New Aspects of Mitochondrial Uncoupling Proteins (UCPs) and Their Roles in Tumorigenesis

Delira Robbins and Yunfeng Zhao *

Department of Pharmacology, Toxicology & Neuroscience, LSU Health Sciences Center 1501 Kings Highway, Shreveport, LA 71130, USA; E-Mail: drobbi@lsuhsc.edu

* Author to whom correspondence should be addressed; E-Mail: yzhao1@lsuhsc.edu; Tel.: +1-318-675-7876; Fax: +1-318-675-7857.

Received: 26 July 2011; in revised form: 9 August 2011 / Accepted: 10 August 2011 / Published: 17 August 2011

Abstract: Uncoupling proteins (UCPs) belong to a family of mitochondrial carrier proteins that are present in the mitochondrial inner membrane. UCP1 was first identified followed by its two homologs, UCP2 and UCP3. The physiological functions of UCP include lowering mitochondrial membrane potential and dissipating metabolic energy as heat. However, UCP can be dysregulated and may contribute to the pathogenesis of metabolic disorders and obesity. Recent studies suggest that UCP also plays a role in neurodegenerative diseases and atherosclerosis. In addition, the widely expressed UCP, UCP2, has been shown to be upregulated in a number of aggressive human cancers. One mechanism of UCP2 upregulation in these cancers is due to oxidative stress, and elevated UCP2 in turn reduces oxidative stress, which provides a growth advantage for these cancers. Nevertheless, new studies suggest UCP2 may interact with oncogenes and tumor suppressor genes, providing a potential new mechanism of how UCP2 contributes to cancer development. In this review, the evidence supporting the role of UCPs in diseases other than diabetes and obesity, the reports on how UCP is regulated in cancer cells, and how UCP may regulate p53 will be discussed.

Keywords: mitochondrial uncoupling; UCP2; cancer; UCP2 regulation
1. Introduction

In vertebrates, energy is mainly produced in the mitochondria via the Citric Acid Cycle coupled with oxidative phosphorylation. The mitochondrial respiration process generates a proton gradient across the mitochondrial inner membrane that establishes the electrochemical potential ($\Delta \psi_m$), which is mainly used for ATP synthesis. However, not all of the energy available in the electrochemical gradient is coupled to ATP synthesis. Some of the energy is consumed by “proton leak” reactions, by which protons pumped into the inner membrane space flow back into the matrix through proton conductance pathways in the inner membrane that bypass the ATP synthase. As a result, energy derived from the metabolic oxidation reaction is dissipated as heat [1–4]. This nonproductive proton leak, termed mitochondrial uncoupling, is physiologically important and accounts for 20–25% of the basal metabolic rate [5,6].

Mitochondrial uncoupling is mediated mainly by uncoupling proteins (UCPs), among those, UCP1 is the first to be identified in brown adipose tissue [7], followed by its four homologs: UCP2 [8] is ubiquitously expressed, UCP3 [9] exists solely in skeletal muscle and the heart, UCP4 [10], and BMCP1 (brain mitochondrial carrier protein-1, [11]) or UCP5 are predominantly expressed in the central nervous system. UCPs are anion carriers across the mitochondrial inner membrane, which bring protons back into the mitochondrial matrix. In addition, UCP1 dissipates redox energy and thereby provides heat to the animal. UCP2 decreases the production of reactive oxygen species [12]. Furthermore, it has been suggested that brain-specific UCP4 and UCP5 play a role in apoptosis in the brain [13,14].

2. UCPs and Non-Cancer Diseases

Mitochondria-generated ATP provides the major fuel for eukaryotic cells. As byproducts, free radicals can be generated within mitochondria during energy production, which could harm cells if not rapidly removed. Mild mitochondrial uncoupling can reduce the generation of free radicals and therefore, protect cells. Mitochondrial uncoupling has been amplified or reduced during the pathogenesis of a number of human diseases due to up- or down-regulation of UCP. The two most studied UCP-associated diseases are diabetes and obesity, and studies of UCP in these two diseases have been thoroughly reviewed.

Non-alcoholic fatty liver disease is another form of metabolic disorder. Park et al. detected UCP2 in young Asian patients, and the results showed that the expression levels of UCP2 were correlated with general pathologic severity [15].

