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Review

The role of compartmentalized signaling pathways in the control of mitochondrial activities in cancer cells

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ABSTRACT

Mitochondria are the powerhouse organelles present in all eukaryotic cells. They play a fundamental role in cell respiration, survival and metabolism. Stimulation of G-protein coupled receptors (GPCRs) by dedicated ligands and consequent activation of the cAMP·PKA pathway finely couple energy production and metabolism to cell growth and survival. Compartmentalization of PKA signaling at mitochondria by A-Kinase Anchor Proteins (AKAPs) ensures efficient transduction of signals generated at the cell membrane to the organelles, controlling important aspects of mitochondrial biology. Emerging evidence implicates mitochondria as essential bioenergetic elements of cancer cells that promote and support tumor growth and metastasis. In this context, mitochondria provide the building blocks for cellular organelles, cytoskeleton and membranes, and supply *all* the metabolic needs for the expansion and dissemination of actively replicating cancer cells. Functional interference with mitochondrial activity deeply impacts on cancer cell survival and proliferation. Therefore, mitochondria represent valuable targets of novel therapeutic approaches for the treatment of cancer patients. Understanding the biology of mitochondria, uncovering the molecular mechanisms regulating mitochondrial activity andmapping the relevant metabolic and signaling networks operating in cancer cells will undoubtly contribute to create a molecular platform to be used for the treatment of proliferative disorders.

Here, we will highlight the emerging roles of signaling pathways acting downstream to GPCRs and their intersection with the ubiquitin proteasome system in the control of mitochondrial activity in different aspects of cancer cell biology.

1. Introduction

Mitochondria are cell autonomous organelles that provide the energy production and all the metabolic needs for most replicating eukaryotic cells. Defective mitochondia have been causally linked to ageing and neurodegenerative disorders [1]. Recently, it has emerged that mitochondria significantly contribute to development and progression of a wide array of human cancers. In tumor cells, mitochondria undergo a profound metabolic switch that supplies sufficient energy for the increased metabolic demands and the building blocks for the assembly of intracellular organelles, cytoskeleton and membranes of newly derived cancer cells. Inhibiting this metabolic reprogramming significantly impacts on the growth and dissemination of several types of human cancer [2,3]. Understanding the mechanisms adopted by actively proliferating cells to sustain their metabolic needs represents a key aspect in the cancer biology field.

In proliferating cells, increased metabolic demands are linked to enhanced energy production andto a rapid adaption of mitochondria to increased metabolic needs. The metabolic reprogramming of growing cells is induced and sustained by signaling events elicited by hormones and growth factors operating at cell membrane and intracellular organelles [4]. Emerging evidence points to a pivotal role of compartmentalized signaling networks in redirecting and supporting the metabolic switch occurring in normal proliferating cells and, more importantly, in rapidly dividing cancer cells. Regulation of signaling events at target sites efficiently and rapidly allows mitochondria to adapt their activity in response to metabolic demands [5–8]. Protein Kinase A (PKA) controls essential aspects of mitochondrial activities. Thus, activation of PKA by cAMP generating systems tightly regulates a wide array of mitochondrial functions, as organelle biogenesis and morphology, gene expression, metabolism, steroidogenesis and survival [9,10]. In mammalian cells, PKA holoenzyme is concentrated atthe membrane,

