SMGroup

Mitochondria and Cancer

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INTRODUCTION

In normal cells, growth and developmental signaling are finely regulated in response to external and internal stimuli directing cells to survival ou death [1]. Deregulation of these signaling pathways has been associated to several human diseases, including diabetes, neurodegenerative disorders, developmental defects and cancer [2]. Cancer is a genetic disease caused by changes in genes that control the way our cells work, especially how they grow and divide. During the multistep development of human tumors, cancer cells acquire among other characteristics, the capacity of sustaining proliferative signaling, replicative immortality, increased genome instability followed by the accumulation mutations, induced angiogenesis, evasion from growth suppressors, deregulation of cellular energetics and resistance to - cell death [2].

Mitochondria integrate and regulate many aspects of cellular metabolism and produce the majority of cellular ATP. The “hydrogen hypothesis” for the first eukaryote cell predicts the symbiosis between a hydrogen-dependent *archaebacterium*, as the host cell, and a hydrogen-producing *eubacterium*, ancestor of modern mitochondria [3,4]. Because of the interaction between mitochondria and the host cell, the mitochondria lost control of some of their functions by transferring part of genome to the nucleus [5]. Still however, mitochondria are crucial for the

eukaryote cell´s viability through cell death regulation, production of reactive oxygen species (ROS), and are involved in the modulation of calcium levels, and the trafficking of small metabolites [6].

In this chapter, we will discuss how mitochondrial dysfunction can initiate a complex cellular reprogramming that supports tumor formation and growth.

THE MITOCHONDRIAL METABOLISM IN CANCER

When Claude and Deduve developed the first techniques for mitochondria isolation, the biochemical knowledge had a great advancement. Metabolic reprogramming is one recognized hallmark of cancer [2]. As evidenced by Otto Warburg in 1956, cancer cells are characterized by increased glycolytic metabolism, specially in hypoxia environments, as a consequence of mitochondrial dysfunctions. Carcinogenesis is associated with decreased levels of mitochondrial proteins and upregulation of glycolytic enzymes [7]. Lehninger and Kennedy started the identification of enzymes involved on fatty acid oxidation (Krebs cycle), and afterwards many other enzymes localized in the matrix or the inner mitochondrial membrane participate in several important metabolic pathways are also known. The citric acid cycle or tricarboxylic acid (TCA cycle) had already been postulated by Krebs in 1937 and takes place inside the mitochondria (Lehninger and Kennedy) and together with the cytochromes identification led to the recognition of mitochondria as the "powerhouse of the cell". Besides that, the urea cycle, dolichol and ubiquinone biosynthesis, heme biosynthesis, part of the reactions leading to steroids and the synthesis of lipids also occur in this organelle. Defects in mitochondrial functions have been associated to the development and possibly progression of cancer.

Defects in Tricarboxylic Acid Cycle Enzymes and Cancer

The enzymes of the TCA cycle, although encoded by nuclear DNA (nDNA), are located in the mitochondrial matrix, with the exception of succinate dehydrogenase, which is located in the inner mitochondrial membrane. Currently, several mutations are being identified in enzymes involved on this pathway both in sporadic as in hereditary cancers. The energy production in melanoma cells occur preferentially through the conversion of glucose to pyruvate that is imported into mitochondria, converted to acetyl-CoA, and utilized by the TCA cycle to generate electron donors and create the proton gradient across the mitochondrial membrane used by ATP synthase to generate ATP [8] or by uncoupling proteins to produce heat [9]. Thus, in the following paragraphs we will discuss some of these mutations and their effects on cancer.

Citrate synthase

The first step of the TCA cycle, the condensation of oxaloacetate and acetyl coenzyme A (AcCoA) to generate citrate is catalyzed by the citrate synthase (CS), and its possible role in cancer is controversial. Despite its increased expression in pancreatic ductal carcinoma [10] and renal oncocytoma [11], cervical cancer cell lines showed reduced expression [12]. However, it is unclear

the role of expression levels in the tumorigenic process. One hypothesis is that the increase in CS activity, through higher levels of citrate, could be an advantage for cancer cells dependent on an increase in fatty acid biosynthesis, such as pancreatic cancers [13], malignant ovarian tumors and ovarian cancer cell lines [14]. On the other hand, the decreased activity / expression levels of CS could induce mitochondrial dysfunctions that trigger tumor-supporting glycolytic switch, usually found in cancer cells. Also the loss of CS in human cervical cancer cells induced morphological changes in epithelial–mesenchymal transition (EMT), which accelerate cancer cell metastasis and proliferation *in vitro* and *in vivo* [12].

Isocitrate dehydrogenase

Eukaryotic cells express three different isoforms of isocitrate dehydrogenases (IDHs): IDH1, IDH_2 and IDH_3. They catalyze the $NADP^+$-dependent oxidative decarboxylation of isocitrate into α-ketoglutarate (α-KG) in the cytosol (IDH1) and mitochondria (IDH_2 and IDH_3). Somatic point mutations of IDH1/2 have been identified in a spectrum of both solid tumors and hematologic malignancies, as for example in colon cancer [15], glioblastoma [16], glioma [17], osteosarcoma [18], prostate cancer [19], B-acute lymphoblastic leukemia [19], acute myeloid leukemia [20] and intrahepatic cholangiocarcinoma [21].

Missense mutations found associated to cancer ($IDH1^{R132}$, $IDH2^{R140}$, and $IDH2^{R172}$) confer a novel gain-of-function to cancer cells, which results ultimately in the reduction of α-KG into the oncometabolite 2- hydroxyglutarate (R-2HG) [22,23], that can promote cytokine independency and thereby blocks differentiation in hematopoietic cells [24]. R-2HG acts as an antagonist on enzymes that utilize α-KG as a cofactor, such as translocases (TETs), JmjC histone demethylases, and prolyl-hydroxylases [25]. Therefore, this metabolite is considered the major contributor to the oncogenic activity of mutated IDHs [6] and analysis of human leukemia and breast cancer found a DNA hyper-methylation as a consequence of expression of mutated IDH and consequently increased R-2HG levels [26,27]. It was also observed that R-2HG accumulation causes changes in histone methylation [28], indicating the role of R-2HG in multiple epigenetic processes.

Succinate dehydrogenase

The SDH is a mitochondrial enzyme complex that participates in both the TCA cycle and electron transport chain. In the TCA cycle, SDH catalyzes the oxydation of succinate to fumarate, which is coupled to the reduction of ubiquinone to ubiquinol in the electron transport chain [29]. Inactivating mutations of SDH subunits have been associated to different types of hereditary and sporadic cancers, including pheochromocytoma [30], renal carcinoma [31], breast cancer [32] and Carney-Stratakis syndrome [33]. Carney-Stratakis syndrome is a familiar syndrome characterized by Paragangliomas and gastrointestinal stromal tumors, and may be caused by loss-of-function mutations in succinate dehydrogenase (SDH). Like described above for IDH mutations the the SDH mutations are believed to promote epigenetics changes by inhibition of both DNA [34,35] and histone demethylases [36] in many types of cancers. Therefore, SDH may

acts as some kind of mitochondrial tumor suppressor and a thereby constitute a key player in cancer cell differentiation.

