Mitochondrial Changes in Cancer

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Contents

Abstract

Mitochondrial structural and functional integrity defines the health of a cell by regulating cellular metabolism. Thus, mitochondria play an important role in both cell proliferation and cell death. Cancer cells are metabolically altered compared to normal cells for their ability to survive better and proliferate faster. Resistance to apoptosis is an important characteristic of cancer cells and given the contribution of mitochondria to apoptosis, it is imperative that mitochondria could behave differently in a tumor situation. The other feature associated with cancer cells is the Warburg effect, which engages a shift in metabolism. Although the Warburg effect often occurs in conjunction with dysfunctional mitochondria, the relationship between mitochondria, the Warburg effect, and cancer cell metabolism is not clearly decoded. Other than these changes, several mitochondrial gene mutations occur in cancer cells, mitochondrial biogenesis is affected and mitochondria see structural and functional variations. In cancer

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pharmacology, targeting mitochondria and mitochondria associated signaling pathways to reduce tumor proliferation is a growing field of interest. This chapter summarizes various changes in mitochondria in relevance to cancer, behavior of mitochondria during tumorigenesis, and the progress on using mitochondria as a therapeutic target for cancer.

Keywords
Apoptosis • Cancer • Mitochondria • Mitochondrial fission • Mitochondrial fusion • Reactive oxygen species

1 Introduction

In routine clinical diagnosis of cancer, a glucose analogue (2-18 fluoro-2-deoxy-Glucose) is used to trace tumor tissue that would uptake more glucose than normal tissues due to its increased necessity for sugars. This technique is based on a hypothesis by Otto Warburg in the 1930s that cancer cells choose a different metabolic route than normal cells (Koppenol et al. 2011; Warburg 1956). This school of thought led to major studies on aerobic glycolysis in tumor cells where cells adapt to a glycolytic pathway to make adenosine triphosphate (ATP) instead of using the regular mitochondrial electron transport chain (ETC). Thus, cancer cells involve increased breakdown of glucose generating raw materials for the synthesis for other macromolecules, helping their rapid growth. Although tumor hypoxia is hypothesized to be a trigger (Gatenby and Gillies 2004), there are evidences where there is a metabolic shift to aerobic glycolysis in free availability of oxygen (Christofk et al. 2008). It is speculated that in cancer, there is a reprogramming of the cells driven by oncogenes into a proliferative metabolism, resembling an embryonic program (Vander Heiden et al. 2009) with upregulation of glycolytic enzymes (Christofk et al. 2008). Glycolysis under aerobic conditions makes cells acidic due to increased production of lactate as a result of glycolytic cycles, but this excess lactate is postulated to be a fuel for mitochondrial oxidative phosphorylation (Sonveaux et al. 2008). This phenomenon is proposed to be used by certain cancer cells in a reverse Warburg effect, where cancer cells induce Warburg effect in neighboring stromal cells and in turn receive lactate and pyruvate for oxidative phosphorylation (Pavlides et al. 2009). All these metabolic altercations point to an altered mitochondrial function in tumor cells that has led to years of research in this field with respect to ATP production and beyond (Boland et al. 2013). This chapter summarizes the important changes in mitochondria associated with onset and progression of cancer such as mitochondrial DNA (mtDNA) mutations, mitochondrial reactive oxygen species (ROS), mitochondrial mass regulation, and mitochondrial dynamics. The chapter also discusses and summarizes major cancer drug classes that target mitochondria (Table 1).