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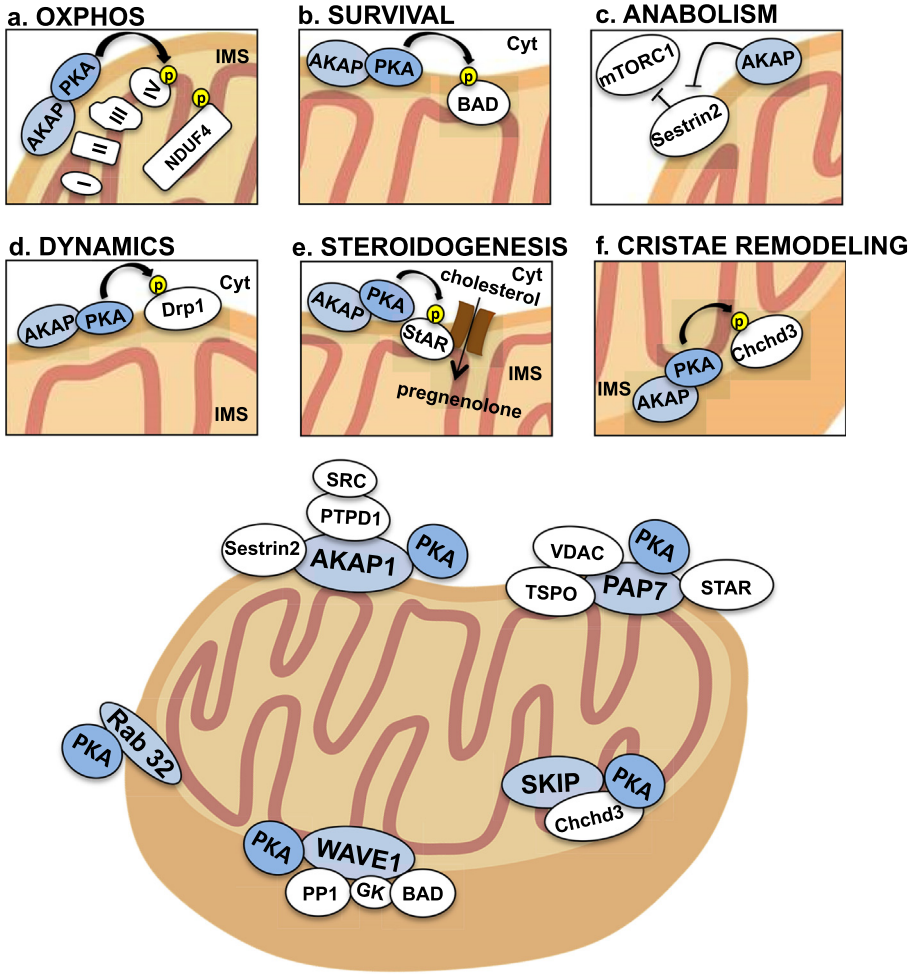

Fig. 1. Mitochondrial AKAPs regulate organelle activity. Distinct families of AKAPs have been identified at the mitochondrial compartments. AKAPs assemble multifunctional molecular platforms at the OMM and within the mitochondrial compartment that include not only PKA, but also other non-PKA partners. Phosphorylation of mitochondrial subtsrates by PKA controls essential aspects of organelle physiology. **a**. PKA phosphorylation of components of the respiratory chain positively regulates oxidative ATP synthesis.**b**. BAD binds to- and inactivates anti-apoptotic Bcl-2 homologs, promoting apoptosis. Phosphorylation and inactivation of BAD at the OMM by AKAP-anchored PKA prevents BAD/Bcl-2 interaction and inhibits apoptosis. **c**. Sestrin2 is a stress-induced anti-oxidant gene product that acts as inhibitor of mTORC1. By targeting sestrin2 to mitochondria, AKAP1 relieves the inhibitory constrain on mTORC1 and promotes anabolism and tumor cell proliferation. **d**. Phosphorylation and inactivation of the pro-fission protein Drp1 promotes mitochondrial fusion. **e**. Transport of cholesterol from cytosol (cyt) to intermembrane space (IMS) is stimulated by PKA-dependent phosphorylation of mitochondrial StAR protein. Consequent conversion of cholesterol to pregnenolone by the mitochondrial sidechain cleavage enzyme system (P450scc) is required for steroid biosynthesis. **f**. Phosphorylation of ChChd3 by SKIP-associated PKA within the mitochondrial compartment is essential for maintaining mitochondrial cristae integrity/remodeling.

cytoskeleton and organelles, including mitochondria, by direct interactions with A-Kinase-Anchor-Proteins (AKAPs). AKAPs are a group of scaffold proteins that assemble signaling enzymes, adaptor molecules and mRNAs, and create intracellular sites where the signals are kinetically and spatially transmitted to downstream target subtsrates, eliciting major biological responses [11]. In the last few years, it has been found that different classes of AKAPs locally orchestrate signaling events at mitochondria. Activation and integration of distinct signal pathways by AKAPs at mitochondria efficiently couple hormone stimulation to mitochondrial activities, supporting metabolism and survival, and providing an efficient system to rapidly adapt mitochondrial activity to changes in metabolic demands. For their essential role in mitochondrial metabolism, AKAPs are currently being considered as therapeutic targets for proliferative disorders, including cancer [12–14].

