BBA - Molecular Basis of Disease 1867 (2021) 166016

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Cancer cell metabolism: Rewiring the mitochondrial hub

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ARTICLE INFO

Keywords:
Metabolism
Mitochondria
mtDNA
Metabolic pathways
Cancer

ABSTRACT

To adapt to tumoral environment conditions or even to escape chemotherapy, cells rapidly reprogram their metabolism to handle adversities and survive. Given the rapid rise of studies uncovering novel insights and therapeutic opportunities based on the role of mitochondria in tumor metabolic programing and therapeutics, this review summarizes most significant developments in the field. Taking in mind the key role of mitochondria on carcinogenesis and tumor progression due to their involvement on tumor plasticity, metabolic remodeling, and signaling re-wiring, those organelles are also potential therapeutic targets. Among other topics, we address the recent data intersecting mitochondria as of prognostic value and staging in cancer, by mitochondrial DNA (mtDNA) determination, and current inhibitors developments targeting mtDNA, OXPHOS machinery and metabolic pathways. We contribute for a holistic view of the role of mitochondria metabolism and directed therapeutics to understand tumor metabolism, to circumvent therapy resistance, and to control tumor development.

Abbreviations: 2-DG, 2-Deoxyglucose; 2-HG, D-2-hydroxyglutarate; 3BP, 3-Bromopyruvate; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AIF, apoptosis inducing factor; AKT, serine–threonine kinase; AMPK, AMP-activated protein kinase; ASL, argininosuccinate lyase; ASS1, argininosuccinate synthetase 1; BER, base excision repair; BPTES, Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide; CAFs, cancer-associated fibroblasts; COX, mitochondrial cytochrome C oxidase; DAMPS, damage-associated molecular patterns; DCA, dichloroacetic acid; DCFDA, 2′,7′–dichlorofluorescin diacetate fluorogenic dye; DddA, deaminase belonging to the SCP1.201-like family; DHODH, dihydroorotate dehydrogenase; D-loop, displacement loop; EMT, epithelial mesenchymal transition; ETC, electron transport chain; FABP5, fatty acid binding protein; FAO, fatty acid oxidation; FCCP, carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone; FH, fumarate hydratase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GLS, glutaminase; GLUD1, glutamate dehydrogenase 1; GLUT, glucose transporters; GOT2, glutamic-oxalo-acetic transaminase 2; GSH, glutathione; HER2, human epidermal growth factor receptor 2; HIF-1, hypoxia inducible factor 1; HK1, hexokinase 1; HK2, hexokinase 2; HSPD1, heat shock protein family D (Hsp60) member 1; IDH1, isocitrate dehydrogenase; IDH2, isocitrate dehydrogenase 2; IF1, inhibitory factor 1; IFN, type I interferon; IKK, IκB kinase; IMM, inner mitochondrial membrane; LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; LKB1, tumor suppressor liver kinase B1; MCT, monocarboxylate transporters; MDP, mitochondrial-derived peptides; MILS, maternally inherited Leigh syndrome; MitoMet, mitochondrial-targeted metformin; MitoTam, mitochondrial-targeted derivative of tamoxifen; MitoVES, mitochondria-targeted analog of vitamin E succinate; MOTS-c, mitochondrial open reading frame of the 12S rRNA-c; MPC, mitochondrial pyruvate carrier; MPP^+, 1-methyl-4-phenylpyridinium ion; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; MT-ND1, mitochondrially encoded NADH dehydrogenase 1; MT-ND5, mitochondrially encoded NADH dehydrogenase 5; MT-ND6, mitochondrially encoded NADH dehydrogenase 6; NADH, nicotinamide adenine dinucleotide, reduced form; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form; NDI, analog of complex I; nDNA, nuclear DNA; NFE2L2, nuclear factor, erythroid 2 like 2; NF-kB, nuclear factor kappa B; NOTCH1, Notch 1 receptor; NRF1, nuclear respiratory factor 1; NRF2, nuclear respiratory factor 2; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase enzyme; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructokinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PHD, prolyl hydroxylase; PKM2, pyruvate kinase isozymes M2; POLB, DNA polymerase beta; POLG, DNA polymerase gamma; PSTMB, 1-(phenylseleno)-4-(trifluoromethyl) benzene; PTEN, phosphatase and tensin homolog; RISP, Rieske iron-sulfur protein; ROS, reactive oxygen species; SCO2, mitochondrial synthesis of cytochrome *c* oxidase 2; SDH, succinate dehydrogenase; SHLP2, small humanin-like peptide 2; SHLPs 1–6, small humanin-like peptides; SLC1A3, glutamate-aspartate transporter; sORF, short open reading frame; TALENs, transcription activator-like effector nucleases; T-ALL, acute lymphoblastic T-cell leukemia; TCA, tricarboxylic acid; TFAM, mitochondrial transcription factor A; TPP^+, triphenylphosphonium; Tregs, regulatory T cells; UbQ, ubiquinone; UQCRB, ubiquinol cytochrome *c* reductase binding protein; VDAC, voltage-dependent anion channel; ZFNs, zin-finger nucleases.

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https://doi.org/10.1016/j.bbadis.2020.166016
Received 1 September 2020; Received in revised form 12 November 2020; Accepted 15 November 2020
Available online 25 November 2020

1. Cancer metabolic transformations and mitochondria

1.1. Tumor cells metabolic reprogramming and the mitochondrial hub

1.1.1. Cancer metabolic rewiring

The metabolic changes that occur in cell malignant transformation are distinctive and, currently, recognized as a hallmark of carcinogenesis [1]. Otto Warburg first reported that cancer cells produce energy preferentially by glycolysis in detriment of oxidative phosphorylation (OXPHOS), even in the presence of oxygen [2,3]. This metabolic switch in cancer cells towards the "aerobic glycolysis", also known as "Warburg effect", increases glucose uptake, mediated *via* glucose transporters (GLUT), with pyruvate being oxidized to lactate. This phenomenon was initially thought to be a consequence of an irreversible OXPHOS impairment. The journey that allowed the conception of the first tumor-specific metabolic phenotype by Otto Warburg was recently revisited [4]. While it became widely accepted that glycolysis displays important role in carcinogenesis, mitochondria are increasingly acknowledged as key organelle and a crucial mediator in all steps, as those organelles interconnect multiple intracellular pathways [5,6]. In fact, those same pathways may be active simultaneously emphasizing the possible need to target both and the metabolic plasticity in cancer cells [7]. Below it is described the intersection of mitochondria in crucial metabolic pathways that are at the basis of plastic behavior of cancer cells, targets, and available drugs or drug candidates.

1.1.2. Lactate as a fuel source

One of the common features of cancer cells is that, even under normoxic conditions, they exhibited increased uptake of glucose and lactate accumulation. Cancer cells are traditionally thought to mostly rely on glycolysis. In tumor cells that rely on the "Warburg effect", glucose is converted to pyruvate, which is then reduced to lactate instead of being transported into mitochondria. This reaction is catalyzed by lactate dehydrogenase A (LDHA), which is stimulated by hypoxia inducible factor 1 (HIF-1) [8,9], with the regeneration of nicotinamide adenine dinucleotide, reduced form (NADH) to NAD^+ that is necessary to

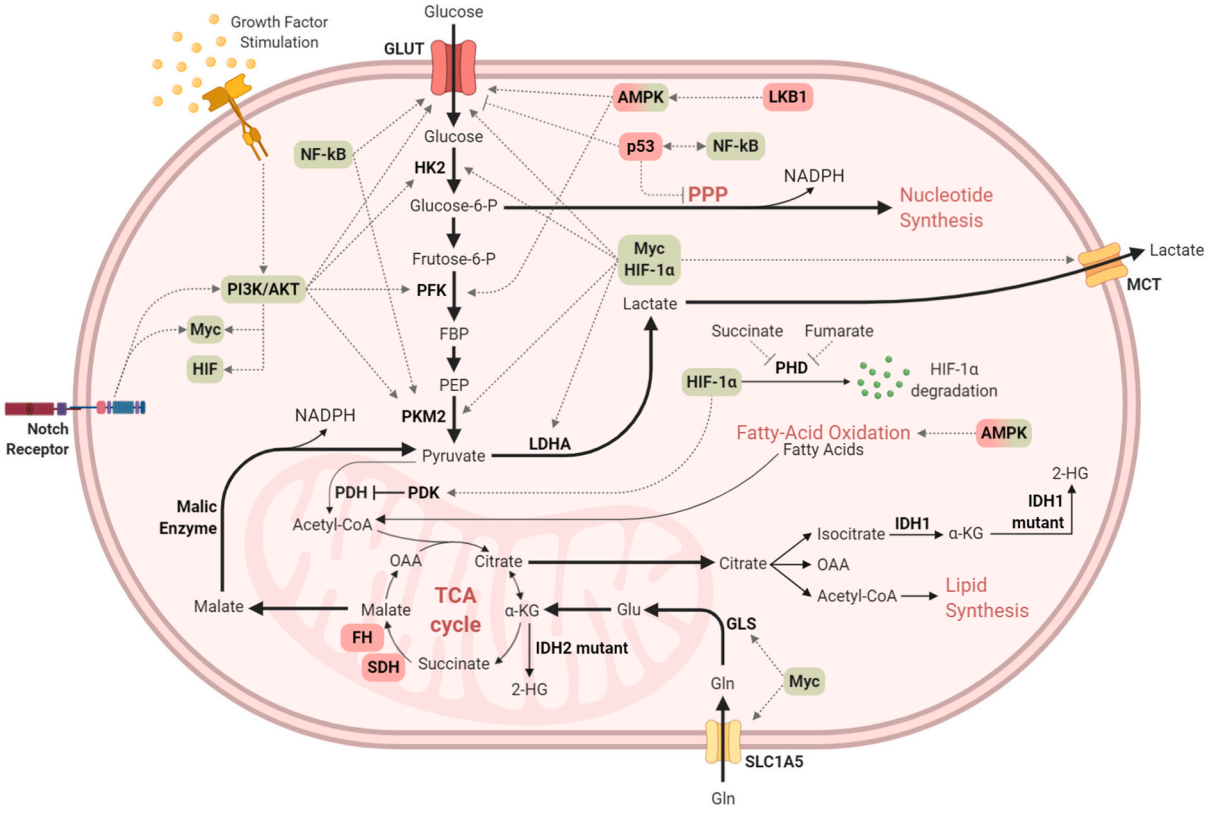

Fig. 1. Metabolic remodeling in cancer cells. The metabolic reprogramming in cancer cells is characterized by two major adjustments in energy metabolism: increased glycolysis and increased use of glutamine as an energy source. This metabolic shift occurs due to oncogenic changes in several signaling pathways. Growths factors lead to the activation of PI3K/AKT, which promotes the increased uptake of glucose through GLUTs, increased activity of key glycolytic enzymes, and induces the upregulation of HIF-1 and Myc transcription factors. Both HIF-1 and Myc promote an increase in the glycolytic pathway, in lactate production and MCT-mediated lactate extrusion, contributing to the microenvironment acidification. Myc also favors glutaminolysis to support NADPH production and lipid synthesis, and increases transcription of transporters such as SLC5A5. NF-kB favors glycolysis by interacting with transcription factors such as p53, being able to modulate each other, thus affecting cancer metabolism. p53 is a tumor suppressor that inhibits glycolysis, glucose uptake and PPP, and is usually silenced in cancer promoting uncontrolled proliferation of tumor cells. AMPK plays a dual role in carcinogenesis, being dependent on cellular context. After being activated by LKB1, AMPK can induce glycolysis and glucose uptake, or it can stimulate fatty acid oxidation and OXPHOS while inhibiting glycolysis. Notch pathway plays a dual role in cancer, and its hyperactivation can promote a metabolic shift towards a glycolytic phenotype through the activation of PI3/Akt signaling and Myc. Succinate and fumarate accumulation due to FH and SDH oncogenic mutations induces a pseudo-hypoxic response and leads to glycolytic enzymes activation, through inhibition of prolyl hydratase enzyme, which signals HIF-1α degradation. Furthermore, IDH mutations promote the accumulation of 2-HG, which leads to tumorigenesis. Oncogenes are represented in green and tumor suppressors in red. Abbreviations: AKT - serine/threonine-protein kinase; AMPK - AMP-activated protein kinase; FBP - fructose-1,6-bisphosphate; FH - fumarate hydratase; Gln - glutamine; GLS - glutaminase; Glu - glutamate; GLUT - glucose transporter; HIF - hypoxia-inducible factor; HK2 - Hexokinase 2; IDH - Isocitrate dehydrogenase; LDHA - lactate dehydrogenase A; LKB1 - tumor suppressor liver kinase B1; MCT - monocarboxylate transporter; NF-kB - nuclear factor kappa B; OAA - oxaloacetate; PDH - pyruvate dehydrogenase; PDK - pyruvate dehydrogenase kinase; PEP - phosphoenolpyruvate; PFK - phosphofructokinase; PHD - prolyl hydroxylase; PI3K - phosphoinositide 3-kinase; PKM2 - pyruvate kinase muscle 2; PPP - pentose phosphate pathway; SDH - succinate dehydrogenase; α-KG - alpha-ketoglutarate; 2-HG - D-2-hydroxyglutarate.

maintain a high glycolytic flux [10]. However, in cancer, restoration of NAD^+ pool is not the only advantage of pyruvate oxidation to lactate. This metabolite, together with the associated H^+ production, is secreted to the microenvironment *via* monocarboxylate transporters (MCT), resulting in decreased pH of the extracellular environment and to an increased concentration of lactate that can reach 10–30 mM [11,12]. This phenomenon contributes to oncogenesis by increasing the activity of pro-invasion factors and stimulating tumor cell invasion, immunosuppression, angiogenesis, and metastasis [13–15], ultimately leading to poor prognosis in some types of cancer [11,16,17].

