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Review

Expression and putative role of mitochondrial transport proteins in cancer☆

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ABSTRACT

Cancer cells undergo major changes in energy and biosynthetic metabolism. One of them is the Warburg effect, in which pyruvate is used for fermentation rather for oxidative phosphorylation. Another major one is their increased reliance on glutamine, which helps to replenish the pool of Krebs cycle metabolites used for other purposes, such as amino acid or lipid biosynthesis. Mitochondria are central to these alterations, as the biochemical pathways linking these processes run through these organelles. Two membranes, an outer and inner membrane, surround mitochondria, the latter being impermeable to most organic compounds. Therefore, a large number of transport proteins are needed to link the biochemical pathways of the cytosol and mitochondrial matrix. Since the transport steps are relatively slow, it is expected that many of these transport steps are altered when cells become cancerous. In this review, changes in expression and regulation of these transport proteins are discussed as well as the role of the transported substrates. This article is part of a Special Issue entitled Mitochondria in Cancer, edited by Giuseppe Gasparre, Rodrigue Rossignol and Pierre Sonveaux.

1. Alterations of mitochondrial metabolism

It has been long established that metabolism of cancer cells is different from that of normal cells. In recent years, interest in this aspect of cancer has significantly increased and has lead to the provocative proposal that cancer is a metabolic disease, caused by metabolic defects [1,2]. Whether or not this is true, alterations of cellular metabolism represent a prominent hallmark of all cancers [3]. Most of these changes directly or indirectly involve mitochondria, thus making these organelles central players in defining the phenotypic characteristics of cancer cells. There is no consensus on the causal relationships between alterations occurring in mitochondria and carcinogenesis, but parts of the puzzle are gradually starting to come together.

In 1920s, Otto Warburg made an observation, which became one of the most famous, but at the same time highly misinterpreted and controversial observations in cancer biology. He found that cancer cells, unlike normal cells, maintain high levels of glycolysis even under conditions of sufficient oxygenation, or, in other words, they bypass the Pasteur effect. Warburg named this phenomenon “aerobic fermentation”, but nowadays it is generally known as the “Warburg effect” – a term proposed by Efraim Racker in 1972 [4–6].

Warburg proposed the most straightforward and self-evident explanation: cancer cells need to rely glycolysis, because their respiratory chain does not function properly. Moreover, he stated that the defect in respiratory chain is the only primary cause of cancer, and all other manifestations are secondary to it. Nowadays we know that this “self-evident” explanation is wrong: cancer cells, in most cases, possess fully functional respiratory chains, which are responsible for the majority of ATP production [7,8]. Up-regulated glycolysis, however, serves other metabolic processes, providing building blocks for biosynthetic processes in the cell (Fig. 1). The Warburg effect is clearly the most famous metabolic phenotype in cancer, but definitely not the only one. Another important feature of most cancer cells is their increased reliance on glutamine, which is the most abundant amino acid in blood serum. Increased glutaminolysis helps to replenish the pool of Krebs cycle metabolites used for other purposes, such as amino acid or lipid biosynthesis [9–11]. In addition, mitochondria provide many crucial metabolites for iron sulfur cluster assembly, heme synthesis, sterol and lipid synthesis, and amino acid synthesis, degradation and interconversions – pathways, which can be highly relevant for cancer metabolism [12–17]. Moreover, mitochondria are key players in initiation and execution of apoptosis, and cancer cells need to deal with this aspect of mitochondrial function as well [18–20].

In this review we will discuss metabolite transport in processes altered in cancer, focusing on those aspects of metabolism that involve metabolite transport across the inner membrane of mitochondria and on the roles of the transported molecules in these processes. We do not

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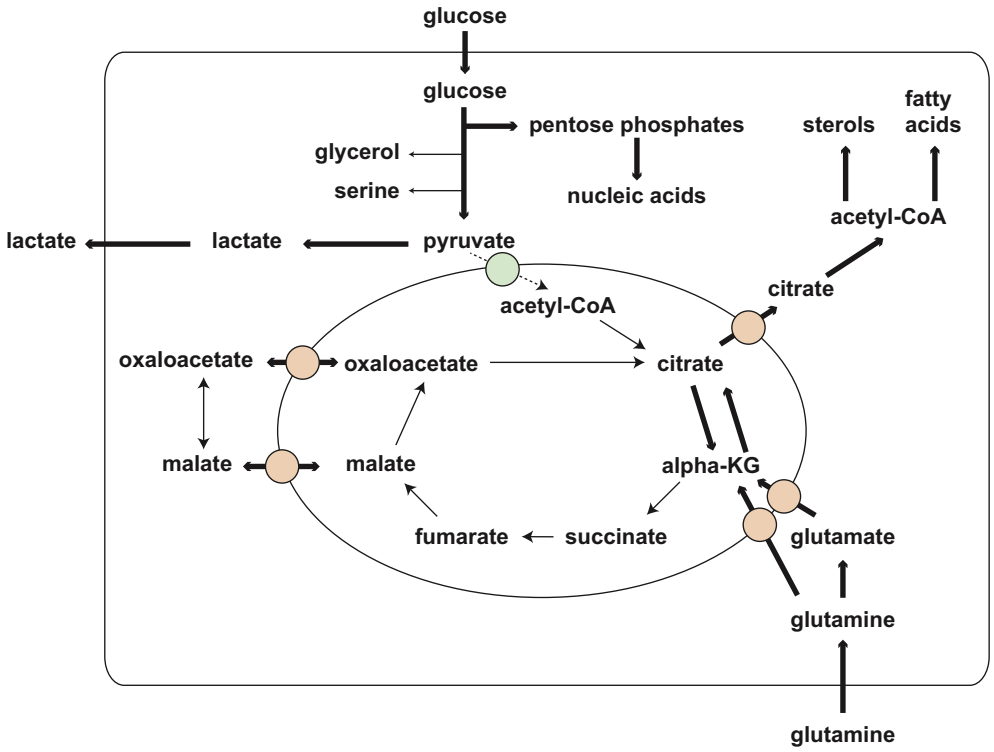

Fig. 1. Main metabolic alterations in cancer cells.Glucose is the main energy source both in normal and cancer cells, but its metabolism in cancer cell is typically shifted towards anaerobic glycolysis, ending with increased lactate production even in the presence of sufficient oxygen (Warburg effect). Increased glycolysis serves to provide substrates for synthesis of some amino acids and for pentose phosphate pathway, which is needed for increased nucleotide synthesis in cancer cells. However, the Krebs cycle remains essential as a source of metabolites for amino acid and lipid production. The pool of metabolites in Krebs cycle is partly replenished by a supply of alpha-ketoglutarate derived from glutamine and glutamate. Increased glutamine catabolism (glutaminolysis) is an important characteristic of most cancer cells.Reactions and pathways that are activated in cancer cells are shown as thick arrows; the ones that are down-regulated are indicated with dashed lines; normal reactions are displayed as thin arrows. Mitochondrial carriers are shown as filled circles, where green indicates that a carrier has anticancer properties, whereas the red ones support cancer growth.

intend to give a comprehensive overview of cancer cell metabolism, which can be found in numerous excellent reviews devoted to this topic [7,8,21–34]. It is important to note that speaking about “typical metabolism of cancer cells” can be dangerous, as cancer cells are extremely heterogeneous. Even within a single tumor there are gradients of gases, metabolites and growth factors. Moreover, tumors are highly heterogeneous in their cellular components: besides malignantly transformed cells, they contain normal cells of the tissue, infiltrating immune cells, blood vessels and other components [35,36]. This heterogeneity is rarely taken into consideration in a typical study, but it could explain some of the controversies and contradictory results in the studies discussed in this review.

2. Mitochondrial carriers

The mitochondrial inner membrane is impermeable for most small hydrophilic molecules, and thus specialized transport proteins are required for them to traverse the membrane. Most of them belong to the solute carrier 25 (SLC25) family, which in humans consists of 53 members (Table 1) [37–40]. One important exception is the mitochondrial pyruvate carrier, which belongs to a different membrane protein family and is most likely a heterodimer of two related subunits [41]. Other mitochondrial carriers are monomeric in structure and function with the exception of the mitochondrial aspartate/glutamate carrier, which is a structural dimer through dimerization of the N-terminal regulatory domain, but the carrier domains are not interacting [37,42].

The members of the SLC25 family transport nucleotides (including ATP and ADP), amino acids, carboxylates, small inorganic ions and cofactors (vitamins). For nearly half of them, however, the substrate specificities have not been determined [38]. The role of mitochondrial carriers goes beyond transport functions. Two mitochondrial carrier subfamilies have a role in calcium regulation of the mitochondrion, the mitochondrial aspartate/glutamate carrier [42–46] and ATP-Mg/Pi carrier [47–49]. Mitochondrial uncoupling protein 1, which also belongs to the SLC25 family, is responsible for non-shivering thermogenesis; other uncoupling proteins may play a role in antioxidant defense, although the latter is controversial [50–52].

Cancer cells have alterations both in sensitivity to apoptosis and in mitochondrial metabolic pathways. It is, therefore, not surprising that many members of the mitochondrial carrier family are involved in progression of cancer. The role of metabolic alterations involving mitochondria in cancer is well established, but there is little known about the role of mitochondrial carriers in this process. In this review, we will summarize published evidence on their role in cancer and on their potential as therapeutic targets.

3. Di and tricarboxylate transporters

The mitochondrial citrate carrier (CIC), encoded by the SLC25A1 gene, is located at the crossroad of multiple metabolic pathways that are important in cancer (Fig. 2). Its physiological role is to exchange cytosolic malate against citrate or other tricarboxylates, such as isocitrate or cis-aconitate, produced in mitochondria. Citrate transported into the cytosol has multiple metabolic roles. It can be cleaved by ATP citrate lyase in the presence of ATP and CoA to yield acetyl-CoA and oxaloacetate. Oxaloacetate is converted further to malate, which can be imported to mitochondria (by citrate or dicarboxylate carriers) or cleaved by malic enzyme to produce NADPH, which in turn is used in a number of biosynthetic processes (Fig. 2). Another product of the ATP citrate lyase, acetyl-CoA, is used for biosynthesis of fatty acids and sterols, which makes citrate carrier especially important for rapidly proliferating cells with an increased demand for membrane lipids.

Table 1
Expression and role of mitochondrial carriers in cancer.

Gene	Protein name	Expression in cancer	Physiological effects in cancer cells
SLC25A1	Mitochondrial citrate carrier (CIC)	Expression is increased in many cancers [57,58] High expression correlates with poor survival in lung cancer [58,61] SLC25A1 is a transcriptional target of oncogenic p53 mutants [58]	Promotes growth of tumor cells [57] Pharmacological inhibition decreases proliferation of cancer cells and has anti-tumor effect *in vivo* [57,60] Chemical inhibitors of SLC25A1 reduce tumor growth and increase sensitivity to cisplatin in p53 mutant cell lines [58,61] Associated with chemotherapy resistance in ovarian cancer cell lines [59] Inhibited by doxorubicine (explains mitochondriotoxic effects of this anticancer substance) [62] Plays a role in TNFα- and IFNγ-triggered inflammation [194]
SLC25A3	Mitochondrial phosphate carrier (PHC)	Can be used as diagnostic marker of chronic myeloid leukemia progression [100]	Overexpression promotes cytochrome c release and apoptosis [97] Depletion has anti-apoptotic effects [97,195]
SLC25A4	Mitochondrial ADP/ATP carrier 1 (AAC1)	Expression is lowered in severe cervical carcinoma [196] Expression is progressively down-regulated in patients with prostate cancer [96]	Regulates opening of mitochondrial permeability transition pore [83] Overexpression promotes apoptosis in cultured cancer cells and suppresses tumor growth *in vivo* [83] Knock-down induces cell death in human glioblastoma cell line [85]
SLC25A5	Mitochondrial ADP/ATP carrier-2 (AAC2)	Expression is increased in proliferating cells, including cancer cells [81,197] One of the lymphatic metastasis-associated genes in human hepatocellular carcinoma [198]	shRNA-based knockdown of SLC25A5 inhibits cancer cell growth in vitro and in vivo [86] Silencing facilitates pro-apoptotic effect of a chemotherapeutic lonidamine [197] Was proposed to be a promising chemotherapeutic target [72,73,86,197]
SLC25A6	Mitochondrial ADP/ATP carrier-3 (AAC3)		Has a pro-apoptotic effect in human cancer cells [79] Overexpression increases cancer cell sensitivity to ionidamine and staurosporine [78]
SLC25A8	Mitochondrial uncoupling protein 2 (UCP2)	High in a variety of cancers [109–111] In breast cancer patients, higher UCP2 expression correlates with poor prognosis [112]	Knockdown or inhibition of UCP2 promotes apoptosis and increases chemotherapeutic sensitivity in many cancer cells [112–114] Overexpression in colon cancer cells increases their resistance to chemotherapeutics [115] Mice with UCP2 knockout had reduced risk of skin tumor formation *in vivo* [116]
SLC25A9	Mitochondrial uncoupling protein 3 (UCP3)	Expression is high in some cancers, such as renal cell carcinoma [120,121]	Overexpression of UCP3 in keratinocytes reduces carcinogenesis in human and mouse skin [122,123] High expression levels are associated with tumor-induced cachexia [124–128]
SLC25A10	Mitochondrial dicarboxylate carrier (DIC)	Up-regulated in many cancers [66]	Knockdown of SLC25A10 reduces malignant phenotype of cancer cells and caused a shift in their metabolism from glycolysis towards oxidative phosphorylation [66] Deletion of SLC25A10 is predicted to reduce cancer cell growth by an *in silico* metabolic analysis [199]
SLC25A12	Aspartate-glutamate carrier 1 (AGC1), aralar		May play an important role in cancer cell metabolism due to its role in regeneration of the cytosolic glutathione [45]
SLC25A13	Aspartate-glutamate carrier 2 (AGC2), citrin		AGC2 deficiency contributes to carcinogenesis in liver in some Asian populations [135–137]
SLC25A14	Brain mitochondrial carrier protein 1 (BMCP-1) or mitochondrial uncoupling protein 5 (UCP5)	High expression in colon cancer [131]	
SLC25A19	Mitochondrial thiamine pyrophosphate carrier	Up-regulated in breast cancer [200]	Might mediate toxic effects of some nucleoside analogs used in anticancer therapies [201]
SLC25A20	Mitochondrial carnitine/acylcarnitine carrier (CAC)	Down-regulated in bladder cancer [180]	
SLC25A21	Mitochondrial Oxodicarboxylate carrier (ODC)		Deletion of chromosome region containing SLC25A21 was reported in lung cancer [69] SNPs in SLC25A21region correlate with breast cancer risk in women receiving menopausal hormone replacement therapy [70]
SLC25A22	Mitochondrial glutamate carrier 1 (GC1)	GC1 is up-regulated in colorectal cancer. High expression correlates with poor prognosis in patients [134]	GC1 knockdown reduces proliferation and migration of cancer cells and their tumor formation capacity in nude mice [134]
SLC25A23	Calcium-binding mitochondrial carrier protein 3 (SCaMC-3) or mitochondrial ATP-Mg/Pi carrier protein 2 (APC2)	Overexpressed in many cancers [92] Progressively down-regulated in patients with prostate cancer [96]	
SLC25A24	Calcium-binding mitochondrial carrier protein 1 (SCaMC-1) or mitochondrial ATP-Mg/Pi carrier protein 1 (APC1)	Overexpressed in many cancers [92]	
SLC25A25	Calcium-binding mitochondrial carrier protein (SCaMC-2) or Mitochondrial ATP-Mg/Pi carrier protein 3 (APC3)	Overexpressed in many cancers [92]	
SLC25A26	S-adenosylmethionine mitochondrial carrier protein (SAMC)	Consistently down-regulated in cervical carcinomas [179]	
SLC25A27	Mitochondrial uncoupling protein 4 (UCP4)	Up-regulated in breast cancer [202]	Promotes cell survival and inhibits apoptosis [130,131]