This review will focus on the dynamic connections between compartmentalized cAMP signaling and mitochondrial activity, with important implications in the control of cancer cell growth and metabolism.

2. Compartmentalized cAMP signaling

cAMP represents the prototypic second messenger generated at cell membrane by GPCR-activated adenylate cyclase. In eukaryotes, the major cAMP-responsive enzyme is protein kinase A (PKA). PKA is a tetrameric holoenzyme composed of two regulatory subunits (R) and two catalytic moieties (C). The binding of cAMP to R dissociates the holoenzyme and releases the C subunit. Phosphorylation of intracellular substrates by C subunit controls a wide array of cellular functions, including respiration and metabolism. The composition and the biochemical properties of the R/C subunits allows the generation of distinct classes of PKA holenzymes with individual sensitivities to cAMP and differential tissues and cellular distributions. In this context, the rate of PKA activation and the persistence and magnitude of cAMP signals increase the specificity and sensitivity of cells to distinct GPCR activators [15–20]. Another layer of complexity in the cAMP signaling system is represented by the PKA anchor proteins (AKAPs). AKAPs act as scaffold proteins that bind and target PKA holoenzymes to distinct intracellular compartments. AKAPs employ a PKA-binding motif that tethers the R subunit of PKA holoenzyme and a targeting module that localizes the AKAP/kinase complex to a given organelle, membrane or cytoskeletal element. By spatially distributing PKA holoenzymes within the cell, AKAPs efficiently control the propagation of cAMP signals from sites of signal generation to downstream substrates/effectors [21,22]. AKAPs also assemble multienzyme complexes which include not only PKA holoenzymes, but also components of the cAMP generating systems (receptors and adenylate cyclase), effectors (PKA and Epac) and attenuating enzymes, such as cAMP-directed phosphodiesterases (PDEs) and protein phosphatases (PPs). Moreover, AKAPs complexes include adaptor molecules, mRNAs and effector enzymes distinct from PKA.The complexes assembled by AKAPs, namely ‘transduceosomes’, generate highly specialized intracellular microenvironments where different signaling pathways converge and focus, exerting biological effects in response to stimulation by hormones, cytokines, neurotransmitters and growth factors. This signaling apparatus operates in multi-cellular organisms and evolved as a duplication of ancient linear unicellular systems, where the stimulation of signaling enzymes and adapter proteins occurred in a single step within the same intracellular location.

Pharmacological or genetic interference with the dynamic assembly of AKAPs complexes in living organisms profoundly impacts on key physiological processes underlying metabolism, respiration, growth, differentiation and development [5,11,23–25].

3. Mitochondrial cAMP signaling: mechanisms and actors

Activation of the PKA pathway controls essential aspects of mitochondrial physiology, including respiration, survival, metabolism, organelle biogenesis and dynamics. Several mitochondrial AKAPs have been isolated and functionally characterized [9,10] (Fig. 1). Among these, AKAP1 represents the prototypic mitochondrial AKAP that is mechanistically linked to essential aspects of mitochondrial metabolism and dynamics. AKAP1 binds and targets PKA to the outer mitochondrial membrane (OMM). AKAP1 mRNA undergoes alternative splicing that generates different variants of AKAP1 which include AKAP121, AKAP100 and AKAP84. All splice variants share the NH_2-terminal core that incorporates the PKA binding motif, but diverge at their C-terminus. The first 30 N-terminal residues (MT domain) of the AKAP1 products mediates the interaction of the proteins with the OMM. Addition of an hydrophobic 33-residue modifier segment upstream to the MT domain by alternative splicing generates a protein that is targeted to the endoplasmic reticulum (ER). The dynamic shift in the localization of AKAP1-assembled signaling complexes between ER and mitochodria functionally links the two organelles in control of Ca^{2+} homeostasis and cell respiration [5,26]. This represents an evolutionary-conserved mechanism that redirects cAMP signaling from one organelle to another in response to specific metabolic requirements or stress conditions. However, the presence of a conserved ER targeting domain at the N-terminus of AKAP1 has been questioned [27].

