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From old to new — Repurposing drugs to target mitochondrial energy metabolism in cancer

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Abstract

Although we have entered the era of personalized medicine and tailored therapies, drugs that target a large variety of cancers regardless of individual patient differences would be a major advance nonetheless. This review article summarizes current concepts and therapeutic opportunities in the area of targeting aerobic mitochondrial energy metabolism in cancer. Old drugs previously used for diseases other than cancer, such as antibiotics and antidiabetics, have the potential to inhibit the growth of various tumor entities. Many drugs are reported to influence mitochondrial metabolism. However, here we consider only those drugs which predominantly inhibit oxidative phosphorylation.

Keywords

Aerobic mitochondrial energy metabolism; Oxidative phosphorylation complex; Antibiotic; Antidiabetic; Chemotherapeutic

1 Introduction

Cancer is one of the most devastating and intractable diseases. For example, it is the second causing deaths in the United States [1]. During the last decade, substantial progress has been made in genetic diagnostics, especially in the area of exome and whole-genome sequencing [2]. Moreover, the development of RNA sequencing is enabling elucidation of the function of genetic variants whose pathogenic relevance has been unclear [3,4]. These technical advances have also led to significant cost reductions, thus providing the foundation for personalized / precision medicine in the treatment of cancer [5]. However, because of the enormous heterogeneity and numerous inter-individual genetic differences,

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new therapies usually target only very small patient cohorts. An emerging broad-spectrum approach to cancer therapy depends on the fact that many tumors are characterized by enhanced glycolysis and low but mostly functional oxidative phosphorylation (OXPHOS), a phenotype first described by the Nobel laureate Otto Warburg more than 80 years ago [6,7]. Therefore, metabolic therapies have the potential to be applied against a vast array of tumor entities.

There is increasing evidence that several drugs with potent antitumor activity act *via* targeting mitochondrial aerobic metabolism. Possible targets include the five OXPHOS complexes, mitochondrial translation, and mitochondrial biogenesis. Other parameters of mitochondrial function such as mitochondrial morphology may also be impacted by these drugs, but the experimental evidence is sparse and inconclusive in terms of therapeutic significance.

The Warburg effect describes the abnormality wherein cancer cells generate energy predominantly *via* glycolysis even if sufficient oxygen is present. It seems a paradox that tumors use inefficient glycolysis instead of OXPHOS for energy production, but there are several explanations for why the principal pathway of ATP generation is reprogrammed in cancer cells. Foremost, aerobic glycolysis is not as inefficient as is often assumed. Although it is correct that the amount of ATP generated per molecule of glucose is low, the rate of glucose metabolism is high in cancer cells. The production of lactate from glucose occurs 10–100 times faster than the complete oxidation of glucose in mitochondria, therefore ATP production is similar [8].

Many tumors are characterized by low OXPHOS. However, the reasons for this pathology differ between cancer entities. Some tumors carry pathogenic mutations in mtDNA-encoded complex I subunits (*e.g.* renal oncocytomas) or nuclear-encoded complex II subunits (*e.g.* pheochromocytomas and paragangliomas); others show a reduction of all OXPHOS complexes, with a reduction of mtDNA copy number; and still others have low mitochondrial mass [9–13]. The genetic cause of this downregulation remains elusive in many cases. Many entities show a homogenous reduction of OXPHOS, such as oncocytic tumors, neuroblastomas, renal cell carcinomas and astrocytic brain tumors [10,11,14]. However, only a subset of carcinomas and melanomas is OXPHOS deficient, the others retaining a functional OXPHOS system [15–20]. The OXPHOS dependence of certain cancer subtypes is influenced either by genetic alterations and/or tumor microenvironment. For example, KRAS driven in lung cancer showed increased glucose contribution to the tricarboxylic acid (TCA) cycle relative to normal lung tissue [21]. Furthermore, alterations in components of the SWI/ SNF chromatin complex including SMARCA4 are frequently detected in lung cancer. Tumors with SMARCA4 mutations are characterized by enhanced OXPHOS as well as respiratory capacity and are therefore sensitive to OXPHOS inhibition [22]. In contrast to Phosphatase and tensin homolog (PTEN) wild type prostate cancer cells, mitochondria of PTEN-null cells consume ATP through complex V, instead of producing it, which resulted in genotype specific sensitivity to complex I inhibition *in vitro* [23].

BTB and CNC homology1 (BACH1), a haem-binding transcription factor that is increased in expression in tumors from patients with triple negative breast cancer, decreases glucose

utilization in the TCA cycle and downregulates expression of OXPHOS genes. Thus, BACH1 gene expression inversely correlates with OXPHOS gene expression in tumors from patients with breast cancer [24].

Moreover, cancer cells have the capacity to use a variety of substrates to fuel the mitochondrial respiration (fatty acids, glutamine, lactate, acetate…) [25–28]. This has been demonstrated for example *in vivo* in human cancer patients and diverse animal models *via* infusion of 13C-labelled substrates [25–27].

Cells exposed to acidosis largely rely upon mitochondrial metabolism for energy generation to the extent that metabolic intermediates are redirected away from several other critical metabolic processes, including ribose and glutathione synthesis [29]. The metabolic adaptation of cancer cells to chronic acidosis causes a shift from glucose to glutamine metabolism and glutamine fueled OXPHOS in different tumor cell lines [30]. Furthermore, lactate produced by enhanced glycolysis can also be used as a metabolic fuel by oxidative cancer cells [26,31,32] but also nearly all normal tissues [27].

In all these scenarios the tumor microenviornment has to be taken in consideration. The tumor microenvironment is characterized by different factors such as an increased level of lactate and/or CO_2, produced by tumor cells. As shown in lung cancer, a hypercapnic tumor environment reduces mitochondrial respiration, leading to chemoresistance [178]. Cancer-associated fibroblasts (CAFs) are the major cellular stromal component of many solid tumors. For example in prostate cancer (PCa), CAFs establish a metabolic symbiosis with PCa cells, contributing to cancer aggressiveness through lactate shuttle. Cancer cells are even able to hijack CAF-derived functional mitochondria through the formation of cellular bridges [179].

In this article, we discuss the therapeutic potential of targeting mitochondrial energy metabolism and the mechanisms behind the various approaches.