(continued on next page)

Table 1 *(continued)*

Gene	Protein name	Expression in cancer	Physiological effects in cancer cells
		Correlates with prognostic markers in breast carcinomas [131]	
SLC25A28	Mitoferrin-2 (MFRN2)		SLC25A28 knockdown reduces sensitivity of human glioma cells to arsenic trioxide treatment [163] and squamous carcinoma cells to photodynamic therapy [164]
SLC25A30	Kidney mitochondrial carrier protein 1 or uncoupling protein 6 (UCP6)	High expression associated with tumorigenesis induced by gestational arsenic exposure in mice [181]	
SLC25A31	Mitochondrial ADP/ATP carrier 4 (AAC4)		Has anti-apoptotic effect in cancer cells, protecting them from chemotherapeutics ionidamine and staurosporine [78]
SLC25A33	Solute carrier family 25 member 33 or pyrimidine nucleotide carrier 1 (PNC1)		Promotes cell growth and survival by controlling mitochondrial genome and preventing mitochondrial dysfunction. Overexpression may play a role in oncogenesis [182,183]
SLC25A36	Solute carrier family 25 member 36 or pyrimidine nucleotide carrier 2 (PNC2)	Up-regulated in cervical carcinomas [184]	
SLC25A37	Mitoferrin-1 (MFRN)	Progressively up-regulated in patients with prostate cancer-associated fatigue [96] Up-regulated in refractory anemia with ring sideroblasts (RARS) [165]	
SLC25A38	Solute carrier family 25 member 38	Up-regulated in refractory anemia with ring sideroblasts (RARS) [165] and in acute lymphoblastic leukemia [186]	
SLC25A43	Solute carrier family 25 member 43	Frequently deleted or down-regulated in HER2-positive breast cancer and other cancers [169,170]	Influences cell cycle progression and cell proliferation rate [169,172] Knockdown of SLC25A43 reduces sensitivity to chemotherapeutics in breast cancer cell lines [171]
SLC25A47	Solute carrier family 25 member 47 or hepatocellular carcinoma down-regulated mitochondrial carrier protein	Expression is lowered in hepatocellular carcinoma [173]	
SLC25A49	Mitochondrial carrier homolog 1 (MTCH1)		Regulates opening of the mitochondrial permeability transition pore [97]
SLC25A50	Mitochondrial carrier homolog 2 (MTCH2)	Expression is lowered in some cancers [176]	Regulates opening of the mitochondrial permeability transition pore and interacts with truncated BID to promote apoptosis [97,175] siRNA-mediated knockdown increases invasive properties of gastric cancer cells [178] Induction of its expression reduces tumorigenicity of cancer cells and leads to their growth arrest [203]
SLC25A52	Mitochondrial carrier triple repeat protein 2 (MCART2)	SNPs in SLC25A52 region correlate with breast cancer risk in women receiving menopausal hormone replacement therapy [70]	

Citrate-malate exchange is also the main component of citrate-malate and isocitrate-oxoglutarate shuttles. Besides that, cytosolic citrate regulates rate of glycolysis by affecting activity of phosphofructokinase [53–55] and plays an important role in cytokine-induced inflammatory pathways [56].

Considering this, it is not surprising that expression of citrate carrier is increased in most cancers [57–59]. Overexpression of citrate carrier in cancer cell lines was found to increase their tumorigenic potential, whereas its pharmacological inhibition by its substrate analogue 1,2,3-benzenetricarboxylate [60] reduced their proliferation rate and tumorigenicity *in vitro* and *in vivo* after injection of cancer in nude mice. Treatment with benzenetricarboxylate reduced tumor growth in mice without any significant toxicity. The same effect was achieved using transfection of cancer cells with dominant-negative form of CIC [57]. Expression of SLC25A1 was associated with chemotherapy resistance in ovarian cancers [59], whereas its inhibition enhanced tumor sensitivity to platinum-based chemotherapeutics [58].

Another evidence for the role of citrate carrier in tumors is its up-regulation in cells harboring oncogenic mutations in p53. Transcription of SLC25A1 is increased as a direct consequence of these p53 mutations and its inhibition reduces their oncogenic activity [58]. It is tempting to speculate that overexpression of SLC25A1 can explain some of the tumorigenic effects of mutated p53 and that its pharmacological inhibition can help to overcome oncogenic potential of mutated p53 [61]. Citrate carrier has yet another link to cancer: it is inhibited by a chemotherapeutic doxorubicin, a medication used in cancer therapy [62]. This, on one hand, can contribute to its mode of action, but may also be responsible for some of its adverse effects [63].

The exact mechanism by which citrate carrier promotes tumorigenicity remains unclear. The initial assumption of its role in lipid production [64] was questioned by Catalina-Rodrigues et al. [57]. Although the ability of cells to convert glucose into fatty acids was significantly reduced after inhibition of citrate carrier, overall lipid levels were not significantly affected. Instead, the authors linked reduced tumorigenic phenotype of the cells to impairment of their mitochondrial physiology [57,61].

Malate is another important metabolite, participating in a number of essential processes. Its conversion to pyruvate catalyzed by $NADP^+$-dependent malate dehydrogenase (also known as malic enzyme) is one of the sources of reduced NADPH, an essential cofactor of biosynthetic processes. Transport of malate is also part of the aspartate-malate shuttle, involved in the import of reducing equivalents produced during glycolysis into mitochondria. Cytosolic NADH and NADPH are not able to cross the inner mitochondrial membrane because there is no dedicated transporter. Instead, they are used by cytosolic malate dehydrogenase to reduce cytosolic oxaloacetate to malate, which is imported into mitochondria and converted to oxaloacetate there, reducing NAD^+ and leading to a net import of reducing equivalents. This pathway might be especially important for energy metabolism of cancer cells, due to up-regulated glycolysis [45,65].

Malate is transported into and out of mitochondria by at least two more carriers, besides CIC: the dicarboxylate carrier DIC (SLC25A10) and oxoglutarate carrier OGC (SLC25A11) (Table 1, Fig. 2). The mitochondrial dicarboxylate carrier is up-regulated in many cancers.

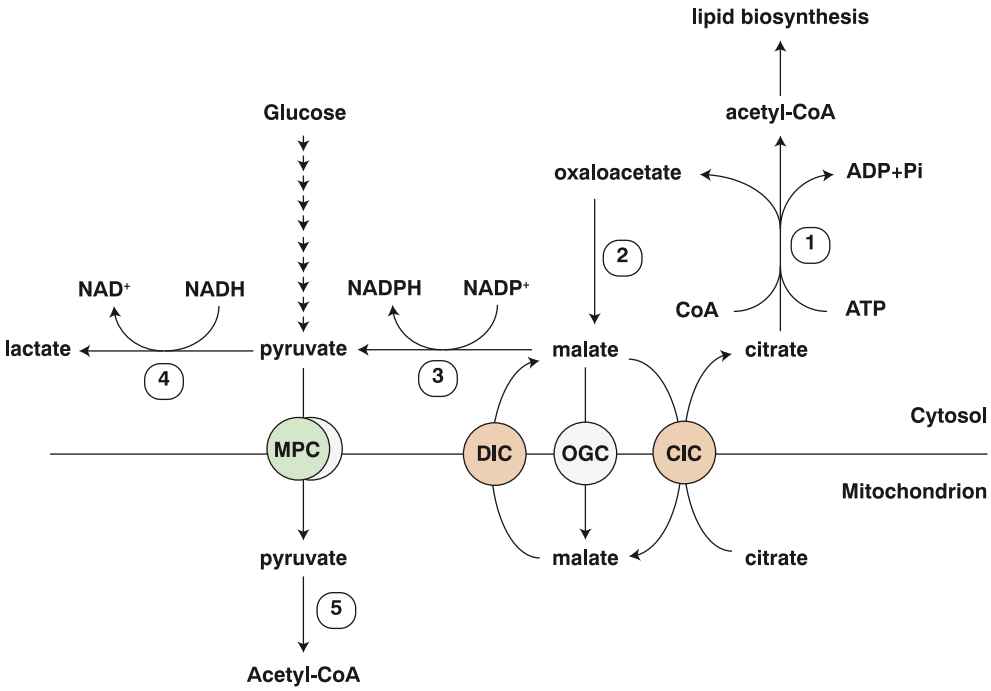

Fig. 2. The role of carboxylate transport in cellular metabolism.Acetyl-CoA is required for lipid biosynthesis in cytosol. Acetyl-CoA derived from pyruvate in mitochondria cannot cross the inner mitochondria membrane. Instead, citrate is exported by citrate carrier in exchange to cytosolic malate and serves as a source of cytosolic acetyl-CoA. Oxaloacetate produced in this reaction is converted to malate, which can enter the mitochondrion with the aid of citrate, oxoglutarate or dicarboxylate carrier. It can also serve as a source of reduced NADPH, an essential cofactor for various biosynthetic processes. Pyruvate formed in this reaction enters mitochondria using mitochondrial pyruvate carrier and can be converted to produce mitochondrial acetyl-CoA. Typically, cancer cells have reduced activity of mitochondrial pyruvate carrier and increased expression of the dicarboxylate and citrate carriers.MPC, mitochondrial pyruvate carrier; DIC, dicarboxylate carrier; OGC, oxoglutarate carrier; CIC, citrate carrier. Carriers promoting cancer cell growth are shown as red circles; carriers with anti-tumorigenic properties are shown as green circles; carriers, whose role in cancer is unknown, are displayed as white circles. The following enzymes are indicated with numbers: 1, ATP citrate lyase; 2, malate dehydrogenase; 3, malic enzyme (malate dehydrogenase (oxaloacetate-decarboxylating) ($NADP^+$)); 4, lactate dehydrogenase; 5, pyruvate dehydrogenase. Not all reaction products and substrates are shown for the purpose of clarity.

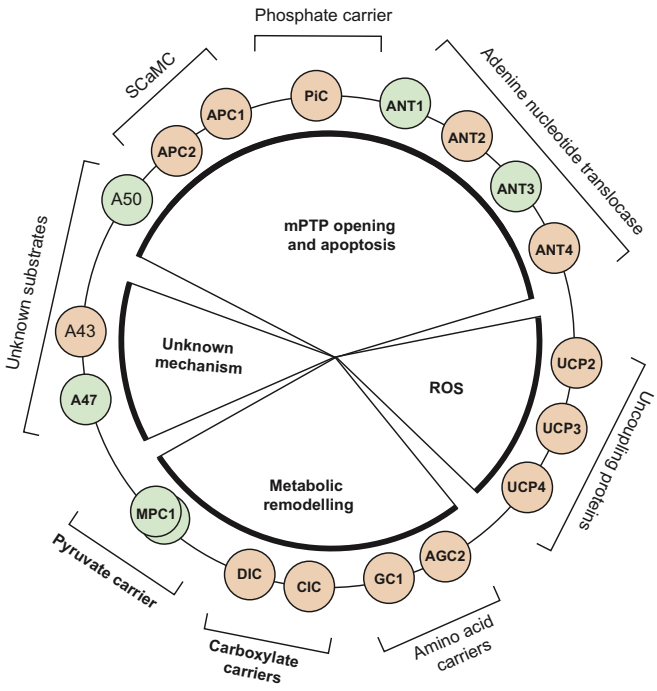

Fig. 3. Multiple roles of mitochondrial carriers in cancer.Selected carriers are classified according to their role in cancer and the underlying molecular mechanisms. Mitochondrial carriers supporting tumor growth and/or typically overexpressed in cancers are shown as red circles; the ones that are typically suppressed in cancer and have antitumorigenic properties are in green. SLC25 family members SLC25A43, SLC25A47 and SLC25A50 are labelled as A43, A47 and A50, respectively.

Its knockdown in cancer cells caused metabolic shift towards less glycolytic phenotype, reduced their malignancy and increased sensitivity to anticancer agent cisplatin [66]. There were no studies directly linking oxoglutarate carrier and cancer, but it was shown to be involved in regulation of apoptosis, potentially by interacting with Bcl-2 [67,68].

Mitochondrial 2-oxodicarboxylate carrier (ODC), encoded by the SLC25A21 gene, transports several oxodicarboxylates, such as 2-oxoadipate, 2-oxoglutarate, 2-oxopimelate and others. Chromosomal region containing SLC25A21 (14q13.3) was found to be frequently deleted in lung cancer [69] and two single nucleotide polymorphisms in the SLC25A21 gene were associated with an increased risk of breast cancer in women receiving hormone replacement therapy [70].

4. Mitochondrial ADP/ATP carriers

The mitochondrial ADP/ATP carrier (AAC), also called adenine nucleotide translocase, exist in four isoforms (AAC1-AAC4) encoded by SLC25A4, SLC25A5, SLC25A6 and SLC25A31, respectively (Table 1) [71,72]. Its main role is to import ADP from the cytosol and to export ATP produced in the mitochondrial matrix by ATP synthase. However, under certain conditions, when mitochondrial ATP production is impaired, AAC2 can deliver ATP produced by glycolysis into mitochondria for maintenance of membrane potential and other essential functions [73].

