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Review

Mitochondrial metabolism and energy sensing in tumor progression☆

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ABSTRACT

Energy homeostasis is pivotal for cell fate since metabolic regulation, cell proliferation and death are strongly dependent on the balance between catabolic and anabolic pathways. In particular, metabolic and energetic changes have been observed in cancer cells even before the discovery of oncogenes and tumor suppressors, but have been neglected for a long time. Instead, during the past 20 years a renaissance of the study of tumor metabolism has led to a revised and more accurate sight of the metabolic landscape of cancer cells. In this scenario, genetic, biochemical and clinical evidences place mitochondria as key actors in cancer metabolic restructuring, not only because there are energy and biosynthetic intermediates manufacturers, but also because occurrence of mutations in metabolic enzymes encoded by both nuclear and mitochondrial DNA has been associated to different types of cancer. Here we provide an overview of the possible mechanisms modulating mitochondrial energy production and homeostasis in the intriguing scenario of neoplastic cells, focusing on the double-edged role of 5′-AMP activated protein kinase in cancer metabolism. This article is part of a Special Issue entitled Mitochondria in Cancer, edited by Giuseppe Gasparre, Rodrigue Rossignol and Pierre Sonveaux.

1. Introduction

In 1964, the pioneering studies of Hans A. Krebs indicated that adenosine monophosphate (AMP) levels may be a crucial factor in determining whether glycolysis or gluconeogenesis predominates in cell metabolism [1]. During the same period, Atkinson and coll. proposed that the fate of an intermediate metabolite towards energy-yielding, -demanding or -storing process may depend on the balance among concentrations of the adenine nucleotides [2]. In this study, the adenylate energy charge (AEC) was conceptualized as a quantitative parameter of the cell energy state regulating the intermediates flux through metabolic pathways [2]. AEC is defined by the effective concentrations of adenine nucleotides [(ATP) + 0.5 (ADP)]/[(ATP) + (ADP) + (AMP)] and ranges between 0.87 and 0.94 values for most of cells in metabolic steady state conditions [3]. Such values are reached through the balance between combustion of fuel sources to produce energy (catabolism) and ability to consume it to synthesize macromolecules (anabolism). AEC directly controls the switch between catabolic and anabolic pathways, since adenine nucleotides also act as allosteric modulators of specific metabolic enzymes (i.e. phosphofructokinase 1 and pyruvate kinase for glycolysis, pyruvate dehydrogenase, citrate synthase and α-ketoglutarate dehydrogenase for tricarboxylic acid (TCA) cycle; pyruvate carboxylase for anaplerotic reactions; fructose 1,6 bisphosphatase for gluconeogenesis; other enzymes involved in glycogen, fatty acid and nucleotides metabolism) [3]. Interestingly, mitochondria host most of these pathways providing a compartmentalized metabolic hub in communication with the rest of the cell. For a long time, it has been assumed that cellular adenine nucleotides levels were in a permanent steady state and that, consequently, AEC value was constant. However, this hypothesis was in contrast with the evidence that certain enzymes were regulated in response to changes in adenine nucleotide levels. Indeed, recent studies showed that adenine nucleotides concentrations are determined by oscillations and large local fluctuations, although the AEC value is usually maintained within a narrow physiological range [4]. Such balance

Abbreviations: ACSL3, Acyl-CoA synthase long chain family member 3; ADP, adenosine diphosphate; AEC, adenylate energy charge; AK, adenylate kinase; AMP, adenosine monophosphate; AMPK, AMP activated kinase; ANT, adenine nucleotide translocator; ATP, adenosine triphosphate; CaMKKβ, calmodulin-dependent protein kinase kinase β; CK, creatine kinase; CoA, coenzyme A; CPT1a, carnitine palmitoyltransferase 1a; Erk, extracellular signal–regulated kinase; $FADH_2$, reduced flavin adenine dinucleotide; FAO, fatty acid oxidation; FAS, fatty acid synthesis; Her2, human epidermal growth factor receptor 2; HIF1α, hypoxia inducible factor 1α; LKB1, liver kinase B1; mtDNA, mitochondrial DNA; mTORC1, mammalian Target Of Rapamycin Complex 1; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; OXPHOS, oxidative phosphorylation; PCr, phosphocreatine; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA, protein kinase A; PTEN, Phosphatase and tensin homolog; ROS, reactive oxygen species; Rsk, Ribosomal S6 kinase; TAK1, transforming growth factor-β activated kinase 1; TCA, tricarboxylic acid.

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permits a fine regulation of cell metabolism, leading to the activation of catabolism in order to prevent ATP depletion before a critical drop of AEC values and the generation of metabolic intermediates for anabolic reactions when AEC is close to 1 [5]. Since AEC is involved in the control of multiple essential pathways, the maintenance of energy homeostasis results critical for cell's fate in both physiological and pathological conditions. In this review, we will describe the mitochondrial contribution to energy production and homeostasis and how changes in AEC are perceived by specific sensing systems. In this frame, the role of 5′-AMP activated protein kinase in carcinogenesis and tumor progression will be revisited.

2. Energy homeostasis in non-cancer cells

In animal cells, ATP is mainly produced by glycolysis in the cytosol and by oxidative phosphorylation (OXPHOS) into the mitochondria, where complete glucose oxidation takes place. Glycolysis is a catabolic process that provides energy (ATP), reduced molecules (NADH) and metabolites feeding various anabolic pathways. Extracellular glucose is up taken into the cell through GLUT transporters and metabolized to pyruvate in the cytosol. The fate of the latter largely depends on cellular oxygen availability. Under normoxic conditions, glycolytic pyruvate enters into the TCA cycle and reduced equivalents (NADH and $FADH_2$) are generated to feed the OXPHOS activity for ATP production. Other catabolic pathways such as fatty acid oxidation (FAO) and amino acid degradation replenish TCA cycle with Acetyl-Coenzyme A (Acetyl-CoA) and pyruvate. The same pathways produce metabolic intermediates required for ATP-consuming reactions for the biosynthesis of amino acid, nucleotides, fatty acids and sugars [3]. When O_2 tension is low and OXPHOS is slowed down, pyruvate is mainly transformed into lactate through lactic fermentation that upon NADH oxidation restores the NAD^+ pool needed to drive glycolysis [3]. Mammalian OXPHOS system comprises five multiprotein complexes (complexes I to V) and two mobile electron carriers (ubiquinone and cytochrome *c*) embedded in the lipid bilayer of the inner mitochondrial membrane. Complexes I to IV allow the electron transfer from NADH and $FADH_2$ to molecular oxygen, while generating a proton gradient across the inner mitochondrial membrane that is dissipated to synthesize ATP by Complex V or F_1F_O ATPase (CV; EC 3.6.1.3) [6–8]. This enzyme is composed by two-coupled rotary motors: (i) the hydrophilic domain F_1 binds adenine nucleotides and Pi; (ii) the membrane-embedded hydrophobic F_O domain constitutes the ion-translocating portion. These domains are connected by a central and a peripheral stalk, being the former the key rotary element transferring energy from F_O to F_1 and *vice versa* [9]. Under peculiar conditions (i.e. lack of oxygen or dysfunctional respiratory chain), CV can also hydrolyze ATP acting as a proton pump and generating a transmembrane ionic gradient [8,10]. This process can be repressed by the protein IF_1 [11], a non-competitive unidirectional inhibitor of ATP hydrolysis, displaying no inhibitory activity on ATP synthesis in presence of a mitochondrial electrochemical gradient [8]. Indeed, the reversible inhibition of ATP hydrolase activity of CV is pH dependent and plays a crucial role in the presence of respiratory chain dysfunctions. Under this latter condition, cells must manage equilibrium between the maintenance of mitochondrial membrane potential, in order to prevent massive uncontrolled mitophagy, and to sustain a proper AEC avoiding an excessive consumption of glycolytic ATP. Beside the inhibition of ATP hydrolase activity, recent studies indicate that IF_1 can also suppress ATP synthesis activity of CV [12,13], being regulated also at transcription level in a tissue specific manner or through post-translational modifications such as acetylation, succinylation and phosphorylation [14]. These regulatory mechanisms link CV activity to the redox status of the cell, through mitochondrial sirtuins [15,16], and to the calcium signaling *via* protein kinase-A (PKA) [13]. In fact, PKA seems to play a critical role in the regulation of mitochondrial function being able to trigger the activity of respiratory complexes and to inhibit IF_1, thus allowing an efficient and coordinated ATP synthesis [17].

Newly synthesized ATP molecules are exchanged with cytosolic ADP and P_i across the inner mitochondrial membrane into the cytosol. A member of the solute carrier family named adenine nucleotide translocator (ANT) catalyzes the ATP/ADP transfer, whereas P_i is exchanged with OH^- *via* the phosphate transporter [18]. In humans, four ANT isoforms (ANT1-4) are present, with ANT3 expressed ubiquitously at low levels and the other isoforms in a tissue-specific manner [19]. Interestingly, ANT2 is specifically expressed either in undifferentiated cells or in tissues that are able to regenerate, and is considered a marker of cell proliferation [19]. ANT transporters catalyze the electrogenic and not energy dependent ATP^{4-}/ADP^{3-} exchange coupled to the OXPHOS activity and driven by the mitochondrial membrane potential. In presence of a functional OXPHOS system, the ADP/ATP ratio can be up to 100 fold smaller in the cytosol rather than that into the mitochondrial matrix. Conversely, when mitochondria are completely depolarized, ANT proceeds with a high activity transferring at equal rates ADP and ATP in both directions [20]. Mitochondrial ATP translocated into the cytosol must be available for anabolic reactions, although in high energy demanding cells the diffusion rates of ATP or ADP may be insufficient to distribute ATP properly in different cell compartments [21]. To overcome this deficiency, cells evolved an energy buffering strategy based on phosphocreatine-creatine kinase (PCr-CK) and adenylate kinase (AK) systems, connecting ATP production processes (glycolysis and OXPHOS) with subcellular sites of ATP utilization [22]. In particular, AK catalyzes the interconversion of the adenine nucleotides allowing their functional distribution in intracellular compartments [23]. This biochemical step reaction is crucial to induce relatively large changes in AMP/ATP ratio that regulates the activity of key enzymes in metabolism and mediates intracellular AMP signaling by 5′-AMP activated protein kinase (AMPK) [23].

