World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i11.3232

World J Gastroenterol 2015 March 21; 21(11): 3232-3238
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Mitochondrial uncoupling protein 2 and pancreatic cancer: A new potential target therapy

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Author contributions: All authors contributed to the conceptual design of the manuscript and data interpretation; Donadelli M reviewed and summarized aspects of the literature that formed the basis of the manuscript; Palmieri M and Dando I carefully revised the manuscript; Dando I and Dalla Pozza E created illustrations; all authors also provided critical analysis of the discussed literature and gave final approval of the manuscript.

Supported by grants from Associazione Italiana Ricerca Cancro, Milan, Italy; Fondazione CariPaRo, Padova, Italy; and Ministero dell'Istruzione, dell'Università e della Ricerca, Rome, Italy.

Conflict-of-interest: The authors declare that they have no conflict of interest

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Received: October 14, 2014
Peer-review started: October 14, 2014
First decision: December 11, 2014
Revised: December 18, 2014
Accepted: February 5, 2015
Article in press: February 5, 2015
Published online: March 21, 2015

Abstract

Overall 5-years survival of pancreatic cancer patients is nearly 5%, making this cancer type one of the most lethal neoplasia. Furthermore, the incidence rate of pancreatic cancer has a growing trend that determines a constant increase in the number of deceases caused by this pathology. The poor prognosis of pancreatic cancer is mainly caused by delayed diagnosis, early metastasis of tumor, and resistance to almost all tested cytotoxic drugs. In this respect, the identification of novel potential targets for new and efficient therapies should be strongly encouraged in order to improve the clinical management of pancreatic cancer. Some studies have shown that the mitochondrial uncoupling protein 2 (UCP2) is over-expressed in pancreatic cancer as compared to adjacent normal tissues. In addition, recent discoveries established a key role of UCP2 in protecting cancer cells from an excessive production of mitochondrial superoxide ions and in the promotion of cancer cell metabolic reprogramming, including aerobic glycolysis stimulation, promotion of cancer progression. These observations together with the demonstration that UCP2 repression can synergize with standard chemotherapy to inhibit pancreatic cancer cell growth provide the molecular rationale to consider UCP2 as a potential therapeutic target for pancreatic cancer. In this editorial, recent advances describing the relationship between cancer development and mitochondrial UCP2 activity are critically provided.

Key words: Uncoupling protein 2; Target therapy; Reactive oxygen species; Metabolism; Pancreatic cancer

Core tip: The dramatic poor prognosis of pancreatic cancer forces towards the identification of novel efficient therapeutic targets against this neoplasia. Overexpression of uncoupling protein 2 (UCP2) and its functional involvement in cancer development, reactive oxygen species production, and cancer metabolic reprogramming may represent the rationale and the

starting point for future drug design projects focused on the identification of specific UCP2 inhibitors as innovative therapeutic tool against pancreatic cancer.

Donadelli M, Dando I, Dalla Pozza E, Palmieri M. Mitochondrial uncoupling protein 2 and pancreatic cancer: A new potential target therapy. *World J Gastroenterol* 2015; 21(11): 3232-3238 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i11/3232.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i11.3232

