FEBS Letters

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REVIEW ARTICLE

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

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(Received 15 May 2019, revised 8 July 2019, accepted 12 July 2019, available online 1 August 2019)

doi:10.1002/1873-3468.13546

Edited by László Nagy

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 because 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. The present review summarizes the latest findings of UCP2 with respect to obesity, diabetes and cancer.

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

Uncoupling proteins (UCPs), located in the mitochondrial inner membrane, belong to the mitochondrial transporter family SLC25 [1]. There are five members in the UCP family: UCP1 was identified and discovered in brown adipose tissue. UCP1 is a proton transporter allowing mitochondrial membrane potential to be transduced to heat [2]. UCP2, a homolog of UCP1, was described in 1997 [3]. By contrast to UCP1, UCP2 is expressed in many organs and tissues in the body, including the skin [4], brain[5], liver [6] and kidney [7]. UCP2 is also considered as an antioxidant because it suppresses the generation of reactive oxygen species (ROS) in mitochondria [8]. UCP3 is distributed in the skeletal muscle and heart (slightly), participating in the regulation of skeletal muscle respiration [9] and pH flash frequency in skeletal muscle fibers [10]. UCP4 and UCP5 are mainly located in the brain [11,12] and play important roles in energy homeostasis and neuroprotection [13].

UCP1 exists in large amounts, comprising up to 10% of membrane proteins in brown adipose tissues, whereas other UCPs are present in much smaller amounts [14]. Similar to UCP1, other UCPs can also catalyze net proton conductance when activated by fatty acids [14]. Besides protons, UCP2 and UCP3 can transport anions across the mitochondrial inner membrane [15]. Mitochondria are the major source of superoxide production as a result of the 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.

Abbreviations
mTOR, mechanistic target of rapamycin; PFKFB2, phosphofructokinase 2/fructose-2,6-bisphosphatase 2; PKC, protein kinase C; ROS, reactive oxygen species; UCP, uncoupling protein.

The *UCP2* gene is located in chromosome 1 of rats, chromosome 7 of mice and chromosome 11 of human beings [16]. 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 [17], hypertension [18], diabetes [19,20], obesity [21] and cancer [22].

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 [23]. UCP2 can be regulated by miRNAs to influence tumor metabolism and chemoresistance [24]. UCP2 is also regulated by growth hormones [25]. In addition, the activity of UCP2 can be regulated by several factors including ROS, free fatty acids, purine nucleotides, coenzyme Q, etc., as neatly summarized in a recent review [26]. In brief, free fatty acids are required for the activation of the anion carrier UCP2 [27]. 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 [14]. Purine (guanine) nucleotides directly bind to UCP2 and the binding site faces the intermembrane space of mitochondria and UCP2 activity is inhibited [27]. It has been suggested that coenzyme Q could affect UCP2 activity in two ways: (i) by cooperating with fatty acids to mediate proton transfer in its oxidized form and (ii) by generating ROS and 4-hydroxynonenal in its reduced form [26]. Overall, UCP2 is responsive to and subsequently regulates metabolic alterations in the body, which makes it a potential target for metabolic diseases, including obesity, diabetes and cancer.

UCP2 and obesity

Obesity, comprising a chronic metabolic disorder caused by the interactions among genetic factors, epigenetic factors, environmental factors and lifestyle [28], 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 [29]. Mechanisms of UCP2-mediated regulation of obesity include but are not limited to (i) UCP2 indirectly activating the melanocortin-4 receptor, therefore inhibiting food intake and increasing energy expenditure [30] and (ii) UCP2 negatively regulating glucose-dependent insulin secretion in pancreatic β cells [31] and positively regulating glucagon secretion from pancreatic α cells [32]. In terms of weight loss, there is a positive correlation between weight loss and *UCP2* expression [33].

The gene polymorphism of *UCP2* may serve as an endogenous risk factor for obesity. Three polymorphisms in the *UCP2* gene have been studied the most: 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-bp insertion (I)/deletion (D) in exon 8.

Among various ethnicities, the UCP2 −866G/A polymorphism has been found to be associated with obesity [34,35]. The GG genotype is associated with an increased risk of obesity among Egyptians [36] and white Europeans [37]. The haplotype containing the −866G allele is associated with childhood obesity in the UK [38]. By contrast, the A allele of −866G/A polymorphism has a protective effect on obesity and being overweight, especially in European populations [39,40]. The possible responsible 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 to the A allele, resulting in increased ROS generation, as well as decreased insulin secretion and energy expenditure, and, consequently, an increased accumulation of body fat in the G allele individuals [41].