It is currently known that some cancer cells have the ability to uptake lactate, using it for amino acid formation and as a fuel for oxidative mitochondrial metabolism [18,19]. Taking into account the heterogeneity present within and between tumors [20], it was proposed that glycolytic cells work in symbiosis with oxidative cells, with the former exporting lactate to the extracellular microenvironment and the latter ones importing it [21]. Tumor cells do so by taking advantage of the lactate shuttle with the upregulation of MCT transporters expression, being MCT1 and MCT4 the isoforms most widely expressed in tumor cells. Although both isoforms are bidirectional proton-linked transporters, in cancer, MCT4 is predominantly responsible for lactate export, and MCT1 for its import [19,22] (Fig. 1). The heterogeneity found in solid tumors is regulated by the conditions of the microenvironment such as the concentration of oxygen, being the regions near blood vessels better oxygenated, and the ones in the center more hypoxic [20]. In breast cancer, the increased uptake of lactate only occurs in regions of the tumor where oxygen is present [23]. Furthermore, the expression of GLUT1 and MCT4 is upregulated in cells exposed to hypoxia, in a hypoxia inducible factor 1 subunit alpha (HIF-1α) dependent manner [24,25], whereas a higher expression of MCT1 was found in oxygenated cancer cells [22]. Interestingly, MCT2 was shown to be primarily expressed in the cytosol of various cancer cells, suggesting that it might be localized within organelles, such as mitochondria [26–28]. As MCT2 has also high affinity for pyruvate, this may allow mitochondrial uptake of pyruvate, thus providing more substrate for oxidative phosphorylation [27].

Upon lactate uptake, oxidative cancer cells convert lactate into pyruvate by lactate dehydrogenase B (LDHB), also originating NADH as a byproduct [19,22]. Chen et al. demonstrated that in H460 cells, LDHB has higher activity in isolated mitochondrial lysates comparing with whole-cell lysates, suggesting that its activity could be more concentrated in mitochondria. The same study also suggested that pyruvate re-oxidation leads to the formation of Acetyl-CoA, being a source of carbons for lipid biosynthesis during proliferation [29]. Several studies support that circulating lactate contributes to the generation of tricarboxylic acid (TCA) cycle intermediaries in cancer [19,30], as described by Faubert et al. in human lung cancer [19]. Thus, pyruvate is used by the TCA cycle, while NADH by the electron transport chain (ETC) in mitochondria and, consequently, leads to ATP production through OXPHOS. It is important to mention that this is not a static process, meaning that even the same cell, under different conditions, remodel its own metabolism to fulfill the needs for energy and biosynthetic precursors. In fact, new evidence highlights this, as only a double knockout of LDHA/B genes abrogates lactate production in persistent cells rewiring their metabolism to OXPHOS to escape death, and only partially abolishing tumor growth, thus becoming extremely sensitive to the mitochondrial Complex I inhibitor phenformin [31].

The tumor microenvironment is constituted by a variety of cells such as malignant cancer cells, cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, and non-cancer stroma cells [12]. It is also believed that there is a cross-talk between cancer cells and stromal cells, a process known as the "reverse Warburg effect" [32]. CAFs are recruited by cancer cells through reactive oxygen species (ROS) production to the surrounding area, which ultimately leads to changes in their metabolic behavior [33]. There is some evidence that, in some cancers, aerobic glycolysis occurs in CAFs, exporting lactate to the microenvironment, which is then accumulated by oxidative cancer cells. Accordingly, it was observed that the expression of MCT4 is upregulated in CAFs of breast [34], head and neck [35], and lung [19] cancers, among other glycolytic markers such as LDH and pyruvate kinase isozymes M2 (PKM2) [36]. Because of that, CAFs have been associated with metastasis, as well as to tumor progression and invasion [12,37].

Although lactate was initially considered a waste product of glycolysis, the accumulated evidences described above emphasize lactate as a crucial regulator of cancer development, maintenance, and metastasis [19,38–40], being an important energy fuel and an active signaling molecule [41].

1.1.3. Glutaminolysis and amino acid metabolism

Besides having an increased glucose consumption, another metabolic feature of cancer cells is an upregulation of glutamine uptake and metabolism [42]. Glutamine is the most abundant amino acid in human blood, and most cancer cells utilize it at much higher rates than other amino acids, despite being a non-essential amino acid [43]. This dependence was shown by inducing glutamine deprivation, which results in growth arrest and cell death [44–46].

Glutamine can be used as a precursor for the synthesis of amino acids, nucleotides, proteins, and lipids, which are needed to cell growth and proliferation [47,48]. Once internalized by the cell, glutamine is deaminated by glutaminase (GLS) to glutamate and ammonia (Fig. 1). Glutamate is then converted in α-ketoglutarate, an anaplerotic substrate which replenishes TCA cycle intermediates [49,50] in mitochondria, a process known as glutaminolysis. Furthermore, the upregulation of glutaminolysis also leads to an increase of glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH), key molecules for redox balance maintenance and biosynthetic pathways, in the case of the latter [47,51]. It was recently described that hypoxia induces GLS1 expression in colorectal cancer cells, which in turn is associated with a poor prognosis, and with an increased risk of metastasis [52].

Ippolito et al. demonstrated that docetaxel-resistant PC3-DR prostate cancer cells, present an increased uptake of glutamine and exhibited a higher rate of OXPHOS. So, data suggest that these cells remodel their metabolism towards a more oxidative phenotype in order to survive to docetaxel treatment [53]. Moreover, Ko et al. proposed a metabolic coupling between endothelial cells and tumor stroma, in which CAFs goes through an apoptotic program and release glutamine to the microenvironment which, in turn, is up taken by tumor cells. When CAFs and tumor cells were co-cultured, glutamine induced an increase in mitochondrial mass of MCF-7 cells, while having the opposite effect on the fibroblasts [54].

Glutamate plays an important role in the biosynthesis of alanine, aspartate, proline and serine, which are then used for arginine, asparagine, cysteine and glycine synthesis. It was recently described that the inhibition of glutamate dehydrogenase 1 (GLUD1), a mitochondrial enzyme responsible for glutamate metabolism, promotes an imbalance on redox homeostasis [51], and also leads to the attenuation of cancer cell proliferation and tumor growth [51,55]. Interestingly, Spinelli et al. showed in breast cancer cells that GLUD1 can operate reversibly by assimilating ammonia to generate amino acids [56]. This work reveals that, although ammonia is potentially toxic in cells, it can support tumor biomass in certain cancers by being an important nitrogen source. Furthermore, urea cycle, the pathway that converts ammonia into urea to be excreted from de body, was observed to be suppressed in several tumors [57]. It is described that argininosuccinate synthetase 1 (ASS1) and argininosuccinate lyase (ASL), urea cycle genes, are silenced in some tumors [58,59], which ultimately leads to nitrogen diversion into aspartate for nucleotide biosynthesis. However, this causes a vulnerability in cancer cells, since the suppression of this metabolic pathway prevent the synthesis of arginine [60], an amino acid that is a component of the urea cycle. Arginine is involved in the biosynthesis of proteins, nucleotides, glutamate, among others, being critical for the tumor growth. Thus, these cells are dependent on arginine uptake from

circulation, being sensitive to its depletion [61,62]. This particularity has been tested in clinical trials as a therapeutic approach in some cancers [63,64].

Several other amino acids have been pointed out as important players in tumor growth and proliferation. For instance, serine participate in purine and lipid biosynthesis [65,66], mitochondrial protein translation [67], among others [68]. Moreover, serine metabolism to glycine is important for one-carbon metabolism, being this process important to sustain the high proliferative rate of tumor cells [69,70]. Aspartate, which is generated from glutamate-derived nitrogen and oxaloacetate by the mitochondrial glutamic-oxaloacetic transaminase 2 (GOT2), is known to be involved in providing electrons between mitochondria and the cytosol *via* malate–aspartate shuttle. Comparing to other amino acids, aspartate concentration in plasma is one of the lowest. Thus, it is believed that aspartate biosynthesis is the most relevant source of this amino acid, since it is described that, in proliferating cells, aspartate is inefficiently transported [71]. It was recently described a connection between aspartate biosynthesis and the ETC, suggesting that providing electrons acceptors for aspartate biosynthesis is an essential role of ETC in proliferative cells [71,72]. Indeed, aspartate levels are found diminished in ETC-inhibition-sensitive cancer cell lines [73]. In pancreatic cancer cells, GOT2 support most of aspartate production even under hypoxic conditions, while mitochondria maintain respiratory activity [74], suggesting that mitochondrial activity is essential for the proliferation of this cancer type, independently of oxygen availability. In opposition, aspartate production is suppressed by HIF-1 by repressing cytosolic mitochondrial glutamic-oxaloacetic transaminase and GOT2, at least in clear cell renal cell carcinoma [75].

Although a subset of cancer cells show resistance to ETC-inhibitors with dependency on aspartate import and enhanced expression of the SLC1A3 glutamate-aspartate transporter [73,76], the use of SLC1A3 inhibitors restored cells sensitivity to ETC inhibitors [73]. Aspartate is important for purine and pyrimidine nucleotides synthesis, and inhibition of aspartate biosynthesis in breast and pancreatic cancer cells was shown to inhibit tumor growth [77,78]. Cellular redox status of pancreatic cancer cells is also regulated by aspartate following its conversion to oxaloacetate, malate and finally to pyruvate enables the increase of NADPH/$NADP^+$ ratio and GSH levels [78].

Based on these observations, glutamine metabolism can be considered as a second metabolic shift in tumor cells [79], supporting the complexity and heterogeneity that exists between and within a tumor. As in other cases, mitochondria appear as a central hub involved in the remodeling of amino acid metabolism.

1.1.4. Metabolic reprogramming activation

During the last decades, it has been demonstrated that the Warburg effect is more closely related to alterations in signaling pathways than to mitochondrial defects. The metabolic shift that occurs in cancer has been explained by some molecular mechanisms involving the HIF-1 pathway, oncogenes (MYC, AKT, RAS and NF-kB), and tumor suppressor genes (p53, AMPK, succinate dehydrogenase and fumarate hydratase) [80].

The PI3K/AKT pathway is one of the most commonly activated oncogenic signaling pathways in tumors, having a central role in regulating cell proliferation and survival, cancer cell invasion [81], and also cancer metabolism [82]. The best-known effector downstream of PI3K is serine–threonine kinase (AKT), which has been shown to be sufficient to stimulate glycolysis [82]. AKT activation facilitates the uptake of glucose by up-regulation and/or by membrane translocation of GLUT1 and GLUT4, which are the primary glucose transporters [83–85]. The upregulation of AKT signaling is also known to promote the activity of key glycolytic enzymes by phosphorylation, such as hexokinase and phosphofructokinase (PFK) (Fig. 1) [86,87]. Hexokinase 2 (HK2) phosphorylation by AKT increases its association to the voltage-dependent anion channel (VDAC), which increases the efficiency and speed of glycolysis [88]. Moreover, HK2-VDAC association promotes the maintenance of the closed state of the mitochondrial permeability transition pore (mPTP), preventing cytochrome *c* release and protecting cells from apoptosis [89,90]. In addition, AKT was demonstrated to be present in the mitochondria, being detected within the outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM) and also in the mitochondrial matrix [91]. It participates in mitochondrial bioenergetics regulation and accumulates in mitochondria in a membrane potential-dependent manner [92]. Moreover, Pelicano et al. suggested that mitochondrial respiration defects lead to the activation of the AKT signaling pathway. In this study, the authors observed that NADH levels increased upon mitochondrial respiration depletion, leading to the inactivation of the phosphatase and tensin homolog (PTEN), a tumor suppressor, by a redox modulation which, in turn, causes AKT activation [93]. AKT also promotes the upregulation of HIF-1 and Myc [79].

HIF-1 is a transcription factor that is induced under hypoxic conditions, and regulates many cellular responses and processes such as cell proliferation, angiogenesis, energy production, inflammation, among others [94,95]. HIF-1 induces glycolysis, together with downregulation of OXPHOS by slowing-down the pyruvate conversion in acetyl-CoA. This happens because HIF-1 promotes the transcription of glycolytic enzymes such as hexokinase 1 (HK1) and HK2; glucose transporters (GLUT1 and GLUT3) [96,97] which induce an increase in glucose uptake; and also LDHA and lactate transporters, promoting the production and extrusion of lactate and contributing to the microenvironment acidification (Fig. 1). Moreover, HIF-1 also induces the increase of pyruvate dehydrogenase kinase (PDK) levels, which inhibits pyruvate dehydrogenase enzyme (PDH), ultimately leading to the diversion of pyruvate from mitochondria [98]. HIF-1α is sensitive to oxygen, being rapidly degraded in normoxic conditions, and stabilized in hypoxic conditions. However, in human cancers, its levels are upregulated even when sufficient levels of oxygen are present [99], a term called “pseudohypoxia” [94]. This further might explain the Warburg effect, where glycolysis is upregulated even in the presence of oxygen.