Mouse AKAP121 and its human (AKAP149) and Drosophila orthologs (MDI) possess a KH domain located at their C-terminus which mediates interaction with nuclear-encoded mRNAs [28–30]. AKAP1 binding to mRNA and ribosomes at the OMM promotes efficient translation and co-import of mitochondrial proteins into the organelles, with important implications for global protein synthesis and mitochondrial physiology [31–33]. Importantly, AKAP1 complexes include not only PKA, but also protein tyrosine kinases (Src), phosphatase (PP1, PTPD1), phosphodiesterases, mRNA and adenylate cyclase. The transduction unit assembled by AKAP1 supports mitochondrial homeostasis, metabolism, respiration and survival [34,35].

A wide number of mitochondrial proteins have been identified and functionally characterized as PKA substrates. Thus, in metabolically active cells, hormone stimulation induces PKA-mediated phosphorylation of different components of the oxidative phosphorylation machinery (OXPHO). The signaling circuitry activated by AKAP1/PKA complex at mitochondria favors allosteric regulation of the respiratory enzymes by newly synthesized ATP moieties, significantly impacting on global respiration, thermogenesis and ATP synthesis. Moreover, growth factor-induced phosphorylation of mitochondrial proteins by AKAP1-assembled src tyrosine kinase further contributes to the regulation of mitochondrial activity, integrating distinct signaling pathways travelling from membrane to the organelles [27].

One role of AKAP1 regulated cAMP signaling in cell survival has been explored mechanistically. BAD is a BH3 proapoptotic Bcl-2 family member that interacts with- and inactivates anti-apoptotic Bcl-2 homologs. In the presence of death stimuli, inhibition of Bcl-2 activity by BAD induces mitochondrial cristae disruption, mitochondrial swelling and release of cytochrome *c* from the organelles, with consequent activation of caspases and induction of apoptosis. In contrast, survival stimuli activate ser/thr protein kinases that promote phosphorylation and inactivation of BAD, thereby inhibiting cell death. BAD has been isolated in complex with AKAP1 and PKA. In response tosurvival signals, AKAP121 selectively enhances cAMP-PKA signaling to mitochondria favouring PKA phosphorylation of BAD at Ser155 and preventing its association with- and inhibition of- the anti-apoptotic Bcl-2 protein [36,37]. This is especially important for cells subjected to stress conditions or serum deprivation. In proliferating cells, instead, activation of PKA maygenerate divergent biological responses that favor apoptosis. Thus, mitochondrial survivin, also named IAP (inhibitor of apoptosis), interacts with its homolog XIAP and with the co-factor hepatitis B X-interacting protein (HBXIP). The trimeric complex has strong cytoprotective effects and inhibits apoptosis. Activation of PKA induces phosphorylation of cytosolic IAP within the XIAP-interacting domain (Ser20). IAP phosphorylation prevents the formation of the IAP/XIAP complex and stimulates cell death. PKA action is counteracted by a pool of mitochondrial ser/thr-phosphatase (PP2A) that dephosphorylates IAP and promotes survival. Mutations of IAP at the PKA site stabilize IAP/XIAP complex and inhibit the apoptotic machinery. This ultimately contributes to tumor growth and dissemination *in vivo* [38].

The biological activities mediated by AKAP1 at mitochondria are modulated by the ubiquitin proteasome system (UPS). Following hypoxic insult, the RING E3 ubiquitin ligase Siah2 rapidly accumulates within cells, leading to ubiquitination and proteolysis of PHD2 (prolyl hydroxylase), an enzyme that under normoxic conditions negatively controls the stability of the hypoxia sensor HIF-1α (Hypoxia Inducible Factor-1α) [39,40]. Removing PHD2, Siah2 increases the levels of HIF-1α and promotes the HIF1α-dependent transcription of several genes, as vascular endothelial growth factor (VEGF), tumor growth factor β (TGFβ) and erythropoietin. These growth factors promote vascularization, erythropoiesis and metabolism of ischaemic tissue, preventing further irreversible tissue damage. An important event that occurs during hypoxia is the downregulation of mitochondrial activities. This reduces mitochondrial oxidative stress in the presence of low oxygen levels. This mechanism requires Siah2-dependent ubiquitination and proteolysis of AKAP1. Degradation of AKAP1 by the UPS rapidly attenuates the oxidative metabolism, promoting adaptation of cells to accidental hypoxic conditions [41].