Many FDA-approved drugs initially used for the treatment of noncancer illnesses are now being repurposed for tumor therapy in light of increased knowledge about their mechanisms of action. Drugs with minimal side effects on whole-body metabolism exploit the Warburg effect in cancer cells. However, certain traditional chemotherapeutics may act by inhibiting aerobic mitochondrial energy metabolism. This review focuses on very concrete changes of mitochondrial energy function. Only FDA-approved drugs that affect specific mitochondrial components or functions - OXPHOS complexes; oxygen consumption; enzymatic activity; mitochondrial replication, transcription or translation; mitochondrial fission and fusion; or mitochondrial biogenesis - are considered for their ability to target tumor metabolism (Fig. 1).

2 Antimicrobial agents

Growing clinical and pre-clinical evidence indicates that many commonly used antimicrobial (AM) therapeutics such as antibiotics, antiparasitics and antifungal drugs have anticancer effects against a wide spectrum of solid tumors and blood cancers (*e.g.* breast, brain, cervix, lung, kidney, ovary, retinoblastoma, multiple myeloma and leukemia).

As shown in various studies, the underlying anticancer mechanisms of AMs are linked to their effects on key proteins involved in glycolysis, the response to DNA damage, protein degradation, angiogenesis, autophagy, the cell cycle and different signaling pathways [33–39]. However, a particularly important aspect of the anticancer effects of AM therapy is the interference with mitochondrial function [38,40–51] (Table 1). The endosymbiotic hypothesis proposes that mitochondria originated from bacteria; consequently, several antibiotics target these cellular organelles, too. AMs alter mitochondrial function by reducing mitochondrial biogenesis, altering mitochondrial morphology, lowering ATP production and increasing the level of reactive oxygen species (ROS), ultimately resulting in energy stress and anti-proliferative and pro-apoptotic effects. *In vitro* studies showed that cancer cells depleted of mitochondrial DNA (ρ0) are resistant to AMs in terms of suppression of cell proliferation or induction of apoptosis, emphasizing that AMs specifically target mitochondria [41,43–47,52]. In fact, AMs can cause mitochondrial dysfunction in both normal [53] and cancer cells [36,38,40,41,43,44,46,48,49,54–62], although rapidly dividing malignant cells with high energy demands are more sensitive to AMs [38,42,43,54,56,58–61,63,64] (Table 1).

Examples of AMs that suppress cancer by altering mitochondrial aerobic metabolism are provided below in more detail. Members of the Tetracycline and Chloramphenicol family of commonly used antibiotics inhibit both mitochondrial and bacterial translation [36,38,41,43,46,49,50,57–59,65]. Consistent with inhibition of mitochondrial translation, these antibiotics reduce the activities of OXPHOS complexes I, IV and V, which contain mitochondrially encoded subunits [41,46,59,60]. The antibiotic Bedaquiline, originally developed to eradicate aerobic bacteria, targets mitochondrial and bacterial ATP synthase [54,55]. Atovaquone, an antimalarial drug, is an inhibitor of OXPHOS complex III [62,66]. Ivermectin, a treatment for many types of parasites, inhibits complex I activity [42,44]. Pyrvinium pamoate, an anti-pinworm and anti-malarial medication, inhibits the mitochondrial NADH-fumarate reductase system, which is composed of complex I and II [39,45,67,68]. Itraconazole, a broad-spectrum anti-fungal agent, binds to mitochondrial protein voltage-dependent anion-selective channel 1 (VDAC1) and reduces the level of ATP production [69,70]. Additionally, other classes of antimicrobial agents such as quinolones, aminoglycosides, β-lactams and oxazolidinones also cause mitochondrial dysfunction in mammalian cells [53,71], although their effects on aerobic metabolism in cancer cells are barely investigated.

Remarkably, pre-clinical and clinical studies revealed that AMs such as Doxycycline, Tigecycline, Azithromycin, Chloramphenicol, Atovaquone and Bedaquiline can effectively target cancer stem cells (CSCs) of different types of cancers [36,54,57,72–74] (Table 1). For example in CML, Tigecycline targets the more oxidative, long-term leukemic stem cells that are hardly sensitive to Imatinib, a protein kinase inhibitor used in CML therapy, which targets more mature progenitors [51]. CSCs are associated with cancer initiation, progression, metastasis, tumor recurrence and drug resistance. Interestingly, CSCs have a high level of reliance on mitochondrial function [73–77]. For example, breast cancer-derived CSCs express an abundance of mitochondrial proteins involved in beta-oxidation, ketone body metabolism, mitochondrial biogenesis, the stress response to hypoxia, and inhibition of autophagy/mitophagy [74,77]. Interestingly, Farge et al. reported that an OXPHOS-

dependent energetic flexibility may be more responsible for chemoresistance rather than cellular quiescence or stage of maturity of CSCs. Based on *in vitro* and *in vivo* findings, chemoresistant AML cells showed high OXPHOS status compared to AML chemosensitive cells. In this context, Tigecycline sensitized high OXPHOS AML cells to the chemotherapy [50].

In conclusion, AMs are promising as part of a multimodal treatment regimen to improve the efficacy of classic anticancer therapies and to overcome CSC-based drug resistance. Combinations of AMs can sensitize cancer cells and CSCs to classic chemo or radiation therapies [36,41,43,58,66,74]. Although most data support the potent anticancer mechanisms of AMs, caution is required. Some clinical studies have shown associations between certain AMs and increased cancer risk, likely due to altered organ microbiota, attenuated immune surveillance and increased inflammation [79–82].

3 Antidiabetic drugs

Metformin (*N,N*-dimethylbiguanide) is an inexpensive generic drug and one of the most commonly used therapies for type 2 diabetes. Indeed, it accounts for around 120 million prescriptions per year worldwide. Its long track record of tolerability and known pharmacokinetics assure an excellent safety profile [83].

The antidiabetic effect of Metformin derives from its capacity to lower the blood glucose concentration by (i) inhibiting hepatic gluconeogenesis [84], (ii) improving insulin sensitivity in muscle and (iii) lowering the free fatty acid concentration in plasma [85].