Fumarate hydratase

In the TCA cycle the conversion of fumarate to malate is catalyzed by fumarate hydratase (FH). Germline mutations of FH were observed in hereditary leiomyomatosis and renal cell cancer characterized by multiple cutaneous benign smooth muscle tumors of the uterus [37], aggressive renal cell carcinomas [38], and testicular cancer [39]. FH deletion in sub-types of neuroblastoma [40] and downregulated in glioblastoma [38] or sporadic clear cell carcinoma [41], again like above for SDH, suggest a possible role as a tumor suppressor. Similarly to IDH and SDH mutants, FH-deficient cancer cells accumulate fumarate, which can inhibit several OG-dependent enzymes [42], and histone and DNA demethylases [35]. In addition to its epigenetic role, fumarate in excess can covalently bind to cysteine residues of proteins, in a process called succination [43,44]. Several proteins are succinated in FH-deficient cells, including aconitase [45], Kelch-like ECH-associated protein 1 (Keap1) [46] and GSH [44] and this phenomenon is linked to increased oxidative stress in FH-deficient cancer cells.

Malic enzyme

Malic enzyme (ME) links the glycolytic and citric acid cycle that is important for NADPH production and glutamine metabolism. ME catalyze the conversion of malate into pyruvate and CO_2, accompanied by the production of NADH or NADPH. Three isoforms have been identified: the cytosolic ME1 and the mitochondrial ME2 and ME3. The relation between ME expression and cancer is recently. The knockdown of ME2 in K562 cells led to erythroid differentiation in the model of chronic myelogenous leucemia [47]. The expression of ME2 increases during melanoma progression and its knockout attenuated melanoma cell proliferation, anchorage-independent growth *in vitro* and tumor cell growth *in vivo* [48]. In lung cells the knockdown of ME2 suppresses tumor growth and induces differentiation [49].

Defects in Oxidative Phosphorylation and Cancer

Cancer cells are metabolically adapted for rapid growth and proliferation under hypoxic conditions [50]. The observed differences in the mitochondria of transformed versus non-transformed cells are: 1. the ultrastructure of mitochondria [51,52], 2. the decrease of cellular mitochondrial numbers and 3. changes in the enzyme expression levels or enzyme activity status reported above [7]. Oxidative phosphorylation (OXPHOS), that takes place in mitochondria, is the process of electron transfer from NADH or $FADH_2$ to O_2 by a series of electron carriers that culminates in the major source of ATP in aerobic organisms. The OXPHOS system is composed by five subunit complexes embedded in the mitochondria inner membrane — NADH: ubiquinone oxidoreductase (complex I), succinate: ubiquinone oxidoreductase (complex II), ubiquinol: cytochrome c oxidoreductase (complex III), cytochrome c oxidase (complex IV) and F0 F1-ATP-synthase (complex V) [53]. The activity of enzymes involved in this process is decreased in several

cancer cells [7]. Decreased content or functions of OXPHOS complexes have been associated with renal cell carcinoma [11] and can lead to enhanced ROS production.

Studies have shown a decreased activity of cytochrome oxidase in colon tumors [54], colonic adenocarcinoma [54,55], hepatoma [56] and especially at the COX III protein. Thus, a defect in cytochrome-c oxidase can cause enhanced ROS levels and a subsequent increase in mtDNA damage. In contrast, increased expression levels of the poly(A)-rich m-RNA of COX IV, I and II have been observed in rat hepatoma [57].

Significant reduction in the expression of beta-F1-ATPase has also been observed in breast and gastric adenocarcinomas, as well as in squamous esophageal and lung carcinomas [58]. The alpha subunit of mitochondrial F(1)F(0)-ATP synthase has been shown to be downregulated in colorectal carcinomas [59,60]. Studies have also revealed reduced expression of the beta 1-subunit of Na-K-ATPase in carcinoma cell lines derived from colon, breast, kidney and pancreas [61].

For space restriction the fatty acid metabolism, urea cycle, lipid biosynthesis/metabolism, biosynthesis of ubiquinol and Fe–S Centers processes and their relation with cancer will not be discussed in this chapter and are exceptionally discussed in recently reviews [62,63].

The Warburg Effect and Energy Homeostasis

Otto Warburg in 1956 hypothesized that metabolism was specific adapted for cancer cells through mitochondrial defects that inhibited their ability to effectively oxidize glucose carbon to CO_2 [64]. In normal cells under aerobic condition pyruvate is transported to the mitochondria and oxidized, but in anaerobic condition pyruvate is converted to lactate in the cytosol. As hypothesized by Warburg, cancer cells undergo metabolic reprogramming to perform anerobic glycolysis through metabolic changes in the relative balance of glycolysis/fermentation and respiration [65]. Despite the fact that tumors exhibit relatively normal levels of oxidative phosphorylation [66], some studies showed that the glucose uptake is increased, and the relative levels of fermentation and lactic acid production increase as well [32,66]. Cancer cells are very well adapted to promote tumor growth and survival, once the balance between aerobic and anaerobic conditions is variable and may be altered in response to environmental conditions such as hypoxia or low extracellular glucose. In melanoma cells the glutamine is used as a source for the TCA cycle intermediates under hypoxic conditions [66]. Although glucose is typically the principal source of energy in melanoma cells, mitochondria also utilize glutamine as an alternative anaplerotic substrate for the TCA cycle [66]. Glutamine is also required for rapid growth and serves as a source of ATP and biosynthetic intermediates in different types of cancers [67].

MITOPHAGY AND TUMOR SUPPRESSION

The autophagy process is a non-selective degradation to recycle obsolete cytoplasmic materials such as organelles, proteins, lipid droplets and pathogens [68]. Its pro-survival function may enable cancer cells to adapt to hostile environments and resist cancer therapy [69-71].

The process for specific removal of damaged or superfluous mitochondria is known as mitophagy [72]. Due to the critical role of mitochondria in energy metabolism, Ca^{2+} signaling, redox control and cell death, deregulated mitophagy can potentially impact a variety of diseases, including neurodegeneration and cancer. In early stages of tumorigenesis, autophagy works as a "tumor suppressor process" by limiting ROS-driven genomic instability and preventing necrosis-associated inflammation [73-75]. Moreover, by removing damaged mitochondria in conditions of stress, mitophagy prevents the accumulation of toxic ROS, which may propagate damage to other macromolecules and contribute to tumor initiation [76-78]. In addition, given that mitochondrial DNA mutations are also incited by mitochondrial ROS production, mitophagy may be a mechanism to decrease the rate of mtDNA mutations, which would be passed to daughter cells and could therefore contribute to cancer progression [79].

Many proteins that impact the mitophagy process are downregulated in different types of tumors. Through protein-protein interactions BNIP3 promotes cell death, regulate mitochondrial fragmentation and mitophagy [80,81]. Despite the fact that BNIP3 is silenced in pancreatic cancer, in normal cells BNIP3 protects against tumorigenesis by controlling intracellular levels of ROS and in pancreatic cancer cells its expression is lost thereby leading to the accumulation of ROS and increased DNA damage [82]. In hepatocellular carcinomas, BNIP3 silencing has been linked to a poor prognosis [83]. Another example is PARKIN, which works as a tumor suppressor and is mutated or down-regulated in glioblastoma, breast, ovarian, colorectal, hepatocellular and pancreatic tumors [84-88].