Besides that, they are involved in regulation of cell death and were believed to be a component of the mitochondrial permeability transition pore, although this view has been questioned by several studies [74–77]. Although there is no agreement on the molecular mechanism by which AAC isoforms regulate cell death, there is no doubt that their overexpression or knockdown modulates sensitivity of cells to apoptotic stimuli. Despite a high degree of homology (about 80% pairwise identity), different isoforms have opposite effects on cell survival.

According to current view, AAC1 and AAC3 are pro-apoptotic, whereas AAC2 and AAC4 are anti-apoptotic (Fig. 3) [73,78–80].

AAC1 (encoded by SLC25A4) is expressed predominantly in brain, heart and skeletal muscle [81] and is the main pro-apoptotic AAC isoform. Accordingly, expression of AAC1 was found to be low in many cancers [82,83] and its overexpression induced apoptosis in several breast cancer cell lines, most probably, in an NF-kB-dependent manner [83,84]. Overexpression of AAC1 also inhibited tumorigenicity of cancer cells *in vivo*, significantly reducing tumor size in nude mice [83]. Unexpectedly, lowering of AAC1 expression in human glioblastoma cells caused a similar effect, which was not dependent on its ATP/ADP transport function [85].

On the contrary, overexpression of AAC2 does not induce apoptosis [80], whereas its down-regulation does [86]. AAC2 is up-regulated in most cancers and can serve as an indicator of carcinogenesis [73,82]. Knock-down of the SLC25A5 gene encoding AAC2 inhibited growth of breast cancer cells both *in vitro* and *in vivo* [86]. The mechanisms of this effect are not clear. AAC2 is highly expressed in normal undifferentiated and proliferating cells and may play a role in importing glycolytically produced ATP from cytosol into mitochondria [73,81,82]. Although cancer cells generally maintain high levels of oxidative phosphorylation in mitochondria (as discussed above), this function of AAC2 may become critical for cancer cell survival under hypoxic conditions in insufficiently oxygenated layers of solid tumors. Another hypothesis suggests that dysregulation of AAC isoforms could contribute to carcinogenesis by affecting nucleotide pools in mitochondria and thus leading to instability of the mitochondrial genome [73].

AAC3 is expressed ubiquitously and in many regards resembles AAC1. Overexpression of AAC3, similarly to AAC1, induces apoptosis in cultured cells and sensitizes cancer cells to chemotherapeutics cisplatin and melphalan, as well as antiproliferative agent all-trans retinoic acid [78,79,87,88]. AAC3 is selectively required for initiation of tumor necrosis factor alpha (TNFa)-induced apoptosis and its disruption can prevent cytochrome c release and membrane potential dissipation triggered by TNFa treatment [89].

AAC4 is predominantly expressed in testicular germ cells, liver and brain [71,90]. Its role in cancer has not been studied in much detail, but it was shown to cause anti-apoptotic effects in cultured cancer cells, similarly to AAC2. Overexpression of AAC2 also reduced cancer cell sensitivity to chemotherapeutics ionidamine and staurosporine [78].

To conclude, the four AAC isoforms, despite high similarity, have opposing effects on apoptosis and cell survival (Fig. 3). Cancer cells tend to up-regulate anti-apoptotic isoform AAC2, while suppressing pro-apoptotic AAC1. However, a significant controversy remains about the molecular mechanisms mediating AAC effects on cell death and tumorigenicity.

5. ATP-Mg/phosphate carriers

Mitochondrial ATP-Mg/phosphate carriers (APC1-APC4), also known as calcium-binding mitochondrial carriers (SCaMC1-4), are encoded by the SLC25A24, SLC25A23, SLC25A25 and SLC25A41 genes, respectively (Table 1, Fig. 3). They are activated by an increase in cytosolic calcium and transport Mg-ATP or Mg-ADP in both directions across the inner mitochondrial membrane in exchange for inorganic phosphate (Pi). Thus, unlike AAC, they mediate electroneutral net import or export of adenine nucleotides [49].

There are at least three mechanisms that might link this subfamily of carriers to carcinogenesis. It has been long known that the total mitochondrial adenine nucleotide pool regulates opening of the mitochondrial permeability transition pore (mPTP) [91], and ATP-Mg/phosphate carriers might thus contribute to the regulation of cell survival. In addition, phosphate release from mitochondria could contribute to buffering calcium in cytosol and thus as well prevent opening of the permeability transition pore [92]. Finally, it has been initially proposed that changes in adenine nucleotide pools in mitochondria by the transport activity of AAC might affect replication and maintenance of the mitochondrial genome [73], but this is likely to be true for ATP-Mg/Pi carriers as well.

APC1 (SCaMC-1/SLC25A24) was found to be up-regulated in many cancer cell lines, tumors and rapidly proliferating cells [92,93]. The carrier was not essential for cell proliferation, but demonstrated a strong cytoprotective effect under oxidative stress and calcium overload conditions. Knockdown of APC1 increased cancer cell sensitivity to oxidative stress-induced apoptosis, while its overexpression protected them from death. The cytoprotective effect of the carrier was attributed both to an increase in mitochondrial calcium buffering capacity and to adenine nucleotide transport function of the protein. Selective inhibition of APC1 was thus suggested to be a promising anticancer strategy [92].

There is not much data on the role of other ATP-Mg/phosphate carrier isoforms in cancer, although several gene expression studies suggest that they might play similar important roles. For example, high expression of APC2 (SCaMC-3/SLC25A23) was associated with poor 5-year survival and included in a set of prognostic markers in patients with diffuse large B cell lymphoma [94]. Its mRNA levels were also significantly up-regulated in tissue samples of patients with colorectal cancer [95] and associated with cancer-related fatigue in patients with prostate cancer [96].

6. Phosphate carrier

Mitochondrial phosphate carrier (PiC), encoded by the SLC25A3 gene (Fig. 3), transports inorganic phosphate from cytosol into mitochondrial matrix together with a proton. The phosphate carrier regulates cytochrome c release from mitochondria and its knockdown has anti-apoptotic effect, probably, by direct interaction with the components of the mitochondrial permeability transition pore [97]. Knockout of the SLC25A3 gene in mouse heart did not block mPTP opening completely, but caused its partial desensitization to calcium-induced apoptosis [98]. These results suggest that phosphate carrier, similarly to AAC and ATP-Mg/phosphate carriers, could be involved in mPTP opening and thus in tumorigenesis. There are no data directly supporting this hypothesis, but activity of the phosphate carrier was found to be increased in rat hepatoma [99] and SLC25A3, along with several other genes, was found to be differentially expressed in early and late chronic phase of chronic myeloid leukemia (Table 1) [100].

7. Uncoupling proteins

The term “uncoupling proteins” refers to a group of six related proteins (UCP1-UCP6, encoded by SLC25A7, SLC25A8, SLC25A9, SLC25A27, SLC25A14 and SLC25A30, respectively), which dissipate mitochondrial membrane potential and thus uncouple oxidation of substrates from ADP phosphorylation (Table 1). The five uncoupling proteins may have different physiological functions, and uncoupling has not been shown conclusively for most of them. Moreover, the molecular mechanism of uncoupling is not fully understood and the substrates of the uncoupling proteins remain unknown. Deregulation of uncoupling proteins' expression has been associated with a number of pathological states [8,51,52,101–103].

The best studied one, UCP1, is expressed mostly in brown adipose tissue and thymus and responsible for non-shivering thermogenesis. To date, there are no studies directly linking UCP1 to cancer (except of its expression in brown fat tumors, hibernomas) [104].

UCP2 is a ubiquitously expressed protein. Its function is not fully defined, but it was shown to export several C4 metabolites (such as malate, oxaloacetate, aspartate and malonate) out of mitochondria in an *in vitro* transport assay [105] and to play a role in antioxidant defense, insulin production and immunity [106–108]. Many studies found strong evidence on its role in supporting tumor growth. Significant up-regulation of UCP2 expression was observed in many

cancers, including colon cancer [109], head, neck, skin, pancreas and prostate cancers [110], breast cancer and most other tumors [111]. In breast cancer patients, higher UCP2 expression correlated with poor prognosis [112]. Knockdown or inhibition of UCP2 promoted apoptosis and increased sensitivity to anticancer drugs in hepatocellular carcinoma, colon and breast cancer cells [112–114], while its overexpression in colon cancer cells increased their resistance to chemotherapeutics *in vitro* and in mouse xenografts [115]. UCP2 knockout in mice significantly reduced formation of benign and malignant skin tumors *in vivo* [116]. Accordingly, overexpression of UCP2 in breast cancer cells increased their tumorigenic phenotype, both *in vitro* and *in vivo* in a mouse xenograft model [111].

However, the view of the UCP2 as a typical tumor-promoting carrier has been questioned by several other studies. In some, although not all, lung cancer cells expression of UCP2 was lower than in normal cells [110,117] and its low expression was associated with chemotherapy resistance in lung cancer patients [117]. Overexpression of UCP2 was reported to repress malignant properties of mouse and human cancer cell lines *in vitro* and when injected in nude mice [118]. UCP2 knockout mice were more prone to development of colon tumors than their wild type littermates [119]. These seemingly controversial findings can be explained, at least in part, by the dual role that UCP2 plays in tumor origin and progression. Mild mitochondrial uncoupling has been proposed to lower ROS formation by respiratory chain [50]. At the initial stages of tumorigenesis, down-regulation of UCP2 can increase ROS formation, and promote tumor growth, whereas overexpression of UCP2 at later stages of tumor progression protects them from apoptosis and reduces their sensitivity to damaging agents [51,103]. Given the high degree of controversy surrounding the function of UCP2, its role in cancer has not been fully defined.

UCP3 is normally expressed in skeletal muscle and heart. It may play a similar role as UCP2 in several cancers, although the role of UCP2 is more established and well studied. UCP3 expression is high in some cancers, such as renal cell carcinoma [120,121]. Interestingly, overexpression of UCP3 suppressed carcinogenesis in human and mouse keratinocytes [122,123]. Many studies point out that high UCP3 expression is associated with muscle wasting in tumor-induced cachexia [124–128].

UCP4 is a brain-specific protein and its role in cancer is controversial. Neuronal differentiation studies using mouse stem cells have demonstrated that UCP4 is mostly expressed in differentiated non-proliferating cells, and that its expression in most cancer cell lines is low [129]. On the other hand, overexpression of UCP4 was demonstrated to stimulate cell proliferation and inhibit apoptosis, most likely, in an extracellular signal-regulated kinase (ERK)-dependent manner [130]. Moreover, positivity for UCP4 correlated with prognostic markers in breast carcinomas [131].

8. Amino acid carriers

There is surprisingly little known about mitochondrial carriers transporting amino acids. Only carriers for arginine, lysine, aspartate and glutamate have been identified (Table 1), whereas carriers required for transport of essential amino acids, as well as cysteine and glutamine are missing [37,132]. This is especially unfortunate, because amino acids are among the most cancer-relevant substrates.

There are at least 4 carriers that transport glutamate into mitochondria: glutamate carriers 1 and 2 (SLC25A22 and SLC25A18, respectively) and aspartate/glutamate carriers 1 and 2 (SLC25A12 and SLC25A13) [43,45,46,133]. Expression of glutamate carrier 1 (SLC25A22) is increased in colorectal cancer and correlates with poor prognosis in patients. Its knockdown reduces cancer cell proliferation and migration *in vitro*, as well as tumor formation in nude mice [134]. Deficiency of aspartate-glutamate carrier-2, citrullinemia, caused by mutations in the SLC25A13 gene, significantly increases risk of hepatic cancer in patients, at least in some Asian populations [135–137].

Bioinformatic analysis shows that the aspartate-glutamate carrier 1 (AGC1) gene (SLC25A12) is frequently mutated, amplified or deleted in many cancers, and its mRNA levels are often elevated. Along with malate transporters, AGC participates in malate-aspartate shuttle, which transfers reducing equivalents from cytosol to mitochondria, and thus might play a special role in redox homeostasis of cancer cells. Besides that, it may play a role in antioxidant defence by supplying substrates for cytosolic production of NADPH used for regeneration of glutathione [45]. Although there is no direct experimental evidence that targeting AGC can be beneficial for cancer treatment, its role in cellular metabolism and indirect bioinformatic data suggest that it may be another promising oncotarget.

Glutamine is the most abundant amino acid in blood serum, and a significant increase of glutamine catabolism (glutaminolysis) is a classical hallmark of many cancers [9,10,138–140]. Mitochondrial glutamine carrier has not been identified, although its activity has been extensively studied by transport assays for almost half a century [141–143]. There is no doubt that there is a specialised carrier for this amino acid, at least in some cell types, but glutamine can be also deaminated to glutamate in the cytosol and imported into mitochondria in this form [141,144]. Glutaminolysis fuels the Krebs cycle and acts to replenish metabolites used for other metabolic purposes. Besides its obvious metabolic role, increased glutaminolysis was proposed to play a role in buffering pH changes caused by excessive glycolytic lactate production [145]. According to this hypothesis, ammonium produced by glutamine conversion to glutamate prevents acidification of extracellular surroundings and thus promotes survival of cancer cells. Regardless of the mechanism, the role of glutamine in cancer is undoubted and glutamine carrier would be one of the most promising anticancer targets, once discovered.

9. Mitochondrial pyruvate carrier

A recently identified transporter for cytosolic pyruvate does not belong to the SCL25 family, but its function is especially relevant for cancer and it attracted significant attention in recent years [146–150]. The fate of cytosolic pyruvate is at the decision point between oxidative and anaerobic metabolism and is dramatically different between normal and cancer cells. In normal cells, under aerobic conditions pyruvate is transported into mitochondria, where it is oxidatively decarboxylated by the pyruvate dehydrogenase complex to produce acetyl-CoA, which then enters Krebs cycle. Anaerobic NADH-dependent reduction of pyruvate catalyzed by cytosolic lactate dehydrogenase produces lactate, which is normally exported from the cell. Otto Warburg's observation of increased lactate production in cancer cells under aerobic conditions was one of the most important observations in the field and established the entire paradigm of mitochondrial dysfunction in cancer. There are several mechanisms that can cause this phenotype in cancer cells, and deregulation of mitochondrial pyruvate carrier is one of them.

The identity of the mitochondrial pyruvate carrier (MPC) was discovered in 2012 by Herzig et al. [41] and Bricker et al. [151]. In mammals, it consists of two homologous subunits, MPC1 and MPC2, which do not belong to the SLC25 family and most likely function together as a heterodimer.

