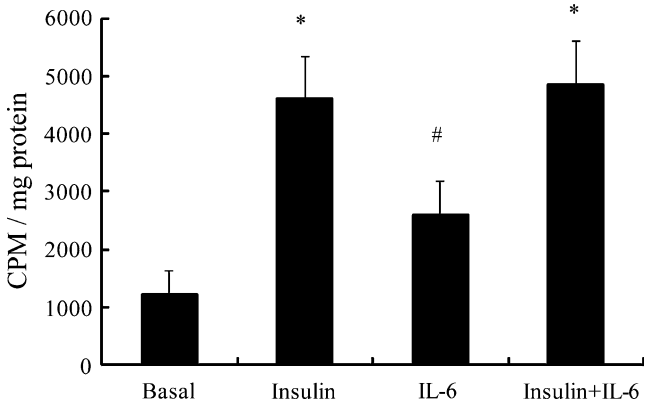

Fig. 5 Rate of glucose transport in IL-6-treated cells. Fully differentiated 3T3-L1 adipocytes were incubated with 20 ng/mL recombinant mouse IL-6 for 24 h. Basal glucose transport and insulin-stimulated glucose transport are shown. Basal rate refers to the rate of glucose transport in the absence of insulin. *, significantly increased glucose uptake in IL-6-treated 3T3-L1 cells compared to untreated control cells (n=6). (P<0.05, t-test)

Discussion

Several studies have reported that administration of IL-6 in healthy humans increased systemic lipolysis (van Hall et al. 2003; Lyngsø et al. 2002). Here, we showed the direct lipolytic effect of IL-6 in differentiated adipocytes, which might be involved in obesity-related high lipolytic capacity and exercise-induced lipolysis. Enhanced fatty acid metabolism may lead to an increase in ATP production. However, in the current study, we found that the ATP content in IL-6-treated adipocytes was markedly decreased. Concomitantly,

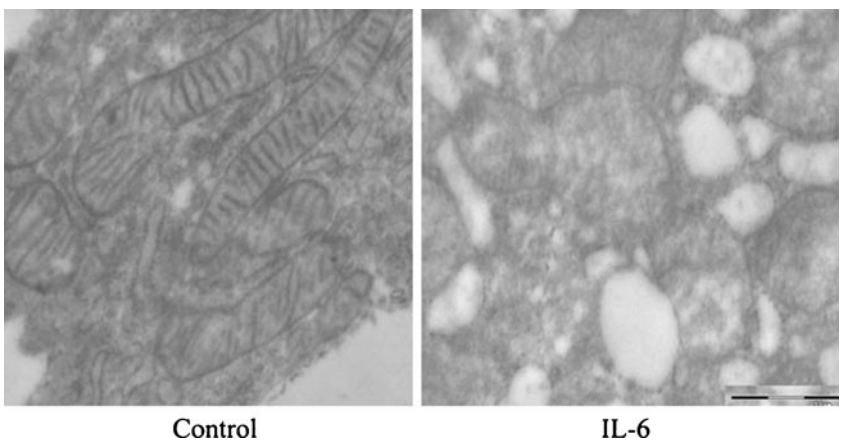

Fig. 4 Effect of IL-6 on mitochondrial morphology. Mitochondrial ultrastructure in IL-6-treated adipocytes and control cells was visualized using transmission electron microscopy (×50,000 magnification). The scale bar in the bottom right corner is 1 μm

