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Mitochondrial and metabolic alterations in cancer cells

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ABSTRACT

Metabolic alterations have been observed in many cancer types. The deregulated metabolism has thus become an emerging hallmark of the disease, where the metabolism is frequently rewired to aerobic glycolysis. This has led to the concept of "metabolic reprogramming", which has therefore been extensively studied. Over the years, it has been characterized the enhancement of aerobic glycolysis, where key mutations in some of the enzymes of the TCA cycle, and the increased glucose uptake, are used by cancer cells to achieve a "metabolic phenotype" useful to gain a proliferation advantage. Many studies have highlighted in detail the signaling pathways and the molecular mechanisms responsible for the glycolytic switch. However, glycolysis is not the only metabolic process that cancer cells rely on. Oxidative Phosphorylation (OXPHOS), gluconeogenesis or the beta-oxidation of fatty acids (FAO) may be involved in the development and progression of several tumors. In some cases, these metabolisms are even more crucial than aerobic glycolysis for the tumor survival. This review will focus on the contribution of these alterations of metabolism to the development and survival of cancers. We will also analyze the molecular mechanisms by which the balance between these metabolic processes may be regulated, as well as some of the therapeutical approaches that can derive from their study.

1. Introduction: cancer and glycolisis

The study of cancer is an ever-growing field, where over the years new concepts and altered physiological processes have been associated with the disease. Metabolism has been extensively studied in relation to cancer, and in particular the ability of tumor cells to rewire and rearrange metabolism in order to have a better growth advantage, survival and invasion capacities. Altered metabolism has for these reasons been acknowledged as one of the 'new' hallmarks of cancer (Fouad and Aanei, 2017; Hanahan and Weinberg, 2000). The first observations of cancer cells metabolism alteration came in 1920 by Otto Warburg and led to the discovery, in several types of cancer, of the so called 'Warburg Effect', where the cells can turn their metabolism towards anaerobic glycolysis, even in the presence of oxygen. In order to adapt their metabolism to the ever-demanding cancer cells growth, the cells develop a plethora of mechanisms, which have been extensively studied over the years (Liberti and Locasale, 2016). They can vary between upregulation of glycolytic enzymes, improved glucose uptake, and down-regulation of oxidative phosphorylation. These processes, as well as the anabolic processes involved in cancer cells, are briefly summarized in Fig. 1. These processes result in what has been defined as a 'metabolic switch' that favors anaerobic glycolysis as a primary metabolic pathway in cancer cells (Yu et al., 2017). The concept of 'metabolic reprogramming' has thus become prominent in cancer research, highlighting how tumor cells are able to rewire their metabolic processes. However, glycolysis is not the only metabolic process that becomes "highjacked" by tumor cells. And even the metabolic processes that have been thought to be downregulated in cancer, such as oxidative phosphorylation (OXPHOS), may play a role in tumor growth and survival. In fact, while it is true that in some cases, a higher OXPHOS rate is related to a better prognosis (Frederick et al., 2020), and that OXPHOS is down-regulated in several cancers, there is evidence of tumors in which OXPHOS is not just used by the cancer cells, but it is upregulated (Evans et al., 2021; Zacksenhaus et al., 2017). Indeed, it has been reported that cancer cells are able to shift their metabolism towards the oxidation of a specific substrate such as succinate in order to sustain tumor progression (Schöpf et al., 2020). Furthermore, other types of metabolisms, such as beta-oxidation of fatty acids and even alteration in specific metabolites such as amino acids, can be used by the same cancer cells to ensure their survival, growth, and to promote invasion. While the concept of 'metabolic switch' that drives

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cancer metabolism towards glycolysis is a well-established concept, also every metabolic process apart from glycolysis has a unique and proper 'switch', intended as a key molecular event, that enhances the metabolic phenotype. The whole concept of 'metabolic reprogramming', then, may need to be adjusted in order to also reflect the different types of switches. This review will focus on the several metabolic alterations apart from glycolysis, and on the molecular mechanisms underlying the various 'switches' that may be activated in cancer. We will also briefly highlight some of the possible therapeutic opportunities that may come from the detailed understanding of the aforementioned molecular basis of metabolisms.

2. Mitochondria in cancer

2.1. The renewed role of the mitochondrion in tumors

Until recent years, the "Warburg effect" was considered the main actor playing in cancer metabolism. It overshadowed other important molecular mediators of metabolism, many of them pertaining to mitochondria. The root of this misjudgment refers to the early notions that surrounded the Warburg effect, for which the ability acquired by malignant cells, responsible for the glycolytic switch, would derive from mitochondrial defects (Warburg, 1956; Warburg et al., 1927). Despite the crucial contribution that this framework generated in the understanding of cancer development (Kubota, 2001), further studies have highlighted that mitochondrial functions play a pivotal role in each step of the process, from transformation to drug-resistance (Cairns et al., 2011; Vyas et al., 2016; Wallace, 2012) (Fig. 2).

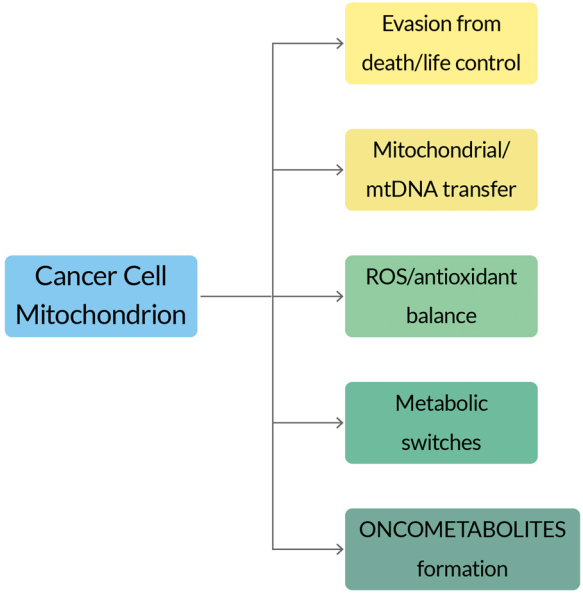

Fig. 2. Cancer and mitochondria. Schematic diagram highlighting the mechanisms by which mitochondria can impact cancer growth and survival. The indicated features have an impact on cancer cell growth and progression, as mitochondria act as direct regulators of pro-tumoral mechanisms.

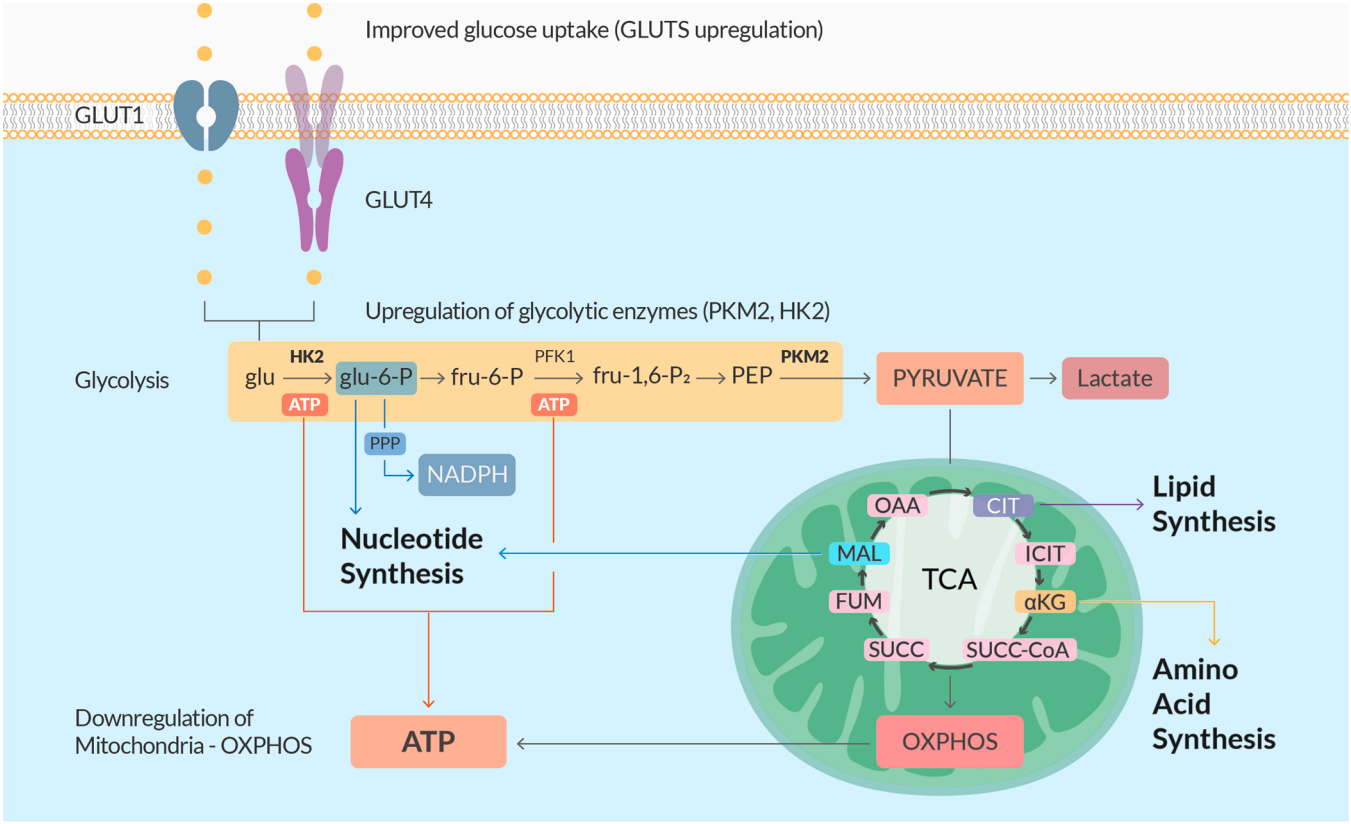

Fig. 1. Cancer and Glycolysis. Schematic diagram showing the most common mechanisms of the glycolytic switch in cancer. In cancer cells, enhanced glycolysis may derive from the upregulation of glucose transporters (such as GLUT1, already present on the cell membrane or GLUT4, that needs translocation from the cytoplasm) in order to increase glucose uptake. This is usually coupled with an increase (in either expression or activity) in key glycolytic enzymes, such as the rate-limiting ones (highlighted in bold) Hexokinase 2 (HK2), and Pyruvate Kinase (shift to the more active isoform PKM2). As a result, glycolysis becomes the main energy source for the cells even in aerobic conditions, and in an overproduction of lactate. The basic Warburg effect observed in cancer cells also involves downregulation of the mitochondrial energy processes TCA and OXPHOS, obtained through an impairment of the mitochondrial function. Figure also briefly shows the basic anabolic processes used in cancer cells, as well as their way, using the Pentose Phosphate Pathway (PPP), to achieve more NADPH production.

In fact, in tumors, the mitochondria may exert many key functions as dynamic regulators of all malignant cellular processes, mainly through a metabolic rewiring strategy (Fendt et al., 2013; Wise et al., 2011). The mitochondrial plasticity potential represents a fundamental tool exploited by tumor cells in all steps of oncogenic occurrence (neoplastic transformation, tumor development and progression, metastatic dissemination and therapeutic response), according to their ever-changing needs (Vyas et al., 2016; Wallace, 2012). In fact, proliferating cells use mitochondria as metabolic machinery to satisfy, the elevated bioenergetic requirements through ATP production, as well as the higher anabolic demand, in terms of building blocks and biosynthesis of macromolecules (nucleotides, lipids and proteins).

The readaptation of mitochondrial metabolism in cancer is regulated by the following mechanisms and an overview of them is shown in Fig. 2.

2.2. ROS production

Among the earlier events of malignant transformation, there is the overproduction of reactive oxygen species (ROS); this is considered one of the major stimuli for tumor onset and progression (Kumari et al., 2018) and mitochondria are considered the main site of ROS production. Because of both, their high reactivity as genotoxic agents (Buechter, 1988) and the intracellular signaling regulating capacity (Gius and Spitz, 2006; Waris and Ahsan, 2006), an accumulation of mitochondrial ROS (mtROS) is linked to the acquisition of an oncogenic phenotype (Sabharwal and Schumacker, 2014). MtROS are generated at the level of the TCA cycle and the Electron Transport Chain (ETC), coupled to NADPH oxidase (Galvan et al., 2017). The superoxide overproduced by cancer cells is rapidly dismuted in H_2O_2 by SOD1/2 (superoxide dismutase 1/2), required for oxidation of some cysteine residues of regulating proteins (among them the best known are Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN), the Src homology 2 domain containing protein tyrosine phosphatase-2 SHP2 and MAPK-phosphatases (MPKs, the dual-specificity protein phosphatases that deactivate MAP kinases), that are responsible for altering redox signaling thus sustaining initiation, survival, and invasion phases of carcinogenesis (Guo et al., 2020).

2.3. Maintenance of redox homeostasis

The imbalance of redox homeostasis, due to high levels of ROS, drives the activation of a programmed cell death signaling (Redza-Dutordoir and Averill-Bates, 2016). The maintenance of a redox balance is therefore fundamental for tumor homeostasis and survival, and for metastatic dissemination (Lignitto et al., 2019; Sayin et al., 2019; Wiel et al., 2019). In order to achieve ROS scavenging, cancers use mechanisms that may be non-enzymatic, such as through NADPH and reduced glutathione (GSH), or enzymatic (e.g., SOD, catalase, GSH peroxidase-GPX-). At the transcriptional level, in many cancer types plays a key role in the redox balance maintenance the up-regulation of NF-E2–related factor 2 (NRF2), by either gain-of-function mutations or degradation of its inactivating ligand Kelch-like ECH-associated protein 1 (KEAP1) (Lignitto et al., 2019; Sayin et al., 2019; Wiel et al., 2019). In other types of tumors is instead involved an enhanced antioxidant capacity, via the pentose phosphate pathway (PPP) and NADPH related production, by up-regulation of TP53 induced glycolysis regulatory phosphatase gene (TIGAR) (Lee et al., 2014).

2.4. Oncometabolites formation

Fumarate, succinate, and the enantiomers of 2-hydroxy-glutarate (2-HG) are the main known oncometabolites acting as transforming factors (Dang et al., 2009). In fact, they are used by cancer cells to progress in tumor development (Thompson, 2009). Their abundance is due to mutations occurred in genes encoding for TCA cycle enzymes, such as succinate dehydrogenase (SDH) and fumarate hydratase (FH), isocitrate dehydrogenase 1 and 2 (IDH1/2) (Dang et al., 2009; Ye et al., 2018), malate or lactate dehydrogenase (Engqvist et al., 2014). They are all involved in a metabolic reprogramming that ensure cancer cell proliferation and tumor progression and aggressiveness. Severe hypoxic conditions have been found to be related with high levels of 2-HG (Intlekofer et al., 2015), the specific mechanism by which the tumorigenic effect is exerted remains to be fully characterized, but they involve DNA methylation and inhibition of DNA repair, as seen in gliomas (Reiter-Brennan et al., 2018). Interestingly, all these oncometabolites are considered competitors of α-ketoglutarate in inhibiting enzymes, such as α-ketoglutarate-dependent dioxygenases, which include also negative regulators of the hypoxia inducible factor (HIF), and regulators involved in DNA methylation and epigenetic modifications such as hypermethylations of cell differentiation-related genes (Baksh and Finley, 2021; Losman et al., 2013). In some cases, TCA cycle enzymes have been shown to modulate gene expression by directly altering specific histones (Martínez-Reyes and Chandel, 2020; Xu et al., 2021; Zhang et al., 2019).

2.5. mtDNA mutations and nuclear DNA mutations affecting mitochondria

The mitochondrial genome (mtDNA) only encodes for 13 proteins involved in the OXPHOS program. Almost all of the remaining mitochondrial proteome is encoded by the nuclear genome. Therefore, mtDNA mutations result in OXPHOS alterations, but the other mitochondrial functions are under nuclear DNA control and their regulatory mechanisms are not yet fully understood. A detailed discussion on mtDNA mutations can be found in this recent review (Hertweck and Dasgupta, 2017).

2.6. Evasion from "life and death cycle" control

The implication of mitochondria in the regulation of the intrinsic apoptosis pathway is well-established (Ciccarese and Ciminale, 2017). Briefly, the balance between apoptosis inhibitors and effectors when is shifted versus the inhibitors conveys on triggering the anti-apoptotic members of the Bcl-2 family that act by binding the pro-apoptotic effectors, such as Bak and Bax, inlaid in the outer mitochondrial membrane (OMM) and preserving its integrity. Once the OMM integrity is disrupted, the release of pro-apoptotic effectors, such as cytochrome c, is allowed thus triggering the apoptotic program through the activation of the caspases cascade. The altered mitochondrial outer membrane permeabilization (MOMP) and mitochondrial permeability transition (MPT) as well as a decrease in mitochondrial membrane potential and the telomere erosion are early irreversible steps of the apoptotic process. In fact, all of these processes have causative roles for the triggering of the programmed cell death (Czabotar et al., 2014; Izzo et al., 2016; Singhapol et al., 2013).

2.7. Mitochondria and TME-cells metabolism

Mitochondria are sensors of different types of stress, such as nutrient depletion, acidosis, hypoxia, energy imbalance (Khacho et al., 2014; Liesa and Shirihai, 2013; McElroy and Chandel, 2017; Petricca et al., 2019). For these reasons, mitochondria are defined as the guardian of metabolism. The crosstalk between mitochondria of cancer cells and metabolism of the tumor microenvironment (TME) cells, including endothelial, stromal and immune (CTLs, regulatory T and myeloid) cells, is (Li et al., 2019b; Makowski et al., 2020; Ryan and O'Neill, 2020) another hallmark of tumors, developed to survive in limiting conditions. In this regard, recent studies confirmed that limiting levels of oxygen and glucose do not block the increase of tumor bulk. This occurs thanks to mitochondrial adaptations, which allow to alter signaling pathways affecting gene expression, such as HIFs, required for the metabolic

rewiring, and so for tumor survival (Hollinshead et al., 2020; Jacobs et al., 2008; Mukherjee et al., 2020; Reinfeld et al., 2021). As a response to tumor development, the mitochondria mediate the release of danger-signaling products (such as ATP, ROS, mtDNA) that allow recognition of cancer cells by immune cells. In fact, mtROS are necessary to trigger the activation of T-cells, subsequently to T-cell receptor binding, and are also necessary for the activation of some transcription factors, including NF-kB and nuclear factor of activated T-cells 1 (NFAT), required for a good T-cells functionality (Sena et al., 2013; Weinberg et al., 2015). ROS and mtDNA are also important in inducing the inflammasome activation, a key part of the anticancer immunity program (Mills et al., 2016).

2.8. Mitochondrial dynamics, cross-link with metabolism

A high mitochondrial turnover characterizes many types of cancer cells (Grasso et al., 2020) and the plasticity potential of these organelles reflects their dynamic nature. In fact, mitochondria are capable to move inside the cell, and to interact with each other, creating the so-called "mitochondrial network", and even with other types of cellular organelles (Vafai and Mootha, 2012). Mitochondria are also capable to transfer themselves in neighboring cells (Dong et al., 2017). The mitochondrial network undergoes a finely-tuned quality control mechanism, including fusion and fission events and mitochondrial biogenesis and mitophagy, the basic processes through which they fuse, divide, renovate and eliminate their dysfunctional portions and waste (Chan, 2012; Iorio et al., 2022; Mao et al., 2013). Hence, a dynamic balance of biogenesis, fission, fusion, and degradation processes is pivotal for the correct maintenance of healthy mitochondrial pools.

Mitophagy has a central role in the occurrence of some fundamental metabolic features of cancer cells. In fact, a direct relationship exists between compromised mitochondria and decrease in tumor development and progression. Severe defect of mitochondria functionality, such as in mitophagy, are related to remission in different types of tumor models (Guo et al., 2013; Joshi et al., 2015; Rao et al., 2014; Rosenfeldt et al., 2013). There is evidence that maintaining the integrity of a dynamic mitochondrial hub, as well as a functional mitophagy, support the efficiency of mitochondrial metabolism. In fact, it has been demonstrated that the increase in metabolism and signaling functions, because of aberrant mitochondria functions such as in mitophagy, results in decreased progress to malignancy in different types of tumor models (Kimmelman and White, 2017). Other evidences have shown that the differentiation of a particular cell population inside the tumor, such as folliculin (FLCN)-deficient oncocytic BHD (Birt-Hogg-Dubé syndrome) tumors, results in the accumulation of a functional mitochondria pool and increased cell survival. In this process, activation of mTORC1 alongside mitochondrial biogenesis, can regulate the mitophagy rate (Hasumi et al., 2012).

From another point of view, the fission/fusion events contribute to the removal of ROS-overproducing and dysfunctional mitochondria, to elicit a ROS reduction (Galluzzi et al., 2017), and obtain an advantage in terms of survival. It has also been reported that hypoxia activates mitochondrial fission events to promote damaged mitochondria elimination by mitophagy, lowering mtROS production to a harmless level (Fuhrmann and Brüne, 2017). Recent data have demonstrated that mitochondrial dynamics remain intact in severely hypoxic pancreatic ductal adenocarcinoma (PDAC) cancer cells and assume a pivotal role in cell growth and mitochondrial oxidative activity (Hollinshead et al., 2020). This well explain why dysregulation of these processes is directly connected to cell viability. Transmission electron microscopy (TEM) analyses have demonstrated that human pancreas adenocarcinoma (8988 T) cells are capable to maintain their overall fission, fusion and degradation balance, thus maintaining integrity of mitochondrial pools, in terms of number and morphology, under severe hypoxic conditions. In accord with this, cells in low-oxygen environment exhibited a significant drop in mitochondrial mass. Interestingly, the cristae number and density were found as indicative of mitochondrial fitness (Hollinshead et al., 2020). However, the generalization that mitochondrial fragmentation impairs the respiratory function and is fatal to cell viability were found to be less accurate. Dynamin-related protein 1 (Drp1) promotes mitochondrial fission and quality control and inhibition of Drp1- mediated mitochondrial fission can also affect mitochondrial function (Liesa and Shirihai, 2013). For example, epithelioid cervix carcinoma (HeLa) cells with down-regulation of Drp1 expression show a decrease of both, complex IV activity and state-3 (maximal ATP synthesis) and state-4 respiration (proton leak or uncoupling) (Benard et al., 2007). Accordingly, other recent evidences have shown that the inhibition of mitochondrial fission may represent a promising new therapeutic approach for pancreatic cancer (Courtois et al., 2021).

Interestingly, cancer cells have been shown to elicit an intercellular communication based on mitochondria, that has been defined "mitocommunication". This may consist on a horizontal transfer of mitochondrial material, such as mtDNA, proteins or even whole organelles, through nanotubular-tunneling structures, extracellular vehicles, or gap junctions (Guescini et al., 2010; Mistry et al., 2019). In line with this, recent studies focused on mitochondrial transfer have shown that this process can restore the tumorigenic capacity in mito-ablated (ρ0) cells (that lack mitochondrial DNA and are therefore incapable of aerobic ATP synthesis) (Dong et al., 2017). In addition, recent evidences highlighted the involvement of a mitochondria-to-nucleus communication, known as retrograde mitochondrial response (MRR), in the latest stages of tumor progression where MRR can trigger a nuclear response that leads to activation of the survival pathway mediated by NF-kB (Desai et al., 2020).