The first data on MPC1 expression in cancer come from Schell et al. [152]. For the first time, they noted down-regulation of MPC1 in many cancers and its correlation with poor prognosis in patients. Interestingly, re-expression of MPC1 and MPC2 in colon cancer cells reduced signs of tumorigenicity in cells grown under low-attachment conditions, without affecting growth in adherent cell culture [152]. Biochemically, pharmacological inhibition of MPC shifted metabolism from oxidative phosphorylation towards glycolysis, promoting the Warburg effect in cancer cells. Unexpectedly, this treatment also increased resistance of prostate cancer cells to chemotherapeutic cisplatin [153]. Mitochondrial pyruvate carrier was found to be one of the main targets of

lonidamine, a potent anticancer drug, whose mode of action was previously unknown [154,155].

10. Mitochondrial iron transporters

Iron is one of the central elements required for cancer cell growth and proliferation [156,157]. Mitochondria play a key role in cellular iron metabolism, being responsible for heme and iron-sulfur cluster biosynthesis, and transport of iron into mitochondria is tightly regulated. Two members of the SLC25 family, mitoferrins 1 (SLC25A37) and 2 (SLC25A28), are required for iron import into mitochondria [158–160]. Although the question is whether the transported species is free iron [37], changes in expression of these genes led to severe alterations of iron homeostasis [161,162].

In theory, mitoferrins may play a central role in iron homeostasis in cancer cells and can be very important oncotargets. However, to date, there are only few studies linking mitoferrins 1 and 2 directly to cancer.

Expression of mitoferrin-2 influences effects of several anticancer treatment approaches. Silencing of the mitoferrin-2 gene SLC25A28 reduced sensitivity of human glioma cells to arsenic trioxide treatment [163] and squamous carcinoma cells to photodynamic therapy [164]. Mitoferrin-1 (SLC25A37) is overexpressed in refractory anemia with ring sideroblasts (RARS) [165–167], and progressively associated with fatigue in prostate cancer patients receiving radiotherapy [96,168]. We believe that question of iron transport into mitochondria requires more attention.

11. Carriers with unknown substrate specificities

The SLC25 family in humans consists of 53 members, but the substrate specificity of many carriers has not been assigned and in some cases is disputed (Table 1) [38]. Some carriers, whose substrate specificities are unknown, have been nevertheless associated with different pathological conditions, including cancer (Fig. 3) [63].

Several studies demonstrated association of SLC25A43 with several tumor types. Chromosomal region containing SLC25A43 is frequently deleted in some breast tumors, cervical and lung cancers [169] or the gene is transcriptionally repressed [170]. Knockdown of SLC25A43 reduces sensitivity to chemotherapeutics in breast cancer cell lines [171]. Interestingly, this mitochondrial protein exerts its effects by influencing cell cycle progression and cell proliferation rate [169,172].

SLC25A47, a hepatocellular carcinoma-down-regulated protein, has a self-descriptive name, suggesting its involvement at least in some forms of hepatic cancer [173]. Its substrate and mechanism of action in cancer are unknown, but it was proposed to be a liver-specific uncoupling protein, and it might, similarly to other uncoupling proteins, regulate ROS production [173,174].

Mitochondrial carrier homologs 1 and 2 (MTCH1 and MTCH2), encoded by SLC25A49 and SLC25A50, were shown to regulate apoptosis by modulating activity of the mitochondrial permeability transition pore [97]. MTCH2 directly interacts with mitochondrial pro-apoptotic protein truncated BID (tBID) and recruits it to mitochondria to activate apoptosis [175]. In agreement with its pro-apoptotic role, some cancer cells tend to down-regulate MTCH2 by overexpressing its regulatory miRNA [176]. Single nucleotide polymorphisms (SNPs) in the SLC25A50 gene are associated with high risk of endometrial cancer [177]. Bioinformatic analysis revealed that MTCH2 is tightly transcriptionally regulated in multiple solid cancers. Its knockdown in gastric cancer cells increased their invasive properties, without significantly affecting proliferation rate [178].

12. Other carriers

There is increasing evidence that other carriers can be associated with cancer as well. For example, carnitine-acylcarnitine carrier/SLC25A20 is downregulated in bladder cancer, while expression of S-adenosylmethionine carrier/SLC25A26 is low in cervical carcinomas [179,180]. High expression of uncoupling protein 6/SLC25A30 is associated with carcinogenesis induced by arsenic exposure in mice [181]. Pyrimidine nucleotide carrier PNC1/SLC25A33 deserves a special attention, as it was shown to promote cancer cell proliferation, invasiveness and increase their size [182,183]. Both pyrimidine nucleotide carriers 1 and 2 (SLC25A33 and SLC25A36) are upregulated in some cancers [182,184]. SLC25A38 (a potential glycine transporter required for heme biosynthesis [185]) is upregulated in acute lymphoblastic leukemia [186]. Information about some other carriers with potential links to cancer is summarised in Table 1.

13. Concluding remarks

Despite almost a century of interest in the role of mitochondria in cancer, there are still no effective anticancer agents that target mitochondria. Their development and the continued investigation of the fundamental mechanisms of carcinogenesis are hindered by a few technical and conceptual difficulties, some of which are particularly relevant for studying the role of mitochondrial carriers in cancer.

First, most of the bioinformatics data on carrier expression in cancer cells or tissues relies on high-throughput transcriptomics data (in most cases, on microarrays). These data shed light on the importance of transcriptional regulation in cancer, but should be analyzed with care, as steady-state mRNA levels of mitochondrial carriers do not always correlate with protein levels. This has been reported, for example, for uncoupling proteins and it is possible that other carriers can be regulated predominantly on a translational level as well [187,188].

Another source of potentially misleading data has to do with the nature of the experimental model. Many studies, for obvious reasons, were performed using cultured cells. Whilst this approach provides valuable information about genetics and molecular biology of cancer, the physiological and biochemical properties of cultured cells can be dramatically different from cancer tissues *in situ*. First of all, tumors (especially the solid ones) are never uniform. Depending on their size, several layers of cells with dramatically different properties can be found within the same tumor [35]. Accordingly, metabolism of cells in different layers of a solid tumor can be dramatically different, due to differences in oxygen and nutrient supply, proliferation state etc. A well-known problem of cultured cells, which is generally largely ignored, is their oxygenation. Within the body, cells are exposed to 1–11% of oxygen, which is dramatically different from 21% oxygen in cell culture and can have serious physiological implications [189]. Within tumors, these values can differ from the “normal conditions” in cell culture incubator even more dramatically. It is generally believed to be acceptable for most of the cell biology studies, but should be considered remarkably carefully in studies looking for minor differences in biochemical pathways that differ cancer cells from normal ones and make them targetable by metabolism-affecting drugs.

Following the same line of thought, what would we call a “cancer cell” in an *in vitro* experiment? Out of the classical 6 cancer “hallmarks” proposed by Hanahan and Weinberg in 2000 [190], at least 5 are shared by benign tumors [191], and are hardly applicable to cell culture conditions. In most cases, “cancer cells” are very different from “cells derived from cancer tissues and cultured under non-physiological conditions for limitless number of generations afterwards”. At the same time, the most practically-relevant targetable metabolic and biochemical features of cancer cells are shared with normal fast-proliferating cells [29]. This does not mean that the results of cell culture-based studies are irrelevant, but special attention is needed to distinguish between cancer-specific and conditions-induced metabolic changes.

There is no doubt that expression of some mitochondrial carriers is altered in a variety of cancers. However, the reason for these changes is not obvious. Theoretically, there are three possibilities. First, changes in expression of mitochondrial carriers can represent an adaptation of cancer cells to their metabolic challenges. Second, these changes can

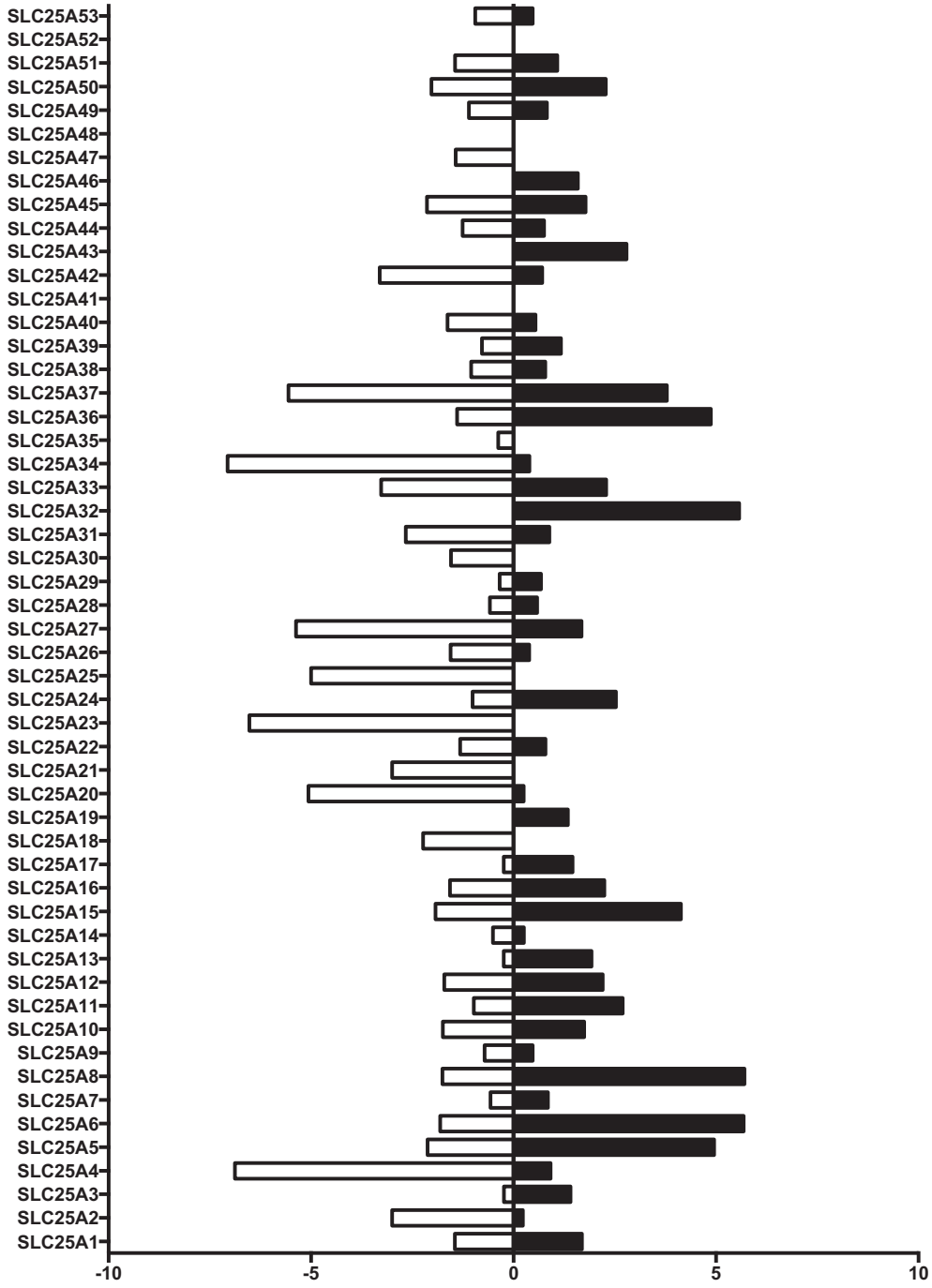

Fig. 4. Number of datasets in the Oncomine database that demonstrate significant up- or down-regulation of expression in cancer.Percentage of all studies in Oncomine database demonstrating change in expression of carriers in cancer is shown. Number of studies in which expression in cancer is higher than in the normal tissue is plotted to the right of the Y-axis (black bars). Number of studies in which the carrier is down-regulated in cancer is shown to the left of the Y-axis (white bars).

contribute to *de novo* formation of tumors. Finally, mitochondrial carriers can be innocent bystanders and indirect targets of unrelated regulatory circuits and pathways.

In its current state, the field seems to support strongly the first option. According to the most straightforward explanation, cancer cells need to adapt their substrate fluxes to challenges caused by fast proliferation and low oxygenation of cells within tumors. Besides that, they need to silence pro-apoptotic and up-regulate anti-apoptotic factors. There are many examples of carriers that fit perfectly to this model. Citrate carrier is up-regulated in many cancers, because it transports physiologically important substrates [57,58]. AAC1 and AAC3 are down-regulated, because they are pro-apoptotic molecules [79,83]. Expression of uncoupling protein-2 is high at advanced stages of cancer, because it may protect cancer cells from ROS formation [51].

However, there is increasing evidence for the alternative possibility, namely, that increased levels of certain metabolites can contribute to epigenetic and metabolic reprogramming of cells and formation of their malignant phenotype. Increased formation of reactive oxygen species and destabilisation of mitochondrial genome can be also involved in pathogenesis and origination of tumors. This view is supported by multiple associations between mutations in certain carriers with the frequency of cancer, even though the underlying molecular mechanisms are often unknown [69,70,135,136]. Another important line of evidence is coming from transgenic mouse models. Knockout or over-

expression of certain carriers reduces or increases frequency of tumor formation *in vivo* (see Table 1), suggesting that carriers, even if not directly being the cause of cancer, can significantly contribute to its pathogenesis [116,119].

The third option is rarely taken into consideration, but relatively high inconsistency of SLC25 gene expression in cancer suggests that at least in some cases their up- or down-regulation may not have much physiological meaning. The Oncomine database is a popular resource combining transcriptomics data from different cancer studies [192]. We analysed the database searching for datasets, which demonstrate significant up- or down-regulation of each carrier. Not surprisingly, for most of the carriers there were studies demonstrating both increase or decrease of expression (at least, on a transcriptional level) in different cancers (Fig. 4). It cannot be excluded that in some cases seemingly physiologically meaningful carrier up- or down-regulation represents a selection of "convenient" results, which are easy to explain by a simple mechanistic model. Overall, it must be noted that causative relationships between expression of mitochondrial carriers and manifestations of cancer are missing in many cases.

Similarly, physiological consequences of carrier inactivation can vary dramatically depending on the type of cancer and other conditions. Achilles' project is a comprehensive study, in which consequences of RNAi-mediated knockdown or CRISPR-Cas9 knockout were analysed in more than 200 cancer cell lines [193]. For nearly all of the carriers, consequences of their inactivation in different cell lines varied dramatically, often having opposite results on cell survival in different cancers.

