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UCP2 gene polymorphisms in obesity and diabetes, and the role of UCP2 in cancer

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Abstract

Mitochondria are the primary sites for ATP synthesis and free radical generation in organisms. Abnormal mitochondrial metabolism contributes to many diseases, including obesity, diabetes, and cancer. UCP2 is an ion/anion transporter located in mitochondrial inner membrane, and has a crucial role in regulating oxidative stress, cellular metabolism, cell proliferation, and cell death. polymorphisms of the UCP2 gene have been associated with diabetes and obesity, as UCP2 is involved in energy expenditure and insulin secretion. Moreover, UCP2 gene expression is often amplified in cancers, and increased UCP2 expression contributes to cancer growth, cancer metabolism, anti-apoptosis, and drug resistance. This article will summarize the latest findings of UCP2 on obesity, diabetes, and cancer.

Keywords: UCP2, obesity, diabetes, cancer, polymorphism, mitochondria

1. Introduction

Uncoupling proteins (UCPs), located in mitochondrial inner membrane, belong to the mitochondrial transporter family SLC25 (Palmieri, 2013). There are five members in the UCP family: UCP1 is the first to be identified and discovered in brown adipose tissue. UCP1 is a proton transporter allowing mitochondrial membrane potential to be transduced to heat (Rial et al., 1998). UCP2, one homolog of UCP1 was described in 1997 (Fleury et al., 1997). In contrast to UCP1, UCP2 is expressed in many organs and tissues in the body, including skin (Mori et al., 2008), brain (Shen et al., 2017), liver (Iannucci et al., 2016), and kidney (de Souza et al., 2015). UCP2 is also considered as an antioxidant since it suppresses the generation of reactive oxygen species (ROS) in mitochondria (Cadenas 2018). UCP3 is distributed in skeletal muscle and heart (a little) which participates in the regulation of skeletal muscle respiration (Boss et al., 2018) and pH flash frequency in skeletal muscle fibers (McBride et al., 2019). UCP4 and UCP5 are mainly located in the brain (Mao et al., 1999; Yu et al., 2000), and they play an important role in energy homeostasis and neuroprotection (Ramsden et al., 2012).

UCP1 exists in large amounts, up to 10% of membrane proteins in brown adipose tissues, whereas other UCPs are present in much smaller amounts (Brand and Esteves, 2005). Similar to UCP1, other UCPs can also catalyze net proton conductance when activated by fatty acids (Brand and Esteves, 2005). Besides protons, UCP2 and UCP3 can transport anions across the mitochondrial inner membrane (Echtay et al., 1999). Mitochondria are the major source of superoxide production due to one-electron reduction of oxygen. This reaction correlates with the levels of mitochondrial membrane potential. Therefore, the uncoupling effect caused by UCPs can lower mitochondrial superoxide production.

The UCP2 gene is located in chromosome 1 of rats, chromosome 7 of mice, and chromosome 11 of human beings (Kaisaki et al., 1998). Genetic polymorphism of UCP2 has been reported. Gene polymorphism, different from mutation, is an inherited variation in DNA sequence among populations, which may cause a change in the structure/function/activity of the gene product. UCP2 gene polymorphisms may play a pathological role in human diseases, such as

cardiovascular disease (Tian et al., 2018), hypertension (Ji et al., 2004), diabetes (Zhou et al., 2018), obesity (Kaabi 2018), and cancer (Marques et al., 2017).