THE CONNECTION BETWEEN METABOLISM AND APOPTOSIS

Mitochondria are not only the major hubs for metabolic pathways, but also are central to programmed cell death pathways. Cell renewal is counterbalanced by apoptosis of functionally inactive cells as a strategy to remove mutated, infected or damaged cells [89]. After apoptotic stimulus cytochrome-C is released to the cytoplasm, through membrane permeabilization and thereby triggers downstream apoptotic pathways. This process occurs via activation of the pro-apoptotic members of the BCL-2 family: Bax and Bak [90]. Therefore, in cancer cells, in general, the expression of anti-apoptotic protein is increased [91], and such amplification plays a major a role in resistance development to traditional cytotoxic chemotherapy [92]. The regulation of BCL-2 members occurs on genomic, translational, and post-translational levels. For example, BAD phosphorylation on serines 112 and 136 is exacerbated in glioblastomas, prostate cancers, and melanomas due to a combination of increased oncogenic MAPK signaling and PTEN mutation or activity downregulation [93].

p53, the "guardian of the genome", is a transcription factor that regulates cellular responses to multiple stress factors, including DNA damage, oncogene activation, cell cycle and metabolic defects [94]. During chronic stress or in response to deficient DNA repair, pro-apoptotic signaling, mediated by p53 acts to promote cell death [95]. This occurs mainly through the transcriptional

induction of pro-apoptotic members of BCL-2 family members, BAX, Noxa, and PUMA (96-98] as well as through inhibitory physical interaction with the anti-apoptotic proteins BCL-xL and BCL-2 [99,100].

PTEN is a tumor suppressor and one of the most frequently inactivated proteins in cancer [101]. PTEN inactivation results in an increased phosphorylation and activation of AKT, resulting in decreased apoptosis and increased cell cycle progression and survival [102-104]. The effects of PTEN inactivation in apoptosis occur indirectly (AKT pathway) through the pro-apoptotic proteins Bad, caspase 9 and Foxo1 which are inactivated by phosphorylation [105,106].

Post-transcriptionally, several cancer-associated miRNAs are involved in the control of the BCL-2 family. For example, expression of miR-15a and miR-16-1 is reduced in about two thirds of B-cell chronic lymphocytic leukemia (CLL) cases, resulting in overexpression of the anti-apoptotic protein BCL-2, and therefore contributes to the establishment of disease [107]. Other miRNAs in CLL, such as miR-181a/b, attenuate BCL-2 and BCL-xL expression and are markers of chemotherapeutic success [35].

One of the major metabolic adaptations of cancer cells has been associated to resistance to apoptosis and deprivation of the utilization of glucose [108], glutamine [109] and fatty acids [110]. One link between metabolism, apoptosis, and mitochondria involves the interaction of hexokinase (HK) with voltage-dependent anion channel 1 (VDAC1) proteins, which helps to prevent apoptosis [111] and the increase in the enzymatic capacity of HK, due to high local concentrations of ATP released by the mitochondria [112]. The elevated formation of the HK/VDAC complex has been observed in many forms of cancer [113]. In summary, mitochondrial or mitochondrial-associated protein expression and activity are regulated at the genomic, translational, and post-translational levels in signaling pathways altered in cancer cells.

MITOCHONDRIAL DNA MUTATION, AGING AND CANCER

Mitochondrial DNA (MtDNA) has been completely sequenced and is a 16.6 kb circular double-stranded DNA molecule, which is present at a high copy number per cell and coding for 37 genes [114]. Somatic mtDNA mutations in both coding and non-coding regions have been found in several human cancers including colon, breast, lung, prostate, liver, pancreas, kidney, thyroid and brain as well as in gastric carcinoma or ovarian cancer [115] and are usually associated with bioenergetics defects and aging [116]. The generation of mutations is probably due to the oxidation of DNA bases by free radicals, especially during cellular energy production [117]. In normal tissues, the mutations have been associated with advancing age. The A189G and T408A mutations were found in skeletal muscle from aged individuals [118,119]. The *substantia nigra* of normal human brains also revealed mitochondrial somatic mutations in both neurons and glia [120].

Tan and colleagues (2012) demonstrated, by sequencing mitochondrial DNA from of breast cancer and normal tissues of the same patient, that the occurrence of somatic mutations in 74% of

the patients, with the majority of the mutations locating to the control regions (D-loop) of mtDNA. Transcriptional promoters are located in the D-loop, which is the major control site for mtDNA expression, [121]. Mutations in the D-loop were also identified in colorectal [122,123], ovarian [124], hepatocellular [125], pancreatic [126], gastric carcinoma [127,128], prostate [129], lung [130], brain [131] and other types of cancers. Petros and colleagues [132] used cybrid transfer to generate a PC3 prostate cancer cell line with the ATPase 6 gene mutated (T8993G). The T8993G mutation causes impaired mitochondrial ATPase synthesis and therefore increases ROS levels, which may lead to an increased DNA damage. Additionally, the mutant T8993G cybrids generated tumors seven times larger than the wild-type cells (T8993T). Thus, this ATP6 mutation actively contributes to tumor progression.

Additionally, the increase of mtDNA copy number is a self-protective mechanism of tumor cells to prevent apoptosis, since a reduced mtDNA copy number tends to increases ROS levels in tumor cells as well as the tumor cells' sensitivity to chemotherapeutic drugs and the rate of apoptosis [133]. In conclusion, mtDNA has an important role in the development of cancer and further work is required to identify the most frequent types of mutations and understand their functional consequences in cancer as well as the aging process.

MITOCHONDRIA AND RADICAL OXYGEN SPECIES

Mitochondria represent an important source for intracellular ROS production [134]. The electrochemical proton (H^+) gradient across the inner mitochondrial membrane, that drives ATP production, is indirectly involved in ROS formation in response to the build-up of reduced intermediaries along the respiratory chain, such as $FMNH_2$, $FADH_2$, $CoQH_2$, NADH or cytochrome c Fe^{2+}. These compounds are formed predominantly at complexes I and III of the ETC, where electrons react with oxygen to produce superoxide anions [135]. The ROS levels increase after respiratory chain arrest as the result of: a) inhibition of OxPhos, b) inhibition of respiratory chain complexes, c) excess of oxidizable substrate, d) saturation of the respiratory complexes, or e) defects in the oxidant scavenging systems. The inhibition of the complexes I to IV either by use of specific inhibitors, or through introduction of specific mutations, resulted in the production of significantly higher levels of superoxides [136,137].

ROS are involved in mitochondria redox signaling and under pathological conditions, the increase of ROS levels contributes to the initiation of cancer and to progression of the tumor phenotype. Excessive ROS can impair cellular functions through the oxidation of lipids, proteins or DNA [138]. Low levels of oxidants act as signal transduction messengers in redox signaling pathways, which have important roles in the regulation of cell function, including proliferation. In the leukemic stem cell population of acute myeloid leukemia (AML) patients low ROS levels were observed and a low glycolytic activity [139]. However in the blast AML cells there was a significant increase in ROS formation and a constant oxidative stress [140].

The phosphoinositide 3-kinase (PI3K) pathway that is involved in proliferation, survival, and

cellular mobility is hyper-activated in many cancers [141]. Intracellular level of ROS can affect the PI3K pathway by Akt activation [142] or by inactivation of the PI3K negative regulator PTEN (phosphatase and tensin homolog deleted on chromosome 10 protein). PTEN is oxidized in the active site cysteine resulting in the inactivation of PTEN´s phosphatase activity [143,144].