Myc, an oncogene that is frequently induced in many human cancers [100], is also strongly involved in the regulation of cell metabolism by inducing the transcription of genes such as GLUT1, HK2, LDHA, and MCTs. Furthermore, it also increases the expression of glutaminase [101] and glutamine transporters [102], favoring glutaminolysis to support NADPH production and lipid synthesis. It is also described that Myc plays a role in inducing mitochondrial biogenesis and function, which ultimately leads to increased respiration and ATP production. Myc stimulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [103] and mitochondrial transcription factor A (TFAM) [104] and, moreover, Graves et al. showed that fibroblast lacking *myc* presented smaller and fewer mitochondria, with a poorly interconnected network [105]. Myc stimulates both metabolic pathways, and this could be important for cell adaptation to different tumor microenvironments, since it is also described that Myc can work in cooperation with HIF-1 in increasing glycolysis under hypoxic conditions [106].

The oncogene nuclear factor kappa B (NF-kB) also plays a role in the metabolic remodeling of cancer cells, stimulating the transcription of genes related with glycolysis. Reports have showed that this occurs by a cross talking with transcription factors such as HIF-1 and p53 [107,108]. Indeed, p53 suppression leads to NF-κB activity enhancement, by utilizing members of the IκB kinase (IKK), and consequently glycolysis stimulation and GLUT3 upregulation. Moreover, NF-κB was shown to be essential for oncogene-induced cell transformation [109]. Other reports also suggest that the classical NF-kB pathway induces the upregulating of glycolytic genes and PKM2, with HIF-1 being required for RelA binding to PKM2 promoter [110]. Furthermore, in lymphoma, NF-kB was shown to promote GLUT1 translocation to the plasma membrane [111]. Moreover, NF-kB also regulates mitochondrial respiration critically dependent on p53 status. As such, Johnson et al. in both $p53^{-/-}$ mouse embryo fibroblasts and p53-null human non–small-cell lung

carcinoma H1299 cells showed that oxygen consumption and ATP levels were compromised after NF-κB member RelA translocation into the mitochondria. Mechanistically, is thought that the interaction with mitochondrial transcription factors repressed mitochondrial genes as cytochrome *c* and cytochrome *b* oxidase III [108]. Oppositely, Mauro et al. reported on a glucose starvation model that NF-kB can increase p53 which activates OXPHOS through upregulation of mitochondrial synthesis of cytochrome *c* oxidase 2 (SCO2), a subunit of the mitochondrial cytochrome C oxidase (COX) complex and suppress glycolysis, whereas RelA loss reverses OXPHOS activity and enhanced glucose transporters GLUT1, 3 and 4. A synergistic effect was observed in tumor growth upon RelA loss and metformin treatment [112]. Thus, is NF-kB and p53 modulate each other on a context basis [107,113], which has implications to tumor cell metabolism.

Tumor suppressor genes code for proteins that normally operate to restrict cellular growth and division, repair DNA errors and promote programmed cell death (apoptosis). They are usually silenced in cancer, which stimulates cells to grow in an uncontrolled way. For instance, p53 plays an important role as a defense mechanism against tumor development, being involved in the regulation of apoptosis, DNA repair mechanisms, among others [114]. It is also involved in metabolic stress response, promoting OXPHOS and inhibiting glycolysis in normal conditions. However, in cancer, the phenotype may vary depending on mutation and tissue type, since different p53 mutants were shown to have different metabolic behaviors [115]. p53 is involved in the inhibition of GLUT1 and GLUT2 transcription, and is also responsible for the upregulation of TIGAR, an apoptosis regulator that decreases the levels of fructose-2,6-bisphosphate [80,116]. Moreover, in response to stress, p53 translocates to mitochondria, where it displaces inhibitors of pro-apoptotic channel-forming proteins [117]. Another tumor suppressor gene that also has an important role in metabolic remodeling is AMP-activated protein kinase (AMPK). AMPK is activated under stress conditions, such as nutrient deprivation and hypoxia, and functions as a cellular sensor of AMP. AMPK promotes OXPHOS and inhibits proliferation when the ratio of AMP/ATP is high [118,119]. AMPK activation mainly occurs through phosphorylation at Thr172, through the tumor suppressor liver kinase B1 (LKB1) [120,121], although it can also be phosphorylated at other sites by other kinases. AMPK plays a dual role in carcinogenesis, as a large number of studies support the idea that AMPK plays an inhibitory role in the growth of cancer, and many other reports suggest a tumor-promoting effect [122–124]. Under stress conditions and with the objective of restoring the cellular energy balance, AMPK goes through biological changes such as suppressing mTORC1 signaling and inducing fatty acid oxidation (FAO) [118]. mTOR suppression supports cell survival in stress conditions, since this pathway is critical for autophagy inhibition and protein synthesis stimulation [125]. AMPK activation can also lead to increased uptake of glucose, since it was found that it can promote GLUT4 translocation to the plasma membrane [126]. Jiang et al. reported that AMPKα is localized and interacts with mitochondria exerting a stimulatory effect of OXPHOS and FAO oxidation while it inhibits glycolysis. This leads to the arrest of cancer growth *in vitro* as *in vivo*, underscoring a suppressor function of mitochondrial AMPKα [124]. Previous work from Faubert et al. also suggested the antitumorigenic role of AMPK in lymphoma through a HIF-1α-mediated glycolysis inhibition process [127]. In acute lymphoblastic T-cell leukemia (T-ALL), it was previously demonstrated that these cells depend less on glycolysis that normal T-cells. Due to Notch signaling, AMPK was more active, restricted mTOR pathway and compromised glycolysis while promoting mitochondrial oxidative metabolism by upregulation of complex I expression, to sustain T-ALL cells survival [128]. Therefore, AMPK persistent activation can support tumor survival by regulation of cells bioenergetics [128–130] through reprogramming energy metabolism. Thus, these data indicate that AMPK pro- or anti-tumoral activity is very dependent of cellular context. Accordingly, a recent study suggest that dormant ER^+ breast cancer cells possess upregulated AMPK levels and treatment with the anti-diabetes drug metformin also drives AMPK induction and fatty acid oxidation, rendering cells survival advantages [131]. AMPK influences mitochondrial homeostasis, since it also plays a role in mitochondrial dynamics by inducing fission, and in mitochondrial turnover by recycling of damaged mitochondria [132,133]. Moreover, it also promotes mitochondrial biogenesis through interaction with PGC-1α and nuclear respiratory factor 1 and 2 (NRF1 and NRF2), important transcription factors that control respiratory chain complexes encoding genes [134,135]. In prostate cancer, AMPK increased PGC-1α, OXPHOS activity, as well as glycolysis upon androgen treatment [136]. It was recently described that ROS are a physiological activator of AMPK and, in turn, AMPK activation promotes a decrease in ROS levels by inducing a PGC-1α-dependent antioxidant response [137].

The Notch pathway plays a dual role in cancer with studies reporting oncogenic or tumor suppressor function [138]. Studies in T-ALL revealed that approximately 60% of patients present an aberrant expression of NOTCH1, and gain-of-function mutations are commonly found [139]. Furthermore, a gene expression analysis revealed that Notch 1 receptor (NOTCH1) induces leukemic cell growth by regulating directly the transcription of anabolic genes involved in a variety of processes, such as nucleotide and amino acid metabolism [140]. Reports suggest that NOTCH1 promotes glycolysis mediated by Myc and AMPK activation [139,141]. Notch signaling deregulation is also found in solid tumors, but is highly dependent on the contexts, and on other signaling pathways. Thus, Notch can promote or suppress tumorigenesis in a cancer stage- or type-dependent manner [138]. A study in MCF-7 cells, a breast cancer cell line, revealed that hyperactivation of Notch induces a metabolic shift towards a glycolytic phenotype through the activation of PI3/Akt signaling [142]. Besides this Notch effect on cell metabolism, a non-canonical Notch signaling activation of AKT by a recombinant ligand Jagged 1 in triple negative breast cancer cell lines was recently reported. Moreover, Jagged 1 increased mitochondrial respiration, while Notch is reported to co-localize in the mitochondria [143]. Thus, these data convey the idea that the Notch pathway may also modulate tumors metabolic adaptation and mitochondrial function.

Mutations that interfere with oncogenes and/or tumor suppressor genes and their signaling pathways promote alterations in cell metabolism, and it is known that cancer cells accumulate them to remove environmental constraints. The above data suggest that glycolysis and OXPHOS in tumors are not mutually exclusive, and both are needed for cell growth and maintenance.

1.1.5. Tricarboxylic acid cycle enzymes and mitochondrial respiratory chain complexes

Succinate dehydrogenase (SDH) and fumarate hydratase (FH) are enzymes involved in the TCA cycle, being responsible for the conversion of succinate to fumarate and fumarate to malate, respectively. SDH is also a functional member (Complex II) of the ETC [144]. Several studies identified them both as tumor suppressors, and oncogenic mutations lead to the accumulation of their substrates [144,145]. The increase in the levels of succinate and fumarate induces a pseudo-hypoxic response and leads to glycolytic enzymes activation, through inhibition of prolyl hydratase enzyme, which signals HIF-1α degradation [79]. In SDH-deficient renal cell carcinoma tumors, the loss of SDH induces the inhibition of the TCA cycle, promoting the generation of lactate from pyruvate in high amounts. Furthermore, their mitochondria present fewer cristae when compared to mitochondria from normal kidney tissue, where SDHB was present [146].

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2), responsible for converting isocitrate to α-ketoglutarate *via* oxidative decarboxylation, and are also known to be mutated in several cancers [147–149]. IDH1 is localized in the cytosol and peroxisomes, while IDH2 is mitochondrial. It is believed that the mutations cause a neomorphic enzyme activity [150], and result in the conversion of α-ketoglutarate into D-2-hydroxyglutarate (2-HG) using NADPH as co-factor [150,151]. The accumulation of 2-HG inhibits α-ketoglutarate-dependent dioxygenases,

proteins that are involved in the regulation of cellular epigenetic status and differentiation [152]. Thus, alterations promoted by IDH1 and IDH2 mutations may lead to tumorigenesis by altering the epigenetic patterns and the fates of progenitor or stem cells [150].

Changes in the complexes of mitochondrial electron transport chain are also identified in cancer. Complex I is the main entry point of electrons in the ETC and plays an important role in generating and maintaining the mitochondrial membrane potential, which support the synthesis of ATP. Moreover, Complex I also plays a role in maintaining the cellular NAD^+ pool and the ratio of NAD^+/NADH, which in turn is important for the synthesis of some precursors, such as aspartate (see Section 1.1.3) [153], and for the induction of adaptative mechanisms to hypoxia through HIF-1α (Warburg effect). Upon the inhibition of Complex I, decreased α-ketoglutarate dehydrogenase activity occurs because of NADH accumulation, promoting the increase of α-ketoglutarate/succinate ratio. Thus, as α-ketoglutarate acts as a substrate of prolyl-hydroxylases, that are responsible for HIF-1α degradation, it promotes arrest of tumor growth [154,155]. However, there are mutations in mitochondrial DNA (mtDNA) that induce OXPHOS defects that actually have a pro-tumorigenic effect [156]. For instance, heteroplasmic mitochondrial-encoded NADH dehydrogenase 5 (MT-ND5) mutation induces the activation of PI3K/Akt pathway and increase resistance to apoptosis; and mitochondrial-encoded NADH dehydrogenase 6 (MT-ND6) mutations promote the formation of ROS, Complex I deficient activity and increased metastatic potential [157]. The controversial behavior of Complex I in cancer has been explained as being dependent on the severity and type of the OXPHOS disfunction. Porcelli et al. suggested that a complete inhibition of Complex I is necessary to have an antitumorigenic effect, while a mildly dysfunction in its activity (caused by mtDNA mutations) allows the formation of tumors in the same rate that cancer cells with normal mtDNA [158,159].

As explained previously in this section, Complex II represents a connection point between TCA cycle and the ETC. Although it does not directly contribute to proton gradients across the mitochondrial membrane, it transfers electrons from succinate to ubiquinone (UbQ), which is then reduced to ubiquinol and reduces Complex III and IV [160]. Complex II mutations have been found to result in increased ROS production, not only directly but also indirectly *via* reverse electron transfer through Complex I [161,162]. In turn, the increased ROS formation results in genomic instability and metabolic stress, promoting tumorigenesis [163,164]. Several reports found mutations in Complex II in various types of cancer, including pheochromocytoma, paraganglioma, gastrointestinal stromal tumors, and renal tumors [165,166].

Complex III activity is also altered in some cancers, such as ovarian and breast cancer [167,168]. Complex III is a source of ROS, producing superoxide in the mitochondrial intermembrane space and believed to be involved in promoting the proliferation and survival of cancer cells. During hypoxia, superoxide anion produced by Complex III plays a role in stabilizing HIF-1α independently of OXPHOS activity by inhibiting the activity of prolyl hydroxylase (PHD) [169–171]. In breast cancer, it has been shown that its activity was decreased in metastatic and aggressive cancer cell lines, which is associated with an up-regulation of Rieske iron-sulfur protein (RISP), a vital part of electron transfer through Complex III. Owens et al. showed that a reduction in the invasion capacity and alterations of mitochondrial function in MCF-7 (breast cancer) and 143B (osteosarcoma) cell lines were observed when RISP was silenced [168]. Furthermore, Bhattacharya et al. demonstrated that inhibiting Complex III in glioblastoma multiforme cells results in generation of oxidative stress accompanied by DNA damage and cell cycle arrest [172].