Table 1 List of drugs targeting mitochondria in cancer

Drug classes	Targeted mitochondrial component/process
1-methyl-4-phenylpyridinium, Vitamin K	mtDNA/mtDNA replication-copy number inhibition (Sasaki et al. 2008; Umeda et al. 2000; Neuzil et al. 2007)
ABT-263, Gossypol, antimycin A, alpha-tocopheryl	Bcl-2 family/BH3 domain mimetics (Kang et al. 2010; Neuzil et al. 2007)
Metformin (biguanide)	Mitochondrial complex I/inhibition of ATP production (El-Mir et al. 2000; Owen et al. 2000)
Phenformin (biguanide)	Mitochondrial complex I/inhibition of ATP production (Birsoy et al. 2014)
VLX600	ETC inhibitor/inhibition of ATP production (Zhang et al. 2014)
Tigecycline	ETC inhibitor/inhibition of ATP production (Skrtic et al. 2011)
bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide)	Glutaminase inhibitor/inhibition of biosynthetic pathways (Le et al. 2012)
Compound 968	Glutaminase inhibitor/inhibition of biosynthetic pathways (Le et al. 2012)
Chloroquine	Autophagy inhibitor/inhibition of mitophagy (Balic et al. 2014)
Antioxidants	ROS inhibition/mitochondrial ROS scavenging (Bjelakovic and Gluud 2007)
Inhibitors of antioxidants	Antioxidant inhibition/selective tumor cell death (Raj et al. 2011; Glasauer et al. 2014)

2 Mitochondrial Mutations in Cancer Cells

Each cell contains numerous mitochondria, and every mitochondrion has its own DNA (mtDNA) in multiple copies. Mammalian cells contain about 1000–10,000 copies of mtDNA which can replicate independent of cellular division (Lightowlers et al. 1997). Mitochondria can accumulate somatic mutations and lead to a heteroplasmic state where mitochondria with dissimilar DNA content co-exist. Mutations in mitochondrial DNA contribute to mitochondrial function, especially ROS production, and hence it is important to consider mitochondrial DNA as an important factor in tumorigenesis.

The mitochondrial genome has been sequenced and characterized (Blanchard and Schmidt 1996; Grivell 1983), and several mutations in mtDNA have been associated with cancers in human tissues (Chatterjee et al. 2006). A list of major cancers and associated mtDNA mutations is provided in Table 2 (Abu-Amero et al. 2005; Fliss et al. 2000; Habano et al. 1999; Jeronimo et al. 2001; Jones et al. 2001; Maximo et al. 2002; Polyak et al. 1998; Sanchez-Cespedes et al. 2001; Canter et al. 2005; Parrella et al. 2001; Petros et al. 2005; Wong et al. 2003). Mitochondrial mutations (both homoplasmic and heteroplasmic) have been

Table 2 List of mitochondrial gene mutations and relevant cancers

Major cancer types	Mitochondrial gene affected
Bladder	Cyt b, ND3 (Fliss et al. 2000)
Colon	ND1, ND5, COX I, COX II, COX III, Cyt b (Polyak et al. 1998; Jones et al. 2001; Habano et al. 1999)
Pancreas	ND1, ND2, ND3, ND4, ND6, COX I, COX II, COX III, ATPase, Cyt b (Jones et al. 2001; Jeronimo et al. 2001)
Ovary	Cyt b (Liu et al. 2013)
Thyroid	Cyt b, ND1, ND2, ND3, ND4, ND5, ND6, COX II, COX III (Abu-Amero et al. 2005)
Breast	ND4, ND5 (Canter et al. 2005; Parrella et al. 2001)
Head and neck	ND4 (Fliss et al. 2000)
Medulloblastoma	ND4L (Wong et al. 2003)
Prostrate	ND1, ND5 COX I (Jeronimo et al. 2001; Petros et al. 2005)

detected in body fluids of cancer patients (Chinnery et al. 2002; Fliss et al. 2000). Although normal subjects are reported to display age-associated accumulation of mitochondrial mutations (Cormio et al. 2005), mtDNA mutations are highly prevalent in cancer tissues. mtDNA coded enzymes contributing to mitochondrial oxidative phosphorylation (Luciakova and Kuzela 1992) are reported defective in tumor situations, which could possibly lead to deregulation of ROS production from the mitochondria. Thus, mtDNA mutations could contribute to solid tumors by favoring the Warburg phenomenon and by playing a role in apoptosis. These mutations can be traced along with tumors and thus could be used as markers for identifying types of tumors. However, it is not clear if mtDNA mutations themselves can drive tumor growth or merely provide an advantage to cancer cells. This is one key area awaiting extensive research in order to understand the mtDNA mutations and their relation to tumorigenesis.