Protein phosphatase 2A (PP2A) and protein tyrosine phosphatase 1B (PTP1B) are also involved in Akt dephosphorylation and / inactivation [145]. ROS have been shown to also inhibit PTP1B and PP2A activity [146]. Thereby, PTP1B and PP2A inhibition increases Akt activity, resulting in increased anchorage-independent growth and cell survival and inhibition of apoptosis [102-104,147,148].

Several oncogenes have been associated to increased ROS levels. In murine embryonic fibroblasts (MEFs) immortalized by a dominant negative p53 and transformed ectopically with Myr-Akt, HRasV12 conferred increased mROS-dependent soft-agar colony formation through regulation of the ERK/MAPK signaling pathway [149]. The levels of ROS may vary according to cell type, mutation status, and oncogene expression levels. Deregulated expression of c-Myc increases ROS production, thereby leading either to transformation in some cells types or ROS-induced apoptosis in others [150,151].

In solid tumors the O_2 levels fluctuates spatially and temporarily from normoxic to hypoxic due to the lack of an efficient tumor vascularization, which causes a diminished local supply of O_2. During malignancy, the increased mitochondrial ROS production in cancer cells is mainly due to hypoxia which leads to the expression and activation of hypoxia inducible factors (HIFs), that allow tumor cells to better adapt to their oxygen depleted microenvironment. The levels of ROS increase tumor-initiating or cancer stem cell (CSC) numbers through expression of HIF-2α and its upregualtion of this transcription factors targets, which include Oct-4, c-Myc and Nanog in many types of cancers [152].

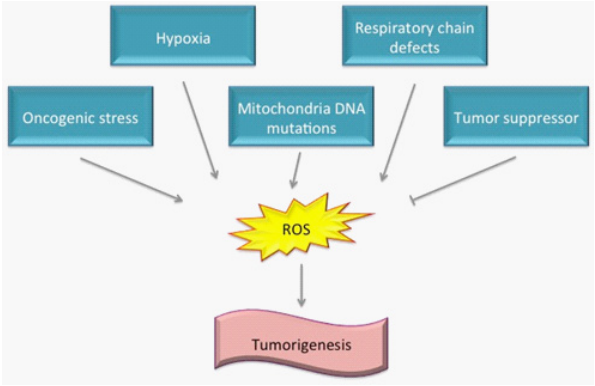

Figure 1: Modulation of mitochondrial reactive oxygen species levels. Mitochondrial reactive oxygen species (ROS) have been shown to be regulated by hypoxia, respiratory chain defects, oncogenic stress, mitochondrial DNA mutations and tumor suppressor gene inactivation.

MITOCHONDRIAL PATHWAYS AS EMERGING PHARMACOLOGICAL TARGETS IN CANCER THERAPY

It has been suggested that during tumorigenesis cancer cells energy metabolism suffers several alterations that in turn contribute to the further progression of the transformation process. Furthermore, mutations or the depletion of the entire mitochondrial genome can contribute to the development of chemotherapy resistance in malignant tumors [153]. Another form of contribution to tumorigenesis is the mitochondria´s loss of function of apoptosis, the major form of programmed cell death in mammals. Evasion from apoptosis is required for both neoplastic transformation and sustained growth of tumor cells [2] and also contributes to the cancer cells resistance to cytotoxic cancer therapies [154].

Glucose and glutamine are the major fuels to facilitate tumor progression in glioblastoma multiforme (GBM) [155]. Current chemotherapy agents, high-dose radiation treatments and cytomegalovirus infection can create a tumor microenvironment rich in glucose and glutamine ([156-159]. In this context, metabolic therapies designed to target aerobic fermentation present a promising strategy to kill cancer cells while enhancing the health of normal brain and body cells. A calorie restricted ketogenic diet has been reported to reduce fermentable fuels in the tumor microenvironment and to promote anti-angiogenic, anti-inflammatory and pro-apoptotic effects [160]. Furthermore, glycolysis inhibitors have recently been tested as potential anti-cancer drugs. 2-Deoxyglucose and 3-bromopyruvate are inactive glucose analogs that promote cell death of cancer cells through hexokinase II inhibition, thereby leading to mitochondrial defects [108,161-163]).

Spontaneous healthy mitochondrial transfer to cells without mtDNA (p^0 cells) can be promoted *in vitro* and can rescue the respiration deficiency [164]. The replacement of mitochondria using microinjection has been shown to improve embryo maturation and to minimize injury in rabbit hearts submitted to ischemic-reperfusion. Mitochondria purified from untransformed mammary epithelial MCF-12A cells, were successfully injected into human breast cancer cell lines and suppressed cancer cell proliferation accompanied by increased sensitivity to doxorubicin, abraxane, or carboplatin chemotherapy [165]. Therefore, mitochondrial manipulation in cells creates the possibility of new cancer treatments that envision cancer cell apoptosis and increased drug sensitivity.

The voltage gated potassium channel Kv1.3 and the big-potassium (BK) channel are mitochondrial proteins involved on potassium transport and are associated with cell death by serving as targets for pro-apoptotic Bax and Bak proteins. MitoKv1.3 expression was observed in different mitochondria of cancer cells including human lymphoma [166], pancreas [167], glioma [168], breast [169], melanoma [170], prostate [171], gastric [172] and colon cancers [173]. mitoKv1.3 is inhibited by Bax and Bak, which bind directly to the pore of the channel, thereby resulting in the hyperpolarization of the inner mitochondrial membrane, ROS formation

and release of cytochrome c to the cytoplasm, ultimately causing apoptotic cell death [174]. As mitoKv1.3 acts downstream of Bax and Bak, drugs that directly inhibit mitoKv1.3 (charybdotoxin and margatoxin) may serve as a new class of drugs for the treatment of tumors, as demonstrated by *in vivo* treatment of mouse melanoma and *ex vivo* human chronic leukemia B cells [175].

Chemotherapy is able to cure many patients with malignancies, but, ever so often fails. Therefore the demand for novel therapeutic approaches and the quest to identify new cancer drug targets is a ongoing, long-term challenge. In this context, the fact that mitochondrial dysfunctions provide survival advantages to cancer cells, raise the tempting opportunity to explore mitochondrial pathways as new and promising targets for innovative therapeutic interventions.