The effects of the Ala55Val polymorphism on obesity are 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 [42,43]. However, in the aboriginal populations in Taiwan, the Val55 allele shows an increased risk of obesity compared to the Ala55 allele [44]. Another study from Taiwan reports that the Ala55Val polymorphism is associated with morbid obesity and weight loss [45]. In addition, obese patients carrying the TT or CT genotype show greater weight loss compared to the CC genotypes after the LAGB (laparoscopic adjustable gastric banding) surgery [45].

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 the female group [46].

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 and resulting in

decreased UCP2 activity [46]. The ethnic/gender discrepancy might occur because: (i) UCP2 regulated proteins could be different; (ii) environmental factors vary in different regions; and (ii) there are body fat differences between male and female.

The association between the 45-bp insertion (I)/deletion (D) polymorphism and obesity is found mainly among Asians and the results demonstrate regional and gender differences. The D/D genotype is the most widely distributed in eastern Saudi Arabia and is associated with severe obesity [21]. Among Indonesians, the D/I genotype and the I allele reduce the risk of obesity in the female group, whereas the I/I genotype and I allele are risk factors for obesity in the male group [46]. In a Malaysian study, the I allele is a risk factor for obesity among Malaysian women [47]. In Iranian [48] and Turkish [49] studies, the I/I genotype and I allele also demonstrate a higher risk for obesity compared to the D/D genotype.

The location of this polymorphism in the 3′-UTR in exon 8 is assumed 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 [37].

In summary, although controversy exists, higher UCP2 expression levels could enhance energy expenditure, therefore reducing the risk of obesity. The association between the *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. Future studies could aim to investigate: (i) whether UCP2 conveys other transport activity in addition to functioning as an ion/anion transporter; (ii) whether there any effector protein binding to UCP2 and mediating its action; and (iii) where UCP2 stands in the broader consideration of mitochondria-to-nucleus signaling regulating obesity?

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 and type 2 diabetes. As a result of 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 [50]. This suppression of insulin secretion by upregulated UCP2 increases the risk of type 2 diabetes in humans [51].

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

The results demonstrate that individuals with the AA genotype and A allele of the −866G/A polymorphism have an increased risk for diabetes in Austrian [52], Italian [53], American [54] and Indian [55] populations. The A allele of −866G/A is associated with higher promoter activity of *UCP2* in β-cells [51,52], 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 [56] and American [57] populations. The VV genotype shows increased insulin resistance in those individuals 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 [58,59].

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 [19,20]. The 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 [19,20]. In an Iranian study, the 45-bp I/D polymorphism of the *UCP2* gene is shown to be associated with the metabolic syndrome, which is being recognized as a risk factor for insulin resistance [48].

The exact mechanism of how the 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 [48].

In summary, the impact of UCP2 deregulation on diabetes is likely the net result of two apparently opposite effects: decreasing UCP2 activity increases ATP production and insulin secretion, whereas decreased UCP2 activity can also increase ROS generation leading to the damage in insulin-secreting β-cells. Future directions may include an investigation of (i) the precise mechanism for UCP2 with respect to regulating insulin secretion; (ii) the role of UCP2 deregulation in insulin-resistant diabetes; and (iii) the other signaling molecules that UCP2 may regulate during the pathogenesis of diabetes.

A schematic diagram regarding the role of UCP2 in diabetes is shown in Fig. 1.

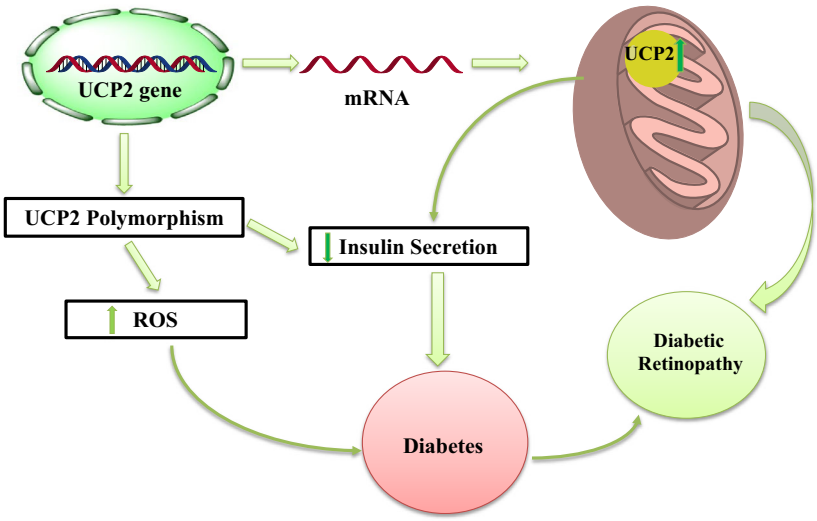

Fig. 1. *UCP2* and its polymorphism in diabetes mellitus and diabetic complications. The *UCP2* gene polymorphism could be associated with diabetes, which may be a result of the effect of UCP2 on pancreatic β-cell function, fasting insulin, insulin sensitivity and insulin secretion indices in the body.

