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Uncoupling Protein 2 and Metabolic Diseases

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Abstract

Mitochondria are fascinating organelles involved in various cellular-metabolic activities that are integral for mammalian development. Although they perform diverse, yet interconnected functions, mitochondria are remarkably regulated by complex signaling networks. Therefore, it is not surprising that mitochondrial dysfunction is involved in plethora of diseases, including neurodegenerative and metabolic disorders. One of the many factors that lead to mitochondrial-associated metabolic diseases is the uncoupling protein-2, a family of mitochondrial anion proteins present in the inner mitochondrial membrane. Since their discovery, uncoupling proteins have attracted considerable attention due to their involvement in mitochondrial-mediated oxidative stress and energy metabolism.

This review attempts to provide a summary of recent developments in the field of uncoupling protein 2 relating to mitochondrial associated metabolic diseases.

Keywords

Uncoupling proteins; mitochondrial dysfunction; metabolic disorder; cancer; obesity; diabetes

1. Introduction

The increase in the prevalence of metabolic syndrome among the US population constitutes a serious threat to public health. Metabolic syndrome is not a ‘disease’ per se. Instead, metabolic syndrome is a group of metabolic abnormalities which are associated with high blood sugar, elevated blood pressure, excess body fat, and abnormal cholesterol levels, which can ultimately lead to plethora of diseases, such as diabetes, obesity, cardiovascular disease and cancer. Moreover, since these diseases are associated with increased mortality and morbidity rates, metabolic syndrome is a consequential life-threatening condition [1–6]. One of the many factors that lead to this condition is the alteration of uncoupling protein-2 (UCP2) [7–9].

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Uncoupling proteins (UCPs) are a family of mitochondrial proteins present in the inner mitochondrial membrane whose physiological role is to transport the protons back into the mitochondrial matrix [8–11]. In recent times, there has been immense interest in defining the role of uncoupling proteins; UCP2 is often dysregulated in various metabolic conditions. Mutations in UCP2 show association with congenital hyperinsulinism and obesity, while studies from our lab and the labs of other medical institutions have shown that UCP2 is overexpressed in many aggressive cancers [12–17]. Since a growing body of evidence supports the emerging functions of UCP2 in metabolic diseases, the aim of this integrative review is to collate the evidence and summarize the role of UCP2 in metabolic syndromes, mainly, diabetes, obesity and cancer.

2. Uncoupling Proteins: What are they?

UCPs are proteins encoded by nuclear DNA and located in the inner mitochondrial membrane. Mitochondrial respiration results in the extrusion of the protons (H^+) out of the mitochondria and into the intermembrane space, establishing the mitochondrial membrane potential that drives the ATP synthase. UCPs pump the protons from the intermembrane space into the mitochondrial matrix and thereby dissipate the proton gradient, reduce the ATP production and diminish superoxide production. Hence, UCPs appear to play important roles in redox regulation, mitochondrial and metabolic processes [18–20].

2.1 The family of UCPs

Among the family of UCPs, UCP1 is well-characterized with known functions and is almost exclusively present in the mitochondria of brown adipocytes [21,22]. It accounts for up to 8% of total mitochondrial protein. UCP1 was first discovered in 1997 and has since been characterized as a mitochondrial membrane transporter essential to nonshivering thermogenesis. Cold, thyroid hormone, norepinephrine, adrenergic stimulation, and cyclic adenosine monophosphate (cAMP) can increase UCP1 gene expression. In addition, UCP1 gene expression is enhanced by fatty acids and inhibited by purine nucleotides (GDP, ATP, ADP). It plays important roles in regulation of energy expenditure, thermogenesis, mitochondrial membrane potential, and ROS. Since these mechanisms are associated with diabetes, obesity, UCP1 is an excellent candidate gene for the pathogenesis of diabetes and obesity.