However, despite the efforts in better understanding cancer metabolism, and given the flexibility of mitochondrial functions and dynamics in supporting cancer development and the adaptative response related resistance, further studies are needed in order to leverage these processes to develop an effective cancer therapy.

3. The role of OXPHOS from tumor progression to therapy resistance

In the last few years, the concept of a dynamic metabolic heterogeneity of neoplastic cells, due to the diversity of carbon fuels, is emerging as an alternative to a univocal permanent metabolic switch.

Several studies highlighted that in cancer cells mitochondria are still functionally active and are capable to maintain OXPHOS capacity (Frezza and Gottlieb, 2009; Jose et al., 2011). For instance, they are a primary ATP source in some breast cancer (Guppy et al., 2002). Moreover, it has also been demonstrated that glycolytic neoplastic cells not only retain OXPHOS but are able to restore oxidative metabolism under glycolysis-inhibited conditions (Bonnet et al., 2007; Fantin et al., 2006).

Indeed, a growing body of evidence supports a dual ability of tumors to utilize both the glycolytic and oxidative metabolic pathways (Martin-Valencia et al., 2012; Obre and Rossignol, 2015). Alternative carbon sources, such as glutamine, serine/glycine and fatty acids, are the oxidizable substrates for the TCA cycle anaplerotic pathway.

Interestingly, in cancer cells a new OXPHOS metabolic profile has been found. Several studies on lymphocytic B-cells and a subtype of melanoma overexpressing the peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) showed a clear OXPHOS gene-expression pattern (Monti et al., 2005), related to the expression of ETC units and TCA cycle enzymes (Caro et al., 2012; Haq et al., 2013; Vazquez et al., 2013). In these tumors the PGC-1α gene has been shown to be under control of the melanocyte specific transcription factor (MITF), resulting in enhanced PGC-1α dependent mitochondrial respiration. Maintaining elevated the OXPHOS rate, supports tumor progression and spreading. In recent studies, several types of tumors have been shown to acquire a stronger OXPHOS dependence and an increase in aggressiveness (Hollinshead et al., 2020). Furthermore, a mitochondrial switch to OXPHOS phenotype, expressed through ETC overload, has been shown to be

involved in promoting the migration and invasive potential, clonogenicity of cancer cells and metastasis formation (Porporato et al., 2014). In addition, novel findings on the metabolic switch of cancer stem cells (CSCs) and on the epithelial-to-mesenchymal transition (EMT, a process enabling cancer spread through metastatic dissemination) demonstrated an overall increase in mitochondrial functions and the utilization of OXPHOS as the preferred metabolism to produce energy in CSCs, thus revealing the OXPHOS addiction as a necessary process to maintain tumorigenic potential and acquire aggressiveness (García-Heredia and Carnero, 2020; Lai et al., 2020). A growing body of evidence demonstrates a direct link between OXPHOS and resistance to therapy. In fact, the use of inhibitors of certain pathways, such as the pro-glycolytic MAPKs (Corazao-Rozas et al., 2016) or the pro-mitosis aurora kinases (Zhang et al., 2021c), induces chemoresistance and a sustained OXPHOS- addiction as alternative mechanisms to promote tumor cells survival.

Furthermore, in cancer, a metabolic heterogeneity has also been found, in fact, the same oncogenic driver can elicit different metabolic pathways, even in the same tissue, while in distinct tissues the activation of different oncogenic molecules leads to a similar metabolic profile (Mayers et al., 2016; Yuneva et al., 2012). The mTORC1 pathway has been found deeply involved in the direct control of mitochondrial functions and dynamics, such as mitochondrial biogenesis (Khan et al., 2017). Furthermore, a signaling network that implies alterations of LKB1/AMPK axis in tumorigenesis, has also been established. The role assumed by AMPK, as metabolic stress sensor and mitochondrial homeostasis master regulator, allows to exert both, pro- or anti-tumor functions. In the presence of distinct tumor-driven oncogenic patterns, AMPK mediates ULK1-driven upregulation of mitophagy, necessary for cell survival during starvation (Faubert et al., 2015), or activates PGC-1α-mediated mitochondrial biogenesis, as well as fission/fusion dynamics, ensuring to the cancer cell a metabolic plasticity (Faubert et al., 2015). Several works have also suggested that the Bcl-2 pathway, beyond its role as inhibitor of programmed cell death, is implicated in promotion of a pro-survival oxidant state, potentiating ETC activity in leukemia cells, by promoting cytochrome c oxidase (COX) activity on respiratory complex IV. Bcl-2 physically interacts with the COX Va subunit, leading to Complex IV and V assembly and, thus, to mitochondrial respiration (Chen and Pervaiz, 2007).

Moreover, together with the activation of KRAS and the loss of p53 (Biancur et al., 2021; Zhu et al., 2021), has been observed the sustained expression or up-regulation of other genes encoding not only for glycolytic enzymes but also for ETC subunits and TCA cycle components (Ducker et al., 2016; Martínez-Reyes and Chandel, 2020; Oshima et al., 2020). Consequently to a higher rate of ETC activation, the mitochondrion releases a higher amount of ROS and, at the same time mediates a PGC-1α-dependent increased level of antioxidant response.

3.1. OXPHOS and the potential advantages of Supercomplexes formation

The components of the respiratory machinery, the ETC complexes, consist of factors and subunits assembled or disassembled depending on the ETC tasks. Their structure and organization sustain cancer cells with an oxidative metabolic profile to support their needs, resulting in an elevated rate of respiration and an antioxidant counterbalance, respect to the higher levels of ROS production, in line with the ROS rheostat theory (Raimondi et al., 2020). Although the strict correlation between the metabolic switches and mitochondrial complexes composition and activity are still under investigation, altogether these evidences drive to the renewed concept of a tumor promoting role for mitochondrial respiration (Fig. 3).

mtDNA encodes for 13 proteins, such as the ETC proteins and the COX subunits, that are essential for the OXPHOS-machinery. Mutations in mtDNA and nuclear genes encoding for proteins implied in mitochondrial respiration, occur in OXPHOS-dependent cancer cells, leading to an increased ROS production and to an overall OXPHOS upregulation (Schon et al., 2012). Mutations in Mitochondrial Respiratory Complex I, most commonly on ND2 or ND6 subunits, are selected mutations that enhance the ETC activity, resulting in a higher rate of respiration and an improved ROS-scavenging mechanism; these changes are demonstrated to be also implicated in metastatic dissemination (Raimondi et al., 2020). Furthermore, several reports have shown a hierarchical higher level of organization of the Complexes in “Supercomplexes” (Acín-Pérez et al., 2008; Schägger and Pfeiffer, 2000). In fact, it has been reported that the individual respiratory chain complexes can undergo mutual assembly to form the quaternary structures of the Supercomplexes, distributed within the folds of the inner mitochondrial membrane. (Enríquez, 2016). For example, the assembly of Complex I is often also revealed with Complex III and IV, forming the functional element so-called ‘respirasome’, or even with other Supercomplexes (Schägger and Pfeiffer, 2001). Interestingly, it has been shown that the shape of mitochondrial cristae determines the respiratory chain Supercomplex formation and this is strictly related to respiratory efficiency, in terms of a more efficient electron transfer activity (Cogliati et al., 2013). As a result, the increasing efficiency of ETC Complexes and Supercomplexes decreases ROS accumulation below the critical toxic threshold and manages redox balance to promote cancer cell survival (Hollinshead et al., 2020; Ikeda et al., 2019).

In favor of the OXPHOS-dependence by some tumors, a direct implication of Supercomplexes assembly in tumorigenesis of breast and

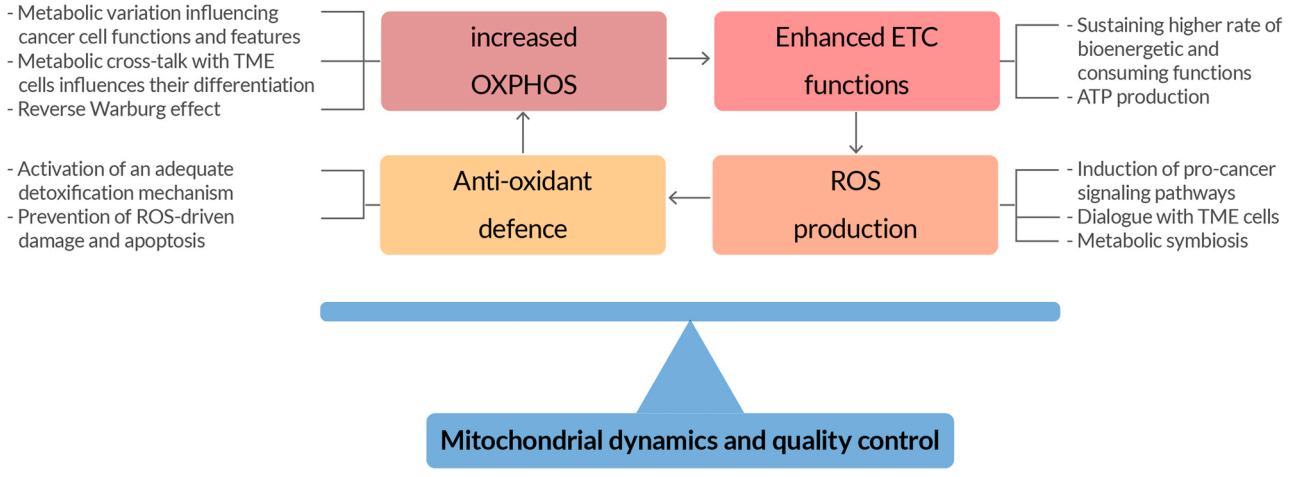

Fig. 3. Mitochondrial molecular mechanisms leading to cancer progression. Mitochondrial dynamics and quality control regulate the balance between OXPHOS, ETC functions, ROS production and anti-oxidant defense, pointing out to the importance of mitochondria in this field.

endometrial cancers has recently been demonstrated, together with increased hypoxia tolerance and metabolic alterations (Ikeda et al., 2019). Furthermore, respiratory Supercomplexes are required to promote severely hypoxic pancreatic ductal adenocarcinoma (PDAC), maintaining intact mitochondrial efficiency, such as membrane potential, morphology, and the oxidative metabolic activity needed for key metabolites synthesis and tumor growth, in vitro and in vivo (Hollinshead et al., 2020). In particular, authors showed that this phenotype relies on the presence and the functionality of mitochondrial respiration. Hollinshead and collegues, disrupted the assembly of respiratory Supercomplex by the genetic targeting of SCAF1 (supercomplex assembly factor 1, also known as COX7A2L), thus reducing the overall mitochondrial efficiency, without affecting the expression of individual ETC complexes. These results demonstrate a direct dependence of mitochondrial respiration and efficiency on Supercomplex structures to preserve healthy mitochondrial pools, hypothesized by the authors to enable the most efficient use of the low levels of oxygen available (Hollinshead et al., 2020). Furthermore, the analyses of ROS production in order to confirm the role of Supercomplexes in maintaining ETC efficiency in vivo, have suggested that the lack of Supercomplexes formation increases ROS-mediated damage and cell death as a result of impaired ETC efficiency (Hollinshead et al., 2020). This confirms that cancer cells have evolved mechanisms to reduce mtROS and the related cytotoxic damage threshold (Humpton et al., 2019).

3.2. OXPHOS and therapeutic strategies

The OXPHOS-addictions may render tumors sensitive to OXPHOS inhibitors. Targeting ETC components, thus inducing levels of ROS capable to trigger cell death (Dong and Neuzil, 2019), is an interesting possibility to target cancer cells. Most of the ETC inhibitors that have been studied target Complex I and have demonstrated efficacy in several tumors. Among them there are: metformin (Wheaton et al., 2014), compound ME-344 (Quintela-Fandino et al., 2020), and the more recent IACS10759 (Carter et al., 2020), used also to prevent resistance in leukemia therapy (Panina et al., 2020). Furthermore, targeting Supercomplexes formation, induces cancer cells to undergo ROS-mediated damage and cell death. Recent works have shown that the inhibition of the Supercomplexes, and respirasome assembly, affects the electron transfer efficiency, and results in an impaired mitochondrial respiratory capacity, specifically targeting hypoxic PDAC metabolism and proliferation, as well as tumor growth in vivo (Hollinshead et al., 2020).

A burgeoning interest is ongoing on the search for a selective therapy targeting cancer cells and sparing normal ones. It has been reported that cancer cells are dependent on cytosolic NADH for ATP production (Lee et al., 2020b). Also, clinical data regarding patients with loss of LKB1 and treated with platinum-based anticancer drugs show a higher sensitivity to oxidative damage. These observations are in good agreement with the concept that tumorigenesis requires a specific mtROS level, versus a lower cytosolic counterpart, to elicit the best pro-tumoral mitogenic signaling. In order to increase mtROS above the harmful level, the use of antioxidants inhibitors could represent a selective strategy to eliminate cancer cells (Ciccarese and Ciminale, 2017; Silic-Benussi et al., 2018). In a further recent study, Ciccarese and colleagues analyzed engineered nanoparticles (NPs), capable of killing cancer cells by altering their metabolic flux and redox homeostasis; the authors showed a selective effect for these nanoparticles on malignant cells with low side effects on the healthy counterpart (Ciccarese et al., 2020). In this regard, new engineered NPs with metals, as well as arsenic-, iron-oxide-, manganese-, are capable to penetrate subcellular structures and efficiently trigger cancer cell death, by increasing ROS production through directly reducing the activity of ETC complexes, thus resulting in mitochondrial function impairment (Ashrafi Hafez et al., 2019; He et al., 2016; Subastri et al., 2018).

Moreover, Lee and colleagues found that cancer cells show a direct dependence of autophagy activation on an OXPHOS-driven ATP production. In this study, the authors observed how some cells of the tumorigenic pool were killed by chemotherapy, but at the same time the cancer cells were able to later acquire resistance and survive anticancer drug treatment through autophagy induction; this event was demonstrated to be linked to OXPHOS activation. So, OXPHOS inhibition may guarantee anti-cancer drug efficacy and reverse drug resistance (Lee et al., 2020b). Given that ATP depletion in mitotic cells causes cycle arrest by disrupting energy homeostasis (Park et al., 2018), multi-approach therapies, including OXPHOS targeting, seem to be interesting tools to face cancer growth (Kosaisawe et al., 2021). Therapeutic targeting of ETC components (complex I, II, III, IV or ATP synthase), has been demonstrated to potentiate the anticancer efficacy of alisertib and others mitotic kinase inhibitors, as a consequence of a resulting highly OXPHOS-addicted status and a severe energy drop in ATP-dependent mitotic cells. The combinatorial use of metformin and alisertib also synergistically reduces in vivo tumor growth (Zhang et al., 2021c).

3.3. Metabolic reprogramming occurs in the tumor microenvironment: OXPHOS-glycolysis, a mutual interaction?

Mitochondrial metabolism also seems to differently influence differentiation of TAMs (tumor-associated macrophages), the main tumor microenvironment (TME) constituent, which plays a fundamental role in tumor growth, development, invasion, and metastasis (Liu et al., 2021).

To circumvent nutrient competition, cancer cells activate a strategy based on a metabolic crosstalk, directly stimulating the TME-cells through the release of ROS. An important feature, known as the “reverse Warburg effect”, regulates the metabolic interplay between the tumor bulk and its TME, such as CAFs (cancer-associated fibroblasts) and MSCs (mesenchymal stromal cells), as well as the peripheric cell population. As seen in melanomas and lung cancers, it has been reported the existence of an OXPHOS-dependent (tumor bulk) and an OXPHOS-independent (the external cell population of the tumor, as well as its microenvironment) cell population. In this context, it is established a metabolic cross-talk between the OXPHOS-dependent cells and the glycolysis-dependent ones, defined ‘metabolic symbiosis’. This mutual interaction acts via a positive feedback loop where lactate, a byproduct of the glycolytic pathway, is captured by the OXPHOS-dependent neighboring cells, which in turn stimulate them to increase the glycolytic rate, through a ROS-mediate mechanism (Duda et al., 2020; Ho et al., 2012). Although these processes are not yet well characterized, these types of metabolic symbioses are redefining the role of aerobic glycolysis in cancer (Ma and Zong, 2020).

The mechanisms of increased OXPHOS described in this section, ultimately resulting in increased cancer metabolism, are integrated with all the other processes regulated by mitochondria, including ROS production, activation of the antioxidant response and enhanced ETC functions (as summarized in Fig. 3). Mitochondrial dynamics, as well as their quality control, act as regulators of the balance between all these mechanisms. for this reason, their role in cancer should be further investigated.

4. Fatty acid oxidation and cancer

Fatty Acid Oxidation (FAO) is the process that breaks down a fatty acid into Acetyl-CoA units. The process takes place in the mitochondrial matrix and couples the cyclic and progressive shortening of fatty acids with the production of Acetyl-CoA (which enters the Krebs Cycle and is oxidized to generate ATP), NADH and FADH2 (used for ATP production in the electron transport chain). FAO can also target unsaturated and polyunsaturated fatty acids, requiring in this case additional enzymatic steps. FAO regulation is strictly related to the nutritional status and to the relative abundance of lipids: the higher the concentration of free fatty acids, the higher will be the rates of cellular uptake and oxidation of fatty acids (Schulz, 2013).

FAO takes place at the peroxisomal level as well, and targets the very long, or branched fatty acids that mitochondria cannot process (Schrader et al., 2015). The metabolites coming from peroxisomal FAO can migrate to the mitochondria for further metabolic processing, and several studies have also shown that the peroxisomes and mitochondria can interact in order to coordinate their activities (Schrader et al., 2015; Visser et al., 2007; Wanders et al., 2016).

Cancers with a very fast rate of growth, rely on FAO for their metabolic demands, and many types of tumors use it for survival, proliferation, and invasion (Maher et al., 2018; Monaco, 2017; Pacella et al., 2018). This is the case of gastrointestinal (GI) cancers, pancreatic cancers, and metastatic breast cancers, in which reports have shown an overall increase in FAO (Aiderus et al., 2018; Hou et al., 2020; Jariwala et al., 2021; Lee et al., 2020a; Lin et al., 2020). This is usually coupled with a decreased glucose availability, and not necessarily with an increase in OXPHOS. More than that, the most aggressive tumors show an upregulated FAO. Evidence came from early studies in GI cancer, where the in vivo investigation on the relation between obesity and cancer (induced by high fat diet) highlighted increased oxygen consumption, but reduced respiratory rates, thus pointing to a shift towards fat metabolism (Khasawneh et al., 2009). Moreover, as shown in several studies in colon cancer, inhibiting the synthesis of fatty acids through blockage of carnitine palmitoyltransferase 1 (CPT1) or 3-ketoacyl-CoA thiolase (3-KAT), the rate limiting enzymes of the FAO process (Jariwala et al., 2021; Maher et al., 2018)(Young et al., 2021), have been effective to achieve cancer regression.

The various types of cancer can increase mitochondrial FAO using several different mechanisms, both alone and in combination. They include: *Increased Fatty acids uptake, Lipolysis, De novo Fatty Acid Synthesis, Fatty Acids Activation, Peroxisomal FAO.*

4.1. Increased fatty acids uptake

Similarly to the principle on increasing glucose uptake, in order to increase aerobic glycolysis, increasing fatty acid uptake leads to increased FAO in cancers. In addition, increasing lipids uptake has the effect of reducing the amount of glucose taken up and utilized by the tumor cells (Li et al., 2021a; Liu et al., 2010; Lupien et al., 2020). Studies in ovarian and bladder cancers showed, in cisplatin-resistant tumor cells, that the metabolic index (intended as the ratio of fatty acids uptake versus glucose incorporation) was shifted towards FA, and consequent FAO, implying that an aggressive tumor relies preferentially on FAO rather than glycolysis (Jin et al., 2018; Li et al., 2021a). Cancer cells, then, can acquire the needed fatty acids through uptake of dietary lipids or through the uptake of exogenous fatty acids released by cancer-associated adipocytes (CAA) (Nieman et al., 2011), or they are obtained from the tumor microenvironment (Kolonin, 2021). A possible molecular mediator of this process is the membrane protein CD36/SR-B2, responsible for 50% of the FA uptake in human and mice (Hao et al., 2020). It is localized in caveolae, and actually needs them for its activity. The protein acts as a scavenger receptor, causing the internalization of the FA via an endocytosis process. The precise mechanisms by which the fatty acids pass through the plasma membrane is still unclear. Nevertheless, prostate and ovarian cancers with an increased lipid metabolism exhibit high levels of CD36, implying its importance for lipid uptake in tumors (Glatz and Luiken, 2017) (Hao et al., 2020).

4.2. Lipolysis

Tumor cells can enhance the process of lipolysis, that normally hydrolyze triglycerides into glycerol and then free fatty acids, in order to obtain more substrates for FAO and an enhanced metabolic response. One key enzyme for this process is Lipoprotein Lipase (LPL), which is a limiting enzyme for the lipolysis process and hydrolyzes triacylglycerols and phospholipids from lipoproteins (Kuemmerle et al., 2011). Indeed, several types of cancers such as triple-negative breast cancer and cervical cancer, have increased levels of LPL, pointing out to a major availability of fatty acids (Abumrad et al., 2021; Senga et al., 2018; Zhang et al., 2020b). It is important to note that LPL is an extracellular enzyme, usually expressed in the tumor microenvironment: this means that cancer cells have to increase their lipid uptake, mainly by increasing CD36, in order to obtain the fatty acids derived from lipolysis. LPL can also increase cancer cells lipids uptake with a different mechanism that involves the upregulation of the very low-density lipoprotein receptor (VLDLR): a recent study in breast cancer cell lines highlighted a mechanism in which they work in concert to rapidly internalize lipoproteins (Campion et al., 2020), making the cells resistant to drugs by targeting the synthesis of fatty acids. VLDLR has thus been found to be a very important mediator of the whole process, causing the internalization by cancer cells of lipoproteins that will then be degraded into fatty acids (He et al., 2010; Kim et al., 2017).