3. Energy sensing and AMPK

In order to maintain the physiological AEC value and to face changes in energy homeostasis (ADP/ATP and AMP/ATP ratios) cells have developed a sensitive molecular system that integrates multiple upstream inputs and regulates enzymes activity and transcriptional responses. The core enzyme of such system is AMPK, an evolutionarily conserved kinase whose activity is regulated in response to the variations of energy charge [24]. In mammals, AMPK is a heterotrimeric protein composed of one catalytic (α1 or α2) and two regulatory subunits (β1 or β2 and γ1, γ2 or γ3), leading to the generation of 12 possible combinations of the enzyme. Very little is known about these different isoforms, although there are some indications that they may have various functions, different subcellular localizations and may be subjected to specific regulation [25]. The overall function of AMPK is to restore AEC when intracellular levels of ATP drops down, as in response to mitochondrial dysfunctions or stress conditions. When activated, AMPK promotes catabolic processes, i.e. glucose uptake, glycolysis, FAO, mitochondrial biogenesis and OXPHOS and autophagy, while preventing ATP consuming anabolic biosynthetic reactions (Fig. 1) [24]. Hence, this sensor is a molecular switch orchestrating the overall metabolic status of the cell and its activation must be tightly controlled. In fact, phosphorylation of the conserved Thr172 within the activation loop of the kinase domain is required for AMPK activation. At least three different mechanisms of Thr172 phosphorylation have been described: (i) the AMP-dependent phosphorylation *via* liver kinase B1 (LKB1) (ii) the calcium-dependent phosphorylation *via* the calmodulin-dependent protein kinase kinase β (CaMKKβ); (iii) hormonal activation *via* transforming growth factor-β-activated kinase-1 (TAK1) (Fig. 1) [26]. The most common mechanism of inactivation of AMPK consists in the dephosphorylation of Thr172 by upstream phosphatases, although several other emerging regulation mechanisms have been recently described including inhibitory phosphorylation, ubiquitination, oxidation and subcellular compartmentalization (Fig. 1) [26]. Lastly, AMPK is allosterically regulated by AMP and, to a lesser extent, by ADP, which can bind the CBS domain

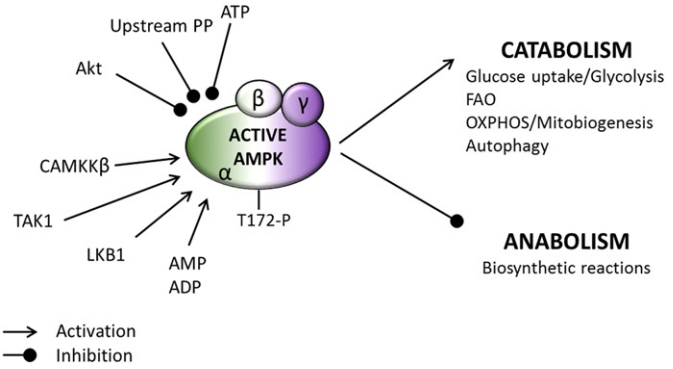

Fig. 1. Mechanisms of AMPK regulation and its downstream pathways. AMPK is a heterotrimeric kinase formed by one catalytic subunit (α) and two regulatory subunits (β and γ). The phosphorylation of the conserved Thr172 is required for AMPK activation and can be mediated by LKB1, CaMKKβ and TAK1. Dephosphorylation of Thr172 provided by upstream protein phosphatases (PP) or phosphorylation of other regulatory residues by Akt switch off this enzyme. Allosteric activation is mediated by AMP, whereas ATP binding suppresses AMPK activation. Active AMPK is required to sustain a catabolic metabolism while the biosynthetic reactions are inhibited in order to maintain a functional energetic balance.

of the γ subunit. Such binding elicits also the LKB1-mediated phosphorylation of Thr172 and protects the same residue from dephosphorylation, concurring to a most stable activation of the kinase (Fig. 1) [24]. Taking into account the central role of AMPK in the modulation of metabolic pathways that concur to the cell energetic rewiring under peculiar stress conditions, it is not surprising that this protein has been widely linked to a variety of pathological context, including cancer [26].

4. Metabolic reprogramming of cancer cells

One of the hallmark of neoplastic cells is their ability to reprogram metabolism in response to the abnormal requirement of building blocks necessary for uncontrolled cell proliferation and to adapt to the ever-changing microenvironment in which tumors grow [27]. The classical example of a rewired metabolic pathway in cancer is the Warburg effect or aerobic glycolysis [28]. It is well known that cancer cells display an increased glycolytic flux regardless oxygen availability, which confers a significant growth advantage and promotes tumor progression, invasion and metastatic potential. The initial hypothesis of Warburg stated that enhanced glycolysis may derive from a mitochondrial dysfunction, leading to the diffuse idea that neoplastic cells generate their ATP almost exclusively from glycolytic reactions [29]. The Warburg effect definition has been now revisited, since it has been demonstrated that it can be triggered by activation of oncogenes, such BRAF and c-Myc [30,31], loss of tumor suppressors like p53 [32], and activation of the mTORC1 pathway [33]. Nevertheless, it has become evident that mitochondrial function, including ATP production, is required for cell proliferation and tumor progression [34], at least in specific phases such as adaptation to nutrient and oxygen deprivation [35,36], and OXPHOS dependent tumors have been identified [37]. These data clearly indicate that the coexistence of glycolytic-dependent lactate production and functional TCA cycle and OXPHOS activity offers a selective metabolic advantage for cancer cells, providing energy and precursors for anabolic pathways and permitting an unrestrained cell proliferation. Moreover, neoplastic cells are also able to replenish TCA cycle and OXPHOS through FAO and anaplerotic reactions, such as glutaminolysis and pyruvate carboxylation (Fig. 2) [38]. In particular, glutaminolysis feeds the TCA cycle of α-ketoglutarate which, in turn, undergoes reductive carboxylation, providing citrate and Acetyl-CoA that may be used for fatty acid synthesis (FAS; Fig. 2) under stress conditions, such as defective OXPHOS or TCA cycle [39], hypoxia [40,41] or in specific cell types [42,43]. On the other hand, FAO can replenish TCA cycle providing a remarkable amount of "fuel" for ATP synthesis and sustaining the redox potential through NADPH generation [44]. It is interesting to note that FAO has been found critical for maintenance of leukemia initiating cells pool [45] and contributes to glioblastomas and ovarian cancer to feed aerobic respiration under nutrient deprivation [46,47]. Moreover, it has been shown that KRAS regulates fatty acid uptake and FAO through Acyl-CoA synthetase long-chain family member 3 (ACSL3) [48] and that certain Ras-driven cancer cells scavenge lipids to support ATP production under hypoxic stress [49]. Downregulation of key FAO enzymes, such as ACSL3 and carnitine palmitoyltransferase 1a (CPT1a) hampered tumor growth [48,50], indicating that FAO can be envisioned as a target for novel therapeutic strategies. However, as for many others metabolic processes, it must take into account that a balance between FAO and FAS must be maintained in the context of tumor growth, since lipids are essentia l for membrane generation in daughter cells during unrestricted proliferation. Based on these findings, it comes to light that cancer initiation, development, and/or growth strongly rely on metabolic shifts that enable the generation of biosynthetic precursors and ATP.

5. Mitochondrial energy homeostasis in cancer cells

5.1. Energy production – F_1F_O ATPase or Complex V

Several studies pointed out that mitochondrial CV may be a major player in carcinogenesis and tumor progression. Indeed, CV has a pivotal role not only in mitochondrial ATP synthesis, but is also strictly involved in the maintenance of mitochondrial membrane potential through its ATP hydrolytic function, in the shaping of mitochondrial *cristae* and in the regulation of the final phases of apoptosis events, being part of the mitochondrial permeability transition pore [51]. A first link between the modulation of CV activity and tumor progression is represented by the occurrence of somatic mutations in mitochondrial DNA (mtDNA) genes *MT-ATP6* and *MT-ATP8*, encoding for two subunits embedded in the inner mitochondrial membrane and belonging to the F_O domain of the enzyme. Such mutations have been reported in different types of cancer (Table 1) but their functional significance has been only partially elucidated. In fact, similar to mutations hitting other mtDNA genes, nucleotide variants in *MT-ATP6* and *MT-ATP8* genes effect on enzyme function depends on mutation type and mutant load, being mtDNA mutations subjected to the threshold effect [52]. Moreover, it is now well established that highly damaging somatic mtDNA mutations are subjected to negative selection in tumors [53], with the only remarkable exception of oncocytomas [54]. In this regard, only 4/45 indels have been found in *MT-ATP6* and *MT-ATP8* genes, and most of the mutations are missense or silent variants (Table 1), implying a mild impact on ATPase activity and not on its structure. Functional studies on the effect of such mutations placed in the context of cancer cells are still missing. To date only the well-characterized pathogenic m.8993T>G/*MT-ATP6* mutation, known to repress ATP synthesis and to trigger mitochondrial reactive oxygen species (ROS) production, has been investigated in prostate cancer cell background [55]. Homoplasmic mutant cells were more tumorigenic in immunodeficient mice and into the bone microenvironment, indicating an active role of this mutation in prostate cancer etiology and metastasis formation [55,56]. However, the m.8993T>G/*MT-ATP6* mutation has never been reported in tumor samples so far, suggesting that it may be counter-selected in patients, most likely because of its severe detrimental effect on CV activity. Despite the fact that the severity of mtDNA nucleotide variants may be attenuated in a condition of heteroplasmy, mutations remains fixed genetic lesions that seem to not satisfy the required metabolic plasticity of cancer cells. Moreover, it is reasonable to hypothesize that a minimum function of the CV is required for cell survival and that the modulation of its subunits expression may permit a more controlled regulation of ATP production. Indeed, the catalytic β subunit (ATP5B protein) of the enzyme has been found downregulated in some types of cancer [57–59] and it has been correlated with poor prognosis in terms of invasiveness,