The control of AKAP1 stability by UPS is also important for mitochondrial dynamics. Mitochondria are dynamic organelles that undergo fusion or fission, changing their shape, number and intracellular distribution in response to fluctuations in metabolic demands. The remodeling of mitochondrial morphology is rapid and, in some circumstances, quite dramatic. It is vital for mitochondrial activities under specific metabolic needs. The balance between fusion and fission requires the activity of several factors/regulators that actively participate in mitochondrial dynamics. AKAP1/PKA complex controls mitochondria dynamics by directly modulating the activity of the dynamin-related protein 1 (Drp1), a protein that promotes mitochondrial fission. Thus, phosphorylation and inactivation of Drp1 by PKA within the AKAP1 complex promotes elongation of mitochondria and enhances cellular resistance to apoptotic signals. In contrast, dephosphorylation of Drp1 by the calcium-activated ser/thr phosphatase, calcineurin (also known as PP2B), restores Drp1 activity and promotes mitochondrial fission and cell death. Similarly, proteolysis of AKAP121 by the hypoxia-induced Siah2 pathway removes the inhibitory constraint of PKA on the Drp1/fission machinery and leads to mitochondria fragmentation and cell death [42–45]. This exemplifies a regulatory mechanism operated by the AKAP1/PKA signaling module on mitochondria that finely controls dynamic events underlying mitochondrial adaptation to metabolic or environmental stress.

Other AKAPs have been physically and functionally linked to several regulators of mitochondrial physiology, including Rab32, WAVE1, PAP7 and SKIP. RAB32 is a GTPase Rab family member that controls mitochondrial dynamics and ER activityby an AKAP-like mechanism [46–48]. A centrally located 20-residue stretch forms an α-helical wheel that mediates the interaction of Rab32 with PKA, whereas lipid modification of two C-terminal cysteine residues promotes attachment of the protein at the interface between themitochondrial and ER membranes (MAM). Localization of Rab32/PKA complexes at MAM is important for ER calcium homeostasis, mitochondrial dynamics and survival. Thus, interfering with Rab32 expression or activity induces