4.3. De novo fatty acid synthesis

Another way to increase FAO in cancers, other than increasing lipid uptake, is by synthetizing more fatty acids to be oxidized. That allows the cancer cells to survive even in low-nutrient environments (Vogel and Schulze, 2021). Upregulating key genes involved in the *de novo* synthesis, usually a process active at very low levels in most tissues, is the way used by several cancers. This is the case of the fatty acid synthase FASN, a key enzyme, in this process, with a wide array of functions (Fhu and Ali, 2020): it is found overexpressed in several cancers (Madigan et al., 2014) (Cairns et al., 2021; Sena and Denmeade, 2021), usually due to an increase in EGF, HER2, and PI3K/Akt/mTOR mediated pathways (Raab et al., 2021; Wagner et al., 2017) (Jin et al., 2010). This results in enhanced synthesis of fatty acids and increased lipid metabolism. Other molecular mediators involved in this process are the FA-binding proteins (FABPs), that regulate lipid metabolism but have a role in lipid uptake as well. Recent studies highlighted a role for those proteins in cancers: FABP5 is upregulated in prostate, colon and breast cancer, both via epigenetic mechanisms and direct gene upregulation (Liu et al., 2011; Lv et al., 2019; O'Sullivan and Kaczocha, 2020; Senga et al., 2018; Seo et al., 2020; Zhang et al., 2020b). This upregulation of key genes related to lipid synthesis and metabolism, results ultimately in enhanced cancer progression and metastasis, and a shift towards FAO rather than glucose utilization. Another FABP family member, FABP7, is also important for both new FA synthesis and lipolysis: its overexpression in breast cancer causes a dramatic shift in FAO utilization and an increased fatty acid synthesis (Kawashima et al., 2020; Kwong et al., 2019). Moreover, when FABP7 signaling is upregulated (due to PPARα upstream signaling) cancer cells lose the ability to rely on glycolysis for survival, becoming completely dependent from lipid metabolism (Kwong et al., 2019).

De novo fatty acid synthesis can also be dependent on the PI3K/Akt/mTORC1 pathway. The process functions through the Sterol Regulatory Element-binding Proteins (SREBPs), key mediators in the lipid synthesis (Sato, 2010). As seen in hepatic and lung cancers, the mTORC1 mediated pathway directly regulates SREBP1 at the transcriptional and post/translational level, resulting in a direct effect in proliferation and metastasis (Han et al., 2015; Peterson et al., 2011; Zhang et al., 2020a). Furthermore, mTORC1 can also act as a lipid sensor. In fact, high concentrations of fatty acids have been shown to activate the pathway in a phosphatidic acid (PA) dependent manner (Menon et al., 2017).

4.4. Fatty acids activation

Fatty Acids activation is an additional step to make fatty acids available for the beta-oxidation. A series of enzymes belonging to the long-chain acyl-coenzyme A synthases (ACSLs) family catalyze the conversion of fatty acids into fatty Acyl-CoA, that enter the TCA cycle after the FAO process (Ellis et al., 2010). All of these enzymes are upregulated in several cancers, as shown in different recent studies in breast, prostate, liver, colon and lung cancer (Cao et al., 2010; Ma et al.,

2021; Ndiaye et al., 2020; Radif et al., 2018). Their mechanism of activation varies from transcriptional activation by peroxisome proliferator-activated receptors (PPARs) or nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) (Cao et al., 2010), to post-translational modifications (Vargas et al., 2016), tumor inflammation (Ma et al., 2021) and miRNA activity (Cruz-Gil et al., 2018). The direct effect of this upregulation is represented by the increased lipid accumulation in cancer cells, and the dramatically increased tumor growth and invasive capacity ultimately caused by increased fatty acid metabolism and increased FAO. Each member of the ACSLs family can be involved in a different aspect of the tumor progression: for a wider understanding of this particular subject, we refer the reader to a recent review (Quan et al., 2021).

4.5. Peroxisomal FAO

Peroxisomal FAO is also deeply intertwined with cancer. In fact, the process is downregulated in some tumors, especially the ones that show a high HIF level like the renal carcinoma (Frederiks et al., 2010; Walter et al., 2014). Reduced peroxisomal FAO is generally related to damaged peroxisomes as well, as seen in colon, breast and liver cancer (Kim, 2020). However, reports have shown an increase of peroxisomal FAO in prostate, colon, gastric cancers, and melanoma (Jiang et al., 2003; Jindal et al., 2016; Shen et al., 2020; Valença et al., 2015), pointing out to a tissue-specific role for the process. Nevertheless, peroxisomal FAO has been considered a possible target for prostate cancer therapy, by targeting the α-methylacyl-CoA racemase (AMACR) enzyme, a key mediator of the process (Yevglevskis et al., 2019).

All these mechanisms, pointed towards an upregulation of fatty acid oxidation, often work in combination, in order to sustain a higher lipid metabolism, often at the expense of glycolysis in highly proliferating cancer cells, as seen in breast and prostate cancer. For instance, LPL upregulation (that means more lipids available in the tumor ECM) is followed by CD36 increase (meaning more lipid uptake). An overview of the involved mechanisms is shown in Fig. 4. The combination of therapies targeting the various steps of fatty acid oxidation could be pivotal for the treatment of those cancers with a high growth rate. A possible combination therapy could be represented by the inhibition of a key FAO (both mitochondrial and peroxisomal) enzyme such as CPT1, coupled with FASN targeting, in order to stop *de novo* fatty acid synthesis

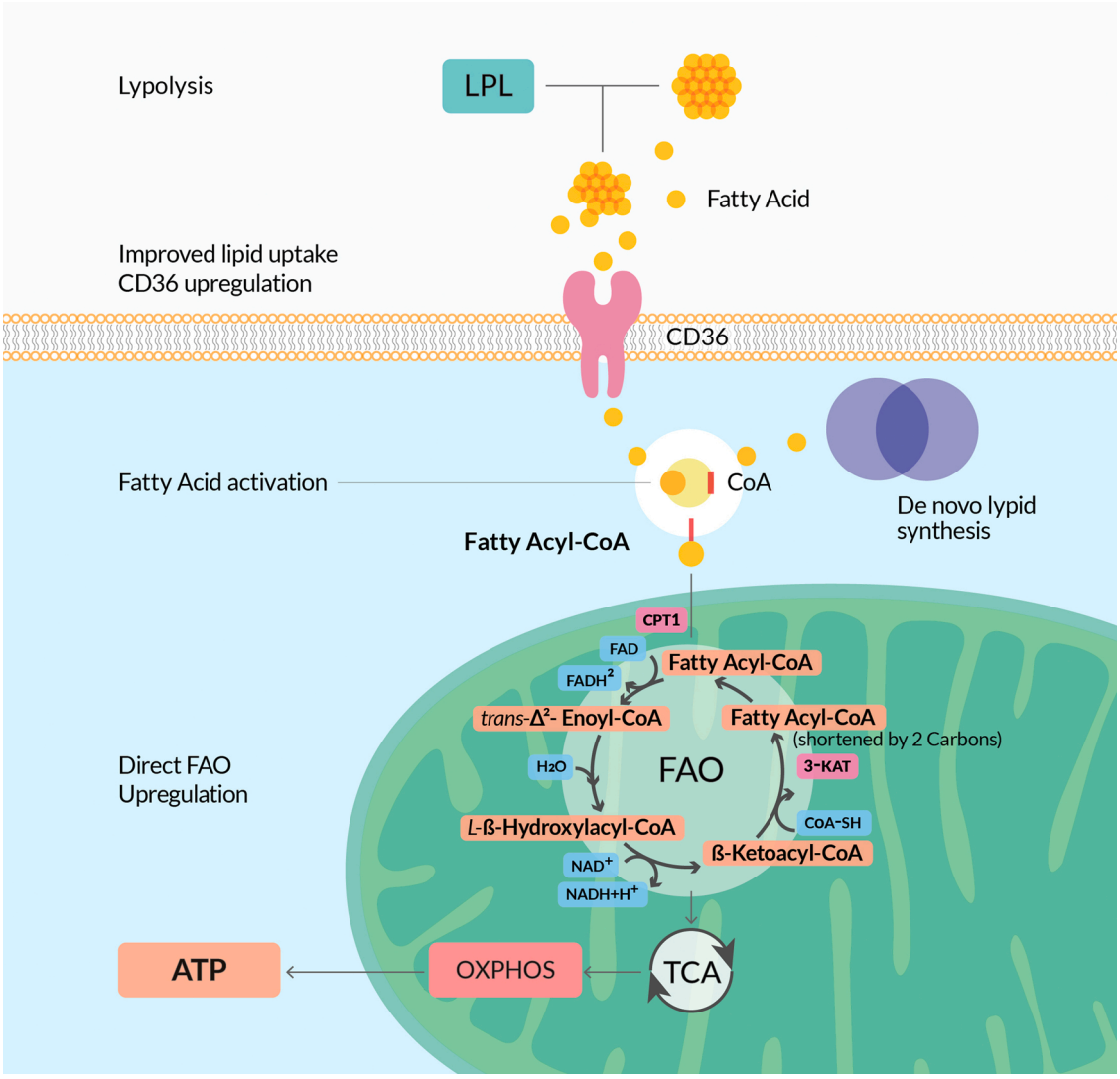

Fig. 4. FAO and Cancer. Summary of the molecular mechanisms found in cancer cells and used to enhance lipid metabolism, in the form of fatty acid oxidation (FAO) for growth and survival. Fatty acids (FA) can be obtained from the tumor microenvironment by "breaking" the extracellular lipoproteins and by enhancing FA uptake in cancer cells via CD36 upregulation. This results in increased FA into the cell. FA deriving from these processes as well as from de novo synthesis, then, undergo the process of activation (upregulated in several cancers), that allows them to enter the FAO process ultimately thus resulting in more ATP production. FAO itself can be enhanced in cancers, by upregulating its rate-limiting enzymes such as CPT1 or 3-KAT.

(new, less toxic FASN inhibitors are currently being used in phase I studies (Zaytseva et al., 2018)), as well as CD36 inhibition to counteract a possible tumor resistance, as recently seen in colorectal cancer (Drury et al., 2020).

5. Alterations in amino acids metabolism and possible therapeutic strategies

The actively proliferating cancer cell is highly demanding for energy. Metabolism of amino acids beyond protein synthesis is one of the mechanisms that cancer cell exploits to match its energy needs. Furthermore, amino acids metabolism is deeply involved with control of normal and cancer cell fate through regulation of cell survival and death (Suraweera et al., 2012).

The metabolism of several amino acids has been implicated in the growth advantage acquired by cancer cells. Many of these amino acids need to be synthesized, including arginine, asparagine, glutamine, glycine, proline, serine, while others, such as methionine, are essential amino acids and, thus, they must be supplied through the diet. In cancer cells, in order to meet their high demand for amino acids, is enhanced the amino acids uptake, through the enhancement of plasma membrane transporters activity (Fuchs and Bode, 2005; Kandasamy et al., 2018, 2021; Liu et al., 2018).

Most of the amino acids analyzed below activates the mammalian target of rapamycin mTOR under the form of the mTORC1 complex. This complex controls protein translation by regulating the activity of the S6K kinase and by phosphorylating, and thus by inhibiting, the negative regulator 4EBP1 of the initiator of protein synthesis complex (Fig. 5a, b). The involvement of mTORC1 functions in cancer have been widely studied, and it is at the center of numerous therapeutical strategies (Popova and Jücker, 2021). The amino acids mechanism of mTORC1 control involves the lysosomal transporter SLC38A9 belonging to the amino acid–polyamine organocation (APC) superfamily of transporters. This is a component of the RAG-Ragulator complex that mediates the activation of mTORC1 (Di Malta et al., 2017) by causing its anchorage to the lysosomal membrane and its interaction with the small GTPase Rheb (Yang et al., 2017).

5.1. Glutamine

Glutamine is a non-essential amino acid; but for some cancer cells it is recognized as a conditionally essential amino acid because they rely on extracellular glutamine for their growth. In fact, in cancer cells glutamine is necessary to sustain the mitochondrial oxidative metabolism and its consumption exceeds its biosynthesis (Cruzat et al., 2018). In cancer cells glutamine is imported through the membrane by amino acid antiporters such as members of the ASCs (Na^+-dependent alanine-serine-cysteine transporters ASCT1 e ASCT2) and SNATs (Na^+-coupled neutral amino acid transporters, SNAT1, SNAT2, SNAT5) subfamilies (Cha et al., 2018; Kandasamy et al., 2018). Glutamine is also imported through the broad specific amino acid transporter Sodium- and chloride-dependent neutral and basic amino acid transporter B(0 +) (ATB0,+, SLC6A14) and the more selective specific amino acid transporter Solute Carrier Family 38 member 5 (SLC38A5) (Sniegowski et al., 2021). The key enzyme in glutamine metabolism is glutaminase 1 (GLS1) that operates deamidation of glutamine to produce glutamate that in the mitochondria sustains the citric cycle after it has been metabolized by several enzymes. Glutamate is than used to synthesize several non-essential amino acids and glutamine is used for purine and pyrimidine biosynthesis. Glutamine exerts an important role also in controlling the redox status of the cell by conditioning the rate of glutathione synthesis. Inhibition of key enzymes of glutamine metabolism, such as GLS1, blocks the cancer cell growth by decreasing glutamine levels and reducing ATP and NADH production (Kodama et al., 2020). GLS1 is in fact upregulated in several cancer types, including liver, breast, melanoma, lung and kidney (Edwards et al., 2021; Feng et al., 2021; Guo et al., 2021a; Jin et al., 2020). Glutamine is also deeply intertwined with the PI3K/Akt/mTORC1 pathway; the amino acid is able to activate mTORC1, both by inhibiting its antagonist AMPK, during the process of glutaminolysis (Bodineau et al., 2021), and by direct activation (Meng et al., 2020). mTORC1 then acts as a downstream effector of glutamine, with the precise mechanism depending on the cell type, and cancer cells are actually able to use this pathway for sustained growth (Meng et al., 2020).

Based on the key role played by glutamine metabolism in cancer cells, numerous therapies that target glutamine for cancer treatment

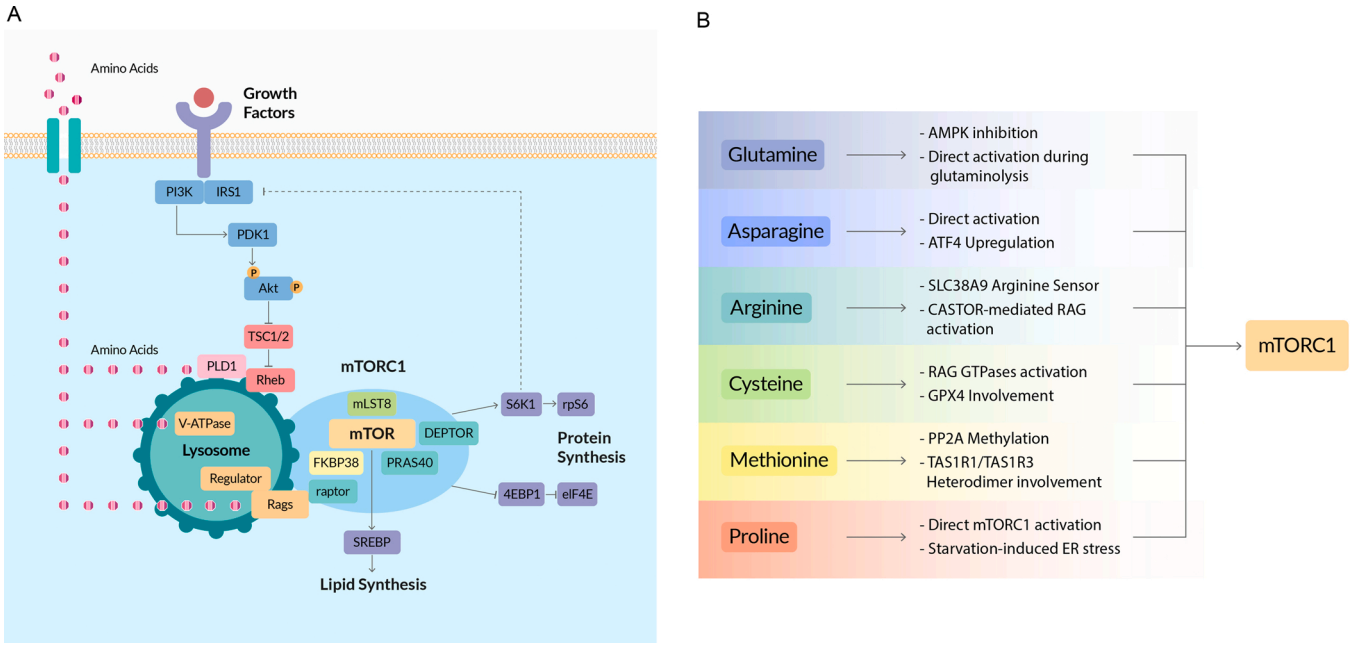

Fig. 5. Amino acids and mTORC1. A: The mTORC1 pathway and its targets, p70S6K and 4EBP1, leading to protein synthesis and mTORC1 effects on lipid metabolism and regulation of the pathway by RAG GTPases. B: Schematic diagram showing the effects of the single amino acids on the activation of the mTORC1 pathway. Each of the listed amino acids is able, with a specific mechanism, to induce cancer growth by activating mTORC1.

have been proposed. Among them the approaches targeting glutamine uptake (see the paragraph dedicated to the transporters as therapeutic targets at the end of this chapter) and glutaminase GLS1 activity are the main targets that have been investigated. Inhibitors of GLS1 have been shown to be effective in reducing the tumor mass in several studies and in particular bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES) and CB-839 are the most promising, the latter being the most advanced in clinical trials (Li et al., 2019a; Pallett et al., 2021; Ren et al., 2020; Wang et al., 2020; Xiang et al., 2015). Furthermore, it has also been studied the glutamate metabolism as a possible target for cancer therapy. Glutamate is converted into α-KG by the glutamate dehydrogenase (GDH) and acts as a nitrogen donor for non-essential amino acids synthesis and production of intermediates of the TCA cycle anaplerotic pathway. To counteract the activity of GDH have been developed several experimental inhibitors that have demonstrated antitumor effects (Jin et al., 2016, 2015). For instance, GDH1 has been targeted by shRNA or the small molecule inhibitor R162 that induced an inhibition of cancer cell proliferation and tumor growth.

5.2. Asparagine

Despite the importance of glutamine for cancer cells, they can adapt to glutamine starvation by using other amino acids, such as asparagine, introduced through the diet (Jiang et al., 2018). Furthermore, asparagine can be used by cancer cells as an amino acid exchange factor. In fact, it can be released by exchange transporters such as ASCT2 in order to absorb glutamine to promote proliferation (Krall et al., 2016). Asparagine is a non-essential amino acid. The key enzyme involved in its synthesis is asparagine synthase (ASNS) (Balasubramanian et al., 2013). This enzyme gene expression is reduced in acute lymphoblastic leukemia (ALL) cells thus they are dependent from the exogenous asparagine introduced with the diet. For this reason, a bacterial asparaginase that hydrolyzes asparagine to aspartic acid is used in ALL therapy to deplete asparagine (Radadiya et al., 2020). Other types of cancer, and in particular solid tumors and sarcomas, have recently been shown to overexpress ASNS, promoting cell growth and metastatic phenotype (Gwinn et al., 2018; Hanada et al., 2021; Knott et al., 2018; Zhu et al., 2017). Thus, ASNS may represent a target for cancer therapy, as seen in recent studies. Besides ASNS, asparagine is also able to regulate mTORC1 activity, either directly or indirectly, (Meng et al., 2020) and to impact the mitochondrial respiration (and subsequent ATP synthesis) via Activating Transcription Factor 4 (ATF4) upregulation (Gwinn et al., 2018), strengthening its importance for cancer development.

5.3. Arginine

Arginine is a conditionally non-essential amino acid that is necessary for the synthesis of nitric oxide and polyamine. It is synthesized via activity of arginine succinate synthase 1 (ASS1) and arginine succinate lyase (ASL) (Chen et al., 2021). In many tumors ASS1 gene expression is repressed thus the cells are dependent on the external supply of arginine. Arginine is taken up into the cells through at least eight known transporters including the cationic amino acid transporters (CAT) and the heteromeric amino acid transporters (Closs et al., 2006, 2004; Fotiadis et al., 2013). Furthermore, abundance of the amino acid activates either the lysosomal transporter SLC38A9 (Wyant et al., 2017), or the Cellular Arginine Sensor for mTORC1 (CASTOR), (Saxton et al., 2016) and promotes its interaction with the RAG GTPases which in turn mediates mTORC1 activation and its signaling (Kim and Kim, 2016; Sancak et al., 2008) that sustains tumor progression. An abnormal arginine metabolism has been associated with cancer progression (Du and Han, 2021; Kuo et al., 2021; Meng et al., 2020; Shi et al., 2021). The lack of arginine, conditions macrophages functions by conditioning their polarization toward the cancer tolerating M2 type (Rath et al., 2014). On the other hand, by reducing the amount of arginine introduced through the diet it is possible to induce cancer cell death by mitochondrial dysregulation, and OXPHOS inhibition, as seen in breast cancer cell lines (Cheng et al., 2018). Moreover, arginine deprivation in cancers is usually followed by a biphasic autophagic response, leading ultimately to cancer cell death, as seen in various tumor cell lines (Szlosarek, 2014). Taken together, these evidences make arginine a possible target for a starvation-based cancer therapy.

5.4. Cysteine

Cysteine is a non-essential amino acid that can be obtained by de novo synthesis from methionine or from protein catabolism. Nevertheless, the main source of cellular cysteine is from cystine introduced through the diet (Bonifácio et al., 2021). In cancer has been observed an increased cystine import respect to normal cells and this increase has been associated to poor prognosis (Bonifácio et al., 2021). Moreover, cysteine appears to be crucial for the adaptation of the tumor cells to hypoxic stress, as seen in ovarian cancer cell lines (Nunes et al., 2021). Cysteine represents a source of carbon for biomass and energy production but it is also a key substrate for glutathione synthesis, thus it contributes to the remodeling of cancer cell metabolism also by controlling the redox state of the cell (Bonifácio et al., 2021). The cellular redox state is also relevant for cancer therapy by conditioning the efficacy of the chemotherapy (El Banna et al., 2019). Cysteine metabolism is intertwined to its transport into the cells. This is mediated by specific transporters such as excitatory amino acid transporter 3 (EAAT3), that is upregulated in brain, colon, lung and prostate cancer (Guo et al., 2021b; Ruiz-Rodado et al., 2021; Ye et al., 2016); cysteine uptake may also be mediated by the cysteine/glutamate antiporter xCT, which is upregulated in several cancer cell lines (Nunes et al., 2021; Ye et al., 2016) and whose activity is regulated by the redox-associated transcription factor NRF2 (Habib et al., 2015), once again pointing out to the importance of cysteine for the tumor cell redox state. Hence, both the redox state depending on cysteine, and the amino acid uptake may be considered potential targets for cancer therapy. Furthermore, cysteine starvation is able to block mTORC1 activation and reduces its lysosomal localization; this causes a decrease in Glutathione Peroxidase 4 (GPX4, a negative regulator of ferroptosis) protein levels, which could be utilized for a ferroptosis-based cancer therapy (Zhang et al., 2021b).