Non-alcoholic steatohepatitis (NASH) has been identified in patients with non-alcoholic fatty liver disease with evidence of inflammation in liver biopsies. The mechanistic progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis is not clear; however the involvement of underlying mitochondrial dysfunction orchestrates the progression due to its role in fatty acid oxidation, ROS generation and ATP synthesis. NASH has been characterized by the accumulation of fatty acids in hepatocytes and oxidative stress [16], decreased ATP production [17], and the induction of proinflammatory cytokines [18]. Serviddio et al. reports that the upregulation of UCP2 protects the liver from excessive fat accumulation, but chronically depletes the liver of ATP, compromising
the response of the liver to acute energy demands, which results in increased susceptibility to ischemia-reperfusion injury [19].

Clinical evidence suggests that UCPs may be associated with diseases distinct from metabolic diseases. For instance, higher expression levels of UCP2 may mediate follicle development in polycystic ovary syndrome [20]. Several well designed studies further suggest that UCP is involved in the pathogenesis of neurodegenerative disease, atherosclerosis, liver disease, etc.

Richard et al. reported the presence of UCP2 mRNA with varying intensities throughout the brain. Marked high intensities were found in the hypothalamus, the ventral septal region, the ventricular region and the cerebellum, suggesting a novel role of UCP in modulating neuroendocrine functions and autonomic responses of the brain [21]. In addition, UCP2-mediated mitochondrial proton leak has been positively correlated with increased oxygen consumption in brain tissues [22]. This regulation of oxygen consumption, suggests that UCP2 may modulate ROS production and influence the process of neurodegeneration [21].

The mRNA expression of UCP2 in the brain suggested neuronal localization [21]. In an animal model of Parkinson’s disease (PD), in which dopamine neurons are depleted by 1-methyl-4-phenyl-1,2,5,6 tetrahydropyridine (MPTP), UCP2 knockout increased whereas UCP2 overexpression decreased MPTP-induced nigral dopamine cell loss. Coenzyme Q10 (CoQ10), a cofactor of mitochondrial metabolism and UCP2 activity [23], induced UCP2-mediated mitochondrial uncoupling in the substantia nigra [24]. When given orally, CoQ10 was shown to reduce dopamine cell loss in both mouse [25] and primate models of PD [24] and potentially slowed the progression of the disease in human patients [26]. As mentioned above, UCP2 protects against dopamine cell loss caused by the mitochondrial complex I toxin MPTP. Consistent with that, degeneration of substantia nigra compacta dopaminergic neurons in human PD is associated with mitochondrial complex I dysfunction and free radical toxicity [27]. These studies demonstrate the importance of UCP2 in normal nigral dopamine cell metabolism, and suggest that UCP2 is important in regulating cell survival and susceptibility to mitochondrial toxins; and may serve as a novel therapeutic target for the prevention and treatment of PD [28].

Not surprising, UCP also plays an important role in Alzheimer’s disease (AD). The expression levels of UCP2, 4, and 5 were significantly reduced in AD patients, which were accompanied by upregulation of nitric oxide synthases (NOS), and resulted in increased oxidative stress and impaired mitochondrial functions. Therefore, to increase the expression level of UCP may help in the treatment of AD [29].

The protective role of UCP2 against atherosclerosis was demonstrated using irradiated low-density lipoprotein receptor-deficient mice (LDLR/-/). These mice were transplanted with bone marrow from either UCP2 deficient mice or wild-type mice, and fed with an atherogenic diet. The results showed that the atherosclerotic lesion size was markedly increased in the mice receiving UCP2 deficient bone marrow, which was accomplished by enhanced oxidative stress [30].

3. UCP and Cancer

Compared with the extensive studies on UCP in diabetes and obesity, the role of UCP (mostly UCP2) in cancer was recently recognized and has attracted more attention. As a matter of fact, the
impact of mitochondrial uncoupling on cellular physiology is not restricted to normal cells; it also plays an important role in the reprogramming of cancer cell metabolism [31].

Early evidence showing that UCP might be important for tumor growth arises from rats which received an inoculation of the Yoshida AH-130 ascites hepatoma cells [11]. The expression levels of both UCP2 and UCP3 mRNAs were increased, suggesting that energy expenditure is associated with tumor growth.