The gene expression of UCP2 is regulated by many factors *in vivo*. UCP2 is responsive to unsaturated fatty acids in food to regulate energy metabolism (Reilly and Thompson, 2000). UCP2 can be regulated by miRNAs to influence tumor metabolism and chemoresistance (Yuan et al., 2015). UCP2 is also regulated by growth hormones (Futawaka et al., 2016). In addition, the activity of UCP2 can be regulated by several factors including ROS, free fatty acids, purine nucleotides, coenzyme Q, etc., which has been nicely summarized in a recent review (Woyda-Ploszczyca and Jarmuszkiewicz, 2017). In brief, as the anion carrier, free fatty acids are required for the activation of UCP2 (Klingenberg and Huang, 1999). It is speculated that superoxide reacts with polyunsaturated fatty acyl chains of membrane phospholipids, resulting in the generation of 4-hydroxynonenal and other reactive alkenals. These reactive alkenals activate the proton conductance activity of UCP2 (Brand and Esteves, 2005). Purine (guanine) nucleotides directly bind to UCP2 and the binding site faces the intermembrane space of mitochondria and UCP2 activity is inhibited (Klingenberg and Huang, 1999). It has been suggested that coenzyme Q could affect UCP2 activity in two ways: cooperating with fatty acids to mediate proton transfer in its oxidized form; and generating ROS and 4-hydroxynonenal in its reduced form (Woyda-Ploszczyca and Jarmuszkiewicz, 2017). Overall, UCP2 is responsive to and then regulates the metabolic alterations in the body, which makes it a potential target for metabolic diseases including obesity, diabetes, and cancer.

2. UCP2 and obesity

Obesity, a chronic metabolic disorder caused by the interactions among genetic factors, epigenetic factors, environmental factors, and lifestyles (Rohde et al., 2018), is becoming a major health problem worldwide. As a mitochondrial transporter regulating glucose/lipid metabolism and energy homeostasis, UCP2 plays an important role in the development and treatment of obesity. UCP2 mRNA levels are often decreased in white adipose tissue in obese individuals compared to their lean controls (Oberkofler et al., 1998). Mechanisms of UCP2-mediated regulation of obesity include but not limited to 1) UCP2 indirectly activates the melanocortin-4 receptor, therefore inhibiting food intake and increasing energy expenditure (Toda and Diano, 2014); 2) UCP2 negatively regulates glucose-dependent insulin secretion in pancreatic β cells (Zhang et al., 2001) and positively regulates glucagon secretion from pancreatic α cells (Allister et al., 2013). In term of weight loss, there is a positive correlation between weight loss and UCP2 expression (Cortes-Oliveira et al., 2017).

The gene polymorphism of UCP2 may serve as an endogenous risk factor for obesity. There are three mostly studied polymorphisms in the UCP2 gene: one is located in the promoter regions (rs659366, -866G/A), one is a missense variant in exon 4 (rs660339, Ala55Val, C/T), and one is a 45-base pair (bp) insertion (I)/deletion (D) in exon 8.

Among various ethnicities, the UCP2 −866G/A polymorphism has been found to be associated with obesity (Srivastava et al., 2010; Martinez-Hervas et al., 2012). The GG genotype is associated with an increased risk of obesity among Egyptians (Hassan et al., 2018) and white Europeans (Esterbauer et al., 2001). The haplotype containing the −866G-allele is associated with childhood obesity in the United Kingdom (Dhamrait et al., 2004). On the other side, the A allele of −866G/A polymorphism has a protective effect on overweight and obesity, especially for the European populations (Brondani et al., 2014; Zhang et al., 2014). The possible mechanism could be attributed to the different expression levels of UCP2 mRNA between the −866G-allele and the A allele in obesity: the G allele has lower UCP2 mRNA/protein expression levels compared with the A allele, resulted in increased reactive oxygen species generation, decreased insulin secretion and energy expenditure, therefore, increased accumulation of body fat in the G-allele individuals (Andersen et al., 2013).

The effects of the Ala55Val polymorphism on obesity is influenced by ethnic and gender differences. Among Italian and Swedish women, the Ala55Val polymorphism of UCP2 gene is not associated with the characteristics of clinical, metabolic, and anthropometric obesity (Maestrini et al., 2003; Mottagui-Tabar et al., 2008). However, in the aboriginal populations in Taiwan, the Val55 allele shows increased the risk of obesity compared to the Ala55 allele (Wang et al., 2004). Another study from Taiwan finds that the Ala55Val polymorphism is associated with morbid obesity and weight loss (Chen et al., 2007). In addition, obese patients carrying TT or CT genotype show greater weight loss compared to the CC genotypes after the LAGB (laparoscopic adjustable gastric banding) surgery (Chen et al., 2007).