A retrospective study suggests Metformin may reduce cancer mortality [86]. Different metabolic pathways are involved in the antitumorigenic effects of Metformin. Metformin leads to activation of AMP-activated protein kinase and inhibition of mammalian target of rapamycin, which results in inhibition of cell proliferation [87]. Moreover, Metformin lowers the blood concentration of insulin and insulin-like growth factor 1; the latter factor is often involved in tumor progression [87,88].

Another promising feature of Metformin is its capacity to target OXPHOS [89]. Evidence suggests Metformin may exert its anti-diabetic effects by targeting complex I of the mitochondrial respiratory chain [90]. Indeed, new studies show that Metformin inhibits the activity of complex I in a wide range of cancers [91–95] (Table 2). Moreover, Metformin reduces the oxygen consumption in different cancer models [91–94,96–99] (Table 2), likely through complex I inhibition. Similarly, ATP production is reduced by Metformin in a broad range of cancers [94,98,100,101]. In other cases, changes in the expression levels of complex I transcripts [102,103], and a lower NADH/NAD ratio were reported [99]. Recent findings suggest that the antiproliferative effect of Metformin is determined by the metabolic environment of the tumor, which can dramatically alter the sensitivity to Metformin [99]. Overall, the most common effects of Metformin on cancer progression are reduced tumor growth and higher apoptotic rate (Table 2).

Other biguanides have also shown anticancer effects. For example, Phenformin is considerably more potent than Metformin in abrogating the electron transport chain in

leukemia cells [104]. However, Phenformin has been withdrawn from clinical use because it can cause severe lactic acidosis, and several fatal cases have been reported [105]. For this reason, studies of its anticancer effects have waned. In colorectal cancer, Phenformin inhibits complex I and oxygen consumption, and increases cancer cell radiosensitivity [106]. Phenformin has also been shown to reduce tumor growth in cancer models characterized by OXPHOS deficiency [107]. Moreover, Phenformin and Oxamate, an inhibitor of lactate dehydrogenase, synergistically decrease respiration and ATP production. Likewise, cell and tumor growth are inhibited by this drug combination [108].

Canaglifozin, another antidiabetic drug, inhibits complex I and cell growth in prostate and lung cancer and it has a synergetic effect with radio- and chemo-therapy [109].

Pioglitazione, also targets mitochondria, inhibits oxygen consumption and shows an anti-proliferative effect in combination with the glycolysis inhibitor 2-deoxyglucose (2DG) [110].

In summary, antidiabetic drugs suppress tumor growth in a broad range of cancer models by targeting mitochondrial complex I (Table 2). For this reason, these drugs could potentially play a primary role in a multi-target metabolic treatment strategy to increase the efficacy of standard therapies or reduce their side effects through a low-dose regimen approach.

4 Classic antitumor agents

Mitochondria can promote or negate the anticancer effects of many commonly used chemotherapeutic drugs. For example, they are essential for exploiting the pro-apoptotic effects of certain drugs, but they are sometimes responsible for the development of drug resistance. In this part of the review, we focus on antitumor agents that specifically target mitochondrial OXPHOS or biogenesis (Table 3).

For decades cisplatin (CPT) has been widely used for the treatment of different types of cancer. In isolated rat mitochondria, CPT induced increased state 2 and 4 respiration [111]. In different gastrointestinal cancers, CPT interferes with mitochondrial bioenergetics by increasing the permeability of the inner mitochondrial membrane, promoting mitochondrial uncoupling, and decreasing OXPHOS function [112]. Along these same lines, rats treated with a single dose of CPT showed a reduction of state 3 respiration and inhibition of complex I and ATP synthase activity [113].

Doxorubicin (DOX) is one of the most effective and widely used anticancer drugs. Its efficacy could be even higher, but the clinical dosage is limited due to the development of delayed, cumulative and dosage-dependent cardiotoxicity [114,115]. DOX has high affinity for cardiolipin, an inner mitochondrial membrane phospholipid, resulting in an elevated concentration of the drug in mitochondria [116]. Moreover, DOX intercalates into mtDNA, causing disruption of genes coding for subunits of OXPHOS complexes [117]. The main cause of the DOX-associated cardiotoxicity is the overproduction of ROS by cardiac mitochondria, coupled with mitochondrial membrane depolarization and mitochondrial dysfunction. In general, treatment with DOX has been associated with decreased expression of some OXPHOS proteins, or with OXPHOS defects, and increased

mitochondrial-mediated apoptosis [114,118]. Interestingly, a recent *in vitro* study showed that preconditioning of cardiomyoblasts with a single nanomolar exposure to DOX induced a beneficial mitochondrial adaptation. The preconditioned cells were less susceptible to DOX toxicity when treated with a second, higher dose of DOX, compared to non-pretreated cells. Nine days after the nanomolar DOX administration, cells showed increased expression of some OXPHOS subunits, but not increased mitochondrial biogenesis [115].

In colon cancer cells treated with DOX, the expression profile of genes involved in mitochondrial energy metabolism was significantly changed. Interestingly, DOX effects were abrogated by complex I deficiency, but not complex II, suggesting that DOX binds to complex I to initiate the apoptotic process [119].

The multi-kinase inhibitor Sorafenib (SFB) is also able to inhibit mitochondrial respiration [120,121]. In neuroblastoma cells, SFB induced loss of mitochondrial transmembrane potential and destabilization of complex I [121]. SFB administered to four children with relapsed and refractory neuroblastoma showed antitumor effects in all four cases, without major adverse effects, although after a short stabilization time, tumor progression was again observed [122]. Addition of the glycolytic inhibitor 2-DG strongly increased the cytotoxicity of SFB in rat hepatocholangiocarcinoma and mouse melanoma cell lines, compared to cells treated with vehicle or SFB alone [120].

Tamoxifen (TAM) is a nonsteroidal anti-estrogenic compound that is widely used in the treatment of estrogen-dependent cancers, including estrogen receptor-positive breast cancer [123]. In breast cancer cells, TAM induced cytochrome c release from mitochondria, reduced the mitochondrial membrane potential and OXPHOS activity, and increased cell death [123]. In isolated rat liver mitochondria, TAM reduced OXPHOS activity and interfered with mitochondrial membrane polarization/depolarization fluctuations in a dose-dependent manner [124]. Moreover, TAM significantly inhibited complex I activity by targeting the flavin mononucleotide site of complex I [125]. In addition, TAM significantly inhibited DNA topoisomerase and mtDNA synthesis, leading to progressive depletion of mtDNA in the liver of mice treated for more than 12 days [126]. Interestingly, TAM-resistant breast cancer cells show a “dormant” profile, with high mtDNA depletion and a very low respiration, compared to TAM-sensitive breast cancer cells [127].