In human studies, most of the results point to UCP2 potentially being associated with the development of colon and breast cancer. Horimoto et al. reported that UCP2 overexpression in malignancy was limited to the colon [32], in which UCP2 expression in human colon tissue increased with the degree of neoplasia. However, their results also showed that high UCP2 levels in colon adenocarcinoma correlated with high oxidant levels, making it hard to explain whether it is a cause or effect relationship between uncoupling and oxidative stress.

Kuai et al. further demonstrated that the levels of both UCP2 mRNA and protein were higher in colon cancer tissue samples than in its adjacent tissue samples [33], and the authors suggested that increased UCP2 expression may be involved in colon cancer metastasis.

However, the first colon tumorigenesis study using UCP2 null mice showed surprising results [34]. The UCP2 null mice developed more colon tumors than the wild-type controls with increased oxidative stress and enhanced NF-κB activation when treated with azoxymethane (AOM), an experimental alkylating carcinogen [35], despite the fact that isolated mitochondria from UCP2-/- cells produced more superoxide/hydrogen peroxide. In our opinion, this study can be improved by checking whether UCP2 is up- or down-regulated during colon tumorigenesis in the wild-type mice. If it is upregulated, then UCP2 transgenic mice might be a better tool to study the role of UCP2 in colon tumorigenesis.

Later studies suggest that UCP2 is also involved in the pathogenesis of other cancers. Sayeed et al. reported a significant association of UCP2 with tumor grade in primary breast cancer [36]. The results are reinforced by the study from Won et al., which demonstrated that UCP2 expression was correlated significantly with histological grade and mitotic count in invasive ductal carcinoma of the breast analyzed from human tissue microarrays [37].

We used a tumor promotion model to study the role of mitochondrial uncoupling in tumor promotion [38]. Our study demonstrated that mitochondrial uncouplers inhibited cell death that arose during tumor promotion. When UCP2 was downregulated using a siRNA approach, cell transformation was suppressed, suggesting UCP2 may serve as a tumor promoter during early tumorigenesis.

Another important role of UCPs in cancer is their contributions to chemoresistance [39,32]. UCPs were upregulated in many chemoresistant cancer cell lines, which may provide a prosurvival advantage to tumor cells via attenuating ROS (reactive oxygen species) generation [40–42], and increasing drug concentrations to kill these cancer cells [43].

4. Regulation of UCP in Cancer Cells

UCP gene regulation is not well understood. UCP can be generally regulated by oxidative stress. When oxidative stress occurs, UCP2 and UCP3 uncoupling activities can be stimulated by superoxide anion, limiting ROS production by the mitochondrial respiratory chain. This in turn decreases superoxide levels and UCP uncoupling activity via a feedback loop [44]. Fatty acids also induced
UCP2 and UCP3 in muscle [45] and fat [46], which was mediated by transcription factors of peroxisome proliferator-activated receptors (PPAR, [47]).

How oncogenes and tumor suppressor genes may regulate UCP should be of great interest to study UCP in cancer. However, such evidence is rare, which deserves more research efforts, since knowing the basic biology of UCP regulation in cancer cells is essential for potential UCP-targeted cancer therapy. One important study utilized well-to-moderately differentiated primary breast tumor cell lines showed that SMAD was recruited to the UCP2 promoter region via the transforming growth factor-beta (TGFβ)/SMAD-dependent pathway [36]. In contrast, in TGFβ-resistant high-grade tumors, potentiation of UCP2 repression fails to occur, contributing to impaired cell differentiation.

5. UCP2 and p53 Signaling

p53, as a pivotal tumor suppressor, can cause apoptotic cell death in response to cellular stress stimuli (e.g., drugs, irradiation, UV, hypoxia) and the expression of viral or cellular oncogenes [48]. Interestingly, a fraction of p53 can translocate to mitochondria under the above mentioned stress conditions [49]. Similarly to nuclear p53, mitochondrial p53 is also able to initiate apoptosis [50]. Since both p53 and UCP2 can regulate and respond to oxidative stress, it is possible that there is a potential interaction between these two proteins.

