Chapter 3
Regulating Mitochondrial Respiration in Cancer

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Abstract Mitochondria are a major focus of research in cancer due to their critical role in tumor physiology and metabolism. Metabolic remodeling is observed in tumor cells, often resulting in increased glycolytic activity, which serves for the generation of adenosine triphosphate (ATP), and as hubs for biosynthesis of key metabolites essential for cancer cell growth and proliferation. Mitochondria, thus, appear as a critical nexus in cancer metabolic alterations. Not only increased overexpression of oncogenes leads to altered mitochondrial respiration due to remodeling of mitochondrial gene expression and substrate channeling, but also particular mutations in components of the respiratory chain trigger an upstream feedback mechanism which also leads to metabolic reshaping in cancer cells. Mitochondrial respiration can thus be controlled by intrinsic and extrinsic mechanisms in cancer cells, which ultimately translates into different abilities to generate mitochondrial ATP. Altered mitochondrial structures and processes can be a target for chemotherapeutics, which are increasingly being developed to specifically target mitochondria in tumors. The present chapter reviews current knowledge on regulation of mitochondrial respiration and overall metabolism and how these specific alterations in the cell powerhouse can be used to eliminate tumors.

Keywords Cancer metabolism · Mitochondria · Oxidative phosphorylation · Respiration · Chemotherapy

3.1 Cancer Metabolism

3.1.1 Overview

Under normal conditions, cells have controlled programs for maintaining homeostasis in tissues, relying normally on aerobic respiration, using cytosolic and mitochondrial metabolisms to produce adenosine triphosphate (ATP) and for the

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biosynthesis of cellular building molecules [311]. Any deviation from these programs may result in an anomalous situation. Tumors, deviations from normal cell homeostasis, contain a mixed cell population, with some showing fast proliferation. Together with unregulated cell growth, tumor cells display loss of contact inhibition, which is necessary for normal tissue formation. Interestingly, both uncontrolled growth and loss of contact inhibition appear to be linked with altered cellular metabolism [187]. The progressive growth of a tumor greatly increases the demand for oxygen and nutrients, resulting in the inability of tumor cells that are distant from blood vessels to be steadily supplied [129]. As a consequence, hypoxic regions are formed within the tumor. Therefore, one of the main mechanisms for the metabolic remodeling observed in cancer cells is an adaptation to a novel environment, where oxygen can be limiting [183]. Malignant cells will survive under hypoxic conditions due to the activity of distinct oncogenic proteins, which induce the expression of specific encoding genes for metabolic proteins and consequently modulate their function in cancer cells [137]. The molecular mechanism behind this adaptation and energy metabolic adjustment is not completely understood and this phenomenon is not general to all cancer cells.

One important characteristic of tumors is the induction of angiogenesis [311]. New vessels are formed in the tumor microenvironment providing oxygen, which, although not as well distributed as in a normal tissue, favors ATP production through oxidative phosphorylation (OXPHOS). Still, most cancer cell types will continue to use glycolysis, which not only provides a survival advantage over non-transformed cells but also ensures the persistence of the most successful cancer cells [128]. Cancer cells manage to adapt from aerobic to anaerobic glycolysis to survive in a new microenvironment, upregulating transporter proteins that extrude lactic acid from the cell into the surrounding extracellular medium, as well as undergoing many other alterations [286]. This phenomenon is widely explored in cancer biology and was termed the Warburg effect [309].

Glycolysis accounts for most of ATP generation in a majority of cancer cell types [203]; however, mitochondrial ATP production in other tumors may be entirely similar to a non-tumor cell. It has been proposed that this switch may be related to specific cell or tissue types, with this metabolic flexibility being important for certain tumors to grow and metastasize [45]. Moreover, a large number of mitochondrial alterations exist in most cancer cells. In fact, tumor cells that show negative mitochondrial alterations are particularly aggressive, showing a rapid growth rate [279]. The downregulation of some mitochondrial proteins in cancer cells, including the OXPHOS machinery, is achieved by distinct mechanisms, specifically activated by the profound hypoxic environment, the loss of tumor-suppressor genes and/or activation of oncogenes, and the direct inhibition of mitochondrial complex subunits [112]. Tumor microenvironment can also dictate the type of metabolic pathway to be predominantly used in cells, which, in turn, gives self-renewal ability to the tumor [20].

Hanahan and Weinberg reformulated their six hallmark signatures of cancer [150], adding the reprogramming of energy metabolism plus the evasion from immune destruction as new cancer features. The “Hallmarks of Cancer” appear now as a signature of the disease which can help in stratification, diagnosis, prognosis, and

treatment: limitless replication potential, sustained angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, tissue invasion, metastasis, metabolic remodeling, and evading immune destruction [151]. [AQ1]

In fact, more and more evidence enhances the importance of cancer metabolism research. It is our objective to understand the mitochondrial alterations in tumorigenesis, namely those altering mitochondrial respiration, and evidence the most promising therapies that target these alterations.

3.1.2 Mitochondrial OXPHOS

Mitochondria are essential organelles for cell survival and growth and are the main producers of cellular ATP via OXPHOS, which provides 15 times more ATP than glycolysis [4]. These organelles are also involved in calcium signaling [148], heme and steroid synthesis [260], and redox homeostasis [149]. The actual mechanism of OXPHOS was mechanistically explained by Peter Mitchell's chemiosmotic hypothesis [217, 218], elucidating the biochemical mechanism of ATP synthesis in mitochondria. Under normal conditions, electrons are transferred from carbohydrates and lipids via nicotinamide adenine dinucleotide (NAD; reduced form) to complex I (NADH dehydrogenase), the major entrance point of electrons in the respiratory chain (or electron transport chain (ETC)), or from succinate to complex II (succinate dehydrogenate), that directly connects the tricarboxylic acid cycle (TCA) to the system [104]. Other components involved in electron entry to ETC are the electron transfer flavoprotein-ubiquinone oxidoreductase (ETF-QO) [327] and glycerol-3-phosphate dehydrogenase (G3PDH) [180]. Coenzyme Q_{10} accepts the electrons from different sources and channels them to complex III (subunit for ubiquinol: cytochrome *c* oxidoreductase) [119]. Electrons then flow through complex III to complex IV (cytochrome *c* oxidase, COX), where oxygen is reduced to water. Protons are pumped from the matrix to the intermembrane space, coupled to electron transport at complexes I, III, and IV, creating an electrochemical gradient, composed of an electric component ($\Delta\Psi m$), being negative inside, and of a pH component (ΔpH), alkaline in the matrix [53]. The proton motive force is then used by complex V (ATP synthase) to produce ATP from adenosine diphosphate (ADP) and phosphate [171]. The ETC is coupled with the phosphorylation system, in order to maximize mitochondrial ATP production and minimize heat production [30]. All these processes must follow strict regulated conditions, otherwise cell death or malignancy can occur. Therefore, under normal conditions, different mechanisms of regulation of mitochondrial respiration exist. One crucial factor is not only the modulation of complex IV isoforms [43], but also the activation of four mitochondrial dehydrogenases, namely flavin adenine dinucleotide (FAD)-glycerol-3-phosphate dehydrogenase [152], pyruvate dehydrogenase phosphatase [83], NAD-isocitrate dehydrogenase [84], and oxoglutarate dehydrogenase [213] by calcium ions, which leads to their stimulation. Mitochondrial respiration regulation depends as well on fusion and fission proteins that are responsible for mitochondrial morphology [15]. Moreover, there are other proteins that are responsible for mitochondrial biogenesis

and degradation, which have a role in regulating mitochondrial respiration [40]. Besides the direct regulation of OXPHOS by proteins, the availability of substrates (NADH, H + /NAD + , ADP/ATP, oxygen gradients, glucose, and glutamine) [135], as well as the interaction with other cellular organelles [77] or even chemicals and drugs, can also impact mitochondrial respiration [16] .

3.1.3 Cancer Metabolism

Metabolism is the sum of all chemical reactions that occur in cells or organisms [116]. In this particular section, energy metabolism in cancer is discussed. The analysis of mitochondrial metabolic alterations is important to better approach the regulatory adaptations that occur in mitochondrial respiration of cancer cells.

Cells exposed to low oxygen availability (hypoxia) upregulate glycolysis, resulting in increased lactic acid production. Cancer cells can preferentially use this pathway, once it generates ATP more rapidly than OXPHOS, even if in far lower amounts [262]. Glycolytic genes are regulated by the hypoxia-inducible factor-1 (HIF-1) ([72]; Fig. 3.1). Within any cell type, HIF-1 controls the expression of a very large number of genes. In particular, HIF-1 modulates the expression of aldolase, phosphoglycerate kinase, phosphofructokinase, lactate dehydrogenase A (LDHA), and lactate-extruding enzyme monocarboxylate transporter 4 (MCT4), as well as hexokinases (Hk1 and Hk2) [57]. At the same time, HIF-1 indirectly inhibits pyruvate conversion to acetyl-coenzyme A (CoA) by leading to an overexpression of pyruvate dehydrogenase kinase 1 (PDK1), which inhibits pyruvate dehydrogenase (PDH) [71]. In mitochondria, HIF inhibits the respiratory chain by targeting a Bcl-2 family member (BNiP3) and by reducing COX activity by upregulating microRNA-210 [257]. In several tumors, impairment of the TCA cycle leads to succinate accumulation, which acts as a signaling molecule and triggers the reactivation of HIF-1 [269]. Due to the lower energy efficacy of aerobic glycolysis, glucose uptake verified in most tumors is higher than in normal tissues [304], with increased expression of glucose transporters (Glut1, Glut3, and other isoforms) [270]. However, when elevated intracellular glucose is available, cells redirect pyruvate towards lipid synthesis, which is necessary for membrane assembly. While in non-tumor cells pyruvate is mostly imported into mitochondria to produce NADH and succinate, which will fuel the ETC in two different sites [6], pyruvate can also be converted to lactate by LDH in the cytosol and extruded, causing extracellular acidification, which is also advantageous to cancer cells as it decreases immune detection and facilitates invasion [320]. Contributing to cancer success, the downregulation of oxidative metabolism can favor malignant cells to evade apoptosis [159].