INTRODUCTION

Pancreatic cancer (PC) ranks amongst the most lethal cancers and has a mortality rate that nearly equals the incidence rate and an overall 5-years survival of approximately 5%[1,2]. Dismally, its mortality rate has been increasing in the last years with a prediction for next years having the same trend. In contrast, in the last decades, an overall reduction in cancer-related mortality in Western countries has been observed for lung, breast, colorectal, and prostate cancers[3]. The reduced cancer mortality for the latter tumors is likely the result of several strategies, including development of early detection, prevention programs, and the discovery of new therapeutic targets and drugs. In the case of PC, because of its low incidence, population-based screening has been considered not feasible[4]. Indeed, the worldwide incidence of all the types of pancreatic cancers (85% of which are adenocarcinomas) ranges from 1 to 10 cases per 100000 people and is generally higher in developed countries and among men. Furthermore, PC has been classified as the eighth leading cause of death for cancer in men and the ninth in women[5]. Pancreatic adenocarcinoma (PDAC), the most aggressive and frequent PC, possesses a variety of hallmarks that include: (1) high rate of KRAS activating mutations; (2) progression from distinct types of precursor lesions; (3) propensity for both local invasion and distant metastasis; (4) extensive stromal reaction (desmoplasia) resulting in a hypovascular and hypoxic microenvironment; (5) reprogramming of cellular metabolism; and (6) tumor immune evasion[6]. More than 90% of all grades pancreatic intraepithelial neoplasia possess KRAS mutations[7]. Instead, the mutational inactivation of the CDKN2A, p53, and SMAD4 tumor suppressors has been detected with increasing frequency in type Ⅱ and type Ⅲ lesions of pancreatic intraepithelial neoplasia, suggesting that they may represent rate-limiting events for tumor progression, while KRAS mutations would contribute to its inception[8]. The epidermal growth factor receptor, the nuclear factor κB, the antiapoptotic protein Bcl-xL, and mitogen-activated protein kinase pathways have also been shown to contribute to KRAS-mediated pancreatic adenocarcinoma, suggesting alternative combinatorial tumorigenic strategies[9-11].

Several efforts made to identify pancreatic tumor biomarkers[12,13] have brought to the identification of the carcinoembryonic antigen and the carbohydrate antigen 19-9, which, however, are considered low sensitive and specific for screening pancreatic cancer at early stages. Despite these advances, more than 90% of patients who have received a diagnosis of pancreatic cancer die from the disease as a result of extensive metastasis (70%) or of bulky primary tumors with limited metastatic disease (30%)[14]. Thus, delayed diagnosis, early metastasis, and resistance to almost all the classes of cytotoxic drugs are considered the main causes of the extremely poor prognosis of PC. For all these reasons, research is now focused on the identification of new prognostic and diagnostic biomarkers and efficient therapeutic targets in order to improve the clinical management of PC. In this respect, we here provide critical comments on the possible usage of the antioxidant mitochondrial uncoupling protein 2 (UCP2) as a new potential target for PC treatment. Several studies have indeed shown that UCP2 is broadly over-expressed in various cancer types and its over-expression is strictly related with the regulation of reactive oxygen species (ROS) and cell metabolism (including autophagy), both processes known to be generally altered in cancer cells.

Uncoupling protein superfamily

Mitochondrial ATP production occurs by coupling the electron transport chain (ETC) with the phosphorylation of ADP into ATP, the so-called oxidative phosphorylation. These two processes are not always efficiently coupled, mainly because of the presence in the inner membrane of mitochondrial transporters, such as uncoupling proteins (UCPs). The UCPs belong to the superfamily of anion transport carriers of the mitochondrial inner membrane[15] and some of them are involved in thermogenesis and regulation of mitochondrial ROS. UCP1 was first discovered and cloned in 1986[16] and is involved in the non-shivering thermogenesis activity of brown adipose tissue (BAT)[17]. Since then, the discovery of UCPs has grown rapidly, UCP1 homologues being found across mammalian species (UCP2 and UCP3) but also in other eukaryotes from plants to animals[18,19]. UCP1, UCP2, and UCP3 are thought to differ in the nature of their uncoupling activity[20,21] and of their potential physiological roles[22]. A rapid overview of data collected on UCP1, 2 and 3 highlights how these proteins differ from each other. First, while UCP1 tissue expression is localized and abundant in BAT, UCP2 has been found in several tissues, including liver, brain, pancreas, adipose tissue, immune cells, spleen, kidney, and the central nervous system[23-25], and UCP3 is mainly present in the skeletal muscle[18]. Also, the physiological role of UCP1 is restricted to thermogenesis, which is unlikely to be the role for UCP2 and 3, as shown by their respective knock-out models[26,27]. UCP2 and 3 have