3 Mitochondrial Reactive Oxygen Species

ROS are a by-product of the electron transport chain at the level of complex I and complex II/III where electrons escape (leak) the canonical pathway of electron transport, and are established to play a role in cellular signaling (Brand 2010; Chen et al. 2003). Reduced levels of antioxidants can also contribute to increased ROS levels in the cells (Hamanaka and Chandel 2010; Schumacker 2006). ROS can have both deleterious and favorable effects on cancer cells depending on the amount as well as rate of generation.

ROS can activate several signaling pathways promoting tumorigenesis and thus play a factor favoring the cancer cells. ROS stabilize hypoxia inducible factor (HIF)-α, an important protein for the survival of tumor cells in extremely hypoxic tumor environment (Jung et al. 2008). Intriguingly, antioxidant treatment of cancer cells can cause suppression of HIF1-α, again indicating the importance of ROS

regulation in tumor microenvironment (Gao et al. 2009). Activation of the hypoxia pathway in cancer cells is also related to metabolic changes. HIF1-α induces the expression of glycolytic enzymes driving the cancer cells to adapt to an alternative ATP generation mechanism (Kim et al. 2006). The other way by which ROS regulate metabolism in cancer cells is by driving the activation of NRF2, a nuclear factor involved in increased production of anabolic enzymes (Mitsuishi et al. 2012). ROS also oxidize pyruvate kinase M2, which in turn drives a pentose pathway flux and increases glutathione levels promoting tumorigenesis (Anastasiou et al. 2011; Israelsen et al. 2013).

ROS regulate signaling pathways in cancer; the most studied one amongst them is the PI3Kinase pathway—a major growth-promoting signal in normal as well as cancer cells (Cantley 2002). The target of ROS within the context of cancer is the phosphatase PTEN, a negative regulator of the PI3Kinase pathway. ROS oxidize an active site cysteine on PTEN leading to the hyper-activation of the pathway (Lee et al. 2002; Leslie et al. 2003). ROS, on the other hand, can also inhibit the phosphatases of this pathway, namely PP2A and PTP1B, that negatively regulate Akt (Ostman et al. 2011), fostering the pathway's activity and thus promoting cell survival and proliferation.

Another role of ROS in cancer cells is induction of oxidative DNA damage leading to the development and progression of tumor in several examples. Patients with increased oxidative damage are more likely to develop tumors (Hagen et al. 1994; Shimoda et al. 1994). The origin of ROS in tumor cells could often be oncogenes themselves (Irani et al. 1997) or increased activity of oxidases or peroxisome activity (Liou and Storz 2010). Mutations in mitochondrial DNA or mitochondrial dysfunction also cause increased levels of ROS. Heteroplasmic mitochondrial DNA mutations in ND (NADH Dehydrogenase) genes are shown to increase ROS production from the mitochondria (Larman et al. 2012). Tumor cells also have an elevated antioxidant response to balance the increased ROS, avoiding apoptosis (Liou and Storz 2010).

As mentioned above, although ROS is a tumor-promoting signal, the levels of ROS clearly define if it is playing a deleterious effect for the cancer cells or an advantage. Given cancer cells carry high levels of ROS, they can be targeted to death by further elevating the levels of ROS using chemicals that produce ROS. Small molecules and alkaloids have been used to target cancer cells (Raj et al. 2011; Shaw et al. 2011; Trachootham et al. 2009). However, a major disadvantage of using ROS as a target for cancer cells stems from the fact that normal cells are also affected by increased ROS, especially in cells that utilize ROS as a physiological molecule (Sena and Chandel 2012; Nagaraj et al. 2012; Owusu-Ansah and Banerjee 2009). Moreover, not all cancer cells elevate ROS levels (Nagaraj et al. 2012; Shaw et al. 2011). Hence, ROS offers a tumor type specific therapeutic scope in cancer biology (discussed at the end of this chapter).