The Warburg effect can be observed even after re-oxygenation of tumors due to the formation of new blood vessels. Warburg initially observed that cancer cells would rather use glycolysis than OXPHOS to obtain most of their energy [309]. The original observation was based on the fact that tumors have elevated levels of glucose consumption and lactate production (Pasteur effect) while in the presence of oxygen [184]. The Warburg effect was observed in vitro and in vivo and is well documented

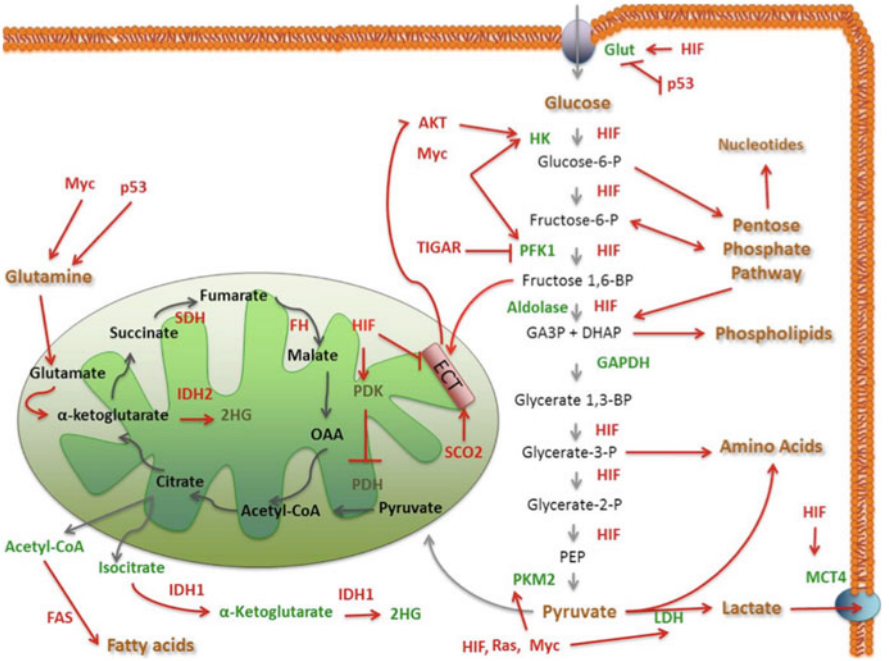

Fig. 3.1 Cancer metabolism. Proliferating cancer cells show upregulation of glucose transporters (Glut) in order to import a large amount of glucose to be processed in glycolysis. Glycolysis is entirely regulated by HIF; however, oncogenes (e.g., Myc and Ras) and suppressor genes (e.g., TP53-induced glycolysis and apoptosis regulator (TIGAR)) ultimately control the flux. The ultimate product of glycolysis is pyruvate, which is normally converted to lactate in cancer cells. Pyruvate can also originate from non-essential amino acids or be converted to acetyl-coenzyme A and enter mitochondria to generate citrate. Due to altered mitochondrial function observed in cancer cells, citrate will mostly leave these organelles to promote lipid synthesis. Other pathways that are altered and important for the survival of cancer cells are the pentose phosphate pathway, which supplies RNA and DNA, but especially the glutamine pathway which fuels cells with other amino acids and proteins. *MCT4* monocarboxylate transporter; *Glucose-6-P* Glucose-6-phosphate; *Fructose-6-P* Fructose-6-phosphate; *Fructose 1,6-BP* Fructose 1,6-biphosphate; *GA3P* Glyceraldehyde-3-phosphate; *DHAP* Dihydroxyacetone phosphate; *Glycerate 1,3-BP* Glycerate 1,3-biphosphate; *Glycerate-3-P* Glycerate 3-phosphate; *Glycerate-2-P* Glycerate-2-phosphate; *PEP* Phosphoenolpyruvate; *2HG* 2-hydroxy-glutarate; *HK* Hexokinase; *PFK1* Phosphofructokinase; *GAPDH* Glyceraldehyde 3-phosphate dehydrogenase; *PKM2* pyruvate kinase isoform 2; *LDH* Lactate dehydrogenase; *IDH1* Isocitrate dehydrogenase isoform 1; *IDH2* Isocitrate dehydrogenase isoform 2; *SCO2* synthesis of cytochrome *c* oxidase deficient homolog 2; *PDK* pyruvate dehydrogenase kinase; *PDH* pyruvate dehydrogenase; *SDH* Succinate dehydrogenase; *FH* Fumarate hydratase; *FAS* Fatty acid synthase; *HIF* Hypoxia inducible factor; *ETC* Electron transport chain

for several tumor types, where the overproduction of lactate leads to the acidification of the tumor microenvironment, being recognized as a major metabolic hallmark of cancer, although many tumors do not have this effect [294]. Therefore, the Warburg effect can originate from an increase in glucose consumption and glycolysis activity and/or downregulation of mitochondrial metabolism [90].

Another phenomenon similar to the Warburg effect but caused by a different event is the Crabtree effect [91]. Fast-growing cells, including tumors, display inhibition of respiration due to an excessive increase of intracellular glucose. The Crabtree effect is considered a short-term and reversible event. The possible advantage of this phenomenon would be the adaptation of cancer cell metabolism to the heterogeneous microenvironment found in tumors [91].

Even if both the Warburg and Crabtree effects were common to all cancer cells, one must take into account that both metabolic effects, as well as other metabolic alterations, are not exclusive to cancer cells, since they can also be observed in activated T lymphocytes and some proliferating normal cells [141]. Moreover, each type of cancer carries its own mutation load and different tissues of origin differently prime tumors to metabolic alterations. In addition, an increase in the glycolytic flux may not directly result from increased expression of glycolytic enzymes, but instead result from altered proteins that co-regulate glycolysis [227].

Within the tumor, some cancer cells quickly interchange the metabolism between fermentation and oxidative metabolism, according to the presence or absence of nutrients and environmental conditions, thus showing a large plasticity [259]. Therefore, tumor cells can behave differently depending on many intrinsic and/or extrinsic factors, which limits the use of metabolic remodeling per se to distinguish a particular type of tumor.

More research must be performed to identify differences between normal and cancer cells and to identify the best therapeutic approaches. In particular, the central role of mitochondria, by modulating several key functions in the cell, deserves special attention. Mitochondria can serve both as a hub for metabolic alterations and as a target for chemotherapeutics.

3.2 Mitochondrial Metabolism Remodeling in Cancer

3.2.1 Biosynthesis and Energy Production

The proliferation of cancer cells is supported not only by altered energy production but also by increased biosynthesis and maintenance of specific redox balance [18]. The remodeling of mitochondrial metabolism is evidenced by the preferential use of glycolysis and the increased usage of biosynthetic pathways, such as those of amino acids and fatty acids [120].

As described earlier, ATP production by mitochondria in most tumor types is diminished. One possible explanation for the disruption of the normal flux of the Krebs cycle may be the channeling of cycle intermediates, including malate and citrate, for other biosynthetic pathways. Both molecules can leave mitochondria, thus deviating the carbon flux. Malate can be used to provide the cytoplasm with NADPH, and citrate is used to support fatty acid and cholesterol synthesis [225]. Moreover, citrate is a crucial sensor of energy level, exerting a negative feedback on the Krebs cycle and glycolysis, slowing or even arresting the two pathways [161].

Another observation to support a low mitochondrial activity in cancer is a decrease of ADP transport to the mitochondrial matrix, as well as the inhibition of ATP synthase [64], decreasing ATP production in mitochondria. In the Krebs cycle, carbon can be dissipated as CO_2, while carbons originating from glycolysis supply precursors for biosynthesis. In truth, there is a waste of carbon by lactate export, although there are several advantages in the process, including evasion from the immune system [80].