UCP2 and cancer

Cancer is the second leading cause of death in the USA. Approximately 1.6 million new cases occur with 600 000 deaths each year [60]. 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 [61]. Furthermore, cancer cells can also obtain energy from more sources than normal cells.

As a result of 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 [62–64]. 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 [65]. As discussed above, the G allele has lower UCP2 mRNA expression levels compared to the A allele, resulting in lower UCP2 protein levels [41], 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 [66]. 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 example, oroxylin A induces mitochondrial permeability transition pore in colon cancer cells through the inhibition of UCP2 in a dose-dependent manner, resulting in increased levels of ROS and apoptosis [67]. Colon cancer cells are found to be more sensitive to oroxylin A treatment after *UCP2* knockdown using small interfering RNAs.

The promotion of cell proliferation is considered as an important mechanism with respect to UCP2 contributing to tumorigenesis. In our study of skin carcinogenesis, UCP2 deficiency clearly suppresses skin cell proliferation as indicated by mitotic cell counts and Ki-67 staining [66]. In hepatocellular carcinoma, cell proliferation is inhibited when UCP2 is downregulated by miR-214 [68].

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 demonstrated how UCP2 participates in shifting oxidative phosphorylation to glycolysis in pancreas cancer cells [69]. The expression levels of the glucose transporter GLUT1 and pyruvate kinase isoform M2 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, a widely used inhibitor of glycolysis [69].

Our group has studied the mechanism of how UCP2 regulates glycolysis during cell transformation [70,71]. 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 [70,71]. In *UCP2* overexpressing cells, the levels of superoxide are decreased, whereas that of hydrogen peroxide is 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 as a result of the redirected cancer metabolism from glycolysis to oxidative phosphorylation [72]. Different results may occur as a result of different endogenous levels of UCP2 in human cancers.

The role of UCP2 in regulating cellular behaviors has been summarized in Fig. 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 and breast cancer [73]. 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 [74].

In breast cancer cells, downregulation of UCP2 increases the sensitivity of cells to cisplatin and tamoxifen treatment [75]. In *UCP2* knockdown cells, cell viability and clonal formation are decreased in conjunction with increases in mitochondrial membrane potential, ROS production and apoptotic cell death. *UCP2* knockdown plus tamoxifen treatment increases autophagic cell death in these cancer cells [75].

Also in breast cancer cells, downregulation of UCP2 via MiR-133a increases the sensitivity of cells to doxorubicin treatment [24]. MiR-133a suppresses UCP2 with respect to both 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 [76]. Patients with relatively low *UCP2* expression are more sensitive to cisplatin treatment and have a better survival rate. A potential mechanism of UCP2-caused chemoresistance is a reduction in the generation of ROS. *UCP2* expression levels may be used as an effective index for predicting the efficacy of chemotherapy when treating ovarian serous carcinoma [76].

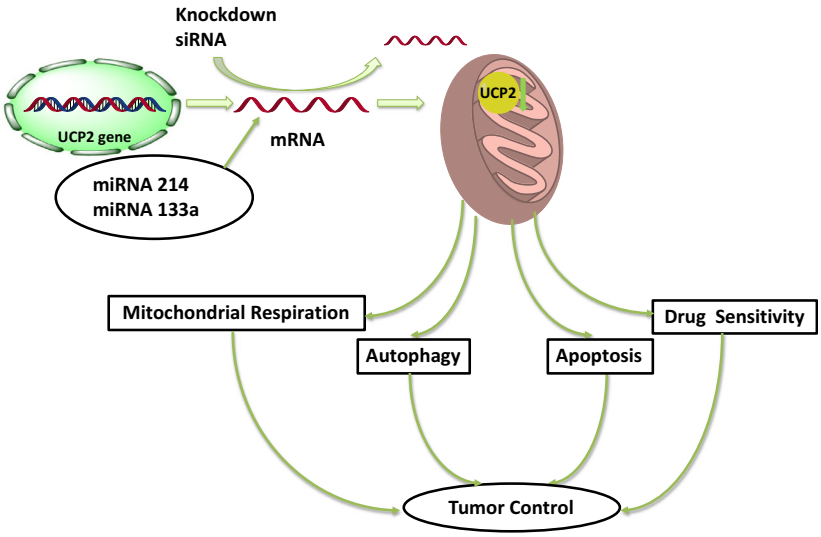

Fig. 2. Changes in tumor cell behaviors after UCP2 inhibition: cells shift from glycolysis to mitochondrial respiration; cell death is enhanced; tumor cells become sensitive to anti-cancer agents.