4 Mitochondrial Dynamics in Cancer

Mitochondria are dynamic organelles undergoing fusion and fission events constantly. The outer membrane consists of mitofusins, Mfn1 and Mfn2 and the inner membrane consists of Opa1, which facilitates fusion and fission in their respective membranes (Karbowski and Youle 2003). Drp1, a dynamin related GTPase is another protein required for mitochondrial fission, which forms rings where mitochondria pinch off from each other (Detmer and Chan 2007).

The shape of mitochondria changes throughout the cell cycle and apoptosis, which relates to their role in cancer (Van den Bogert et al. 1988). During G1-S phase there is an increased oxidative phosphorylation and the function of mitochondria to facilitate cell division. However during S-M phase, given the need of the cell to divide, the mitochondria become fragmented as they are distributed between the daughter cells (Margineantu et al. 2002). It is believed that the G1-S phase networking of mitochondria can regulate the cyclin E levels and thus is essential for cell cycle progression. This also involves membrane polarization and hyperfusion of mitochondria (Mitra et al. 2009). Although cyclin E expression is important for cell cycle progression, how this is driven by mitochondrial hyperfusion is not yet proved. However, ATP and ROS have been ruled out to be playing a major role (Qian et al. 2012). Glycolysis and glutaminolysis are noted to be increased around G1/S phase and which could be linked to the change in mitochondrial dynamics (Qian et al. 2012; Dang 2010). Thus, mitochondrial structural status can contribute to cell cycle progression and a deregulation would affect cell division.

Other than cell cycle, stress signals are documented to alter mitochondrial dynamics. Signaling pathways interact with mitochondrial dynamics and regulate the structure and function of the mitochondria in order to sustain stress. Drugs, UV, production of increased amounts of ATP, and higher rates of oxidative phosphorylation are all known to cause stress-induced hyperfusion to prevent apoptosis and mitophagy (Mitra et al. 2009; Rambold et al. 2011; Tondera et al. 2009). During glucose deprivation, cells switch to oxidative phosphorylation with increased mitochondrial fusion and cristae density as an adaptation for cell survival (Rossignol et al. 2004) in normal as well as tumor producing cells. Hence, such structural changes are relevant to cell survival and division. This was shown in an *in vivo* model Drosophila (Nagaraj et al. 2012), where the oncogene Yorkie (Yki) transcriptionally regulated mitochondrial proteins Opa1 and mitofusin causing increased mitochondrial fusion. This fusion was essential throughout proliferation mediated by Yorkie. This study was extended into human cells where Yap2 expression, a homologue of Yorkie showed hyperfusion. Mitochondrial fusion is also indirectly correlated with decreased levels of ROS (Nagaraj et al. 2012), a contradiction from the general notion that ROS are elevated in tumor cells. Given ROS can induce apoptosis, it can be postulated that mitochondrial fusion is pro-survival and thus helps cancer cell endurance.

Conversely, inhibiting mitochondrial fusion impedes cell growth and proliferation as well as oxidative metabolism (Bach et al. 2003). Hence, it is imperative that

fusion promotes mitochondrial function by increasing the efficiency of oxidative phosphorylation as well as ATP production, and reducing ROS generation. Thus, fusion could also promote mitochondria related metabolic pathways such as the Kreb's cycle, fatty acid oxidation, etc.

Mitochondrial fission, the opposite phenomenon to fusion, has opposite effects on metabolism. It is acknowledged to stunt growth and increase ROS (Nagaraj et al. 2012; Yarosh et al. 2008), which could be the result of compromised respiratory activity. Loss of Drp1, a protein required for fission is also shown to cause deregulation of cyclin E, leading to aberrant proliferation (Parker et al. 2015). Dysregulated Drp1 expression is linked to tumor cell fission (Rehman et al. 2012). Given fission increases ROS production, and the ability of ROS to regulate hypoxia and lactate production, it is an interesting problem to answer how fission contributes to the Warburg effect.