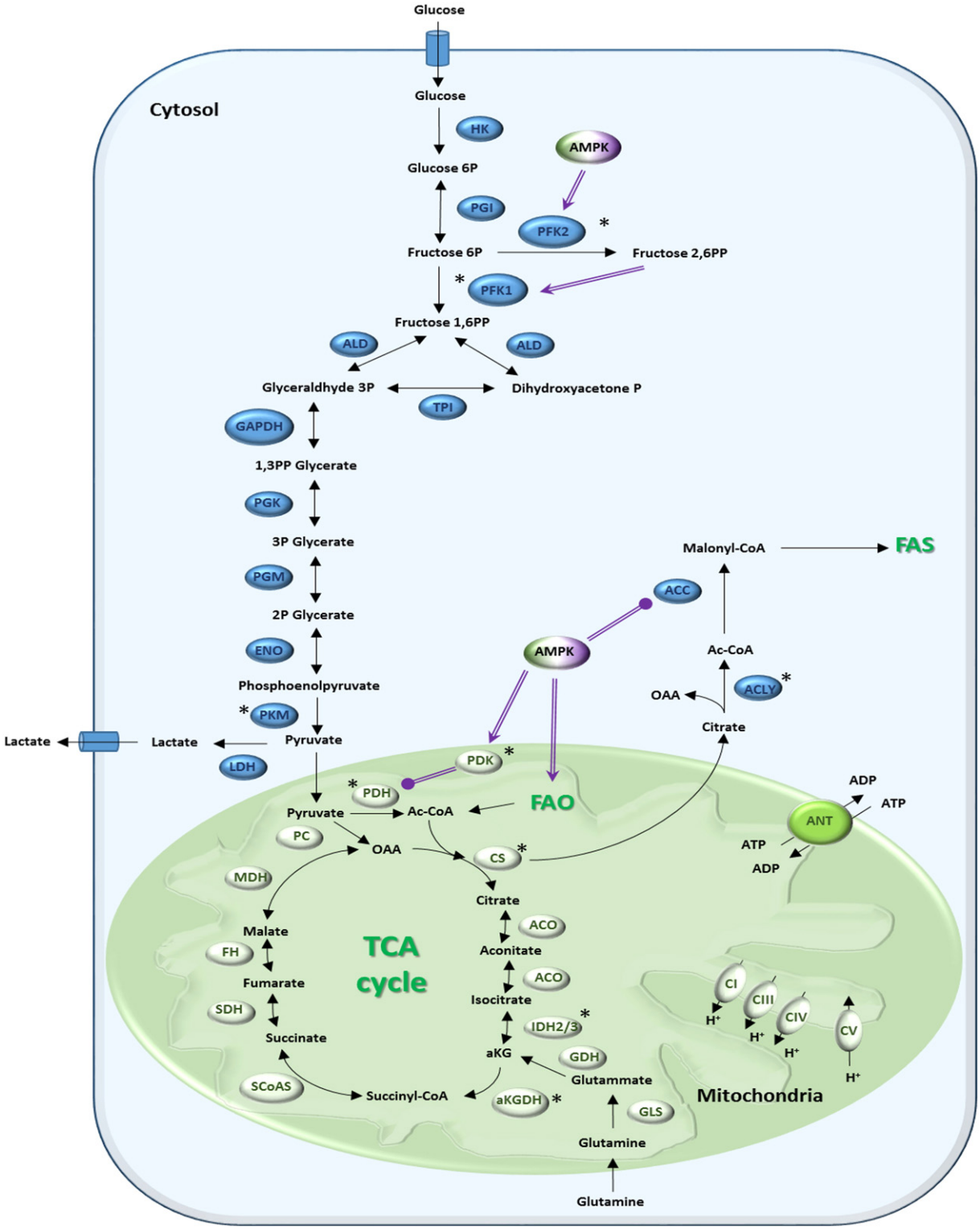

Fig. 2. Metabolic reactions modulated by AMPK activation and energy charge. Several crucial enzymes of glycolysis, FAO, FAS and TCA cycle are tightly controlled by AMPK-mediated phosphorylation or allosteric regulation mediated by adenine nucleotides levels (indicated with *). Such control is evident under physiological conditions, but also during metabolic reprogramming of cancer cells. Enzymes involved in these reactions are: α-ketoglutarate dehydrogenase (αKGDH); acetyl CoA carboxylase (ACC); aconitase (ACO); aldolase (ALD); ATP citrate lyase (ACLY); citrate synthase (CS); enolase (ENO); fumarate hydratase (FH); glutamate dehydrogenase (GDH); glutamine lyase (GLS); glyceraldehyde 3-phosphate dehydrogenase (GAPDH); hexokinase (HK); isocitrate dehydrogenase (IDH); lactate dehydrogenase (LDH); malate dehydrogenase (MDH); OXPHOS complexes (CI-CV); phosphofructokinase (PFK); phosphoglucose isomerase (PGI); phosphoglycerate kinase (PGK); phosphoglyceromutase (PGM); pyruvate dehydrogenase (PDH); pyruvate dehydrogenase kinase (PDK); pyruvic carboxylase (PC); succinate dehydrogenase (SDH); succinyl-CoA synthetase (SCoAS); triose phosphate isomerase (TPI). Black arrows indicate reactions, purple arrows indicate mechanisms of activation/inactivation, cytosolic enzymes are indicated in blue, mitochondrial enzymes are indicated in green.

metastasis formation or patient survival [58,59]. These observations are in line with the revisited Warburg hypothesis, since mitochondrial OXPHOS is frequently repressed, but not absent, in different human carcinomas and often correlates with poor response to chemotherapy, highlighting that a minimal bioenergetic function to sustain tumor progression and malignancy is needed [60]. Reduced expression of ATP5B

Table 1
Mitochondrial DNA mutations in F_1F_o ATP synthase genes found in tumors.
*Table 1 references are listed in Supplementary material.

Mutation	Gene	Amino acid change	Tumor	References*
m.8374A>G	MT-ATP8	Synonym	Head and neck tumor	[100]
m.8429C>A	MT-ATP8	p.L22I	Breast cancer	[113]
m.8439A>C	MT-ATP8	p.Q25P	Breast cancer	[113]
m.8448T>C	MT-ATP8	p.M28T	Breast cancer	[113]
m.8519A>G	MT-ATP8	p.E52K	Breast cancer	[113]
m.8539C>T	MT-ATP6	Synonym	Osteosarcoma	[114]
m.8542T>C	MT-ATP6	p.F6L	Osteosarcoma	[114]
m.8546InsC	MT-ATP6	Frameshift	Osteosarcoma	[114]
m.8592InsG	MT-ATP6	Frameshift	Osteosarcoma	[114]
m.8610T>C	MT-ATP6	Synonym	Pylocystic astrocytoma	[115]
m.8614T>C	MT-ATP6	Synonym	Pylocystic astrocytoma	[115]
m.8617A>G	MT-ATP6	p.I31V	Leukemia	[116]
m.8627C>T	MT-ATP6	p.S34F	Osteosarcoma	[114]
m.8654T>G	MT-ATP6	p.I43S	Osteosarcoma	[114]
m.8684C>T	MT-ATP6	p.T53I	Osteosarcoma	[114]
m.8697G>A	MT-ATP6	Synonym	Pylocystic astrocytoma	[115]
m.8697G>A	MT-ATP6	Synonym	Hürthle cell follicular carcinoma and adenoma; Breast cancer	[113] [117]
m.8704A>G	MT-ATP6	p.M60V	Pylocystic astrocytoma	[115]
m.8778C>G	MT-ATP6	Synonym	Osteosarcoma	[114]
m.8781C>T	MT-ATP6	Synonym	Osteosarcoma	[114]
m.8803A>G	MT-ATP6	p.T93A	Head and neck tumor	[100]
m.8822C>G	MT-ATP6	p.S99C	Osteosarcoma	[114]
m.8832A>G	MT-ATP6	Synonym	Oncocytic pituitary adenoma	[100]
m.8858G>C	MT-ATP6	p.G111A	Breast cancer	[113]
m.8865G>A	MT-ATP6	Synonym	Osteosarcoma	[114]
m.8922InsC	MT-ATP6	Frameshift	Osteosarcoma	[114]
m.8930C>T	MT-ATP6	p.T135M	Oncocytic pituitary adenoma	[100]
m.9000A>C	MT-ATP6	Synonym	Osteosarcoma	[118]
m.9060C>T	MT-ATP6	Synonym	Head and neck tumor; Oncocytic pituitary adenoma	[100]
m.9119T>G	MT-ATP6	p.L198R	Breast cancer	[113]
m.9124DelA	MT-ATP6	Frameshift	Osteosarcoma	[114]
m.9128T>C	MT-ATP6	p.I201T	Osteosarcoma	[114]
m.9130C>G	MT-ATP6	p.L202V	Breast cancer	[113]
m.9139G>A	MT-ATP6	Synonym	Osteosarcoma	[114]
m.9144C>G	MT-ATP6	Synonym	Osteosarcoma	[114]
m.9145G>C	MT-ATP6	p.A207P	Osteosarcoma	[114]
m.9148T>G	MT-ATP6	p.L208V	Osteosarcoma	[114]
m.9149T>C	MT-ATP6	p.L208S	Osteosarcoma	[114]
m.9151A>C	MT-ATP6	p.I209L	Osteosarcoma; Ewing sarcoma	[114] [119]
m.9152T>A	MT-ATP6	p.I209N	Osteosarcoma	[114]
m.9153C>A	MT-ATP6	p.I209M	Osteosarcoma	[114]
m.9182G>A	MT-ATP6	p.S219N	Osteosarcoma	[118]