Alterations and/or mutations in the expression of Complex IV subunits were also found in some types of cancers. It was described that inhibiting Complex IV decreases cell proliferation in glioma and glioblastoma [173]. However, mutations that lead to loss or decreased Complex IV activity were found in colorectal and esophageal cancers, ultimately promoting an upregulation of glycolysis and stimulating invasion [174,175].

Complex V catalytic subunit relative expression is described as downregulated in some cancers compared to the corresponding normal tissue [176,177], which is accompanied by an upregulation of the inhibitory factor 1 (IF1) levels, a protein that regulates the activity of Complex V [178]. Inhibition of Complex V by IF1 leads to a metabolic remodeling towards a more glycolytic phenotype, promotes a mitochondrial hyperpolarization and increases superoxide production, which ultimately leads to an increased cell survival through HIF-1α stabilization [179]. Interestingly, high levels of IF1 have been associated with poor prognosis in lung [180] and stomach [181] cancers, among others [182], but not in breast cancer. In this particular case, it promotes a decrease in cell migration and invasion, being considered a biomarker of good prognosis [183].

The above data highlight how defects or even subtle changes in the mitochondria inherently related members, can lead to mitochondrial abnormal function, predisposing tumor cells to a different bioenergetic signature or redox state. These adaptations can act as a potential pro- or anti-tumor drivers. Thus, one must consider mitochondria role in the specific tumoral cellular context and specific alteration to its normal function, to predict the potential transformations. However, functional ETC supports the OXPHOS activity, which is essential for tumor development. Inhibitors that target ECT directly disrupting mitochondrial respiratory, is an invaluable strategy to kill cancer cells and detailed in Section 2.1.1.

1.2. Mitochondrial DNA and cancer

1.2.1. The mitochondrial genome: mtDNA

Mitochondria contain their own genome, which is maternally inherited. Upon fertilization, paternal mitochondria and mtDNA are eliminated by LC3-dependent autophagy [184]. Interestingly, a recent paper has shown biparental mtDNA transmission in humans. Although this phenomenon is valid in exceptional cases, it could lead to new insights in the mitochondrial field [185]. Mammalian mtDNA is a circular double-stranded DNA rich in CpG motifs and regulated on the level of transcription, translation and protein synthesis. It contains no introns and encodes for 22 tRNAs, 2 rRNAs and 13 subunits of the ETC complexes I, III, IV and V (Fig. 2). Each mtDNA molecule possesses a heavy and a light strand, which are guanine-rich or -poor, respectively. While approximately 93% of the genome represents coding regions, mtDNA contains a non-coding regulatory region, the displacement loop (D-loop) [186]. Each cell contains thousands of copies of mtDNA, an excess of copies relative to the nuclear chromosomes [187]. Unlike nuclear DNA (nDNA), mtDNA molecules are packaged into histone-free nucleoprotein structures called nucleoids, an organizational unit containing a single copy of mtDNA compacted by the mitochondrial TFAM. When nucleoids are highly compacted, mtDNA replication and transcription is inhibited. More elongated nucleoids are associated with ongoing replication and transcription processes [188]. Mitochondrial DNA replication and transcription are orchestrated by nuclear-encoded proteins, probably transferred *en bloc* from mtDNA to nDNA during evolution. In addition to mtDNA compaction function, TFAM is a transcription-initiation factor and regulates mtDNA transcription [189]. TFAM mtDNA binding and transcription is influenced by the CpG sequences in the promoters [190].

Among the 90 proteins present in the respiratory chain of mammals, only 13 are encoded by mtDNA. Additionally, in the past two decades, analysis of the mitochondrial transcriptome demonstrated the presence of small mRNAs, which encode active mitochondrial-derived peptides (MDP). The first peptide identified as encoded by a short open reading frame (sORF) in mtDNA was Humanin [191]. More recently, mitochondrial open reading frame of the 12S rRNA-c (MOTS-c) and small humanin-like peptides (SHLPs 1–6) were also identified as MDPs. Identification of novel short open reading frames in mtDNA indicates a greater mitochondrial genetic repertoire [192,193]. MDPs have been detected in multiple tissue and plasma, and affect mitochondrial

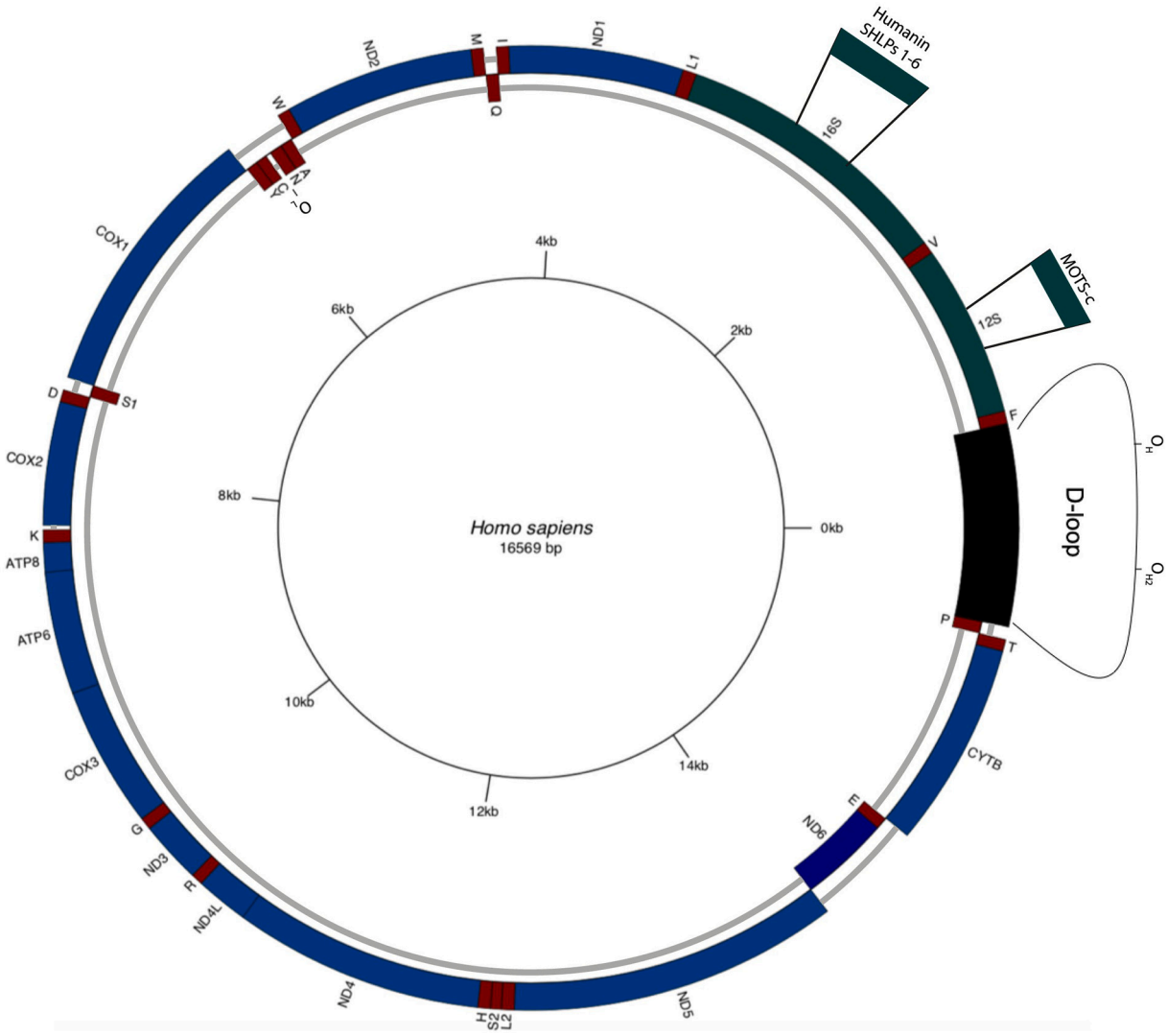

Fig. 2. Human mtDNA map.
Human mtDNA (16.6 kb) showing location of genes. Protein coding genes (blue), ribosomal RNA genes (green) and transfer RNA genes (red). The D-loop regulatory region (black) contains two origins of H-strand replication (OH and OH2), whereas the origin of L-strand replication (OL) is displaced by approximately two thirds of the genome. Mitochondrial-derived peptides (MDP) are encoded in 16S (Humanin and SHLPs 1–6) and 12S (MOTS-c). Image designed using "GenomeVX (Conant, G. C., and K. H. Wolfe. (2007) GenomeVx: simple web-based creation of editable circular chromosome maps, Bioinformatics, in press.) and FoswikiMITOMAP WebGenomeLoci."

bioenergetics and metabolism, playing an important role in aging and age-associated diseases [194]. MOTS-c, is a 16 amino acid peptide conserved in mammalian species. mtDNA-derived MOTS-c is found in different tissues, with the skeletal muscle and fat tissues being its main organ targets. It is also found in the circulation, acting as a systemic hormone. MOTS-c, mediating 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) levels and AMPK activation, increases glycolysis and fatty acid oxidation and decreases mitochondrial respiration. Moreover, MOTS-c treatment prevents insulin resistance in obese mice [193]. Because of the dual genetic origin of respiratory complexes, except for Complex II, a coordination between both genomes is critical to avoid an imbalance. Mitochondria host >1000 nuclear-encoded proteins that regulate their function, as well as mtDNA replication and transcription.

Some of the main regulators of mitochondrial genes expression and function include TFAM, PGC-1, sirtuins, AMPK and mTOR [195–197]. Moreover, due to the crucial role of mitochondria in cellular homeostasis, mechanisms to recognize and respond to mitochondrial stress are also important. Those mechanisms usually rely on retrograde responses, signals emitted by mitochondria and targeting the nucleus to impact gene transcription. Retrograde signaling is carried out by secondary mitochondrial metabolites, transient molecules and damage-associated molecular patterns (DAMPS), such as Ca^{2+}, ROS and Cyt c [198]. However, mtDNA-encoded proteins have never been implicated in mitochondria-nucleus communication until recently. MOTS-c was recognized as a retrograde signaling peptide, which binds to transcription factors in the nucleus, regulating nuclear gene expression. MOTS-c translocates to the nucleus in response to cellular stress and in an AMPK-dependent manner. Within the nucleus, MOTS-c interacts with several transcription factors and modulates nuclear factor, erythroid 2 like 2 (NFE2L2)-target genes. Thus, both genomes regulate each other in a mutual manner [199].

Considering the proximity to ETC, a well-known producer of ROS, the mtDNA is more prone to damage and mutations compared to nDNA. However, mechanisms of mtDNA repair are rather limited in scope. Base excision repair (BER) is the mechanism responsible for oxidative lesions repair and is managed by DNA polymerase gamma (POLG), a key protein involved in mtDNA replication. Other nuclear polymerases have shown supportive role to POLG during the repair of DNA damage. REV3 DNA

polymerase zeta subunit has also been found in mitochondria of tissues and cell lines, and has shown protective effects again UV exposure damage [200]. Complementary to POLG, DNA polymerase beta (POLB), participates in the repair of mtDNA. This nuclear enzyme was detected in mitochondria, and its absence results in lower BER capacity and increased mtDNA damage [201]. The accumulation of damage and mutations of mtDNA has severe consequences for mitochondrial and cellular function, and they give rise to several pathologies including neurodegenerative and cancer.

1.2.2. Mitochondrial DNA and cancer

The number of mtDNA copies per cell varies based on different tissues and on other physiological factors, such as age; it has been found altered in several diseases, including cancer. Large number of mtDNA copies per cell, ranging from 100 to 100,000, its inefficient repair, the oxidative microenvironment and fast replication can increase the rate of mtDNA mutations. It was estimated that 1 in 200 people are carriers of mtDNA alterations, however not all mutations are linked to deleterious phenotypes and pathologies. Thus, mutations in mtDNA lead to phenotypically silent as well as to severe familial diseases. Additionally, alterations in mitochondrial proteins encoded by nDNA also contribute to mitochondrial diseases [202]. The appearance of diseases is conditioned by the level of heteroplasmy, a polyploid state, with a variable proportion of wild-type and mutant mtDNA in a population. Different levels of point mutations are associated with different pathological phenotypes. For a specific mutation in leucine tRNA, the harboring percentage of 3243A>G mutation could lead to different outcomes, from diabetes to perinatal lethality, and it is connected with mitochondrial bioenergetics and structural changes [203].

mtDNA mutations are transversally found in all types of cancer, although its contribution is not totally clear. Somatic non-synonymous mutations are likely to have a higher functional impact [204]. Mutations in mtDNA could appear in coding regions of ETC subunits, promoting destabilization of the OXPHOS system, but also in tRNAs and rRNAs, required for the translation process and consequently for the assembly of individual complexes. Among the encoding regions, Complex I-related genes appeared as the most affected [159,204]. Interestingly, MT-ND5 heteroplasmic frame-shift mutations are associated with a metabolic shift towards glycolysis and tumor growth, whereas homoplasmic state of this mutation inhibits tumor formation [205]. The MT-ND5-coding region has high propensity for mutations, occurring up to 7.5% in several types of tumor [204]. Two different homoplasmic mutations in Complex I-mitochondrially encoded NADH dehydrogenase 1 (MT-ND1) subunit have different impact on cybrid osteosarcoma cell proliferation. While m.3460G>A/MT-ND1 mutation causes a mild decrease in Complex I activity and do not influences tumor growth, the frameshift m.3571insC/MT-ND1 causes a severe Complex I dysfunction, which halts tumor progression. The dissimilar biologic effect was related to the chronic destabilization of HIF-1 and consequent inability to rewiring the metabolism to glycolysis. Interestingly, m.3571insC/MT-ND1 mutation has been reported in oncocytic tumors, which displays Complex I disassembly [159]. A study performed by the Cancer Genome consortium, using whole-genome parallel sequencing of tumor and non-tumor tissue of 5 different cancers, revealed that 43% of tumors harbor somatic mutations. mtDNA mutations levels vary among cancer type, ranging from 13% in glioblastomas to 63% of rectal adenocarcinoma, and being the NADH dehydrogenase complex the most affected [204]. The tumorigenic potential of mtDNA mutations within ETC subunits in cancer seems to be dependent on mutation type, load and degree of OXPHOS dysfunction, playing a neutral, pro or anti-tumorigenic effect [159].