5.5. Methionine

Methionine is an essential amino acid. It is necessary for methylation reactions but it also plays a key role in the cell redox status and for nucleotide synthesis in coordination with the folate cycle, supplying metabolites that lead to the conversion of cysteine (Stipanuk, 2020). Most cancer cells show an increased uptake of methionine, as seen in animal models of leukemia, breast cancer, hepatocellular carcinoma, and neuroblastoma (Hoffman et al., 2019; Hung et al., 2021). Methionine influx into the cells is mediated by the system L-type amino acid transporter (LAT1). This is an amino acid antiporter that mediates methionine influx in exchange for intracellular amino acids, such as glutamine, efflux (Kanai et al., 1998; Meier et al., 2002; Yanagida et al., 2001). Methionine is involved in key aspects of the cancer metabolism such as nucleic acid and chromatin methylation, redox state and polyamine synthesis that favor the rapid cell proliferation (Higuchi et al., 2021). In cancer cells, several enzymes involved in methionine metabolism are also found upregulated, such as methionine synthase, the enzyme directly responsible for methionine biosynthesis (Wu et al., 2017) and the methionine adenosyl transferases, which catalyzes the conversion of methionine into S-adenosylmethionine (SAM), the principal cellular methyl donor (Kargbo, 2021). Methionine is also involved in the mTORC1 pathway modulation through mechanisms mediated by either the methylation of phosphatase 2A (PP2A) (Laxman et al., 2014), or the taste 1 receptor member 1 (TAS1R1)/taste 1 receptor member 3 (TAS1R3) heterodimer, that acts as a methionine sensor and mTORC1 activator through phospholipase C (Zhou et al., 2018). For further

details about the methionine modulation of mTORC1, we refer the reader to a recent review (Kitada et al., 2020). Indeed, many types of cancer are methionine dependent for their growth, an event known as the "Hoffman effect" where the tumors are strictly dependent on exogenous methionine (Lauinger and Kaiser, 2021). While methionine restriction, through a diet that contains a reduced level of methionine respect to a standard diet, is associated with lifespan extension, the complete methionine deprivation from diet has been associated with reduced cancer growth or cancer regression and with increased sensitivity to chemotherapy. Combined with the targeting of methylation, being dependent on methionine (Higuchi et al., 2021), targeting of methionine metabolism could be central for the effectiveness of chemotherapeutic strategies.

5.6. Serine

Serine is a conditionally non-essential amino acid. It can be synthesized as a byproduct of glycolysis or it can be introduced with the diet. It is taken up by the cells from the external environment through the ASCT1 and ASCT2 transporters (Arriza et al., 1993; Scalise et al., 2018; Utsunomiya-Tate et al., 1996). Its metabolism is frequently dysregulated in cancer cells (Montrose et al., 2021). Serine can be converted to glycine by removal of a methyl group that can be used in the folate cycle. Thus, the role of serine in cancer growth depends on its use as source of metabolites which are then used for macromolecules synthesis, such as nucleotides and lipids, beyond its use as building block of proteins. In this regard, serine synthesis is regulated at the transcriptional level by the mTOR/ATF4 axis, as seen in pancreatic cancer (Mesclon et al., 2017), or at the post-translational level by the sirtuins SIRT3 and SIRT5 in colorectal and non-small cell lung cancer (NSCLC), respectively (Montrose et al., 2021; Rinaldi et al., 2021). In colon cancer, serine metabolism is also able to prevent degradation of yes-associated protein (YAP, a central mediator of the Hippo pathway), which in turn promotes cell growth (Zhao et al., 2021). Furthermore, serine contributes to the maintenance of the cell redox state, providing the tumor cells with reductive equivalents (Diehl et al., 2019) and being directly involved in glutathione synthesis (Kurniawan et al., 2020). For all of these reasons, cancer cells consume high amounts of exogenous serine and so serine starvation inhibits cancer cells growth in vitro (Montrose et al., 2021). Serine starvation also slows tumor growth while improving survival in vivo (Tajan et al., 2021).

5.7. Proline

Proline is a conditionally non-essential amino acid. Its transport into the cells is mediated by the brain-specific Na+ -dependent proline transporter PROT (SLC6A7) and the broad-specific Sodium/Imino-acid Transporter 1 (SIT1) (Shafqat et al., 1995; Takanaga et al., 2005; Velaz-Faircloth et al., 1995). Key enzymes involved in proline metabolism are pyrroline-5-carboxylate reductase (PYCR), that catalyzes the final step of proline biosynthesis from glutamate, and proline dehydrogenase (PRODH), that catalyzes the oxidation of proline. Both enzymes have been involved in the progression of several cancers mainly because of an increase of their gene expression, resulting in increased proline metabolism and leading mainly to more ATP production through OXPHOS (Tanner et al., 2018). In particular PYCR activity has been found associated with increased protein synthesis and cancer growth, as seen in several experimental models (Li et al., 2021b). Proline can also be obtained for cancer cell growth from the catabolism of collagen of the extracellular matrix (Olivares et al., 2017). Furthermore, proline hydroxylation of the transcription factor hypoxia-inducible factor (HIF), is one of the main mechanisms of control of cancer cells response to oxygen deprivation (Snell et al., 2014). Thus, proline exerts a control of cancer cell growth also when it undergoes to post-translation modification. To target proline metabolism for cancer therapy, PRODH inhibition has been explored. It has also been observed that inhibition of proline biosynthesis can enhance the efficacy of chemotherapy in some cancers such as colon, breast or hepatocellular carcinomas (Scott et al., 2019). Thus, its inhibition may represent a possible means for cancer therapy. PYCR activity and proline availability are linked to protein translation, by interfering with the mTORC1 pathway; cancer cells that exhibit dependency on exogenous proline have an hyperactivation of the mTORC1/4EBP1 pathway. In this context, proline starvation induces endoplasmic reticulum (ER) stress and a dysregulation of the mTORC1 pathway, 4EBP1 activity, that blocks protein synthesis, and a consequent inhibition of the cancer cells growth (Sahu et al., 2016).

5.8. Amino acids transporters may be targeted for cancer therapy

As we have mentioned earlier, cancer cells are highly demanding for amino acids to support their metabolic rewiring and their growth, thus, amino acids transporters in the cell membrane are frequently upregulated to meet this increased demand. For this reason, they can be targeted for therapeutic purposes. A complication, for the therapeutic targeting of amino acid transporters, arises from their redundancy and their specificity. In fact, some of these transporters are tissue specific while others are broad specific. In fact, many transporters can recognize more than one amino acid. Furthermore, some of the transporters are antiporters meaning that they transport an amino acid for the exchange of another as we have seen earlier in this paper. Finally, different tumors may depend on different amino acid metabolism and amino acid transporters to acquire their growth advantage over normal cells (Scalise et al., 2020). For this reason, their targeting requires prior cancer screening to select the patients who may benefit from the therapy. In the case of glutamine, a further problem is represented by the metabolic adaptations to glutamine deprivation (Reid et al., 2013) that ensure the cancer cells survival and proliferation. Nevertheless, several studies have reported the feasibility of the targeting of glutamine transporters for cancer therapy. Glutamine is imported in cancer cells through several transporters and some of them, such as ASCT2, are highly expressed and critical for their growth and proliferation. Thus, cancer cells are more sensitive to amino acids transporters inhibition respect to normal cells. Table 1 summarizes the most relevant amino acid transporters in cancer cells and the molecules that have been studied or are under evaluation for their targeting.

6. Conclusions

Cell metabolism and even more cancer cell metabolism is a complex matter. Here we have reviewed several metabolic alterations commonly found in cancer cells beyond the Warburg effect and the aerobic glycolysis. Alterations of mitochondria, OXPHOS, fatty acid oxidation or amino acids metabolism are all found in cancer cells. In order to pave the way to the development of novel drugs and therapeutical strategies that, by targeting these alterations, are able to counteract cancer progression, it is necessary an increase of knowledge on the molecular mechanisms at their basis. Furthermore, the various alterations of the cancer cell metabolism that we have reviewed are only a part of all the molecular events that occur in the complex scenario of cancer development and survival. For instance, there are mechanisms of crosstalk between all the metabolic pathways and the oncogenes and tumor-suppressor genes, and these mechanisms may act as "master regulators" of cancer cells growth. These alterations could act as proper "switches" towards a cancer phenotype and may overall become pivotal for the cancer cell to acquire an advantage over normal cells and so they could be targeted for therapeutic purposes. As a consequence, a growing number of drugs is being developed, or repositioned, in order to target the different metabolic aspects of the cancer cell. Table 2 highlights a representative number of compounds/drugs, as well as the phase of the clinical trials in which they are being evaluated. These compounds/drugs target specific aspects of the cancer cells metabolism, and their use (alone or in combination) may be important to boost the cancer therapy efficacy.

Table 1
Amino Acids Transporters and their targeting in cancer. In Bold the transported amino acid more relevant to tumor growth; TNBC, Triple Negative Breast Cancer; CRC, Colorectal Cancer;.

Amino Acid Transporter	*Amino Acid Transported*	*Drug*	*Type of Cancer*	*Phase of Development*	*Reference*
ASCT1 (SLC1A4)	Serine	n.a.	Breast, Lung	Preclinical	(Peng et al., 2021)
ASCT2 (SLC1A5)	Alanine, Serine, Cysteine, **Glutamine**, Asparagine	V-9302, Benzylserine, 2-amino-4-bis(aryloxybenzyl) aminobutanoic acids (AABA)	Gastric, TNBC, Prostate	Preclinical	(Edwards et al., 2021; Jin et al., 2020; Luo et al., 2020; Schulte et al., 2018; Zhang et al., 2020c)
ATB0,+ (SLC6A14)	Serine, Tryptophan	α-methyl-DL-tryptophan	CRC, Breast, Cervix, Pancreatic, Metastasis	Preclinical	(Babu et al., 2015; Coothankandaswamy et al., 2016; Gupta et al., 2006; Karunakaran et al., 2008; McCracken and Edinger, 2015)
CAT1 (SLC7A1)	**Arginine**, Lysine	n.a.	CRC, Chronic Lymphocytic Leukemia Cells	Preclinical	(Lu et al., 2013; Okita et al., 2021; Werner et al., 2019)
CAT2 (SLC7A2)	Arginine	n.a.	Melanoma, Pancreatic, Ovarian	Preclinical	(Li et al., 2017; Sun et al., 2020; Wei et al., 2021; Yang et al., 2020)
LAT1 (SLC7A5)	Leucine, Isoleucine, Valine, Phenylalanine, Methionine, Tryptophan, Histidine, Tyrosine	JPH203	Glioma, Lung, Prostate, Breast, Bladder, Cervix, Skin, Oral, Melanoma	Phase 1, Preclinical	(Janpipatkul et al., 2014; Okano et al., 2018; Shimizu et al., 2015)
LAT2 (SLC7A8)	Glutamine	n.a.	Pancreatic	Preclinical	(Feng et al., 2018)
SNAT1 (SLC38A1)	Glutamine, Serine	n.a.	Breast, Osteosarcoma	Preclinical	(Wang et al., 2013, 2017)
SNAT2 (SLC38A2)	Glutamine	n.a.	TNBC	Preclinical	(Morotti et al., 2019, 2021; Pinilla et al., 2011)
xCT (SLC7A11)	Cystine	PRLX93936, Sorafenib, Sulfasalazine	Glioma, TNBC, CRC, Multiple myeloma, Breast cancer cells	Phase 1 Phase 2	(Chen et al., 2020; Dahlmanns et al., 2017; Hirschhorn and Stockwell, 2019; Ji et al., 2018; Ma et al., 2017; Sehm et al., 2016; Timmerman et al., 2013; Yoshioka et al., 2019)

Table 2
Drugs and compounds targeting cancer metabolism.

Drug name	Mechanism of Action	Metabolic process involved	Cancer type (s)	Clinical stage	Ref
β-Lapachone	ROS overproduction	Mitochondrial Dynamics	Glioblastoma	Phase 1 (completed)	(Beg et al., 2019)
Resveratrol	ROS production, mitochondrial membrane permeabilization. FASN inhibitor	Mitochondrial Dynamics, FAO	Colon cancer, breast cancer	Phase 1	(Zhang et al., 2021a)
Metformin	Glucose metabolism inhibitor, Mitochondrial respiration inhibitor, ETC complex inhibitor, AMPK activator	Glycolysis, OXPHOS	Prostate cancer, Oral Cancer, Breast Cancer	Phase 2–3	(Zhang et al., 2021c)
ME-344	Complex I inhibitor, ETC inhibitor	OXPHOS	Solid Tumors	Phase 1	(Quintela-Fandino et al., 2020)
IACS-010759	Complex I inhibitor through ND1 binding	OXPHOS	Relapsed or Refractory Acute Myeloid Leukemia	Phase 1	(Yap et al., 2019)
Phenformin	ETC complex inhibitor	OXPHOS	Melanoma	Phase 1	(García Rubiño et al., 2019)
CTO	Calcium influx inhibitor	OXPHOS	Glioma	Phase 1	(Bonnefond et al., 2018)
Etomoxir	CPT1 inhibitor	Lipid metabolism – FAO	Liver cancer	Preclinical	(O'Connor et al., 2018)
Perhexiline	CPT1 inhibitor	Lipid metabolism – FAO	Glioblastoma	Preclinical	(Kant et al., 2020)
Quercetin	FASN inhibitor	Lipid metabolism – Fatty acid synthesis	Squamous cells carcinoma	Phase 2	(Vafadar et al., 2020)
Orlistat	FASN inhibitor. LPL inhibitor	Lipid metabolism – Fatty acid synthesis – Lipolysis	Prostate cancer, Breast cancer, colon cancer	Preclinical	(Qi, 2018)
TVB-2640	FASN inhibitor	Lipid metabolism – Fatty acid synthesis	Colon cancer, solid malignant tumors	Phase 2	(Brenner et al., 2015)
CD36 mAB	CD36 inhibitor	Lipid metabolism – Lipid uptake	Prostate cancer, Breast cancer	preclinical	(Feng et al., 2019)
Docetaxel	Inhibition of microtubular depolymerization – Also FABP5 inhibitor	Lipid metabolism – Fatty acid synthesis	Advanced solid tumors	Phase 3	(Jeong et al., 2021)

Authors contribution

Jacopo Di Gregorio, **Sabrina Petricca**, and **Vincenzo Flati**: Conceptualization, Writing – original draft preparation. **Vincenzo Flati** and **Roberto Iorio**: Supervision, **All Authors**: Writing – review & editing,

Declaration of interest

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References

Abumrad, N.A., Cabodevilla, A.G., Samovski, D., Pietka, T., Basu, D., Goldberg, I.J., 2021. Endothelial cell receptors in tissue lipid uptake and metabolism. Circ. Res 128, 433–450.

Acín-Pérez, R., Fernández-Silva, P., Peleato, M.L., Pérez-Martos, A., Enriquez, J.A., 2008. Respiratory active mitochondrial supercomplexes. Mol. Cell 32, 529–539.

Aiderus, A., Black, M.A., Dunbier, A.K., 2018. Fatty acid oxidation is associated with proliferation and prognosis in breast and other cancers. BMC Cancer 18, 805.

Arriza, J.L., Kavanaugh, M.P., Fairman, W.A., Wu, Y.N., Murdoch, G.H., North, R.A., Amara, S.G., 1993. Cloning and expression of a human neutral amino acid transporter with structural similarity to the glutamate transporter gene family. J. Biol. Chem. 268, 15329–15332.

Ashrafi Hafez, A., Naserzadeh, P., Mortazavian, A.M., Mehravi, B., Ashtari, K., Seydi, E., Salimi, A., 2019. Comparison of the effects of MnO(2)-NPs and MnO(2)-MPs on mitochondrial complexes in different organs. Toxicol. Mech. Methods 29, 86–94.

Babu, E., Bhutia, Y.D., Ramachandran, S., Gnanaprakasam, J.P., Prasad, P.D., Thangaraju, M., Ganapathy, V., 2015. Deletion of the amino acid transporter Slc6a14 suppresses tumour growth in spontaneous mouse models of breast cancer. Biochem J. 469, 17–23.

Baksh, S.C., Finley, L.W.S., 2021. Metabolic coordination of cell fate by α-ketoglutarate-dependent dioxygenases. Trends Cell Biol. 31, 24–36.

Balasubramanian, M.N., Butterworth, E.A., Kilberg, M.S., 2013. Asparagine synthetase: regulation by cell stress and involvement in tumor biology. Am. J. Physiol. Endocrinol. Metab. 304, E789–E799.

Beg, M.S., Boothman, D., Khosama, L., Arriaga, Y., Verma, U., Sanjeeviaiah, A., Kazmi, S., Fattah, F., Pilarski, S., Rodriguez, M., Lindsey, D., Linden, S., Schwartz, B., Laheru, D., 2019. 708P - A phase I/Ib, multi-center trial of ARQ-761 (Beta-Lapachone) with gemcitabine/nab-paclitaxel in patients with advanced pancreatic cancer. Ann. Oncol. 30 v271.

Benard, G., Bellance, N., James, D., Parrone, P., Fernandez, H., Letellier, T., Rossignol, R., 2007. Mitochondrial bioenergetics and structural network organization. J. Cell Sci. 120, 838–848.

Biancur, D.E., Kapner, K.S., Yamamoto, K., Banh, R.S., Neggers, J.E., Sohn, A.S.W., Wu, W., Manguso, R.T., Brown, A., Root, D.E., Aguirre, A.J., Kimmelman, A.C., 2021. Functional Genomics Identifies Metabolic Vulnerabilities in Pancreatic Cancer. Cell Metab. 33, 199–210 e198.

Bodineau, C., Tomé, M., Courtois, S., Costa, A.S.H., Sciacovelli, M., Rousseau, B., Richard, E., Vacher, P., Parejo-Pérez, C., Bessede, E., Varon, C., Soubeyran, P., Frezza, C., Murdoch, P.D.S., Villar, V.H., Durán, R.V., 2021. Two parallel pathways connect glutamine metabolism and mTORC1 activity to regulate glutamoptosis. Nat. Commun. 12, 4814.

Bonifácio, V.D.B., Pereira, S.A., Serpa, J., Vicente, J.B., 2021. Cysteine metabolic circuitries: druggable targets in cancer. Br. J. Cancer 124, 862–879.

Bonnefond, M.L., Florent, R., Lenoir, S., Lambert, B., Abeilard, E., Giffard, F., Louis, M. H., Elie, N., Briand, M., Vivien, D., Poulain, L., Gauduchon, P., N'Diaye, M., 2018. Inhibition of store-operated channels by carboxyamidotriazole sensitizes ovarian carcinoma cells to anti-Bclx(L) strategies through Mcl-1 down-regulation. Oncotarget 9, 33896–33911.

Bonnet, S., Archer, S.L., Allalunis-Turner, J., Haromy, A., Beaulieu, C., Thompson, R., Lee, C.T., Lopaschuk, G.D., Puttagunta, L., Bonnet, S., Harry, G., Hashimoto, K., Porter, C.J., Andrade, M.A., Thebaud, B., Michelakis, E.D., 2007. A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer Cell 11, 37–51.

Brenner, A.J., Hoff, D.D.V., Infante, J.R., Patel, M.R., Jones, S.F., Burris, H.A., Rubino, C., McCulloch, W., Zhukova-Harrill, V., Kemble, G., 2015. First-in-human investigation of the oral first-in-class fatty acid synthase (FASN) inhibitor, TVB-2640. J. Clin. Oncol. 33. TPS2615-TPS2615.

Buechter, D.D., 1988. Free radicals and oxygen toxicity. Pharm. Res 5, 253–260.

Cairns, J., Ingle, J.N., Kalari, K.R., Goetz, M.P., Weinshilboum, R.M., Gao, H., Li, H., Ghanat Bari, M., Wang, L., 2021. Anastrozole regulates fatty acid synthase in breast cancer. Mol. Cancer Therapeutics:molcanther 0509, 2021.

Cairns, R.A., Harris, I.S., Mak, T.W., 2011. Regulation of cancer cell metabolism. Nat. Rev. Cancer 11, 85–95.

Campion, O., Al Khalifa, T., Langlois, B., Thevenard-Devy, J., Salesse, S., Savary, K., Schneider, C., Etique, N., Dedieu, S., Devy, J., 2020. Contribution of the low-density lipoprotein receptor family to breast cancer progression. Front Oncol. 10, 882.

Cao, A., Li, H., Zhou, Y., Wu, M., Liu, J., 2010. Long chain acyl-CoA synthetase-3 is a molecular target for peroxisome proliferator-activated receptor delta in HepG2 hepatoma cells. J. Biol. Chem. 285, 16664–16674.

Caro, P., Kishan, A.U., Norberg, E., Stanley, I.A., Chapuy, B., Ficarro, S.B., Polak, K., Tondera, D., Gounarides, J., Yin, H., Zhou, F., Green, M.R., Chen, L., Monti, S., Marto, J.A., Shipp, M.A., Danial, N.N., 2012. Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphoma. Cancer Cell 22, 547–560.

Carter, J.L., Hege, K., Kalpage, H.A., Edwards, H., Hüttemann, M., Taub, J.W., Ge, Y., 2020. Targeting mitochondrial respiration for the treatment of acute myeloid leukemia. *Biochemical Pharmacology*, 182, 114253.

Cha, Y.J., Kim, E.-S., Koo, J.S., 2018. Amino acid transporters and glutamine metabolism in breast cancer. Int. J. Mol. Sci. 19, 907.

Chan, D.C., 2012. Fusion and fission: interlinked processes critical for mitochondrial health. Annu Rev. Genet 46, 265–287.

Chen, C.-L., Hsu, S.-C., Ann, D.K., Yen, Y., Kung, H.-J., 2021. Arginine signaling and cancer metabolism. Cancers 13, 3541.

Chen, M.-C., Hsu, L.-L., Wang, S.-F., Hsu, C.-Y., Lee, H.-C., Tseng, L.-M., 2020. ROS mediate xCT-dependent cell death in human breast cancer cells under glucose deprivation. Cells 9, 1598.

Chen, Z.X., Pervaiz, S., 2007. Bcl-2 induces pro-oxidant state by engaging mitochondrial respiration in tumor cells. Cell Death Differ. 14, 1617–1627.

Cheng, C.-T., Qi, Y., Wang, Y.-C., Chi, K.K., Chung, Y., Ouyang, C., Chen, Y.-R., Oh, M.E., Sheng, X., Tang, Y., Liu, Y.-R., Lin, H.H., Kuo, C.-Y., Schones, D., Vidal, C.M., Chu, J. C.Y., Wang, H.-J., Chen, Y.-H., Miller, K.M., Chu, P., Yen, Y., Jiang, L., Kung, H.-J., Ann, D.K., 2018. Arginine starvation kills tumor cells through aspartate exhaustion and mitochondrial dysfunction. Commun. Biol. 1, 178.

Ciccarese, F., Ciminale, V., 2017. Escaping death: mitochondrial redox homeostasis in cancer cells. Front. Oncol. 7, 117.

Ciccarese, F., Raimondi, V., Sharova, E., Silic-Benussi, M., Ciminale, V., 2020. Nanoparticles as tools to target redox homeostasis in cancer cells. Antioxidants 9 (3), 211.