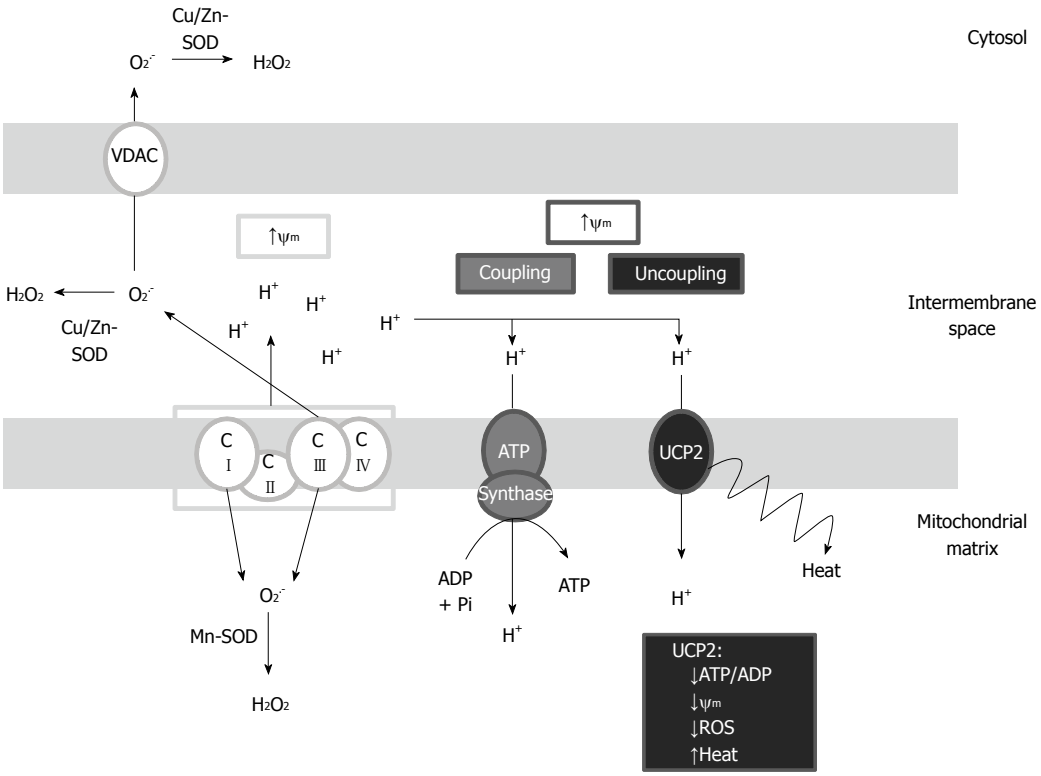

Figure 1 Uncoupling protein 2 uncoupling activity in oxidative phosphorylation. ROS: Reactive oxygen species; UCP2: Uncoupling protein 2; SOD: Superoxide dismutase; Mn-SOD: Manganese-superoxide dismutase.

been involved in a number of postulated functions in energy regulation, including regulation of insulin secretion[28] or ROS production and control of the immune response[26]. The other two members of the UCP superfamily, UCP4 and UCP5, are expressed in a tissue-specific manner and are involved in mitochondrial membrane potential reduction[29].