References

1. Altman BJ, Rathmell JC. Metabolic stress in autophagy and cell death pathways. Cold Spring Harb Perspect Biol. 2012; 4: a008763.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646-674.
3. Martin W, Müller M. The hydrogen hypothesis for the first eukaryote. Nature. 1998; 392: 37-41.
4. Margulis L. On the evolutionary origin and possible mechanism of colchicine-sensitive mitotic movements. Biosystems. 1974; 6: 16-36.
5. Timmis JN, Ayliffe MA, Huang CY, Martin W. Endosymbiotic gene transfer: organelle genomes forge eukaryotic chromosomes. Nat Rev Genet. 2004; 5: 123-135.
6. Gaude E, Frezza C. Defects in mitochondrial metabolism and cancer. Cancer Metab. 2014; 2: 10.
7. Cuezva JM, Krajewska M, de Heredia ML, Krajewski S, Santamaría G. The bioenergetic signature of cancer: a marker of tumor progression. Cancer Res. 2002; 62: 6674-6681.
8. Balaban RS. Regulation of oxidative phosphorylation in the mammalian cell. Am J Physiol. 1990; 258: C377-389.
9. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004; 84: 277-359.
10. Schlichtholz B, Turyn J, Goyke E, Biernacki M, Jaskiewicz K. Enhanced citrate synthase activity in human pancreatic cancer. Pancreas. 2005; 30: 99-104.
11. Simonnet H, Alazard N, Pfeiffer K, Gallou C, Béroud C. Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma. Carcinogenesis. 2002; 23: 759-768.
12. Lin CC, Cheng TL, Tsai WH, Tsai HJ, Hu KH. Loss of the respiratory enzyme citrate synthase directly links the Warburg effect to tumor malignancy. Sci Rep. 2012; 2: 785.
13. Blum R, Kloog Y. Metabolism addiction in pancreatic cancer. Cell Death Dis. 2014; 5: e1065.
14. Chen L, Liu T, Zhou J, Wang Y, Wang X. Citrate synthase expression affects tumor phenotype and drug resistance in human ovarian carcinoma. PLoS One. 2014; 9: e115708.
15. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, et al. The consensus coding sequences of human breast and colorectal cancers. Science. 2006; 314: 268-274.
16. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008; 321:1807-1812.
17. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009; 360: 765-773.
18. Liu X, Kato Y, Kaneko MK, Sugawara M, Ogasawara S. Isocitrate dehydrogenase 2 mutation is a frequent event in osteosarcoma detected by a multi-specific monoclonal antibody MsMab-1. Cancer Med. 2013; 2: 803-814.
19. Kang MR, Kim MS, Oh JE, Kim YR, Song SY. Mutational analysis of IDH1 codon 132 in glioblastomas and other common cancers. Int J Cancer. 2009; 125: 353-355.
20. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009; 361: 1058-1066.

21. Borger DR, Goyal L, Yau T, Poon RT, Ancukiewicz M, et al. Circulating oncometabolite 2-hydroxyglutarate is a potential surrogate biomarker in patients with isocitrate dehydrogenase-mutant intrahepatic cholangiocarcinoma. Clin Cancer Res. 2014; 20: 1884-1890.

22. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009; 462:739–744.

23. Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010; 17: 225-234.

24. Losman JA, Looper RE, Koivunen P, Lee S, Schneider RK. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science. 2013; 339: 1621-1625.

25. Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. EMBO Rep. 2011; 12: 463-469.

26. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012; 483: 474-478.

27. Terunuma A, Putluri N, Mishra P, Mathé EA, Dorsey TH. MYC-driven accumulation of 2-hydroxyglutarate is associated with breast cancer prognosis. J Clin Invest. 2014; 124: 398-412.

28. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012; 483: 474-478.

29. King A, Selak MA, Gottlieb E. Succinate dehydrogenase and fumarate hydratase: linking mitochondrial dysfunction and cancer. Oncogene. 2006; 25: 4675-4682.

30. Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000; 287: 848-851.

31. Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D. Germline SDHB mutations and familial renal cell carcinoma. J Natl Cancer Inst. 2008; 100: 1260-1262.

32. Kim S, Kim do H, Jung WH, Koo JS. Succinate dehydrogenase expression in breast cancer. Springerplus. 2013; 2: 299.

33. Szarek E, Ball ER, Imperiale A, Tsokos M, Faucz FR. Carney triad, SDH-deficient tumors, and Sdhb+/- mice share abnormal mitochondria. Endocr Relat Cancer. 2015; 22: 345-352.

34. Killian JK, Kim SY, Miettinen M, Smith C, Merino M, et al. Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. Cancer Discov. 2013; 3: 648-657.

35. Xiao M, Yang H, Xu W, Ma S, Lin H, et al. Inhibition of alpha-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. Genes Dev. 2012; 26: 1326-1338.

36. Cervera AM, Bayley JP, Devilee P, McCreath KJ. Inhibition of succinate dehydrogenase dysregulates histone modification in mammalian cells. Mol Cancer. 2009; 8: 89.

37. Kiuru M, Launonen V. Hereditary leiomyomatosis and renal cell cancer (HLRCC). Curr Mol Med. 2004; 4: 869-875.

38. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002; 30: 406–410.

39. Carvajal-Carmona LG, Alam NA, Pollard PJ, Jones AM, Barclay E. Adult leydig cell tumors of the testis caused by germline fumarate hydratase mutations. J Clin Endocrinol Metab. 2006; 91: 3071-3075.

40. Bardella C, El-Bahrawy M, Frizzell N, Adam J, Ternette N. Aberrant succination of proteins in fumarate hydratase-deficient mice and HLRCC patients is a robust biomarker of mutation status. J Pathol. 2011; 225: 4-11.

41. Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metab Rev. 2006; 38: 769-789.

42. Zheng L, Mackenzie ED, Karim SA, Hedley A, Blyth K. Reversed argininosuccinate lyase activity in fumarate hydratase-deficient cancer cells. Cancer Metab. 2013; 1: 12.

43. Chen C, Liu Y, Lu C, Cross JR, Morris JP 4th. Cancer-associated IDH2 mutants drive an acute myeloid leukemia that is susceptible to Brd4 inhibition. Genes Dev. 2013; 27: 1974-1985.

44. Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: mechanisms, models, and clinical opportunities. Cancer Discov. 2013; 3: 730-741.

45. Hao HX, Khalimonchuk O, Schraders M, Dephoure N, Bayley JP. SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. Science. 2009; 325: 1139-1142.

46. Rakheja D, Konoplev S, Medeiros LJ, Chen W. IDH mutations in acute myeloid leukemia. Hum Pathol. 2012; 43: 1541-1551.

47. Ren JG, Seth P, Everett P, Clish CB, Sukhatme VP. Induction of erythroid differentiation in human erythroleukemia cells by depletion of malic enzyme 2. PLoS One. 2010; 5.

48. Chang YL, Gao HW, Chiang CP, Wang WM, Huang SM. Human mitochondrial NAD(P)(+)-dependent malic enzyme participates in cutaneous melanoma progression and invasion. J Invest Dermatol. 2015; 135: 807-815.

49. Ren JG, Seth P, Clish CB, Lorkiewicz PK, Higashi RM, et al. Knockdown of Malic Enzyme 2 Suppresses Lung Tumor Growth, Induces Differentiation and Impacts PI3K/AKT Signaling. Scientific Reports. 2014; 4: 5414.

50. Griffiths JR. Causes and consequences of hypoxia and acidity in tumour microenvironments. Bioessays. 2001; 23: 295-296.

51. Hoberman HD. Is there a role for mitochondrial genes in carcinogenesis? Cancer Res. 1975; 35(11 Pt.

52. Springer EL. Comparative study of the cytoplasmic organelles of epithelial cell lines derived from human carcinomas and nonmalignant tissues. Cancer Res. 1980; 40: 803-817.

53. Basak NP, Banerjee S. Mitochondrial dependency in progression of acute myeloid leukemia. Mitochondrion. 2015; 21: 41-48.

54. Cavelier L, Jazin EE, Eriksson I, Prince J, Båve U. Decreased cytochrome-c oxidase activity and lack of age-related accumulation of mitochondrial DNA deletions in the brains of schizophrenics. Genomics. 1995; 29: 217-224.

55. Sun AS, Sepkowitz K, Geller SA. A study of some mitochondrial and peroxisomal enzymes in human colonic adenocarcinoma. Lab Invest. 1981; 44: 13-17.

56. Sun AS, Cederbaum AI. Oxidoreductase activities in normal rat liver, tumor-bearing rat liver, and hepatoma HC-252. Cancer Res. 1980; 40: 4677-4681.