In an Indonesian study, the Ala55Val polymorphism shows a gender effect on the risk of obesity: the TT and CT genotypes reduce the risk of obesity in the male but not in the female group (Surniyantoro et al., 2018).

A possible mechanism of Ala55Val polymorphism-regulated obesity is that this single-nucleotide polymorphism is adjacent to the phosphorylation site of Protein Kinase C (PKC), therefore, interfering with the phosphorylation of UCP2 by PKC, resulting in decreased UCP2 activities (Surniyantoro et al., 2018). The ethnic/gender discrepancy might be due to several reasons: UCP2 regulated proteins could be different; environmental factors vary in different regions; body fat differences between male and female.

The association between the 45-base pair (bp) insertion (I)/deletion (D) polymorphism and obesity is found mainly among Asians and the results show regional and gender differences. The D/D genotype is the most widely distributed in eastern Saudi Arabia and it is associated with severe obesity (Kabbi 2018). Among Indonesians, the D/I genotype and I allele reduce the risk of obesity in the female group; whereas the I/I genotype and I allele are a risk factor for obesity in the male group (Surniyantoro et al., 2018). In a Malaysian study, the I allele is a risk factor for obesity among Malaysian women (Say et al., 2014). In an Iranian (Hashemi et al., 2014) and a Turkish (Oguzkan-Balci et al., 2013) study, the I/I genotype and I allele also show a higher risk for obesity compared to the D/D genotype.

The location of this polymorphism in the 3'UTR in exon 8 is thought to be involved in regulating mRNA transcription or its stability. It is speculated that this polymorphism leads to decreased UCP2 protein levels and lower energy expenditure (Esterbauer et al., 2001).

In summary, although controversies exist, higher UCP2 expression levels could enhance energy expenditure, therefore, reduce the risk of obesity. The association between UCP2 gene polymorphisms and obesity depends on how the polymorphisms affect UCP2 expression/activity levels; however, other factors such as ethnicity, gender, and environment also play an influential role. Futures directions may include: besides functioning as an ion/anion transporter, does UCP2 convey other transport activity? Is there any effector protein binding to UCP2 and mediating its action? Where UCP2 stands in the big picture of mitochondria-to-nucleus signaling regulating obesity?

3. UCP2 and diabetes

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia which is related to genetic inheritance and environmental factors. Diabetes is divided into Type 1 diabetes (T1D) and Type 2 diabetes (T2D). Due to its regulatory role in ATP synthesis, glycolysis, and oxidative stress, it is not surprising that UCP2 plays an important role in the development of diabetes.

Pancreatic β-cells rely heavily on ATP for insulin secretion, therefore, it is often found that there is a negative relationship between UCP2 and glucose-stimulated insulin secretion (Seshadri et al., 2017). This suppression of insulin secretion by upregulated UCP2 increases the risk of T2D in humans (Sasahara et al., 2004).

Similar to obesity, the -866G/A in the promoter region, Ala55Val in exon 4, and 45 bp insertion(I)/deletion(D) in exon 8 are mostly studied for the relationship between UCP2 polymorphisms and diabetes.

Results find that individuals with the AA genotype and A allele of the -866G/A polymorphism have an increased risk for diabetes in Austrian (Krempler et al., 2002), Italian (Sesti et al., 2003), American (Hsu et al., 2008), and Indian populations (Kaul et al., 2015). The A allele of -866G/A is associated with higher promoter activity of UCP2 in β-cells (Krempler et al., 2002; Sasahara et al. 2004), which leads to higher UCP2 expression, lower ATP production, decreased insulin secretion, and increased plasma glucose levels.

For the Ala55Val polymorphism, the Val/Val (VV) genotype is a risk factor for diabetes compared to the Ala/Ala (AA) genotype among Chinese (Xiu et al., 2004) and American (Yu et al., 2005) populations. The VV genotype shows increased insulin resistance in those with impaired glucose homeostasis. The VV genotype has a lower degree of uncoupling, more efficient energy utilization, more production of ROS and more β-cell damage, and lower fat oxidation compared to the AA genotype (Astrup et al., 1999; Walder et al., 1998).