UCP2 and reactive oxygen species

The cellular antioxidant systems include a large set of enzymes and low-molecular-weight compounds that sequester excessively generated ROS or prevent their production by aerobic respiration. Some antioxidant systems can be energetically expensive because of their dependence on both ATP and NADPH usage. The UCP system represents an acute and energetically costly mechanism to decrease ROS production in mitochondria[30]. Indeed, as shown in Figure 1, the uncoupling of oxidative phosphorylation is a short circuit in which the transport of protons from the intermembrane space to the matrix bypasses ATP synthase resulting in a decrease of: (1) mitochondrial inner membrane potential; (2) leakage of electrons from ETC; and (3) consequently, ROS generation. The existence of a strong correlation between mitochondrial membrane potential and ROS production is well known[31]. Minor increases in membrane potential induce ROS formation, whereas slight decreases can substantially diminish their production, without greatly lowering the efficiency of oxidative phosphorylation. Hence, the mild uncoupling of mitochondrial oxidative phosphorylation may represent the first line of defense against oxidative stress[32]. According to this pattern, UCP2 can dissipate the proton gradient to prevent the proton-motive force from becoming excessive, thus decreasing ROS produced by electron transport[33]. Overall, it is estimated that 0.2%-2% of the O_2 consumed in mitochondria is reduced to superoxide by electron leakage. Mitochondrial superoxide ion is considered the initial and leading molecule of ROS signaling and is generally converted into hydrogen peroxide (H_2O_2) by superoxide dismutases. In addition, upon reaction with H_2O superoxide ion can generate hydroxyl radicals ($^{\bullet}HO$) implicated in lipid damage and protein oxidation[34,35]. The electron leakage causing superoxide production can occur both at complex Ⅰ (CⅠ) and complex Ⅲ (CⅢ) of the respiratory chain[36]: at CⅠ, superoxide has been shown to be exclusively directed toward the mitochondrial matrix and converted into membrane-permeable H_2O_2 by manganese-superoxide dismutase (Mn-SOD), while at CⅢ, superoxide is released to both the matrix and the intermembrane space where it can be converted into H_2O_2 by copper/zinc-superoxide dismutase (Cu/Zn-SOD) (Figure 1)[37]. In addition, some evidence indicates that mitochondrial matrix-directed superoxide can be released from mitochondria through voltage dependent anion channels causing an increase of cytosolic ROS[38]. Therefore, UCP2 acts as a sensor of mitochondrial oxidative stress and

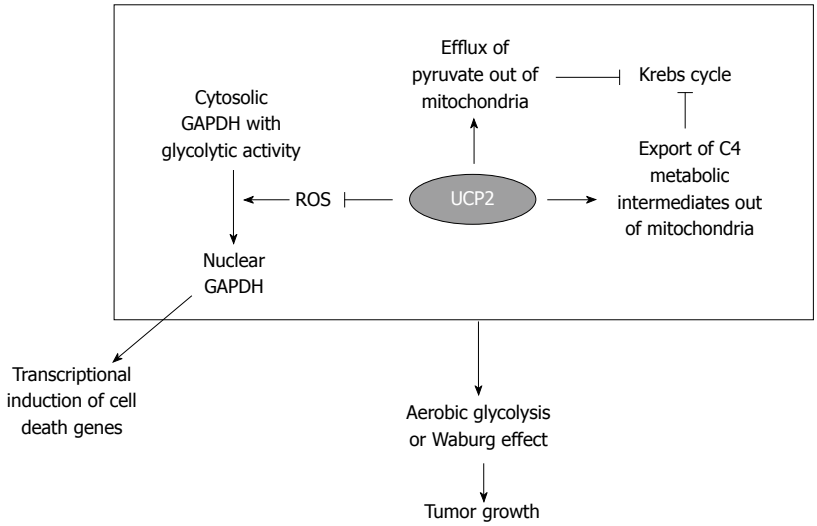

Figure 2 The regulation of cancer metabolism by uncoupling protein 2. ROS: Reactive oxygen species; UCP2: Uncoupling protein 2.

constitutes an important component of local feedback mechanisms generally implicated in cyto-protective activities controlling the production of mitochondrial ROS and regulating redox-sensitive cytosolic signaling pathways.