Closs, E.I., Boissel, J.P., Habermeier, A., Rotmann, A., 2006. Structure and function of cationic amino acid transporters (CATs). J. Membr. Biol. 213, 67–77.

Closs, E.I., Simon, A., Vékony, N., Rotmann, A., 2004. Plasma membrane transporters for arginine. J. Nutr. 134, 2752S–2759S.

Cogliati, S., Frezza, C., Soriano, M.E., Varanita, T., Quintana-Cabrera, R., Corrado, M., Cipolat, S., Costa, V., Casarin, A., Gomes, L.C., Perales-Clemente, E., Salviati, L., Fernandez-Silva, P., Enriquez, J.A., Scorrano, L., 2013. Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency. Cell 155, 160–171.

Coothankandaswamy, V., Cao, S., Xu, Y., Prasad, P.D., Singh, P.K., Reynolds, C.P., Yang, S., Ogura, J., Ganapathy, V., Bhutia, Y.D., 2016. Amino acid transporter SLC6A14 is a novel and effective drug target for pancreatic cancer. Br. J. Pharm. 173, 3292–3306.

Corazao-Rozas, P., Guerreschi, P., André, F., Gabert, P.E., Lancel, S., Dekiouk, S., Fontaine, D., Tardivel, M., Savina, A., Quesnel, B., Mortier, L., Marchetti, P., Kluza, J., 2016. Mitochondrial oxidative phosphorylation controls cancer cell's life and death decisions upon exposure to MAPK inhibitors. Oncotarget 7, 39473–39485.

Courtois, S., de Luxán-Delgado, B., Penin-Peyta, L., Royo-García, A., Parejo-Alonso, B., Jagust, P., Alcalá, S., Rubiolo, J.A., Sánchez, L., Sainz Jr., B., Heeschen, C., Sancho, P., 2021. Inhibition of mitochondrial dynamics preferentially targets pancreatic cancer cells with enhanced tumorigenic and invasive potential. Cancers 13 (4), 698.

Cruz-Gil, S., Sanchez-Martinez, R., Gomez de Cedron, M., Martin-Hernandez, R., Vargas, T., Molina, S., Herranz, J., Davalos, A., Reglero, G., Ramirez de Molina, A., 2018. Targeting the lipid metabolic axis ACSL/SCD in colorectal cancer progression by therapeutic miRNAs: miR-19b-1 role. J. Lipid Res. 59, 14–24.

Cruzat, V., Macedo Rogero, M., Noel Keane, K., Curi, R., Newsholme, P., 2018. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients 10 (11), 1564.

Czabotar, P.E., Lessene, G., Strasser, A., Adams, J.M., 2014. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat. Rev. Mol. Cell Biol. 15, 49–63.

Dahlmanns, M., Yakubov, E., Chen, D., Sehm, T., Rauh, M., Savaskan, N., Wrosch, J.K., 2017. Chemotherapeutic xCT inhibitors sorafenib and erastin unraveled with the synaptic optogenetic function analysis tool. Cell Death Discov. 3, 17030.

Dang, L., White, D.W., Gross, S., Bennett, B.D., Bittinger, M.A., Driggers, E.M., Fantin, V. R., Jang, H.G., Jin, S., Keenan, M.C., Marks, K.M., Prins, R.M., Ward, P.S., Yen, K.E., Liau, L.M., Rabinowitz, J.D., Cantley, L.C., Thompson, C.B., Vander Heiden, M.G., Su, S.M., 2009. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 462, 739–744.

Desai, R., East, D.A., Hardy, L., Faccenda, D., Rigon, M., Crosby, J., Alvarez, M.S., Singh, A., Mainenti, M., Hussey, L.K., Bentham, R., Szabadkai, G., Zappulli, V., Dhoot, G.K., Romano, L.E., Xia, D., Coppens, I., Hamacher-Brady, A., Chapple, J.P., Abeti, R., Fleck, R.A., Vizcay-Barrena, G., Smith, K., Campanella, M., 2020. Mitochondria form contact sites with the nucleus to couple prosurvival retrograde response. Sci. Adv. 6 (51).

Di Malta, C., Siciliano, D., Calcagni, A., Monfregola, J., Punzi, S., Pastore, N., Eastes, A. N., Davis, O., De Cegli, R., Zampelli, A., Di Giovannantonio, L.G., Nusco, E., Platt, N., Guida, A., Ogmundsdottir, M.H., Lanfrancone, L., Perera, R.M., Zoncu, R., Pelicci, P. G., Settembre, C., Ballabio, A., 2017. Transcriptional activation of RagD GTPase controls mTORC1 and promotes cancer growth. Science 356, 1188–1192.

Diehl, F.F., Lewis, C.A., Fiske, B.P., Vander Heiden, M.G., 2019. Cellular redox state constrains serine synthesis and nucleotide production to impact cell proliferation. Nat. Metab. 1, 861–867.

Dong, L., Neuzil, J., 2019. Targeting mitochondria as an anticancer strategy. Cancer Commun. 39, 63.

Dong, L.F., Kovarova, J., Bajzikova, M., Bezawork-Geleta, A., Svec, D., Endaya, B., Sachaphibulkij, K., Coelho, A.R., Sebkova, N., Ruzickova, A., Tan, A.S., Kluckova, K., Judasova, K., Zamecnikova, K., Rychtarcikova, Z., Gopalan, V., Andera, L., Sobol, M., Yan, B., Pattnaik, B., Bhatraju, N., Truksa, J., Stopka, P., Hozak, P., Lam, A.K., Sedlacek, R., Oliveira, P.J., Kubista, M., Agrawal, A., Dvorakova-Hortova, K., Rohlena, J., Berridge, M.V., Neuzil, J., 2017. Horizontal transfer of whole

mitochondria restores tumorigenic potential in mitochondrial DNA-deficient cancer cells. Elife 6 (e22187).
Drury, J., Rychahou, P.G., He, D., Jafari, N., Wang, C., Lee, E.Y., Weiss, H.L., Evers, B.M., Zaytseva, Y.Y., 2020. Inhibition of fatty acid synthase upregulates expression of CD36 to sustain proliferation of colorectal cancer cells. Front. Oncol. 10, 1185.
Du, T., Han, J., 2021. Arginine metabolism and its potential in treatment of colorectal cancer. Front. Cell Dev. Biol. 9 (658861).
Ducker, G.S., Chen, L., Morscher, R.J., Ghergurovich, J.M., Esposito, M., Teng, X., Kang, Y., Rabinowitz, J.D., 2016. Reversal of cytosolic one-carbon flux compensates for loss of the mitochondrial folate pathway. Cell Metab. 23, 1140–1153.
Duda, P., Janczara, J., McCubrey, J.A., Gizak, A., Rakus, D., 2020. The reverse warburg effect is associated with Fbp2-dependent Hif1α regulation in cancer cells stimulated by fibroblasts. Cells 9, 205.
Edwards, D.N., Ngwa, V.M., Raybuck, A.L., Wang, S., Hwang, Y., Kim, L.C., Cho, S.H., Paik, Y., Wang, Q., Zhang, S., Manning, H.C., Rathmell, J.C., Cook, R.S., Boothby, M. R., Chen, J., 2021. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. J. Clin. Invest 131 (4), e140100.
El Banna, N., Hatem, E., Heneman-Masurel, A., Léger, T., Baïlle, D., Vernis, L., Garcia, C., Martineau, S., Dupuy, C., Vagner, S., Camadro, J.M., Huang, M.E., 2019. Redox modifications of cysteine-containing proteins, cell cycle arrest and translation inhibition: involvement in vitamin C-induced breast cancer cell death. Redox Biol. 26, 101290.
Ellis, J.M., Frahm, J.L., Li, L.O., Coleman, R.A., 2010. Acyl-coenzyme A synthetases in metabolic control. Curr. Opin. Lipido 21, 212–217.
Engqvist, M.K., Eßer, C., Maier, A., Lercher, M.J., Maurino, V.G., 2014. Mitochondrial 2-hydroxyglutarate metabolism. Mitochondrion 19 (Pt B), 275–281.
Enríquez, J.A., 2016. Supramolecular organization of respiratory complexes. Annu Rev. Physiol. 78, 533–561.
Evans, K.W., Yuca, E., Scott, S.S., Zhao, M., Paez Arango, N., Cruz Pico, C.X., Saridogan, T., Shariati, M., Class, C.A., Bristow, C.A., Vellano, C.P., Zheng, X., Gonzalez-Angulo, A.M., Su, X., Tapia, C., Chen, K., Akcakanat, A., Lim, B., Tripathy, D., Yap, T.A., Francesco, M.E.D., Draetta, G.F., Jones, P., Heffernan, T.P., Marszalek, J.R., Meric-Bernstam, F., 2021. Oxidative phosphorylation is a metabolic vulnerability in chemotherapy-resistant triple-negative breast cancer. Cancer Res. 81, 5572–5581.
Fantin, V.R., St-Pierre, J., Leder, P., 2006. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 9, 425–434.
Faubert, B., Vincent, E.E., Poffenberger, M.C., Jones, R.G., 2015. The AMP-activated protein kinase (AMPK) and cancer: many faces of a metabolic regulator. Cancer Lett. 356, 165–170.
Fendt, S.M., Bell, E.L., Keibler, M.A., Olenchock, B.A., Mayers, J.R., Wasylenko, T.M., Vokes, N.I., Guarente, L., Vander Heiden, M.G., Stephanopoulos, G., 2013. Reductive glutamine metabolism is a function of the α-ketoglutarate to citrate ratio in cells. Nat. Commun. 4, 2236.
Feng, M., Xiong, G., Cao, Z., Yang, G., Zheng, S., Qiu, J., You, L., Zheng, L., Zhang, T., Zhao, Y., 2018. LAT2 regulates glutamine-dependent mTOR activation to promote glycolysis and chemoresistance in pancreatic cancer. J. Exp. Clin. Cancer Res 37, 274.
Feng, W.W., Wilkins, O., Bang, S., Ung, M., Li, J., An, J., del Genio, C., Canfield, K., DiRenzo, J., Wells, W., Gaur, A., Robey, R.B., Guo, J.Y., Powles, R.L., Sotiriou, C., Pusztai, L., Febbraio, M., Cheng, C., Kinlaw, W.B., Kurokawa, M., 2019. CD36-mediated metabolic rewiring of breast cancer cells promotes resistance to HER2-targeted therapies. Cell Rep. 29, 3405–3420 e3405.
Feng, Y., Pathria, G., Heynen-Genel, S., Jackson, M., James, B., Yin, J., Scott, D.A., Ronai, Z.A., 2021. Identification and characterization of IMD-0354 as a glutamine carrier protein inhibitor in melanoma. Mol. Cancer Ther. 20, 816–832.
Fhu, C.W., Ali, A., 2020. Fatty acid synthase: an emerging target in cancer. Molecules 25 (17), 3935.
Fotiadis, D., Kanai, Y., Palacín, M., 2013. The SLC3 and SLC7 families of amino acid transporters. Mol. Asp. Med 34, 139–158.
Fouad, Y.A., Aanei, C., 2017. Revisiting the hallmarks of cancer. Am. J. Cancer Res 7, 1016–1036.
Frederick, M., Skinner, H.D., Kazi, S.A., Sikora, A.G., Sandulache, V.C., 2020. High expression of oxidative phosphorylation genes predicts improved survival in squamous cell carcinomas of the head and neck and lung. Sci. Rep. 10, 6380.
Frederiks, W.M., Bosch, K.S., Hoeben, K.A., van Marle, J., Langbein, S., 2010. Renal cell carcinoma and oxidative stress: The lack of peroxisomes. Acta Histochem 112, 364–371.
Frezza, C., Gottlieb, E., 2009. Mitochondria in cancer: not just innocent bystanders. Semin Cancer Biol. 19, 4–11.
Fuchs, B.C., Bode, B.P., 2005. Amino acid transporters ASCT2 and LAT1 in cancer: partners in crime? Semin Cancer Biol. 15, 254–266.
Fuhrmann, D.C., Brüne, B., 2017. Mitochondrial composition and function under the control of hypoxia. Redox Biol. 12, 208–215.
Galluzzi, L., Baehrecke, E.H., Ballabio, A., Boya, P., Bravo-San Pedro, J.M., Cecconi, F., Choi, A.M., Chu, C.T., Codogno, P., Colombo, M.I., Cuervo, A.M., Debnath, J., Deretic, V., Dikic, I., Eskelinen, E.L., Fimia, G.M., Fulda, S., Gewirtz, D.A., Green, D. R., Hansen, M., Harper, J.W., Jäättelä, M., Johansen, T., Juhasz, G., Kimmelman, A. C., Kraft, C., Ktistakis, N.T., Kumar, S., Levine, B., Lopez-Otin, C., Madeo, F., Martens, S., Martinez, J., Melendez, A., Mizushima, N., Münz, C., Murphy, L.O., Penninger, J.M., Piacentini, M., Reggiori, F., Rubinsztein, D.C., Ryan, K.M., Santambrogio, L., Scorrano, L., Simon, A.K., Simon, H.U., Simonsen, A., Tavernarakis, N., Tooze, S.A., Yoshimori, T., Yuan, J., Yue, Z., Zhong, Q., Kroemer, G., 2017. Molecular definitions of autophagy and related processes. Embo J. 36, 1811–1836.
Galvan, D.L., Green, N.H., Danesh, F.R., 2017. The hallmarks of mitochondrial dysfunction in chronic kidney disease. Kidney Int 92, 1051–1057.
García-Heredia, J.M., Carnero, A., 2020. Role of mitochondria in cancer stem cell resistance. Cells 9 (7), 1693.
García Rubiño, M.E., Carrillo, E., Ruiz Alcalá, G., Domínguez-Martín, A., J, A.M., Boulaiz, H., 2019. Phenformin as an anticancer agent: challenges and prospects. Int J. Mol. Sci. 20 (13), 3316.
Gius, D., Spitz, D.R., 2006. Redox signaling in cancer biology. Antioxid. Redox Signal 8, 1249–1252.
Glatz, J.F., Luiken, J.J., 2017. From fat to FAT (CD36/SR-B2): Understanding the regulation of cellular fatty acid uptake. Biochimie 136, 21–26.
Grasso, D., Zampieri, L.X., Capelôa, T., Van de Velde, J.A., Sonveaux, P., 2020. Mitochondria in cancer. Cell Stress. 4, 114–146.
Guescini, M., Guidolin, D., Vallorani, L., Casadei, L., Gioacchini, A.M., Tibollo, P., Battistelli, M., Falcieri, E., Battistin, L., Agnati, L.F., Stocchi, V., 2010. C2C12 myoblasts release micro-vesicles containing mtDNA and proteins involved in signal transduction. Exp. Cell Res 316, 1977–1984.
Guo, J., Satoh, K., Tabata, S., Mori, M., Tomita, M., Soga, T., 2021a. Reprogramming of glutamine metabolism via glutamine synthetase silencing induces cisplatin resistance in A2780 ovarian cancer cells. BMC Cancer 21, 174.
Guo, J.Y., Karsli-Uzunbas, G., Mathew, R., Aisner, S.C., Kamphorst, J.J., Strohecker, A. M., Chen, G., Price, S., Lu, W., Teng, X., Snyder, E., Santanam, U., Dipaola, R.S., Jacks, T., Rabinowitz, J.D., White, E., 2013. Autophagy suppresses progression of K-ras-induced lung tumors to oncocytomas and maintains lipid homeostasis. Genes Dev. 27, 1447–1461.
Guo, W., Li, K., Sun, B., Xu, D., Tong, L., Yin, H., Liao, Y., Song, H., Wang, T., Jing, B., Hu, M., Liu, S., Kuang, Y., Ling, J., Li, Q., Wu, Y., Wang, Q., Yao, F., Zhou, B.P., Lin, S.-H., Deng, J., 2021b. Dysregulated glutamate transporter SLC1A1 propels cystine uptake via Xc− for glutathione synthesis in lung cancer. Cancer Res. 81, 552–566.
Guo, Y.J., Pan, W.W., Liu, S.B., Shen, Z.F., Xu, Y., Hu, L.L., 2020. ERK/MAPK signalling pathway and tumorigenesis (Review). Exp. Ther. Med 19, 1997–2007.
Guppy, M., Leedman, P., Zu, X., Russell, V., 2002. Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells. Biochem J. 364, 309–315.
Gupta, N., Prasad, P.D., Ghamande, S., Moore-Martin, P., Herdman, A.V., Martindale, R. G., Podolsky, R., Mager, S., Ganapathy, M.E., Ganapathy, V., 2006. Up-regulation of the amino acid transporter ATB(0,+) (SLC6A14) in carcinoma of the cervix. Gynecol. Oncol. 100, 8–13.
Gwinn, D.M., Lee, A.G., Briones-Martin-Del-Campo, M., Conn, C.S., Simpson, D.R., Scott, A.I., Le, A., Cowan, T.M., Ruggero, D., Sweet-Cordero, E.A., 2018. Oncogenic KRAS regulates amino acid homeostasis and asparagine biosynthesis via ATF4 and alters sensitivity to L-asparaginase. Cancer Cell 33, 91–107 e106.
Habib, E., Linher-Melville, K., Lin, H.-X., Singh, G., 2015. Expression of xCT and activity of system xc− are regulated by NRF2 in human breast cancer cells in response to oxidative stress. *Redox Biology*, 5, 33–42.
Han, J., Li, E., Chen, L., Zhang, Y., Wei, F., Liu, J., Deng, H., Wang, Y., 2015. The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. Nature 524, 243–246.
Hanada, K., Kawada, K., Nishikawa, G., Toda, K., Maekawa, H., Nishikawa, Y., Masui, H., Hirata, W., Okamoto, M., Kiyasu, Y., Honma, S., Ogawa, R., Mizuno, R., Itatani, Y., Miyoshi, H., Sasazuki, T., Shirasawa, S., Taketo, M.M., Obama, K., Sakai, Y., 2021. Dual blockade of macropinocytosis and asparagine bioavailability shows synergistic anti-tumor effects on KRAS-mutant colorectal cancer. Cancer Lett. 522, 129–141.
Hanahan, D., Weinberg, R.A., 2000. The hallmarks of cancer. Cell 100, 57–70.
Hao, J.W., Wang, J., Guo, H., Zhao, Y.Y., Sun, H.H., Li, Y.F., Lai, X.Y., Zhao, N., Wang, X., Xie, C., Hong, L., Huang, X., Wang, H.R., Li, C.B., Liang, B., Chen, S., Zhao, T.J., 2020. CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis. Nat. Commun. 11, 4765.
Haq, R., Yokoyama, S., Hawryluk, E.B., Jönsson, G.B., Frederick, D.T., McHenry, K., Porter, D., Tran, T.-N., Love, K.T., Langer, R., Anderson, D.G., Garraway, L.A., Duncan, L.M., Morton, D.L., Hoon, D.S.B., Wargo, J.A., Song, J.S., Fisher, D.E., 2013. BCL2A1 is a lineage-specific antiapoptotic melanoma oncogene that confers resistance to BRAF inhibition. Proc. Natl. Acad. Sci. 110, 4321–4326.
Hasumi, H., Baba, M., Hasumi, Y., Huang, Y., Oh, H., Hughes, R.M., Klein, M.E., Takikita, S., Nagashima, K., Schmidt, L.S., Linehan, W.M., 2012. Regulation of mitochondrial oxidative metabolism by tumor suppressor FLCN. J. Natl. Cancer Inst. 104, 1750–1764.
He, C., Jiang, S., Jin, H., Chen, S., Lin, G., Yao, H., Wang, X., Mi, P., Ji, Z., Lin, Y., Lin, Z., Liu, G., 2016. Mitochondrial electron transport chain identified as a novel molecular target of SPIO nanoparticles mediated cancer-specific cytotoxicity. Biomaterials 83, 102–114.
He, L., Lu, Y., Wang, P., Zhang, J., Yin, C., Qu, S., 2010. Up-regulated expression of type II very low density lipoprotein receptor correlates with cancer metastasis and has a potential link to β-catenin in different cancers. BMC Cancer 10, 601.
Hertweck, K.L., Dasgupta, S., 2017. The Landscape of mtDNA modifications in cancer: a tale of two cities. Front. Oncol. 7.
Higuchi, T., Han, Q., Sugisawa, N., Yamamoto, J., Yamamoto, N., Hayashi, K., Kimura, H., Miwa, S., Igarashi, K., Bouvet, M., Singh, S.R., Tsuchiya, H., Hoffman, R. M., 2021. Combination methionine-methylation-axis blockade: a novel approach to target the methionine addiction of cancer. Cancer Genom. Proteom. 18, 113–120.
Hirschhorn, T., Stockwell, B.R., 2019. The development of the concept of ferroptosis. Free Radic. Biol. Med 133, 130–143.