There are fewer reports on the 3'-UTR 45-bp I/D polymorphism in diabetes. The I allele and DI genotype are more common in diabetic retinopathy among the Chinese population (Zhou et al., 2018). II and DI genotypes are associated with a higher risk of proliferative diabetic retinopathy, and the DI genotype is associated with a higher risk of non-proliferative diabetic retinopathy (Zhou et al., 2018). In an Iranian study, the 45-bp I/D polymorphism of UCP2 gene is associated with metabolic syndrome, which is being recognized as a risk factor for insulin resistance (Hashemi et al., 2014).

The exact mechanism of how 45-bp I/D polymorphism affects diabetes is unclear. It has been suggested that this 3' UTR variant might be involved in mRNA processing or in transcript stability (Hashemi et al., 2014).

In summary, the impact of UCP2 deregulation on diabetes is likely the net result of two seemingly opposite effects: decreasing UCP2 activity increases ATP production and insulin secretion, but decreased UCP2 activity can also increase ROS generation leading to the damage of insulin-secreting β-cells. Future directions may include: what is the precise mechanism for UCP2 to regulate insulin secretion? What is the role of UCP2 deregulation in insulin-resistant diabetes? What other signaling molecules UCP2 may regulate during the pathogenesis of diabetes?

A schematic diagram on the role of UCP2 in diabetes is shown in Figure 1.

4. UCP2 and cancer

Cancer is the 2nd leading cause of death in the United States. Approximately 1.6 million new cases occur with 600,000 deaths each year (Golemis et al., 2018). Metabolic alterations are one of the hallmarks of cancer. As early as 100 years ago, Otto Warburg observed that even in oxygen-rich conditions, cancer cells would give priority to glycolysis and contain far more energy than surrounding tissues (Warburg et al., 1927). Furthermore, cancer cells can also obtain energy from more sources than normal cells.

Due to its regulatory role in ATP synthesis and cellular metabolism, UCP2 plays an important role in cancer metabolism. UCP2 amplification has been detected in a number of human cancers, including leukemia, skin cancer, pancreatic cancer, non-small cell lung cancer, colon cancer, and hepatocarcinoma (Pitt, 2015; Oleksiewicz et al., 2017; Li et al., 2013). The UCP2 gene polymorphism is also found to be associated with cancer prognosis. The -866G/A polymorphism is associated with the outcomes of colorectal cancer after surgery: the GG genotype has the highest survival rate, whereas the AA genotype is the most detrimental (Jiang et al., 2018). As discussed above, the G allele has lower UCP2 mRNA expression levels compared with the A allele, resulted in lower UCP2 protein levels (Andersen et al., 2013), which further suggests that UCP2 may promote cancer growth and survival.

UCP2 in cancer cell behavior and signaling pathways

To test whether UCP2 promotes skin carcinogenesis, our group has performed a chemically-induced multistage skin carcinogenesis study using UCP2 homozygous knockout and wild-type mice (Li et al., 2015). The results demonstrate that UCP2 deficiency suppresses the formation of both benign and malignant skin tumors, as well as the increases in cutaneous inflammation. However, UCP2 deficiency does not enhance chemical carcinogen-induced apoptosis.

In other studies, targeting UCP2 has been shown to induce apoptosis of tumor cells. For instance, Oroxylin A induces mitochondrial permeability transition pore (MPTP) in colon cancer cells through the inhibition of UCP2 in a dose-dependent manner, resulting in increased levels of ROS and apoptosis (Qiao et al., 2015). In this study, colon cancer cells are more sensitive to Oroxylin A treatment after UCP2 knockdown using siRNAs.

Promoting cell proliferation is considered an important mechanism of UCP2 in contributing to tumorigenesis. In our study of skin carcinogenesis, UCP2 deficiency clearly suppresses skin cell proliferation evidenced by mitotic cell counts and Ki-67 staining (Li et al., 2015). In hepatocellular carcinoma, cell proliferation is inhibited when UCP2 is downregulated by miR-214 (Yu et al., 2016).