UCP2 and cancer metabolism

In 1956, Warburg *et al*[39] proposed that cancer was caused by defects in mitochondria, forcing cells to shift to energy production through glycolysis despite aerobic conditions. This characteristic of cancers is described as the "Warburg effect." Warburg statement is based on the observation that the irreversible injury to mitochondrial respiration is followed by a long fight for existence in which a part of the cells perishes for lack of energy while another part succeeds in replacing the lost respiration energy by developing aerobic glycolysis. The Warburg effect, considered now a hallmark of cancer, plays an important role in the growth of tumors, including gastrointestinal cancers, by remodeling the metabolic profile in order to allow tumor cell survival under adverse conditions[40]. More recently, some scientists tried to create a cellular model of the Warburg effect by developing an epithelial cell line lacking mitochondrial DNA (rho^0)[41]. Among the regulated genes, UCP2 expression was predominantly higher in rho^0 cells suggesting that UCP2 may inhibit ROS accumulation and protect the cells from excessive ROS production induced by mitochondrial defects linked to Warburg effect. In this respect, UCP2 may function as a potential diagnostic marker of cancer associated with the Warburg effect[42]. In addition to its antioxidant role, UCP2 acts as a direct metabolic regulator contributing to the Warburg phenotype. Indeed, as schematically reported in Figure 2, UCP2 has been proposed to function as a uniporter for pyruvate, which promotes pyruvate efflux from mitochondria, restricts mitochondrial respiration, and increases the rate of glycolysis in cancer cells[43]. Furthermore, UCP2 catalyzes the exchange of intramitochondrial C4 metabolites for cytosolic phosphate by an H^+-assisted mechanism, which is stimulated by both the electrical potential (negative inside) and pH gradient (acidic outside) existing across the inner mitochondrial membrane of respiring cells[44]. In particular, by exporting oxaloacetate and related C4 compounds from mitochondria, UCP2 negatively controls the oxidation of acetyl-CoA-producing substrates *via* the Krebs cycle, thus lowering the redox pressure on the mitochondrial respiratory chain, the ATP: ADP ratio, and ROS production. Notably, the mitochondrial concentration of oxaloacetate is usually very low, and its availability regulates the entry of acetyl-CoA into the Krebs cycle. Thus, UCP2 prevents mitochondrial glucose oxidation and favors a higher glucose utilization by aerobic glycolysis. In this context, our research group further confirmed the pro-glycolytic effect of UCP2 demonstrating for the first time that UCP2 can stabilize the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in the cytoplasm of cancer cells[45]. Accordingly, in response to oxidative stress, GAPDH has been demonstrated to undergo protein oxidation of redox-sensitive cysteine residues that stimulates its translocation to cell nuclei[46], where the enzyme favors transcriptional induction of cell death-related genes[47,48]. Thus, the antioxidant effect of UCP2 can inhibit both GAPDH oxidation and nuclear translocation supporting the glycolytic flux and preventing cancer cells from stimulating cell death mechanisms (Figure 2).

UCP2 and pancreatic cancer

A careful analysis of the recent scientific literature concerning the role of UCP2 in tumor development reveals that UCP2 and cancer may have a double relationship. Indeed, a dual regulation of UCP2 expression, depending on the stages of cancer development, has been observed in many tumor types.

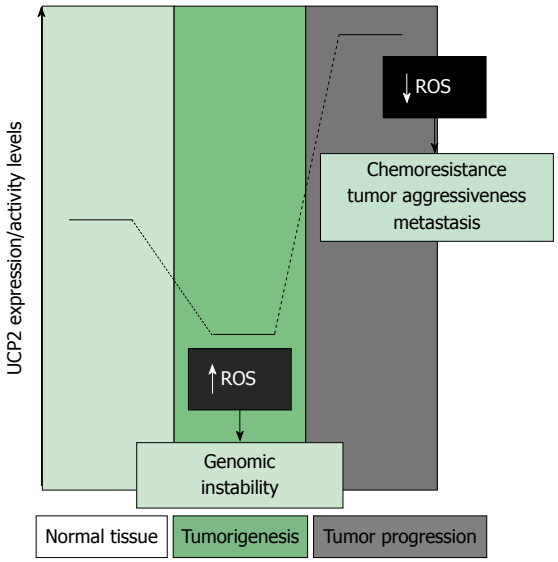

Figure 3 Relation between cancer development and uncoupling protein 2 expression or activity. ROS: Reactive oxygen species; UCP2: Uncoupling protein 2.