and energy production through CV have been linked to the overexpression and activation of IF_1 in a wide panel of human carcinomas and cancer cell lines [14]. Interestingly, some studies report high levels of IF_1 as a predictor of poor prognosis for patients' survival, underscoring its involvement in adaptation to hypoxia, tumor proliferation, invasiveness and metastasis formation [61–63]. How IF_1 regulates mitochondrial function and morphology, and consequently impacts on tumor biology and malignancy, is still not completely understood. IF_1 overexpression prompts mitochondrial *cristae* morphogenesis and blocks their remodeling upon pro-apoptotic insults, preventing the mitochondrial permeability transition pore opening and the release of cytochrome *c* [64]. Moreover, the IF_1-mediated inhibition of CV stimulates a mild ROS production leading to a nuclear preconditioning aimed at preventing cell death and supporting tumorigenesis [12,65]. Such involvement of IF_1 in the apoptotic cascade is crucial in the context of cancer cells that are intrinsically characterized by a resistance to cell death [27]. Besides its role on regulation of apoptosis, increased expression or activation of IF_1 prevents ATP depletion and induces the Warburg effect [12,13,66], although conflicting data have been reported on the exact mechanism through which this protein regulates the OXPHOS function [67,68]. A recent *in vivo* study shows that the expression of an active mutant of human IF_1 in mouse hepatocytes induced a partial OXPHOS defect characterized by a reduced respiration and an inhibition of CV activity [69]. This bioenergetic defect seemed to promote cell proliferation, resistance to apoptosis and a metabolic shift towards glycolysis *via* AMPK activation, generating a predisposing background for primary carcinogenesis hits and favoring tumor progression in liver [69]. Hence, IF_1 has been proposed as a molecular switch of OXPHOS function, which allows the maintenance of the minimal mandatory mitochondrial bioenergetic competence but also the response to altered metabolic request of the cell.

5.2. Mitochondrial transport of adenine nucleotides

As already described, when OXPHOS is active, ATP produced into the mitochondria must be exchanged with ADP to ensure the energy amount sufficient to sustain anabolic reactions, cell growth and survival. In the context of a reprogrammed metabolism in which OXPHOS can be partially repressed and, thus glycolysis is enhanced, mitochondria may suffer a status of energy depletion and ATP must be imported from the cytosol and hydrolyzed to maintain the mitochondrial membrane potential. In this frame, ANT exchangers participate in the regulation of energy homeostasis and may become key player in the regulation of metabolic adaptation of neoplastic cells. Since ANT1, ANT3 and ANT4 isoforms are poorly expressed in proliferating cells their role in human malignancies has been investigated only briefly. Conversely, ANT2 has been found upregulated in several human tumors [70], in neoplastic cell lines [71] and in cancer stem cells [72]. Downregulation of ANT2 in breast cancer cells induced mild ATP depletion, triggered apoptosis, blocked cell cycle progression [73], repressed the expression of HER2/Neu and the PI3K/Akt pathway preventing tumor growth, cell migration and invasiveness [74], and overcame chemoresistance [72]. Similar results have been obtained by the same group also in hepatocellular carcinoma and non-small lung cancer cell models. These data, reinforced by the coordinated expression of ANT2 and glycolytic metabolism, support the hypothesis that this exchanger may be necessary for the import of glycolytic ATP into the mitochondria when the mitochondrial energetic function is repressed, sustaining anabolism and cancer cell proliferation. Indeed, it has been hypothesized that ANT2 may be the only ANT isoform able to import glycolytic ATP into the mitochondria to support anabolic metabolism, since its knock out in mice is embryonically lethal [19] and the expression of its yeast orthologue is restricted to anaerobiosis and essential to sustain cell proliferation on fermentable substrates [19]. However, a recent study shows that ANT2 and ANT3 do not participate in mitochondrial import of ATP in different cancer cell lines [75]. The authors suggest that a possible candidate for the mitochondrial ATP import may be the ATP/Mg-Pi carrier, a non-electrogenic exchanger of adenosine nucleotides. Interestingly, this protein has been found overexpressed in several tumors and cancer cell lines, where it seems to foster tumor growth by preventing mitochondrial permeability transition and lastly apoptosis [76]. This hypothesis is particularly intriguing since an electroneutral exchanger may decreases cytosolic ATP/ADP ratios of proliferating cancer cells stimulating glycolysis and prompting the Warburg effect [75].

6. AMPK: a double-edged sensor in the modulation of cancer cell metabolism

As encountering states of energy depletion during nutrient restriction and hypoxia, neoplastic cells must rewire their metabolism in order to sustain growth and proliferation. Being the orchestra leader of metabolism, it is not surprising that AMPK has been widely involved in tumor initiation, progression and metastasis formation [77,78]. It is interesting to note that the primary AMPK upstream kinase LKB1 is a tumor suppressor, whose germline mutations are causative of the Peutz-Jeghers syndrome, a hereditary condition characterized by

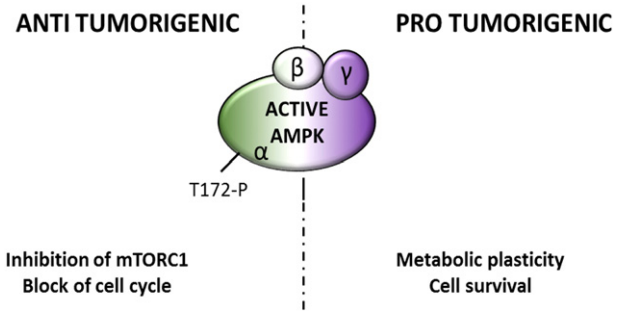

Fig. 3. AMPK, a double-edged kinase in the regulation of tumorigenic potential. Active AMPK may act as pro-tumorigenic inducer fostering metabolic plasticity and autophagy leading to cell survival. On the other hand, AMPK may play an anti-tumorigenic role through the inhibition of mTORC1 signaling and the induction of cell cycle arrest.

predisposition to both benign polyposis and cancer [79]. Moreover, somatic changes in *LKB1* have been associated with melanoma, lung cancer, pancreatic cancer and gynecological cancers [79]. Lying downstream to a well-known tumor suppressor, AMPK has been long suspected to be a tumor suppressor too or, at least, to negatively influence tumor formation and growth. However, recent studies highlight the double-edged nature of AMPK, indicating that its activation can either constrain tumor progression but also promote cancer cell adaptation under specific environmental conditions and in a context-dependent manner (Fig. 3 and Table 2). Differently from *LKB1*, genes encoding for AMPK subunits are rarely mutated in human tumors and there is no association of such mutations with any propensity to develop cancer [25], indicating that AMPK is not a canonical tumor suppressor. Indeed, a recent analysis of the mutation spectrum in AMPK genes in human cancers shows that certain genes such as *PRKAA1* and *PRKAB2* (encoding for α1 and β2 subunits, respectively) are usually amplified, similarly to oncogenes [25]. On the other hand, subunits like AMPKα2 are more prone to accumulate mutations, similar to tumor suppressors, although the functional effects of these mutations have not been investigated [25]. Nonetheless, loss of AMPK caused by genetic ablation is not a sufficient condition to induce cell transformation both *in vitro* and in mouse models [80]. Such differential mutation pattern represents the first line of evidence that AMPK has a double-faced nature and that its involvement in tumor development and progression may be more tangled than its only function as an energy sensor (Fig. 3). To further complicate this scenario, AMPK can be found differentially expressed and/or activated in different types of cancer, at different stages of the diseases and associated with different outcomes and prognosis [77]. This pattern may derive from altered upstream mechanisms. Interestingly, AMPK activation is prevented in melanoma cells with mutant $BRAF^{V600E}$ through a phosphorylation cascade mediated by ERK and Rsk kinases which lead to the inactivation of LKB1 [81]. Moreover, constitutive activation of the PI3K/Akt pathway caused by loss-of-function mutations in *PTEN* have been also shown to repress AMPK activity through the phosphorylation of Ser487 of the α1 subunit [82]. AMPK inhibition results in a defective mitochondrial bioenergetic metabolism and in the stimulation of a compensatory glycolysis, directly contributing to thyroid hyperplasia *in vivo* [83]. Lastly, *PRKAA1* ablation promotes the Warburg effect and Myc-induced lymphomagenesis *in vivo*, inducing biomass accumulation and supporting cell proliferation [84], although the contribution of AMPK in Myc-driven tumorigenesis seems to be context or tissue dependent, as shown in osteosarcoma models [85]. Such divergences may be explained taking into account how AMPK integrates different intracellular and extracellular signaling and its function within the context of metabolic reprogramming and adaptation to hypoxia. On one hand, active AMPK exerts an inhibitory effect on mTOR pathway [86,87] and prevents the biosynthetic processes necessary for cell growth and proliferation, affecting tumor progression and clonal expansion of cancer cells (Fig. 3). Indeed, it has been found that hepatocyte specific *Tak1* KO in mice triggers mTORC1 pathway, suppresses AMPK expression and inhibits autophagy in response to starvation or treatment with metformin [88]. These models spontaneously develop hepatocellular carcinomas, whose formation can be reverted by inhibiting mTORC1 or stimulating autophagy, indicating that TAK1 mediated AMPK activation inhibits tumorigenesis [88]. Conversely, AMPK also seems necessary to sustain the metabolic plasticity of cancer cells during the phases of adaptation to nutrient and oxygen paucity and exposure to oxidative stress (Fig. 3). In fact, upon nutrient deprivation and hypoxia AMPK activation is induced by different signaling pathways, including PI3K/Akt and ROS [89,90], resulting in a metabolic rewiring towards aerobic glycolysis [91], activating autophagy [92,93] and preventing cell death [92,94,95]. However, whether autophagy stimulation represents a pro-survival mechanism or prevents tumor growth is still unclear and may be cell type dependent [93,96]. Emerging studies are showing that blocking autophagy confines aggressive carcinomas into a more benign status of almost quiescent oncocytomas [97,98]. Interestingly, oncocytomas are characterized by the accumulation of disruptive mutations in mtDNA encoded genes, particularly those for respiratory complex I subunits [99,100]. We demonstrated that such mutations induce a severe OXPHOS dysfunction that lead to a profound energetic crisis as attested from imbalanced AMP/ATP ratio and activation of AMPK in presence or deprivation of glucose [101]. Such energetic stress conditions contribute to an increased avidity for glucose, even if complex I defective cells fail to establish a Warburg transcriptional profile because they are not able to stabilize the Hypoxia Inducible Factor 1α (HIF1α) [36,101]. Indeed, in our cell model the activation of AMPK did not modify cell aggressiveness, whereas chemical stabilization of HIF1α partially overcomes the block of tumor growth, indicating that AMPK activation regulates the metabolic reprogramming and induces a compensatory mitochondrial biogenesis in mitochondrial defective cancer cells, but plays a secondary role in tumor progression of aggressive osteosarcoma [101]. On the other hand, aerobic glycolysis can be triggered also in AMPK defective models, being HIF1α the master regulator of the