Next are the UCP2 and UCP3, homologues of UCP1 [23,24]. UCP2 has 59% identity with UCP1 and is ubiquitously expressed. UCP2 is widely present in the mitochondria of adipose tissue, skeletal muscle, spleen, liver, lung, and macrophages. Whereas, UCP3 is specifically expressed in skeletal muscle [25]. Interestingly, UCP2 and UCP3 have 73% identity with each other [24]. UCP3 is 57% identical with UCP1 and after its discovery in 1997, UCP3 was thought to be the skeletal muscle analogue of UCP1. Conversely, UCP4 and UCP5 are very recently discovered, mainly expressed in the neurons of the central nervous system (CNS) and its functions are largely unknown [26,27]. More interestingly, Sukolova and colleagues have identified an invertebrate UCP homologue similar to UCP2 and 3, termed UCP6 [28]. Given the physiological roles of UCPs and their association with various

pathophysiology conditions, there exists an exciting potential for investigation and potential therapeutic applications.

2.2. UCP2: What is special?

An enormous interest has been created since the discovery of UCP2 in 1997. Unlike the other UCPs, the major difference is that UCP2 mRNA is present in many tissues and cell types – adipose tissue, heart, lung, spleen, kidney, thymus, lymphocytes and macrophages [Fleury C et al.]. In mammals, they reduce mitochondrial membrane potential, attenuate mitochondrial ROS production and protect against oxidative damage. Thus, the primary physiological function of UCP2 is redox regulation, ROS handling and immunity [29]. In addition, UCP2 has a role in lipid and fatty acid metabolism, glucose metabolism and transportation of TCA cycle metabolites [30–32]. UCP2 is unique. It is regulated at both transcriptional and translational levels [33,34].

Various studies have demonstrated that free fatty acids induce transcription of UCP2 [35]. As well as increased production of ROS, particularly superoxide can activate UCP2 even in the absence of FFA (Figure 3) [36]. However, the precise pathway through which superoxide activates UCP2 is unknown. Nevertheless, the superoxide-UCP2 pathway is involved in pathogenesis of hyperglycemia, hyperlipidemia and β -cell dysfunction [10]. Several physiological states and pathological conditions (like high-fat diet, stress, exercise, obesity, and diabetes) are known to regulate UCP2 expression and activity [37–39]. Hence, substantial efforts are being made to understand how UCP2 is regulated. In addition, UCP2 is very unstable and has an unusually short half-life (30min) making it a novel protein to explore [40].

2.3. Characteristics of UCP2 gene

The UCP2 gene is located on chromosome 7 of mice and chromosome 11 of humans [10]. Ironically, chromosome 11 is one of the disease-rich chromosomes in humans. Both human and mouse UCP2 genes are located 7–10 kilobases (kb) downstream of UCP3 stop codon and particularly present in exon 2 of several ATG-translational initiation codons. UCP2 coding sequence begins in the exon 3. Furthermore, UCP2 promoter region does not contain a TATA box, a DNA sequence (5'-TATAAA-3') which is typically present within the core promoter region on the DNA. Rather, it contains potential binding motifs for several transcription factors such as specificity protein 1 (Sp1), activator proteins (AP-1, AP-2) and the cyclic AMP response element binding protein (CREB) [9].

UCP2, member of the family of mitochondrial uncoupling proteins have the widest tissue distribution. Since its discovery, UCP2 has been shown to be involved in various cellular and physiological processes. Numerous speculations on the possible role of UCP2 in tissue-specific functions are growing. Furthermore, UCP2 expression is generally increased in response to oxidative stress, which is implicated in several metabolic diseases. Alteration in expression and activity of UCP2 are associated with metabolic diseases (Figure 4).

Typically, cancer, obesity and diabetes are associated with elevated ROS levels, oxidative stress and increased levels of FFA [41]. Cancer has been linked to both obesity and diabetes which provide exciting potential for further investigation [42,43]. Since, ROS and FFA are

important molecular signals that activate UCP2, it is interesting to unravel and explore the relationship between UCP2 and metabolic diseases. Therefore, UCP2 is an important target to combat such diseases.