The tumor-promoting effects of UCP2 can also be attributed to the alterations in glycolysis and signaling pathways. Glycolysis is often boosted in tumor cells. A recent study has demonstrated how UCP2 participates in shifting oxidative phosphorylation to glycolysis in pancreas cancer cells (Brandi et al., 2016). The expression levels of the glucose transporter GLUT1 and pyruvate kinase isoform M2 (PKM2) mRNA are increased after UCP2 stimulation. When UCP2 is inhibited, the components of mitochondrial oxygen consumption such as complex I, complex IV, and complex V are downregulated. Moreover, cancer cells with higher UCP2 expression are more sensitive to 2-deoxy-D-glucose (2-DG), a widely used inhibitor of glycolysis (Brandi et al., 2016).

Our group has studied the mechanism of how UCP2 regulates glycolysis during cell transformation (Sreedhar et al., 2017). In phorbol ester-treated UCP2 overexpressing skin epidermal cells, glycolysis is enhanced, at least partially, through the activation of phosphofructokinase 2/ fructose-2,6-bisphosphatase 2 (PFKFB2), which is mediated by activated Akt. When PFKFB2 is inhibited, cellular metabolism is switched from glycolysis to mitochondrial respiration.

Using the same model, our group has also found that upregulated UCP2 enhances the signaling of PLCγ-1 (Sreedhar et al., 2017). In UCP2 overexpressing cells, the levels of superoxide are decreased whereas that of hydrogen peroxide are increased, concomitantly with increased expression and activity levels of manganese superoxide dismutase. These changes cause increased lipid peroxidation and PLCγ-1 activation.

However, there are controversial results regarding the role of UCP2 in cancer. When UCP2 is overexpressing in a murine melanoma, a human pancreatic and glioblastoma cell line, tumor cell proliferation is inhibited due to redirecting cancer metabolism from glycolysis to oxidative phosphorylation (Esteves et al., 2014). Different results may be due to different endogenous levels of UCP2 in human cancers.

The role of UCP2 in regulating cellular behaviors has been summarized in Figure 2.

UCP2 and drug resistance

Chemotherapy resistance is one of the major reasons for the failure of cancer treatment. Recent studies have found that UCP2 may regulate cancer cell sensitivity to anti-tumor agents.

Gemcitabine is a traditional chemotherapeutic agent to treat pancreatic cancer, non-small cell lung cancer, ovarian cancer, breast cancer (Strouse and Epperla, 2017). Gemcitabine chemoresistance has been linked to UCP2 in several cancer types. In hepatocellular tumors, inhibition of UCP2 increases the sensitivity of cancer cells to gemcitabine, which is accompanied by increases in mitochondrial superoxide levels (Yu et al., 2015).

In breast cancer cells, downregulation of UCP2 increases the sensitivity of cells to cisplatin and tamoxifen treatment (Pons et al., 2015). In UCP2 knockdown cells, cell viability and clonal formation are decreased with the increases in mitochondrial membrane potential, ROS production, and apoptotic cell death. UCP2 knockdown plus tamoxifen treatment increase autophagic cell death in these cancer cells (Pons et al., 2015).

Also in breast cancer cells, downregulation of UCP2 via MiR-133a increases the sensitivity of cells to doxorubicin treatment (Yuan et al., 2015). MiR-133a suppresses UCP2 in both the mRNA and protein levels, leading to inhibiting tumor proliferation *in vitro* and *in vivo*.

It has been reported that the expression levels of UCP2 are associated with cisplatin sensitivity in ovarian serous carcinoma (Kawanishi et al., 2018). Patients with relatively low UCP2 expression are more sensitive to cisplatin treatment and have a better survival rate. The potential mechanism of UCP2-caused chemoresistance is reducing the generation of ROS. UCP2 expression levels may be used as an effective index to predict the efficacy of chemotherapy for ovarian serous carcinoma (Kawanishi et al., 2018).

Neoadjuvant chemotherapy is an effective approach to treat local tumors. The expression levels of UCP2 provide guidance for the use of neoadjuvant chemotherapy in locally advanced uterine cervical cancer (Imai et al., 2017). Patients with higher UCP2 expression levels are relatively resistant to neoadjuvant chemotherapy which can be reversed by using a UCP2 inhibitor (Imai et al., 2017).