A study with 31 samples of gastric cancer 65% carried at least on somatic mtDNA mutation, being 69% related to D-loop region, 27% in ETC subunits-coding region and only 4% in tRNA genes. Overall, tRNA-coding regions encompass the lowest levels of mutations [206,207]. 7472insC in tRNA-Ser(UCN) somatic insertion is likely to induce a clover leaf secondary structure alteration of the tRNA, which leads to Complex I impairment and low oxygen consumption, promoting mitochondrial dysfunction of gastric cancers [206]. Using a cybrid model, homoplasmic mutation within the tRNA-Leu (UUR) affects mitochondrial protein synthesis and is usually found in oncocytomas, a benign senescent-like type of tumor. In osteosarcoma, this mutation has an anti-tumorigenic potential. Osteosarcoma 143B cells harboring tRNA m.3243A.G/MT-TL1 shows impaired oxygen consumption rate, decrease activity of Complex I and Complex I/II-dependent ATP synthesis, and inability to form tumors when injected in nude mice [159]. In oral squamous cell carcinoma, 240 out of 300 patients were found to carry somatic mtDNA mutations. Among them, around 8% were detected in tRNA, which were related with tumor differentiation [207]. The previous study also found that 14% of somatic mutations were in rRNA-coding regions [207].

Large scale mtDNA deletion, known as “common deletion”, is characterized by the loss of 4977 base pairs, from 8470 to 13,447 position. It comprises the elimination of 5 tRNAs and 7 encoding genes of Complex I, IV and V, and is well-described in several types of human cancer [208].

However, most mtDNA mutations are reported to occur in the non-coding D-loop regulatory region. Mutations in the D-loop affect coding sequences and mtDNA transcription and replication, likely affecting the OXPHOS system [209]. The D-loop D310 polycytidine stretch region is more susceptible to oxidative damage, being the hot spot region for mutation in primary tumors [208]. In a study using samples from 22 breast cancer patients, D-loop mutations were detected in 90% of all cases [210]. In another study comparing non-tumor liver tissue and hepatocellular carcinoma tissue of 61 patients, homoplasmic D-loop mutations were found in 40% of cases [211]. The high mutation rate correlated with a poor prognosis and survival among several types of cancer. Since D-Loop is a control region for mitochondrial replication and transcription, its mutation is usually associated with changes in copy number [208].

Besides mtDNA mutations, changes in the content of the mitochondrial genome were detected in several cancers, including breast, renal, thyroid and pancreatic cancer [210,212,213]. Depending on cancer type and its stage, mtDNA copy number can increase or decrease. However, alterations in the mtDNA copy number correlate with increased oxidative stress levels [214]. There is no consensus whether mtDNA depletion presents a gain or loss of tumorigenic potential in *in vitro* or *in vivo* models, as well as in patients with primary tumors [215]. Most of the types of breast cancer exhibit lower mtDNA content [209,210,216,217]. Moreover, low mtDNA content has been associated with epithelial mesenchymal transition (EMT), tumor invasion and metastasis, and aggressiveness. Reduction of mtDNA content triggers retrograde signaling and activation of TGF-β, inducing the mesenchymal transition [218–220]. However, the above findings are still inconclusive. One example is a report using a broad panel of human breast cancer cell lines and about 200 primary breast tumors that did not find any link between EMT genes, types of tumors and mtDNA content [215]. Reduced mtDNA content was also proposed to be implicated in drug response of cancer [221,222].

Studies have also reported the importance of mtDNA release into the cytosol following mitochondria stress, as an important regulator of immune responses including in antiviral responses by activation of interferon genes (STING) [223]. Recently, Field et al. showed that regulatory T cells (Tregs), which depend on lipid metabolism for their survival and function to exert their immunosuppressive effect, overexpress the fatty acid binding protein (FABP5), even in tumors. Inhibition of FABP5 leads to a rewiring of Tregs metabolism towards glycolysis. Mitochondrial dysfunction and particularly mtDNA release lead to the induction of STING-type I interferon (IFN) signals and IL-10, thereby inducing the suppression of Tregs [224]. Moreover, oxidized mtDNA released by ionized radiated cancer cells induce antitumor effect by activation of STING signaling in dendritic cells [225].

Currently, a well-established phenomenon is whole mitochondrial

transfer between cells, allowing for horizontal mtDNA acquisition. In tumors, horizontal mtDNA transfer occurs between microenvironment donor cells to cancer depleted cells (ρ0 cells). The transfer have shown to restore mitochondrial respiration, supercomplex assembly and boost tumor growth *in vivo* relatively to ρ0 cells [226,227]. In fact, mitochondria transfer from endothelial to malignant cells promotes chemoresistance [228], whereas in prostate cancer mitochondria acquisition inhibits the apoptosis of cancer cells [229]. Thus, these results highlight the critical role of mitochondria and OXPHOS importance in tumor progression as well as tumor cells plasticity and escape mechanisms.

1.2.3. Mitochondria biomarkers as prognostic factors

Early diagnosis of cancer remains as one of the major challenges. Nowadays, diagnostic methods are usually invasive or show lack of specificity/sensitivity. Changes in mitochondrial metabolism and mitochondrial apoptosis during tumorigenesis, highlight mitochondria as key player in malignancy. Given that, mitochondria appear as a potential source of tumor biomarkers, which may improve the accuracy of tumor screening, therapeutic guidance and survival.

Lisanti's group employed a bioinformatic approach to identify nuclear-encoded mitochondrial genes that can be used as tumor biomarkers of non-small cell lung cancer. Using samples from 726 patients, 180 mitochondrial biomarkers were validated. The mitochondrial biogenesis gene, heat shock protein family D (Hsp60) member 1 (HSPD1), showed the highest predictive value [230]. Using the same *in silico* strategy, they also found that individual or combined mitochondrial genes, mainly associated with mitochondrial biogenesis and OXPHOS, can predict tumor progression and recurrence, as well as clinical outcomes and patient survival of several types of cancer. Overall, mitochondrial biomarkers can predict high-risk cancer patients in advance, up to 5, 10 or 15 years in ovarian, lung or breast cancer, respectively [230–233]. Analysis of those mitochondrial prognostic factors also allows the stratification of the risk, and consequently personalized medicine.

Due to the metabolic differences between normal and cancer cells, oxidative phosphorylation system arises as potential biomarker source with clinical value in tumorigenesis. Mitochondrial Complex III, especially its ubiquinol cytochrome *c* reductase binding protein (UQCRB) subunit, is a possible prognostic marker in colorectal cancer. UQCRB was detected upregulated in colorectal cancer tissue, both at gene and protein level, compared to non-tumor tissue. Moreover, the increment and copy number gene variation was correlated with clinical stage and pathologic features [234]. Complex IV, along with Complex I, Complex III and ATP synthase, is encoded by nuclear and mitochondrial genes. The ratio between nuclear/mitochondrial-encoded genes of Complex IV changes in parallel with prostate tumor progression. Ovarian, colon, esophageal and breast carcinomas demonstrated the same trend. This study suggests that the shift may be a valuable biomarker to predict tumor evolution even before histological changes [235].

Besides tumor and other tissue biopsies, mtDNA can be further found in body fluids and collected through a less/non-invasive approaches under the form of circulating cell-free mtDNA and extracellular vesicles-containing mtDNA [236].

Extracellular vesicles are critical mediators for intercellular communication and were also found to contain mtDNA. As active carriers of molecular biomarkers, extracellular vesicles containing-mtDNA have potential for detection and monitoring the progression of several pathological states [237].

Although cell-free genomic DNA has been identified as a biomarker in blood-based liquid biopsy in cancer [238], cell-free mtDNA appears to be more stable in circulation, revealing a potential clinical prediction approach worthy to explore. Mair and his colleagues showed that tumor-released cell-free mtDNA detection is a more sensitive method to detect glioblastoma compared to cell-free nDNA. Using digital PCR, the authors verified that mtDNA was detected more frequently and in higher copy number, both in the plasma and urine. Moreover, increased levels of mtDNA in orthotopically implanted xenografts of glioblastoma are correlated with tumor burden and proliferation. mtDNA release is further boosted by temozolomide combined radiotherapy treatment, being related with tumor cell death [239]. In a study with 165 epithelial ovarian cancer patients and 60 healthy women, the serum level of a 79-short fragment and 230-large fragment of mtDNA was significantly increased in cancer patients. The increased levels were positively correlated with FIGO stages and metastatic potential. Furthermore, mtDNA integrity was found to be decreased in the disease group [240]. However, and despite the general trend of increased circulating mtDNA levels in cancer patients, decreased levels of cell-free circulating mtDNA was reported in some cancers, such as renal and hepatocarcinoma [236].

Several clinical trials are now covering the prediction value of cell-free circulating nDNA (clinicaltrials.gov); however, to the best of our knowledge none is taking into consideration specific mtDNA detection as a biomarker in cancer. It is important to define and to uniformize methods of extraction, type of body fluid and molecular analysis to have more coherent results. Distinguish between tumor- and non-tumor-derived mtDNA is also a major point that needs to be well established.

Another study emphasizes that, not a specific mtDNA mutation, but the total acquired genomic mutations demonstrate high prognostic value in prostate tumors. The number and frequency of somatic mtDNA single-nucleotide variances are molecular biomarkers that in combination with Gleason score are useful for risk prediction, and significantly correlate with tumor relapse [241]. A prostate cancer study in South Africa men, using 87 tissue samples, also associated the load of mitochondria mutations and aggressiveness of prostate cancer. Again, total number of mutations was correlated with Gleason score, indicating higher pathological stage and poor prognosis [242]. mtDNA mutation patterns have been associated with various types of cancer. The difficulty to detect mutations in free-cell mitochondrial genome in circulation constrains its use in cancer diagnostic [243].

Circulating levels of mitochondrial-derived peptides, including MOTS-c and humanin, have been identified as biomarkers for several pathologies, usually related with altered metabolism and aging. Since both are implicated with tumorigenic process, mitochondrial-derived peptides may appear as oncopeptides and potential biomarkers in cancer, including non-Hodgkin's lymphomas [244–246]. Humanin has been detected overexpressed in gastric cancer using suppression subtractive hybridization method. Compared to normal tissues, Humanin isoform 3 expression level was about 4-fold higher. The study suggested the role of humanin in chemoresistance and as new biomarker [247]. Moreover, humanin was also shown 20-times upregulated in tumor tissue compared to normal tissue of patients with T2 bladder carcinoma [248]. Small humanin-like peptide 2 (SHLP2) was also detected in plasma. Since it acts as a retrograde signaling molecule, SHLP2 can be used as a mitochondrial biomarker in cancer. In fact, lower levels of SHLP2 were associated with increased risk of prostate cancer. However, this link was only present in white men, demonstrating a racial disparity [249].

2. Exploiting mitochondrial and metabolic targets in cancer cells

2.1. Targeting cancer cell metabolism

As described above numerous metabolic adaptations occur in malignant cells with mitochondria displaying a fundamental role in the transformation that allows tumors to progress and evade therapy. Below, a description of targets and drug development strategy is described.

2.1.1. Aerobic glycolysis and oxidative phosphorylation targets

Considering that one of the main metabolic phenotypes in tumors is their high glycolytic rate, and almost 70% of human cancers present an overexpression of glycolytic enzymes [250], with some tumor

presenting defective or less active mitochondria. Thus, therapeutic approaches have been developed in order to efficiently kill malignant cells by using inhibitors that target the glycolytic pathway. With this approach, some drugs increase mitochondria respiration, which is thought to be also essential to induce tumor cells arrest and death [251]. Although research on cancer metabolism was mainly focused on glycolysis in the past, OXPHOS has also emerged as a potential target in recent years [252]. So, we also revise the OXPHOS targeting approach as some cancer cells still or preferentially rely on this pathway [253], or due to the metabolic shift observed in cancer cells that allows their survival to anti-cancer treatments.