57. Luciaková K, Kuzela S. Increased steady-state levels of several mitochondrial and nuclear gene transcripts in rat hepatoma with a low content of mitochondria. Eur J Biochem. 1992; 205: 1187-1193.

58. Isidoro A, Martínez M, Fernández PL, Ortega AD, Santamaría G. Alteration of the bioenergetic phenotype of mitochondria is a hallmark of breast, gastric, lung and oesophageal cancer. Biochem J. 2004; 378: 17-20.

59. Sakai H, Suzuki T, Maeda M, Takahashi Y, Horikawa N. Up-regulation of Na(+),K(+)-ATPase alpha 3-isoform and down-regulation of the alpha1-isoform in human colorectal cancer. FEBS Lett. 2004; 563: 151-154.

60. Shin YK, Yoo BC, Chang HJ, Jeon E, Hong SH. Down-regulation of mitochondrial F1F0-ATP synthase in human colon cancer cells with induced 5-fluorouracil resistance. Cancer Res. 2005; 65: 3162-3170.

61. Espineda CE, Chang JH, Twiss J, Rajasekaran SA, Rajasekaran AK. Repression of Na,K-ATPase beta1-subunit by the transcription factor snail in carcinoma. Mol Biol Cell. 2004; 15: 1364-1373.

62. Balaban S, Lee LS, Schreuder M, Hoy AJ. Obesity and cancer progression: is there a role of fatty acid metabolism? Biomed Res Int. 2015; 2015: 274585.

63. Madaan K, Kaushik D, Verma T. Hydroxyurea: a key player in cancer chemotherapy. Expert Rev Anticancer Ther. 2012; 12: 19-29.

64. Warburg O. On the origin of cancer cells. Science. 1956; 123: 309-314.

65. Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer. 2011; 11: 325-337.

66. Scott DA, Richardson AD, Filipp FV, Knutzen CA, Chiang GG. Comparative metabolic flux profiling of melanoma cell lines: beyond the Warburg effect. J Biol Chem. 2011; 286: 42626-42634.

67. McGuirk S, Gravel SP, Deblois G, Papadopoli DJ, Faubert B. PGC-1Î± supports glutamine metabolism in breast cancer. Cancer Metab. 2013; 1: 22.

68. Rogov V, Dötsch V, Johansen T, Kirkin V. Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy. Mol Cell. 2014; 53: 167-178.

69. Rosenfeldt MT, Ryan KM. The multiple roles of autophagy in cancer. Carcinogenesis. 2011; 32: 955-963.

70. Rubinsztein DC, Codogno P, Levine B. Autophagy modulation as a potential therapeutic target for diverse diseases. Nat Rev Drug Discov. 2012; 11: 709-730.

71. White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer. 2012; 12: 401-410.

72. Youle RJ, Narendra DP. Mechanisms of mitophagy. Nat Rev Mol Cell Biol. 2011; 12: 9-14.

73. Bray K, Mathew R, Lau A, Kamphorst JJ, Fan J. Autophagy suppresses RIP kinase-dependent necrosis enabling survival to mTOR inhibition. PLoS One. 2012; 7: e41831.

74. Degenhardt K, Mathew R, Beaudoin B, Bray K, Anderson D. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. Cancer Cell. 2006; 10: 51-64.

75. Mathew R, Karp CM, Beaudoin B, Vuong N, Chen G. Autophagy suppresses tumorigenesis through elimination of p62. Cell. 2009; 137: 1062-1075.

76. Komatsu M, Waguri S, Koike M, Sou YS, Ueno T. Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. Cell. 2007; 131: 1149-1163.

77. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell. 2011; 147: 728-741.

78. Sridhar S, Botbol Y, Macian F, Cuervo AM. Autophagy and disease: always two sides to a problem. J Pathol. 2012; 226: 255-273.

79. Chatterjee A, Mambo E, Sidransky D. Mitochondrial DNA mutations in human cancer. Oncogene. 2006; 25: 4663-4674.

80. Erkan M, Kleeff J, Esposito I, Giese T, Ketterer K. Loss of BNIP3 expression is a late event in pancreatic cancer contributing to chemoresistance and worsened prognosis. Oncogene. 2005; 24: 4421-4432.

81. Okami J, Simeone DM, Logsdon CD. Silencing of the hypoxia-inducible cell death protein BNIP3 in pancreatic cancer. Cancer Res. 2004; 64: 5338-5346.

82. Lu SZ, Harrison-Findik DD. Autophagy and cancer. World J Biol Chem. 2013 ;4: 64.

83. Calvisi DF, Ladu S, Gorden A, Farina M, Lee JS, et al. Mechanistic andprognostic significance of aberrant methylation in the molecular pathogenesisof human hepatocellular carcinoma. J Clin Invest. 2007; 117: 2713–2722.

84. Letessier A, Garrido-Urbani S, Ginestier C, Fournier G, Esterni B. Correlated break at PARK2/FRA6E and loss of AF-6/Afadin protein expression are associated with poor outcome in breast cancer. Oncogene. 2007; 26: 298-307.

85. Fujiwara M, Marusawa H, Wang HQ, Iwai A, Ikeuchi K. Parkin as a tumor suppressor gene for hepatocellular carcinoma. Oncogene. 2008; 27: 6002-6011.

86. Veeriah S, Taylor BS, Meng S, Fang F, Yilmaz E. Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies. Nat Genet. 2010; 42: 77-82.

87. Poulogiannis G, McIntyre RE, Dimitriadi M, Apps JR, Wilson CH. PARK2 deletions occur frequently in sporadic colorectal cancer and accelerate adenoma development in Apc mutant mice. Proc Natl Acad Sci U S A. 2010; 107: 15145-15150.

88. Sun X, Liu M, Hao J, Li D, Luo Y. Parkin deficiency contributes to pancreatic tumorigenesis by inducing spindle multipolarity and misorientation. Cell Cycle. 2013; 12: 1133-1141.

89. Sachs L. The control of hematopoiesis and leukemia: from basic biology to the clinic. Proc Natl Acad Sci U S A. 1996; 93: 4742-4749.

90. Green DR, Kroemer G. The pathophysiology of mitochondrial cell death. Science. 2004; 305: 626-629.

91. Portt L, Norman G, Clapp C, Greenwood M, Greenwood MT. Anti-apoptosis and cell survival: a review. Biochim Biophys Acta. 2011; 1813: 238-259.

92. Nessling M, Kern MA, Schadendorf D, Lichter P. Association of genomic imbalances with resistance to therapeutic drugs in human melanoma cell lines. Cytogenet Cell Genet. 1999; 87: 286-290.

93. She QB, Solit DB, Ye Q, O'Reilly KE, Lobo J. The BAD protein integrates survival signaling by EGFR/MAPK and PI3K/Akt kinase pathways in PTEN-deficient tumor cells. Cancer Cell. 2005; 8: 287-297.

94. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol. 2007; 8: 275-283.

95. Vousden KH, Prives C. Blinded by the Light: The Growing Complexity of p53. Cell. 2009; 137: 413-431.

96. Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell. 2001; 7: 683-694.

97. Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. Science. 2000; 288: 1053-1058.

98. Yu J, Zhang L, Hwang PM, Kinzler KW, Vogelstein B. PUMA induces the rapid apoptosis of colorectal cancer cells. Mol Cell. 2001; 7: 673-682.