Several groups [76, 123, 324] have provided evidence of the importance of amino acid metabolism in tumor proliferation, demonstrating that cancer cells have increased glutamine consumption by glutaminolysis when compared with their normal counterparts, although others suggest that this may be an in vitro artifact [223]. Glutamine is the most abundant amino acid in mammals [185] and a major factor in anaplerosis [76]. Oxidation of glutamine was observed to be essential not only for cancer systems but also for normal proliferating cells, such as lymphocytes, enterocytes, and fibroblasts [76]. Glutamine metabolism can be roughly divided into α-nitrogen (Krebs cycle) and γ-nitrogen (nucleotide and hexosamine synthesis) [57]. In the latter reactions, glutamine is converted to glutamate by cytoplasmic or mitochondrial glutaminase. From here, glutamate can follow one of two pathways: as a source of oxaloacetate (OAA) for the Krebs cycle or via transaminase by consuming OAA and generating aspartate, which then leaves mitochondria [223]. OAA is an essential substrate because it leads to citrate production when condensed with acetyl-CoA. After being exported to the cytosol, citrate can be used by ATP citrate lyase (ACL) to produce OAA and acetyl-CoA, essential for cholesterol and fatty acid synthesis and also for modification of chromatin structure [153, 315]. α-Ketoglutarate can also be originated from isocitrate by the action of isocitrate dehydrogenases (IDH1 and IDH2). The two enzymes exist in the cytoplasm and mitochondria, respectively, and, when mutated, convert α-ketoglutarate to 2-hydroxy-glutarate, which is recognized as an oncometabolite [252], Scatena [2012]. **[AQ2]**

Glutamine metabolism can also provide precursors for the synthesis of glutathione (GSH), which serves as a redox buffer against increased oxidative stress, being important for tumors with rapid growth, thus presenting a high production of reactive oxygen species (ROS) [109]. Finally, glutamine is required as a nitrogen donor to produce purine and pyrimidine nucleotides during cell proliferation [123].

Interestingly, the serine pathway, another amino acid biosynthetic flux, has an important role in most estrogen-negative breast cancers [248]. In fact, some tumors showing overexpression of phosphoglycerate dehydrogenase (PHGDH) redirect glycolytic intermediates into serine and glycine metabolism [202].

Besides amino acid metabolism, other metabolic pathways can be altered, including fatty acid β-oxidation. The contribution of β-oxidation to metabolism in cancers was suggested as providing an important source of acetyl-CoA, NADH, H +,and ATP, to sustain energy production and proliferation. However, there is still a large unknown to be investigated [161]. Fatty acid synthesis in normal cells occurs at a low rate, since fatty acids can be easily obtained via blood circulation. However, proliferation of some tumors was still observed even when mitochondrial catabolism of fatty acids originating from the blood stream was not occurring, forcing de novo fatty acid synthesis at very high rates [212] or export of citrate from mitochondria to produce

acetyl-CoA [275]. To support this hypothesis, citrate transport is increased in tumor cells and also associated with glutamine uptake [237]. Moreover, increased lipogenesis in cancer is closely associated with the overexpression and hyperactivity of ACL, acetyl-CoA carboxylase (ACC), or fatty acid synthase (FAS) [186]. Among these proteins, FAS was the most consistently increased in cancer cells, being expressed at low levels in normal cells and tissues [36]. In malignant cells, FAS is involved in lipid production for membrane incorporation, as well as synthesis of lipids for cell signaling, such as phosphatidylinositol-3,4,5-trisphosphate, which activates protein kinase B/Akt leading to cell proliferation and survival [323], lysophosphatidic acid, which stimulates tumor aggressiveness by signaling a family of G-protein-coupled receptors [256], and prostaglandins formed by cyclooxygenases, which support migration and tumor–host interactions [143]. Moreover, fatty acid synthesis participates in the activation of oncogenic pathways, such as Ras, Src, or Wnt [247]. Lipid metabolism also involves important mitochondrial proteins, such as uncoupling protein 2 (UCP2), normally expressed in central and peripheral tissues [88]. Uncoupling proteins have multiple roles, which are tissue-dependent, including heat generation [303], fatty acid derivatives transport [105], and control of oxidative stress [23]. In some tumor models, high expression of UCP2 was observed to be associated with malignancy, increased aerobic glycolysis, and resistance to apoptosis [265].

[AQ3]

Mitochondria are responsible for a significant part of ROS as well as reactive nitrogen species (RNS) generation in cells [38]. Both ROS and RNS act as biological mediators by regulating mitogen-activated protein kinases (MAPKs) essential in signaling pathways involved in cell survival, proliferation, and differentiation [222]. ROS are mostly produced by mitochondrial complexes I and III [51]. Complex II has also been shown to be another source, possibly at the FAD coenzyme present in SDHA [145] or in a mutated SDHC subunit [281].

In malignant cells, ROS promote mitogenic signaling, cell survival, disruption of cell death signaling, epithelial–mesenchymal transition (EMT), metastasis, and chemoresistance [54]. In fact, increased uncontrolled mitochondrial ROS production affects HIF-1 by stabilizing HIF-1α, the oxygen-sensitive subunit, allowing the dimerization with HIF-1β to form an active molecule [85].

The transcription factor p53 regulates ROS production and induces cell death when damage is extensive [253]. Excessive ROS production can damage proteins, lipids, and DNA, leading, in extreme situations, to cell death [299], once ROS production exceeds the capacity of cell antioxidant defenses [54]. In fact, some findings suggest that the mitochondrial antioxidant defenses do not provide efficient removal of ROS, especially H_2O_2, in most tumor tissues [48]. Another mitochondrial source of ROS, which has been associated with carcinogenesis, is p66Sch. This adaptor protein seems to promote increased oxidative stress by inhibiting the mitochondrial enzyme manganese superoxide dismutase (SOD2) activity [233]. On the other hand, SOD2 is an effective antioxidant enzyme with antitumor activity, since its overexpression results in inhibition of tumor growth [14]. In melanoma and some cancer cell types, SOD2 expression was found to be decreased, more likely due to epigenetic silencing [158]. However, other studies are contradictory, showing that SOD2 overexpression in cancers of the gastrointestinal tract is correlated with an invasive and

metastatic profile, resulting in poor prognosis for the patients [169, 250]. Similarly to other proteins, SOD2 has heterogenic expression, probably due to cancer type or developmental stage.

Without having an intrinsic antioxidant activity, the overexpression of the anti-apoptotic Bcl-2 protects against ROS-induced apoptosis by promoting overexpression of antioxidants such as reduced GSH, catalases, and NAD(P)H [194]. At the same time, other studies showed that Bcl-2 induces increased generation of mitochondrial ROS [49]. Even though cancer cells are often shown to have higher ROS production, coupled with high expression of cell antioxidants, the opposite can occur. For instance, a lower than normal generation of mitochondrial ROS was recently correlated to intrinsic chemotherapy resistance of cancer stem cells [92].

Due to the proximity to ROS sources, mitochondrial DNA (mtDNA) is continuously at risk for suffering oxidative damage. In fact, a correlation between altered mitochondrial gene expression and cellular metabolism alteration has been observed in some tumor types. Whereas mtDNA-encoded subunits correspond to catalytic enzymes, nDNA-encoded subunits have functional and structural activities [53]. Thus, the coordination of the expression of nDNA-and mtDNA-encoded genes is essential for normal mitochondrial physiology [53]. In different systems, loss of mtDNA is associated with a decrease in oxygen consumption and increased oxygen tension inside cells [62]. In fact, mutations and altered mtDNA copy number were observed in diverse types of tumors and cancer cell lines (see also Sect. 3.2.3), leading to altered mitochondrial protein expression, morphology, and general physiology [11, 193, 204]. However, since these mutations result in a large range of tissue-dependent phenotypic variation, this complicates the identification of OXPHOS alterations as a unique pathogenic factor [216]. Importantly, mtDNA alterations can even lead to the activation of oncogenes including Ras and a downstream increase in Akt and Erk pathway signaling, besides several metabolic modifications [62].

3.2.2 Oncogenes Vs. Suppressor Genes and Mitochondria

Oncogenes such as Myc, Ras, or Src induce the expression of glucose transporters (Glut), which are associated with tumor invasiveness and metastasis, but also are implicated in the regulation of mitochondrial activity [72]. The Myc gene is essentially engaged in conserved core target genes, which are involved in ribosomal and mitochondrial biogenesis, energy metabolism, and cell cycle regulation [103]. Under normal conditions, Myc stimulates glucose oxidation and lactate production, while under hypoxia, Myc and HIF-1 cooperate to increase pyruvate dehydrogenase kinase 1 (PDK1) activity, leading to OXPHOS inhibition [176]. In addition, Myc can regulate the alternative splicing of the pyruvate kinase (PK) transcript, in favor of isoform M2 (PKM2) [74], which is one of the most regulated enzymes in glycolysis [206] . Pyruvate kinase converts phosphoenolpyruvate to pyruvate and produces ATP in the final step of glycolysis. Pyruvate kinase isoform M2 is the predominant form in many cancer cells [61]. This protein can promote glucose metabolism in cancer cells by increasing lactate production and reducing oxygen consumption [302],

also directly binding to HIF-1, promoting its transcriptional activity [205]. Pyruvate kinase isoform 2 interacts with a specific cell surface marker in cancer stem cells, CD44, whose ablation leads to depletion of GSH and increased generation of intracellular ROS in glycolytic cancer cells [292]. In fact, PKM2 confers cancer cells with resistance to oxidative stress [7]. Regulation of glycolysis by Myc involves several other glycolysis-associated target proteins, including hexokinase 2 (HK2), phosphofructokinase (PFKM), and enolase1 (ENO1) [177]. Loss of Myc results in a profound decrease in the expression of genes involved in metabolism [308], while the activation of Myc and consequent upregulation of glycolysis can direct cells to use other substrates to fuel mitochondria; this allows cancer cells to easily adapt to different environments, including hypoxia and nutrient deprivation [300]. In fact, tumors in which Myc is upregulated are particularly sensitive to the amount of glutamine present, which suggests that Myc is regulated by glutamine metabolism as well [301]. Moreover, Myc induces lipogenic genes contributing to lipid membrane synthesis for fast-growing cells rather than used for fat storage [70]. Therefore, the ability of Myc to induce mitochondrial biogenesis despite glycolysis upregulation makes sense, since cells need a constant supply of amino acids and fatty acids to proliferate, and these are supplied by mitochondria [68]. Interestingly, inhibition of tumorigenesis is obtained after a brief suppression of Myc [164], while in other tumors this is not observed [29]. The evidence suggests that tissue specificity or even mutagenic or epigenetic alterations influence tumor regression following Myc suppression [318, 330].