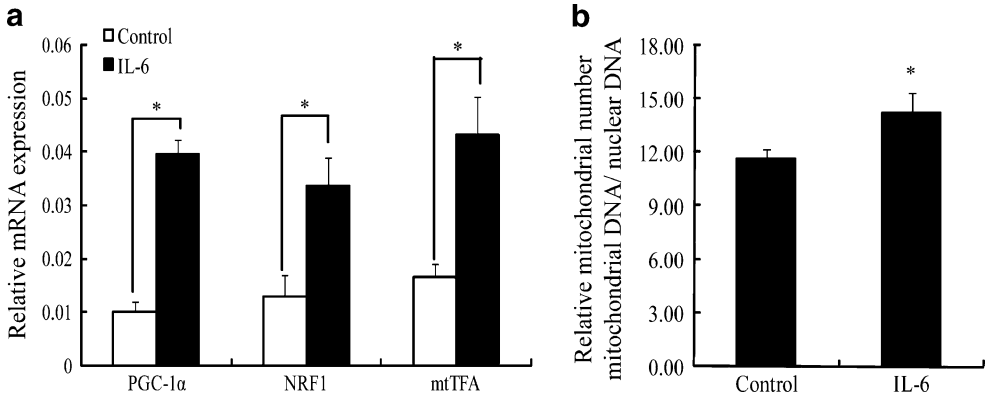

Fig. 6 Effect of IL-6 on mitochondrial biogenesis and mtDNA copy number in 3T3-L1 adipocytes. The mRNA levels of PGC-1α, NRF, and mtTFA were analyzed using real-time quantitative RT-PCR and normalized to β-actin levels (n=6) (**a**). *, P<0.05. The cellular mtDNA content was assessed by real-time qPCR analysis with primers designed to target the *CYTB* and 28S rRNA genes (n=6) (**b**). The ratio of the *CYTB* gene to the 28S rRNA gene reflects the number of mitochondria per cell

mitochondrial membrane potential also observably declined. Normally, fatty acids in the cell are maintained at a constant level depending on the balance of fatty acid availability and utilization. A recent study demonstrated that exposure to fatty acids disrupted mitochondrial fuel homeostasis in cultured myotubes (Koves et al. 2008). The lipid surplus resulted in a disproportionate increase in the rate of incomplete oxidation relative to complete oxidation of fatty acids, and caused the accumulation of even-chain acylcarnitines of short, medium, and long chain length. Obesity, diabetes, and high-fat feeding are also accompanied by high rates of fatty acid catabolism, principally "incomplete" fat oxidation, in which a large proportion of fatty acids entering the mitochondria are only partially degraded (Koves et al. 2008; Muoio and Koves 2007). Additionally, it has been reported that long-chain fatty acids are natural uncouplers of oxidative phosphorylation in mitochondria, which would become apparent under particular physiological or pathological conditions characterized by unusual fatty acid accumulation (Wojtczak and Schönfeld 1993). It is not surprising that treatment of adipocytes with IL-6 may result in excess fatty acids due to increased lipolysis, which might induce the decreased membrane potential and incomplete oxidation of fatty acids; thus reducing ATP production.

Adipocytes treated with IL-6 also displayed increased ROS levels. ROS production is an unavoidable byproduct of oxidative phosphorylation. Accumulation of fatty acids in the vicinity of the mitochondrial matrix, where oxidative processes take place, makes them prone to lipid peroxidation. Uncontrolled increase of these oxidants is detrimental to mitochondria, and damages mitochondrial proteins, DNA, and lipids in membrane components, resulting in mitochondrial morphological abnormalities and reduced oxidative capacity (Schrauwen and Hesselink 2004). As expected, we found that mitochondria in adipocytes incubated with IL-6 appeared swollen and hollow with reduced density and missing cristae. As the mitochondrial matrix and cristae are the main sites of metabolism, it is conceivable that these mitochondria do not contain sufficient space to maintain normal or excessive metabolic needs. Interestingly, the changes in mitochondrial morphology and function in IL-6-treated adipocytes are very similar to those observed in obese rodents and human, which also have chronically elevated IL-6 (Choo et al. 2006; Højlund et al. 2008).