Mitochondrial fission also promotes membrane depolarization, cytochrome c release, and apoptosis. Drp1 promotes Bax oligomerization, possibly allowing fragmented mitochondria to form Bax/Bak openings (Brooks et al. 2007; Montessuit et al. 2010). Other classes of apoptotic proteins, such as Bcl2 family members (Bcl-X_L), promote mitochondrial fission (Li H 2008) and are overexpressed in tumors (Kelly and Strasser 2011). These are predicted to promote a Warburg shift by reducing oxidative phosphorylation. However, their mechanistic connection to mitochondrial activity and metabolic changes is to be explored.

Mitochondrial dynamics (both fusion and fission) contribute to tumor cell proliferation by different mechanisms. However, if these changes can act as cause for tumor progression or if they are a consequence of tumor growth is yet to be understood.

5 Mitochondrial Content in Cancer

Mitochondrial content is decided by two factors in cancer: mitochondrial biogenesis and mitophagy. Signaling pathways, especially the oncogenes, control mitochondrial biogenesis, as established in cell culture systems. However, there is no clear evidence of altered mitochondrial biogenesis in tumors. Yet, given the established roles of oncogenes such as Myc in mitochondrial biogenesis (Li et al. 2005; Morrish and Hockenbery 2014), it is vital to understand the importance of mitochondrial amounts in tumor cells.

Mitochondrial biogenesis involves nuclear factors as well as mitochondrial genes; most of the mitochondrial proteins are synthesized by the nuclear factor and imported to mitochondria, while some enzymes in the ETC are encoded by the mitochondrial genes themselves (Chacinska et al. 2009). It is an essential process for the cells, and the mitochondrial content of the cells depends on the nutrient availability, dividing status and physiological (and/or pathophysiological) state of the cells (Wenz 2013). Mitochondrial biogenesis is controlled by peroxisome-proliferator activator receptor-alpha and gamma (PPARα, PPARγ), nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 (NRF2), and also estrogen

related receptors (ERR) α, β, γ (Scarpulla et al. 2012). PPAR-γ co-activator 1-alpha (PGC-1α), with its partners (PGC-1β, and PRC-PGC related co-activator) termed as the master regulator of mitochondrial biogenesis. It forms a protein complex, controlling and maintaining the expression of mitochondrial biogenesis factors, antioxidants, and several metabolic genes (Dominy et al. 2010).

The role of mitochondrial biogenesis in cancer comes to picture with the discoveries of oncogenes regulating mitochondrial biogenesis through the PGC family. The most well-known oncogene that triggers mitochondrial biogenesis is c-Myc, which control biogenesis through PGC-1β (Zhang et al. 2007). However, tumor related genes such as HIF-1α negatively regulate mitochondrial biogenesis by inhibiting c-Myc (Zhang et al. 2007). PGC-1α activity is upregulated in a subset of melanoma where oxidative phosphorylation dependency is seen (Vazquez et al. 2013). PGC-1β and its targets are upregulated in ALT (Alternative Lengthening of Telomeres) positive tumors (Hu et al. 2012). p53, the tumor suppressor protein negatively regulates mitochondrial biogenesis, again indicating a relation between cancer and mitochondrial function (Sahin et al. 2011).

Taken together, it is not clear whether mitochondrial biogenesis is beneficial for tumor cells or is inhibiting rapid proliferation. Not all tumor cells carry the same metabolic profiles. Thus, tumor mitochondrial biogenesis needs to be studied in specification to the oncogenes involved and the nature of the tumors.

The other process that regulated mitochondrial mass in cancer cells is mitochondrial autophagy. Autophagy is activated in a situation of nutrient deprivation to the cells, and mitophagy is a specific process where mitochondria are targeted for degradation to provide nutrient for cell survival (Rabinowitz and White 2010). Mitochondrial fusion and fission events control mitophagy, where fission facilitates mitophagy by marking them for degradation and fusion keeps the mitochondria healthy, protecting them from mitophagy (Twig et al. 2008). Mitophagy is regulated by two pathways postulated to be tumor suppressors: the Parkin pathway and the BNIP3/NIX pathway (Youle and Narendra 2011; Zhang and Ney 2009). Parkin promotes mitochondrial turnover via fission and assists in mitochondrial transport via microtubules (Narendra et al. 2010; Narendra et al. 2008). Parkin, although is a gene associated with Parkinson's syndrome (Youle and Narendra 2011), is also identified as a tumor suppressor gene in several cancers, and Parkin mutant mice are susceptible to tumors (Cesari et al. 2003; Fujiwara et al. 2008). Parkin promotes oxidative metabolism as a p53 target while inhibiting the development of Warburg effect (Zhang et al. 2011). Although direct evidences of Parkin involved in a tumor scenario via mitophagy are unclear, it can be postulated that Parkin maintains healthy mitochondria balancing metabolism in cells and thus can cause deregulation of metabolism in cancer cells upon its mutation.