Ho, J., de Moura, M.B., Lin, Y., Vincent, G., Thorne, S., Duncan, L.M., Hui-Min, L., Kirkwood, J.M., Becker, D., Van Houten, B., Moschos, S.J., 2012. Importance of glycolysis and oxidative phosphorylation in advanced melanoma. Mol. Cancer 11, 76.
Hoffman, R.M., Stern, P.H., Coalson, D.W., Douglas Wallace, C., Erbe, R.W., 2019. Altered methionine metabolism in cancer cells. In: Hoffman, R.M. (Ed.), Methionine Dependence of Cancer and Aging: Methods and Protocols. Springer New York, New York, NY, pp. 13–26.
Hollinshead, K.E.R., Parker, S.J., Eapen, V.V., Encarnacion-Rosado, J., Sohn, A., Oncu, T., Cammer, M., Mancias, J.D., Kimmelman, A.C., 2020. Respiratory supercomplexes promote mitochondrial efficiency and growth in severely hypoxic pancreatic cancer. Cell Rep. 33, 108231.
Hou, J., Reid, N.E., Tromberg, B.J., Potma, E.O., 2020. Kinetic analysis of lipid metabolism in breast cancer cells via nonlinear optical microscopy. Biophys. J. 119, 258–264.
Humpton, T.J., Alagesan, B., DeNicola, G.M., Lu, D., Yordanov, G.N., Leonhardt, C.S., Yao, M.A., Alagesan, P., Zaatari, M.N., Park, Y., Skepper, J.N., Macleod, K.F., Perez-Mancera, P.A., Murphy, M.P., Evan, G.I., Vousden, K.H., Tuveson, D.A., 2019. Oncogenic KRAS induces NIX-mediated mitophagy to promote pancreatic cancer. Cancer Discov. 9, 1268–1287.
Hung, M.H., Lee, J.S., Ma, C., Diggs, L.P., Heinrich, S., Chang, C.W., Ma, L., Forgues, M., Budhu, A., Chaisaingmongkol, J., Ruchirawat, M., Ruppin, E., Greten, T.F., Wang, X. W., 2021. Tumor methionine metabolism drives T-cell exhaustion in hepatocellular carcinoma. Nat. Commun. 12, 1455.
Ikeda, K., Horie-Inoue, K., Suzuki, T., Hobo, R., Nakasato, N., Takeda, S., Inoue, S., 2019. Mitochondrial supercomplex assembly promotes breast and endometrial tumorigenesis by metabolic alterations and enhanced hypoxia tolerance. Nat. Commun. 10, 4108.
Intlekofer, A.M., Dematteo, R.G., Venneti, S., Finley, L.W., Lu, C., Judkins, A.R., Rustenburg, A.S., Grinaway, P.B., Chodera, J.D., Cross, J.R., Thompson, C.B., 2015. Hypoxia induces production of L-2-hydroxyglutarate. Cell Metab. 22, 304–311.
Iorio, R., Celenza, G., Petricca, S., 2022. Mitophagy: molecular mechanisms, new concepts on parkin activation and the emerging role of AMPK/ULK1 Axis. Cells 11.
Izzo, V., Bravo-San Pedro, J.M., Sica, V., Kroemer, G., Galluzzi, L., 2016. Mitochondrial permeability transition: new findings and persisting uncertainties. Trends Cell Biol. 26, 655–667.
Jacobs, S.R., Herman, C.E., Maciver, N.J., Wofford, J.A., Wieman, H.L., Hammen, J.J., Rathmell, J.C., 2008. Glucose uptake is limiting in T cell activation and requires CD28-mediated Akt-dependent and independent pathways. J. Immunol. 180, 4476–4486.
Janpipatkul, K., Suksen, K., Borwornpinyo, S., Jearawiriyapaisarn, N., Hongeng, S., Piyachaturawat, P., Chairoungdua, A., 2014. Downregulation of LAT1 expression suppresses cholangiocarcinoma cell invasion and migration. Cell Signal 26, 1668–1679.
Jariwala, N., Mehta, G.A., Bhatt, V., Hussein, S., Parker, K.A., Yunus, N., Parker, J.S., Guo, J.Y., Gatza, M.L., 2021. CPT1A and fatty acid β-oxidation are essential for tumor cell growth and survival in hormone receptor-positive breast cancer. NAR Cancer 3 (3), zcab035.
Jeong, D.-W., Lee, S., Chun, Y.-S., 2021. How cancer cells remodel lipid metabolism: strategies targeting transcription factors. Lipids Health Dis. 20, 163.
Ji, X., Qian, J., Rahman, S.M.J., Siska, P.J., Zou, Y., Harris, B.K., Hoeksema, M.D., Trenary, I.A., Heidi, C., Eisenberg, R., Rathmell, J.C., Young, J.D., Massion, P.P., 2018. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. Oncogene 37, 5007–5019.
Jiang, J., Pavlova, N.N., Zhang, J., 2018. Asparagine, a critical limiting metabolite during glutamine starvation. Mol. Cell. Oncol. 5, e1441633.
Jiang, Z., Fanger, G.R., Banner, B.F., Woda, B.A., Algate, P., Dresser, K., Xu, J., Reed, S. G., Rock, K.L., Chu, P.G., 2003. A dietary enzyme: alpha-methylacyl-CoA racemase/P504S is overexpressed in colon carcinoma. Cancer Detect Prev. 27, 422–426.
Jin, H., Wang, S., Zaal, E.A., Wang, C., Wu, H., Bosma, A., Jochems, F., Isima, N., Jin, G., Lieftink, C., Beijersbergen, R., Berkers, C.R., Qin, W., Bernards, R., 2020. A powerful drug combination strategy targeting glutamine addiction for the treatment of human liver cancer. Elife 9, e56749.
Jin, L., Alesi, G.N., Kang, S., 2016. Glutaminolysis as a target for cancer therapy. Oncogene 35, 3619–3625.
Jin, L., Chun, J., Pan, C., Li, D., Lin, R., Alesi, G.N., Wang, X., Kang, H.B., Song, L., Wang, D., Zhang, G., Fan, J., Boggon, T.J., Zhou, L., Kowalski, J., Qu, C.K., Steuer, C. E., Chen, G.Z., Saba, N.F., Boise, L.H., Owonikoko, T.K., Khuri, F.R., Magliocca, K.R., Shin, D.M., Lonial, S., Kang, S., 2018. MAST1 drives cisplatin resistance in human cancers by rewiring cRaf-independent MEK activation. Cancer Cell 34, 315–330 e317.
Jin, L., Li, D., Alesi, G.N., Fan, J., Kang, H.B., Lu, Z., Boggon, T.J., Jin, P., Yi, H., Wright, E.R., Duong, D., Seyfried, N.T., Egnatchik, R., DeBerardinis, R.J., Magliocca, K.R., He, C., Arellano, M.L., Khoury, H.J., Shin, D.M., Khuri, F.R., Kang, S., 2015. Glutamate dehydrogenase 1 signals through antioxidant glutathione peroxidase 1 to regulate redox homeostasis and tumor growth. Cancer Cell 27, 257–270.
Jin, Q., Yuan, L.X., Boulbes, D., Baek, J.M., Wang, Y.N., Gomez-Cabello, D., Hawke, D.H., Yeung, S.C., Lee, M.H., Hortobagyi, G.N., Hung, M.C., Esteva, F.J., 2010. Fatty acid synthase phosphorylation: a novel therapeutic target in HER2-overexpressing breast cancer cells. Breast Cancer Res. 12, R96.
Jindal, Y., Singh, A., Kumar, R., Varma, K., Misra, V., Misra, S.P., Dwivedi, M., 2016. Expression of alpha methylacyl CoA racemase (AMACR) in gastric adenocarcinoma and its correlation with helicobacter pylori Infection. J. Clin. Diagn. Res 10 (10), EC10–EC12.
Jose, C., Bellance, N., Rossignol, R., 2011. Choosing between glycolysis and oxidative phosphorylation: a tumor's dilemma? Biochim Biophys. Acta 1807, 552–561.
Joshi, S., Tolkunov, D., Aviv, H., Hakimi, A.A., Yao, M., Hsieh, J.J., Ganesan, S., Chan, C. S., White, E., 2015. The genomic landscape of renal oncocytoma identifies a metabolic barrier to tumorigenesis. Cell Rep. 13, 1895–1908.
Kanai, Y., Segawa, H., Miyamoto, K., Uchino, H., Takeda, E., Endou, H., 1998. Expression cloning and characterization of a transporter for large neutral amino acids activated by the heavy chain of 4F2 antigen (CD98). J. Biol. Chem. 273, 23629–23632.
Kandasamy, P., Gyimesi, G., Kanai, Y., Hediger, M.A., 2018. Amino acid transporters revisited: new views in health and disease. Trends Biochem Sci. 43, 752–789.
Kandasamy, P., Zlobec, I., Nydegger, D.T., Pujol-Giménez, J., Bhardwaj, R., Shirasawa, S., Tsunoda, T., Hediger, M.A., 2021. Oncogenic KRAS mutations enhance amino acid uptake by colorectal cancer cells via the hippo signaling effector YAP1. Mol. Oncol. 15, 2782–2800.
Kant, S., Kesarwani, P., Guastella, A.R., Kumar, P., Graham, S.F., Buelow, K.L., Nakano, I., Chinnaiyan, P., 2020. Perhexiline demonstrates FYN-mediated antitumor activity in glioblastoma. Mol. Cancer Ther. 19, 1415–1422.
Kargbo, R.B., 2021. Methionine adenosyltransferase inhibitors for the treatment of cancer. ACS Med. Chem. Lett. 12, 180–181.
Karunakaran, S., Umapathy, N.S., Thangaraju, M., Hatanaka, T., Itagaki, S., Munn, D.H., Prasad, P.D., Ganapathy, V., 2008. Interaction of tryptophan derivatives with SLC6A14 (ATB0,+) reveals the potential of the transporter as a drug target for cancer chemotherapy. Biochem J. 414, 343–355.
Kawashima, M., Bensaad, K., Zois, C.E., Barberis, A., Bridges, E., Wigfield, S., Lagerholm, C., Dmitriev, R.I., Tokiwa, M., Toi, M., Papkovsky, D.B., Buffa, F.M., Harris, A.L., 2020. Disruption of hypoxia-inducible fatty acid binding protein 7 induces beige fat-like differentiation and thermogenesis in breast cancer cells. Cancer Metab. 8, 13.
Khacho, M., Tarabay, M., Patten, D., Khacho, P., MacLaurin, J.G., Guadagno, J., Bergeron, R., Cregan, S.P., Harper, M.-E., Park, D.S., Slack, R.S., 2014. Acidosis overrides oxygen deprivation to maintain mitochondrial function and cell survival. Nat. Commun. 5, 3550.
Khan, N.A., Nikkanen, J., Yatsuga, S., Jackson, C., Wang, L., Pradhan, S., Kivelä, R., Pessia, A., Velagapudi, V., Suomalainen, A., 2017. . mTORC1 regulates mitochondrial integrated stress response and mitochondrial myopathy progression. Cell Metab. 26, 419–428 e415.
Khasawneh, J., Schulz, M.D., Walch, A., Rozman, J., Hrabe de Angelis, M., Klingenspor, M., Buck, A., Schwaiger, M., Saur, D., Schmid, R.M., Klöppel, G., Sipos, B., Greten, F.R., Arkan, M.C., 2009. Inflammation and mitochondrial fatty acid beta-oxidation link obesity to early tumor promotion. Proc. Natl. Acad. Sci. USA 106, 3354–3359.
Kim, B.K., Yoo, H.I., Lee, A.R., Choi, K., Yoon, S.K., 2017. Decreased expression of VLDLR is inversely correlated with miR-200c in human colorectal cancer. Mol. Carcinog. 56, 1620–1629.
Kim, J., Kim, E., 2016. Rag GTPase in amino acid signaling. Amino Acids 48, 915–928.
Kim, J.A., 2020. Peroxisome metabolism in cancer. Cells 9 (7), 1692.
Kimmelman, A.C., White, E., 2017. Autophagy and tumor metabolism. Cell Metab. 25, 1037–1043.
Kitada, M., Xu, J., Ogura, Y., Monno, I., Koya, D., 2020. Mechanism of activation of mechanistic target of rapamycin complex 1 by methionine. Front. Cell Dev. Biol. 8 (715).
Knott, S.R.V., Wagenblast, E., Khan, S., Kim, S.Y., Soto, M., Wagner, M., Turgeon, M.O., Fish, L., Erard, N., Gable, A.L., Maceli, A.R., Dickopf, S., Papachristou, E.K., D'Santos, C.S., Carey, L.A., Wilkinson, J.E., Harrell, J.C., Perou, C.M., Goodarzi, H., Poulogiannis, G., Hannon, G.J., 2018. Asparagine bioavailability governs metastasis in a model of breast cancer. Nature 554, 378–381.
Kodama, M., Oshikawa, K., Shimizu, H., Yoshioka, S., Takahashi, M., Izumi, Y., Bamba, T., Tateishi, C., Tomonaga, T., Matsumoto, M., Nakayama, K.I., 2020. A shift in glutamine nitrogen metabolism contributes to the malignant progression of cancer. Nat. Commun. 11, 1320.
Kolonin, M.G., 2021. Bad cholesterol uptake by CD36 in T-cells cripples anti-tumor immune response. Immunometabolism 3, e210028.
Kosaisawe, N., Sparta, B., Pargett, M., Teragawa, C.K., Albeck, J.G., 2021. Transient phases of OXPHOS inhibitor resistance reveal underlying metabolic heterogeneity in single cells. Cell Metab. 33, 649–665 e648.
Krall, A.S., Xu, S., Graeber, T.G., Braas, D., Christofk, H.R., 2016. Asparagine promotes cancer cell proliferation through use as an amino acid exchange factor. Nat. Commun. 7, 11457.
Kubota, K., 2001. From tumor biology to clinical Pet: a review of positron emission tomography (PET) in oncology. Ann. Nucl. Med 15, 471–486.
Kuemmerle, N.B., Rysman, E., Lombardo, P.S., Flanagan, A.J., Lipe, B.C., Wells, W.A., Pettus, J.R., Froehlich, H.M., Memoli, V.A., Morganelli, P.M., Swinnen, J.V., Timmerman, L.A., Chaychi, L., Fricano, C.J., Eisenberg, B.L., Coleman, W.B., Kinlaw, W.B., 2011. Lipoprotein lipase links dietary fat to solid tumor cell proliferation. Mol. Cancer Ther. 10, 427–436.
Kumari, S., Badana, A.K., G, M.M., G, S., Malla, R., 2018. Reactive oxygen species: a key constituent in cancer survival. Biomark. Insights 13, 1177271918755391.
Kuo, M.T., Chen, H.H.W., Feun, L.G., Savaraj, N., 2021. Targeting the proline-glutamine-asparagine-arginine metabolic axis in amino acid starvation cancer therapy. Pharmaceuticals 14 (1), 72.
Kurniawan, H., Franchina, D.G., Guerra, L., Bonetti, L., Baguet, L.S., Grusdat, M., Schlicker, L., Hunewald, O., Dostert, C., Merz, M.P., Binsfeld, C., Duncan, G.S., Farinelle, S., Nonnenmacher, Y., Haight, J., Das Gupta, D., Ewen, A., Taskesen, R., Halder, R., Chen, Y., Jäger, C., Ollert, M., Wilmes, P., Vasiliou, V., Harris, I.S., Knobbe-Thomsen, C.B., Turner, J.D., Mak, T.W., Lohoff, M., Meiser, J., Hiller, K.,

Brenner, D., 2020. Glutathione restricts serine metabolism to preserve regulatory T cell function. Cell Metab. 31, 920–936 e927.
Kwong, S.C., Jamil, A.H.A., Rhodes, A., Taib, N.A., Chung, I., 2019. Metabolic role of fatty acid binding protein 7 in mediating triple-negative breast cancer cell death via PPAR-α signaling. J. Lipid Res 60, 1807–1817.
Lai, X., Li, Q., Wu, F., Lin, J., Chen, J., Zheng, H., Guo, L., 2020. Epithelial-mesenchymal transition and metabolic switching in cancer: lessons from somatic cell reprogramming. Front Cell Dev. Biol. 8, 760.
Lauinger, L., Kaiser, P., 2021. Sensing and signaling of methionine metabolism. Metabolites 11 (2), 83.
Laxman, S., Sutter, B.M., Tu, B.P., 2014. Methionine is a signal of amino acid sufficiency that inhibits autophagy through the methylation of PP2A. Autophagy 10, 386–387.
Lee, J.-S., Oh, S.-J., Choi, H.-J., Kang, J.H., Lee, S.-H., Ha, J.S., Woo, S.M., Jang, H., Lee, H., Kim, S.-Y., 2020a. ATP production relies on fatty acid oxidation rather than glycolysis in pancreatic ductal adenocarcinoma. Cancers 12, 2477.
Lee, J.S., Lee, H., Jang, H., Woo, S.M., Park, J.B., Lee, S.H., Kang, J.H., Kim, H.Y., Song, J., Kim, S.Y., 2020b. Targeting oxidative phosphorylation reverses drug resistance in cancer cells by blocking autophagy recycling. Cells 9.
Lee, P., Vousden, K.H., Cheung, E.C., 2014. TIGAR, TIGAR, burning bright. Cancer Metab. 2, 1.
Li, J., Tan, Y., Zhao, G., Huang, K.-C., Cardenas, H., Matei, D., Cheng, J.-X., 2021a. Metabolic reprogramming from glycolysis to fatty acid uptake and beta-oxidation in platinum-resistant. Cancer Cells bioRxiv, 2021.2005.2017.444564.
Li, L., Meng, Y., Li, Z., Dai, W., Xu, X., Bi, X., Bian, J., 2019a. Discovery and development of small molecule modulators targeting glutamine metabolism. Eur. J. Med Chem. 163, 215–242.
Li, X., Sun, X., Carmeliet, P., 2019b. Hallmarks of endothelial cell metabolism in health and disease. Cell Metab. 30, 414–433.
Li, Y.Y., Wu, C., Shah, S.S., Chen, S.M., Wangpaichitr, M., Kuo, M.T., Feun, L.G., Han, X., Suarez, M., Prince, J., Savaraj, N., 2017. Degradation of AMPK-α1 sensitizes BRAF inhibitor-resistant melanoma cells to arginine deprivation. Mol. Oncol. 11, 1806–1825.
Li, Y., Bie, J., Song, C., Liu, M., Luo., J., 2021b. PYCR, a key enzyme in proline metabolism, functions in tumorigenesis. Amino Acids 53 (12), 1841–1850.
Liberti, M.V., Locasale, J.W., 2016. The warburg effect: how does it benefit cancer cells? Trends Biochem Sci. 41, 211–218.
Liesa, M., Shirihai, O.S., 2013. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 17, 491–506.
Lignitto, L., LeBoeuf, S.E., Homer, H., Jiang, S., Askenazi, M., Karakousi, T.R., Pass, H.I., Bhutkar, A.J., Tsirigos, A., Ueberheide, B., Sayin, V.I., Papagiannakopoulos, T., Pagano, M., 2019. Nrf2 activation promotes lung cancer metastasis by inhibiting the degradation of bach1. Cell 178, 316–329 e318.
Lin, R., Zhang, H., Yuan, Y., He, Q., Zhou, J., Li, S., Sun, Y., Li, D.Y., Qiu, H.-B., Wang, W., Zhuang, Z., Chen, B., Huang, Y., Liu, C., Wang, Y., Cai, S., Ke, Z., He, W., 2020. Fatty acid oxidation controls CD8+ tissue-resident memory T-cell survival in gastric adenocarcinoma. Cancer Immunol. Res. 8, 479–492.
Liu, R.Z., Graham, K., Glubrecht, D.D., Germain, D.R., Mackey, J.R., Godbout, R., 2011. Association of FABP5 expression with poor survival in triple-negative breast cancer: implication for retinoic acid therapy. Am. J. Pathol. 178, 997–1008.
Liu, Y., Xu, R., Gu, H., Zhang, E., Qu, J., Cao, W., Huang, X., Yan, H., He, J., Cai, Z., 2021. Metabolic reprogramming in macrophage responses. Biomark. Res. 9, 1.
Liu, Y., Zhao, T., Li, Z., Wang, L., Yuan, S., Sun, L., 2018. The role of ASCT2 in cancer: a review. Eur. J. Pharm. 837, 81–87.
Liu, Y., Zuckier, L.S., Ghesani, N.V., 2010. Dominant uptake of fatty acid over glucose by prostate cells: a potential new diagnostic and therapeutic approach. Anticancer Res 30, 369–374.
Losman, J.A., Looper, R.E., Koivunen, P., Lee, S., Schneider, R.K., McMahon, C., Cowley, G.S., Root, D.E., Ebert, B.L., Kaelin Jr., W.G., 2013. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science 339, 1621–1625.
Lu, Y., Wang, W., Wang, J., Yang, C., Mao, H., Fu, X., Wu, Y., Cai, J., Han, J., Xu, Z., Zhuang, Z., Liu, Z., Hu, H., Chen, B., 2013. Overexpression of arginine transporter CAT-1 is associated with accumulation of L-arginine and cell growth in human colorectal cancer tissue. PLoS One 8, e73866.
Luo, Z., Xu, J., Sun, J., Huang, H., Zhang, Z., Ma, W., Wan, Z., Liu, Y., Pardeshi, A., Li, S., 2020. Co-delivery of 2-deoxyglucose and a glutamine metabolism inhibitor V9302 via a prodrug micellar formulation for synergistic targeting of metabolism in cancer. Acta Biomater. 105, 239–252.
Lupien, L.E., Bloch, K., Dehairs, J., Traphagen, N.A., Feng, W.W., Davis, W.L., Dennis, T., Swinnen, J.V., Wells, W.A., Smits, N.C., Kuemmerle, N.B., Miller, T.W., Kinlaw, W. B., 2020. Endocytosis of very low-density lipoproteins: an unexpected mechanism for lipid acquisition by breast cancer cells. J. Lipid Res 61, 205–218.
Lv, Q., Wang, G., Zhang, Y., Han, X., Li, H., Le, W., Zhang, M., Ma, C., Wang, P., Ding, Q., 2019. FABP5 regulates the proliferation of clear cell renal cell carcinoma cells via the PI3K/AKT signaling pathway. Int J. Oncol. 54, 1221–1232.
Ma, L., Zong, X., 2020. Metabolic symbiosis in chemoresistance: refocusing the role of aerobic glycolysis. Front Oncol. 10, 5.
Ma, Y., Zhang, X., Alsaidan, O.A., Yang, X., Sulejmani, E., Zha, J., Beharry, Z., Huang, H., Bartlett, M., Lewis, Z., Cai, H., 2021. Long-chain Acyl-CoA synthetase 4-mediated fatty acid metabolism sustains androgen receptor pathway-independent prostate cancer. Mol. Cancer Res 19, 124–135.
Ma, Z., Zhang, H., Lian, M., Yue, C., Dong, G., Jin, Y., Li, R., Wan, H., Wang, R., Wang, Y., Zhai, J., Ma, H., Feng, L., Han, J., Liu, S., Guo, Y., Li, J., Liu, Y., Fang, J., Liu, H., 2017. SLC7A11, a component of cysteine/glutamate transporter, is a novel biomarker for the diagnosis and prognosis in laryngeal squamous cell carcinoma. Oncol. Rep. 38, 3019–3029.
Madigan, A.A., Rycyna, K.J., Parwani, A.V., Datiri, Y.J., Basudan, A.M., Sobek, K.M., Cummings, J.L., Basse, P.H., Bacich, D.J., O'Keefe, D.S., 2014. Novel nuclear localization of fatty acid synthase correlates with prostate cancer aggressiveness. Am. J. Pathol. 184, 2156–2162.
Maher, M., Diesch, J., Casquero, R., Buschbeck, M., 2018. Epigenetic-transcriptional regulation of fatty acid metabolism and its alterations in leukaemia. Front. Genet. 9, 405.
Makowski, L., Chaib, M., Rathmell, J.C., 2020. Immunometabolism: from basic mechanisms to translation. Immunol. Rev. 295, 5–14.
Mao, K., Wang, K., Liu, X., Klionsky, D.J., 2013. The scaffold protein Atg11 recruits fission machinery to drive selective mitochondria degradation by autophagy. Dev. Cell 26, 9–18.
Marin-Valencia, I., Yang, C., Mashimo, T., Cho, S., Baek, H., Yang, X.L., Rajagopalan, K. N., Maddie, M., Vemireddy, V., Zhao, Z., Cai, L., Good, L., Tu, B.P., Hatanpaa, K.J., Mickey, B.E., Matés, J.M., Pascual, J.M., Maher, E.A., Malloy, C.R., Deberardinis, R. J., Bachoo, R.M., 2012. Analysis of tumor metabolism reveals mitochondrial glucose oxidation in genetically diverse human glioblastomas in the mouse brain in vivo. Cell Metab. 15, 827–837.
Martínez-Reyes, I., Chandel, N.S., 2020. Mitochondrial TCA cycle metabolites control physiology and disease. Nat. Commun. 11, 102.
Mayers, J.R., Torrence, M.E., Danai, L.V., Papagiannakopoulos, T., Davidson, S.M., Bauer, M.R., Lau, A.N., Ji, B.W., Dixit, P.D., Hosios, A.M., Muir, A., Chin, C.R., Freinkman, E., Jacks, T., Wolpin, B.M., Vitkup, D., Vander Heiden, M.G., 2016. Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. Science 353, 1161–1165.
McCracken, A.N., Edinger, A.L., 2015. Targeting cancer metabolism at the plasma membrane by limiting amino acid access through SLC6A14. Biochem J. 470, e17–e19.
McElroy, G.S., Chandel, N.S., 2017. Mitochondria control acute and chronic responses to hypoxia. Exp. Cell Res 356, 217–222.
Meier, C., Ristic, Z., Klauser, S., Verrey, F., 2002. Activation of system L heterodimeric amino acid exchangers by intracellular substrates. Embo J. 21, 580–589.
Meng, D., Yang, Q., Wang, H., Melick, C.H., Navlani, R., Frank, A.R., Jewell, J.L., 2020. Glutamine and asparagine activate mTORC1 independently of Rag GTPases. J. Biol. Chem. 295, 2890–2899.
Menon, D., Salloum, D., Bernfeld, E., Gorodetsky, E., Akselrod, A., Frias, M.A., Sudderth, J., Chen, P.H., DeBerardinis, R., Foster, D.A., 2017. Lipid sensing by mTOR complexes via de novo synthesis of phosphatidic acid. J. Biol. Chem. 292, 6303–6311.
Mesclon, F., Lambert-Langlais, S., Carraro, V., Parry, L., Hainault, I., Jousse, C., Maurin, A.C., Bruhat, A., Fafournoux, P., Averous, J., 2017. Decreased ATF4 expression as a mechanism of acquired resistance to long-term amino acid limitation in cancer cells. Oncotarget 8, 27440–27453.
Mills, E.L., Kelly, B., Logan, A., Costa, A.S.H., Varma, M., Bryant, C.E., Tourlomousis, P., Däbritz, J.H.M., Gottlieb, E., Latorre, I., Corr, S.C., McManus, G., Ryan, D., Jacobs, H.T., Szibor, M., Xavier, R.J., Braun, T., Frezza, C., Murphy, M.P., O'Neill, L. A., 2016. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell 167 (457–470), e413.
Mistry, J.J., Marlein, C.R., Moore, J.A., Hellmich, C., Wojtowicz, E.E., Smith, J.G.W., Macaulay, I., Sun, Y., Morfakis, A., Patterson, A., Horton, R.H., Divekar, D., Morris, C.J., Haestier, A., Di Palma, F., Beraza, N., Bowles, K.M., Rushworth, S.A., 2019. ROS-mediated PI3K activation drives mitochondrial transfer from stromal cells to hematopoietic stem cells in response to infection. Proc. Natl. Acad. Sci. USA 116, 24610–24619.
Monaco, M.E., 2017. Fatty acid metabolism in breast cancer subtypes. Oncotarget 8, 29487–29500.
Monti, S., Savage, K.J., Kutok, J.L., Feuerhake, F., Kurtin, P., Mihm, M., Wu, B., Pasqualucci, L., Neuberg, D., Aguiar, R.C., Dal Cin, P., Ladd, C., Pinkus, G.S., Salles, G., Harris, N.L., Dalla-Favera, R., Habermann, T.M., Aster, J.C., Golub, T.R., Shipp, M.A., 2005. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood 105, 1851–1861.
Montrose, D.C., Saha, S., Foronda, M., McNally, E.M., Chen, J., Zhou, X.K., Ha, T., Krumsiek, J., Buyukozkan, M., Verma, A., Elemento, O., Yantiss, R.K., Chen, Q., Gross, S.S., Galluzzi, L., Dow, L.E., Dannenberg, A.J., 2021. Exogenous and endogenous sources of serine contribute to colon cancer metabolism, growth, and resistance to 5-fluorouracil. Cancer Res 81, 2275–2288.
Morotti, M., Bridges, E., Valli, A., Choudhry, H., Sheldon, H., Wigfield, S., Gray, N., Zois, C.E., Grimm, F., Jones, D., Teoh, E.J., Cheng, W.C., Lord, S., Anastasiou, D., Haider, S., McIntyre, A., Goberdhan, D.C.I., Buffa, F., Harris, A.L., 2019. Hypoxia-induced switch in SNAT2/SLC38A2 regulation generates endocrine resistance in breast cancer. Proc. Natl. Acad. Sci. USA 116, 12452–12461.
Morotti, M., Zois, C.E., El-Ansari, R., Craze, M.L., Rakha, E.A., Fan, S.-J., Valli, A., Haider, S., Goberdhan, D.C.I., Green, A.R., Harris, A.L., 2021. Increased expression of glutamine transporter SNAT2/SLC38A2 promotes glutamine dependence and oxidative stress resistance, and is associated with worse prognosis in triple-negative breast cancer. Br. J. Cancer 124, 494–505.
Mukherjee, A., Chiang, C.-Y., Daifotis, H.A., Nieman, K.M., Fahrmann, J.F., Lastra, R.R., Romero, I.L., Fiehn, O., Lengyel, E., 2020. Adipocyte-induced FABP4 expression in ovarian cancer cells promotes metastasis and mediates carboplatin resistance. Cancer Res. 80, 1748–1761.
Ndiaye, H., Liu, J.Y., Hall, A., Minogue, S., Morgan, M.Y., Waugh, M.G., 2020. Immunohistochemical staining reveals differential expression of ACSL3 and ACSL4 in hepatocellular carcinoma and hepatic gastrointestinal metastases. Biosci. Rep. 40 (4), BSR20200219.