It has been reported that the development of mitochondrial dysfunction contributes to the pathogenesis of insulin resistance in adipocytes (Patti and Corvera 2010). However, the effects of IL-6 on glucose transport appear to be equivocal. Some studies have demonstrated an increase in insulin-stimulated glucose transport in IL-6-treated adipocytes (Carey et al. 2006; Stouthard et al. 1996), but others have found the opposite effect (Rotter et al. 2003; Bastard et al. 2002). In the current study, we found that IL-6-treated adipocytes exhibit a reduced mitochondrial function. However, insulin-stimulated glucose uptake was unaltered. Meanwhile, IL-6 significantly increased basal glucose uptake in adipocytes. This result seems to be consistent with the finding that overexpression of IL-6 in mice leads to hypoglycemia, whereas IL-$6^{-/-}$ mice display impaired glucose tolerance (Wallenius et al. 2002; Franckhauser et al. 2008), the underlying mechanism of which is not fully clear. Interestingly, we found that IL-6 simultaneously increased PGC-1α, NRF1, and mtTFA expression in 3T3-L1 adipocytes. PGC-1α is known to regulate the transcription of genes involved in mitochondrial biogenesis and fatty acid oxidation. Increased PGC-1α protein expression leads to an increase in target genes, including NRF-1, which is an intermediate transcription factor that stimulates many nuclear-encoded mitochondrial genes such as mtTFA and activates the duplication of mitochon-

drial DNA molecules (Kelly and Scarpulla 2004). Consistently, we also found that mitochondrial content was significantly elevated in adipocytes treated with IL-6. Therefore, we deduced that enhanced mitochondrial biogenesis in these cells might serve a compensatory role in glucose transport.

In summary, our results demonstrated that IL-6 could exert a direct lipolytic effect and induce mitochondrial dysfunction in adipocytes in vitro. During IL-6 treatment, cellular ATP production was decreased and ROS levels were elevated. However, insulin-stimulated glucose transport was unaltered, and mitochondrial biogenesis was enhanced. Although the exact relationship among IL-6, mitochondrial function, and insulin sensitivity requires further investigation, our data provide new insights into the mechanism underlying IL-6 regulation of fat and glucose metabolism.

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References

Bastard JP, Maachi M, Van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, Robert JJ, Capeau J, Hainque B (2002) Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. J Clin Endocrinol Metab 87 (5):2084–2089

Bournat JC, Brown CW (2010) Mitochondrial dysfunction in obesity. Curr Opin Endocrinol Diabetes Obes 17(5):446–452

Carey AL, Steinberg GR, Macaulay SL, Thomas WG, Holmes AG, Ramm G, Prelovsek O, Hohnen-Behrens C, Watt MJ, James DE, Kemp BE, Pedersen BK, Febbraio MA (2006) Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. Diabetes 55(10):2688–2697

Ceddia RB, Somwar R, Maida A, Fanq X, Bikopouls G, Sweeney G (2005) Globular adiponectin increases GLUT4 translocation and glucose uptake but reduces glycogen synthesis in rat skeletal muscle cells. Diabetologia 48(1):132–139

Chanseaume E, Barquissau V, Salles J, Aucouturier J, Patrac V, Giraudet C, Gryson C, Duché P, Boirie Y, Chardigny JM, Morio B (2010) Muscle mitochondrial oxidative phosphorylation activity, but not content, is altered with abdominal obesity in sedentary men: synergism with changes in insulin sensitivity. J Clin Endocrinol Metab 95(6):2948–2956

Choo HJ, Kim JH, Kwon OB, Lee CS, Mun JY, Han SS, Yoon YS, Yoon G, Choi KM, Ko YG (2006) Mitochondria are impaired in the adipocytes of type 2 diabetic mice. Diabetologia 49(4):784–791

Chow LS, Greenlund LJ, Asmann YW, Short KR, McCrady SK, Levine JA, Nair KS (2007) Impact of endurance training on murine spontaneous activity, muscle mitochondrial DNA abundance, gene transcripts, and function. J Appl Physiol 102 (3):1078–1089

Franckhauser S, Elias I, Rotter Sopasakis V, Ferré T, Nagaev I, Andersson CX, Agudo J, Ruberte J, Bosch F, Smith U (2008) Overexpression of Il6 leads to hyperinsulinaemia, liver inflammation and reduced body weight in mice. Diabetologia 51 (7):1306–1316

Fried SK, Bunkin DA, Greenberg AS (1998) Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 83(3):847–850

Green A, Rumberger JM, Stuart CA, Ruhoff MS (2004) Stimulation of lipolysis by tumor necrosis factor-alpha in 3T3-L1 adipocytes is glucose dependent: implications for long-term regulation of lipolysis. Diabetes 53(1):74–81