Table 2
Effects of AMPK activation on tumor initiation and progression.
*Table 2 references are listed in Supplementary material.

Antitumorigenic effects	References*
Loss of one AMPK allele favors lymphoma occurrence in c-Myc mutant animal models.	[84]
Active AMPK inhibits the mTOR pathway blocking cell cycle and proliferation.	[87,103,120]
Loss of AMPKα2 stimulates murine embryonic fibroblast H-RasV12 mediated transformation and tumorigenesis.	[121]
Tak1 ablation stimulates the spontaneous formation of hepatocellular carcinomas in animal models.	[88]
Reduced expression of AMPK in breast cancer and hepatocellular carcinomas compared to normal tissues.	[122,123]
Loss of AMPKα2 in hepatocellular carcinoma cells stimulates aggressiveness.	[123]
Protumorigenic effects	**References***
Activation of AMPK favors metabolic plasticity in cancer cells.	[124]
Triggering of AMPK pathway promotes cancer cell growth and survival under stress conditions, such as hypoxia and mitochondrial dysfunction.	[92–94,96,125–127]
Active AMPK is highly expressed in triple negative breast cancers.	[128]

transcriptional response [84]. Reduced HIF1α levels and triggering of the Warburg effect have been also found when a mitochondrial dysfunction is induced by OXPHOS complexes inhibitors [102], uncoupling compounds [103] or Myc inhibitors [104], although in these reports HIF1α seems to be directly destabilized upon AMPK activation. Based on these findings, AMPK may be raised to pivotal regulator of cancer cell metabolism and thus it is not surprising that this enzyme has been widely implicated in the processes of carcinogenesis and tumor progression, but remains the piece of an intriguing puzzle still to be built.

7. Concluding remarks

It is now well established that deregulated energy metabolism is an hallmark of cancer [27]. Neoplastic cells adapt to environmental pressure globally rewiring their metabolism in order to sustain the augmented request of energy and macromolecules building blocks. Aerobic glycolysis, FAO and anaplerotic reactions strongly contribute to biosynthetic anabolic pathways in proliferating cells. Such ATP consuming processes must be counterbalanced, in order to maintain AEC values within a physiological range, since its deregulation impact on cell survival. Hence, in cancer cells energy homeostasis must be maintained by sustained catabolism and mitochondrial ATP production. In fact, a growing number of studies report that a certain mitochondrial function is necessary for transformed cells, underscoring its role of metabolic hub that integrate different metabolic routes. Functional OXPHOS is required during specific phases of tumor progression when cancer cells are subjected to nutrient and oxygen deprivation. During these phases, ATP depletion may activate AMPK sustaining metabolic and hypoxic adaptation and thus stimulating mitochondrial biogenesis and autophagy. However, a functionally active AMPK may also represent an inhibiting factor during the first phases of carcinogenesis, since it prevents cell proliferation limiting the mTOR pathway. Based on the current literature, the exact molecular mechanisms through which AMPK affects carcinogenesis and tumor progression are still controversial and debated. The main open questions concern the role of different AMPK isoforms, the context in which AMPK may influence tumor biology and how different oncogenes or tumor suppressors regulate this kinase. It can be hypothesized that, similar to mitochondrial genes coding for OXPHOS complexes subunits, AMPK can be envisioned as an *oncojanus* [105], since it may exert divergent effects in different cell context and during specific phases of tumor progression (Fig. 3). Hence, a precise definition of a therapeutic window is necessary, since a pharmacological targeting of AMPK has been proposed as a feasible approach to prevent or hamper tumor development. Beside the reports on the activation of AMPK mediated by the antidiabetic drug metformin and cancer epidemiology [106,107], a continuously increasing interest in AMPK pharmacological activators and inhibitors has been shown by the scientific community. While specific inhibitors of AMPK are still missing [108], a wide panel of natural and synthetic activators is available, although the vast majority of these compounds acts indirectly since they modulate the AMP/ATP ratio through the inhibition of mitochondrial OXPHOS [109]. An illustrative case is represented by metformin that inhibits respiratory complex I without triggering ROS production [110,111]. This drug is widely and safely used for type 2 diabetes first line therapy and it is currently investigated also for treatment of different types of cancer [112]. Whether the antitumorigenic properties of metformin derive from its action at cellular or systemic level, or in a synergistic manner, is still debated. However, it is extremely intriguing that complex I inhibition and AMPK activation concur during tumor growth arrest as it is now well established that respiratory complex I is required for cancer cell adaptation to metabolic and hypoxic constraints during tumor progression [36,101,105]. In this context, further studies on the effects of AMPK activators on OXPHOS system and the design of novel and more selective AMPK activators and inhibitors are necessary in order to find new, effective and selective strategies to combat cancer development.

Transparency document

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bbabio.2017.02.006.

References

[1] H. Krebs, The Croonian lecture, 1963 gluconeogenesis, Proc. R. Soc. Lond. B Biol. Sci. 159 (1964) 545–564.
[2] D.E. Atkinson, G.M. Walton, Adenosine triphosphate conservation in metabolic regulation rat liver citrate cleavage enzyme, J. Biol. Chem. 242 (1967) 3239–3241.
[3] D.L. Nelson, M.M. Cox, Lehninger Principles of Biochemistry, 2013.
[4] V.C. Ozalp, T.R. Pedersen, L.J. Nielsen, L.F. Olsen, Time-resolved measurements of intracellular ATP in the yeast *Saccharomyces cerevisiae* using a new type of nanobiosensor, J. Biol. Chem. 285 (2010) 37579–37588.
[5] D.E. Atkinson, The energy charge of the adenylate pool as a regulatory parameter interaction with feedback modifiers, Biochemistry (Mosc) 7 (1968) 4030–4034.
[6] P. Mitchell, J. Moyle, Respiration-driven proton translocation in rat liver mitochondria, Biochem. J. 105 (1967) 1147–1162.
[7] R.A. Reid, J. Moyle, P. Mitchell, Synthesis of adenosine triphosphate by a protonmotive force in rat liver mitochondria, Nature 212 (1966) 257–258.
[8] J.E. Walker, The ATP synthase: the understood, the uncertain and the unknown, Biochem. Soc. Trans. 41 (2013) 1–16.
[9] S. Nesci, F. Trombetti, V. Ventrella, A. Pagliarani, Opposite rotation directions in the synthesis and hydrolysis of ATP by the ATP synthase: hints from a subunit asymmetry, J. Membr. Biol. 248 (2015) 163–169.
[10] C. von Ballmoos, A. Wiedenmann, P. Dimroth, Essentials for ATP synthesis by F1F0 ATP synthases, Annu. Rev. Biochem. 78 (2009) 649–672.
[11] M.E. Pullman, G.C. Monroy, A naturally occurring inhibitor of mitochondrial adenosine triphosphatase, J. Biol. Chem. 238 (1963) 3762–3769.
[12] L. Formentini, M. Sánchez-Aragó, L. Sánchez-Cenizo, J.M. Cuezva, The mitochondrial ATPase inhibitory factor 1 triggers a ROS-mediated retrograde prosurvival and proliferative response, Mol. Cell 45 (2012) 731–742.
[13] J. García-Bermúdez, M. Sánchez-Aragó, B. Soldevilla, A. Del Arco, C. Nuevo-Tapioles, J.M. Cuezva, PKA phosphorylates the ATPase inhibitory factor 1 and inactivates its capacity to bind and inhibit the mitochondrial H(+)-ATP synthase, Cell Rep. 12 (2015) 2143–2155.
[14] J. García-Bermúdez, J.M. Cuezva, The ATPase inhibitory factor 1 (IF1): a master regulator of energy metabolism and of cell survival, Biochim. Biophys. Acta 1857 (2016) 1167–1182.
[15] M.J. Rardin, J.C. Newman, J.M. Held, M.P. Cusack, D.J. Sorensen, B. Li, B. Schilling, S.D. Mooney, C.R. Kahn, E. Verdin, B.W. Gibson, Label-free quantitative proteomics of the lysine acetylome in mitochondria identifies substrates of SIRT3 in metabolic pathways, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6601–6606.
[16] J. Park, Y. Chen, D.X. Tishkoff, C. Peng, M. Tan, L. Dai, Z. Xie, Y. Zhang, B.M.M. Zwaans, M.E. Skinner, D.B. Lombard, Y. Zhao, SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways, Mol. Cell 50 (2013) 919–930.
[17] R. Acin-Perez, E. Salazar, M. Kamenetsky, J. Buck, L.R. Levin, G. Manfredi, Cyclic AMP produced inside mitochondria regulates oxidative phosphorylation, Cell Metab. 9 (2009) 265–276.
[18] M. Klingenberg, The ADP and ATP transport in mitochondria and its carrier, Biochim. Biophys. Acta 1778 (2008) 1978–2021.
[19] A. Chevrollier, D. Loiseau, P. Reynier, G. Stepien, Adenine nucleotide translocase 2 is a key mitochondrial protein in cancer metabolism, Biochim. Biophys. Acta 1807 (2011) 562–567.
[20] E. Pfaff, H.W. Heldt, M. Klingenberg, Adenine nucleotide translocation of mitochondria kinetics of the adenine nucleotide exchange, Eur. J. Biochem. 10 (1969) 484–493.
[21] Y.-B. Yan, Creatine kinase in cell cycle regulation and cancer, Amino Acids 48 (2016) 1775–1784.
[22] W.R. Ellington, Evolution and physiological roles of phosphagen systems, Annu. Rev. Physiol. 63 (2001) 289–325.