Nieman, K.M., Kenny, H.A., Penicka, C.V., Ladanyi, A., Buell-Gutbrod, R., Zillhardt, M. R., Romero, I.L., Carey, M.S., Mills, G.B., Hotamisligil, G.S., Yamada, S.D., Peter, M. E., Gwin, K., Lengyel, E., 2011. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat. Med. 17, 1498–1503.
Nunes, S.C., Ramos, C., Santos, I., Mendes, C., Silva, F., Vicente, J.B., Pereira, S.A., Félix, A., Gonçalves, L.G., Serpa, J., 2021. Cysteine boosts fitness under hypoxia-mimicked conditions in ovarian cancer by metabolic reprogramming. Front. Cell Dev. Biol. 9, 722412.
O'Sullivan, S.E., Kaczocha, M., 2020. FABP5 as a novel molecular target in prostate cancer. Drug Disco Today S1359-6446 (20), 30375.
O'Connor, R.S., Guo, L., Ghassemi, S., Snyder, N.W., Worth, A.J., Weng, L., Kam, Y., Philipson, B., Trefely, S., Nunez-Cruz, S., Blair, I.A., June, C.H., Milone, M.C., 2018. The CPT1a inhibitor, etomoxir induces severe oxidative stress at commonly used concentrations. Sci. Rep. 8, 6289.
Obre, E., Rossignol, R., 2015. Emerging concepts in bioenergetics and cancer research: metabolic flexibility, coupling, symbiosis, switch, oxidative tumors, metabolic remodeling, signaling and bioenergetic therapy. Int J. Biochem Cell Biol. 59, 167–181.
Okano, N., Kawai, K., Yamauchi, Y., Kobayashi, T., Naruge, D., Nagashima, F., Endou, H., Furuse, J., 2018. First-in-human phaseIstudy of JPH203 in patients with advanced solid tumors. J. Clin. Oncol. 36, 419-419.
Okita, K., Hara, Y., Okura, H., Hayashi, H., Sasaki, Y., Masuko, S., Kitadai, E., Masuko, K., Yoshimoto, S., Hayashi, N., Sugiura, R., Endo, Y., Okazaki, S., Arai, S., Yoshioka, T., Matsumoto, T., Makino, Y., Komiyama, H., Sakamoto, K., Masuko, T., 2021. Antitumor effects of novel mAbs against cationic amino acid transporter 1 (CAT1) on human CRC with amplified CAT1 gene. Cancer Sci. 112, 563–574.
Olivares, O., Mayers, J.R., Gouirand, V., Torrence, M.E., Gicquel, T., Borge, L., Lac, S., Roques, J., Lavaut, M.-N., Berthezène, P., Rubis, M., Secq, V., Garcia, S., Moutardier, V., Lombardo, D., Iovanna, J.L., Tomasini, R., Guillaumond, F., Vander Heiden, M.G., Vasseur, S., 2017. Collagen-derived proline promotes pancreatic ductal adenocarcinoma cell survival under nutrient limited conditions. Nat. Commun. 8, 16031.
Oshima, N., Ishida, R., Kishimoto, S., Beebe, K., Brender, J.R., Yamamoto, K., Urban, D., Rai, G., Johnson, M.S., Benavides, G., Squadrito, G.L., Crooks, D., Jackson, J., Joshi, A., Mott, B.T., Shrimp, J.H., Moses, M.A., Lee, M.-J., Yuno, A., Lee, T.D., Hu, X., Anderson, T., Kusewitt, D., Hathaway, H.H., Jadhav, A., Picard, D., Trepel, J. B., Mitchell, J.B., Stott, G.M., Moore, W., Simeonov, A., Sklar, L.A., Norenberg, J.P., Linehan, W.M., Maloney, D.J., Dang, C.V., Waterson, A.G., Hall, M., Darley-Usmar, V.M., Krishna, M.C., Neckers, L.M., 2020. Dynamic imaging of LDH inhibition in tumors reveals rapid in vivo metabolic rewiring and vulnerability to combination therapy. Cell Rep. 30, 1798–1810 e1794.
Pacella, I., Procaccini, C., Focaccetti, C., Miacci, S., Timperi, E., Faicchia, D., Severa, M., Rizzo, F., Coccia, E.M., Bonacina, F., Mitro, N., Norata, G.D., Rossetti, G., Ranzani, V., Pagani, M., Giorda, E., Wei, Y., Matarese, G., Barnaba, V., Piconese, S., 2018. Fatty acid metabolism complements glycolysis in the selective regulatory T cell expansion during tumor growth. Proc. Natl. Acad. Sci. USA 115. E6546-e6555.
Pallett, L.J., Dimeloe, S., Sinclair, L.V., Byrne, A.J., Schurich, A., 2021. A glutamine 'tug-of-war': targets to manipulate glutamine metabolism for cancer immunotherapy. Immunother. Adv. 1 (1), ltab010.
Panina, S.B., Pei, J., Baran, N., Konopleva, M., Kirienko, N.V., 2020. Utilizing synergistic potential of mitochondria-targeting drugs for leukemia therapy. Front. Oncol. 10, 435.
Park, Y.Y., Ahn, J.-H., Cho, M.-G., Lee, J.-H., 2018. ATP depletion during mitotic arrest induces mitotic slippage and APC/CCdh1-dependent cyclin B1 degradation. Exp. Mol. Med. 50, 1–14.
Peng, X., Chen, R., Cai, S., Lu, S., Zhang, Y., 2021. SLC1A4: a powerful prognostic marker and promising therapeutic target for HCC. Front Oncol. 11, 650355.
Peterson, T.R., Sengupta, S.S., Harris, T.E., Carmack, A.E., Kang, S.A., Balderas, E., Guertin, D.A., Madden, K.L., Carpenter, A.E., Finck, B.N., Sabatini, D.M., 2011. mTOR complex 1 regulates lipin 1 localization to control the SREBP pathway. Cell 146, 408–420.
Petricca, S., Flati, V., Celenza, G., Di Gregorio, J., Lizzi, A.R., Luzi, C., Cristiano, L., Cinque, B., Rossi, G., Festuccia, C., Iorio, R., 2019. Tebuconazole and econazole act synergistically in mediating mitochondrial stress, energy imbalance, and sequential activation of autophagy and apoptosis in mouse sertoli TM4 cells: possible role of AMPK/ULK1 Axis. Toxicol. Sci. 169, 209–223.
Pinilla, J., Aledo, J.C., Cwiklinski, E., Hyde, R., Taylor, P.M., Hundal, H.S., 2011. SNAT2 transceptor signalling via mTOR: a role in cell growth and proliferation? Front Biosci. (Elite Ed.) 3, 1289–1299.
Popova, N.V., Jücker, M., 2021. The Role of mTOR signaling as a therapeutic target in cancer. Int. J. Mol. Sci. 22, 1743.
Porporato, P.E., Payen, V.L., Pérez-Escuredo, J., De Saedeleer, C.J., Danhier, P., Copetti, T., Dhup, S., Tardy, M., Vazeille, T., Bouzin, C., Feron, O., Michiels, C., Gallez, B., Sonveaux, P., 2014. A mitochondrial switch promotes tumor metastasis. Cell Rep. 8, 754–766.
Qi, X., 2018. Review of the clinical effect of orlistat. IOP Conf. Ser.: Mater. Sci. Eng. 301, 012063.
Quan, J., Bode, A.M., Luo, X., 2021. ACSL family: the regulatory mechanisms and therapeutic implications in cancer. Eur. J. Pharm. 909, 174397.
Quintela-Fandino, M., Morales, S., Cortés-Salgado, A., Manso, L., Apala, J.V., Muñoz, M., Gasol Cudos, A., Salla Fortuny, J., Gion, M., Lopez-Alonso, A., Cortés, J., Guerra, J., Malón, D., Caleiras, E., Mulero, F., Mouron, S., 2020. Randomized phase 0/I Trial of the mitochondrial inhibitor ME-344 or placebo added to bevacizumab in early HER2-negative breast cancer. Clin. Cancer Res 26, 35–45.
Raab, S., Gadault, A., Very, N., Decourcelle, A., Baldini, S., Schulz, C., Mortuaire, M., Lemaire, Q., Hardivillé, S., Dehennaut, V., El Yazidi-Belkoura, I., Vercoutter-Edouart, A.-S., Panasyuk, G., Lefebvre, T., 2021. Dual regulation of fatty acid synthase (FASN) expression by O-GlcNAc transferase (OGT) and mTOR pathway in proliferating liver cancer cells. Cell. Mol. Life Sci. 78, 5397–5413.
Radadiya, A., Zhu, W., Coricello, A., Alcaro, S., Richards, N.G.J., 2020. Improving the treatment of acute lymphoblastic leukemia. Biochemistry 59, 3193–3200.
Radif, Y., Ndiaye, H., Kalantzi, V., Jacobs, R., Hall, A., Minogue, S., Waugh, M.G., 2018. The endogenous subcellular localisations of the long chain fatty acid-activating enzymes ACSL3 and ACSL4 in sarcoma and breast cancer cells. Mol. Cell Biochem 448, 275–286.
Raimondi, V., Ciccarese, F., Ciminale, V., 2020. Oncogenic pathways and the electron transport chain: a dangeROS liaison. Br. J. Cancer 122, 168–181.
Rao, S., Tortola, L., Perlot, T., Wirnsberger, G., Novatchkova, M., Nitsch, R., Sykacek, P., Frank, L., Schramek, D., Komnenovic, V., Sigl, V., Aumayr, K., Schmauss, G., Fellner, N., Handschuh, S., Glösmann, M., Pasierbek, P., Schlederer, M., Resch, G.P., Ma, Y., Yang, H., Popper, H., Kenner, L., Kroemer, G., Penninger, J.M., 2014. A dual role for autophagy in a murine model of lung cancer. Nat. Commun. 5, 3056.
Rath, M., Müller, I., Kropf, P., Closs, E.I., Munder, M., 2014. Metabolism via arginase or nitric oxide synthase: two competing arginine pathways in macrophages. Front. Immunol. 5, 532.
Redza-Dutordoir, M., Averill-Bates, D.A., 2016. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys. Acta 1863, 2977–2992.
Reid, M.A., Wang, W.I., Rosales, K.R., Welliver, M.X., Pan, M., Kong, M., 2013. The B55α subunit of PP2A drives a p53-dependent metabolic adaptation to glutamine deprivation. Mol. Cell 50, 200–211.
Reinfeld, B.I., Madden, M.Z., Wolf, M.M., Chytil, A., Bader, J.E., Patterson, A.R., Sugiura, A., Cohen, A.S., Ali, A., Do, B.T., Muir, A., Lewis, C.A., Hongo, R.A., Young, K.L., Brown, R.E., Todd, V.M., Huffstater, T., Abraham, A., O'Neil, R.T., Wilson, M.H., Xin, F., Tantawy, M.N., Merryman, W.D., Johnson, R.W., Williams, C. S., Mason, E.F., Mason, F.M., Beckermann, K.E., Vander Heiden, M.G., Manning, H. C., Rathmell, J.C., Rathmell, W.K., 2021. Cell-programmed nutrient partitioning in the tumour microenvironment. Nature 593, 282–288.
Reiter-Brennan, C., Semmler, L., Klein, A., 2018. The effects of 2-hydroxyglutarate on the tumorigenesis of gliomas. Conte Oncol. (Pozn.) 22, 215–222.
Ren, L., Ruiz-Rodado, V., Dowdy, T., Huang, S., Issaq, S.H., Beck, J., Wang, H., Tran Hoang, C., Lita, A., Larion, M., LeBlanc, A.K., 2020. Glutaminase-1 (GLS1) inhibition limits metastatic progression in osteosarcoma. Cancer Metab. 8, 4.
Rinaldi, G., Pranzini, E., Van Elsen, J., Broekaert, D., Funk, C.M., Planque, M., Doglioni, G., Altea-Manzano, P., Rossi, M., Geldhof, V., Teoh, S.T., Ross, C., Hunter, K.W., Lunt, S.Y., Grünewald, T.G.P., Fendt, S.M., 2021. In vivo evidence for serine biosynthesis-defined sensitivity of lung metastasis, but not of primary breast tumors, to mTORC1 inhibition. Mol. Cell 81, 386–397 e387.
Rosenfeldt, M.T., O'Prey, J., Morton, J.P., Nixon, C., MacKay, G., Mrowinska, A., Au, A., Rai, T.S., Zheng, L., Ridgway, R., Adams, P.D., Anderson, K.I., Gottlieb, E., Sansom, O.J., Ryan, K.M., 2013. p53 status determines the role of autophagy in pancreatic tumour development. Nature 504, 296–300.
Ruiz-Rodado, V., Dowdy, T., Lita, A., Kramp, T., Zhang, M., Jung, J., Dios-Esponera, A., Herold-Mende, C.C., Camphausen, K., Gilbert, M.R., Larion, M., 2021. Cysteine is a limiting factor for glioma proliferation and survival. bioRxiv 2021, 2001.2008.425930.
Ryan, D.G., O'Neill, L.A.J., 2020. Krebs cycle reborn in macrophage immunometabolism. Annu Rev. Immunol. 38, 289–313.
Sabharwal, S.S., Schumacker, P.T., 2014. Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? Nat. Rev. Cancer 14, 709–721.
Sahu, N., Dela Cruz, D., Gao, M., Sandoval, W., Haverty, P.M., Liu, J., Stephan, J.P., Haley, B., Classon, M., Hatzivassiliou, G., Settleman, J., 2016. Proline starvation induces unresolved ER stress and hinders mTORC1-dependent tumorigenesis. Cell Metab. 24, 753–761.
Sancak, Y., Peterson, T.R., Shaul, Y.D., Lindquist, R.A., Thoreen, C.C., Bar-Peled, L., Sabatini, D.M., 2008. The rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science 320, 1496–1501.
Sato, R., 2010. Sterol metabolism and SREBP activation. Arch. Biochem Biophys. 501, 177–181.
Saxton, R.A., Chantranupong, L., Knockenhauer, K.E., Schwartz, T.U., Sabatini, D.M., 2016. Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. Nature 536, 229–233.
Sayin, V.I., LeBoeuf, S.E., Papagiannakopoulos, T., 2019. Targeting metabolic bottlenecks in lung cancer. Trends Cancer 5, 457–459.
Scalise, M., Console, L., Rovella, F., Galluccio, M., Pochini, L., Indiveri, C., 2020. . Membrane transporters for amino acids as players of cancer metabolic rewiring. Cells 9 (9), 2028.
Scalise, M., Pochini, L., Console, L., Losso, M.A., Indiveri, C., 2018. The human SLC1A5 (ASCT2) amino acid transporter: from function to structure and role in cell biology. Front. Cell Dev. Biol. 6, 96.
Schägger, H., Pfeiffer, K., 2000. Supercomplexes in the respiratory chains of yeast and mammalian mitochondria. Embo J. 19, 1777–1783.
Schägger, H., Pfeiffer, K., 2001. The ratio of oxidative phosphorylation complexes I-V in bovine heart mitochondria and the composition of respiratory chain supercomplexes. J. Biol. Chem. 276, 37861–37867.
Schon, E.A., DiMauro, S., Hirano, M., 2012. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat. Rev. Genet 13, 878–890.
Schöpf, B., Weissensteiner, H., Schäfer, G., Fazzini, F., Charoentong, P., Naschberger, A., Rupp, B., Fendt, L., Bukur, V., Giese, I., Sorn, P., Sant'Anna-Silva, A.C., Iglesias-Gonzalez, J., Sahin, U., Kronenberg, F., Gnaiger, E., Klocker, H., 2020. OXPHOS remodeling in high-grade prostate cancer involves mtDNA mutations and increased succinate oxidation. Nat. Commun. 11, 1487.