Regardless of the exact mechanism, promising results obtained with pharmacological or genetic inhibition of certain carriers should stimulate further research in this direction and validation of other oncotargets. Currently, carriers with the highest chances to become valuable therapeutic targets are citrate carrier (CIC), ADP/ATP carrier (AAC1) and pyruvate carrier. The roles of some other carriers, such as dicarboxylate carrier (SLC25A10), APC1 (ScaMC-1, SLC25A24) and UCP2 (SLC25A8), are less well established, but there are studies pointing out to their importance. Finally, other members of the SLC25 family, such as the mitochondrial thiamine pyrophosphate carrier (SLC25A19), oxoglutarate carrier (SLC25A11), aspartate/glutamate carrier (SLC25A12), SLC25A47, SLC25A50 and others may be promising as well, but are awaiting a more detailed investigation. A promising approach could involve simultaneous targeting of several carriers, which can significantly increase efficiency and specificity of any potential anticancer therapy, but at the moment there are no studies investigating synergy between different mitochondrial transporters.

Transparency Document

The Transparency document associated with this article can be found, in online version.

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References

[1] T.N. Seyfried, R.E. Flores, A.M. Poff, D.P. D'Agostino, Cancer as a metabolic disease: implications for novel therapeutics, Carcinogenesis 35 (2014) 515–527.
[2] H.A. Coller, Is cancer a metabolic disease? Am. J. Pathol. 184 (2014) 4–17.
[3] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[4] E. Racker, Bioenergetics and the problem of tumor growth, Am. Sci. 60 (1972) 56–63.
[5] O. Warburg, On the origin of cancer cells, Science 123 (1956) 309–314.
[6] O. Warburg, F. Wind, E. Negelein, The metabolism of tumors in the body, J. Gen. Physiol. 8 (1927) 519–530.
[7] R. Moreno-Sánchez, A. Marín-Hernández, E. Saavedra, J.P. Pardo, S.J. Ralph, S. Rodríguez-Enríquez, Who controls the ATP supply in cancer cells? Biochemistry lessons to understand cancer energy metabolism, Int. J. Biochem. Cell Biol. 50 (2014) 10–23.
[8] G. Solaini, G. Sgarbi, A. Baracca, Oxidative phosphorylation in cancer cells, Biochim. Biophys. Acta 1807 (2011) 534–542.
[9] D.R. Wise, C.B. Thompson, Glutamine addiction: a new therapeutic target in cancer, Trends Biochem. Sci. 35 (2010) 427–433.
[10] W.W. Souba, Glutamine and cancer, Ann. Surg. 218 (1993) 715–728.
[11] D. Wilmore, J. Rombeau, Glutamine metabolism: nutritional and clinical significance, J. Nutr. (2001) 2539–2542.
[12] S.E. Horvath, G. Daum, Lipids of mitochondria, Prog. Lipid Res. 52 (2013) 590–614.
[13] C. Corbet, O. Feron, Cancer cell metabolism and mitochondria: nutrient plasticity for TCA cycle fueling, Biochim. Biophys. Acta 1868 (2017) 7–15.
[14] D.P. Barupala, S.P. Dzul, P.J. Riggs-Gelasco, T.L. Stemmler, Synthesis, delivery and regulation of eukaryotic heme and Fe−S cluster cofactors, Arch. Biochem. Biophys. 592 (2016) 60–75.
[15] D. Pain, A. Dancis, Roles of Fe−S proteins: from cofactor synthesis to iron homeostasis to protein synthesis, Curr. Opin. Genet. Dev. 38 (2016) 45–51.
[16] J. Stiban, M. So, L.S. Kaguni, Iron-sulfur clusters in mitochondrial metabolism: multifaceted roles of a simple cofactor, Biochemistry (Mosc) 81 (2016) 1066–1080.
[17] L.A. Martin, B.E. Kennedy, B. Karten, Mitochondrial cholesterol: mechanisms of import and effects on mitochondrial function, J. Bioenerg. Biomembr. 48 (2016) 137–151.
[18] M.X. Li, G. Dewson, Mitochondria and apoptosis: emerging concepts, F1000Prime Rep. 7 (2015) 42.
[19] O.C. Ubah, H.M. Wallace, Cancer therapy: targeting mitochondria and other subcellular organelles, Curr. Pharm. Des. 20 (2014) 201–222.
[20] A. Neesse, T.M. Gress, P. Michl, Therapeutic targeting of apoptotic pathways: novel aspects in pancreatic cancer, Curr. Pharm. Biotechnol. 13 (2012) 2273–2282.
[21] I.A. Barbosa, N.G. Machado, A.J. Skildum, P.M. Scott, P.J. Oliveira, Mitochondrial remodeling in cancer metabolism and survival: potential for new therapies, Biochim. Biophys. Acta Rev. Cancer 1826 (2012) 238–254.
[22] C. Frezza, E. Gottlieb, Mitochondria in cancer: not just innocent bystanders, Semin. Cancer Biol. 19 (2009) 4–11.
[23] E.E. Ramsay, P.J. Hogg, P.J. Dilda, Mitochondrial metabolism inhibitors for cancer therapy, Pharm. Res. 28 (2011) 2731–2744.
[24] M.L. Verschoor, R. Ungard, A. Harbottle, J.P. Jakupciak, R.L. Parr, G. Singh, Mitochondria and cancer: past, present, and future, 2013 (2013).
[25] C. Frezza, The role of mitochondria in the oncogenic signal transduction, Int. J. Biochem. Cell Biol. 48 (2014) 11–17.
[26] D.C. Wallace, Mitochondria and cancer, Nat. Rev. Cancer 12 (2012) 685–698.
[27] M.V. Liberti, J.W. Locasale, The Warburg effect: how does it benefit cancer cells? Trends Biochem. Sci. 41 (2016) 211–218.
[28] D. Senyilmaz, A.A. Teleman, Chicken or the egg: Warburg effect and mitochondrial dysfunction, F1000Prime Rep. 7 (2015) 41.
[29] P.S. Ward, C.B. Thompson, Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate, Cancer Cell 21 (2012) 297–308.
[30] H. Joo, H.H. Kim, T. Kim, E. Kim, J.K. Park, S.-J. Park, H.J. Kim, The mitochondrial Warburg effect: a cancer enigma, Interdiscip. Bio Cent. 1 (2009) 1–21.
[31] M.D. Hirschey, R.J. DeBerardinis, A.M.E. Diehl, J.E. Drew, C. Frezza, M.F. Green, L.W. Jones, Y.H. Ko, A. Le, M.A. Lea, J.W. Locasale, V.D. Longo, C.A. Lyssiotis, E. McDonnell, M. Mehrmohamadi, G. Michelotti, V. Muralidhar, M.P. Murphy, P.L. Pedersen, B. Poore, et al., Dysregulated metabolism contributes to oncogenesis, Semin. Cancer Biol. 35 (2015) S129–S150.
[32] M. Sciacovelli, E. Gaude, M. Hilvo, C. Frezza, The Metabolic Alterations of Cancer Cells, first ed., Elsevier Inc., 2014.
[33] L.M. Phan, S.-C.J. Yeung, M.-H. Lee, Cancer metabolic reprogramming: importance, main features, and potentials for precise targeted anti-cancer therapies, Cancer Biol. Med. 11 (2014) 1–19.
[34] Y. Zhang, J.M. Yang, Altered energy metabolism in cancer: a unique opportunity for therapeutic intervention, Cancer Biol. Ther. 14 (2013) 81–89.
[35] C.R. Thoma, M. Zimmermann, I. Agarkova, J.M. Kelm, W. Krek, 3D cell culture systems modeling tumor growth determinants in cancer target discovery, Adv. Drug Deliv. Rev. 69–70 (2014) 29–41.
[36] S. Romero-Garcia, J.S. Lopez-Gonzalez, J.L. Báez-Viveros, D. Aguilar-Cazares, H. Prado-Garcia, Tumor cell metabolism: an integral view, Cancer Biol. Ther. 12 (2011) 939–948.
[37] E.R.S. Kunji, Structural and Mechanistic Aspects of Mitochondrial Transport Proteins, Elsevier, 2012, pp. 174–205.
[38] F. Palmieri, The mitochondrial transporter family SLC25: identification, properties and physiopathology, Mol. Asp. Med. 34 (2013) 465–484.
[39] A.J. Robinson, C. Overy, E.R.S. Kunji, The mechanism of transport by mitochondrial carriers based on analysis of symmetry, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 17766–17771.
[40] C.L. Pierri, F. Palmieri, A. De Grassi, Single-nucleotide evolution quantifies the importance of each site along the structure of mitochondrial carriers, Cell. Mol. Life Sci. 71 (2014) 349–364.
[41] S. Herzig, E. Raemy, S. Montessuit, J.-L. Veuthey, N. Zamboni, B. Westermann,