A number of studies have established the key role that UCP2 has in tumorigenesis and in chemoresistance. The generally accepted thesis envisages that, during the first stages of tumorigenesis, UCP2 is repressed to allow ROS accumulation and genomic instability, while it is triggered or over-expressed in the following stages of cancer development, determining chemoresistance and tumor aggressiveness by defending cancer cells from apoptosis through the negative regulation of mitochondrial ROS production (Figure 3)[49-51]. Accordingly, UCP2-null mice have a predisposition for enhanced tumorigenesis in the proximal colon, providing the first *in vivo* confirmation of a link between mitochondrial uncoupling proteins and cancer[52], while highly expressed UCP2 is associated with metastatic colon cancer and tumor aggressiveness[53]. The dual and opposite regulation of UCP2 expression in various stages of tumor development has also been demonstrated in breast cancer. In this system, the repression of UCPs by estrogens, a major risk factor for breast cancer initiation, may play a key role in estrogen-induced breast carcinogenesis[54]. On the contrary, the enhanced expression of UCP2 has been correlated to breast cancer progression. Indeed, a significant correlation between UCP2 levels and tumor grade-associated functional phenotypes has been found in a large number of breast cancer patients (n = 234)[55]. Concerning PC, some studies have shown that the protein level of UCP2 is significantly higher in human PC samples than in the adjacent normal tissues, suggesting that UCP2 may promote tumor growth in this tumor type[56]. An extensive study on Oncomine data sets addressed to analyze the UCP2 expression level in a number of cancer types, including pancreatic cancer, has revealed that UCP2 is over-expressed in ovarian, bladder, esophageal, testicular, kidney, colorectal, lung, breast, leukemia, prostate, as well as pancreas cancers[42]. This study has concluded that UCP2 over-expression is a general phenomenon linked to the progression of human cancers. Along this line of evidence, our research group has demonstrated that increased expression of UCP2 mRNA directly correlates with resistance to gemcitabine treatment, in a panel of pancreatic adenocarcinoma cell lines, and that the *UCP2* gene is induced by gemcitabine, demonstrating that the antioxidant effect of UCP2 plays a critical role in pancreatic cancer cell resistance to standard chemotherapy. We have also shown that UCP2 inhibition has a synergistic antiproliferative effect with gemcitabine in pancreatic adenocarcinoma cell growth[57]. Despite the availability of the above described data on the relationship between UCP2 expression/activity and PC, we believe that further studies need to be performed in order to better clarify the functional role of UCP2 in PC tumorigenesis and progression. Of crucial importance will be analyses on proteome and metabolic profiles of pancreatic cancer cells after knock-down or over-expression of UCP2 and clinical studies correlating UCP2 expression with clinicopathological factors and prognosis outcome on PC patients.

CONCLUSION

UCP2 over-expression may be considered a strategy adopted by cancer cells to protect themselves from excessive ROS production and to support the Warburg effect by reprogramming cancer cell metabolism. Thus, UCP2 inhibition can represent a therapeutic opportunity, in association to radio- or chemo-therapy, to treat tumors resistant to traditional therapy, such as PC. For this reason, we believe that UCP2 may be considered a potential target therapy for this tumor type. However, an efficient and specific UCP2 inhibitor is not yet available. The tools currently used in research studies to inhibit UCP2 are the genetic repression of *UCP2* mRNA by a specific siRNA or the inhibition of UCP2 activity by genipin, a natural aglycon derived from geniposide, an iridoid glycoside extracted from the fruit of *gardenia jasminoides*. Genipin, however, has unspecific pharmacological properties including anti-inflammatory and antidepressant-like effects[58]. Thus, drug design research to identify or synthetize a specific and effective UCP2 inhibitor should be strongly encouraged in order to counteract progression of pancreatic cancer and of many other tumor types over-expressing this protein, which is crucial for their aggressive phenotype.

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P- Reviewer: Fu DL, Giovannetti E, Stefaniak T, Su WC
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ISSN 1007-9327