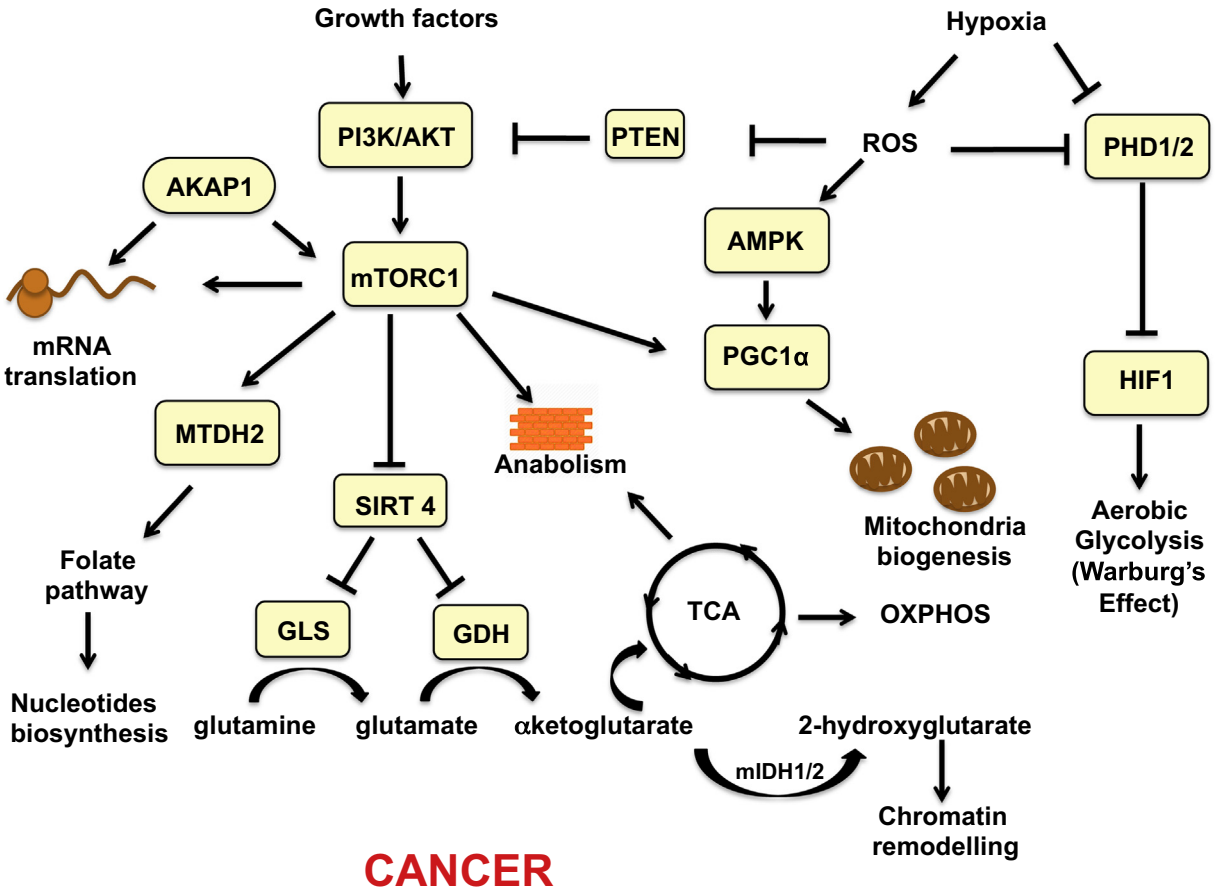

Fig. 2. Integration of signaling inputs and metabolic pathways in cancer cells. Aberrant activation of the PI3K/AKT pathway increases the mTOR-dependent anabolic route, inducing mitochondrial biogenesis and transcriptional repression of SIRT4. By removing the inhibitory constrain of SIRT4 on glutaminase (GLS) and glutamate dehydrogenase (GDH), mTOR supports α-ketoglutarate production and the TCA cycle. In some cancer types, aberrant conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG) by mutated IDH1/2 induced chromating remodeling and transcription of cancer-associated genes. PI3K/AKT/mTOR pathway also activates the methylentetrahydrofolate dehydrogenase 2 (MTDHD2)-dependent folate pathway, thereby promoting nucleotide biosynthesis. mTOR upregulates PGC1a-dependent mitochondrial biogenesis and anabolism. Mitochondrial AKAP1 promotes translation and positively contributes to mTOR-dependent signaling cascade. Activation of AMP-regulated kinase (AMPK) by ROS stimulates a PGC-1α-dependent antioxidant circuitry that further supports mitochondrial homeostasis and metabolism. Elevation of ROS levels also inhibits prolyl hydroxylases (PHDs) and leads to accumulation of HIF1. HIF1-depedent upregulation of glycolytic enzymes contributes to the Warburg's effect.

fragmentation and drastic collapse of mitochondria around the microtubule organizing center (MTOC), impeding movement of the organelles along the neurites and activating the cell death pathway.

WAVE1 (Wiskott-Aldrich syndrome protein verprolin homologous-1) is a PKA anchor protein expressed in neurons where itcontrols actin polymerization and cytoskeletal remodeling [49–51]. In mature neurons, WAVE1 is maintained in its inactive state by direct phosphorylation by Cdk5, a cyclin-dependent kinase family member. Stimulation of neurons with NMDA (N-Methyl-D-Aspartate) promotes proteolysis of the regulatory subunit of CDK5 and de-phosphorylation of WAVE1. Dephosphorylated, active WAVE1 translocates from actin filaments to mitochondria. Bound to mitochondria, WAVE1 induces organelle fission and trafficking along filopodia, promoting filopodia outgrowth and spine morphogenesis, a prerequisite for synaptic activity and plasticity. The mechanisms regulating localization of WAVE1 to mitochondria possibly involve interaction with mitochondrial BAD family members. These nucleate multivalent complexes on mitochondria that include glucokinase (GK), WAVE1 and other PKA-regulated substrates/effectors. The complexes assembled by BAD on mitochondria act as metabolic sensors for nutrient availability and stress stimuli, optimally integrating glycolytic machinery and respiration with the organelle network and apoptotic pathway [52–54].

Peripheral-type benzodiazepine receptor-associated protein (PAP7) is a mitochondrial AKAP that selectively binds and targets type I PKA holoenzyme (PKAR1A) to the OMM [55–57]. A macromolecular complex including translocator protein (TSPO), the voltage-dependent anion chanel (VDAC-1), PAP7 and type I-PKA holoenzyme (PKAR1A) has been isolated from mitochondria and biochemically characterized. PAP7 is present in all mammalian tissues and cells, with predominant expression in steroidogenic tissues, such as testis and adrenal gland. PAP7 myristoylation is required for OMM binding, where it regulates cholesterol flux from cytosol to mitochondria. PAP7 favours a PKA-directed phosphorylation and catalytic activation of steroidogenesis acute regulatory protein (StAR) at mitochondria, leading to cholesterol transport into the organelles. Interfering with PAP7-mediated cAMP signaling profoundly affects hormone-induced cholesterol transport into mitochondria and downregulates steroidogenesis in endocrine cells. In adrenal tumor cells, PAP7 participates in the PKAR1A-dependent mitogenic signaling, supporting tumorigenesis and hormone-independent hypercortisolism.