The role of UCP2 in tumor progression and drug resistance has been summarized in Figure 3.

The UCP2 inhibitor genipin as an anti-cancer drug candidate

Genipin, found in *Gardenis* fruits, is the product of geniposide after hydrolysis by β-glucosidase. Genipin is identified as an inhibitor of UCP2 uncoupling activity in 2006 (Zhang et al., 2006) and its potential anti-tumor activities have been studied since then.
In glioblastoma cells, genipin treatment activates the intrinsic apoptotic pathway in a dose-dependent and time-dependent manner through UCP2-regulated mitochondrial ROS production (Ahani et al., 2018).

Genipin has the ability to alter glucose metabolism to achieve anti-tumor effects. In breast cancer cells, ^{18}F-FDG uptake is reduced dose- and time-dependently by genipin through decreasing both glycolytic flux and mitochondrial oxidative respiration with the increase in ROS generation (Cho et al., 2016).

Since genipin is a natural cross-linker its derivatives (in which the hydroxyl at position C10 or C1 is substituted) with reduced cross-linking activity have also been developed. In pancreatic carcinoma cells, the derivatives with a replacement of C1 (1-OH) do not induce apoptosis in cancer cells; whereas the derivatives with a replacement of C10 (10-OH) induce ROS generation and apoptosis in cancer cells. These results indicate that 1-OH is critical to ensure genipin's anti-tumor activity (Yang et al., 2016).

Genipin can also increase the sensitivity of cancer cells to other treatments. In pancreatic cancer cells, genipin synergizes the mTOR inhibitor everolimus in inducing apoptosis via enhancing the nuclear translocation of the cytosolic glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Dando et al., 2017). mTOR (the mechanistic target of rapamycin), a serine/threonine protein kinase, plays a central role regulating fundamental cellular processes including protein synthesis/turn over, cellular metabolism, etc. (Saxton and Sabatini, 2017). Dysregulated mTOR signaling is implicated in the etiology of human diseases such as diabetes and cancer. In many cancers, mTOR becomes hyperactive and a class of mTOR inhibitors (rapalogs) have been approved to treat advanced kidney cancers (Saxton and Sabatini, 2017). In ovarian serous carcinoma cell, sensitivity to carboplatin treatment is increased when these cells are treated with genipin (Kawanishi et al., 2018).

Concluding remarks

In this review, we have summarized recent findings on the role of UCP2 in obesity, diabetes, and cancer. The polymorphisms of UCP2 play an important role in obesity and diabetes, which may serve as a biomarker for these two diseases. Amplification of UCP2 is often observed in cancers. UCP2 influences cell proliferation, apoptosis, autophagy, and drug sensitivity by regulating ROS generation and cellular metabolism. These new studies further help understand how UCP2 contributes to the disease progression as well as how to target UCP2 in treating these diseases.