[23] P. Dzeja, A. Terzic, Adenylate kinase and AMP signaling networks: metabolic monitoring, signal communication and body energy sensing, Int. J. Mol. Sci. 10 (2009) 1729–1772.
[24] D.G. Hardie, AMPK–sensing energy while talking to other signaling pathways, Cell Metab. 20 (2014) 939–952.
[25] F.A. Ross, C. MacKintosh, D.G. Hardie, AMP-activated protein kinase: a cellular energy sensor that comes in 12 flavours, FEBS J. 283 (2016) 2987–3001.
[26] S.-M. Jeon, Regulation and function of AMPK in physiology and diseases, Exp. Mol. Med. 48 (2016), e245. .
[27] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[28] O. Warburg, On the origin of cancer cells, Science 123 (1956) 309–314.
[29] O. Warburg, On respiratory impairment in cancer cells, Science 124 (1956) 269–270.
[30] H.-B. Kang, J. Fan, R. Lin, S. Elf, Q. Ji, L. Zhao, L. Jin, J.H. Seo, C. Shan, J.L. Arbiser, C. Cohen, D. Brat, H.M. Miziorko, E. Kim, O. Abdel-Wahab, T. Merghoub, S. Fröhling, C. Scholl, P. Tamayo, D.A. Barbie, et al., Metabolic rewiring by oncogenic BRAF V600E links ketogenesis pathway to BRAF-MEK1 signaling, Mol. Cell 59 (2015) 345–358.
[31] Y. Fan, K.G. Dickman, W.-X. Zong, Akt and c-Myc differentially activate cellular metabolic programs and prime cells to bioenergetic inhibition, J. Biol. Chem. 285 (2010) 7324–7333.
[32] W. Ma, H.J. Sung, J.Y. Park, S. Matoba, P.M. Hwang, A pivotal role for p53: balancing aerobic respiration and glycolysis, J. Bioenerg. Biomembr. 39 (2007) 243–246.
[33] Q. Sun, X. Chen, J. Ma, H. Peng, F. Wang, X. Zha, Y. Wang, Y. Jing, H. Yang, R. Chen, L. Chang, Y. Zhang, J. Goto, H. Onda, T. Chen, M.-R. Wang, Y. Lu, H. You, D. Kwiatkowski, H. Zhang, Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 4129–4134.
[34] F. Weinberg, R. Hamanaka, W.W. Wheaton, S. Weinberg, J. Joseph, M. Lopez, B. Kalyanaraman, G.M. Mutlu, G.R.S. Budinger, N.S. Chandel, Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 8788–8793.
[35] K. Smolková, L. Plecitá-Hlavatá, N. Bellance, G. Benard, R. Rossignol, P. Ježek, Waves of gene regulation suppress and then restore oxidative phosphorylation in cancer cells, Int. J. Biochem. Cell Biol. 43 (2011) 950–968.
[36] C. Calabrese, L. Iommarini, I. Kurelac, M.A. Calvaruso, M. Capristo, P.-L. Lollini, P. Nanni, C. Bergamini, G. Nicoletti, C.D. Giovanni, A. Ghelli, V. Giorgio, M.F. Caratozzolo, F. Marzano, C. Manzari, C.M. Betts, V. Carelli, C. Ceccarelli, M. Attimonelli, G. Romeo, et al., Respiratory complex I is essential to induce a Warburg profile in mitochondria-defective tumor cells, Cancer Metab. 1 (2013) 11.
[37] A. Hall, K.D. Meyle, M.K. Lange, M. Klima, M. Sanderhoff, C. Dahl, C. Abildgaard, K. Thorup, S.M. Moghimi, P.B. Jensen, J. Bartek, P. Guldberg, C. Christensen, Dysfunctional oxidative phosphorylation makes malignant melanoma cells addicted to glycolysis driven by the (V600E)BRAF oncogene, Oncotarget 4 (2013) 584–599.
[38] R.J. DeBerardinis, A. Mancuso, E. Daikhin, I. Nissim, M. Yudkoff, S. Wehrli, C.B. Thompson, Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 19345–19350.
[39] A.R. Mullen, W.W. Wheaton, E.S. Jin, P.-H. Chen, L.B. Sullivan, T. Cheng, Y. Yang, W.M. Linehan, N.S. Chandel, R.J. DeBerardinis, Reductive carboxylation supports growth in tumour cells with defective mitochondria, Nature 481 (2011) 385–388.
[40] C.M. Metallo, P.A. Gameiro, E.L. Bell, K.R. Mattaini, J. Yang, K. Hiller, C.M. Jewell, Z.R. Johnson, D.J. Irvine, L. Guarente, J.K. Kelleher, M.G. Vander Heiden, O. Iliopoulos, G. Stephanopoulos, Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia, Nature 481 (2011) 380–384.
[41] D.R. Wise, P.S. Ward, J.E.S. Shay, J.R. Cross, J.J. Gruber, U.M. Sachdeva, J.M. Platt, R.G. DeMatteo, M.C. Simon, C.B. Thompson, Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of α-ketoglutarate to citrate to support cell growth and viability, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 19611–19616.
[42] D.R. Wise, R.J. DeBerardinis, A. Mancuso, N. Sayed, X.-Y. Zhang, H.K. Pfeiffer, I. Nissim, E. Daikhin, M. Yudkoff, S.B. McMahon, C.B. Thompson, Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 18782–18787.
[43] M. Yuneva, N. Zamboni, P. Oefner, R. Sachidanandam, Y. Lazebnik, Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells, J. Cell Biol. 178 (2007) 93–105.
[44] A. Carracedo, L.C. Cantley, P.P. Pandolfi, Cancer metabolism: fatty acid oxidation in the limelight, Nat. Rev. Cancer 13 (2013) 227–232.
[45] I. Samudio, R. Harmancey, M. Fiegl, H. Kantarjian, M. Konopleva, B. Korchin, K. Kaluarachchi, W. Bornmann, S. Duvvuri, H. Taegtmeyer, M. Andreeff, Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction, J. Clin. Invest. 120 (2010) 142–156.
[46] H. Lin, S. Patel, V.S. Affleck, I. Wilson, D.M. Turnbull, A.R. Joshi, R. Maxwell, E.A. Stoll, Fatty Acid Oxidation is Required for the Respiration and Proliferation of Malignant Glioma Cells, Neuro-Oncol., 2016.
[47] K.M. Nieman, H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-Gutbrod, M.R. Zillhardt, I.L. Romero, M.S. Carey, G.B. Mills, G.S. Hotamisligil, S.D. Yamada, M.E. Peter, K. Gwin, E. Lengyel, Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med. 17 (2011) 1498–1503.
[48] M.S. Padanad, G. Konstantinidou, N. Venkateswaran, M. Melegari, S. Rindhe, M. Mitsche, C. Yang, K. Batten, K.E. Huffman, J. Liu, X. Tang, J. Rodriguez-Canales, N. Kalhor, J.W. Shay, J.D. Minna, J. McDonald, I.I. Wistuba, R.J. DeBerardinis, P.P. Scaglioni, Fatty acid oxidation mediated by Acyl-CoA synthetase long chain 3 is required for mutant KRAS lung tumorigenesis, Cell Rep. 16 (2016) 1614–1628.
[49] J.J. Kamphorst, J.R. Cross, J. Fan, E. de Stanchina, R. Mathew, E.P. White, C.B. Thompson, J.D. Rabinowitz, Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 8882–8887.