Another oncogenic protein is Ras, which is mutated in one quarter of all cancers, leading to increased aggressiveness [255]. Ras is associated with metabolic alterations, increased lactic acid accumulation, altered expression of mitochondrial genes, increased ROS production, and significantly decreased OXPHOS activity [124]. Specifically, mitochondrial dysfunction was associated with mitochondrial localization of STAT3, which is regulated by oncogenic Ras, and at the same time promotes mitochondrial respiration and an increase in glycolytic activity [139, 254].

Ras is activated by growth factors to transduce proliferation signals, mediating important pathways such as PI3K/Akt and MAPK [3, 255]. Similarly to Myc, the PI3K/Akt pathway can lead to glycolytic upregulation by diverse ways, including by increasing Glut1 expression [13], stimulating phosphofructokinase activity and increasing the association of hexokinase with mitochondria [258]. Both PI3K/Akt/mTOR and MAPK pathways were shown to be involved in lipogenesis [319]. Increased glycolytic activity is intrinsically associated with the activation of Akt for cell survival [107]. This protein can stimulate glycolysis in a dose-dependent manner, which is correlated with tumor aggressiveness in vivo [107]. Together with a high activity of the PI3K/Akt pathway, the inactivation of phosphatase and tensin homolog (PTEN), a negative regulator of PI3K pathway is often also found [108]. Moreover, the hyperactivity of Akt can also lead to the increase of mammalian target of rapamycin (mTOR) activity, which in turn increases nutrient uptake during tumor cell proliferation [106]. Furthermore, Akt is important in lipid metabolism, activating enzymes involved in cholesterol synthesis, such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase and HMG-CoA reductase, and in fatty acids biosynthesis, namely FAS and stearoyl-CoA desaturase [246].

Low intracellular glucose or glutamine levels often result in lower ATP production and increased AMP levels [215]. AMP-activated protein kinase (AMPK) is an ATP sensor that is activated during metabolic stress, promoting cell survival by blocking the cell cycle progression or by inducing biosynthetic pathways for proliferation under harsh conditions. AMPK also participates in the inactivation of mTOR, through phosphorylation of tuberous sclerosis complex subunit 2 (TSC2) [69]. In a regular cell environment, when nutrients are not limiting, cells accumulate biomass and, in some cases, proliferate [333]. Several proteins are involved in this process, including insulin growth factor 1 (IGF-1), epidermal growth factor (EGF), or platelet-derived growth factor (PDGF), which are often absent in cancer [311]. In fact, some cancer cells can proliferate without external growth stimuli, altering the normal function of their downstream targets, Akt and mTOR [311]. Therefore, the mTORC1 complex senses the nutritional status of the cell, linking nutrient availability with proliferative activity [60]. On the other hand, mTORC2 activates Akt, which in turn promotes glycolytic activity, through phosphorylation of several proteins including hexokinase II, and also inhibits apoptosis by activating FoxO3A [114]. FoxO3A can also be activated downstream of HIF-1 during hypoxia, inhibiting a set of nuclear-encoded mitochondrial genes and consequently decreasing mitochondrial mass, oxygen consumption, and ROS production and promoting cell survival [167].

The switch to glycolysis in cancer cells is also associated with the inactivation of the tumor suppressor p53 [140], occurring via defective trans-activation of TP53-induced glycolysis and apoptosis regulator (TIGAR), which is an isoform of 6-phosphofructo-2-kinase with the ability to inhibit glycolysis and ROS generation [103]. Similarly to TIGAR, the mitochondrial protein SCO2, which promotes mitochondrial respiration by inducing the correct assembly of COX complex, is induced by p53, favoring mitochondrial respiration [17]. Moreover, PGC-1α can bind to p53 and modulate the transactivation of pro-arrest and metabolic genes [271]. Silencing or alteration of p53 activity can occur during the development of some types of tumors, especially during hypoxia, impacting the response of cells to DNA damage [274]. Interestingly, a p53-responsive gene, Lpin1, induced following DNA damage and glucose deprivation, is involved in the regulation of fatty acid oxidation in mouse C2C12 myoblasts [10]. On the other hand, p53 can accelerate the development of nearby capillary networks and contribute to minimizing hypoxia, through the consequent inactivation of thrombospondin (Tsp-1), a potent anti-angiogenic molecule [188]. Similarly to Myc, p53 promotes glutamine utilization by upregulating glutaminase 2 [157], but as opposed to the former, it can have an inhibitory effect on the expression of Glut1 and Glut4 [267]. Interestingly, the overexpression of Glut1 was shown to inhibit p53 and Puma activities during growth factor induction [329].

Some TCA cycle enzymes can act as tumor suppressors, including succinate dehydrogenase (SDH) and fumarate hydratase (FH), which convert succinate to fumarate and fumarate to malate, respectively [138]. Interestingly, oncogenic mutations in SDH and FH can result in hypoxia-like response and glycolysis activation due to substrate accumulation, resulting in the development of paragangliomas (PGLs) as well as leiomyomatosis and renal cell carcinoma, respectively [32].

Sirtuins, proteins with de-acetylase activity, also modulate metabolism in cancer. Sirtuin 1 (Sirt1) was found altered in some cancer types, although the data are controversial whether this protein works as a tumor suppressor or as a promoter [82]. Sirtuin 1 acts as tumor promoter when inhibiting the activity of p53 through deacetylation at the C-terminal K382 residue [305]. Interestingly, Sirt1 and PGC-1α can activate HIF2α, and consequently reprogram the metabolism of cancer cells by inhibiting the supply of fatty acids and pyruvate to mitochondrial metabolism, besides the upregulation of angiogenesis via expression of vascular endothelial growth factor (VEGF) [181]. On the other hand, Sirt1 can act as a tumor suppressor by regulating c-Myc, decreasing its activity [27]. Interestingly, both Sirt1 and fatty acid oxidation can be controlled by β-adrenergic/cAMP signaling [47].

Other sirtuins were also pointed out as having a role in tumorigenesis, namely Sirt3 and Sirt5, mitochondrially located sirtuins. Sirtuin 5 (Sirt5) overexpression was identified in pancreatic cancer [231], while a decrease in Sirt3 expression/activity leads to increased ROS production, a shift towards glycolysis metabolism, and tumor growth [117]. Furthermore, a number of studies showed that Sirt3 can control mitochondrial ATP production, possibly through regulating complex I activity [132]. In addition, Sirt3 decreases cyclophilin D (cypD) activity, promoting its dissociation from the adenine nucleotide translocator 1 (ANT1). Sirtuin 3 can also promote the separation of hexokinase II from the outer membrane voltage-dependent anion channel (VDAC), resulting in increased OXPHOS [277]. Sirtuin 3 can prevent oxidative stress through IDH2 activation and decrease chromosomal instability caused by ROS generation through increasing the activity of SOD2 [295, 322]. Both effects may be considered tumor-suppressant activities.

3.2.3 Mitochondrial OXPHOS in Cancer

Mitochondrial OXPHOS complexes are organized in large supermolecular structures, constituted by a diverse number of subunits. Defects in specific complex subunits can alter electron flux through the chain ([208]; Fig. 3.2). Some studies demonstrated the relationship between mitochondrial structure and metabolic state when cells were forced to use OXPHOS to synthesize ATP. In the absence of glucose, some cancer cell lines rapidly show morphological adaptations to the new substrate availability, namely by increasing the synthesis of OXPHOS components, cristae content, and elongation and ramification of mitochondrial network [261]. When cancer cells are made to rely more on glycolysis, the mitochondrial structure appears to become more fragmented [147]. Interestingly, a correlation between decreased levels of fusion proteins MFN2, MFN1, or OPA1 and inhibition of Krebs cycle, decrease of OXPHOS, and stimulation of glycolysis and lactic fermentation was previously observed [52].