Author Contributions

JL, RJ, XC, and YZ wrote the manuscript.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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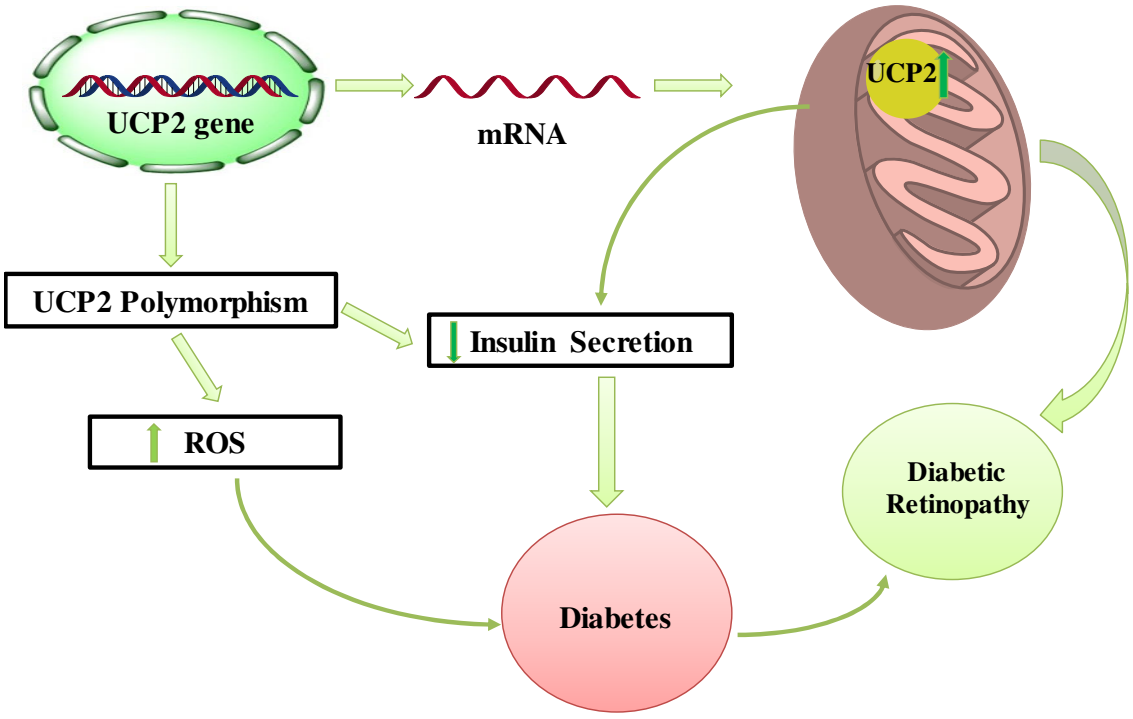

Figure 1. UCP2 and its polymorphism in diabetes mellitus and diabetic complications. UCP2 gene polymorphism could be associated with diabetes which may be due to the effect of UCP2 on pancreatic β-cell function, fasting insulin, insulin sensitivity, insulin secretion indexes in the body.