[50] G.-J. Sung, H.-K. Choi, S. Kwak, J.-H. Song, H. Ko, H.-G. Yoon, H.-B. Kang, K.-C. Choi, Targeting CPT1A enhances metabolic therapy in human melanoma cells with the BRAF V600E mutation, Int. J. Biochem. Cell Biol. 81 (2016) 76–81.
[51] P. Bernardi, A. Rasola, M. Forte, G. Lippe, The mitochondrial permeability transition pore: channel formation by F-ATP synthase, integration in signal transduction, and role in pathophysiology, Physiol. Rev. 95 (2015) 1111–1155.
[52] L. Iommarini, M.A. Calvaruso, I. Kurelac, G. Gasparre, A.M. Porcelli, Complex I impairment in mitochondrial diseases and cancer: parallel roads leading to different outcomes, Int. J. Biochem. Cell Biol. 45 (2013) 47–63.
[53] Y.S. Ju, L.B. Alexandrov, M. Gerstung, I. Martincorena, S. Nik-Zainal, M. Ramakrishna, H.R. Davies, E. Papaemmanuil, G. Gundem, A. Shlien, N. Bolli, S. Behjati, P.S. Tarpey, J. Nangalia, C.E. Massie, A.P. Butler, J.W. Teague, G.S. Vassiliou, A.R. Green, M.-Q. Du, et al., Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer, elife 3 (2014).
[54] G. Gasparre, G. Romeo, M. Rugolo, A.M. Porcelli, Learning from oncocytic tumors: why choose inefficient mitochondria? Biochim. Biophys. Acta 1807 (2011) 633–642.
[55] J.A. Petros, A.K. Baumann, E. Ruiz-Pesini, M.B. Amin, C.Q. Sun, J. Hall, S. Lim, M.M. Issa, W.D. Flanders, S.H. Hosseini, F.F. Marshall, D.C. Wallace, mtDNA mutations increase tumorigenicity in prostate cancer, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 719–724.
[56] R.S. Arnold, C.Q. Sun, J.C. Richards, G. Grigoriev, I.M. Coleman, P.S. Nelson, C.-L. Hsieh, J.K. Lee, Z. Xu, A. Rogatko, A.O. Osunkoya, M. Zayzafoon, L. Chung, J.A. Petros, Mitochondrial DNA mutation stimulates prostate cancer growth in bone stromal environment, Prostate 69 (2009) 1–11.
[57] A. Isidoro, M. Martínez, P.L. Fernández, A.D. Ortega, G. Santamaría, M. Chamorro, J.C. Reed, J.M. Cuezva, Alteration of the bioenergetic phenotype of mitochondria is a hallmark of breast, gastric, lung and oesophageal cancer, Biochem. J. 378 (2004) 17–20.
[58] J. Sun, Z.-L. Yang, X. Miao, Q. Zou, J. Li, L. Liang, G. Zeng, S. Chen, ATP5b and β2-microglobulin are predictive markers for the prognosis of patients with gallbladder cancer, J. Mol. Histol. 46 (2015) 57–65.
[59] P.-C. Lin, J.-K. Lin, S.-H. Yang, H.-S. Wang, A.F.-Y. Li, S.-C. Chang, Expression of beta-F1-ATPase and mitochondrial transcription factor A and the change in mitochondrial DNA content in colorectal cancer: clinical data analysis and evidence from an in vitro study, Int. J. Color. Dis. 23 (2008) 1223–1232.
[60] M. Sánchez-Aragó, M. Chamorro, J.M. Cuezva, Selection of cancer cells with repressed mitochondria triggers colon cancer progression, Carcinogenesis 31 (2010) 567–576.
[61] Y.-X. Gao, L. Chen, X.-G. Hu, H.-B. Wu, Y.-H. Cui, X. Zhang, Y. Wang, X.-D. Liu, X.-W. Bian, ATPase inhibitory factor 1 expression is an independent prognostic factor in non-small cell lung cancer, Am. J. Cancer Res. 6 (2016) 1141–1148.
[62] R. Song, H. Song, Y. Liang, D. Yin, H. Zhang, T. Zheng, J. Wang, Z. Lu, X. Song, T. Pei, Y. Qin, Y. Li, C. Xie, B. Sun, H. Shi, S. Li, X. Meng, G. Yang, S. Pan, J. Zhu, et al., Reciprocal activation between ATPase inhibitory factor 1 and NF-κB drives hepatocellular carcinoma angiogenesis and metastasis, Hepatol. Baltim. Md 60 (2014) 1659–1673.
[63] T. Yin, L. Lu, Z. Xiong, S. Wei, D. Cui, ATPase inhibitory factor 1 is a prognostic marker and contributes to proliferation and invasion of human gastric cancer cells, Biomed. Pharmacother. 70 (2015) 90–96.
[64] M. Campanella, E. Casswell, S. Chong, Z. Farah, M.R. Wieckowski, A.Y. Abramov, A. Tinker, M.R. Duchen, Regulation of mitochondrial structure and function by the F1Fo-ATPase inhibitor protein, IF1, Cell Metab. 8 (2008) 13–25.
[65] M. Sánchez-Aragó, L. Formentini, I. Martínez-Reyes, J. García-Bermudez, F. Santacatterina, L. Sánchez-Cenizo, I.M. Willers, M. Aldea, L. Nájera, A. Juarránz, E.C. López, J. Clofent, C. Navarro, E. Espinosa, J.M. Cuezva, Expression, regulation and clinical relevance of the ATPase inhibitory factor 1 in human cancers, Oncogenesis 2 (2013), e46. .
[66] L. Sánchez-Cenizo, L. Formentini, M. Aldea, A.D. Ortega, P. García-Huerta, M. Sánchez-Aragó, J.M. Cuezva, Up-regulation of the ATPase inhibitory factor 1 (IF1) of the mitochondrial H^+-ATP synthase in human tumors mediates the metabolic shift of cancer cells to a Warburg phenotype, J. Biol. Chem. 285 (2010) 25308–25313.
[67] M. Fujikawa, H. Imamura, J. Nakamura, M. Yoshida, Assessing actual contribution of IF1, inhibitor of mitochondrial FoF1, to ATP homeostasis, cell growth, mitochondrial morphology, and cell viability, J. Biol. Chem. 287 (2012) 18781–18787.
[68] S. Barbato, G. Sgarbi, G. Gorini, A. Baracca, G. Solaini, The inhibitor protein (IF1) of the F1F0-ATPase modulates human osteosarcoma cell bioenergetics, J. Biol. Chem. 290 (2015) 6338–6348.
[69] F. Santacatterina, L. Sánchez-Cenizo, L. Formentini, M.A. Mobasher, E. Casas, C.B. Rueda, I. Martínez-Reyes, C. Núñez de Arenas, J. García-Bermúdez, J.M. Zapata, M. Sánchez-Aragó, J. Satrústegui, Á.M. Valverde, J.M. Cuezva, Down-regulation of oxidative phosphorylation in the liver by expression of the ATPase inhibitory factor 1 induces a tumor-promoter metabolic state, Oncotarget 7 (2016) 490–508.
[70] H. Faure Vigny, A. Heddi, S. Giraud, D. Chautard, G. Stepien, Expression of oxidative phosphorylation genes in renal tumors and tumoral cell lines, Mol. Carcinog. 16 (1996) 165–172.
[71] S. Giraud, C. Bonod-Bidaud, M. Wesolowski-Louvel, G. Stepien, Expression of human ANT2 gene in highly proliferative cells: GRBOX, a new transcriptional element, is involved in the regulation of glycolytic ATP import into mitochondria, J. Mol. Biol. 281 (1998) 409–418.
[72] J.Y. Jang, M.K. Kim, Y.K. Jeon, Y.K. Joung, K.D. Park, C.W. Kim, Adenovirus adenine nucleotide translocator-2 shRNA effectively induces apoptosis and enhances