E.R.S. Kunji, J.-C. Martinou, Identification and functional expression of the mitochondrial pyruvate carrier, Science 337 (2012) 93–96 (80-.).
[42] C. Thangaratnarajah, J.J. Ruprecht, E.R.S. Kunji, Calcium-induced conformational changes of the regulatory domain of human mitochondrial aspartate/glutamate carriers, Nat. Commun. 5 (2014) 5491.
[43] L. Palmieri, B. Pardo, F.M. Lasorsa, A. del Arco, K. Kobayashi, M. Iijima, M.J. Runswick, J.E. Walker, T. Saheki, J. Satrustegui, F. Palmieri, Citrin and aralar1 are Ca(2 +)-stimulated aspartate/glutamate transporters in mitochondria, EMBO J. 20 (2001) 5060–5069.
[44] S.P.D. Harborne, J.J. Ruprecht, E.R.S. Kunji, Calcium-induced conformational changes in the regulatory domain of the human mitochondrial ATP-Mg/Pi carrier, Biochim. Biophys. Acta 1847 (2015) 1245–1253.
[45] N.D. Amoedo, G. Punzi, E. Obre, D. Lacombe, A. De Grassi, C.L. Pierri, R. Rossignol, AGC1/2, the mitochondrial aspartate-glutamate carriers, Biochim. Biophys. Acta 1863 (2016) 2394–2412.
[46] A. Menga, V. Iacobazzi, V. Infantino, M.L. Avantaggiati, F. Palmieri, The mitochondrial aspartate/glutamate carrier isoform 1 gene expression is regulated by CREB in neuronal cells, Int. J. Biochem. Cell Biol. 60 (2015) 157–166.
[47] M.T. Nosek, J.R. Aprille, ATP-Mg/Pi carrier activity in rat liver mitochondria, Arch. Biochem. Biophys. 296 (1992) 691–697.
[48] G. Fiermonte, F. De Leonardis, S. Todisco, L. Palmieri, F.M. Lasorsa, F. Palmieri, Identification of the mitochondrial ATP-Mg/Pi transporter: bacterial expression, reconstitution, functional characterization, and tissue distribution, J. Biol. Chem. 279 (2004) 30722–30730.
[49] E.N. Maldonado, J.J. Lemasters, ATP/ADP ratio, the missed connection between mitochondria and the Warburg effect, Mitochondrion 19 Pt A (2014) 78–84.
[50] M.D. Brand, T.C. Esteves, Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3, Cell Metab. 2 (2005) 85–93.
[51] M. Donadelli, I. Dando, E. Dalla Pozza, M. Palmieri, Mitochondrial uncoupling protein 2 and pancreatic cancer: a new potential target therapy, World J. Gastroenterol. 21 (2015) 3232–3238.
[52] J.M. Argiles, S. Busquets, F.J. Lopez-Soriano, The role of uncoupling proteins in pathophysiological states, Biochem. Biophys. Res. Commun. 293 (2002) 1145–1152.
[53] J. Sun, S. Aluvila, R. Kotaria, J.A. Mayor, D.E. Walters, R.S. Kaplan, Mitochondrial and plasma membrane citrate transporters: discovery of selective inhibitors and application to structure/function analysis, Mol. Cell. Pharmacol. 2 (2010) 101–110.
[54] G.V. Gnoni, P. Priore, M.J.H. Geelen, L. Siculella, The mitochondrial citrate carrier: metabolic role and regulation of its activity and expression, IUBMB Life 61 (2009) 987–994.
[55] S. Edvardson, V. Porcelli, C. Jalas, D. Soiferman, Y. Kellner, A. Shaag, S.H. Korman, C.L. Pierri, P. Scarcia, N.D. Fraenkel, R. Segel, A. Schechter, A. Frumkin, O. Pines, A. Saada, L. Palmieri, O. Elpeleg, Agenesis of corpus callosum and optic nerve hypoplasia due to mutations in SLC25A1 encoding the mitochondrial citrate transporter, J. Med. Genet. 50 (2013) 240–245.
[56] V. Infantino, V. Iacobazzi, A. Menga, M.L. Avantaggiati, F. Palmieri, A key role of the mitochondrial citrate carrier (SLC25A1) in TNFα- and IFNγ-triggered inflammation, Biochim. Biophys. Acta 1839 (2014) 1–9.
[57] O. Catalina-Rodriguez, V.K. Kolukula, Y. Tomita, A. Preet, F. Palmieri, A. Wellstein, S. Byers, A.J. Giaccia, E. Glasgow, C. Albanese, M.L. Avantaggiati, The mitochondrial citrate transporter, CIC, is essential for mitochondrial homeostasis, Oncotarget 3 (2012) 1220–1235.
[58] V.K. Kolukula, G. Sahu, A. Wellstein, O.C. Rodriguez, A. Preet, V. Iacobazzi, G.D. Orazi, C. Albanese, M.L. Avantaggiati, SLC25A1, or CIC, is a novel transcriptional target of mutant p53 and a negative tumor prognostic marker, Oncotarget 5 (2014) 1212–1225.
[59] L. Cheng, W. Lu, B. Kulkarni, T. Pejovic, X. Yan, J.H. Chiang, L. Hood, K. Odunsi, B. Lin, Analysis of chemotherapy response programs in ovarian cancers by the next-generation sequencing technologies, Gynecol. Oncol. 117 (2010) 159–169.
[60] S. Aluvila, J. Sun, D.H.T. Harrison, D.E. Walters, R.S. Kaplan, Inhibitors of the mitochondrial citrate transport protein: validation of the role of substrate binding residues and discovery of the first purely competitive inhibitor, Mol. Pharmacol. 77 (2010) 26–34.
[61] C. Albanese, M.L. Avantaggiati, The SLC25A1-p53 mutant crosstalk, Aging (Albany NY) 7 (2015) 519–520.
[62] I. Stipani, M.I. Capalbo, V. Zara, Effect of anthracycline antibiotics on the reconstituted mitochondrial tricarboxylate carrier, Biochem. Biophys. Res. Commun. 164 (1989) 1281–1287.
[63] M. Gutiérrez-Aguilar, C.P. Baines, Physiological and pathological roles of mitochondrial SLC25 carriers, Biochem. J. 454 (2013) 371–386.
[64] G. Hatzivassiliou, F. Zhao, D.E. Bauer, C. Andreadis, A.N. Shaw, D. Dhanak, S.R. Hingorani, D.A. Tuveson, C.B. Thompson, ATP citrate lyase inhibition can suppress tumor cell growth, Cancer Cell 8 (2005) 311–321.
[65] E.M. Palmieri, I. Spera, A. Menga, V. Infantino, V. Porcelli, V. Iacobazzi, C.L. Pierri, D.C. Hooper, F. Palmieri, A. Castegna, Acetylation of human mitochondrial citrate carrier modulates mitochondrial citrate/malate exchange activity to sustain NADPH production during macrophage activation, Biochim. Biophys. Acta 1847 (2015) 729–738.
[66] X. Zhou, J.A. Paredes, S. Krishnan, S. Curbo, A. Karlsson, The mitochondrial carrier SLC25A10 regulates cancer cell growth, Oncotarget 6 (2015) 9271–9283.
[67] M. Gallo, D. Park, D.S. Luciani, K. Kida, F. Palmieri, O.E. Blacque, J.D. Johnson, D.L. Riddle, MISC-1/OGC links mitochondrial metabolism, apoptosis and insulin secretion, PLoS One 6 (2011) e17827.
[68] H.M. Wilkins, K. Marquardt, L.H. Lash, D.A. Linseman, Bcl-2 is a novel interacting partner for the 2-oxoglutarate carrier and a key regulator of mitochondrial glutathione, Free Radic. Biol. Med. 52 (2012) 410–419.
[69] T. Harris, Q. Pan, J. Sironi, D. Lutz, J. Tian, J. Sapkar, R. Perez-Soler, S. Keller, J. Locker, Both gene amplification and allelic loss occur at 14q133 in lung cancer, Clin. Cancer Res. 17 (2011) 690–699.
[70] A. Rudolph, R. Hein, S. Lindström, L. Beckmann, S. Behrens, J. Liu, H. Aschard, M.K. Bolla, J. Wang, T. Truong, E. Cordina-Duverger, F. Menegaux, T. Brüning, V. Harth, W.Y. Lo, G. Severi, L. Baglietto, M. Southey, S.J. Chanock, J. Lissowska, et al., Genetic modifiers of menopausal hormone replacement therapy and breast cancer risk: A genome-wide interaction study, Endocr. Relat. Cancer 20 (2013) 875–887.
[71] V. Dolce, P. Scarcia, D. Iacopetta, F. Palmieri, A fourth ADP/ATP carrier isoform in man: identification, bacterial expression, functional characterization and tissue distribution, FEBS Lett. 579 (2005) 633–637.
[72] S. Todisco, M.A. Di Noia, A. Onofrio, G. Parisi, G. Punzi, G. Redavid, A. De Grassi, C.L. Pierri, Identification of new highly selective inhibitors of the human ADP/ATP carriers by molecular docking and in vitro transport assays, Biochem. Pharmacol. 100 (2016) 112–132.
[73] A. Chevrollier, D. Loiseau, P. Reynier, G. Stepien, Adenine nucleotide translocase 2 is a key mitochondrial protein in cancer metabolism, Biochim. Biophys. Acta Bioenerg. 1807 (2011) 562–567.
[74] A.P. Halestrap, C. Brenner, The adenine nucleotide translocase: a central component of the mitochondrial permeability transition pore and key player in cell death, Curr. Med. Chem. 10 (2003) 1507–1525.
[75] J.E. Kokoszka, K.G. Waymire, S.E. Levy, J.E. Sligh, J. Cai, D.P. Jones, G.R. MacGregor, C.W. Douglas, The ADP/ATP translocator is not essential for the mitochondrial permeability transition pore, Nature 427 (2004) 461–465.
[76] C. Brenner, S. Grimm, The permeability transition pore complex in cancer cell death, Oncogene 25 (2006) 4744–4756.
[77] C. Brenner, K. Subramaniam, C. Pertuiset, S. Pervaiz, Adenine nucleotide translocase family: four isoforms for apoptosis modulation in cancer, Oncogene 30 (2011) 883–895.
[78] C. Gallerne, Z. Touat, Z.X. Chen, C. Martel, E. Mayola, O. Sharaf el dein, N. Buron, M. Le Bras, E. Jacotot, A. Borgne-Sanchez, A. Lemoine, C. Lemaire, S. Pervaiz, C. Brenner, The fourth isoform of the adenine nucleotide translocator inhibits mitochondrial apoptosis in cancer cells, Int. J. Biochem. Cell Biol. 42 (2010) 623–629.
[79] M. Zamora, M. Granell, T. Mampel, O. Viñas, Adenine nucleotide translocase 3 (ANT3) overexpression induces apoptosis in cultured cells, FEBS Lett. 563 (2004) 155–160.
[80] M.K.A. Bauer, A. Schubert, O. Rocks, S. Grimm, Adenine nucleotide translocase-1, a component of the permeability transition pore, can dominantly induce apoptosis, J. Cell Biol. 147 (1999) 1493–1501.
[81] G. Stepien, Differential expression of adenine nucleotide translocator isoforms in mammalian tissues and during muscle cell differentiation, J. Biol. Chem. 267 (1992) 14592–14597.
[82] A. Chevrollier, D. Loiseau, B. Chabi, G. Renier, O. Douay, Y. Malthièry, G. Stepien, ANT2 isoform required for cancer cell glycolysis, J. Bioenerg. Biomembr. 37 (2005) 307–317.
[83] J.-Y. Jang, Y. Choi, Y.-K. Jeon, K.C.Y. Aung, C.-W. Kim, Over-expression of adenine nucleotide translocase 1 (ANT1) induces apoptosis and tumor regression in vivo, BMC Cancer 8 (2008) 160.
[84] M. Zamora, C. Merono, O. Vinas, T. Mampel, Recruitment of NF-kappaB into mitochondria is involved in adenine nucleotide translocase 1 (ANT1)-induced apoptosis, J. Biol. Chem. 279 (2004) 38415–38423.
[85] A. Lena, M. Rechichi, A. Salvetti, D. Vecchio, M. Evangelista, G. Rainaldi, V. Gremigni, L. Rossi, The silencing of adenine nucleotide translocase isoform 1 induces oxidative stress and programmed cell death in ADF human glioblastoma cells, FEBS J. 277 (2010) 2853–2867.
[86] J.-Y. Jang, Y. Choi, Y.-K. Jeon, C.-W. Kim, Suppression of adenine nucleotide translocase-2 by vector-based siRNA in human breast cancer cells induces apoptosis and inhibits tumor growth in vitro and in vivo, Breast Cancer Res. 10 (2008) R11.
[87] O. Sharaf el dein, C. Gallerne, C. Brenner, C. Lemaire, Increased expression of VDAC1 sensitizes carcinoma cells to apoptosis induced by DNA cross-linking agents, Biochem. Pharmacol. 83 (2012) 1172–1182.
[88] M. Zamora, J.A. Ortega, L. Alana, O. Vinas, T. Mampel, Apoptotic and anti-proliferative effects of all-trans retinoic acid adenine nucleotide translocase sensitizes HeLa cells to all-trans retinoic acid, Exp. Cell Res. 312 (2006) 1813–1819.
[89] Z. Yang, W. Cheng, L. Hong, W. Chen, Y. Wang, S. Lin, J. Han, H. Zhou, J. Gu, Adenine nucleotide (ADP/ATP) translocase 3 participates in the tumor necrosis factor induced apoptosis of MCF-7 cells, Mol. Biol. Cell 18 (2007) 4681–4689.
[90] J.V. Brower, N. Rodic, T. Seki, M. Jorgensen, N. Fliess, A.T. Yachnis, J.R. McCarrey, S.P. Oh, N. Terada, Evolutionarily conserved mammalian adenine nucleotide translocase 4 is essential for spermatogenesis, J. Biol. Chem. 282 (2007) 29658–29666.
[91] M. Zoratti, I. Szabo, The mitochondrial permeability transition, Biochim. Biophys. Acta 1241 (1995) 139–176.
[92] J. Traba, A. Del Arco, M. Duchen, G. Szabadkai, J. Satrústegui, SCaMC-1 Promotes Cancer Cell Survival by Desensitizing Mitochondrial Permeability Transition via ATP/ADP-mediated Matrix Ca(2 +) Buffering, (2012), pp. 650–660.
[93] Y.-W. Chen, H.-C. Chou, P.-C. Lyu, H.-S. Yin, F.-L. Huang, W.-S.W. Chang, C.-Y. Fan, I.-F. Tu, T.-C. Lai, S.-T. Lin, Y.-C. Lu, C.-L. Wu, S.-H. Huang, H.-L. Chan, Mitochondrial proteomics analysis of tumorigenic and metastatic breast cancer markers, Funct. Integr. Genomics 11 (2011) 225–239.
[94] S.J. Kim, I. Sohn, I.-G. Do, S.H. Jung, Y.H. Ko, H.Y. Yoo, S. Paik, W.S. Kim, Gene