A few studies have suggested that this may indeed occur. Derdak et al. demonstrated that UCP2 inhibited apoptosis of colon cancer cells by suppressing the phosphorylation of p53 within the transactivating domain via suppressing ROS [43]. Won et al. had a different observation. They reported that high UCP2 expression in invasive breast ductal carcinoma was associated with high p53 nuclear expression [37]. However, the antibody against p53 used (DO-7) can detect both wild-type and mutant p53, and p53 is highly mutated in these tumors [51]. Therefore, it is not clear if the highly expressed p53 was wild-type or mutant or both.

Our studies using the skin carcinogenesis model revealed that during early tumor promotion, the tumor suppressor p53 translocated to mitochondria and physically interacted with a primary antioxidant defense enzyme, manganese superoxide dismutase (MnSOD), leading to suppression of its superoxide scavenging activity, as well as, increases in ROS levels [52]. Thus, in addition to the direct apoptotic activity of mitochondria p53, the ability to induce ROS accumulation might serve as a positive feed-back loop and play an essential role in the p53-mediated apoptosis pathway.

Given these facts, we further examined the role of UCP2 in tumor promoter-induced p53 mitochondrial translocation and cell transformation. Downregulation of UCP2 expression using a transfection with specific siRNA to UCP2 induced translocation of a small amount of p53 to mitochondria, and also enhanced tumor promoter-induced p53 mitochondrial translocation whereas cell transformation was reduced [38]. These data indicated that UCP2-mediated mild mitochondrial uncoupling may serve as a tumor promoting event.

The elevated levels of UCP2 in cancer cells may be a result of long-term selection during tumorigenesis, since any event that results in UCP2 upregulation could help cells escape from apoptosis mediated by the p53 signaling. Given the fact that mitochondrial uncoupling could cause dissipation of the mitochondrial potential, a decrease in mitochondrial ROS, and a reduction in p53’s response to oxidative stress, it is reasonable to propose that mitochondrial uncoupling may provide cancer cells with a prosurvival advantage via suppressing the p53 mediated apoptosis pathway.
6. Conclusions

It has been suggested that dysregulation of UCP is involved in the pathogenesis of not only diabetes and obesity, but also neurodegenerative disease, atherosclerosis, and cancer. Among these diseases, it is very likely that UCP can protect against neurodegeneration, but exacerbate the progression of the other diseases. In cancer, elevated UCP contributes not only to chemoresistance, but also to early transformation. Therefore, targeting UCP could serve as a promising approach for both cancer prevention and therapy.

References

1. Brand, M.D. The proton leak across the mitochondrial innermembrane. *Biochim. Biophys. Acta* 1990, 1018, 128–133.
2. Brand, M.D.; Chien, L.F.; Ainscow, E.K.; Rolfe, D.F.S.; Porter, R.K. The causes and functions of mitochondrial proton leak. *Biochim. Biophys. Acta* 1994, 1187, 132–139.
3. Brown, G.C.; Brand, M.D. On the nature of the mitochondrial proton leak. *Biochim. Biophys. Acta* 1991, 1059, 55–62.
4. Brand, M.D.; Brindle, K.M.; Buckingham, J.A.; Harper, J.A.; Rolfe, D.F.S.; Stuart, J.A. The significance and mechanism of mitochondrial proton conductance. *Int. J. Obes. Relat. Metab. Disord.* 1999, 23, S4–S11.
5. Porter, R.K.; Brand, M.D. Causes of differences in respiration rate of hepatocytes from mammals of different body mass. *Am. J. Physiol.* 1995, 269, R1213–R1224.
6. Rolfe, D.F.S.; Newman, J.M.B.; Buckingham, J.A.; Clark, M.G.; Brand, M.D. Contribution of mitochondrial proton leak to respiration rate in working skeletal muscle and liver and to SMR. *Am. J. Physiol.* 1999, 276, C692–C699.
7. Bouillaud, F.; Ricquier, D.; Thibault, J.; Weissenbach, J. Molecular approach to thermogenesis in brown adipose tissue: cDNA cloning of the mitochondrial uncoupling protein. *Proc. Natl. Acad. Sci. USA* 1985, 82, 445–448.
8. Fleury, C.; Neverova, M.; Collins, S.; Raimbault, S.; Champigny, O.; Levi-Meyrueis, C.; Bouillard, F.; Seldin, M.F.; Surwit, R.S.; Ricquier, D.; *et al*. Uncoupling protein-2: A novel gene linked to obesity and hyperinsulinemia. *Nat. Genet.* 1997, 15, 269–272.
9. Boss, O.; Samec, S.; Paoloni-Giacobino, A.; Rossier, C.; Dulloo, A.; Seydoux, J.; Muzzin, P.; Giacobino, J.P. Uncoupling protein-3: A new member of the mitochondrial carrier family with tissue-specific expression. *FEBS Lett.* 1997, 408, 39–42.
10. Mao, W.; Yu, X.X.; Zhong, A.; Li, W.; Brush, J.; Sherwood, S.W.; Adams, S.H.; Pan, G. UCP4, a novel brain-specific mitochondrial protein that reduces membrane potential in mammalian cells. *FEBS Lett.* 1999, 443, 326–330.
11. Sanchis, D.; Fleury, C.; Chomiki, N.; Goubert, M.; Huang, Q.; Neverova, M.; Gregoire, F.; Easlick, J.; Raimbault, S.; Levi-Meyrueis, C.; *et al*. BMCP1, a novel mitochondrial carrier with high expression in the central nervous system of humans and rodents, and respiration uncoupling activity in recombinant yeast. *J. Biol. Chem.* 1998, 273, 34611–34615.
12. Goglia, F.; Skulachev, V.P. A function for novel uncoupling proteins: antioxidant defense of mitochondrial matrix by translocating fatty acid peroxides from the inner to the outer membrane leaflet. *FASEB J.* 2003, 17, 1585–1591.