One characteristic of some cancer cells is higher $\Delta\Psi m$ when compared with normal counterparts [175]. Mechanistically, this can be explained by mitochondrial membrane composition alterations, decreased proton influx, or a decreased activity of ATP synthase, among other causes [283]. In addition, cells usually regulate their

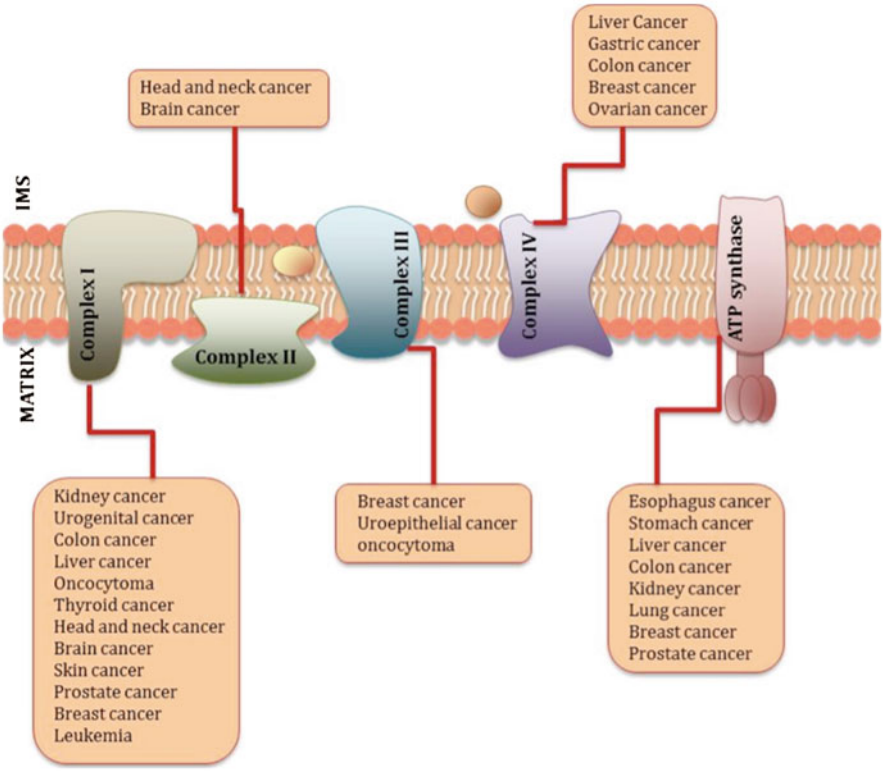

Fig. 3.2 Different cancer types associated with specific mitochondrial respiratory chain complex alterations. *IMS* mitochondrial intermembrane space

$\Delta\Psi m$ under a certain threshold to avoid the formation of ROS by the respiratory chain, while in cancer cells, an incomplete OXPHOS may lead to higher $\Delta\Psi m$ and increased ROS production [306]. Moreover, the expression of mitochondrial proteins involved in OXPHOS appears to be decreased. Besides the inhibition of OXPHOS by intrinsic cellular signaling, mtDNA and/or nuclear gene mutations or damaged enzymes can also result in lower respiration [48]. Downregulation of mitochondrial proteins leads to general reduction of OXPHOS activity, especially complex I, suggesting that at least in some cases, defective mitochondrial activity is associated with altered cellular metabolism [126].

Mitochondrial complex I is a major site of oxygen superoxide anion production, being also involved in apoptosis and age-related diseases [235]. Moreover, complex I can be regulated by hormones, growth factors, and neurotransmitters [235]. Complex I subunits have been shown to have more significant mutations than any other complex in mitochondria, leading to the development of several diseases, including cancer. Mutations in nuclear or mtDNA genes encoding complex I subunits may result in deficient complex I activity, with ROS overproduction and, consequently, upregulation of nuclear genes such as Mcl-1, HIF-1α, and VEGF [57]. As already

described, these three genes regulate alterations in cell metabolism and metastatic potential [162]. Loss or reduced expression of GRIM-19 and NDUFS3 complex I subunits are present in primary renal cell carcinomas and urogenital tumors [154] and in highly invasive breast carcinoma [288]. Mutations in mitochondrial NADH dehydrogenase (ND) subunit 1 gene are present in patients with renal adenocarcinoma [48], colorectal carcinoma [325], hepatocellular carcinoma [195], and thyroid carcinoma, contributing to a decrease in enzymatic activity [25]. Mutations in the subunits ND2 and ND4–6 are present in thyroid cancer cell lines and renal oncocytomas [127], which also show low oxygen consumption, increased ROS production, and glucose dependency, besides fast tumor growth [236]. Particularly, the demethylation of the D-loop regulates ND2 expression in colorectal cancer [113], while mutations in ND subunit 4 have been identified not only in acute myeloid leukemia, but also in head and neck squamous cell carcinoma [67]. Finally, complex I subunit ND6 was described to be decreased in prostate cancer [66].

Complex I is also a caspase-3 and Calpain 10 substrate. Caspase-3 cleaves the largest subunit of the complex (p75), inhibiting its activity leading to mitochondrial membrane potential disruption and ROS production [174]. Upon increased calcium accumulation, Calpain10 inhibits complex I [9]. Complex I dysfunction can also promote fibroblast activation, through increased ROS generation, and melanoma cell invasiveness [291]. In extreme situations, where complex I is lost, oxiphilic tumors and oncocytomas can be originated, showing upregulation of the other mitochondrial complexes [331]. Mitochondrial complex I is, in fact, considered a sensible pacemaker of mitochondrial respiration [235].

Mutations in nuclear-encoded complex II subunits were associated with the occurrence of specific tumors [156]. Complex II, or SDH, is composed of four distinct subunits (SDHA, SDHB, SDHC, and SDHD) and is the only complex totally encoded by nuclear DNA. Loss of function or mutations in SDHB, SDHD, and SDHC (although in a lesser degree) can result in head and neck PGLs, extra-adrenal PGLs, and pheochromocytomas [35]. Tumors appear to be more aggressive when mutated SDHB is present, having a poor prognosis and metastatic potential [35]. Many mutations in complex II that are associated with cancer development occur in an iron–sulfur (Fe–S)-containing subunit. These tumors exhibit high levels of HIF-1α expression, promoting the downregulation of SDHB expression [46]. Hypoxia can further inhibit complex II activity, promoting an increase in ROS [201]. Mutations in SDHC can result in increased superoxide anion production and consequent oxidative stress, increased glucose consumption and genomic instability [281]. Interestingly, the downregulation of complex II subunits does not promote cell death; however, specific inhibition promotes it [197, 198].

Complex III has also been implicated in carcinogenesis, by being involved in generating ROS that is required for HIF hypoxic activation [179]. Complex III mutations in cytochrome *b* are found in human breast cancer cells [293] and murine and human uroepithelial carcinoma, which have in common increased ROS and lactate production, high oxygen consumption and induction of tumor growth, invasiveness, and immune system detection escape [73]. Although complex III is present in low amounts in oncocytoma [25] and breast cancer [251], UQCRFS1 (encoding RISP

525 protein) and UQCRH (encoding Hinge protein) complex III subunits were found to
526 be overexpressed in human breast cancer cell lines and primary tumors [232].
527 Complex IV (COX) is the terminal step in the ETC, responsible for the conversion
528 of O_2 to H_2O [160]. In fact, the expression of COX subunits is regulated by oxy-
529 gen [121]. Therefore, it was suggested that reduced oxygen levels lead to isoform
530 rearrangement, where COXIV-1 is degraded by mitochondrial protease LON and
531 COXIV-2 is increased, resulting in optimization of COX activity for the new hypoxic
532 condition with minimal ROS production [34, 121]. However, virtually all oxygen is
533 consumed and the decrease of hydroxylase activity would result in activation of the
534 HIF pathway [297]. Consequently, differential expression of COX subunits, namely
535 low expression of COXII and high expression of COXI and COXIII, was detected
536 in hepatoma, colon, and prostate cancer [1, 155, 289]. High expression of COXI is
537 also associated with gastric tumorigenesis and ex vivo de-differentiation [207], while
538 mutations in COXI are associated with prostate cancer [241]. In 40 % of breast and
539 ovarian tumors, a decrease in COX subunit II expression was identified [86]. The
540 COXVa subunit has a role in migration and invasion of non-small-cell lung carci-
541 noma cells [55]. A metastasis-associated mechanism, involving Wnt/Snail signaling,
542 suppresses mitochondrial respiration and COX activity, inducing a metabolic switch
543 to glycolysis and pyruvate carboxylase expression [196]. Interestingly, expression
544 of COX levels varies significantly between tissues, being higher in the liver [115].
545 Whether this impact regulates COX activity/role in cancers in the liver versus other
546 tissues remains to be known.
547 The downregulation of β-F1-ATPase is considered a feature of liver, kidney, colon,
548 breast, and many other human carcinomas, where its reduction was correlated with
549 increased expression of some glycolytic markers [63, 163]. Specifically, alterations
550 of ATP6 subunit were found in prostate cancer [1], as well as in in vitro tumor
551 models with decreased respiration rates, high proliferation, and significant resistance
552 to apoptosis [276]. The natural inhibitor Factor 1 (IF1) of ATP synthase is also
553 overexpressed in human cancer cells [264]. Altogether, overexpression of IF1, the
554 limited expression of the catalytic β subunit, and upregulation of glycolytic proteins
555 lead to inhibition of ATP synthase activity [96].
556 Interestingly, the most aggressive cancers have little or no mtDNA content [211].
557 Indeed, although ρ^0 cells, which lack mtDNA, have similar mitochondrial mem-
558 brane potential to cancer cells [211], the former have increased capacity to invade
559 neighboring tissues and promote metastasis [211].