The first step to metabolize glucose involves its transport to the cell, which is done by GLUTs, that are often overexpressed in tumor cells [254]. Taking this into consideration, several studies were conducted to inhibit these transporters. Small molecules such as phloretin, fasentin and STF-31 were discovered and have shown promising results in inhibiting glucose transport and inducing apoptosis in some types of cancer [255–257].

3-Bromopyruvate (3BP), a pyruvate analog, is an alkylating agent that has a broad-spectrum inhibitor activity that targets multiple metabolic enzymes, such as HK2, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), LDH, among others [258,259]. It is up taken by tumor cells by MCTs [259], which are preferentially abundant in several cancer cells. 3BP inhibits HK2 enzymatic activity through a covalent modification, and this event is also believed to trigger apoptosis by inducing HK2 dissociation from mitochondria and the release of the apoptosis inducing factor (AIF) [260]. Additionally, recent evidence demonstrated that 3BP decreases HK2 mRNA and protein levels [261]. The same study also suggested that this compound promotes a decrease on the expression of GAPDH protein levels, as well as LDH. Furthermore, treatment with 3BP promotes pyruvylation of GAPDH, which results in an enzymatic loss of function both *in vitro* and *in vivo* [262–264]. In addition to inhibiting glycolysis, 3BP also causes oxidative stress and depletes cellular GSH [265,266]. A recent study using rat and human metastatic prostate cancer cell lines has shown that 3BP was able to inhibit their mobility, which was accompanied by decrease in the ATP and GSH content [267]. Moreover, synergistic effects using 3BP combined with other compounds are also described. In doxorubicin-resistant neuroblastoma cells, 3BP seems to enhance their response to doxorubicin, suggesting 3BP as a useful mean to overcome chemotherapy resistance in human neuroblastoma [268]. The glucose analog 2-Deoxyglucose (2-DG) inhibits glycolysis by competitive inhibition of glucose transport through GLUTs [269]. When inside the cell, it is phosphorylated by HK2 to 2-Deoxy-D-glucose-6-phosphate, which cannot be further metabolize and accumulates within the cell, causing product inhibition of HK2 [270]. These events lead to the depletion in cellular ATP, decreased biosynthetic precursor production, blocked cell cycle, and even cell death [271,272]. Some studies described that, in combination with mTOR inhibitor PF-04691502 or PI3-kinase, 2-DG is able to promote a metabolic shift from aerobic glycolysis to OXPHOS, causing strong cytotoxicity in primary effusion lymphoma cells [273]. Several reports have shown synergistic effects of 2-DG combined with different drugs, which also target mitochondria, such as cisplatin, doxorubicin, paclitaxel, among others, in different types of cancer [269]. One example is, when combined with metformin, 2-DG promotes a decrease in the cellular growth of ovarian cancer cells [274].

Given the recognized involvement of LDH in tumor metabolism as development, and thus a potential target in cancer therapy, several inhibitors have been developed that target the enzyme directly. Nevertheless, their efficacy has proven to be limited because the *in vivo* activity and/or specificity is insufficient. However, drugs such as oxamate, a classical LDH inhibitor, in combination with the Complex I inhibitor phenformin demonstrated anti-cancer synergistic effect [275]. In medulloblastoma, oxamate inhibits glycolysis and stimulate OXPHOS while inhibit cells proliferation but, unfortunately, at concentration not advisable for clinical practice [276]. Despite this, ongoing efforts identified novel drugs candidates. The 1-(phenylseleno)-4-(trifluoromethyl) benzene (PSTMB) show potent inhibitory effect by impairing cancer cells growth while promoting apoptosis on a ROS-dependent mechanism [277]. In another study, Oshima et al. showed that the LDH inhibitor NCI-066 was able to slow down tumor growth. Interestingly, a stunning tumor metabolic rewiring from glycolysis to aerobic respiration occurred upon LDH inhibition. The combined inhibition of LDH and a specific mitochondrial Complex I (IACS-010759) expands the antitumoral activity while directing cell to a quiescent state [278]. IACS-010759 applicability as an anticancer therapy is examined in more detail below. Therefore, these data support the need of simultaneously target glycolysis and OXPHOS pathways to potentiate anticancer responses.

Lonidamine is a derivate of indazole-3-carboxylic acid that has antitumor and pro-apoptotic activity. Its mechanism of action is still not clear, but it is described as an inhibitor of HK2. Subsequent studies uncovered additional targets for lonidamine, such as the MCT, the mitochondrial pyruvate carrier (MPC), the ETC, and the mitochondrial permeability transition pore [279]. It was described that in combination with other drugs such as doxorubicin, lonidamine induced better anticancer effects, potentiating response to doxorubicin in ovarian, prostate and breast cancer [280]. Despite its anti-cancer efficacy, lonidamine has significant pancreatic and hepatic toxicities [281] and, upon examination of its effect in cancer patients, it provided no significant survival benefit, although it slightly increases the tumor response to radiation and chemotherapy [282].

Dichloroacetic acid (DCA), a structural analog of pyruvate, stimulates the activity of PDH by blocking its inhibitor, the PDK, which results in an increased delivery of pyruvate into mitochondria [283]. Thus, DCA promotes a metabolic shift from glycolysis to OXPHOS, stimulating O_2 consumption, which makes cancer cells more susceptible to hypoxia-specific chemotherapy [251]. This metabolic shift was observed *in vitro* and *in vivo* mouse models of glioblastoma multiforme [284] or in multiple myeloma cells lines [285]. Furthermore, this compound also induces depolarization of mitochondria, reverting membrane potential to basal levels of non-cancerous cells, and increases ROS production, promoting a number of pro-apoptotic changes in cancer cells [286,287]. Another antitumoral potential mechanism of DCA involves lowering lactate accumulation and the consequent acidosis [288,289]. This is quite important, since lactate plays a role in tumor growth, metastasis, and immunosuppression, as well as in the well-established association of acidosis with poor prognosis and survival [290]. DCA administration in rodents harboring human tumor xenografts led to a decrease in cell proliferation and increased host survival [291]. Several reports have shown DCA clinical activity against some types of cancer, such as glioblastoma and colon cancer [292,293], and synergistic effects of DCA combined with different drugs was also observed [294–297]. Furthermore, DCA treatment was able to overcome sorafenib chemoresistance in highly glycolysis-addicted hepatocellular carcinoma cells [298], and oxaliplatin chemoresistance in colorectal cancer cells [299,300]. Over the years, the interest on mitochondrial OXPHOS-targeting therapeutics has been raising with OXPHOS emerging as a promising target approach in recent years and reinforced by the metabolic reprogramming of tumor cells.

Mitocans are small compounds that induce apoptosis of cancer cells by targeting and destabilizing mitochondria. According to their molecular target, mitocans are classified into several classes. Among mitocans, class 5 includes electron transport chain-targeting drugs [301].

As mentioned in Section 1.1.5, Complex I is involved in energy and ROS production, maintenance of NAD^+/NADH ratio or HIF-1α stabilization [71]. Thus, Complex I inhibitors may decrease ATP synthesis, change ROS levels, inhibit biosynthetic pathways, and prevent hypoxia, leading to antitumorigenic activity. Most of the inhibitors are uncharged hydrophobic molecules that target the ubiquinone-binding region of the complex in a competitive manner [301].

Deguelin and other rotenoid-analogues of rotenone, directly inhibit

Complex I and cause defective respiration and apoptosis, showing anti-tumor activity. These molecules, due to their hydrophobicity, readily cross the blood-brain barrier of mammalians promoting neurotoxicity and conditioning their use [301,302].

Tamoxifen is an antagonist of estrogen receptor and is currently used as adjuvant in the treatment of hormone-dependent breast cancer. Furthermore, Tamoxifen was also reported to inhibit Complex I at the flavin site, which promote an increase of ROS, impair mitochondrial respiration, and increase AMP and AMP/ATP ratio. The anticancer activity was also observed in non-estrogen-dependent tumors. However, developed resistance to tamoxifen treatment remains a major clinical issue [303,304]. The novel mitochondrial-targeted derivative of tamoxifen (MitoTam), by use of the triphenylphosphonium (TPP^{+})-tagged, suppresses human epidermal growth factor receptor 2 (HER2)-^{high}, also called erb-b2 receptor tyrosine kinase, breast tumors *in vitro* and *in vivo*, unlike its parental compound tamoxifen (Fig. 3). MitoTam

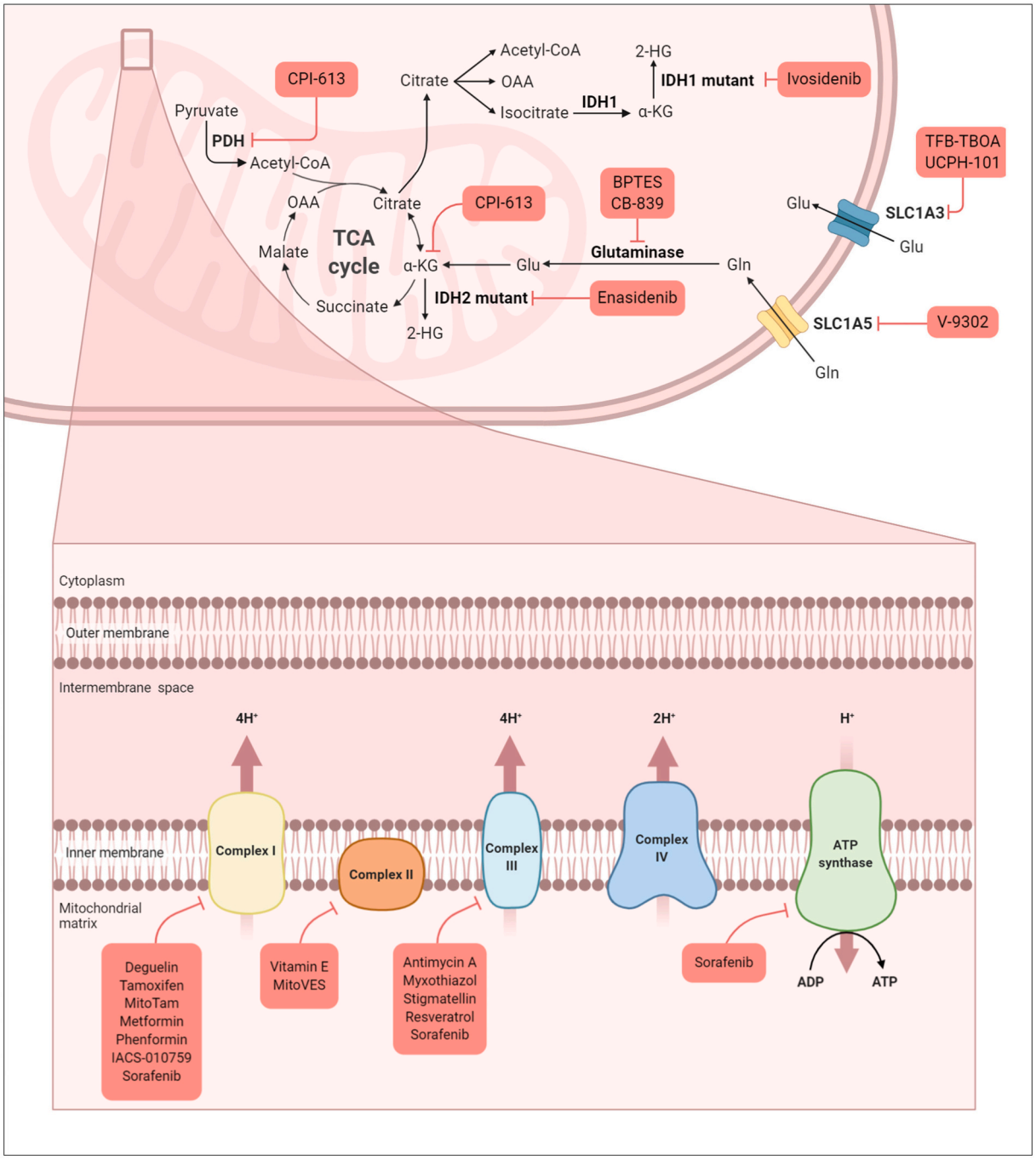

Fig. 3. Chemotherapeutic agents targeting metabolic alterations in cancer cells. Inhibition of enzymes related with TCA cycle using drugs such as CPI-613, Ivosidenib and Enasidenib reveal a great anti-tumor approach. Other agents that target amino acids uptake and metabolism (for example, BPTES, CB-839, TFB-TBOA, UCPH-101, V-9302) compromise cancer cell survival and proliferation, and some of them are already on clinical trials. Inhibition of OXPHOS through targeting of complex I (Deguelin, Tamoxifen, MitoTam, Metformin, Phenformin, IACS-010759, Sorafenib), complex II (Vitamin E, MitoVES), Complex III (Antimycin A; Myxothiazol, Stigmatellin, Resveratrol, Sorafenib) and/or ATP synthase (Sorafenib) are also a promising therapeutic strategies to efficiently kill cancer cells. Nevertheless, cancer cells modulate their metabolism, and combined therapy may promote increased efficacy. Abbreviations: Gln – glutamine; Glu – glutamate; IDH - Isocitrate dehydrogenase; LDHA - lactate dehydrogenase A; OAA – oxaloacetate; PDH pyruvate dehydrogenase; α-KG – alfa-ketoglutarate; 2-HG - D-2-hydroxyglutarate.

accumulates at the matrix/IMM interface and suppresses Complex I-dependent respiration, as well as disrupts respirasome and other supercomplexes, without suppression of other individual ETC subunits. The treatment with MitoTam shortly induced mitochondrial ROS, which mediate cell death-induction effect. Five-fold lower concentrations of MitoTam, when compared to tamoxifen, inhibited growth of $HER2^{high}$ breast tumors in different mouse strains Moreover, sub-micromolar doses of MitoTam reverted spontaneous tumors, without re-incidence up to 8 months. Upon research and pre-clinical trial phases, MitoTam has shown promising results against triple negative breast carcinomas in a Phase I clinical trial [305].