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 [77]. Patients with higher *UCP2* expression levels are relatively resistant to neoadjuvant chemotherapy which can be reversed using a UCP2 inhibitor [77].

The role of UCP2 in tumor progression and drug resistance is summarized in Fig. 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 was identified as an inhibitor of UCP2 uncoupling activity in 2006 [78] and its potential anti-tumor activities have been studied subsequently.

In glioblastoma cells, genipin treatment activates the intrinsic apoptotic pathway in a dose-dependent and time-dependent manner via UCP2-regulated mitochondrial ROS production [79].

Genipin has the ability to alter glucose metabolism and achieve anti-tumor effects. In breast cancer cells, ^{18}F-FDG uptake is reduced both dose- and time-dependently by genipin via a decrease in glycolytic flux and mitochondrial oxidative respiration and an increase in ROS generation [80].

Because genipin is a natural cross-linker, 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, derivatives with a replacement of C1 (1-OH) do not induce apoptosis in cancer cells, whereas derivatives with a replacement of C10 (10-OH) induce ROS generation and apoptosis in cancer cells. These results indicate that 1-OH is critical for ensuring the anti-tumor activity of genipin [81].

Genipin can also increase the sensitivity of cancer cells to other treatments. In pancreatic cancer cells, genipin synergizes the mechanistic target of rapamycin (mTOR) inhibitor everolimus with respect to inducing apoptosis by enhancing nuclear translocation of the cytosolic glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase [82]. mTOR, a serine/threonine protein kinase, plays a central role in the regulation of fundamental cellular processes including protein synthesis/turnover, cellular metabolism, etc. [83]. 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 for treating advanced kidney cancers [83]. In ovarian serous carcinoma cells, sensitivity to carboplatin treatment is increased when these cells are treated with genipin [76].

Concluding remarks

In this review, we have summarized recent findings regarding the role of UCP2 in obesity, diabetes and cancer. The polymorphisms of *UCP2* play important roles 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

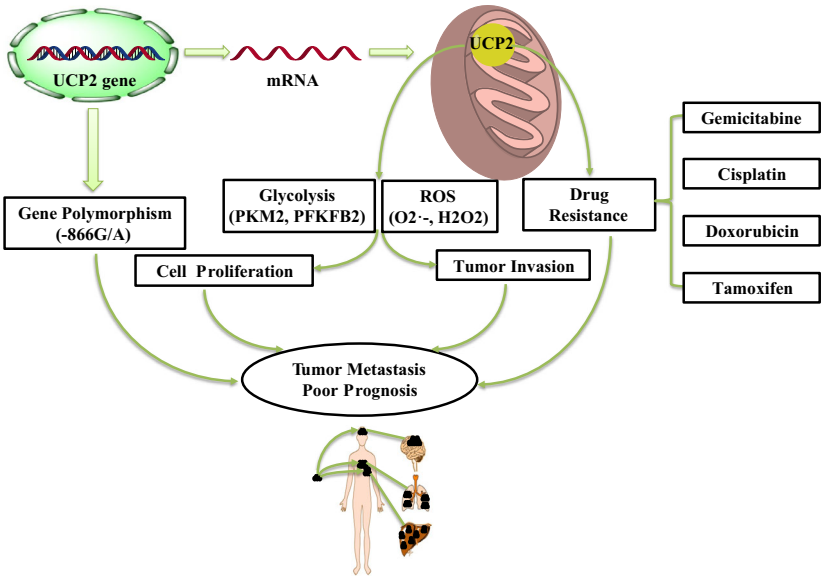

Fig. 3. The effect of UCP2 on tumorigenesis is manifested in many aspects. The *UCP2* gene polymorphism may be associated with tumorigenesis. UCP2 can accelerate the proliferation and invasion of cancer cells via enhanced glycolysis. UCP2 also reduces the sensitivity of cancer cells to drugs, ultimately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

sensitivity by regulating ROS generation and cellular metabolism. These new studies further help us to understand how UCP2 contributes to disease progression, as well as how to target UCP2 when treating these diseases.

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