Recently, TAM has been conjugated with a tag that selectively delivers it to mitochondria (MitoTam). MitoTam has been proven to inhibit complex I and to be more effective in reducing the growth of breast cancer xenografts *in vivo* compared to TAM, especially of xenografts expressing high levels of human epidermal growth factor receptor 2, an oncogene associated with development of resistance and poor prognosis, and implicated in upregulation of complex I activity in breast cancer [128]. MitoTam kills cancer cells without inducing senescence, and increases the amount of cell death of senescent cells, compared to other chemotherapeutics. Usually, senescent cells, including senescent cancer cells, are able to escape the immune system; thus, MitoTam is a promising new molecule for the treatment of breast cancer, and it is currently entering a phase I clinical trial [129].

5 Other FDA-approved agents and some novel compounds

This section focuses on compounds which do not belong to the categories discussed above and which could be repurposed for cancer therapy based on their anti-mitochondrial effects. In addition, several novel compounds targeting mitochondrial bioenergetics are discussed.

Cancer growth and proliferation rely on intracellular iron availability, thus iron has been suggested as an anticancer target. Iron is also essential for mitochondria, which utilize this metal for synthesis of cofactors involved in the function of oxidation-reduction enzymes, and for DNA synthesis and repair [130,131].

Deferiprone (DFP) is an orally administered iron chelator used clinically for the treatment of thalassemia, Friedreich's ataxia and kidney disease. DFP is also able to reduce the proliferation and migration of metastatic and non-metastatic prostate cancer cells. Moreover, DFP lowered the respiration rate as well as the expression and activity of mitochondrial aconitase in these cells [131] (Table 4).

VLX600, a recently designed iron chelator, interferes with intracellular iron metabolism. Iron chelation leads to inhibition of mitochondrial respiration, bioenergetic failure and cell death. VLX600 enhances the glycolytic pathway and decreases respiration and oxygen consumption [48,132,133]. Inhibition of mitochondrial respiration with VLX600 reduced human colon carcinoma cell growth *in vitro*, and mouse colon tumor xenograft growth *in vivo*, both in cells with or without K-Ras mutation [48]. Moreover, VLX600 has been reported to inhibit the growth of breast cancer and colon carcinoma cells, both in 3D spheroids and in 2D monolayers, and to be more potent than other iron chelators [132,133] (Table 4). VLX600 was tested *in vivo* with other compounds that are routinely used for clinical management of colon carcinoma patients. Synergy was observed with irinotecan and oxaliplatin, whereas additive effects were shown in combination with 5-fluorouracil [132]. In gastrointestinal stromal tumors, VLX600 increased the antitumor effect of Imatinib [134]. A phase I clinical trial performed on different types of advanced refractory carcinomas showed that VLX600 is generally well tolerated [135].

Another metal with important functions in cancer cell proliferation and invasion is copper. Tetrathiomolybdate (TM) is a copper-chelating drug currently used in the treatment of copper overload disorder. TM has also shown antitumor effects by reducing both angiogenesis and mitochondrial ATP production. TM reduces mitochondrial respiration *via* inhibition of the copper-dependent mitochondrial activity of complex IV and degradation of Hypoxia-inducible factor 1α [136,137]. Prolonged copper depletion (by another copper chelator, triethylene tetramine) caused mitochondrial damage, oxidative stress and apoptosis in neuroblastoma cells *in vitro* [138]. Similarly, neuroblastoma cells treated with TM showed reduced mitochondrial respiration and cell proliferation [139]. Moreover, TM showed high specificity, selectively inhibiting neuroblastoma cell growth, and not the growth of normal fibroblasts and neuronal cells [139] (Table 4).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs worldwide (*e.g.* Aspirin, Ibuprofen, and Diclofenac). It is widely accepted that Aspirin, in particular, reduces the risk of developing cancer [140]. Besides the anti-

inflammatory properties of NSAIDs, based on their inhibition of prostaglandin-synthesizing cyclooxygenase 1 and 2 [141], these compounds are considered to possess antitumor activity by inducing apoptosis *via* mitochondrial dysfunction and ROS production [142–144]. However, only a few studies have looked in detail into the effects NSAIDs may have on mitochondrial respiration in cancer models. The results indicate that a reduction of mitochondrial bioenergetics triggering oxidative stress seems to be the underlying molecular mechanism contributing to the reduced cell proliferation and thus apoptosis caused by NSAIDs. For example, Diclofenac produced strong inhibition of complex I in colorectal adenocarcinoma cells, followed by Piroxicam, Aspirin, Indomethacin, and Ibuprofen [145]. More specifically, complex I inhibition due to Aspirin and Indomethacin has been linked to reduced ATP production and cell proliferation in liver cancer and colorectal adenocarcinoma, respectively [146,147]. Moreover, in BRAF V600E mutated melanoma cells Diclofenac reduced proliferation partly due to inhibition of respiration [148]. However, the potency of those NSAIDs to reduce complex I activity is positively correlated with gastrointestinal side effects, except in the case of Diclofenac, which is relatively safe in terms of gastrointestinal toxicity but very potent in inhibiting complex I [145]. Besides inhibiting complex I, Aspirin also affects complex IV activity, leading to reduced ATP production and consequently reduced cell proliferation of human hepatoma cells [147] (Table 4).