3. UCP2 in obesity

The expression of UCP2 and the propensity for obesity has been an interesting topic of debate especially when more than one third of adults are considered obese in the US [44]. Energy, another word for “calories” is directly proportional to obesity. Energy balance is the number of calories consumed while eating and drinking compared to energy burned through physical activity. Thus, maintaining the right energy balance is important for a healthy living. The important part of energy balance is the amount of energy out (physical activity) of the body. When energy intake exceeds energy expenditure, the excess fat is stored in body resulting in weight gain and obesity. Obesity is becoming a serious health concern worldwide and has been associated with poor mental health, reduced quality of life, increased risk of hypertension, coronary heart disease, stroke and diabetes. Recently, the discovery of UCP2 has gained popularity in the field of obesity research. Interestingly, the chromosome region of UCP2 is linked to obesity and diabetes [45]. Given that UCP2 is highly expressed in skeletal muscles and human adipose tissue, an involvement in energy regulation is suggested, particularly fatty acid and lipid metabolism. In various studies, UCP2 is shown to be upregulated in adipose tissue of obesity-resistant mice [46]. Several other studies have shown the involvement of UCP2 in the regulation of diet, thyroid hormones and fatty acids. In a study by Walder et al. [13] UCP2 polymorphism was shown to be associated with energy metabolism and obesity in humans. DNA sequencing of UCP2 revealed polymorphisms Ala→Val substitution in exon 4 and 45 bp insertion/deletion in the 3'-untranslated region of exon 8 of *UCP2* that contributed to a variation in metabolic rate and overall body fat content. In 1997, Millet et al. demonstrated a positive correlation between UCP2 mRNA levels in adipose tissue and body mass index (BMI) in humans [47]. These studies therefore confirm an association between UCP2 overexpression and obesity. However, despite the controversies surrounding the biological role of UCP2, there are conflicting evidence to which we and others have demonstrated a strong correlation in UCP2 overexpression and fatty acid signaling and lipid metabolism. Specifically, UCP2 expression can be increased by fatty acids or dietary fat consumption. Therefore, UCP2 is a potential candidate gene for understanding diet-induced obesity. Thus, UCP2 has attracted enormous interest as therapeutic targets for treatment of obesity. However, further investigation is needed to define the role of UCP2 in metabolic regulation.

4. UCP2 in diabetes

Every year about 1.4 million people are diagnosed with diabetes. Diabetes remains the seventh leading cause of death in the US [48]. Numerous comorbid conditions have been associated with diabetes. Having diabetes means you are more likely to have certain conditions (high blood pressure, high cholesterol) that increase the chances of having a heart disease, stroke, and obesity [49,50]. In fact, diabetes has become an epidemic worldwide. Diabetes mellitus, a group of metabolic diseases characterized by high blood glucose (sugar) is typically divided into two subtypes: Type I insulin dependent and Type II insulin non-