Another group of Complex I inhibitors, biguanides, which includes the well-known anti-diabetic drug, metformin, are hydrophilic positively charged molecules that promote a non-competitive inhibition. The antiproliferative effect is achieved by the inhibition of Complex I, which is supported by the lack of sensitivity when the analog of complex I (NDI) is overexpressed in tumor cells [306,307]. Complex I inhibition lowers mitochondrial membrane potential and mitochondrial respiration, causing decreased ATP synthesis and AMP accumulation. ATP depletion further leads to AMPK activation. Metformin-dependent Complex I inhibition promotes proliferation arrest and cell death, though those effects were specifically detected under nutrients deprivation conditions. HIF-1α stabilization is also affected by metformin treatment. Consequently, HIF-1α downstream target genes are reduced, hampering metabolic adaptation of tumor cells [307,308]. NAD^+/NADH balance is also affected by metformin treatment, leading to a decrease in aspartate levels and, consequently, anti-proliferative effects. Indeed, increasing doses of metformin, which are expected to be tolerable in humans, dose-dependently inhibit A549-lung tumors. The effect was associated with decreased levels of NAD^+ and aspartate in tumors [307]. Metformin-conjugated molecules, prepared by tagging TPP^+, are more selectively accumulated in cancer cells, which enhances anti-proliferative effects, through induction of ROS and AMPK activation. MitoMet, mitochondrial-targeted metformin, exhibited an increased efficacy by 4 orders of magnitude in comparison with metformin [306]. Moreover, metformin acts as an adjuvant therapy and sensitize cancer cells to other treatments. Repurposing metformin as an antineoplastic agent is an interesting approach due to its known safety profile. Although metformin has shown inhibitory effects on cell proliferation *in vitro* at supraphysiological concentrations, environment modulates its effects and the concentration found in treated human patients and mouse tumors are able to inhibit Complex I-dependent ETC activity *in vivo*. Metabolic alterations induced by metformin treatment in mice and human tissues are found in glucose-limited conditions, which are not usually used in typical cell culture media [307,309]. Treatment of human lymphoma and colon carcinoma cells with AZD3965, a MCT1 inhibitor, promoted a metabolic shift by blocking glycolysis and inducing mitochondrial oxidative PDH flux, thus sensitizing cells to metformin [310]. Similarly, recent studies reported that treatment with syrosingopine, an anti-hypertensive drug and inhibitor of MCT1 and MCT4, also sensitizes cancer cells to metformin. Benjamin et al. described that a combination treatment of syrosingopine and metformin results in glycolysis and mitochondrial inhibition, which impairs NAD^+ regeneration, induces ATP depletion and promotes cancer cells death [311,312]. Underscoring this, multiple clinical trials using metformin in a context of cancer are currently being under development. In fact, by August 2020, 354 clinical trials involving metformin treatment in several types of tumors have been registered at clinicaltrials.gov.

Another biguanide, phenformin, also inhibits Complex I and despite higher affinity to mitochondrial membrane, which leads to a greater antineoplastic activity, this molecule was associated to increased lactic acidosis, which severely limits its clinical use [308,313].

IACS-010759 likely mimics the biguanide functional group, inhibiting Complex I at the sub-nanomolar to nanomolar range. By targeting Complex I, IACS-010759 decreased mitochondrial respiration and intracellular nucleotide pools in blood cells of chronic lymphocytic leukemia patients. However, the consequently increase of glycolysis limited cell death. Combination treatment with the glycolysis inhibitor 2-DG synergistically promote cell death [314]. In addition, IACS-010759 also promoted cell death of brain cancer and acute myeloid leukemia, possibly trough energy depletion and reduced aspartate synthesis, while *in vivo* also blunted tumors growth [315]. The selective Complex I inhibitor IACS-010759 is orally bioavailable and is under clinical trials evaluation for acute myeloid leukemia and advanced solid tumors (NCT02882321, NCT03291938). Both trials comprised an induction and a maintenance phase, characterized by once-daily dose for a week and twice-weekly dosing, respectively. To the present, no severe side-effects were detected. Nonetheless, lactate levels were increased, which is evidence that Complex I is targeted, it did not altered acidosis levels [316].

Complex II is the smallest of ETC complexes and is exclusively encoded by nuclear genes. Vitamin E group, epitomized by α-tocopheryl succinate, is characterized by a high selectivity for cancer cells and for apoptosis induction, suppressing the growth of several carcinomas [317]. Vitamin E analogs act as Bcl-2 homology domain 3 mimetic, interacting with the BH3 domains of Bcl-2 and Bcl-xL and inhibiting their anti-apoptotic function. Moreover, and probably of major importance, this group of compounds interacts with UbQ site of Complex II, interfering with UbQ function and inducing apoptosis. A strong interaction between α-tocopheryl succinate and the UbQ site induces proton leakage, generation of ROS and malignant cell-selective apoptosis [318]. Knockout experiments of SDHC subunit of Complex II demonstrate inefficient ROS generation and apoptosis induction of vitamin E analogs, pointing to Complex II as the main target (Fig. 3) [319]. MitoVES, a TPP^+-modified mitochondria-targeted analog of vitamin E succinate, showed increased anti-cancer activity when compared with the parent compound. While maintaining selectivity for malignant cells, MitoVES accumulates at the interphase of the mitochondrial matrix and the IMM, inducing oxidative stress, and triggering mitochondria-dependent apoptosis. In two *in vivo* pre-clinical cancer models, MitoVES efficiently suppressed tumor growth, and was even able to reduce tumor size [320].

Accordingly to what was described in Section 1.1.5, Complex III mediates the transfer of electrons between both electron carriers, from UbQ to cyt c, and, along with Complex I, are the major sources of mitochondrial superoxide. Grape seed extract targets Complex III and shows antiproliferative effects in head and neck cancer. Shrotriya et al. showed that this extract decreases Complex III activity and increased mitochondrial ROS parallelly with GSH depletion. Induction of AMPK and inhibition of Akt/mTOR pathway was also reported, which in turn increased autophagy of tumor cells. Overall, oxidative and metabolic stress promoted autophagy and apoptotic cell death in head and neck squamous cell carcinoma [321]. Inhibitors of Complex III, such as myxothiazol, stigmatellin and antimycin A, induce p53-dependent apoptosis in cancer cells, which was mediated by pyrimidine pool depletion. To note, specific inhibitors of other ETC complexes did not show the same effect, unlike dihydroorotate dehydrogenase (DHODH) inhibitors [322]. DHODH catalyzes the fourth and only mitochondrial step of the *de novo* pyrimidine synthesis pathway, which is intimately coupled with the ETC, requiring UbQ as the direct electron acceptor and functional Complex III for UbQ redox-cycling. Indeed, DHODH dysfunction resulting from ETC impairment leads to cell cycle arrest and tumor growth inhibition *in vivo* [4,323].

Several compounds can be grouped in a different category, as they can target multiple complexes of the ETC. Another plant-derived polyphenol, resveratrol, efficiently inhibits multiple ETC complexes, especially Complex III. Sorafenib, marketed under the name Nexavar, also inhibits Complex II and Complex III activity, as well as ATP synthase, at low micromolar doses, in addition to its multi-kinase inhibition properties. The inhibitory capacity leads to PINK-Parkin-mediated apoptosis [324]. In patients with advanced hepatocellular carcinoma, a phase III clinical trial (NCT00105443) showed that sorafenib prolongs overall survival by almost 3 months. Sorafenib's effects could be explained by

the conjugation of both mechanisms of action.

Overall, pharmacological ETC inhibition potentially decreases mitochondrial respiration, mitochondrial membrane potential, ATP and biomolecules synthesis, and increases ROS levels. Consequently, those compounds induce apoptotic death of cancer cells. However, cancer cells modulate their metabolism, shifting to a glycolytic pattern, upon ETC inhibitors treatment, resulting in resistance to cell death [304,314,321]. The use of this strategy as co-adjuvant therapy, may promote increased efficacy [324]. Moreover, ETC inhibitors are a crucial treatment in specific situations, such as, target subpopulations of tumor microenvironment with limit access of glucose, target highly OXPHOS-depend cancer cells [325] and target quiescent cancer cells responsible for tumor relapse, which rely on OXPHOS metabolism [319,326].

2.1.2. Tricarboxylic acid and amino acids approaches

As described in the above sections, cancer cells can take advantage of the TCA cycle and amino acids to remodel their metabolism and survive even in harsh conditions. Thus, targeting such pathways could also represent a good strategy to efficiently kill malignant cells.

CPI-613 is a lipoate analog that inhibits PDH and the α-ketoglutarate dehydrogenase complexes [327]. This compound is known to activate pyruvate dehydrogenase kinases PDK 1–4 that, by phosphorylation, are responsible for PDH inactivation in cancer cells (Fig. 3). CPI-613 also induces a mitochondrial ROS burst that targets α-ketoglutarate dehydrogenase complexes, promoting its inactivation by glutathionylation of sulfhydryl groups [327,328]. CPI-613 lead to the induction of cell death pathways in H460 cancer cells due to mitochondrial metabolism disruption [327], and diminished the ability of ovarian cancer stem cells to form spheroids [329]. Importantly, CPI-613 treatment increased the median survival rates of patients with recurrent acute myeloid leukemia in clinical trials, and it also re-sensitized cancer cells to cytotoxic agents [330,331]. Several clinical trials using CPI-613 are ongoing for the treatment of some cancers, such as metastatic pancreatic cancer (NCT01835041) and metastatic colorectal cancer (NCT02232152), among others.

As described in the previous sections, several types of cancer rely mainly on aerobic glycolysis. Thus, it is not surprising that the MPC, the gatekeeper for pyruvate entry into mitochondria, present reduced levels and/or activity in tumor cells. Then, cancer therapies would need to stimulate MPC activity or expression [332]. However, there are now recent studies that demonstrate that MPC inhibition can have antitumoral effects. Bader et al. showed that MPC inhibition in androgen receptor-driven prostate cancer promotes a delay in tumor growth [333]. Tompkins et al. found out that MPC levels are highly expressed in hepatocellular carcinoma, and MPC disruption limited glutamine availability for GSH synthesis [334]. Corbet et al. showed that MPC inhibition blocks lactate uptake and has an adjuvant effect when combined with radiotherapy (28). These reports suggest that MPC inhibitors could be a good therapeutic approach to the treatment of some specific cancer types.

IDH1 and IDH2 mutations occur in some types of cancer, including acute myeloid leukemia and glioma [335,336], and studies have been done in order to properly target them. Ivosidenib and enasidenib are selective and first-in-class inhibitors of mutated IDH1 and mutated IDH2, respectively (Fig. 3). Preclinical studies, *in vitro* and *in vivo*, demonstrated that, upon treatment with ivosidenib, intracellular levels of 2-HG decreased and the myeloid differentiation block was released in leukemic cells that possess mutant IDH1 [337,338]. Enasidenib inhibits mutant IDH2 by stabilizing the open conformation of the enzyme, impeding the formation of 2-HG [339]. Similar to ivosidenib, treatment with enasidenib induces a decrease in the 2-HG intracellular levels *in vitro* and *in vivo*, and acts as a differentiation agent [339]. Both ivosidenib and enasidenib were recently approved by the United States Food and Drug Administration for the treatment of adult patients with relapsed/refractory acute myeloid leukemia with IDH1 or IDH2 mutations, respectively [340,341]. Several other clinical trials using these inhibitors are also ongoing for the treatment of cholangiocarcinoma [342], advanced solid tumors [343], among others [338,344].

Since many cancers have an upregulation of glutamine uptake and metabolism, inhibitors of those pathways have been developed and studied. SLC1A5 is a glutamine transporter, thus is an attractive target for cancer treatment. V-9302 was recently found as a selective inhibitor of this transporter, and its use resulted in increased cell death and increased oxidative stress, as well as attenuated cancer cell growth and proliferation, both *in vitro* and *in vivo* [345]. This data demonstrates that targeting glutamine uptake could be a viable approach for cancer treatment. Focusing on glutamine metabolism, Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES) was found as a selective inhibitor of glutaminase and had been described as having minimal off-target effects. It is thought that BPTES inhibits glutaminase by disabling the phosphate-dependent activation of the enzyme [346,347], and studies have shown that it promotes a decrease in cell growth *in vitro*, and prolonged the survival of a mice model of hepatocellular carcinoma [348]. However, some factors limit the use of BPTES for clinical development, such as low solubility and poor metabolic stability [49]. Several BPTES-derivatives were then developed, such as CB-839, which is a more potent allosteric inhibitor of glutaminase. Treatment with CB-839 showed an antiproliferative activity both *in vitro* and *in vivo* models of breast cancer, and it was also demonstrated that this compound also affected TCA cycle reprogramming and amino acid synthesis (Fig. 3) [349]. Thus, CB-839 is undergoing clinical trials for the treatment of multiple types of tumors as a combination therapy [49,350].

