The antioxidant mitochondrial protein UCP2 promotes cancer development connecting the Warburg effect and autophagy

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Uncoupling proteins (UCPs) are mitochondrial anion transporter proteins localized into the mitochondrial inner membrane.[1] Currently, five UCP family members have been identified in mammals. Among them, UCP2 is widely distributed throughout the organism, suggesting different and wide functions for this mitochondrial uncoupling protein.[2] Basically, the antioxidant role of UCP2 is due to its capability to decrease the mitochondrial potential and to dissipate the proton gradient. This prevents the proton-motive force from becoming excessive, thus decreasing reactive oxygen species (ROS), especially superoxide ions, produced by leakage of electrons from the mitochondrial transport chain.[3] UCP2 is a redox sensitive protein functioning as a mitochondrial redox sensor. As a result of oxidation, UCP2 is activated becoming an important component of antioxidant feedback mechanisms commonly implicated in cyto-protective events controlling the production of mitochondrial ROS and regulating redox-sensitive cytosolic signaling pathways.

UCP2 participates to the development of several diseases, including many types of cancers in which it is generally over-expressed.[4] In tumors, some studies have well established the key role that UCP2 has in both tumorigenesis and chemoresistance.[5] Indeed, during the first stages of tumorigenesis UCP2 is down-regulated likely to allow ROS increase and genomic instability, while it is triggered and over-expressed in the later stages of cancer development, causing resistance of malignant cells to therapies and tumor aggressiveness mainly through anti-apoptotic mechanisms induced by the attenuation of ROS production.

The antioxidant function of UCP2 can be considered a crossroad between the Warburg effect and autophagy regulation in cancer cells (Figure 1). Xu *et al.* stated that mitochondrial uncoupling mediated by UCPs leads the shift of cancer cell metabolism from mitochondrial oxidative phosphorylation (OXPHOS) to aerobic glycolysis.[6] The authors associate the production of mitochondrial ROS determined by a deficiency of MnSOD enzyme to the stimulation of mitochondrial uncoupling and of aerobic glycolysis. In this way, the Warburg effect can be considered as a metabolic adaptation of cancer cells bearing antioxidant-deficient mitochondria. It's worth noting that data presented by Xu *et al.* support the previous knowledge concerning the UCP2 involvement in the maintenance of the Warburg effect in cancer cells, as demonstrated by the high production of lactate after overexpression of uncoupling proteins.[7] In addition to the antioxidant properties of UCPs by allowing the flux of protons from the intermembrane space to the mitochondrial matrix, the channel formed by these proteins can also promote the mitochondrial efflux towards the cytosol of pyruvate and of Krebs cycle intermediates, thus limiting the mitochondrial oxidation of glucose and supporting the Warburg effect.[8] We have recently found that the antioxidant UCP2 induces the expression of GLUT1 and pyruvate kinase isoform M2 (PKM2) sustaining the glycolytic phenotype of pancreatic adenocarcinoma cells and sensitizing cancer cells to the glycolysis inhibitor 2-deoxy-D-glucose. Furthermore, we observed that UCP2 reduces mitochondrial oxygen consumption and OXPHOS functionality acting as a crucial mediator in cancer cellular bioenergetic shift from OXPHOS to the glycolytic pathway.[9]

Together with the regulation of the cellular metabolism, another highly debated topic in cancer research is the regulation of autophagy, a process determining the lysosomal degradation of proteins and cytoplasmic organelles. This event is largely involved in the control of tumor progression and many efforts are directed in order to explore the regulation of autophagy as a possible therapeutic opportunity. Our recent studies demonstrated that mitochondrial uncoupling mediated by UCP2 inhibits autophagic cell death making pancreatic adenocarcinoma cells particularly resistant to the anticancer drug gemcitabine.[10,11] We have functionally associated this phenomenon with the UCP2-mediated cytosolic stabilization of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH).[11] Indeed, ROS produced by inhibition of UCP2 are able to stimulate the oxidation of this glycolytic enzyme determining its conformational changes, which favor its translocation into the nucleus where it can subsequently activate the expression of GAPDH-regulated genes, as the crucial autophagic gene Atg12. Therefore, the observation that UCPs can prevent the

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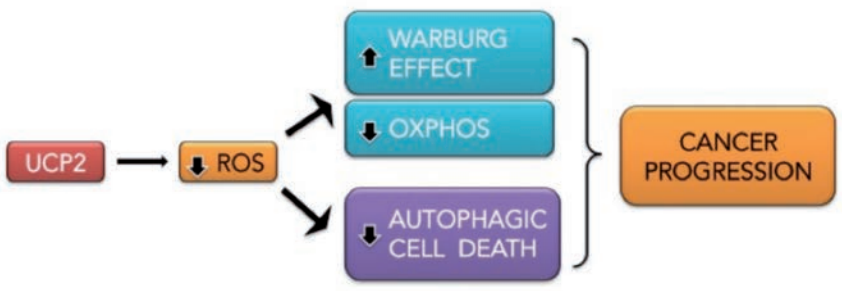

Figure 1. Schematic representation of the involvement of UCP2 in both the metabolic shift from mitochondrial oxidative phosphorylation to aerobic glycolysis and autophagy blockage in order to sustain cancer development.

formation of autophagic vesicles and the activation of autophagic genes concurrently stabilizing the glycolytic enzyme GAPDH in the cytosol, where glycolysis takes place, makes mitochondrial uncoupling a functional crossroad between the Warburg effect and the inhibition of autophagy. Altogether these observations provide a rational explanation for the oncogenic roles of UCP2, whose overexpression in cancer cells can be considered a valuable therapeutic opportunity for the identification of novel target therapies.

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