Cannabinoids are another group of compounds which have gained interest for their use in cancer treatment and which are currently used to relieve cancer-associated pain and chemotherapy-induced nausea and vomiting [149]. Besides their palliative effects, phytocannabinoids, synthetic cannabinoids, and enhancers of endogenous cannabinoids have all been reported to possess antitumor activity. The major anti-cancerogenic effects shown *in vitro* and *in vivo* include reduction of proliferation, induction of apoptosis and autophagy, inhibition of invasion and angiogenesis, enhancement of tumor immune surveillance, and improved chemosensitivity to anticancer drugs [149,150]. Regarding the induction of apoptosis, cannabinoids have been reported to induce mitochondrial damage and increase ROS production [151–153]. However, as in the case of NSAIDs, less is known about the direct effects of cannabinoids on mitochondrial respiration and bioenergetics in cancer cells. Whyte et al. investigated the effect of Δ9-tetra-hydrocannabinol (Δ9-THC) and Δ8-tetrahydrocannabinol (Δ8-THC) on mitochondrial respiration in an *in vitro* model of human oral squamous cell carcinoma with high resistance to chemotherapeutic drugs [154]. The respiration of Tu183 cells decreased dose-dependently after Δ9-THC and Δ8-THC treatment, with the former being more efficacious in inhibiting oxygen consumption. As a consequence of reduced respiration, Δ9-THC decreased cellular ATP levels by 64% compared to control cells (Table 4). A possible mechanism by which Δ9-THC interferes with mitochondrial respiration could be its potential to interfere with mitochondrial respiratory chain complexes, as shown in mitochondria isolated from rat heart and liver [151,152]. However, caution is needed with respect to Δ9-THC. Even though cannabinoids have a favorable drug safety profile, the current clinical use of Δ9-THC is limited to its psychoactivity [149]. Thus, nonpsychoactive cannabinoids, such as cannabidiol, could represent an alternative to Δ9-THC.

Anti-epileptic drugs as well as antidepressants are known to cause mitochondrial toxicity and thus can be contraindicated in patients with mitochondrial diseases [155]. Regarding cancer, however, the mitochondrial toxicity of those drugs could selectively kill cancer cells at certain concentrations. For instance, the anti-epileptic drug Valproate reduced respiration and led to dysfunctional mitochondrial ATP production in hepatocellular carcinoma cells accompanied by increased cell death [156]. The tricyclic antidepressants Clomipramine, Norclomipramine, Amitriptyline and Doxepin significantly reduced cellular respiration of astrocytoma cells [157] (Table 4).

Besides well-characterized and often prescribed drugs, like the ones described so far, two novel compounds, IACS-010759 and BAY 87-2243, have been claimed to be antitumor agents based on their ability to selectively inhibit complex I activity *in vitro* and *in vivo*. The former has been studied in preclinical models of OXPHOS-dependent acute myeloid leukemia (AML), low-glycolytic glioblastoma and neuroblastoma as well as OXPHOS enriched melanoma brain metastasis [158,159]. IACS-010759 robustly inhibited cell viability and induced apoptosis, most likely due to OXPHOS inhibition leading to energy depletion and reduced nucleotide biosynthesis. *In vivo*, treatment of AML and brain cancer with IACS-010759 resulted in potent inhibition of tumor growth at well-tolerated doses (Table 4). Based on these findings, the effects of IACS-010759 on relapsed/refractory AML and solid tumors are currently under investigation in phase I clinical trials. Another small molecule selectively targeting mitochondrial respiration is BAY 87-2243. Inhibition of mitochondrial complex I by BAY 87-2243 leads to decreased mitochondrial respiration, cellular ATP levels, and thus cell death in melanoma cells. Furthermore, BAY 87-2243 reduced tumor growth in several BRAF-mutant mouse xenografts and patient-derived melanoma mouse models [160] (Table 4). Another new small molecule inhibitor of OXPHOS is Gboxin, which interacts with OXPHOS complexes and thereby seems to inhibit complex V. It decreases growth of glioblastoma cells *in vitro* and *in vivo*. Furthermore, a wide range of cancer cell lines were Gboxin-sensitive whereas non tumor cells were not affected. Only one medulloblastoma cell line and primary mouse malignant peripheral nerve sheath tumor cells were Gboxin resistant. In various glioblastoma models treatment with Gboxin for over one month did not lead to obvious toxicity, making this novel compound a promising candidate for metabolic targeting of a wide range of cancers [161].

6 Discussion

The broad variety of tumor entities and plethora of inter-individual differences highlight the importance of identifying therapies able to effectively target pathologies shared by numerous cancer types. Since many solid cancers exhibit the Warburg effect, metabolic therapies potentially could eradicate tumors regardless of their genetic background. Although, numerous studies have shown that drugs which interfere with mitochondrial function can have antitumor effects, it remains to be demonstrated whether drugs which increase mitochondrial function might also have beneficial effects on tumor therapy. It seems that many cancers have low but functional OXPHOS and are sensitive to changes (up or down) of mitochondrial energy metabolism. Therefore, it is not surprising that fenofibrates initially used for lowering blood lipid levels and known to increase mitochondrial biogenesis show antitumor properties [162,163]. The therapeutic efficacy of inhibitors of mitochondrial

energy metabolism might be explained by the fact that tumors frequently have low residual OXPHOS activity that can be further repressed in the tumor cells to deleterious levels by various drugs. However, increasing mitochondrial mass and concomitant OX-PHOS activity might influence drug resistance [164]. In addition, it is not clear if respiring tumors or tumors with high metabolic flexibility, as for example subgroups of melanomas, are prone to inhibition of aerobic mitochondrial energy metabolism [15,17,165,166]. A recent study on brain melanoma metastasis indicated that also cancer tissues with a high OXPHOS content can be targeted by OXOHOS inhibitors [159].

Some “old” and “new” drugs might be of special interest because of their widespread use and/or beneficial effects on the overall health of cancer patients. Long-term follow-up studies showed that regular daily Aspirin use reduces the incidence, distant metastasis and mortality of some cancers after approximately 5 years [167–169]. A “new” drug class that might be of special interest for cancer patients are cannabinoids. It is known that they can positively influence mood, appetite and pain [170], three factors which are very important in advanced-stage tumor patients [171]. A limitation of new compounds inhibiting OX-PHOS is that their safety still needs to be demonstrated in preclinical but also clinical studies. For example a clinical study with BAY 87-2243 in cancer patients was prematurely terminated due to the occurrence of adverse events (re-occurrence of the adverse event vomiting despite dose reduction and change in formulation of the compound; Clinical-Trials.gov Identifier: NCT01297530).