expression profiles for the prediction of progression-free survival in diffuse large B cell lymphoma: results of a DASL assay, Ann. Hematol. 93 (2014) 437–447.
[95] E.A.H. Kheirelseid, K.H. Chang, J. Newell, M.J. Kerin, N. Miller, Identification of endogenous control genes for normalisation of real-time quantitative PCR data in colorectal cancer, BMC Mol. Biol. 11 (2010) 12.
[96] C.-P. Hsiao, D. Wang, A. Kaushal, L. Saligan, Mitochondria-related gene expression changes are associated with fatigue in patients with nonmetastatic prostate cancer receiving external beam radiation therapy, Cancer Nurs. 36 (2015) 189–197.
[97] S. Alcalá, M. Klee, J. Fernández, A. Fleischer, F.X. Pimentel-Muiños, A high-throughput screening for mammalian cell death effectors identifies the mitochondrial phosphate carrier as a regulator of cytochrome c release, Oncogene 27 (2008) 44–54.
[98] J.Q. Kwong, J. Davis, C.P. Baines, M.A. Sargent, J. Karch, X. Wang, T. Huang, J.D. Molkentin, Genetic deletion of the mitochondrial phosphate carrier desensitizes the mitochondrial permeability transition pore and causes cardiomyopathy, Cell Death Differ. 21 (2014) 1209–1217.
[99] E. Tkacova, S. Kuzela, Elevated phosphate transporting activity and phosphate carrier content in mitochondria of rat hepatoma with high glycolytic capacity, Biochem. Int. 11 (1985) 45–50.
[100] V.G. Oehler, K.Y. Yeung, Y.E. Choi, R.E. Bumgarner, A.E. Raftery, P. Radich, W. Dc, J.P. Radich, The derivation of diagnostic markers of chronic myeloid leukemia progression from microarray data, 114 (2013) 3292–3298.
[101] G. Baffy, Uncoupling protein-2 and cancer, Mitochondrion 10 (2010) 243–252.
[102] G. Baffy, Z. Derdak, S.C. Robson, Mitochondrial recoupling: a novel therapeutic strategy for cancer? Br. J. Cancer 105 (2011) 469–474.
[103] D. Robbins, Y. Zhao, New aspects of mitochondrial uncoupling proteins (UCPs) and their roles in tumorigenesis, Int. J. Mol. Sci. 12 (2011) 5285–5293.
[104] U.C. Kozak, W. Held, D. Kreutter, L.P. Kozak, Adrenergic regulation of the mitochondrial uncoupling protein gene in brown fat tumor cells, Mol. Endocrinol. 6 (1992) 763–772.
[105] A. Vozza, G. Parisi, F. De Leonardis, F.M. Lasorsa, A. Castegna, D. Amorese, R. Marmo, V.M. Calcagnile, L. Palmieri, D. Ricquier, E. Paradies, P. Scarcia, F. Palmieri, F. Bouillaud, G. Fiermonte, UCP2 transports C4 metabolites out of mitochondria, regulating glucose and glutamine oxidation, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 960–965.
[106] D. Arsenijevic, H. Onuma, C. Pecqueur, S. Raimbault, B.S. Manning, B. Miroux, E. Couplan, M.C. Alves-Guerra, M. Goubern, R. Surwit, F. Bouillaud, D. Richard, S. Collins, D. Ricquier, Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production, Nat. Genet. 26 (2000) 435–439.
[107] F. Criscuolo, M. del M. Gonzalez-Barroso, F. Bouillaud, D. Ricquier, B. Miroux, G. Sorci, Mitochondrial uncoupling proteins: new perspectives for evolutionary ecologists, Am. Nat. 166 (2005) 686–699.
[108] C.Y. Zhang, G. Baffy, P. Perret, S. Krauss, O. Peroni, D. Grujic, T. Hagen, A.J. Vidal-Puig, O. Boss, Y.B. Kim, X.X. Zheng, M.B. Wheeler, G.I. Shulman, C.B. Chan, B.B. Lowell, Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, beta cell dysfunction, and type 2 diabetes, Cell 105 (2001) 745–755.
[109] X.-Y. Kuai, Z.-Y. Ji, H.-J. Zhang, Mitochondrial uncoupling protein 2 expression in colon cancer and its clinical significance, World J. Gastroenterol. 16 (2010) 5773–5778.
[110] W. Li, K. Nichols, C.-A. Nathan, Y. Zhao, Mitochondrial uncoupling protein 2 is up-regulated in human head and neck, skin, pancreatic, and prostate tumors, Cancer Biomark. 13 (2013) 377–383.
[111] V. Ayyasamy, K.M. Owens, M.M. Desouki, P. Liang, A. Bakin, K. Thangaraj, D.J. Buchsbaum, A.F. LoBuglio, K.K. Singh, Cellular model of Warburg effect identifies tumor promoting function of UCP2 in breast cancer and its suppression by genipin, PLoS One 6 (2011).
[112] D.G. Pons, M. Nadal-Serrano, M. Torrens-Mas, A. Valle, J. Oliver, P. Roca, UCP2 inhibition sensitizes breast cancer cells to therapeutic agents by increasing oxidative stress, Free Radic. Biol. Med. 86 (2015) 67–77.
[113] C. Qiao, L. Wei, Q. Dai, Y. Zhou, Q. Yin, Z. Li, Y. Xiao, Q. Guo, N. Lu, UCP2-related mitochondrial pathway participates in oroxylin A-induced apoptosis in human colon cancer cells, J. Cell. Physiol. 230 (2015) 1054–1063.
[114] G. Yu, J. Liu, K. Xu, J. Dong, Uncoupling protein 2 mediates resistance to gemcitabine-induced apoptosis in hepatocellular carcinoma cell lines, Biosci. Rep. 35 (2015).
[115] Z. Derdak, N.M. Mark, G. Beldi, S.C. Robson, J.R. Wands, G. Baffy, The mitochondrial uncoupling protein-2 promotes chemoresistance in cancer cells, Cancer Res. 68 (2008) 2813–2819.
[116] W. Li, C. Zhang, K. Jackson, X. Shen, R. Jin, G. Li, C.G. Kevil, X. Gu, R. Shi, Y. Zhao, UCP2 knockout suppresses mouse skin carcinogenesis, Cancer Prev. Res. (Phila.) 8 (2015) 487–491.
[117] W.-P. Su, Y.-C. Lo, J.-J. Yan, I.-C. Liao, P.-J. Tsai, H.-C. Wang, H.-H. Yeh, C.-C. Lin, H.H.W. Chen, W.-W. Lai, W.-C. Su, Mitochondrial uncoupling protein 2 regulates the effects of paclitaxel on Stat3 activation and cellular survival in lung cancer cells, Carcinogenesis 33 (2012) 2065–2075.
[118] P. Esteves, C. Pecqueur, C. Ransy, C. Esnous, V. Lenoir, F. Bouillaud, A.-L. Bulteau, A. Lombes, C. Prip-Buus, D. Ricquier, M.-C. Alves-Guerra, Mitochondrial retrograde signaling mediated by UCP2 inhibits cancer cell proliferation and tumorigenesis, Cancer Res. 74 (2014) 3971–3982.
[119] Z. Derdak, P. Fulop, E. Sabo, R. Tavares, E.P. Berthiaume, M.B. Resnick, G. Paragh, J.R. Wands, G. Baffy, Enhanced colon tumor induction in uncoupling protein-2 deficient mice is associated with NF-kappaB activation and oxidative stress, Carcinogenesis 27 (2006) 956–961.
[120] N. Braun, D. Klumpp, J. Hennenlotter, J. Bedke, C. Duranton, M. Bleif, S.M. Huber, UCP-3 uncoupling protein confers hypoxia resistance to renal epithelial cells and is upregulated in renal cell carcinoma, Sci. Rep. 5 (2015) 13450.
[121] H.Y. Lim, Y.M. Yip, E. Chiong, H.Y. Tiong, B. Halliwell, K. Esuvaranathan, K.P. Wong, Metabolic signatures of renal cell carcinoma, Biochem. Biophys. Res. Commun. 460 (2015) 938–943.
[122] S.M. Nowinski, A. Solmonson, J.E. Rundhaug, O. Rho, J. Cho, C.U. Lago, C.L. Riley, S. Lee, S. Kohno, C.K. Dao, T. Nikawa, S.B. Bratton, C.W. Wright, S.M. Fischer, J. DiGiovanni, E.M. Mills, Mitochondrial uncoupling links lipid catabolism to Akt inhibition and resistance to tumorigenesis, Nat. Commun. 6 (2015) 8137.
[123] C.U. Lago, S.M. Nowinski, J.E. Rundhaug, M.E. Pfeiffer, K. Kiguchi, K. Hirasaka, X. Yang, E.M. Abramson, S.B. Bratton, O. Rho, R. Colavitti, M.A. Kenaston, T. Nikawa, C. Trempus, J. Digiovanni, S.M. Fischer, E.M. Mills, Mitochondrial respiratory uncoupling promotes keratinocyte differentiation and blocks skin carcinogenesis, Oncogene 31 (2012) 4725–4731.
[124] S. Busquets, V. Almendro, E. Barreiro, M. Figueras, J.M. Argiles, F.J. Lopez-Soriano, Activation of UCPs gene expression in skeletal muscle can be independent on both circulating fatty acids and food intake Involvement of ROS in a model of mouse cancer cachexia, FEBS Lett. 579 (2005) 717–722.
[125] D. Antunes, A.I. Padrao, E. Maciel, D. Santinha, P. Oliveira, R. Vitorino, D. Moreira-Goncalves, B. Colaco, M.J. Pires, C. Nunes, L.L. Santos, F. Amado, J.A. Duarte, M.R. Domingues, R. Ferreira, Molecular insights into mitochondrial dysfunction in cancer-related muscle wasting, Biochim. Biophys. Acta 1841 (2014) 896–905.
[126] D. Sanchis, S. Busquets, B. Alvarez, D. Ricquier, F.J. Lopez-Soriano, J.M. Argiles, Skeletal muscle UCP2 and UCP3 gene expression in a rat cancer cachexia model, FEBS Lett. 436 (1998) 415–418.
[127] S. Busquets, N. Carbo, V. Almendro, M. Figueras, F.J. Lopez-Soriano, J.M. Argiles, Hyperlipemia: a role in regulating UCP3 gene expression in skeletal muscle during cancer cachexia? FEBS Lett. 505 (2001) 255–258.
[128] C. Bing, M. Brown, P. King, P. Collins, M.J. Tisdale, G. Williams, Increased gene expression of brown fat uncoupling protein (UCP)1 and skeletal muscle UCP2 and UCP3 in MAC16-induced cancer cachexia, Cancer Res. 60 (2000) 2405–2410.
[129] A. Rupprecht, D. Sittner, A. Smorodchenko, K.E. Hilse, J. Goyn, R. Moldzio, A.E.M. Seiler, A.U. Bräuer, E.E. Pohl, Uncoupling protein 2 and 4 expression pattern during stem cell differentiation provides new insight into their putative function, PLoS One 9 (2014) 1–10.
[130] Z. Wei, S. Chigurupati, P. Bagsiyao, A. Henriquez, S.L. Chan, The brain uncoupling protein UCP4 attenuates mitochondrial toxin-induced cell death: role of extracellular signal-regulated kinases in bioenergetics adaptation and cell survival, Neurotox. Res. 16 (2009) 14–29.
[131] M. Gonidi, A.M. Athanassiadou, E. Patsouris, A. Tsipis, S. Dimopoulos, V. Kyriakidou, G. Chelidonis, P. Athanassiadou, Mitochondrial UCP4 and bcl-2 expression in imprints of breast carcinomas: relationship with DNA ploidy and classical prognostic factors, Pathol. Res. Pract. 207 (2011) 377–382.
[132] V. Porcelli, G. FIERMONTE, A. Longo, F. Palmieri, The human gene SLC25A29, of solute carrier family 25, encodes a mitochondrial transporter of basic amino acids, J. Biol. Chem. (2014).
[133] G. Fiermonte, L. Palmieri, S. Todisco, G. Agrimi, F. Palmieri, J.E. Walker, Identification of the mitochondrial glutamate transporter bacterial expression, reconstitution, functional characterization, and tissue distribution of two human isoforms, J. Biol. Chem. 277 (2002) 19289–19294.
[134] C.C. Wong, Y. Qian, X. Li, J. Xu, W. Kang, J.H. Tong, K.-F. To, Y. Jin, W. Li, H. Chen, M.Y. Go, J.-L. Wu, K.W. Cheng, S.S. Ng, J.J. Sung, Z. Cai, J. Yu, SLC25A22 promotes proliferation and survival of colorectal cancer cells with KRAS mutations, and xenograft tumor progression in mice, via intracellular synthesis of aspartate, Gastroenterology (2016).
[135] K.-W. Chang, H.-L. Chen, Y.-H. Chien, T.-C. Chen, C.-T. Yeh, SLC25A13 gene mutations in Taiwanese patients with non-viral hepatocellular carcinoma, Mol. Genet. Metab. 103 (2011) 293–296.
[136] H. Dong, H. Zhang, J. Liang, H. Yan, Y. Chen, Y. Shen, Y. Kong, S. Wang, G. Zhao, W. Jin, Digital karyotyping reveals probable target genes at 7q213 locus in hepatocellular carcinoma, BMC Med. Genet. 4 (2011) 1–8.
[137] C.-W. Tsai, C.-C. Yang, H.-L. Chen, W.-L. Hwu, M.-Z. Wu, K.-L. Liu, M.-S. Wu, Homozygous SLC25A13 mutation in a Taiwanese patient with adult-onset citrullinemia complicated with steatosis and hepatocellular carcinoma, J. Formos. Med. Assoc. 105 (2006) 852–856.
[138] C.T. Hensley, A.T. Wasti, R.J. Deberardinis, Review series glutamine and cancer: cell biology, physiology, and clinical opportunities, 123 (2013).
[139] M. Yuneva, Finding an “Achilles' heel” of cancer: the role of glucose and glutamine metabolism in the survival of transformed cells, Cell Cycle 7 (2008) 2083–2089.
[140] L. Alberghina, D. Gaglio, Redox control of glutamine utilization in cancer, Cell Death Dis. 5 (2014) e1561.
[141] Z. Kovacević, J.D. McGivan, J.B. Chappell, Conditions for activity of glutaminase in kidney mitochondria, Biochem. J. 118 (1970) 265–274.
[142] M. Molina, J.A. Segura, J.C. Aledo, M.A. Medina, I. Núnez de Castro, J. Márquez, Glutamine transport by vesicles isolated from tumour-cell mitochondrial inner membrane, Biochem. J. 308 (Pt 2) (1995) 629–633.
[143] Z. Kovacević, K. Bajin, Z. Kovacevic, K. Bajin, Kinetics of glutamine-efflux from liver mitochondria loaded with the 14C-Labeled substrate, Biochim. Biophys. Acta 687 (1982) 291–295.
[144] E. Kvamme, I.A. Torgner, B. Roberg, Kinetics and localization of brain phosphate activated glutaminase, J. Neurosci. Res. 66 (2001) 951–958.
[145] W. Huang, W. Choi, Y. Chen, Q. Zhang, H. Deng, W. He, Y. Shi, A proposed role for glutamine in cancer cell growth through acid resistance, Cell Res. 23 (2013) 724–727.