13. Mattson, M.P.; Kroemer, G. Mitochondria in cell death: novel targets for neuroprotection and cardioprotection. *Trends Mol. Med.* 2003, 9, 196–205.

14. Mattson, M.P.; Liu, D. Mitochondrial potassium channels and uncoupling proteins in synaptic plasticity and neuronal cell death. *Biochem. Biophys. Res. Commun.* 2003, 304, 539–549.

15. Park, J.W.; Jeong, G.; Kim, S.J.; Kim, M.K.; Park, S.M. Predictors reflecting the pathological severity of non-alcoholic fatty liver disease: Comprehensive study of clinical and immunohistochemical findings in younger Asian patients. *J. Gastroenterol. Hepatol.* 2007, 4, 491–497.

16. Day, C.P.; James, O.F. Steatohepatitis: a tale of two “hits”? *Gastroenterology* 1998, 114, 842–845.

17. Cortez-Pinto, H.; Chatham, J.; Chacko, V.P.; Arnold, C.; Rashid, A.; Diehl, A.M. Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. *JAMA* 1999, 282, 1659–1664.

18. Tomita, K.; Tamiya, G.; Ando, S.; Ohsumi, K.; Chiyto, T.; Mizutani, A.; Kitamura, N.; Toda, K.; Kaneko, T.; Horie, Y.; et al. Tumor necrosis factor alpha signaling through activation of Kupffer cells plays an essential role in liver fibrosis of non-alcoholic steatohepatitis in mice. *Gut* 2006, 55, 415–424.

19. Serviddio, G.; Bellanti, F.; Tamborra, R.; Rollo, T.; Capitanio, N.; Romano, A.D.; Sastre, J.; Vendemiaile, G.; Altomare, E. Uncoupling protein-2 (UCP2) induces mitochondrial proton leak and increases susceptibility of non-alcoholic steatohepatitis (NASH) liver to ischaemia-reperfusion injury. *Gut* 2008, 57, 957–965.

20. Liu, Y.; Jiang, H.; He, L.Y.; Huang, W.J.; He, X.Y.; Xing, F.Q. Abnormal expression of uncoupling protein-2 correlates with CYP11A1 expression in polycystic ovary syndrome. *Reprod. Fertil. Dev.* 2011, 4, 520–526.

21. Richard, D.; Rivest, R.; Huang, Q.; Bouillaud, F.; Sanchis, D.; Champigny, O.; Ricquier, D. Distribution of the uncoupling protein 2 mRNA in the mouse brain. *J. Comp. Neurol.* 1998, 397, 549–560.