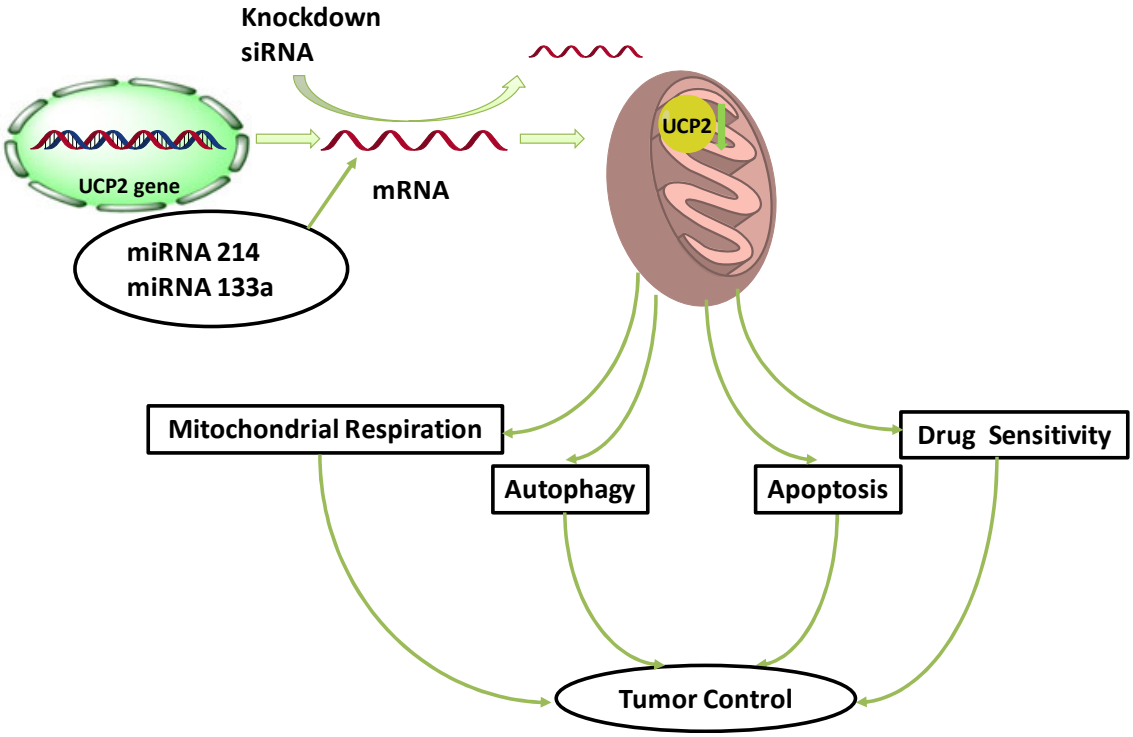

Figure 2. Changes in tumor cell behaviors after UCP2 inhibition: cells shift from glycolysis to mitochondrial respiration; cell death is enhanced; tumor cells become sensitive to anti-cancer agents.

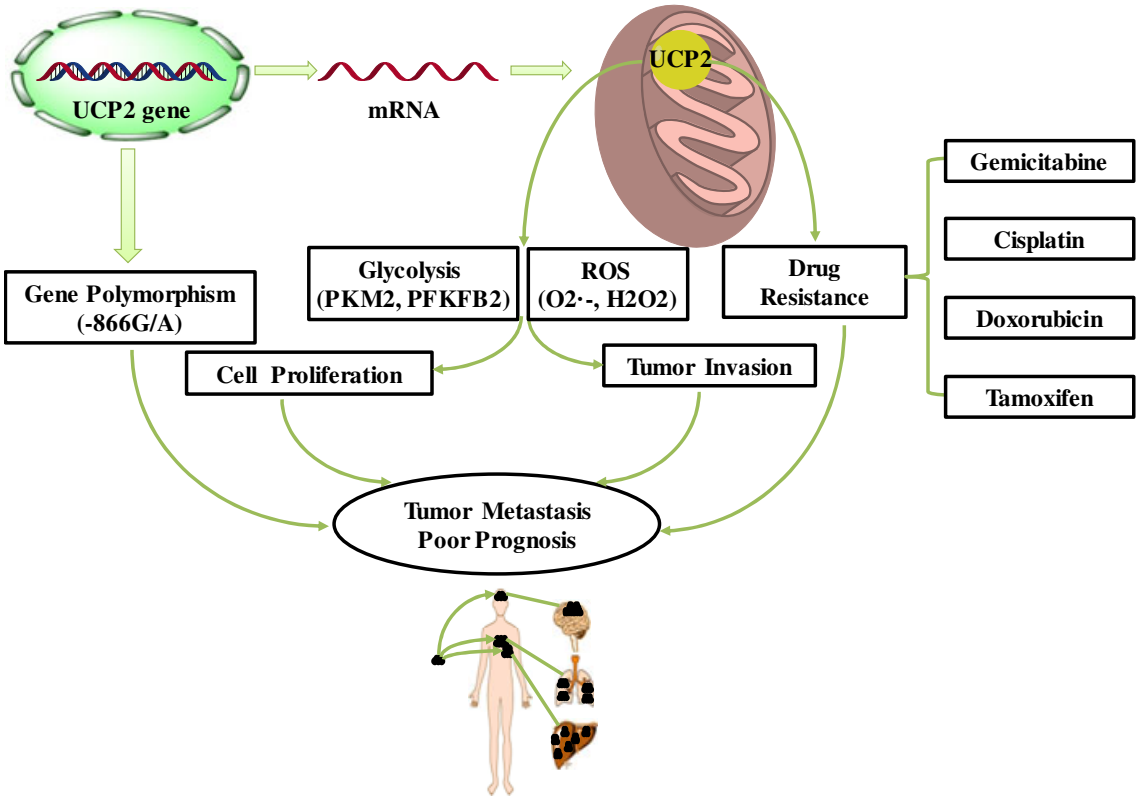

Figure 3. The effect of UCP2 on tumorigenesis is manifested in many aspects. UCP2 gene polymorphism may be associated with tumorigenesis. UCP2 can accelerate the proliferation and invasion of cancer cells via enhanced glycolysis. UCP2 also reduces the sensitivity of cancer cells to drugs, ultimately leading to chemotherapy resistance.