Approaches targeting glutamate uptake and metabolism have also been investigated. TFB-TBOA and UCPH-101 are small molecule inhibitors of the SLC1A3 glutamate-aspartate transporter (Fig. 3) [73,351]. A study on a patient-derived xenograft model of head and neck squamous cell carcinoma revealed that, upon treatment with TFB-TBOA, a decrease in cancer cell proliferation and reduced tumor growth were observed [352]. Regarding glutamate metabolism, the small molecule inhibitor R162m, a glutamate dehydrogenase 1 inhibitor, was recently discovered. Jin et al. demonstrated that this compound promotes a decrease in cell proliferation and disrupts the redox balance in H1299 and MDA-MB231 cells [51].

2.2. Approaches for mtDNA as a druggable target

Conventional anti-cancer therapies utilize mechanisms such as DNA intercalation, microtubule disruption or folate inhibition. Since cancer is still a disease lacking efficient treatment, new therapeutic approaches are needed [353]. Mitocans that interfere with mtDNA, such as Vitamin K_3 (2-methyl-1, 4 naphthoquinone, also known as menadione) or fialuridine, are grouped into class 8 and have been tested for their antiproliferative and anti-cancer potential. These agents can inhibit transcription and expression of the mitochondrially coded ETC subunits, suppressing assembly of respiratory complexes and supercomplexes, and, consequently, blocking mitochondrial respiration [301]. Recent studies demonstrated that mtDNA-devoid cancer cells acquire mitochondria from tumor microenvironment cells to repopulate their mtDNA playload. Only upon achieve a minimum threshold of mtDNA and mitochondrial respiration, cancer cells can proliferate and initiate tumor formation. These papers highlight the importance of functional mtDNA in tumor progression [226,227,323].

As aforementioned, MitoVES promotes apoptosis and suppressed tumor growth but also affects mtDNA, an effect not observed for the untargeted α-tocopheryl succinate. At sub-apoptotic concentrations ($\leq$3 μM), the MitoVES agent suppresses the level of mtDNA transcripts, in particular the regulatory region of mtDNA, the D-loop. Derived from this inhibition, mtDNA-encoded ETC subunits were also found decreased, and mitochondrial function and respiration were affected [354]. Moreover, 1-methyl-4-phenylpyridinium ion (MPP^+), a neurotoxin that inhibits Complex I, was also associated with D-loop destabilization.

Upon recognition of D-loop, MPP^+ interferes with mtDNA replication and promotes mtDNA depletion, independently of Complex I inhibition [355]. This compound demonstrated increased toxicity to lung cancer by affecting overall mitochondria function and being relative safe to normal cells *in vitro* [356]. Currently, to our knowledge, no clinical trials have been attempted yet for these compounds. However, the data highlighted the possibility of developing compounds that directly interfere with mtDNA as a useful approach. Accordingly, the rhodacyanine dye analog MKT-77 damages mtDNA of CX-1 carcinoma cells, without hampering nDNA [357] and inhibit the growth of tumor xenografts as renal or prostate carcinoma [358]. Although tolerable toxicity in animals has been described, renal toxicity was reported in a phase I clinical trial [359], thus compromising further trials. POLG is a key protein involved in mtDNA replication since it is the irreplaceable replicative polymerase in mitochondria. In human cells, POLG is a heterodimer constituting a catalytic subunit and 2 accessory subunits, and is also responsible for mtDNA damage repair mechanisms [186]. Vitamin K_3 inhibited POLG activity but did not show any effect on other DNA polymerases. The compound was tested in several cancer cell lines, demonstrating a wide effect as antitumor agent, due to inhibition of mtDNA replication and repair [360]. In a phase I clinical trial, intermittent administration of vitamin K_3 to patients with colorectal, breast cancer or lung cancer was well-tolerated without displaying major side-effects at doses shown to inhibit tumor growth *in vitro* [361,362]. Despite the promising results, a vitamin K_3 and mitomycin C in combination regime not only failed to offer benefits to not only failed to offer benefits to lung and gastrointestinal cancer patients as hematologic toxicity was observed [362,363]. Despite this, the administration of vitamin K_3 and vitamin C demonstrated synergistic effect by delaying the disease prostate specific antigen marker increase in a clinical phase I/IIa trial of end stage prostate cancer patients [364].

Similarly, the thymidine analog fialuridine disrupted PLOG and mtDNA replication in HepG2 hepatocyte carcinoma cells. Consequently, fialuridine induced mitochondrial structural defects [365]. Despite the positive effects observed in initial studies against chronic hepatitis B, a subsequent trial demonstrated a severe toxicity characterized by hepatic failure and mitochondrial damage [366].

Acute myeloid leukemia cells are known to rely on mitochondrial respiration, which is supported by increased mitochondrial biogenesis. Thus, those cells are more susceptible to mitochondrial-targeted therapy, including mtDNA-directed agents. POLG of several leukemia cell lines was targeted with the antimetabolite 2′3′-dideoxycytidine, resulting in decreased mtDNA content, mitochondrial-encoded ETC subunits and increased cytotoxicity. 2′3′-dideoxycytidine also abolished tumor growth and decreased tumor size *in vivo*, without affecting normal mouse hematopoiesis [367]. POLG was found to be increased in pancreatic patients and treatment of cells lines with 2′3′-dideoxycytidine prompted mitochondrial dysfunction, mtDNA depletion and increased total ROS, measured by the 2′,7′–dichlorofluorescin diacetate (DCFDA) fluorogenic dye, as well as oxidative DNA damage [368].

Broad spectrum of nucleoside reverse transcriptase inhibitors used in antiretroviral therapy showed mitochondrial toxicity. Inhibition of POLG is the most likely underlying mechanism, which causes mtDNA mutations and deletion. Thus, strategies to directed these drugs to cancer cells should be tested to potentiate their use as chemotherapeutic drugs [369]. Doxorubicin treatment, as well as mitotoxic 2-DG and carbonyl cyanide 4-trifluoromethoxy)phenylhydrazone (FCCP), an OXPHOS uncoupler, decreased mtDNA content in leukemic cells, but not normal blood nor solid tumor cells [370]. Moreover, the anthracycline daunorubicin showed mtDNA deletion effects in lung cancer cells. The lack of response and increased resistance in mtDNA-devoid cells suggests that mtDNA is the target of this drug [371,372].

Besides mtDNA replication and transcription, mitochondrial protein translation occurs on mitochondrial ribosomes and is initiated under the control of mitochondrial initiation factors mtIF2 and mtIF3. This step is followed by elongation, which also uses its own elongation factors, such as EFTu, EFTs and EFGM [373]. The impact of inhibiting mitochondrial translation as an anticancer therapy was evaluated in several studies. Tigecycline, a potent inhibitor of the bacterial ribosome, also targets mammalian mitochondrial ribosomes blocking mitochondrial translation, but not cytoplasmic translation. Tigecycline treatment involved mitochondrial dysfunction, oxidative stress, proliferation inhibition and apoptosis activation in leukemic, renal, and ovarian cancer cells. Anticancer efficacy of mitochondrial translation by tigecycline was also demonstrated by tumor growth inhibition in several xenograft mouse models. The therapeutic effect was similar to the one promoted by EFTu knockdown [374–376]. Furthermore, tigecycline potentiates chemotherapeutic efficacy of cisplatin, both *in vitro* and *in vivo* [376]. Doxycycline, another tetracycline antibiotic, that also inhibits mitochondrial protein translation, is described as a promising anticancer drug. In fact, in the last years, several studies provided evidenced that doxycycline targets cancer stem cells [377–379]. The inhibitory effect in spheroids formation was transversal in a broad panel of cancer cells lines as breast, ovarian, lung, melanoma, prostate, pancreas and glioblastoma [377]. Of notice, tigecycline also exhibited similar effects. Additionally, doxycycline hampered mitochondrial respiration and glycolytic activity of MCF-7 breast cancer cells and radio-sensitizes cancer stem cells [378]. In A549 lung adenocarcinoma cancer cell line, doxycycline was shown to inhibit mitochondrial protein synthesis, decrease mitochondrial membrane potential and cells proliferation but not changed mtDNA copy number. The effects where potentiated by gemcitabine combination which also lead to apoptosis induction [380]. Furthermore, combination of doxycycline (1 μM), azithromycin (1 μM) plus vitamin C (250 μM) potentiated the inhibition of cancer stem cells propagation, compromised mitochondrial respiration and ATP production-associated oxygen consumption rate of MCF-7 cells although, the glycolytic reserve was decreased and glycolysis increased [379]. In a recent Phase II window pilot trial, doxycycline reduced cancer stem cells population in early breast cancer patients, as observed by a decrease of the stem cell marker CD44 [381]. Currently, an ongoing phase II clinical trial is exploring the potential of treating patients with localized breast or uterine cancer with metformin hydrochloride and doxycycline (NCT02874430).

Humanin, a 24-aminoacid peptide encoded by an open-reading frame of mtDNA could have a potential therapeutic impact. It has been demonstrated that humanin is cytoprotective in several cell types and tissues, decreasing apoptosis. However, the dual role of humanin in tumor growth seems to be tumor-dependent. Some studies suggested that humanin contributes for tumor progression and chemoresistance [247,382,383], whereas others demonstrated its inhibitory effect in tumorigenesis, alone or as an adjuvant therapy [384,385]. Thus, humanin mechanism and as a potential target in cancer should be further investigated.

No curative treatments are available for mtDNA-encoded disorders, since it is hard to modify the mtDNA sequence in mammalian cells. New methods to remove and replace defective mtDNA sequences are now emerging and are likely to enhance outcomes of mitochondrial-associated diseases [202]. Understanding the value of mtDNA mutations, mainly pathogenic mutation, and why and how diverse heteroplasmic levels behave differently in terms of biological outcomes, is crucial for development of new treatment methods. Gene-based approaches have been developed to treat mtDNA heteroplasmic conditions and involve either replacement of mutant with wild-type mtDNA, degradation of mutant mtDNA or targeting of specific mutations.

A prominent therapeutic strategy for mtDNA diseases are based on allotopic nucleus expression of mitochondrial proteins *via* gene therapy or in nuclease targeting of mtDNA mutations. The later consists on the targeted degradation of mutant mtDNA, allowing the repopulation by wild-type mtDNA. However, this nuclease-based therapy depends on the presence of unique restriction sites. Transcription activator-like effector nucleases (TALENs) and zin-finger nucleases (ZFNs) can be engineered to target specific mtDNA sequences. Those approaches, which promote mutant mtDNA destruction instead of repair, have been extensively

reviewed in [386,387], and out of scope of this review. Although the difficulties to use CRISPR-cas9 system to target mtDNA mutations, conditioned by the delivery of a guide RNA into mitochondria, Mok and his team have recently discovered an enzyme, that converts C to U, meaning a C-T conversion in mtDNA. The enzyme acts on double-strand DNA, after being split into two pieces and linked to programmable DNA-binding proteins to bind on specific sites of the genome, allowing their activation at specific sites [388].

The recent advances open new therapeutic opportunities and overcome some drawbacks, that for years conditioned the evolution in mtDNA targeting therapeutic field. Notwithstanding those techniques are a great promise, showing positive results, both *in vivo* and *in vitro*, they are far from being employed in cancer treatments.

3. Final remarks

The lessons from the last decades should prompt us towards to the undoubtedly need to tackle tumors metabolic liabilities, most likely, in combination with current used therapies. The metabolic profile and reprograming in tumors reflect the molecular adaptation facing the constant microenvironment changing conditions. One must integrate the cross talk between cancer and stromal cells, cancer cells plasticity or emergence of less predominant phenotypes following antitumoral treatments. The undeniable convergent central role of mitochondria, although nowadays already recognized, in oncometabolism, as tumor features for their development and flexibility, should be more than never a focus of attention. Thus, the development of improved drugs directed to metabolic targets, particularly mitochondria-related ones, holds a great promise to improve the success of anticancer treatments.

Funding statement

Work in the authors' laboratory is funded by FEDER (ERDF)—European Regional Development Fund through the COMPETE 2020—Operational Programme for Competitiveness and Internationalisation (POCI), Portugal 2020, and by FCT – Fundação para a Ciência e a Tecnologia (FCT), under the project POCI-01-0145-FEDER-016390 [CANCEL STEM], and through the COMPETE 2020 - Operational Programme for Competitiveness and Internationalisation and Portuguese national funds *via* FCT – Fundação para a Ciência e a Tecnologia, under project[s] POCI UIDB/04539/2020. Also, Gabriela L. Oliveira is supported by project "Summer Course in Interdisciplinary Research, Development and Innovation in Cellular and Molecular Metabolism" (15-20/7/245), funded by FCT and Directorate General for Higher Education (DGES).

CRediT authorship contribution statement

Gabriela L. Oliveira: Writing – original draft. **Ana R. Coelho:** Writing – original draft, Visualization. **Ricardo Marques:** Conceptualization, Visualization, Writing – review & editing. **Paulo J. Oliveira:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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