22. Rolfe, D.F.S.; Hulbert, A.J.; Brand, M.D. Characteristics of mitochondrial proton leak and control of oxidative phosphorylation in the major oxygen-consuming tissues of the rat. *Biochim. Biophys. Acta* 1994, 1118, 405–416.

23. Echtay, K.S.; Winkler, E.; Klingenberg, M. Coenzyme Q is an obligatory cofactor for uncoupling protein function. *Nature* 2000, 408, 609–613.

24. Horvath, T.L.; Diano, S.; Leranth, C.; Garcia-Segura, L.M.; Cowley, M.A.; Shanabrough, M.; Elsworthy, J.D.; Sotonyi, P.; Roth, R.H.; Dietrich, E.H.; et al. Coenzyme Q induces nigral mitochondrial uncoupling and prevents dopamine cell loss in a primate model of Parkinson’s disease. *Endocrinology* 2003, 144, 2757–2760.

25. Beal, M.F.; Matthews, R.T.; Tieleman, A.; Shults, C.W. Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3, tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. *Brain Res.* 1998, 783, 109–114.
26. Shults, C.W.; Oakes, D.; Kieburtz, K.; Beal, M.F.; Haas, R.; Plumb, S.; Juncos, J.L.; Nutt, J.; Shoulson, I.; Carter, J.; et al. Effects of coenzyme Q10 in early Parkinson disease: Evidence of slowing of the functional decline. *Arch. Neurol.* **2002**, *59*, 1541–1550.

27. Dauer, W.; Przedborski, S. Parkinson's disease: Mechanisms and models. *Neuron* **2003**, *39*, 889–909.

28. Andrews, Z.B.; Horvath, B.; Barnstable, C.J.; Elsworth, J.; Yang, L.; Beal, M.F.; Roth, R.H.; Matthews, R.T.; Horvath, T.L. Uncoupling protein-2 is critical for nigral dopamine cell survival in a mouse model of Parkinson's disease. *J. Neurosci.* **2005**, *25*, 184–191.

29. de la Monte, S.M.; Wands, J.R. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. *J. Alzheimers Dis.* **2006**, *9*, 167–181.

30. Blanc, J.; Alves-Guerra, M.C.; Esposito, B.; Roussel, S.; Gourdy, P.; Ricquier, D.; Tedgui, A.; Miroux, B.; Mallat, Z. Protective role of uncoupling protein 2 in atherosclerosis. *Circulation* **2003**, *107*, 388–390.

31. Samudio, I.; Fieggl, M.; Andreeff, M. Mitochondrial uncoupling and the warburg effect: Molecular basis for the reprogramming of cancer cell metabolism. *Cancer Res.* **2009**, *69*, 2163–2166.

32. Horimoto, M.; Resnick, M.B.; Konkin, T.A.; Routhier, J.; Wands, J.R.; Baffy, G. Expression of uncoupling protein-2 in human colon cancer. *Clin. Cancer Res.* **2004**, *10*, 6203–6207.

33. Kuai, X.Y.; Ji, Z.Y.; Zhang, H.J. Mitochondrial uncoupling protein 2 expression in colon cancer and its clinical significance. *World J. Gastroenterol.* **2010**, *16*, 5773–5778.

34. Bai, Y.; Onuma, H.; Bai, X.; Medvedev, A.V.; Misukonis, M.; Weinberg, J.B.; Cao, W.; Robidoux, J.; Floering, L.M.; Daniel, K.W.; et al. Persistent nuclear factor-kappa B activation in Ucp2-/- mice leads to enhanced nitric oxide and inflammatory cytokine production. *J. Biol. Chem.* **2005**, *280*, 19062–19069.

35. Derdak, Z.; Fulop, P.; Sabo, E.; Tavares, R.; Berthiaume, E.; Resnick, M.; Paragh, G.; Wands, J.; Baffy, G. Enhanced colon tumour induction in uncoupling protein-2 deficient mice is associated with NF-κB activation and oxidative stress. *Carcinogenesis* **2006**, *27*, 956–961.

36. Sayeed, A.; Meng, Z.; Luciani, G.; Chen, L.-C.; Bennington, J.L.; Dairkee, S.H. Negative regulation of UCP2 by TGFβ signaling characterizes low and intermediate-grade primary breast cancer. *Cell Death Dis.* **2010**, *1*, doi:10.1038/cddis.2010.30.