Regardless of the mode of downregulation of aerobic mitochondrial energy metabolism, complex I seems to be affected in almost all instances. Also, downregulation of mitochondrial biogenesis, replication, transcription and translation, and mtDNA deletion and depletion all can cause reduction of complex I. In addition, the supercomplex organization of the respiratory chain leads to the paradox that most complex III defects also cause secondary loss of complex I assembly and activity [172,173]. NDUFS1, a subunit of mitochondrial complex I can be cleaved by caspase 3. Therefore, complex I can play an important role in apoptosis [174]. The killer lymphocyte protease granzyme A accesses the mitochondrial matrix to cleave NDUFS3, an iron-sulfur subunit of the NADH:ubiquinone oxidoreductase complex I [175]. Natural killer lymphocytes represent the first line of defense against tumor cells [176]. Low levels of complex I and complex I defects seem to confer a growth advantage and anti-apoptotic state on tumor cells; however, total knock down of complex I with the reported drugs seems to be deleterious to tumor cells.

The treatment with OXPHOS inhibitors might not only target cancer cells but also cancer associated cells such as immune cells. For example, T-regulatory cells induce their OXPHOS in an acidic environment and thereby might promote immune tolerance during tissue injury and impair anti-cancer immunity [177]. In this way, cancers can hijack a physiologic mechanism of self-tolerance. Thus, OXPHOS inhibitors might exert their anti-proliferative effects *in vivo* by different mechanisms.

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7 Conclusion

Inhibition of aerobic mitochondrial energy metabolism represents an attractive therapeutic opportunity against cancer, and repurposing of “old” drugs in tumor therapy holds the potential to effectively kill a broad variety of tumor entities, especially when combined with classic therapeutics.

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Abbreviations

AM	antimicrobial therapeutic
AML	acute myeloid leukemia
AMP	adenosine monophosphate
ATP	adenosine triphosphate
BACH1	BTB and CNC homology1
CAFs	Cancer-associated fibroblasts
CPT	cisplatin
CSC	cancer stem cell
DFP	Deferiprone
DOX	Doxorubicin
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
mtDNA	mitochondrial deoxyribonucleic acid
NAD	nicotinamide adenine dinucleotide
NSAID	Non-steroidal anti-inflammatory drug
OXPHOS	oxidative phosphorylation
PCa	prostate cancer
PTEN	Phosphatase and tensin homolog
RNA	ribonucleic acid
ROS	reactive oxygen species

SFB	Sorafenib
TCA	tricarboxylic acid
TAM	Tamoxifen
TM	Tetrathiomolybdate
VDAC1	voltage-dependent anion-selective channel 1
2DG	2-deoxyglucose
Δ9-THC	Δ9-tetrahydrocannabinol
Δ8-THC	Δ8-tetrahydrocannabinol

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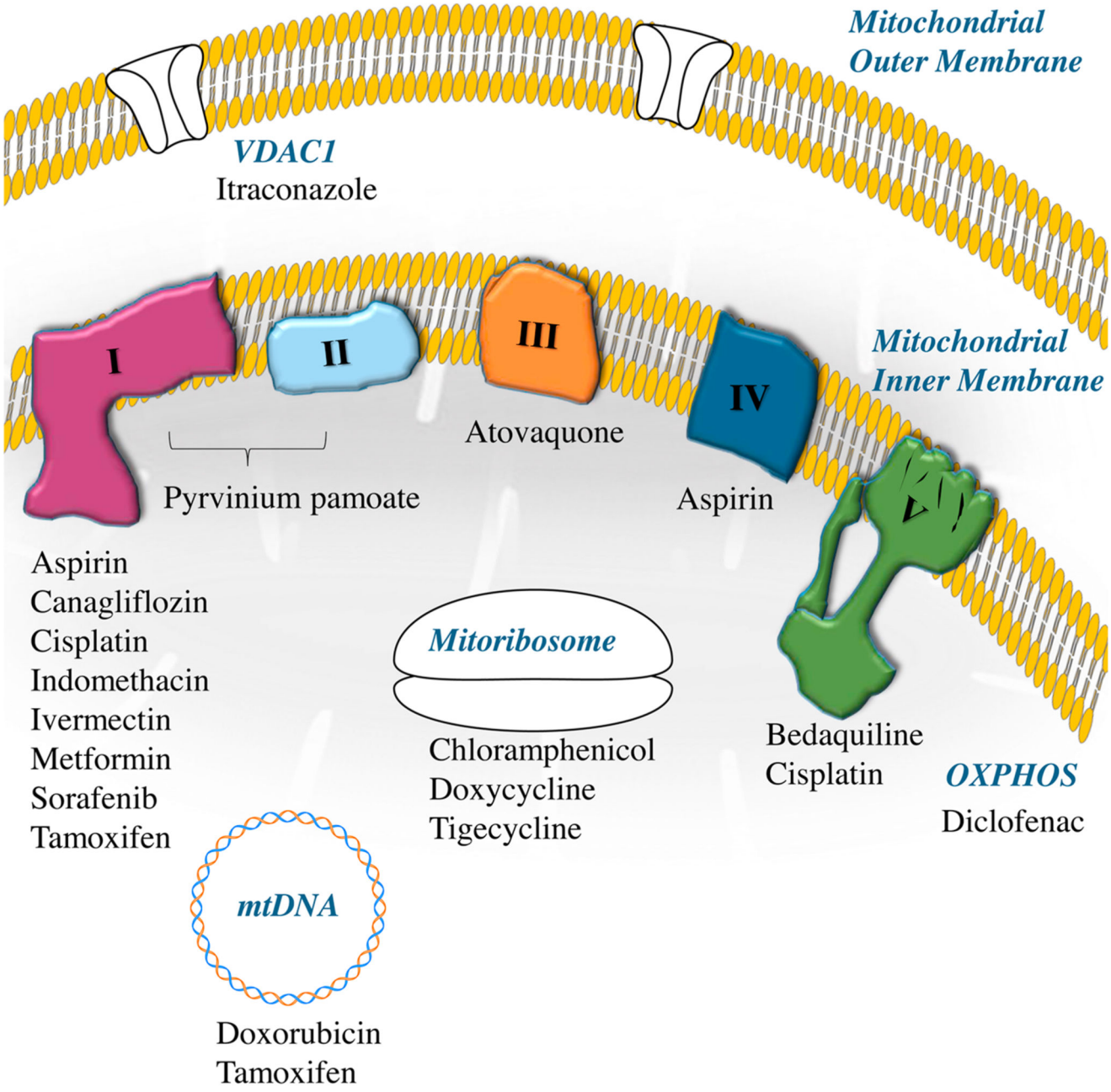

Fig. 1.