[146] T. Bender, J.C. Martinou, The mitochondrial pyruvate carrier in health and disease: to carry or not to carry? Biochim. Biophys. Acta, Mol. Cell Res. (2015) 1–7.
[147] B. Vanderperre, T. Bender, E.R.S. Kunji, J.-C. Martinou, Mitochondrial pyruvate import and its effects on homeostasis, Curr. Opin. Cell Biol. 33 (2015) 35–41.
[148] A.J. Rauckhorst, E.B. Taylor, Mitochondrial pyruvate carrier function and cancer metabolism, Curr. Opin. Genet. Dev. 38 (2016) 102–109.
[149] K.S. McCommis, B.N. Finck, Mitochondrial pyruvate transport: a historical perspective and future research directions, Biochem. J. 466 (2015) 443–454.
[150] J.C. Schell, J. Rutter, The long and winding road to the mitochondrial pyruvate carrier, Cancer Metab. 1 (2013) 6.
[151] D.K. Bricker, E.B. Taylor, J.C. Schell, T. Orsak, A. Boutron, Y.-C. Chen, J.E. Cox, C.M. Cardon, J.G. Van Vranken, N. Dephoure, C. Redin, S. Boudina, S.P. Gygi, M. Brivet, C.S. Thummel, J. Rutter, A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, Drosophila, and humans, Science 337 (2012) 96–100.
[152] J.C. Schell, K.A. Olson, L. Jiang, A.J. Hawkins, J.G. VanVranken, J. Xie, R.A. Egnatchik, E.G. Earl, R.J. DeBerardinis, J. Rutter, A role for the mitochondrial pyruvate carrier as a repressor of the warburg effect and colon cancer cell growth, Mol. Cell 56 (2014) 400–413.
[153] Y. Zhong, X. Li, D. Yu, X. Li, Y. Li, Y. Long, Y. Yuan, Z. Ji, M. Zhang, J.-G. Wen, J.M. Nesland, Z. Suo, Application of mitochondrial pyruvate carrier blocker UK5099 creates metabolic reprogram and greater stem-like properties in LnCap prostate cancer cells in vitro, Oncotarget 6 (2015) 37758–37769.
[154] B. Nancolas, L. Guo, R. Zhou, K. Nath, D.S. Nelson, D.B. Leeper, I.A. Blair, J.D. Glickson, A.P. Halestrap, The anti-tumour agent lonidamine is a potent inhibitor of the mitochondrial pyruvate carrier and plasma membrane monocarboxylate transporters, Biochem. J. 473 (2016) 929–936.
[155] K. Nath, L. Guo, B. Nancolas, D.S. Nelson, A.A. Shestov, S.-C. Lee, J. Roman, R. Zhou, D.B. Leeper, A.P. Halestrap, I.A. Blair, J.D. Glickson, Mechanism of antineoplastic activity of lonidamine, Biochim. Biophys. Acta 1866 (2016) 151–162.
[156] R.L. Elliott, Cancer: tumor iron metabolism, mitochondrial dysfunction and tumor immunosuppression; “A tight partnership—was Warburg correct?”, J. Cancer Ther. 3 (2012) 278–311.
[157] S.V. Torti, Iron and cancer: more ore to be mined, 13 (2013) 342–355.
[158] G.C. Shaw, J.J. Cope, L. Li, K. Corson, C. Hersey, G.E. Ackermann, B. Gwynn, A.J. Lambert, R.A. Wingert, D. Traver, N.S. Trede, B.A. Barut, Y. Zhou, E. Minet, A. Donovan, A. Brownlie, R. Balzan, M.J. Weiss, L.L. Peters, J. Kaplan, et al., Mitoferrin is essential for erythroid iron assimilation, Nature 440 (2006) 96–100.
[159] P.N. Paradkar, K.B. Zumbrennen, B.H. Paw, D.M. Ward, J. Kaplan, Regulation of mitochondrial iron import through differential turnover of mitoferrin 1 and mitoferrin 2, Mol. Cell. Biol. 29 (2009) 1007–1016.
[160] U. Muhlenhoff, B. Hoffmann, N. Richter, N. Rietzschel, F. Spantgar, O. Stehling, M.A. Uzarska, R. Lill, Compartmentalization of iron between mitochondria and the cytosol and its regulation, Eur. J. Cell Biol. 94 (2015) 292–308.
[161] T.A. Rouault, Mitochondrial iron overload: causes and consequences, Curr. Opin. Genet. Dev. 38 (2016) 31–37.
[162] M.-B. Troadec, D. Warner, J. Wallace, K. Thomas, G.J. Spangrude, J. Phillips, O. Khalimonchuk, B.H. Paw, D.M. Ward, J. Kaplan, Targeted deletion of the mouse Mitoferrin1 gene: from anemia to protoporphyria, Blood 117 (2011) 5494–5502.
[163] C. Wang, X. Chen, H. Zou, X. Chen, Y. Liu, S. Zhao, The roles of mitoferrin-2 in the process of arsenic trioxide-induced cell damage in human gliomas, Eur. J. Med. Res. 19 (2014) 49.
[164] H.-I. Hung, J.M. Schwartz, E.N. Maldonado, J.J. Lemasters, A.-L. Nieminen, Mitoferrin-2-dependent mitochondrial iron uptake sensitizes human head and neck squamous carcinoma cells to photodynamic therapy, J. Biol. Chem. 288 (2013) 677–686.
[165] M. del Rey, R. Benito, C. Fontanillo, F.J. Campos-Laborie, K. Janusz, T. Velasco-Hernandez, M. Abaigar, M. Hernandez, R. Cuello, D. Borrego, D. Martin-Zanca, J. De Las Rivas, K.I. Mills, J.M. Hernandez-Rivas, Deregulation of genes related to iron and mitochondrial metabolism in refractory anemia with ring sideroblasts, PLoS One 10 (2015) e0126555.
[166] H. Dolatshad, A. Pellagatti, M. Fernandez-Mercado, B.H. Yip, L. Malcovati, M. Attwood, B. Przychodzen, N. Sahgal, A.A. Kanapin, H. Lockstone, L. Scifo, P. Vandenberghe, E. Papaemmanuil, C.W.J. Smith, P.J. Campbell, S. Ogawa, J.P. Maciejewski, M. Cazzola, K.I. Savage, J. Boultwood, Disruption of SF3B1 results in deregulated expression and splicing of key genes and pathways in myelodysplastic syndrome hematopoietic stem and progenitor cells, Leukemia 29 (2015) 1092–1103.
[167] V. Visconte, N. Avishai, R. Mahfouz, A. Tabarroki, J. Cowen, R. Sharghi-Moshtaghin, M. Hitomi, H.J. Rogers, E. Hasrouni, J. Phillips, M.A. Sekeres, A.H. Heuer, Y. Saunthararajah, J. Barnard, R.V. Tiu, Distinct iron architecture in SF3B1-mutant myelodysplastic syndrome patients is linked to an SLC25A37 splice variant with a retained intron, Leukemia 29 (2015) 188–195.
[168] C.-P. Hsiao, D. Wang, A. Kaushal, M.-K. Chen, L. Saligan, Differential expression of genes related to mitochondrial biogenesis and bioenergetics in fatigued prostate cancer men receiving external beam radiation therapy, J. Pain Symptom Manag. 48 (2014) 1080–1090.
[169] E. Tina, B. Lindqvist, M. Gabrielson, Z. Lubovac, P. Wegman, S. Wingren, The mitochondrial transporter SLC25A43 is frequently deleted and may influence cell proliferation in HER2-positive breast tumors, BMC Cancer 12 (2012) 350.
[170] B.M. Lindqvist, S.A. Farkas, S. Wingren, T.K. Nilsson, DNA methylation pattern of the SLC25A43 gene in breast cancer, Epigenetics 7 (2012) 300–306.
[171] M. Gabrielson, E. Tina, The mitochondrial transport protein SLC25A43 affects drug efficacy and drug-induced cell cycle arrest in breast cancer cell lines, Oncol. Rep. 29 (2013) 1268–1274.
[172] M. Gabrielson, E. Reizer, O. Stål, E. Tina, Mitochondrial regulation of cell cycle progression through {SLC25A43}, Biochem. Biophys. Res. Commun. 469 (2016) 1090–1096.
[173] M.G.K. Tan, L.L.P.J. Ooi, S.E. Aw, K.M. Hui, Cloning and identification of hepatocellular carcinoma down-regulated mitochondrial carrier protein, a novel liver-specific uncoupling protein, J. Biol. Chem. 279 (2004) 45235–45244.
[174] X. Jin, Y. Da Yang, K. Chen, Z.Y. Lv, L. Zheng, Y.P. Liu, S.H. Chen, C.H. Yu, X.Y. Jiang, C.Y. Zhang, Y.M. Li, HDMCP uncouples yeast mitochondrial respiration and alleviates steatosis in L02 and hepG2 cells by decreasing ATP and H2O2 levels: a novel mechanism for NAFLD, J. Hepatol. 50 (2009) 1019–1028.
[175] C. Katz, Y. Zaltsman-Amir, Y. Mostizky, N. Kollet, A. Gross, A. Friedler, Molecular basis of the interaction between proapoptotic truncated BID (tBID) protein and mitochondrial carrier homologue 2 (MTCH2) protein: key players in mitochondrial death pathway, J. Biol. Chem. 287 (2012) 15016–15023.
[176] M. Arigoni, G. Barutello, F. Riccardo, E. Ercole, D. Cantarella, F. Orso, L. Conti, S. Lanzardo, D. Taverna, I. Merighi, R.A. Calogero, F. Cavallo, E. Quaglino, miR-135b coordinates progression of ErbB2-driven mammary carcinomas through suppression of MID1 and MTCH2, Am. J. Pathol. 182 (2013) 2058–2070.
[177] R.J. Delahanty, A. Beeghly-Fadiel, Y.-B. Xiang, J. Long, Q. Cai, W. Wen, W.-H. Xu, H. Cai, J. He, Y.-T. Gao, W. Zheng, X.O. Shu, Association of obesity-related genetic variants with endometrial cancer risk: a report from the Shanghai endometrial cancer genetics study, Am. J. Epidemiol. 174 (2011) 1115–1126.
[178] K. Yu, K. Ganesan, L.K. Tan, M. Laban, J. Wu, X.D. Zhao, H. Li, C.H.W. Leung, Y. Zhu, C.L. Wei, S.C. Hooi, L. Miller, P. Tan, A precisely regulated gene expression cassette potently modulates metastasis and survival in multiple solid cancers, PLoS Genet. 4 (2008) e1000129.
[179] M. Lando, S.M. Wilting, K. Snipstad, T. Clancy, M. Bierkens, E.-K. Aarnes, M. Holden, T. Stokke, K. Sundfør, R. Holm, G.B. Kristensen, R.D.M. Steenbergen, H. Lyng, Identification of eight candidate target genes of the recurrent 3p12–p14 loss in cervical cancer by integrative genomic profiling, J. Pathol. 230 (2013) 59–69.
[180] W.T. Kim, S.J. Yun, C. Yan, P. Jeong, Y.H. Kim, I.-S. Lee, H.-W. Kang, S. Park, S.-K. Moon, Y.-H. Choi, Y.D. Choi, I.Y. Kim, J. Kim, W.-J. Kim, Metabolic pathway signatures associated with urinary metabolite biomarkers differentiate bladder cancer patients from healthy controls, Yonsei Med. J. 57 (2016) 865–871.
[181] K. Nohara, Y. Tateishi, T. Suzuki, K. Okamura, H. Murai, S. Takumi, F. Maekawa, N. Nishimura, M. Kobori, T. Ito, Late-onset increases in oxidative stress and other tumorigenic activities and tumors with a Ha-ras mutation in the liver of adult male C3H mice gestationally exposed to arsenic, Toxicol. Sci. 129 (2012) 293–304.
[182] S. Floyd, C. Favre, F.M. Lasorsa, M. Leahy, G. Trigiante, P. Stroebel, A. Marx, G. Loughran, K. O'Callaghan, C.M.T. Marobbio, D.J. Slotboom, E.R.S. Kunji, F. Palmieri, R. O'Connor, The insulin-like growth factor-I-mTOR signaling pathway induces the mitochondrial pyrimidine nucleotide carrier to promote cell growth, Mol. Biol. Cell 18 (2007) 3545–3555.
[183] C. Favre, A. Zhdanov, M. Leahy, D. Papkovsky, R. O'Connor, Mitochondrial pyrimidine nucleotide carrier (PNC1) regulates mitochondrial biogenesis and the invasive phenotype of cancer cells, Oncogene 29 (2010) 3964–3976.
[184] S.M. Wilting, J. de Wilde, C.J.L.M. Meijer, J. Berkhof, Y. Yi, W.N. van Wieringen, B.J.M. Braakhuis, G.A. Meijer, B. Ylstra, P.J.F. Snijders, R.D.M. Steenbergen, Integrated genomic and transcriptional profiling identifies chromosomal loci with altered gene expression in cervical cancer, Genes Chromosom. Cancer 47 (2008) 890–905.
[185] P. Lunetti, F. Damiano, G. De Benedetto, L. Siculella, A. Pennetta, L. Muto, E. Paradies, C.M.T. Marobbio, V. Dolce, L. Capobianco, Characterization of human and yeast mitochondrial glycine carriers with implications for heme biosynthesis and anemia, J. Biol. Chem. 291 (2016) 19746–19759.
[186] H. Chen, Q. Lu, Y. Zhang, C. Zhang, H. Zhang, H. Xu, Overexpression of SLC25A38 protein on acute lymphoblastic leukemia cells, Oncol. Lett. 7 (2014) 1422–1426.
[187] C. Pecqueur, M.C. Alves-Guerra, C. Gelly, C. Lévi-Meyrueis, E. Couplan, S. Collins, D. Ricquier, F. Bouillaud, B. Miroux, Uncoupling protein 2, in vivo distribution, induction upon oxidative stress, and evidence for translational regulation, J. Biol. Chem. 276 (2001) 8705–8712.
[188] C. Hurtaud, C. Gelly, F. Bouillaud, C. Lévi-Meyrueis, Translation control of UCP2 synthesis by the upstream open reading frame, Cell. Mol. Life Sci. 63 (2006) 1780–1789.
[189] L.M. Tiede, E.A. Cook, B. Morsey, H.S. Fox, Oxygen matters: tissue culture oxygen levels affect mitochondrial function and structure as well as responses to HIV viroproteins, Cell Death Dis. 2 (2011) e246.
[190] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, Cell 100 (2000) 57–70.
[191] Y. Lazebnik, What are the hallmarks of cancer? Nat. Rev. Cancer 10 (2010) 232–233.
[192] D.R. Rhodes, J. Yu, K. Shanker, N. Deshpande, R. Varambally, D. Ghosh, T. Barrette, A. Pandey, A.M. Chinnaiyan, ONCOMINE: a cancer microarray database and integrated data-mining platform, Neoplasia 6 (2004) 1–6.
[193] G.S. Cowley, B.A. Weir, F. Vazquez, P. Tamayo, J.A. Scott, S. Rusin, A. East-Seletsky, L.D. Ali, W.F. Gerath, S.E. Pantel, P.H. Lizotte, G. Jiang, J. Hsiao, A. Tsherniak, E. Dwinell, S. Aoyama, M. Okamoto, W. Harrington, E. Gelfand, T.M. Green, et al., Parallel genome-scale loss of function screens in 216 cancer cell lines for the identification of context-specific genetic dependencies, Sci. Data 1 (2014) 140035.
[194] V. Infantino, V. Iacobazzi, A. Menga, M.L. Avantaggiati, F. Palmieri, A key role of the mitochondrial citrate carrier (SLC25A1) in TNFalpha- and IFNgamma-triggered inflammation, Biochim. Biophys. Acta 1839 (2014) 1217–1225.
[195] S. Büttner, D. Ruli, F.-N. Vögtle, L. Galluzzi, B. Moitzi, T. Eisenberg, O. Kepp, L. Habernig, D. Carmona-Gutierrez, P. Rockenfeller, P. Laun, M. Breitenbach, C. Khoury, K.-U. Fröhlich, G. Rechberger, C. Meisinger, G. Kroemer, F. Madeo, A

yeast BH3-only protein mediates the mitochondrial pathway of apoptosis, EMBO J. 30 (2011) 2779–2792.

[196] Y. Yuan, P. Guo-Qing, T. Yan, Y. Hong-Lin, H. Gong-Hua, Z. Cai-Gao, A study of PKM2, PFK-1, and ANT1 expressions in cervical biopsy tissues in China, Med. Oncol. 29 (2012) 2904–2910.

[197] M. Le Bras, A. Borgne-Sanchez, Z. Touat, O.S. El Dein, A. Deniaud, E. Maillier, G. Lecellier, D. Rebouillat, C. Lemaire, G. Kroemer, E. Jacotot, C. Brenner, Chemosensitization by knockdown of adenine nucleotide translocase-2, Cancer Res. 66 (2006) 9143–9152.

[198] C.F. Lee, Z.Q. Ling, T. Zhao, S.H. Fang, W.C. Chang, S.C. Lee, K.R. Lee, Genomic-wide analysis of lymphatic metastasis-associated genes in human hepatocellular carcinoma, World J. Gastroenterol. 15 (2009) 356–365.

[199] E. Motamedian, G. Ghavami, S. Sardari, Investigation on metabolism of cisplatin resistant ovarian cancer using a genome scale metabolic model and microarray data, Iran J. Basic Med. Sci. 18 (2015) 267–276.

[200] J.A. Zastre, B.S. Hanberry, R.L. Sweet, A.C. McGinnis, K.R. Venuti, M.G. Bartlett, R. Govindarajan, Up-regulation of vitamin B1 homeostasis genes in breast cancer, J. Nutr. Biochem. 24 (2013) 1616–1624.

[201] V. Dolce, G. Fiermonte, M.J. Runswick, F. Palmieri, J.E. Walker, The human mitochondrial deoxynucleotide carrier and its role in the toxicity of nucleoside antivirals, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 2284–2288.

[202] F.M. Santandreu, A. Valle, S. Fernandez de Mattos, P. Roca, J. Oliver, Hydrogen peroxide regulates the mitochondrial content of uncoupling protein 5 in colon cancer cells, Cell. Physiol. Biochem. 24 (2009) 379–390.

[203] R. Leibowitz-Amit, G. Tsarfaty, Y. Abargil, G.M. Yerushalmi, J. Horev, I. Tsarfaty, Mimp, a mitochondrial carrier homologue, inhibits Met-HGF/SF-induced scattering and tumorigenicity by altering Met-HGF/SF signaling pathways, Cancer Res. 66 (2006) 8687–8697.