560 *3.2.4 Tumor Oxygen Gradients and Mitochondrial Respiration*

561 Evidence suggests that cancer cells and the other microenvironment constituents
562 co-evolve during the process of carcinogenesis [245]. The expression of metabolic
563 biomarkers is altered according to the distance from the nearest vessels [280]. In fact,
564 increased glucose uptake, hypoxia, and acidosis are not always fairly distributed in
565 the tumor [56]. The microenvironment of tumors is heterogeneous due to inefficient
566 blood supply, creating nutritional as well as metabolic gradients inside the tumor

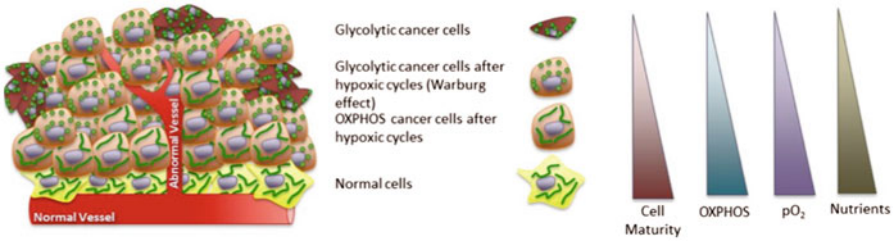

Fig. 3.3 Mitochondrial metabolism and dependence on oxygen and nutrient gradients within the tumor. The cycles of hypoxia or lack of nutrients can result in different cell metabolism used for adenosine triphosphate (ATP) production. Cancer cells under higher stress preferentially use glycolysis instead of oxidative phosphorylation (OXPHOS), while others with mild strain can maintain their mitochondrial ATP production. Moreover, such mitochondrial metabolic changes can also influence the maturity of the cell, if it is more or less differentiated. Mitochondria are represented as *round* or *filamentous green* bodies

[287]. Oxygen gradient in tumors can be created from both passive physical diffusion and oxygen consumption resulting from cellular activity (Fig. 3.3; [75]). Another possible reason for the differences in oxygen distribution and consequent acidosis in tumors has to do with malformed vasculature [39]. Peripheral cells present high proliferative capacity with full nutritional capacity supplied by blood, while cells with low blood supply present a less active mitochondrial metabolism [102]. In fact, the most aggressive tumors are those found under hypoxic conditions, where they suffer cycles of hypoxia and re-oxygenation [87]. Metabolic demand, vessel morphology, hemoglobin oxygen saturation, and blood flow rate can lead to differential hypoxia cycling in tumors [280]. An increasing distance from the source of nutrients will first promote decreased cell proliferation and later result in its stimulation [119]. The hypoxic core is also the site where cancer stem cells are thought to be maintained in an undifferentiated state [242], thus restraining their oxidative metabolism, again suggesting a close relationship between tumor hypoxic cores and cell immaturity.

As described previously, HIF-1 is activated and modulates the mitochondrial respiratory chain by regulating COX. Therefore, at low oxygen availability, the COXIV-2 isoform is more active and more efficient in using oxygen [121]. These observations explain mitochondrial activity and ATP production even under hypoxic conditions. However, a negative correlation between oxygen gradients and ROS generation is often found in the tumor microenvironment. In fact, cells under a high ROS-prone environment must upregulate antioxidant defenses in order to modulate the malignant phenotype, allowing them at the same time to escape from cell death induction [234]. A signaling gradient of declining transforming growth factor beta-1 (TGF-β1) concentration, which is important during development, is also often deregulated in human tumors. Mitochondrial ATP synthesis can be modulated by TGF-β1, stimulated through ANT1 and ANT2 regulation [191, 200], or inhibited via cyclooxygenase-2 (COX-2) and prostaglandin (PG) E2 [50]. The latter signaling pathway is connected with increased inflammation, ROS generation, altered cytokine/chemokine expression, and enhanced signaling via nuclear factor kappa B (NFkB), which combined results in increased risk factors for carcinogenesis [170].

Besides the variability of oxygen tension within the tumor microenvironment, cancer-associated fibroblasts (CAFs) are able to mimic hypoxia, expressing HIF-1 without real oxygen deprivation [298]. Interestingly, TGF-β signaling and consequent metabolic reprogramming of CAFs are activated due to the loss of caveolin-1 (Cav-1) [44]. In CAFs, glycolytic enzymes are upregulated, while OXPHOS pathway is downregulated leading to overproduction of pyruvate and lactate that will fuel the surrounding cancer cells' metabolism, a phenomenon called "reverse Warburg effect" [26]. Moreover, Cav-1 seems to contribute to glucose uptake and ATP generation, through HMGA1-mediated Glut3 transcription [146]. Therefore, these results can help to explain the existence of cancer cells showing increased aerobic glycolysis in oxygenated tumor regions. Indeed, CAFs can even mediate EMT and enhance the motility response of cancer cells [131].

Unfortunately, much needs to be done to confirm the present ideas, especially the reverse Warburg effect in vivo. Measuring oxygen gradients in intact tumors has also been hard, making the identification of gradients in mitochondrial respiration difficult. Some techniques to measure oxygen gradients are available, including measuring oxygen supply at the microvessel level by using microelectrodes and phosphorescent lifetime imaging with *p*O2-calibrated dyes [280]. Immunohistochemistry aimed at evaluating hypoxia gradients by detecting hypoxic markers is another possible technical approach [263].

From the previous sections, it is evident that mitochondria and the process of carcinogenesis are interconnected. Whether mitochondrial alterations are causally linked with cancer or are merely a small component of a larger metabolic remodeling is still under debate, although it appears that mitochondrial alterations are a piece of a more complex puzzle. Whatever the mechanism is, it is clear that mitochondria are important targets in cancer therapy. Therefore, the design and synthesis of effective pharmaceutical agents that would directly target mitochondrial alterations and decrease tumor size can be achieved. In addition, the differential metabolism used by normal and cancer cells can provide knowledge to discover new drugs with little or no side effects on normal cells.

3.3 Targeting Tumor Mitochondria—Closing Down the Factory

Distinct approaches to control cancer are available such as surgery, radiotherapy, and hormone and biological therapies. However, in many cases, those methods are clearly not fully effective, so chemotherapy is usually another tool to eradicate cancer. Unfortunately, the low specificity and the fact that the drugs currently in use have uncomfortable side effects drive the search for more effective and selective drugs.

Guchelaar et al. [142] and Decaudin et al. [78] were the first to point out mitochondria as a potential target for anticancer drugs, proposing the modulation of extrinsic and intrinsic regulators and finding developing chemotherapeutics that would act on mitochondria. Later, a new term, mitocan, was coined to refer to all compounds that exert their action by targeting mitochondria.

The first goal in chemotherapy administration is reached when the drug is selectively accumulated by the tumor. Furthermore, the drug needs to get in the tumor cell and reach mitochondria. The selective accumulation of promising anticancer molecules inside mitochondria of tumor cells, thus sparing normal cells, is a key point in the design of novel molecules [220]. The design of mitochondrial-directed agents, by either chemical conjugation or targeting transporters, has demonstrated promising efficacy; however, their specificity is still discussed. New agents specifically target cancer cells when fused with peptides that recognize cancer-cell-specific surface receptors or internalized through the plasma membrane due to the biological activity of the molecule. Furthermore, if the agent contains a lipophilic cationic moiety, its accumulation by polarized mitochondria, which are negatively charged in the matrix, increases several fold [122]. Thus, the extent to which a drug may interact or even bind to subcellular components, such as membranes and cell organelles, depends on the physicochemical properties of the drug. In order to reduce undesirable side effects, which may result from the drug being accumulated in wrong tissues or in normal cells, or even in wrong organelles, efficient mitochondria-specific delivery systems have been proposed.

To specifically target mitochondria, distinct approaches can be found, including delocalized lipophilic cations (DLCs), mitochondrial targeting sequence (MTs)-containing polypeptides, synthetic peptides and amino-based transporters, and vesicle-based carriers, as reviewed by Weissig and Souza [314]. Unfortunately, many of these strategies can fail if the compound does not reach tumor cells. In fact, several potent anticancer candidates have been shelved due to low solubility and low membrane permeability. It is not easy to design a drug that would combine all essential properties regarding bioavailability and high pharmacological activity [314]. The mechanism by which mitochondrial drugs trigger apoptosis depends on the molecular mitochondrial target site. Nowadays, the vast majority of conventional anticancer drugs activate death pathways, using multiple activation routes (e.g., p53 or death receptors) in order to exert their cytotoxic action [89]. Many of these agents fail due to disruption of endogenous apoptosis-inducing pathways in tumor cells. Newer and more specific therapies have become more prevalent in the treatment of specific cancers as the molecular mechanisms of carcinogenesis become better characterized.

3.3.1 Targeting Mitochondrial Feeding

Although not technically mitocans, some compounds will target different steps of the glycolytic pathway, preferentially affecting those tumors that rely on glycolysis. Inhibition of glycolysis can lead to increased tumor susceptibility to common anticancer agents with minimal effects on normal cells [136]. For example, ATP depletion and consequent death by dephosphorylation of pro-apoptotic BAD protein as well as BAX-induced outer mitochondrial membrane permeabilization were observed when the energy-depleting agent 3-bromopyruvate (3BrPA) and glucose analog 2-deoxy-D-glucose (2DG) were used together [79, 328].