Targeting mitochondrial aerobic metabolism by FDA-approved agents for cancer treatment. Abbreviations: I, Complex I; II, Complex II; III, Complex III; IV, Complex IV; V, Complex V. OXPHOS, oxidative phosphorylation; mtDNA, mitochondrial DNA; Mitoribosome, mitochondrial ribosome; VDAC1, voltage-dependent anion-selective channel 1.

Table 1

Effects of FDA-approved anti-microbial agents on mitochondrial aerobic metabolism of cancer cells in *in vitro*, preclinical and clinical studies.

Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
		Atovaquone		
Breast	*In vitro*	↓ Complex III, ↓ respiration, ↓ ATP production, ↓ MIT mass	↓ CG & CSCs	[62]
Squamous cell carcinoma, colon, lung & pharynx	*In vitro*/*in vivo* + /- radiation treatment	↓ Complex III, ↓ respiration	↓ CG & TG, ↑ sensitization to radiation	[66]
		Bedaquiline		
Breast	*In vitro*	↓ Respiration, ↓ ATP production	↓ CSC propagation & survival, a little or no effect on viability of cancer / normal cells	[54]
Lung	*In vitro*/*in vivo*	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[55]
		Chloramphenicol		
Multiple myeloma	*In vitro*	↓ ATP production	↓ CG, ↑ apoptosis	[56]
		Doxycycline		
Breast	*In vitro* +/- chemotherapy	↓ MIT biogenesis	↓ hypoxic CSCs, ↑ sensitization to chemotherapy	[74]
Breast	*In vitro* +/- radiation treatment	↓ Protein synthesis, ↓ respiration & ATP production	↑ sensitization CSCs to radiation	[36]
Breast	Clinical	No change in level of MIT marker	↓ Stemness markers, no difference in level of proliferation	[72]
Cervical	*In vitro*/*in vivo*	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[35]
Glioblastoma	*In vitro* / *in vivo* +/- chemotherapy	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ sensitization to chemotherapy	[58]
Glioma	*In vitro*	↓ Protein synthesis, ↓ respiration	↓ CG	[65]
		Itraconazole		
Glioblastoma	*In vitro*/*in vivo*	Interaction with VDAC1	↓ CG & TG	[70]
		Ivermectin		
Chronic myeloid leukemia	*In vitro* / *in vivo*	↓ Complex I activity, ↓ respiration	↓ CG & TG, ↑ apoptosis	[42]
Glioblastoma	*In vitro*/*in vivo*	↓ Complex I, ↓ respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[44]
Renal	*In vitro*/*in vivo*	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[64]
		Pyrvinium pamoate		
Breast, pancreatic, colon & cervical cancer	*In vitro*/*in vivo* +/- glycolysis inhibitor	↓ ATP production	↓ CG & TG, ↑ apoptosis	[39]
Lymphoma	*In vitro*	↓ Complex I, ↓ respiration, ↓ ATP production	↑ Apoptosis	[47]
Phase-chronic myeloid leukemia	*In vitro* / *in vivo* +/- targeted therapy	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ effect of targeted therapy	[45]
Myeloma / erythroleukemia	*In vitro*	↓ Complex I, ↓ respiration, ↓ ATP production	↓ CG	[67]
		Tetracycline analogues (doxycycline & COL-3)		

Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
Adenocarcinomas of alveolar, pancreatic & colon	*In vitro*	↓ MIT protein synthesis, ↓ complex IV activity	↓ CG, higher cytotoxicity of COL-3 compared to doxycycline	[59]
		Tigecycline		
Acute lymphoblastic leukemia	*In vitro* / *in vivo*+/- chemotherapy	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis, ↑ sensitization to chemotherapy	[52]
Acute myeloid leukemia	*In vitro* / *in vivo*	↓ MIT protein synthesis, ↓ respiration, ↓ complex I & IV activity	↓ CG & TG, targeting leukemia stem cells	[60]
Acute myeloid leukemia	*In vitro* / *in vivo*+/- chemotherapy	↓ MIT mass, ↓ respiration	↓ CG & TG, ↑ apoptosis, ↑ sensitization to chemotherapy	[50]
Chronic myeloid leukemia	*In vitro*	↓ MIT protein synthesis, ↓ respiration	↓ CG, ↑ apoptosis, overcoming drug resistance	[38]
Chronic myeloid leukemia	*In vitro*/*in vivo* +/- targeted therapy	↓ MIT protein synthesis, ↓ respiration	↓ CG, ↓ TG in combination with protein kinase inhibitor	[51]
OXPHOS-Large B-cell lymphoma	*In vitro*	↓ Complex I, ↓ respiration	↓ CG	[49]
Lung	*In vitro/in vivo*	↓ Respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[61]
Ovarian	*In vitro* / *in vivo* + /- chemotherapy	↓ MIT protein synthesis, ↓ respiration	↓ CG & TG, ↑ sensitization to chemotherapy	[43]
Retinoblastoma	*In vitro*/*in vivo*	↓ MIT protein synthesis, ↓ respiration, ↓ activities of complex I & IV, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[46]
Renal cell carcinoma	*In vitro*/*in vivo* +/- chemotherapy	↓ MIT protein synthesis, ↓ activities of complex I, IV & V	↓ CG & TG, ↑ sensitization to chemotherapy	[41]

Abbreviations: CG, Cell growth; CSC, Cancer stem cell; MIT, mitochondrial; TG, Tumor growth; VDAC1, voltage-dependent anion-selective channel 1. Signs: &, and; ↓, Decrease; ↑, Increase; +, In combination with; -, Without.

Table 2

Effects of FDA-approved anti-diabetic agents on mitochondrial aerobic metabolism of cancer cells in *in vitro*, preclinical and clinical studies.

Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
		Canagliflozin		
Prostate & lung	*In vitro*/*in vivo* +/- radiation & chemotherapy	↓ Complex I activity, ↓ ATP production	↓ CG	[109]
		Metformin		
Breast	*In vitro*	↓ Complex I activity, ↓ respiration	↓ CG	[92]
Breast, gastric & osteosarcoma	*In vitro*/*in vivo* +/- glycolysis inhibitor	↓ ATP, ↓ expression of components of complex I	↑ Cell death, ↓ TG in combination with glycolysis inhibitor	[101]
Breast	Clinical	↑ OXPHOS relevant gene transcription in a subset of patients	Resistant to metformin treatment in subset of patients with OXPHOS transcriptional response	[102]
Colon	*In vitro*/*in vivo*	↓ Complex I activity, ↓ respiration	↓ CG & TG	[93]
Leukemic cells	*In vitro*/*in vivo*	↓ Complex I activity, ↓ respiration, ↓ ATP production	↓ CG & TG, ↑ apoptosis	[94]
Lung, Colon	*In vitro*	↓ ATP production, ↓ respiration	↓ CG	[98]
Ovarian	*In vitro/in vivo*/clinical	Alteration in MIT metabolism in patient and mouse ovarian tumors, ↓ ATP	↓ Cell viability, ↓ TG	[100]
Ovarian	*In vitro*	↓ Respiration	↓ CG	[97]
Prostate	*In vitro* +/- glycolysis inhibitor	↓ Complex I activity	↑ Apoptosis & arrest of cell cycle	[95]
Prostate	*In vitro*/*in vivo*	↓ Respiration	↓ CG	[91]
Thyroid	*In vitro*/*in vivo*	↓ Respiration	↓ TG	[96]
Breast, cervical, lung, bone	*In vitro*/*in vivo*	↓ Complex I activity, ↓ respiration	↓ CG, ↓ TG	[99]
		Pioglitazone		
Prostate	*In vitro* +/- glycolysis inhibitor	↓ Respiration	↓ CG, ↑ efficacy + glycolysis inhibitor on spheroid model	[110]

Abbreviations: CG, Cell growth; MIT, mitochondrial; TG, Tumor growth. Signs: &, and; ↓, Decrease; ↑, Increase; +, In combination with; -, Without.

Table 3

Effects of FDA-approved antitumor agents on mitochondrial aerobic metabolism of cancer cells in *in vitro* and preclinical studies.

Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
		Cisplatin		
Gastrointestinal cancer	*In vitro*	OXPHOS uncoupling, ↑ state 2, 3 & 4 respiration	↑ Apoptosis	[112]
		Doxorubicin		
Colon	*In vitro*	Modulation OXPHOS genes	↑ Apoptosis	[119]
		Sorafenib		
Neuroblastoma	*In vitro*	Destabilization of complex I, ↓ respiration	↑ Apoptosis	[121]
		Tamoxifen		
Breast	*In vitro*/*in vivo* mitochondrially targeting tamoxifen	↓ Complex I	↓ TG, ↑ general cell death	[128]

Abbreviations: TG, Tumor growth. Signs: &, and; ↓, Decrease; ↑, Increase.

Table 4

Effects of further FDA-approved agents and some novel compounds on mitochondrial aerobic metabolism of cancer cells in *in vitro* and preclinical studies.

Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
Antiepileptic drugs				
		Valproate		
Liver	*In vitro*	↓ Respiration, ↓ ATP production	↓ CG	[156]
		Cannabinoids		
		Δ9 -tetrahydrocannabinol and Δ8 -tetrahydrocannabinol		
Oral squamous cell carcinoma	*In vitro*	↓ Respiration, ↓ ATP production	↑ Apoptosis	[154]
		Chelating agents		
		Deferiprone		
Prostate cancer	*In vitro*	↓ Respiration, ↓ ATP production	↓ CG & cell migrations	[131]
		Tetrathiomolybdate		
Endometrial adenocarcinoma	*In vitro* +/- glycolysis inhibitor	↓ Complex IV activity, ↓ respiration	No effect on CG without combination with glycolysis inhibitor	[136]
Neuroblastoma	*In vitro* +/- Akt kinase inhibitor	↓ Respiration, ↓ ATP production	↓ CG	[139]
		VLX600		
Colon carcinoma	*In vitro/in vivo* (+ /-K-Ras mutation)	↓ Respiration	↓ CG & TG in combination with tigecycline	[48]
Colon carcinoma	*In vitro/ex vivo/in vivo*	↓ Respiration, ↓ compelex I, II & IV activities	↓ CG, ↓ TG	[132]
Colon carcinoma & breast cancer	*In vitro*	↓ Respiration, ↓ complex IV activity	↓ CG	[133]
Gastrointestinal stromal tumor Non-steroidal anti-inflammatory drugs (NSAIDs)	*In vivo* ± Imatinib	↓ Respiration	↓ CG & TG, ↑ apoptosis	[134]
		Aspirin		
Liver	*In vitro*	↓ Complex I & IV activities, ↓ ATP production	↓ CG	[147]
		Diclofenac		
Melanoma	*In vitro* +/- vemurafenib	↓ Respiration	↓ CG	[148]
		Indomethacin		
Colorectal adenocarcinoma	*In vitro*	↓ Complex I activity, ↓ ATP production	↓ CG	[146]
		Novel compounds		
		BAY 87-2243		
Melanoma	*In vitro/in vivo*	↓ Complex I activity, ↓ ATP production	↓ CG, ↓ TG	[160]

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Type of cancer	Type of study	Effects on mitochondrial aerobic metabolism	Effects on cancer progression	Ref
		IACS-010759		
Acute myeloid leukemia, low glycolytic glioblastoma & neuroblastoma	*In vitro/in vivo*	↓ Complex I activity, ↓ ATP production	↓ CG, ↓ TG, ↑ survival	[158]
Brain metastasis of MAPK inhibitor-resistant intracranial melanoma	*In vivo*		↑ Survival; ↓ brain metastasis	[159]
		Gboxin		
Glioblastoma	*In vitro*/*in vivo*	↓ Respiration, ↓ complex V activity	↓ CG, ↓ TG, ↑ survival	[161]

Abbreviations: CG, Cell growth; TG, Tumor growth. Signs: &, and; ↓, Decrease; ↑, Increase; +, In combination with; –, Without.