Højlund K, Mogensen M, Sahlin K, Beck-Nielsen H (2008) Mitochondrial dysfunction in type 2 diabetes and obesity. Endocrinol Metab Clin North Am 37(3):713–731

Kelly DP, Scarpulla RC (2004) Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes Dev 18 (4):357–368

Kim JA, Wei Y, Sowers JR (2008) Role of mitochondrial dysfunction in insulin resistance. Circ Res 102(4):401–414

Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, Lopaschuk GD, Muoio DM (2008) Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. Cell Metab 7(1):45–56

Lyngsø D, Simonsen L, Bülow J (2002) Interleukin-6 production in human subcutaneous abdominal adipose tissue: the effect of exercise. J Physiol 543(Pt 1):373–378

Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW (1997) Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 82(12):4196–4200

Muoio DM, Koves TR (2007) Skeletal muscle adaptation to fatty acid depends on coordinated actions of the PPARs and PGC1 alpha: implications for metabolic disease. Appl Physiol Nutr Metab 32 (5):874–883

Patti ME, Corvera S (2010) The role of mitochondria in the pathogenesis of type 2 diabetes. Endocr Rev 31(3):364–395

Pedersen BK, Fischer CP (2007) Beneficial health effects of exercise —the role of IL-6 as a myokine. Trends Pharmacol Sci 28 (4):152–156

Rong JX, Qiu Y, Hansen MK, Zhu L, Zhang V, Xie M, Okamoto Y, Mattie MD, Higashiyama H, Asano S, Strum JC, Ryan TE (2007) Adipose mitochondrial biogenesis is suppressed in db/db and high-fat diet–fed mice and improved by rosiglitazone. Diabetes 56(7):1751–1760

Rotter V, Nagaev I, Smith U (2003) Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. J Biol Chem 278(46):45777–45784

Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A, Gelman S (2000) Raised interleukin-6 levels in obese patients. Obes Res 8(9):673–675

Schrauwen P, Hesselink MK (2004) Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes. Diabetes 53 (6):1412–1417

Sopasakis VR, Sandqvist M, Gustafson B, Hammarstedt A, Schmelz M, Yang X, Jansson PA, Smith U (2004) High local concentrations and effects on differentiation implicate interleukin-6 as a paracrine regulator. Obes Res 12(3):454–460

Spiegelman BM (2007) Transcriptional control of mitochondrial energy metabolism through the PGC1 coactivators. Novartis Found Symp 287:60–63, discussion 63–69

Stouthard JM, Oude Elferink RP, Sauerwein HP (1996) Interleukin-6 enhances glucose transport in 3T3-L1 adipocytes. Biochem Biophys Res Commun 220(2):241–245

Student AK, Hsu RY, Lane MD (1980) Induction of fatty acid synthetase synthesis in differentiating 3T3-L1 preadipocytes. J Biol Chem 255(10):4745–4750

van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, Hiscock N, Møller K, Saltin B, Febbraio MA, Pedersen BK (2003) Interleukin-6 stimulates lipolysis and fat oxidation in humans. J Clin Endocrinol Metab 88(7):3005–3010

Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE (2001) Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res 9(7):414–417

Wallenius V, Wallenius K, Ahrén B, Rudling M, Carlsten H, Dickson SL, Ohlsson C, Jansson JO (2002) Interleukin-6-deficient mice develop mature-onset obesity. Nat Med 8(1):75–79

Wilson-Fritch L, Nicoloro S, Chouinard M, Lazar MA, Chui PC, Leszyk J, Straubhaar J, Czech MP, Corvera S (2004) Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone. J Clin Invest 114(9):1281–1289

Wojtczak L, Schönfeld P (1993) Effect of fatty acids on energy coupling processes in mitochondria. Biochim Biophys Acta 1183 (1):41–57

Wolsk E, Mygind H, Grøndahl TS, Pedersen BK, van Hall G (2010) IL-6 selectively stimulates fat metabolism in human skeletal muscle. Am J Physiol Endocrinol Metab 299(5):E832–E840