dependent. Diabetes results either from an adequate insulin production, or because body's cells do not respond to insulin. Insulin is a hormone secreted into the bloodstream to normalize blood-glucose concentration post a carbohydrate-rich meal. β -cells of the pancreas secrete insulin. Thus, insulin plays a crucial role in maintaining glucose homeostasis. UCP2 is also highly expressed in the pancreatic β -cells and UCP2 is well known to be a negative regulator of insulin [Fleury C et al.]. That is, increased expression of UCP2 in pancreatic β -cells results in decreased levels of glucose-stimulated insulin secretion (GSIS) leading to dysfunction and development of type-II diabetes [51–53]. Pancreatic β -cells sense glucose after a carbohydrate rich meal. Glucose is then transported into the β -cells by glucose transporters and subsequently oxidized by the metabolic pathways (Glycolysis, TCA cycle, ETC and oxidative phosphorylation) to ultimately generate ATP via the ATP synthase. The resultant increase in the ATP releases insulin. During hyperglycemic conditions, glucose metabolism and mitochondrial membrane potential are enhanced and subsequently, superoxide produced in the mitochondrial matrix is elevated. In turn, UCP2 expression is increased. By virtue, of its uncoupling activity, UCP2 decreases ATP production, reduces mitochondrial membrane potential and suppresses generation of superoxide. Therefore, it is a regulator of glucose metabolism and insulin secretion [54–57]. Consistent with this idea, UCP2 expression is markedly increased in the pancreas of animal model for type II diabetes. Other independent pathways can activate UCP2. A functional polymorphism in the UCP2 promoter region (866G/A) is associated with enhanced UCP2 activity. Interestingly, this polymorphism is associated with β -cell dysfunction, diabetes and obesity [58]. Not surprisingly, this functional polymorphism in the human UCP2 promoter increases the risk of obesity. Another study showed an association between Ala55Val (rs660339) polymorphism in UCP2 gene and the risk of type II DM [59]. Moreover, UCP2 knockout mice exhibited hyperinsulinemia and hypoglycemia, suggesting an involvement of UCP2 in insulin secretion and glucose metabolism [60]. Therefore, UCP2 represents a potential candidate in understanding diabetes.

5. UCP2 in cancer

Cancer has been one of the biggest challenges of modern medicine. Cancer is not a single disease, rather a name given to a collection of related diseases, where the cells divide abnormally and uncontrollably and spread into the surrounding tissues. Cancer is the second leading cause of mortality and morbidity worldwide. In 1971, cancer was thought to be primarily a genetic disease caused by mutation in DNA and a 'war on cancer' was declared by then US President Richard Nixon [61–62]. Since cancer is a disease in DNA, it was thought that mutated genes resulted in cancer. However, no single mutation or combination of mutations was identified as required for initiating the disease. Scientists concluded that cancer is more of a mutational complexity and that cancer is not a genetic disease alone. Later, cancer was thought to be resulting from defective metabolism. With the advent of science and technology, cancer is considered as genetic, epigenetic and a metabolic disease. In addition, aging, lifestyle (smoking, diet, obesity), environmental factors (chemicals, radiations), infectious agents (human papillomavirus, Epstein-Barr virus) are risk factors for cancer [63,65]. In recent times, cancer research has seen remarkable progress. Breakthroughs in cancer treatments like Immunotherapy and personalized medicine as a

treatment for cancer are fueling new hope [66–69]. Our lab has been doing extensive research supporting the role of UCP2 in cancer [12,17,69]. In this paper, we review a few of the most recent works from our lab and the labs of other institutions in UCP2 upregulation and the metabolic reprogramming associated with cancer.