99. Leu JI, Dumont P, Hafey M, Murphy ME, George DL. Mitochondrial p53 activates Bak and causes disruption of a Bak-Mcl1 complex. Nat Cell Biol. 2004; 6: 443-450.

100. Mihara M, Erster S, Zaika A, Petrenko O, Chittenden T. p53 has a direct apoptogenic role at the mitochondria. Mol Cell. 2003; 11: 577-590.

101. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013; 6: 1.

102. Datta SR, Brunet A, Greenberg ME. Cellular survival: a play in three Akts. Genes Dev. 1999; 13: 2905-2927.

103. Dudgeon C, Wang P, Sun X, Peng R, Sun Q. PUMA induction by FoxO3a mediates the anticancer activities of the broad-range kinase inhibitor UCN-01. Mol Cancer Ther. 2010; 9: 2893-2902.

104. Steelman LS, Bertrand FE, McCubrey JA. The complexity of PTEN: mutation, marker and potential target for therapeutic intervention. Expert Opin Ther Targets. 2004; 8: 537-550.

105. Modur V, Nagarajan R, Evers BM, Milbrandt J. FOXO proteins regulate tumor necrosis factor-related apoptosis inducing ligand expression. Implications for PTEN mutation in prostate cancer. J Biol Chem. 2002; 277: 47928-47937.

106. Weng L, Brown J, Eng C. PTEN induces apoptosis and cell cycle arrest through phosphoinositol-3-kinase/Akt-dependent and -independent pathways. Hum Mol Genet. 2001; 10: 237-242.

107. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A. 2005; 102: 13944-13949.

108. Xu RH, Pelicano H, Zhou Y, Carew JS, Feng L. Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. Cancer Res. 2005; 65: 613-621.

109. Matés JM, Segura JA, Alonso FJ, Márquez J. Pathways from glutamine to apoptosis. Front Biosci. 2006; 11: 3164-3180.

110. Carracedo A, Cantley LC, Pandolfi PP. Cancer metabolism: fatty acid oxidation in the limelight. Nat Rev Cancer. 2013; 13: 227-232.

111. Shoshan-Barmatz V, Israelson A, Brdiczka D, Sheu SS. The voltage-dependent anion channel (VDAC): function in intracellular signalling, cell life and cell death. Curr Pharm Des. 2006; 12: 2249-2270.

112. Galluzzi L, Kepp O, Tajeddine N, Kroemer G. Disruption of the hexokinase-VDAC complex for tumor therapy. Oncogene. 2008; 27: 4633-4635.

113. Mathupala SP, Ko YH, Pedersen PL. Hexokinase II: cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria. Oncogene. 2006; 25: 4777-4786.

114. Wallace DC. Why do we still have a maternally inherited mitochondrial DNA? Insights from evolutionary medicine. Annu Rev Biochem. 2007; 76: 781–821.

115. Chatterjee A, Mambo E, Sidransky D. Mitochondrial DNA mutations in human cancer. Oncogene. 2006; 25: 4663-4674.

116. Linnane AW, Marzuki S, Ozawa T, Tanaka M. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. Lancet. 1989; 1: 642-645.

117. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956; 11: 298-300.

118. Del Bo R, Bordoni A, Martinelli Boneschi F, Crimi M, Sciacco M. Evidence and age-related distribution of mtDNA D-loop point mutations in skeletal muscle from healthy subjects and mitochondrial patients. J Neurol Sci. 2002; 202: 85-91.

119. Cormio A, Milella F, Vecchiet J, Felzani G, Gadaleta MN. Mitochondrial DNA mutations in RRF of healthy subjects of different age. Neurobiol Aging. 2005; 26: 655-664.

120. Cantuti-Castelvetri I, Lin MT, Zheng K, Keller-McGandy CE, Betensky RA. Somatic mitochondrial DNA mutations in single neurons and glia. Neurobiol Aging. 2005; 26: 1343-1355.

121. Miyazono F, Schneider PM, Metzger R, Warnecke-Eberz U, Baldus SE. Mutations in the mitochondrial DNA D-Loop region occur frequently in adenocarcinoma in Barrett's esophagus. Oncogene. 2002; 21: 3780-3783.

122. Alonso A, Martin P, Albarran C, Aquilera B, Garcia O. Detection of somatic mutations in the mitochondrial DNA control region of colorectal and gastric tumors by heteroduplex and single-strand conformation analysis. Electrophoresis. 1997; 18: 682-685.

123. Habano W, Nakamura S, Sugai T. Microsatellite instability in the mitochondrial DNA of colorectal carcinomas: evidence for mismatch repair systems in mitochondrial genome. Oncogene. 1998; 17: 1931-1937.

124. Liu H, Hu YP, Savaraj N, Priebe W, Lampidis TJ. Hypersensitization of tumor cells to glycolytic inhibitors. Biochemistry. 2001; 40: 5542-5547.

125. Nomoto S, Sanchez-Cespedes M, Sidransky D. Identification of mtDNA mutations in human cancer. Methods Mol Biol. 2002; 197: 107-117.

126. Jones JB, Song JJ, Hempen PM, Parmigiani G, Hruban RH. Detection of mitochondrial DNA mutations in pancreatic cancer offers a "mass"-ive advantage over detection of nuclear DNA mutations. Cancer Res. 2001; 61: 1299-1304.

127. Zhao YB, Yang HY, Zhang XW, Chen GY. Mutation in D-loop region of mitochondrial DNA in gastric cancer and its significance. World J Gastroenterol. 2005; 11: 3304-3306.

128. Wu CW, Yin PH, Hung WY, Li AF, Li SH. Mitochondrial DNA mutations and mitochondrial DNA depletion in gastric cancer. Genes Chromosomes Cancer. 2005; 44: 19-28.

129. Jessie BC, Sun CQ, Irons HR, Marshall FF, Wallace DC. Accumulation of mitochondrial DNA deletions in the malignant prostate of patients of different ages. Exp Gerontol. 2001; 37: 169-174.

130. Sanchez-Cespedes M, Parrella P, Nomoto S, Cohen D, Xiao Y. Identification of a mononucleotide repeat as a major target for mitochondrial DNA alterations in human tumors. Cancer Res. 2001; 61: 7015-7019.

131. Montanini L, Regna-Gladin C, Eoli M, Albarosa R, Carrara F. Instability of mitochondrial DNA and MRI and clinical correlations in malignant gliomas. J Neurooncol. 2005; 74: 87-89.

132. Petros JA, Baumann AK, Ruiz-Pesini E, Amin MB, Sun CQ. mtDNA mutations increase tumorigenicity in prostate cancer. Proc Natl Acad Sci U S A. 2005; 102: 719-724.

133. Mei H, Sun S, Bai Y, Chen Y, Chai R. Reduced mtDNA copy number increases the sensitivity of tumor cells to chemotherapeutic drugs. Cell Death Dis. 2015; 6: e1710.

134. Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol. 2003; 552: 335-344.

135. Finkel T. Signal transduction by reactive oxygen species. J Cell Biol. 2011; 194: 7-15.

136. Turrens JF. Superoxide production by the mitochondrial respiratory chain. Biosci Rep. 1997; 17: 3-8.

137. Paddenberg R, Ishaq B, Goldenberg A, Faulhammer P, Rose F. Essential role of complex II of the respiratory chain in hypoxia-induced ROS generation in the pulmonary vasculature. Am J Physiol Lung Cell Mol Physiol. 2003; 284: L710-719.