Schrader, M., Godinho, L.F., Costello, J.L., Islinger, M., 2015. The different facets of organelle interplay-an overview of organelle interactions. Front Cell Dev. Biol. 3, 56.
Schulte, M.L., Fu, A., Zhao, P., Li, J., Geng, L., Smith, S.T., Kondo, J., Coffey, R.J., Johnson, M.O., Rathmell, J.C., Sharick, J.T., Skala, M.C., Smith, J.A., Berlin, J., Washington, M.K., Nickels, M.L., Manning, H.C., 2018. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. Nat. Med 24, 194–202.
Schulz, H., 2013. Fatty acid oxidation. In: Lennarz, W.J., Lane, M.D. (Eds.), Encyclopedia of Biological Chemistry, Second ed. Academic Press, Waltham, pp. 281–284.
Scott, G.K., Yau, C., Becker, B.C., Khateeb, S., Mahoney, S., Jensen, M.B., Hann, B., Cowen, B.J., Pegan, S.D., Benz, C.C., 2019. Targeting mitochondrial proline dehydrogenase with a suicide inhibitor to exploit synthetic lethal interactions with p53 upregulation and glutaminase inhibition. Mol. Cancer Ther. 18, 1374–1385.
Sehm, T., Rauh, M., Wiendieck, K., Buchfelder, M., Eyüpoglu, I.Y., Savaskan, N.E., 2016. Temozolomide toxicity operates in a xCT/SLC7a11 dependent manner and is fostered by ferroptosis. Oncotarget 7, 74630–74647.
Sena, L.A., Denmeade, S.R., 2021. Fatty acid synthesis in prostate cancer: vulnerability or epiphenomenon? Cancer Res. 81, 4385–4393.
Sena, L.A., Li, S., Jairaman, A., Prakriya, M., Ezponda, T., Hildeman, D.A., Wang, C.R., Schumacker, P.T., Licht, J.D., Perlman, H., Bryce, P.J., Chandel, N.S., 2013. Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. Immunity 38, 225–236.
Senga, S., Kobayashi, N., Kawaguchi, K., Ando, A., Fujii, H., 2018. Fatty acid-binding protein 5 (FABP5) promotes lipolysis of lipid droplets, de novo fatty acid (FA) synthesis and activation of nuclear factor-kappa B (NF-κB) signaling in cancer cells. Biochim Biophys. Acta Mol. Cell Biol. Lipids 1863, 1057–1067.
Seo, J., Jeong, D.W., Park, J.W., Lee, K.W., Fukuda, J., Chun, Y.S., 2020. Fatty-acid-induced FABP5/HIF-1 reprograms lipid metabolism and enhances the proliferation of liver cancer cells. Commun. Biol. 3, 638.
Shafqat, S., Velaz-Faircloth, M., Henzi, V.A., Whitney, K.D., Yang-Feng, T.L., Seldin, M. F., Fremeau Jr., R.T., 1995. Human brain-specific L-proline transporter: molecular cloning, functional expression, and chromosomal localization of the gene in human and mouse genomes. Mol. Pharm. 48, 219–229.
Shen, S., Faouzi, S., Souquere, S., Roy, S., Routier, E., Libenciuc, C., André, F., Pierron, G., Scoazec, J.Y., Robert, C., 2020. Melanoma persister cells are tolerant to BRAF/MEK inhibitors via ACOX1-mediated fatty acid oxidation. Cell Rep. 33, 108421.
Shi, L.-Y., Wang, Y.-Y., Jing, Y., Xu, M.-H., Zhu, Z.-T., Wang, Q.-J., 2021. Abnormal arginine metabolism is associated with prognosis in patients of gastric cancer. Transl. Cancer Res. 10, 2451–2469.
Shimizu, A., Kaira, K., Kato, M., Yasuda, M., Takahashi, A., Tominaga, H., Oriuchi, N., Nagamori, S., Kanai, Y., Oyama, T., Asao, T., Ishikawa, O., 2015. Prognostic significance of L-type amino acid transporter 1 (LAT1) expression in cutaneous melanoma. Melanoma Res 25, 399–405.
Silic-Benussi, M., Scattolin, G., Cavallari, I., Minuzzo, S., del Bianco, P., Francescato, S., Basso, G., Indraccolo, S., D'Agostino, D.M., Ciminale, V., 2018. Selective killing of human T-ALL cells: an integrated approach targeting redox homeostasis and the OMA1/OPA1 axis. Cell Death Dis. 9, 822.
Singhapol, C., Pal, D., Czapiewski, R., Porika, M., Nelson, G., Saretzki, G.C., 2013. Mitochondrial telomerase protects cancer cells from nuclear DNA damage and apoptosis. PLoS One 8, e52989.
Snell, C.E., Turley, H., McIntyre, A., Li, D., Masiero, M., Schofield, C.J., Gatter, K.C., Harris, A.L., Pezzella, F., 2014. Proline-hydroxylated hypoxia-inducible factor 1α (HIF-1α) upregulation in human tumours. PLoS One 9, e88955.
Sniegowski, T., Korac, K., Bhutia, Y.D., Ganapathy, V., 2021. SLC6A14 and SLC38A5 drive the glutaminolysis and serine–glycine–one-carbon pathways in cancer. Pharmaceuticals 14, 216.
Stipanuk, M.H., 2020. Metabolism of sulfur-containing amino acids: how the body copes with excess methionine, cysteine, and sulfide. J. Nutr. 150, 2494S–2505S.
Subastri, A., Arun, V., Sharma, P., Preedia Babu, E., Suyavaran, A., Nithyananthan, S., Alshammari, G.M., Aristatile, B., Dharuman, V., Thirunavukkarasu, C., 2018. Synthesis and characterisation of arsenic nanoparticles and its interaction with DNA and cytotoxic potential on breast cancer cells. Chem. Biol. Inter. 295, 73–83.
Sun, T., Bi, F., Liu, Z., Yang, Q., 2020. SLC7A2 serves as a potential biomarker and therapeutic target for ovarian cancer. Aging (Albany NY) 12, 13281–13296.
Suraweera, A., Münch, C., Hanssum, A., Bertolotti, A., 2012. Failure of amino acid homeostasis causes cell death following proteasome inhibition. Mol. Cell 48, 242–253.
Szlosarek, P.W., 2014. Arginine deprivation and autophagic cell death in cancer. Proc. Natl. Acad. Sci. 111, 14015–14016.
Tajan, M., Hennequart, M., Cheung, E.C., Zani, F., Hock, A.K., Legrave, N., Maddocks, O. D.K., Ridgway, R.A., Athineos, D., Suárez-Bonnet, A., Ludwig, R.L., Novellasdemunt, L., Angelis, N., Li, V.S.W., Vlachogiannis, G., Valeri, N., Mainolfi, N., Suri, V., Friedman, A., Manfredi, M., Blyth, K., Sansom, O.J., Vousden, K.H., 2021. Serine synthesis pathway inhibition cooperates with dietary serine and glycine limitation for cancer therapy. Nat. Commun. 12, 366.
Takanaga, H., Mackenzie, B., Suzuki, Y., Hediger, M.A., 2005. Identification of mammalian proline transporter SIT1 (SLC6A20) with characteristics of classical system imino. J. Biol. Chem. 280, 8974–8984.
Tanner, J.J., Fendt, S.M., Becker, D.F., 2018. The proline cycle as a potential cancer therapy target. Biochemistry 57, 3433–3444.
Thompson, C.B., 2009. Metabolic enzymes as oncogenes or tumor suppressors. N. Engl. J. Med 360, 813–815.
Timmerman, L.A., Holton, T., Yuneva, M., Louie, R.J., Padró, M., Daemen, A., Hu, M., Chan, D.A., Ethier, S.P., van 't Veer, L.J., Polyak, K., McCormick, F., Gray, J.W., 2013. Glutamine sensitivity analysis identifies the xCT antiporter as a common triple-negative breast tumor therapeutic target. Cancer Cell 24, 450–465.
Utsunomiya-Tate, N., Endou, H., Kanai, Y., 1996. Cloning and functional characterization of a system ASC-like Na+-dependent neutral amino acid transporter. J. Biol. Chem. 271, 14883–14890.
Vafadar, A., Shabaninejad, Z., Movahedpour, A., Fallahi, F., Taghavipour, M., Ghasemi, Y., Akbari, M., Shafiee, A., Hajighadimi, S., Moradizarmehri, S., Razi, E., Savardashtaki, A., Mirzaei, H., 2020. Quercetin and cancer: new insights into its therapeutic effects on ovarian cancer cells. Cell Biosci. 10, 32.
Vafai, S.B., Mootha, V.K., 2012. Mitochondrial disorders as windows into an ancient organelle. Nature 491, 374–383.
Valença, I., Pértega-Gomes, N., Vizcaino, J.R., Henrique, R.M., Lopes, C., Baltazar, F., Ribeiro, D., 2015. Localization of MCT2 at peroxisomes is associated with malignant transformation in prostate cancer. J. Cell Mol. Med 19, 723–733.
Vargas, T., Moreno-Rubio, J., Herranz, J., Cejas, P., Molina, S., Mendiola, M., Burgos, E., Custodio, A.B., De Miguel, M., Martín-Hernández, R., Reglero, G., Feliu, J., Ramírez de Molina, A., 2016. 3'UTR polymorphism in ACSL1 gene correlates with expression levels and poor clinical outcome in colon cancer patients. PLoS One 11, e0168423.
Vazquez, F., Lim, J.H., Chim, H., Bhalla, K., Girnun, G., Pierce, K., Clish, C.B., Granter, S. R., Widlund, H.R., Spiegelman, B.M., Puigserver, P., 2013. PGC1α expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. Cancer Cell 23, 287–301.
Velaz-Faircloth, M., Guadaño-Ferraz, A., Henzi, V.A., Fremeau Jr., R.T., 1995. Mammalian brain-specific L-proline transporter. Neuronal localization of mRNA and enrichment of transporter protein in synaptic plasma membranes. J. Biol. Chem. 270, 15755–15761.
Visser, W.F., van Roermund, C.W., Ijlst, L., Waterham, H.R., Wanders, R.J., 2007. Metabolite transport across the peroxisomal membrane. Biochem J. 401, 365–375.
Vogel, F.C.E., Schulze, A., 2021. Fatty acid synthesis enables brain metastasis. Nat. Cancer 2, 374–376.
Vyas, S., Zaganjor, E., Haigis, M.C., 2016. Mitochondria and cancer. Cell 166, 555–566.
Wagner, R., Stübiger, G., Veigel, D., Wuczkowski, M., Lanzerstorfer, P., Weghuber, J., Karteris, E., Nowikovsky, K., Wilfinger-Lutz, N., Singer, C.F., Colomer, R., Benhamú, B., López-Rodríguez, M.L., Valent, P., Grunt, T.W., 2017. Multi-level suppression of receptor-PI3K-mTORC1 by fatty acid synthase inhibitors is crucial for their efficacy against ovarian cancer cells. Oncotarget 8, 11600–11613.
Wallace, D.C., 2012. Mitochondria and cancer. Nat. Rev. Cancer 12, 685–698.
Walter, K.M., Schönenberger, M.J., Trötzmüller, M., Horn, M., Elsässer, H.P., Moser, A. B., Lucas, M.S., Schwarz, T., Gerber, P.A., Faust, P.L., Moch, H., Köfeler, H.C., Krek, W., Kovacs, W.J., 2014. Hif-2α promotes degradation of mammalian peroxisomes by selective autophagy. Cell Metab. 20, 882–897.
Wanders, R.J.A., Waterham, H.R., Ferdinandusse, S., 2016. Metabolic interplay between peroxisomes and other subcellular organelles including mitochondria and the endoplasmic reticulum. Front. Cell Dev. Biol. 3, 83.
Wang, K., Cao, F., Fang, W., Hu, Y., Chen, Y., Ding, H., Yu, G., 2013. Activation of SNAT1/SLC38A1 in human breast cancer: correlation with p-Akt overexpression. BMC Cancer 13, 343.
Wang, M., Liu, Y., Fang, W., Liu, K., Jiao, X., Wang, Z., Wang, J., Zang, Y.S., 2017. Increased SNAT1 is a marker of human osteosarcoma and potential therapeutic target. Oncotarget 8, 78930–78939.
Wang, Z., Liu, F., Fan, N., Zhou, C., Li, D., Macvicar, T., Dong, Q., Bruns, C.J., Zhao, Y., 2020. Targeting glutaminolysis: new perspectives to understand cancer development and novel strategies for potential target therapies. Front. Oncol. 10.
Warburg, O., 1956. On the origin of cancer cells. Science 123, 309–314.
Warburg, O., Wind, F., Negelein, E., 1927. The metabolism of tumors in the body. J. Gen. Physiol. 8, 519–530.
Waris, G., Ahsan, H., 2006. Reactive oxygen species: role in the development of cancer and various chronic conditions. J. Carcinog. 5, 14.
Wei, Z., Liu, X., Cheng, C., Yu, W., Yi, P., 2021. Metabolism of amino acids in cancer. Front. Cell Dev. Biol. 8, 603837.
Weinberg, S.E., Sena, L.A., Chandel, N.S., 2015. Mitochondria in the regulation of innate and adaptive immunity. Immunity 42, 406–417.
Werner, A., Pieh, D., Echchannaoui, H., Rupp, J., Rajalingam, K., Theobald, M., Closs, E. I., Munder, M., 2019. Cationic amino acid transporter-1-mediated arginine uptake is essential for chronic lymphocytic leukemia cell proliferation and viability. Front Oncol. 9, 1268.
Wheaton, W.W., Weinberg, S.E., Hamanaka, R.B., Soberanes, S., Sullivan, L.B., Anso, E., Glasauer, A., Dufour, E., Mutlu, G.M., Budigner, G.S., Chandel, N.S., 2014. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. Elife 3, e02242.
Wiel, C., Le Gal, K., Ibrahim, M.X., Jahangir, C.A., Kashif, M., Yao, H., Ziegler, D.V., Xu, X., Ghosh, T., Mondal, T., Kanduri, C., Lindahl, P., Sayin, V.I., Bergo, M.O., 2019. BACH1 stabilization by antioxidants stimulates lung cancer metastasis. Cell 178, 330–345 e322.
Wise, D.R., Ward, P.S., Shay, J.E., Cross, J.R., Gruber, J.J., Sachdeva, U.M., Platt, J.M., DeMatteo, R.G., Simon, M.C., Thompson, C.B., 2011. Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of α-ketoglutarate to citrate to support cell growth and viability. Proc. Natl. Acad. Sci. USA 108, 19611–19616.
Wu, B., Liu, K., Yang, J.P., Hu, Y., Zhang, J., He, J.X., 2017. The association between methionine synthase A2756G polymorphism and hematological cancer: a meta-analysis. Medicine 96, e7469.
Wyant, G.A., Abu-Remaileh, M., Wolfson, R.L., Chen, W.W., Freinkman, E., Danai, L.V., Vander Heiden, M.G., Sabatini, D.M., 2017. mTORC1 activator SLC38A9 is required to efflux essential amino acids from lysosomes and use protein as a nutrient. Cell 171, 642–654 e612.

Xiang, Y., Stine, Z.E., Xia, J., Lu, Y., O'Connor, R.S., Altman, B.J., Hsieh, A.L., Gouw, A. M., Thomas, A.G., Gao, P., Sun, L., Song, L., Yan, B., Slusher, B.S., Zhuo, J., Ooi, L.L., Lee, C.G., Mancuso, A., McCallion, A.S., Le, A., Milone, M.C., Rayport, S., Felsher, D. W., Dang, C.V., 2015. Targeted inhibition of tumor-specific glutaminase diminishes cell-autonomous tumorigenesis. J. Clin. Invest 125, 2293–2306.

Xu, D., Shao, F., Bian, X., Meng, Y., Liang, T., Lu, Z., 2021. The evolving landscape of noncanonical functions of metabolic enzymes in cancer and other pathologies. Cell Metab. 33, 33–50.

Yanagida, O., Kanai, Y., Chairoungdua, A., Kim, D.K., Segawa, H., Nii, T., Cha, S.H., Matsuo, H., Fukushima, J., Fukasawa, Y., Tani, Y., Taketani, Y., Uchino, H., Kim, J. Y., Inatomi, J., Okayasu, I., Miyamoto, K., Takeda, E., Goya, T., Endou, H., 2001. Human L-type amino acid transporter 1 (LAT1): characterization of function and expression in tumor cell lines. Biochim Biophys. Acta 1514, 291–302.

Yang, H., Jiang, X., Li, B., Yang, H.J., Miller, M., Yang, A., Dhar, A., Pavletich, N.P., 2017. Mechanisms of mTORC1 activation by RHEB and inhibition by PRAS40. Nature 552, 368–373.

Yang, J.S., Wang, C.C., Qiu, J.D., Ren, B., You, L., 2020. Arginine metabolism: a potential target in pancreatic cancer therapy. Chin. Med J. (Engl.) 134, 28–37.

Yap, T.A., Ahnert, J.R., Piha-Paul, S.A., Fu, S., Janku, F., Karp, D.D., Naing, A., Dumbrava, E.E.I., Pant, S., Subbiah, V., Tsimberidou, A.M., Hong, D.S., Rose, K.M., Xu, Q., Vellano, C.P., Mahendra, M., Jones, P., Francesco, M.E.D., Marszalek, J.R., Meric-Bernstam, F., 2019. Phase I trial of IACS-010759 (IACS), a potent, selective inhibitor of complex I of the mitochondrial electron transport chain, in patients (pts) with advanced solid tumors. J. Clin. Oncol. 37, 3014-3014.

Ye, D., Guan, K.L., Xiong, Y., 2018. Metabolism, activity, and targeting of D- and L-2-hydroxyglutarates. Trends Cancer 4, 151–165.

Ye, J.-l, Gao, C.-q, Li, X.-g, Jin, C.-l, Wang, D., Shu, G., Wang, W.-c, Kong, X.-f, Yao, K., Yan, H.-c, Wang, X.-q, 2016. EAAT3 promotes amino acid transport and proliferation of porcine intestinal epithelial cells. Oncotarget 7 (25), 38681–38692.

Yevglevskis, M., Nathubhai, A., Wadda, K., Lee, G.L., Al-Rawi, S., Jiao, T., Mitchell, P.J., James, T.D., Threadgill, M.D., Woodman, T.J., Lloyd, M.D., 2019. Novel 2-arylth-iopropanoyl-CoA inhibitors of α-methylacyl-CoA racemase 1A (AMACR; P504S) as potential anti-prostate cancer agents. Bioorg. Chem. 92, 103263.

Yoshioka, R., Fujieda, Y., Suzuki, Y., Kanno, O., Nagahira, A., Honda, T., Murakawa, M., Yukiura, H., 2019. Novel mouse model for evaluating in vivo efficacy of xCT inhibitor. J. Pharmacol. Sci. 140, 242–247.

Young, R.S.E., Bowman, A.P., Williams, E.D., Tousignant, K.D., Bidgood, C.L., Narreddula, V.R., Gupta, R., Marshall, D.L., Poad, B.L.J., Nelson, C.C., Ellis, S.R., Heeren, R.M.A., Sadowski, M.C., Blanksby, S.J., 2021. Apocryphal FADS2 activity promotes fatty acid diversification in cancer. Cell Rep. 34, 108738.

Yu, L., Chen, X., Sun, X., Wang, L., Chen, S., 2017. The glycolytic switch in tumors: how many players are involved? J. Cancer 8, 3430–3440.

Yuneva, M.O., Fan, T.W., Allen, T.D., Higashi, R.M., Ferraris, D.V., Tsukamoto, T., Matés, J.M., Alonso, F.J., Wang, C., Seo, Y., Chen, X., Bishop, J.M., 2012. The metabolic profile of tumors depends on both the responsible genetic lesion and tissue type. Cell Metab. 15, 157–170.

Zacksenhaus, E., Shrestha, M., Liu, J.C., Vorobieva, I., Chung, P.E.D., Ju, Y., Nir, U., Jiang, Z., 2017. Mitochondrial OXPHOS induced by RB1 deficiency in breast cancer: implications for anabolic metabolism, stemness, and metastasis. Trends Cancer 3, 768–779.

Zaytseva, Y.Y., Rychahou, P.G., Le, A.T., Scott, T.L., Flight, R.M., Kim, J.T., Harris, J., Liu, J., Wang, C., Morris, A.J., Sivakumaran, T.A., Fan, T., Moseley, H., Gao, T., Lee, E.Y., Weiss, H.L., Heuer, T.S., Kemble, G., Evers, M., 2018. Preclinical evaluation of novel fatty acid synthase inhibitors in primary colorectal cancer cells and a patient-derived xenograft model of colorectal cancer. Oncotarget 9, 24787–24800.

Zhang, B., Wu, J., Guo, P., Wang, Y., Fang, Z., Tian, J., Yu, Y., Teng, W., Luo, Y., Li, Y., 2020a. Down-regulation of SREBP via PI3K/AKT/mTOR pathway inhibits the proliferation and invasion of non-small-cell lung cancer cells. Onco Targets Ther. 13, 8951–8961.

Zhang, C., Liao, Y., Liu, P., Du, Q., Liang, Y., Ooi, S., Qin, S., He, S., Yao, S., Wang, W., 2020b. FABP5 promotes lymph node metastasis in cervical cancer by reprogramming fatty acid metabolism. Theranostics 10, 6561–6580.

Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., Liu, W., Kim, S., Lee, S., Perez-Neut, M., Ding, J., Czyz, D., Hu, R., Ye, Z., He, M., Zheng, Y.G., Shuman, H.A., Dai, L., Ren, B., Roeder, R.G., Becker, L., Zhao, Y., 2019. Metabolic regulation of gene expression by histone lactylation. Nature 574, 575–580.

Zhang, L.-X., Li, C.-X., Kakar, M.U., Khan, M.S., Wu, P.-F., Amir, R.M., Dai, D.-F., Naveed, M., Li, Q.-Y., Saeed, M., Shen, J.-Q., Rajput, S.A., Li, J.-H., 2021a. Resveratrol (RV): a pharmacological review and call for further research. Biomed. Pharmacother. 143, 112164.

Zhang, Y., Swanda, R.V., Nie, L., Liu, X., Wang, C., Lee, H., Lei, G., Mao, C., Koppula, P., Cheng, W., Zhang, J., Xiao, Z., Zhuang, L., Fang, B., Chen, J., Qian, S.-B., Gan, B., 2021b. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. Nat. Commun. 12, 1589.

Zhang, Z., Liu, R., Shuai, Y., Huang, Y., Jin, R., Wang, X., Luo, J., 2020c. ASCT2 (SLC1A5)-dependent glutamine uptake is involved in the progression of head and neck squamous cell carcinoma. Br. J. Cancer 122, 82–93.

Zhang, Z., Zeng, D., Zhang, W., Chen, A., Lei, J., Liu, F., Deng, B., Zhuo, J., He, B., Yan, M., Lei, X., Wang, S., Lam, E.W.F., Liu, Q., Wang, Z., 2021c. Modulation of oxidative phosphorylation augments antineoplastic activity of mitotic aurora kinase inhibition. Cell Death Dis. 12, 893.

Zhao, X., Fu, J., Hu, B., Chen, L., Wang, J., Fang, J., Ge, C., Lin, H., Pan, K., Fu, L., Wang, L., Du, J., Xu, W., 2021. Serine metabolism regulates YAP activity through USP7 in colon cancer. Front. Cell Dev. Biol. 9, 639111.

Zhou, Y., Zhou, Z., Peng, J., Loor, J.J., 2018. Methionine and valine activate the mammalian target of rapamycin complex 1 pathway through heterodimeric amino acid taste receptor (TAS1R1/TAS1R3) and intracellular Ca(2+) in bovine mammary epithelial cells. J. Dairy Sci. 101, 11354–11363.

Zhu, X.G., Chudnovskiy, A., Baudrier, L., Prizer, B., Liu, Y., Ostendorf, B.N., Yamaguchi, N., Arab, A., Tavora, B., Timson, R., Heissel, S., de Stanchina, E., Molina, H., Victora, G.D., Goodarzi, H., Birsoy, K., 2021. Functional genomics in vivo reveal metabolic dependencies of pancreatic cancer cells. Cell Metab. 33, 211–221 e216.

Zhu, Y., Li, T., Ramos da Silva, S., Lee, J.J., Lu, C., Eoh, H., Jung, J.U., Gao, S.J., 2017. A critical role of glutamine and asparagine γ-nitrogen in nucleotide biosynthesis in cancer cells hijacked by an oncogenic virus. mBio 8 (4), e01179.