Uncoupling protein 2 is often upregulated in various pathological conditions. It is no surprise that tumor cells have high oxidative stress, and increase in ROS levels in cancer cells play an important role in tumor promotion, proliferation and differentiation. Since the physiological proteins of UCPs are involved in energy-dissipation, it has been speculated to be involved in tumor promotion [70]. Mitochondria, one of the most important organelles, is often dysregulated in cancers. Furthermore, mitochondrial dysregulation is associated with tumor survival, proliferation and differentiation [71–73]. Since mitochondria are the leading source of ROS production, there is a strong correlation between mitochondrial dysfunction and oxidative stress [74–76]. Thus, the higher the mitochondrial membrane potential, the higher is the ROS production. Since, the uncoupling activity induced by UCP2 expression can inhibit the mitochondrial membrane potential, and ROS production as well, they act as natural antioxidants. Consistent with this proposal, upregulation of UCP2 in cancer is known to decrease ROS production leading to chemo-resistance [77–78]. Z. Derdak in 2008 demonstrated that overexpression of UCP2 promoted chemo-resistance [77]. A more recent study demonstrated that knockout of UCP2 sensitized breast cancer cells to chemotherapeutic agents by increasing ROS, thus suggesting an inter-talk between UCP2 expression levels and oxidative stress [79]. This suggests that UCP2 could be a marker of chemo-resistance. We and others have shown that UCP2 is upregulated in many aggressive human cancers. Most of the studies in humans point to the upregulation of UCP2 in breast, prostate, skin, head and neck and colon cancers [17,80]. However, the exact role of UCP2 upregulation in cancer remains unclear. Paradoxically, superoxide is thought to induce the expression of UCP2, and elevated UCP2 in turn decreases ROS production. It is hard to explain whether UCP2 upregulation is the cause or the effect of oxidative stress and/or cancer. To determine the exact role of UCP2 upregulation in skin tumorigenesis, we performed a chemically-induced skin tumorigenesis study using wild type and UCP2 knockout mice [79]. Our results demonstrated that knockout of UCP2 suppressed skin formation in the animal model in vivo, suggesting UCP2 might serve as a tumor promoter and that increased UCP2 expression confer pro-survival advantage for cancer cells. One possible growth advantage of UCP2 overexpression in cancer is the UCP2-induced chemo-resistance. Another growing speculation is existence of a link between UCP2 expression and cancer cell metabolism [81,82,31]. Since, UCP2 can ‘uncouple’ or disengage electron transport chain (ETC) from ATP synthesis, and the fact that UCP2 is upregulated in aggressive cancers, it is hypothesized that UCP2 overexpression could affect energy metabolism in cancer cells. Interestingly, it has been demonstrated that UCP2 exports TCA cycle metabolites out of the mitochondria [31], thus preventing mitochondrial glucose oxidation and favoring aerobic glycolysis. Consistent with this explanation, we have found that UCP2 overexpressed JB6 cells show enhanced glycolysis leading to lactic acid production. Thus, UCP2 overexpression may sustain the Warburg effect in cancer cells. Furthermore, fatty acids are shown to activate UCP2 expression and cancer cells often exhibit enhanced fatty acid oxidation, leading to speculation on the association between

UCP2 expression and fatty acid oxidation in cancer [83]. These studies demonstrate a critical role of UCP2 in cancer cell energy metabolism. C. Pecquer et al. showed that UCP2 controls proliferation by promoting fatty acid oxidation and limiting glycolysis-derived pyruvate utilization [84]. Therefore, UCP2 expression may promote a metabolic switch thus regulating fatty acid oxidation and glucose metabolism in favor of tumorigenesis. In conclusion, tumor promotion, metabolic reprogramming, chemo-resistance, and redox regulation are some of the advantages of UCP2 overexpression in cancers. Overall, various studies demonstrate that UCP2 overexpression promotes cancer cell survival and adaption and targeting UCP2 could serve as a potential therapeutic approach for cancer prevention and/or therapy.

6. UCP2 and inflammatory diseases

UCP2 is shown to regulate ROS production in the inflammatory system [85]. Moreover, UCP2 is highly expressed in macrophages. Knockout of UCP2 in mice increased ROS production in macrophages and these mice were resistant to *Toxoplasma gondii* infection. This suggested that UCP2 $-/-$ favored macrophage activity and can fight infection. LPS stimulation produced less ROS in macrophages overexpressing UCP2 [86]. In addition, UCP2 $-/-$ mice also developed more severe autoimmune encephalomyelitis and diabetes [87,88]. Given the importance of inflammation in development of atherosclerosis, cardiovascular disease, cancer and multiple sclerosis, and since UCP2 is a crucial regulator of mitochondrial ROS production, it is speculated to be a regulator of susceptibility to chronic inflammatory diseases. Our studies have demonstrated a plausible role of UCP2 in promoting inflammation. In our chemically-induced skin carcinogenesis study using UCP2 $-/-$ mice and wild-type mice, we found that squamous cell carcinoma metastasis is only found in wild-type animals but not in UCP2 $-/-$ mice, thus suggesting that UCP2 may be promoting skin carcinogenesis [69]. Furthermore, these metastasized tumors were surrounded by neutrophils and increased expression of pro-inflammatory chemokines and cytokines. This may suggest that UCP2 may also promote inflammation in favor of tumor metastasis. Because UCP2 is also expressed in neutrophils, lymphocytes and dendritic cells, UCP2 may therefore have an important role in regulation of inflammation [89].