chemosensitivity by the down-regulation of ABCG2 in breast cancer stem-like cells, Exp. Mol. Med. 44 (2012) 251–259.
[73] 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.
[74] J.-Y. Jang, Y.-K. Jeon, C.-W. Kim, Degradation of HER2/neu by ANT2 shRNA suppresses migration and invasiveness of breast cancer cells, BMC Cancer 10 (2010) 391.
[75] E.N. Maldonado, D.N. DeHart, J. Patnaik, S.C. Klatt, M.B. Gooz, J.J. Lemasters, ATP/ADP turnover and import of glycolytic ATP into mitochondria in cancer cells is independent of the adenine nucleotide translocator, J. Biol. Chem. 291 (2016) 19642–19650.
[76] J. Traba, A. Del Arco, M.R. Duchen, G. Szabadkai, J. Satrústegui, SCaMC-1 promotes cancer cell survival by desensitizing mitochondrial permeability transition via ATP/ADP-mediated matrix Ca(2+) buffering, Cell Death Differ. 19 (2012) 650–660.
[77] D.G. Hardie, Molecular pathways: is AMPK a friend or a foe in cancer? Clin. Cancer Res. 21 (2015) 3836–3840.
[78] N. Li, D. Huang, N. Lu, L. Luo, Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (review), Oncol. Rep. 34 (2015) 2821–2826.
[79] B.Y. Shorning, A.R. Clarke, Energy sensing and cancer: LKB1 function and lessons learnt from Peutz-Jeghers syndrome, Semin. Cell Dev. Biol. 52 (2016) 21–29.
[80] K.R. Laderoute, K. Amin, J.M. Calaoagan, M. Knapp, T. Le, J. Orduna, M. Foretz, B. Viollet, 5′-AMP-activated protein kinase (AMPK) is induced by low-oxygen and glucose deprivation conditions found in solid-tumor microenvironments, Mol. Cell. Biol. 26 (2006) 5336–5347.
[81] B. Zheng, J.H. Jeong, J.M. Asara, Y.-Y. Yuan, S.R. Granter, L. Chin, L.C. Cantley, Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation, Mol. Cell 33 (2009) 237–247.
[82] S.A. Hawley, F.A. Ross, G.J. Gowans, P. Tibarewal, N.R. Leslie, D.G. Hardie, Phosphorylation by Akt within the ST loop of AMPK-α1 down-regulates its activation in tumour cells, Biochem. J. 459 (2014) 275–287.
[83] V.G. Antico Arciuch, M.A. Russo, K.S. Kang, A. Di Cristofano, Inhibition of AMPK and Krebs cycle gene expression drives metabolic remodeling of Pten-deficient preneoplastic thyroid cells, Cancer Res. 73 (2013) 5459–5472.
[84] B. Faubert, G. Boily, S. Izreig, T. Griss, B. Samborska, Z. Dong, F. Dupuy, C. Chambers, B.J. Fuerth, B. Viollet, O.A. Mamer, D. Avizonis, R.J. DeBerardinis, P.M. Siegel, R.G. Jones, AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo, Cell Metab. 17 (2013) 113–124.
[85] L. Liu, J. Ulbrich, J. Müller, T. Wüstefeld, L. Aeberhard, T.R. Kress, N. Muthalagu, L. Rycak, R. Rudalska, R. Moll, S. Kempa, L. Zender, M. Eilers, D.J. Murphy, Deregulated MYC expression induces dependence upon AMPK-related kinase 5, Nature 483 (2012) 608–612.
[86] D.M. Gwinn, D.B. Shackelford, D.F. Egan, M.M. Mihaylova, A. Mery, D.S. Vasquez, B.E. Turk, R.J. Shaw, AMPK phosphorylation of raptor mediates a metabolic checkpoint, Mol. Cell 30 (2008) 214–226.
[87] R.G. Jones, D.R. Plas, S. Kubek, M. Buzzai, J. Mu, Y. Xu, M.J. Birnbaum, C.B. Thompson, AMP-activated protein kinase induces a p53-dependent metabolic checkpoint, Mol. Cell 18 (2005) 283–293.
[88] S. Inokuchi-Shimizu, E.J. Park, Y.S. Roh, L. Yang, B. Zhang, J. Song, S. Liang, M. Pimienta, K. Taniguchi, X. Wu, K. Asahina, W. Lagakos, M.R. Mackey, S. Akira, M.H. Ellisman, D.D. Sears, J.M. Olefsky, M. Karin, D.A. Brenner, E. Seki, TAK1-mediated autophagy and fatty acid oxidation prevent hepatosteatosis and tumorigenesis, J. Clin. Invest. 124 (2014) 3566–3578.
[89] B.M. Emerling, F. Weinberg, C. Snyder, Z. Burgess, G.M. Mutlu, B. Viollet, G.R.S. Budinger, N.S. Chandel, Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio, Free Radic. Biol. Med. 46 (2009) 1386–1391.
[90] P.T. Mungai, G.B. Waypa, A. Jairaman, M. Prakriya, D. Dokic, M.K. Ball, P.T. Schumacker, Hypoxia triggers AMPK activation through reactive oxygen species-mediated activation of calcium release-activated calcium channels, Mol. Cell. Biol. 31 (2011) 3531–3545.
[91] C.-A. Wu, Y. Chao, S.-G. Shiah, W.-W. Lin, Nutrient deprivation induces the Warburg effect through ROS/AMPK-dependent activation of pyruvate dehydrogenase kinase, Biochim. Biophys. Acta 1833 (2013) 1147–1156.
[92] S.E. Kim, H.-J. Park, H.K. Jeong, M.-J. Kim, M. Kim, O.-N. Bae, S.-H. Baek, Autophagy sustains the survival of human pancreatic cancer PANC-1 cells under extreme nutrient deprivation conditions, Biochem. Biophys. Res. Commun. 463 (2015) 205–210.
[93] I. Papandreou, A.L. Lim, K. Laderoute, N.C. Denko, Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L, Cell Death Differ. 15 (2008) 1572–1581.
[94] K. Kato, T. Ogura, A. Kishimoto, Y. Minegishi, N. Nakajima, M. Miyazaki, H. Esumi, Critical roles of AMP-activated protein kinase in constitutive tolerance of cancer cells to nutrient deprivation and tumor formation, Oncogene 21 (2002) 6082–6090.
[95] R.J. Shaw, M. Kosmatka, N. Bardeesy, R.L. Hurley, L.A. Witters, R.A. DePinho, L.C. Cantley, The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 3329–3335.
[96] E. Possik, Z. Jalali, Y. Nouët, M. Yan, M.-C. Gingras, K. Schmeisser, L. Panaite, F. Dupuy, D. Kharitidi, L. Chotard, R.G. Jones, D.H. Hall, A. Pause, Folliculin regulates ampk-dependent autophagy and metabolic stress survival, PLoS Genet. 10 (2014), e1004273. .
[97] G. Karsli-Uzunbas, J.Y. Guo, S. Price, X. Teng, S.V. Laddha, S. Khor, N.Y. Kalaany, T. Jacks, C.S. Chan, J.D. Rabinowitz, E. White, Autophagy is required for glucose homeostasis and lung tumor maintenance, Cancer Discov. 4 (2014) 914–927.
[98] A.M. Strohecker, J.Y. Guo, G. Karsli-Uzunbas, S.M. Price, G.J. Chen, R. Mathew, M. McMahon, E. White, Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors, Cancer Discov. 3 (2013) 1272–1285.
[99] G. Gasparre, A.M. Porcelli, E. Bonora, L.F. Pennisi, M. Toller, L. Iommarini, A. Ghelli, M. Moretti, C.M. Betts, G.N. Martinelli, A.R. Ceroni, F. Curcio, V. Carelli, M. Rugolo, G. Tallini, G. Romeo, Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncocytic phenotype in thyroid tumors, Proc. Natl. Acad. Sci. 104 (2007) 9001–9006.
[100] A.M. Porcelli, A. Ghelli, C. Ceccarelli, M. Lang, G. Cenacchi, M. Capristo, L.F. Pennisi, I. Morra, E. Ciccarelli, A. Melcarne, A. Bartoletti-Stella, N. Salfi, G. Tallini, A. Martinuzzi, V. Carelli, M. Attimonelli, M. Rugolo, G. Romeo, G. Gasparre, The genetic and metabolic signature of oncocytic transformation implicates HIF1alpha destabilization, Hum. Mol. Genet. 19 (2010) 1019–1032.
[101] L. Iommarini, I. Kurelac, M. Capristo, M.A. Calvaruso, V. Giorgio, C. Bergamini, A. Ghelli, P. Nanni, C. De Giovanni, V. Carelli, R. Fato, P.L. Lollini, M. Rugolo, G. Gasparre, A.M. Porcelli, Different mtDNA mutations modify tumor progression in dependence of the degree of respiratory complex I impairment, Hum. Mol. Genet. 23 (2014) 1453–1466.
[102] C.-C. Hsu, C.-H. Wang, L.-C. Wu, C.-Y. Hsia, C.-W. Chi, P.-H. Yin, C.-J. Chang, M.-T. Sung, Y.-H. Wei, S.-H. Lu, H.-C. Lee, Mitochondrial dysfunction represses HIF-1α protein synthesis through AMPK activation in human hepatoma HepG2 cells, Biochim. Biophys. Acta 1830 (2013) 4743–4751.
[103] J.L. Figarola, J. Singhal, J.D. Tompkins, G.W. Rogers, C. Warden, D. Horne, A.D. Riggs, S. Awasthi, S.S. Singhal, SR4 uncouples mitochondrial oxidative phosphorylation, modulates AMP-dependent kinase (AMPK)-mammalian target of rapamycin (mTOR) signaling, and inhibits proliferation of HepG2 hepatocarcinoma cells, J. Biol. Chem. 290 (2015) 30321–30341.
[104] H. Wang, L. Sharma, J. Lu, P. Finch, S. Fletcher, E.V. Prochownik, Structurally diverse c-Myc inhibitors share a common mechanism of action involving ATP depletion, Oncotarget 6 (2015) 15857–15870.
[105] G. Gasparre, I. Kurelac, M. Capristo, L. Iommarini, A. Ghelli, C. Ceccarelli, G. Nicoletti, P. Nanni, C. De Giovanni, K. Scotlandi, C.M. Betts, V. Carelli, P.L. Lollini, G. Romeo, M. Rugolo, A.M. Porcelli, A mutation threshold distinguishes the antitumorigenic effects of the mitochondrial gene MTND1, an oncojanus function, Cancer Res. 71 (2011) 6220–6229.
[106] G. Zhou, R. Myers, Y. Li, Y. Chen, X. Shen, J. Fenyk-Melody, M. Wu, J. Ventre, T. Doebber, N. Fujii, N. Musi, M.F. Hirshman, L.J. Goodyear, D.E. Moller, Role of AMP-activated protein kinase in mechanism of metformin action, J. Clin. Invest. 108 (2001) 1167–1174.
[107] J.M.M. Evans, L.A. Donnelly, A.M. Emslie-Smith, D.R. Alessi, A.D. Morris, Metformin and reduced risk of cancer in diabetic patients, BMJ 330 (2005) 1304–1305.
[108] B. Viollet, S. Horman, J. Leclerc, L. Lantier, M. Foretz, M. Billaud, S. Giri, F. Andreelli, AMPK inhibition in health and disease, Crit. Rev. Biochem. Mol. Biol. 45 (2010) 276–295.
[109] D.G. Hardie, AMP-activated protein kinase: maintaining energy homeostasis at the cellular and whole-body levels, Annu. Rev. Nutr. 34 (2014) 31–55.
[110] H.R. Bridges, A.J.Y. Jones, M.N. Pollak, J. Hirst, Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria, Biochem. J. 462 (2014) 475–487.
[111] C. Batandier, B. Guigas, D. Detaille, M.-Y. El-Mir, E. Fontaine, M. Rigoulet, X.M. Leverve, The ROS production induced by a reverse-electron flux at respiratory-chain complex 1 is hampered by metformin, J. Bioenerg. Biomembr. 38 (2006) 33–42.
[112] M. Foretz, B. Guigas, L. Bertrand, M. Pollak, B. Viollet, Metformin: from mechanisms of action to therapies, Cell Metab. 20 (2014) 953–966.