138. Murphy MP, Holmgren A, Larsson NG, Halliwell B, Chang CJ. Unraveling the biological roles of reactive oxygen species. Cell Metab. 2011; 13: 361-366.

139. Lagadinou ED, Sach A, Callahan K, Rossi RM, Neering SJ. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. Cell Stem Cell. 2013; 12: 329-341.

140. Zhou FL, Zhang WG, Wei YC, Meng S, Bai GG. Involvement of oxidative stress in the relapse of acute myeloid leukemia. J Biol Chem. 2010; 285: 15010-15015.

141. Cantley LC1. The phosphoinositide 3-kinase pathway. Science. 2002; 296: 1655-1657.

142. Nemoto S, Finkel T. Redox regulation of forkhead proteins through a p66shc-dependent signaling pathway. Science. 2002; 295: 2450-2452.

143. Lee SR, Yang KS, Kwon J, Lee C, Jeong W. Reversible inactivation of the tumor suppressor PTEN by H2O2. J Biol Chem. 2002; 277: 20336-20342.

144. Leslie NR, Bennett D, Lindsay YE, Stewart H, Gray A. Redox regulation of PI 3-kinase signalling via inactivation of PTEN. EMBO J. 2003; 22: 5501-5510.

145. Rao RK, Clayton LW. Regulation of protein phosphatase 2A by hydrogen peroxide and glutathionylation. Biochem Biophys Res Commun. 2002; 293: 610-616.

146. Ostman A, Frijhoff J, Sandin A, Böhmer FD. Regulation of protein tyrosine phosphatases by reversible oxidation. J Biochem. 2011; 150: 345-356.

147. Salmeen A, Andersen JN, Myers MP, Meng TC, Hinks JA. Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate. Nature. 2003; 423: 769-773.

148. Lou YW, Chen YY, Hsu SF, Chen RK, Lee CL. Redox regulation of the protein tyrosine phosphatase PTP1B in cancer cells. FEBS J. 2008; 275: 69-88.

149. Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proc Natl Acad Sci U S A. 2010; 107: 8788-8793.

150. Vafa O, Wade M, Kern S, Beeche M, Pandita TK. c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. Mol Cell. 2002; 9: 1031-1044.

151. Tanaka H, Matsumura I, Ezoe S, Satoh Y, Sakamaki T. E2F1 and c-Myc potentiate apoptosis through inhibition of NF-kappaB activity that facilitates MnSOD-mediated ROS elimination. Mol Cell. 2002; 9: 1017-1029.

152. Li Z, Rich JN. Hypoxia and hypoxia inducible factors in cancer stem cell maintenance. Curr Top Microbiol Immunol. 2010; 345: 21-30.

153. Guaragnella N, Giannattasio S, Moro L. Mitochondrial dysfunction in cancer chemoresistance. Biochem Pharmacol. 2014; 92: 62-72.

154. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer. 2002; 2: 647-656.

155. Seyfried TN, Mukherjee P. Targeting energy metabolism in brain cancer: review and hypothesis. Nutr Metab (Lond). 2005; 2: 30.

156. Williamson CD, Colberg-Poley AM. Access of viral proteins to mitochondria via mitochondria-associated membranes. Rev Med Virol. 2009; 19: 147-164.

157. Bozidis P, Williamson CD, Wong DS, Colberg-Poley AM. Trafficking of UL37 proteins into mitochondrion-associated membranes during permissive human cytomegalovirus infection. J Virol. 2010; 84: 7898–7903.

158. Yu Y, Clippinger AJ, Alwine JC. Viral effects on metabolism: changes in glucose and glutamine utilization during human cytomegalovirus infection. Trends Microbiol. 2011; 19: 360-367.

159. Szerlip N, Rutter C, Ram N, Yovino S, Kwok Y. Factors impacting volumetric white matter changes following whole brain radiation therapy. J Neurooncol. 2011; 103: 111-119.

160. Seyfried TN, Flores R, Poff AM, D'Agostino DP, Mukherjee P. Metabolic therapy: a new paradigm for managing malignant brain cancer. Cancer Lett. 2015; 356: 289-300.

161. Liu H, Savaraj N, Priebe W, Lampidis TJ. Hypoxia increases tumor cell sensitivity to glycolytic inhibitors: a strategy for solid tumor therapy (Model C). Biochem Pharmacol. 2002; 64: 1745-1751.

162. Liu VW, Shi HH, Cheung AN, Chiu PM, Leung TW. High incidence of somatic mitochondrial DNA mutations in human ovarian carcinomas. Cancer Res. 2001; 61: 5998-6001.

163. Maher JC, Krishan A, Lampidis TJ. Greater cell cycle inhibition and cytotoxicity induced by 2-deoxy-D-glucose in tumor cells treated under hypoxic vs aerobic conditions. Cancer Chemother Pharmacol. 2004; 53: 116–122.

164. Spees JL, Olson SD, Whitney MJ, Prockop DJ. Mitochondrial transfer between cells can rescue aerobic respiration. Proc Natl Acad Sci U S A. 2006; 103: 1283-1288.

165. Elliott RL, Jiang XP, Head JF. Mitochondria organelle transplantation: introductionof normal epithelial mitochondria into human cancer cells inhibits proliferationand increases drug sensitivity. Breast Cancer Res Treat. 2012; 136: 347-354.

166. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403: 503-511.

167. Brevet M, Fucks D, Chatelain D, Regimbeau JM, Delcenserie R. Deregulation of 2 potassium channels in pancreas adenocarcinomas: implication of KV1.3 gene promoter methylation. Pancreas. 2009; 38: 649-654.

168. Bielanska J, Hernández-Losa J, Pérez-Verdaguer M, Moline T, Somoza R. Voltage-dependent potassium channels Kv1.3 and Kv1.5 in human cancer. Curr Cancer Drug Targets. 2009; 9: 904-914.

169. Abdul M, Santo A, Hoosein N. Activity of potassium channel-blockers in breast cancer. Anticancer Res. 2003; 23: 3347-3351.

170. Artym VV, Petty HR. Molecular proximity of Kv1.3 voltage-gated potassium channels and beta(1)-integrins on the plasma membrane of melanoma cells: effects of cell adherence and channel blockers. J Gen Physiol. 2002; 120: 29-37.

171. Abdul M, Hoosein N. Reduced Kv1.3 potassium channel expression in human prostate cancer. J Membr Biol. 2006; 214: 99-102.

172. Lan M, Shi Y, Han Z, Hao Z, Pan Y. Expression of delayed rectifier potassium channels and their possible roles in proliferation of human gastric cancer cells. Cancer Biol Ther. 2005; 4: 1342-1347.

173. Abdul M, Hoosein N. Voltage-gated potassium ion channels in colon cancer. Oncol Rep. 2002; 9: 961-964.

174. Szabó I, Bock J, Grassmé H, Soddemann M, Wilker B. Mitochondrial potassium channel Kv1.3 mediates Bax-induced apoptosis in lymphocytes. Proc Natl Acad Sci U S A. 2008; 105: 14861-14866.

175. Leanza L, Venturini E, Kadow S, Carpinteiro A, Gulbins E. Targeting a mitochondrial potassium channel to fight cancer. Cell Calcium. 2015; 58: 131-138.