BNIP3 and NIX are redox-sensing hypoxia inducible genes promoting mitophagy (Zhang and Ney 2009). These proteins directly interact with the autophagy protein LC3 as adaptors targeting mitochondria for degradation (Hanna et al. 2012). They reduce mitochondrial mass in hypoxic condition by inducing mitophagy helping the cells regulate excessive ROS production in a state of hypoxia (Tracy et al. 2007). BNIP3 and NIX are characterized as

dysregulated in several tumors. In certain malignant tumors, the expression of these genes decreases, whereas pre-malignant stages see an increase (Okami et al. 2004; Tan et al. 2007; Sowter et al. 2003). Loss of BNIP3 promotes tumors in mouse models, and hence it is considered to be a tumor suppressor (Chourasia and Macleod 2015). Similar to Parkin, BNIP3 and NIX proteins are considered to control mitochondrial turnover. Although it is established that Parkin and BNIP3/NIX pathways control mitophagy in tumor scenarios, a definitive mechanism for the effect of mitophagy in cancer is yet to emerge. Mitophagy is also directly related to aging as cancer mutations accumulate with age and the development of tumor progresses. Hence mitophagy and aging work *in tandem* in cancer situations. However, targeting mitophagy offers an advantage in tumor therapy over apoptosis and general autophagy due to specificity.

Along with the above discussed major mitochondrial changes, retrograde signals from mitochondria to the nucleus (Wallace 2012), and oncogenic control of mitochondria by oncogenes, such as Myc and KRas, and tumors suppressors, such as p53 and RB (Sherr and McCormick 2002; Vousden and Prives 2009; Dang 2010), also bring about mitochondrial changes in tumor situations. Although it is now established that mitochondrial changes occur in cancer cells, how these changes affect tumor growth and how they can be manipulated to achieve cancer therapy still require specific research.

6 Targeting Mitochondria for Cancer Therapy

Given the multilevel involvement of mitochondria in cancer, researchers have used several ways to target mitochondria for cancer therapy.

Mitochondrial DNA is targeted by drugs that reduce the copy number of mitochondrial DNA or by inhibiting replication. Vitamin K3 (menadione) (Sasaki et al. 2008) inhibits DNA polymerase gamma, which is important for replication of mitochondrial DNA. Parkinsonian toxin 1-methyl-4-phenylpyridinium reduces the copy number of mtDNA by destabilizing the structure (Umeda et al. 2000; Neuzil et al. 2007).

Dysregulated ROS production from mitochondria in cancer is another target for therapy. However, the human trials have not had great success (Bjelakovic and Gluud 2007) as they fail to inhibit the mitochondrial generated ROS. Another problem with the antioxidant drugs is that normal cells such as immune cells also produce ROS for physiological functions. Nevertheless, another approach in ROS based therapeutic experiments is using the ability of cancer cells to produce more antioxidants and ROS. Hence, inhibition of antioxidants in cancer cells could lead to excessive ROS in cancer cells and cause selective killing of cancer cells (Raj et al. 2011; Glasauer et al. 2014).

The Bcl-2 family of proteins consists of pro and anti-survival factors (Youle and Strasser 2008). Cell death is favored in the absence of pro-survival factors. Mimetic drugs that target BH3 domains of these proteins, the domain that interacts with Bax/Bak proteins (Youle and Strasser 2008), are used to target tumors. Drugs such

as ABT-263, Gossypol, antimycin A, alpha-tocopheryl succinates are some examples of Bcl-2 family targets that induce mitochondria mediated cell death, partly due to their interaction with the BH3 domain (Kang et al. 2010; Neuzil et al. 2007).