3BrPA is a lactic acid analog known for its alkylating activity, selectively targeting hepatocellular carcinoma cells in vitro [182]. In vivo,3BrPA suppresses metastatic lung tumors with no apparent side effects [130]. This compound suppresses glycolysis by inhibiting the activity of hexokinase and by interfering with VDAC–hexokinase interaction. 3BrPA is believed to enter the cancer cell via lactic acid transporters that are overexpressed in these cells [238], and inhibits SDH activity and mitochondrial respiration [182]. 3BrPA alone promotes cell death of AS-30D hepatocellular carcinoma cells which exhibit the "Warburg effect," while in combination with other chemotherapeutics, such as [Cu(isaepy)2], a DLC-like molecule, inhibits mitochondrial oxygen consumption and produces ROS leading to cell death [118, 237]. Moreover, an in vivo antitumor effect in hepatic and pancreatic cancer was observed in combination with the 90-kDa heat-shock protein (HSP90) inhibitor geldanamycin [42]. 2DG, in turn, is a non-metabolizable glucose analog used in human lymphoma cells to inhibit glucose metabolism and which, in combination with tumor necrosis factors (TNF), induces apoptosis [134]. 2DG suppresses intracellular ATP and potentiates phosphatidylserine exposure induced by Fas [134]. Certain pancreatic tumors, with specific Glut-1 expression profiles, were shown to be susceptible to 2DG, due to greater accumulation of this drug [209]. 2DGwas also used as adjuvant in combination with ETC blockers, which were particularly effective against colon cancer cells [28].

Dichloroacetate (DCA), structurally similar to pyruvate, stimulates OXPHOS through inhibition of pyruvate dehydrogenase kinase (PDK), hence activating pyruvate dehydrogenase (PDH) and shifting metabolism from glycolysis to glucose oxidation. Michelakis et al. [214] observed that DCA leads to mitochondrial depolarization and increased mitochondrial ROS generation, leading to death of glioblastoma multiforme cells, both in vitro and in vivo. The mechanism of action involves targeting PDK II, highly expressed in this type of cancer. When associated with irradiation or etoposide, DCA induces apoptosis of glioma cancer stem cells in vitro, inducing the overexpression of BH3-only proteins (Bad, Noxa, and Puma), while reducing their growth in vivo [226]. Interestingly, DCA has higher activity in cells with defective mitochondria, presenting an effective synergistic effect with other mitocans [285]. Unfortunately, DCA does not have a selective activity, acting on both cancer and normal cells, although DCA has also been used to treat mitochondrial diseases [285]. Therefore, this compound is not a good solution in cancer cells with functional mitochondria, suggesting that DCA may benefit only a selected subset of patients. Another strategy to control glycolysis is through the suppression of glucose transports. Sensitizing tumor cells with phloretin, a glucose transporter inhibitor, enhanced the activity of daunorubicin [41].

Lipid metabolism has been a potential target for antitumor therapy with enzymes such as FAS, ACC, or ACL being good targets. Their downregulation was shown to decrease the proliferation of tumors [290]. Moreover, statins, the cholesterol-lowering agents, were shown to reduce the incidence of some cancers, and also to improve chemotherapy efficacy [33]. Palmitoylcarnitine and carnitine can induce apoptosis in transformed cells by increasing the synthesis of ceramide, a pro-apoptotic lipid, as well as by inducing glucose and fatty acid oxidation, leading to mitochondrial ROS production [316].

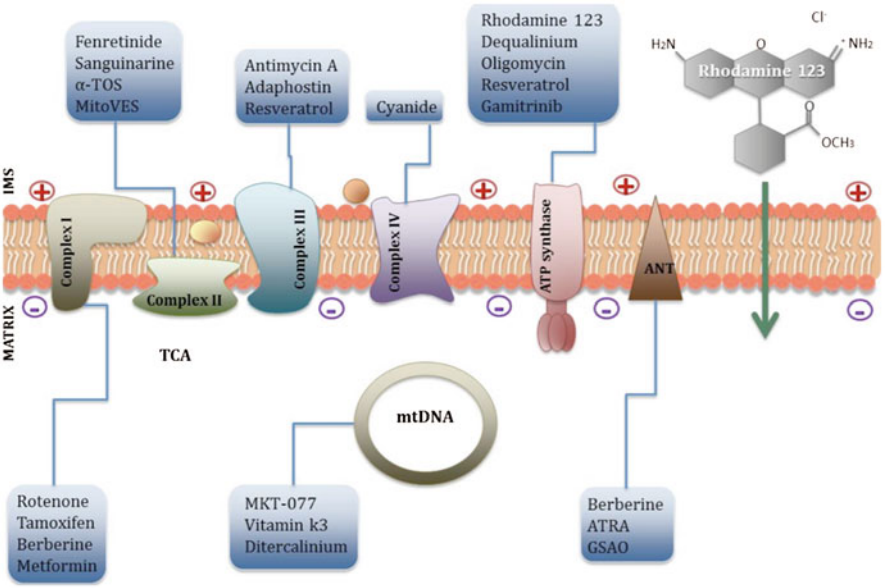

Fig. 3.4 Mitochondria-targeting agents. Cancer cells have altered metabolism, conferring benefits for cell survival and chemotherapy resistance. Several agents are currently under clinical trial to selectively target mitochondria in tumor cells and alter their physiology. One strategy is by using the higher mitochondrial membrane potential ($\Delta\Psi m$) normally found in several tumors (e.g., Rhodamine 123). Several agents target components of the respiratory chain, the adenine nucleotide translocator (ANT), or mitochondrial DNA (mtDNA). Disturbance of mitochondrial function in cancer cells can result in the induction of apoptotic cell death. *TCA* Tricarboxylic acid cycle, *ATRA* All-trans retinoic acid, *GSAO* glutathione-coupled trivalent arsenical, *α-TOS* α-Tocopheryl succinate, *IMS* mitochondrial intermembrane space

For some cancer types, the inhibition of glycolysis per se is not enough, since cancer cells can adapt by remodeling their metabolism with tumor recurrence likely to occur . In those cases, targeting different metabolic pathways may be the solution.

3.3.2 Targeting Mitochondria

By taking advantage of mitochondrial alterations in several cancer types, specific mitochondrially targeted agents can be designed (Fig. 3.4). For example, some cancer cells present higher $\Delta\Psi m$ when compared with non-tumor counterparts [8]. Thus, positively charged lipophilic molecules can be designed to accumulate inside mitochondria, disrupting the organelle and causing cell death. For example, the positively charged Rhodamine-123 is preferentially accumulated in mitochondria of cancer cells, showing a higher degree of toxicity towards them [221]. Rhodamine-123 and analogs are a clear example of using a biophysical characteristic of mitochondria in cancer cells (i.e., higher $\Delta\Psi m$) to undergo selective toxicity and accumulation [190]. Once accumulated by mitochondria in cancer cells, $\Delta\Psi m$ is disturbed and

Rhodamine-123 inhibits the F_0F_1-ATPase [219]. Rhodamine-123 has also been used in conjugation with other compounds, such as 2DG, in the treatment of human breast carcinoma. The two compounds jointly inhibit the growth of cancer cells, whereas no toxicity was observed in normal cells [24]. A similar effect was observed during in vivo studies, suggesting that the disturbance of OXPHOS and glycolytic pathways in tumor cells can be an effective treatment [19]. Cyanine analogs, including MKT-077, are also preferentially accumulated in tumors with higher $\Delta\Psi m$ [312]. Although tested during phase I clinical trials, further trials with MKT-077 were stopped due to renal toxicity in some patients [31, 312].

Berberine, a phytoalkaloid presenting a positive charge in its structure, is accumulated in tumor cells at low concentrations [273]. Berberine targets the respiratory chain by inhibiting mitochondrial complex I and interferes as well with the mitochondrial phosphorylative system [239], especially with the ANT [240]. Berberine also induces apoptosis by increasing ROS production, leading to overexpression of p53 and downstream apoptotic proteins [166]. Another phytochemical, sanguinarine, disrupts mitochondrial calcium loading capacity and increases p53 expression [272]. Sanguinarine interferes with the mitochondrial respiratory chain, namely at complex II [12], and causes ROS-induced DNA damage [58], GSH depletion, and cleavage of poly (ADP-ribose) polymerase and beta-catenin [59]. Dequalinium and F16 are other lipophilic cations with mitochondrial disruptive effects [111, 313]. However, there are no current clinical trials with any of these molecules.