7. UCP2 in neurodegenerative diseases

A heterogeneous group of disorders characterized by progressive loss of structure and function of nervous system are collectively termed neurodegenerative diseases. Neurodegenerative diseases affect millions of people worldwide. Various studies link UCP2 and neurodegeneration and aging [90]. Aging is one of the largest risk factors for predisposition to pathogenesis of neurodegenerative diseases, and it has been speculated that UCP2 overexpression may slow the aging process and may be protective in neurodegenerative diseases. Since, UCP2 is involved in protection against oxidative stress and oxidative stress is associated with several types of neurodegenerative diseases [91], UCP2 is speculated to play a neuroprotective role. UCP2, localized to the inner mitochondrial membrane is expressed in the mitochondria of the brain as well. Andrews et al. [92] have demonstrated that UCP2 promotes survival of dopaminergic neurons in a Parkinson's disease model by inhibiting ROS generation. Overexpression of human UCP2 in

mice has lower dopaminergic cell loss against MPTP toxicity [92]. Accumulating evidence supports an inverse correlation between UCP2 expression in CNS and ROS generation [93–100]. Another study showed that overexpression of hUCP2 decreased oxidative stress and extended lifespan in adult fly neurons [101]. These results suggest a protective role of UCP2 in neurodegenerative diseases. There is accumulating evidence that UCP2 expression could be a potential therapeutic target.

8. Concluding remarks and Prospects

UCP2, a member of the inner mitochondrial membrane anion transporter superfamily is involved in uncoupling respiration from ATP synthesis. They play crucial roles in the regulation of energy metabolism, energy expenditure, and ROS production, which are related to above pathologies. Hence, they are important targets for the treatment and/or prevention of metabolic disorders. Targeting processes that lead to UCP2 overexpression or polymorphism could be a promising therapeutic strategy. Since UCP2 is ubiquitously expressed, understanding the exact tissue-specific role played by UCP2 is of great importance. Ongoing efforts remain to further develop drugs that specifically target UCP2 expression. Given the enormous interest in the role of UCP2 in health and diseases, UCP2 is thought to be a potential therapeutic target for several diseases. Although the exact mechanistic role of UCP2 in metabolic diseases is not completely understood, evidence points out to the involvement of UCP2 in cancer, diabetes, obesity, aging and neurodegenerative diseases. Although it plays different roles in the regulation of these diseases, UCP2 is nevertheless an interesting candidate in the treatment of these metabolic diseases. From the therapeutic perspective, tissue specific control of UCP2 is instrumental and holds great promise in the near future.

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Highlights

- Uncoupling protein 2 (UCP2) is one of the new players implied in mitochondrial associated metabolic disorders.
- Why UCP2 might be special in these disorders are summarized.
- How UCP2 contributes to cancer cell growth especially skin tumorigenesis, is largely discussed.

Figure 1.

Mitochondrial oxidative phosphorylation system

Reduced cofactors such as NADH⁺ and FADH₂ donate electrons to protein complexes (ETC) embedded on the inner mitochondrial membrane. Energy used from the electron transport is used to pump protons across the inner mitochondrial membrane, setting up a membrane potential that drives the ATP synthase to generate ATP. Uncoupling proteins are anion transporters, also present in the inner mitochondrial membrane that transport protons back into the mitochondrial matrix allowing them to bypass ATP synthase, thereby generating heat instead of ATP.

Figure 2.

Structure of Uncoupling proteins

Uncoupling proteins and other mitochondrial anion transporters share similar structure.

UCPs are made up of six transmembrane domains that are linked by hydrophilic segments.

Every third domain is made up of two α -helices and a polar domain.

Figure 3.
Schematic diagram of uncoupling protein 2 activation

Figure 4.
The role of UCP2 in various metabolic diseases