37. Won, K.Y.; Kim, G.Y.; Kim, Y.W.; Lim, S.-J.; Song, J.Y. Uncoupling Protein 2 (UCP2) and p53 expression in invasive ductal carcinoma of breast. *Korean J. Pathol.* **2010**, *44*, 565–570.

38. Wang, F.; Fu, X.; Chen, X.; Chen, X.; Zhao, Y. Mitochondrial uncoupling inhibits p53 mitochondrial translocation in TPA-challenged skin epidermal JB6 cells. *PLoS One* **2010**, *5*, doi:10.1371/journal.pone.0013459.

39. Harper, M.E.; Antoniou, A.; Villalobos-menuey, E.; Russo, A.; Trauger, R.; Vendemelio, M.; George, A.; Bartholomew, R.; Carlo, D.; Shaikh, A.; et al. Characterization of a novel metabolic strategy used by drug-resistant tumor cells. *FASEB J.* **2002**, *16*, 1550–1557.

40. Nègre-Salvayre, A.; Hirtz, C.; Carrera, G.; Cazenave, R.; Troy, M.; Salvayre, R.; Pénicaud, L.; Casteilla, L. A role for uncoupling protein-2 as a regulator of mitochondrial hydrogen peroxide generation. *FASEB J.* **1997**, *11*, 809–815.
41. Kowaltowski, A.J.; Costa, A.D.; Vercesi, A.E. Activation of the potato plant uncoupling mitochondrial protein inhibits reactive oxygen species generation by the respiratory chain. *FEBS Lett.* 1998, 425, 213–216.

42. Kowaltowski, A.J.; de Souza-Pinto, N.C.; Castilho, R.F.; Vercesi, A.E. Mitochondria and reactive oxygen species. *Free Radic. Biol. Med.* 2009, 47, 333–343.

43. Derdak, Z.; Mark, N.M.; Beldi, G.; Robson, S.C.; Wands, J.R. The mitochondrial uncoupling protein-2 promotes chemoresistance in cancer cells. *Cancer Res.* 2008, 68, 2813–2819.

44. Green, K.; Brand, M.D.; Murphy, M.P. Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes. *Diabetes* 2004, 53, S110–S118.

45. Samec, S.; Seydoux, J.; Dulloo, A.G. Post-starvation gene expression of skeletal muscle uncoupling protein 2 and uncoupling protein 3 in response to dietary fat levels and fatty acid composition: a link with insulin resistance. *Diabetes* 1999, 48, 436–441.

46. Rodriguez, V.M.; Portillo, M.P.; Picó, C.; Macarulla, M.T.; Palou, A. Olive oil feeding up-regulates uncoupling protein genes in rat brown adipose tissue and skeletal muscle. *Am. J. Clin. Nutr.* 2002, 75, 213–220.

47. Murray, A.J.; Panagia, M.; Hauton, D.; Gibbons, G.F.; Clarke, K. Plasma free fatty acids and peroxisome proliferator-activated receptor alpha in the control of myocardial uncoupling protein levels. *Diabetes* 2005, 54, 3496–3502.

48. Levine, J.J. p53, the cellular gatekeeper for growth and division. *Cell* 1997, 88, 323–331.

49. Moll, U.M.; Zaikam, A. Nuclear and mitochondrial apoptotic pathways of p53. *FEBS Lett.* 2001, 493, 65–69.

50. Mihara, M.; Erster, S.; Zaika, A.; Petrenko, O.; Chittenden, T.; Pancoska, P.; Moll, U.M. p53 has a direct apoptogenic role at the mitochondria. *Mol. Cell* 2003, 11, 577–590.

51. Lukas, J.; Niu, N.; Press, M.F. p53 mutations and expression in breast carcinoma in situ. *Am. J. Pathol.* 2000, 156, 183–191.

52. Zhao, Y.; Chaiswing, L.; Velez, J.M.; Batinic-Haberle, I.; Colburn, N.H.; Oberley, T.D.; St Clair, D.K. p53 translocation to mitochondria precedes its nuclear translocation and targets mitochondrial oxidative defense protein-manganese superoxide dismutase. *Cancer Res.* 2005, 65, 3745–3750.

© 2011 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).