Agents that interfere with mitochondrial respiration, including OXPHOS uncouplers cause cell death due to bioenergetic disruption . Numerous inhibitors of the mitochondrial respiratory chain are used as tools to better understand mitochondrial respiration; however, in general, these mitochondrial poisons are toxic in vivo, due to their nonspecific activity. Classic mitochondrial poisons include rotenone (complex I), antimycin A (complex III), cyanide (complex IV), and oligomycin (complex V, or ATP-synthase), besides protonophores such as carbonylcyanide trifluoromethoxyphenylhydrazone (FCCP) [97]. These and other mitochondrial inhibitors decrease the capacity to stimulate ROS production and apoptosis of cancer cells. For example, tamoxifen targets complex I [224], fenretinide inhibits complex II [65], and complex III is predominantly inhibited by adaphostin [192]. Alternative molecules presenting lower toxicity have been developed: α-Tocopheryl succinate (α-TOS) is a vitamin E analog capable of preferentially targeting mitochondria in cancer cells, inducing proliferation arrest [249]. α-Tocopheryl succinate is tumor-selective due to its ester structure, since the hydrolysis of α-TOS to α-tocopherol occurs in normal cells but not in tumor cells [168]. Moreover, α-TOS induces cell death by targeting the ubiquinone-binding site at complex II, causing electron leakage, stimulating ROS generation and killing malignant cells at nontoxic concentrations for normal cells [100, 230]. α-Tocopheryl succinate facilitates the translocation of Bax from the cytosol to mitochondria and subsequent cytochrome *c* release [321]. α-Tocopheryl succinate also induces apoptosis in proliferating endothelial cells by causing oxidative damage and suppressing angiogenesis in vitro and in vivo in different breast cancer models [99]. Another compound with a similar activity to α-TOS is mitoVES [101].

Resveratrol is polyphenolic phytoalexin, found in the skin of red grapes, berries, and peanuts, and which presents with chemotherapeutic and chemopreventive properties [165]. Resveratrol induces the redistribution of Fas/CD95 and TRAIL receptors in lipid rafts in colon carcinoma cells [81]. Resveratrol also decreases ROS production by competing with coenzyme Q and decreasing complex III activity [332]. Nitric oxide production, caspase activation, and p53 are also necessary for the mechanism of action of resveratrol in tumor cells [178]. In normal cells, resveratrol increases mitochondrial capacity by activation of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α), which in turn stimulates sirtuin 1 (SIRT1) [189]. Nevertheless, structure–activity studies showed that resveratrol can interfere with mitochondrial ATP synthesis by binding to F1-ATPase, which may contribute to cell death induction [133]. Resveratrol has a low bioavailability [307]; hence, structural modifications may increase its clinical usefulness. In fact, a complex between triphenylphosphonium and resveratrol leads to mitochondrial accumulation of this compound [21]. Resveratrol is currently under clinical evaluation for colon cancer and multiple myeloma treatments [144, 282]. Moreover, resveratrol and other polyphenols are claimed to activate Sirt 3 [132]. Upregulation of this mitochondrial sirtuin may have a similar effect to that of DCA, which increases mitochondrial metabolism and disturbs cancer cell homeostasis.

Both hormones, insulin and insulin-like growth factor, are associated with a range of cancers [244]. Evidence shows that obese and diabetic individuals are a risk group for the development of cancer, and also have a worse prognosis in the event of the disease. Metformin is an anti-glycemic agent used in type 2 diabetes, thought to decrease cancer incidence [296]. Metformin is an AMPK activator and inhibits complex I in human breast cancer in situ [317], also increasing tumor cell sensitivity to chemotherapy [125]. However, caution is required in patients with diabetes since the use of metformin as adjuvant may not be as effective, because these patients may already have a long-term prescription [199]. Metformin also compromises the growth of breast cancer tumors in mice, by modulating endoribonuclease Dicer (DICER), through mir33a upregulation and by targeting c-Myc [22].

Other drugs can target other mitochondrial structures. Lonidamine is an inhibitor of aerobic glucose utilization and can also directly interact with hexokinase [110]. Arsenic trioxide (As_2O_3) triggers cancer cell death by inhibiting thioredoxin reductase and promoting oxidative stress [93], which has been shown to be effective against acute promyelocytic leukemia (APL) [5]. Arsenic trioxide has also been used in combination with all-trans retinoic acid (ATRA) showing a synergistic effect against APL mouse models [210]. ATRA is a natural derivative of vitamin A, which stimulates the expression of retinoic acid receptor-responsive genes [210]. This compound suppresses mitochondrial respiration, decreases $\Delta\Psi m$, and triggers ANT-dependent MPT and cell death independent from nuclear receptor binding, suggesting another potential mechanism of action is involved [228]. The potential of As_2O_3 and ATRA in the treatment of other cancer types is also being explored [326]. A GSH-coupled trivalent arsenical compound (GSAO) causes apoptosis in angiogenic endothelial cells both in vitro and in vivo, although it was initially suggested that proliferating cancer cells would be targeted as well [98]. However,

low toxicity towards the latter was observed [98]. GSAO can inhibit ATP/ADP transport by cross-linking two of the three matrix-facing cysteine thiols in the ANT. This will lead to ATP depletion, ROS generation, and ultimately mitochondrial depolarization and apoptosis [98]. Angiogenic cells can often circumvent many therapies; however, these cells have a decreased capacity to buffer the arsenical moiety by expressing low MRP1/2 [37]. GSAO is currently in clinical trials in cancer patients and promising results are anticipated [37, 94] .

HSP90 is not normally present in mitochondria of normal cells; however, this chaperone is upregulated in mitochondria in cancer cells, due to a possible induction by Ras and Akt oncogenes [243]. HSP-90 is an ATPase-directed molecular chaperone that supervises protein folding during cellular stress responses, with the protein complexes involved in cell proliferation and cell survival [243]. The molecular chaperone Hsp90 provides an attractive target for therapeutic interventions in cancer. Shepherdin is a peptidomimetic that is easily accumulated in mitochondria, and which is an antagonist of the complex between Hsp90 and survivin (cell cycle-regulating protein), plus other additional client proteins such as TRAP-1 [278]. Shepherdin inhibits Hsp90 chaperone activity via an ATP competition mechanism and kills cancer cells by inducing the mitochondrial permeability transition (MPT) [278]. Shepherdin showed no toxicity for brain and liver mitochondria in several human cancers [172, 243]. Gamitrinib was conceived by coupling an HSP90 inhibitor to lipophilic cationic moieties. Gamitrinib specifically targets mitochondria in cancer cells, and antagonizes the ATPase activity of HSP90. Gamitrinib causes the death of cancer cells and suppresses tumor growth in vivo, with no apparent effect on normal counterparts [173].

Some test compounds specifically target mtDNA. A vitamin K sub-type, vitamin k3, is a synthetic compound that has been described to inhibit DNA polymerase Υ, thus disturbing mtDNA replication and promoting ROS generation leading to apoptosis [266]. However, vitamin k3 can interfere with calcium homeostasis and decrease GSH levels as well [95]. In vitro studies demonstrated that vitamin k3 displayed antitumor activity against pancreatic and breast cancer cells [2]. Ditercalinium is another agent which is preferentially accumulated in mitochondria, and that targets mtDNA, inhibiting replication [229]. After treatment with ditercalinium, ultrastructural studies showed a depletion of mtDNA and loss of mitochondrial cristae [268]. Agents that disturb mtDNA are predicted to affect mitochondrial respiration by leading to loss of OXPHOS subunits encoded by the mitochondrial genome.

3.4 Concluding Remarks

The present chapter demonstrates that the profound metabolic remodeling of cancer cells, including mitochondrial rearrangement, not only is an indirect response to cell survival or proliferation but also can be controlled by specific cell signaling [310]. Nevertheless, there are no specific mitochondrial or metabolic alterations common to all cancer types, although the activation of different metabolic pathways results in similar phenotypes. There are no doubts that mitochondrial deregulation and

metabolism remodeling are important hallmarks of cancer cells; however, as pointed out, there are other cases where an altered metabolic pattern is not observed. Besides, many proteins involved in carcinogenesis have dual and opposite functions even inside the same tumor. It is also important to take into account the model that is being used to evaluate the protein activity, since many of them vary their behavior between in vitro and in vivo situations [334]. The large number of functions mitochondria have in cells implies that many of those may be altered during cancer, some of which will contribute to carcinogenesis while others will act as tumor suppressors. The mitochondrial respiratory chain has an important function not only in the context of ATP production, but also in maintaining a determined redox balance. A specific tumor signature requires that each one of these functions is altered somehow to respond to metabolic and survival cues. In the traditional model, a decrease in mitochondrial ATP production, resulting from different factors such as a hypoxic environment or low glucose, will drive the generation of malignant mitochondrial ROS production and trigger mitochondrial biogenesis [253]. Mitochondrial respiration can then be regulated by differential expression of OXPHOS subunits or by upstream signaling and/or metabolic pathways. By its turn, inhibition or stimulation of mitochondrial respiration can feed back onto other cancer cell pathways or even increase genomic instability, thus contributing to higher aggressiveness.

Targeting mitochondria in tumors based on specific respiratory alterations or components implies a type of knowledge that we may not have at the moment. Even inside the same tumor mass, mitochondrial respiration is different according to the oxygen gradient. In the absence of oxygen, mitochondria can still maintain $\Delta\Psi m$ by the reverse action of ATP synthase [284]. This means that compounds targeting the respiratory chain will not work; instead, the inhibition of the ATP synthase in a selective manner in tumor cells is a solution in the future.

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Chapter 3: Author Query

AQ1. We have changed “limitless replicate potential” to “limitless replication potential”. Please check.

AQ2. Please provide a full reference in the reference list for the citation Scatena 2012 or delete the citation.

AQ3. Should “synthesis” be changed to “synthase”? Please check.

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