Given ATP generation is essential for normal cells as well as tumor cells (Zu and Guppy 2004), mitochondrial bioenergetic targeting drugs need to be specifically targeted to tumor cells. Poorly perfused tumors which make ATP (Rumsey et al. 1990) are an apt target for drugs that inhibit ATP production given it would cause cell death in such poorly perfused tumors only. The antidiabetic drug, metformin, a biguanide, is thought to be such a candidate to target ATP production without affecting the normal tissue. Metformin decreases hepatic gluconeogenesis and brings down insulin levels (Bailey and Turner 1996). Metformin has many effects on cancer cells. It decreases blood glucose and insulin levels, and inhibits the growth of tumors that are insulin dependent (Pollak 2014). It acts on the mitochondrial complex I (El-Mir et al. 2000; Owen et al. 2000). It also impairs glycolysis by decreasing the activity of enzyme hexokinase 2, an important enzyme to carry out glycolysis (Salani et al. 2013). Thus, metformin is believed to inhibit tumor growth by lowering glucose supply, acting on complex I and thereby reducing ATP production. The dosages and complete mechanism of action for this drug are still under investigation in clinical trials. Another drug similar to metformin is phenformin, a biguanide that also inhibits mitochondrial complex I (Birsoy et al. 2014). It has higher affinity to mitochondria and recently shown to work better than metformin in breast tumors (Appleyard et al. 2012). Although lactose acidosis is a drawback of phenformin, there are evidences that the drug can be used in combination with BRAF inhibitors to control melanomas effectively (Yuan et al. 2013). Hence, phenformin also makes an attractive candidate for clinical trials.

One of the classes of drugs also tried on inhibiting ATP production is VLX600, an ETC inhibitor. This is shown to reduce colon cancer tumor growth (Zhang et al. 2014) at experimental levels. Mitochondrial protein translation is targeted by certain drugs such as tigecycline that reduces the expression of 13 subunits of ETC. This drug has been efficient on leukemic cells that survive primarily on mitochondrial ATP production (Skrtic et al. 2011). Mitochondrial chaperones, such as heat shock proteins, are targeted by drugs such as Gamitrinib, which are modified to accumulate in mitochondria and reduce the activity of HSP90 and ATPase-1, thus reducing energy production of mitochondria.

Another target in mitochondrial cancer drugs is biosynthetic pathways. The glutamine addicted tumors are formed mostly due to Myc and Kras (Gaglio et al. 2011). Such tumors can be targeted by using inhibitors of glumatinases that use glutamine in their reaction to continue the tricarboxylic acid cycle. Glutaminase inhibitors such as bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide) or compound 968 (Le et al. 2012) already attenuate tumor growth. Mitophagy also produces raw materials for the mitochondrial TCA cycle as discussed in the review before. Several autophagy inhibitors are on trials and chloroquine is one such drug

(Balic et al. 2014). Targeting mitophagy specifically would be a safer option for such treatments given the toxicity associated with autophagy drugs.

Several mitochondria related protein specific inhibitors, such as hexokinase inhibitors (Ben Sahra et al. 2010; Chen et al. 2009; Mathupala et al. 2006), VDAC, and ANT inhibitors, are also reportedly used as mitochondrial targets in cancers (Belzacq et al. 2001; Don et al. 2003).

In conclusion, although there are several attempts to target mitochondria in cancer, the efficiency has been low due to the lack of complete understanding of the role of mitochondria in cancer. Mitochondria are complex organelles and they undergo drastic structural and functional changes during tumor development. As every cancer is defined by its own oncogenic signals, and every signal will have a different effect on mitochondria, there is a tremendous difference in how mitochondria are affected in each scenario. Like the saying—*one glove does not fit all*, there is a need to understand specific changes in mitochondria in specific cancers and target processes with one or a combination of drugs effectively.

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