Sphingosine kinase type 1-interacting protein (SKIP, SPHKAP) was originally identified as a negative regulator of sphingosine kinase 1 activity [58]. Biochemical analyses unveiled that SKIP operates as *a bona fide* AKAP that binds with high affinity the PKAR1A [59]. Mapping analysis identified two conserved AKAP amphipathic helical wheel domains at the C-terminus of the protein that might simultaneously

interact with two PKAR1A holoenzyme moieties [59]. Localization studies demonstrated that a significant fraction of SKIP/PKAR1A complexes could be present within the mitochondrial compartment [58]. Several mitochondrial interactors of SKIP have been identified, including ChChd3, ChChd6, SAM50, MTX1, and MTX2. ChChd3 (Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 3), a peripheral component of the intermembrane space essential for maintaining mitochondrial cristae integrity (see below), has been identified as direct substrate of PKA. Phosphorylation of ChChd3 by PKA requires SKIP, suggesting that mitochondrial SKIP/PKA complexes have relevant physiological roles in cristae integrity/remodeling and mitochondrial activities [60].

4. Mitochondrial biogenesis, mitophagy and dynamics in cancer cells

Cellular mitochondrial content plays a central role in metabolic adaptation of cells to stress conditions and other changes in the microenvironment. The number of mitochondria is tightly controlled by two distinct highly conserved mechanisms: biogenesis and mitophagy. Both events work in an interconnected and dynamic way to ensure mitochondrial mass, function and quality control [61,62]. In cancer cells, both mechanisms are crucial for development and progression of a malignant tumor lesion [63–65].

Mitochondrial biogenesis is regulated by a wide array of factors and stimuli. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) is the master regulator of the transcriptional program that governs mitochondria biogenesis [66,67] (Fig. 2). PGC1α is rapidly activated following cellular transformation by a variety of oncogenes, including c-Myc. In normal proliferating cells, c-Myc activation by growth factors promotes mitochondrial biogenesis that, in turn, enhances respiration, survival and metabolism, contributing to the increased energy demands. This mechanism is overstimulated in cancer cells bearing oncogenic mutations of c-Myc, leading to massive mitochondrial biogenesis that efficiently couples the metabolic needs of cancer cells to aerobic glycolysis and biosynthetic pathways. Interfering with the PGC1α-dependent transcriptional program negatively impacts on cancer growth [68]. Moreover, c-Myc activates the AMPK-related protein ARK5, which is involved in the maintenance of mitochondrial energy homeostasis [69]. The transcriptional activity of c-Myc is amplified by transcriptional co-activators, such as AMY 1. AMY 1 is a Myc-associated protein that has been also found in complex with AKAP1 and functionally linked to spermatogenesis [70]. A role of AKAP1 on AMY-dependent regulation of c-Myc has not been addressed. PGC1α transcription and accumulation is induced by the mammalian target of rapamycin (mTOR). By modulating PGC1α levels, mTOR directly controls mitochondrial biogenesis [66,71]. Additionally, mTOR phosphorylation inhibits the activity of 4E-binding proteins (4E-BPs), a group of translational inhibitors that affects the synthesis of nuclear-encoded mitochondrial proteins.

In this context, AKAP1 has been recently identified as a novel c-Myc target. A cis-acting element within the AKAP1 gene promoter is required for c-Myc upregulation of AKAP1 transcription [8]. AKAP1 acts as a central signaling hub on mitochondria, finely coupling respiration, biosynthetic pathways, translation and survival [5,28]. c-Myc-mediated upregulation of AKAP1 is a molecular signature in a wide array of Myc-overexpressing human cancers, and AKAP1 levels correlate with the malignant phenotype and poor survival of cancer patients [8]. Interestingly, AKAP1 positively regulates mTOR. Thus, AKAP1 interacts with sestrin2, a stress-induced gene product that negatively regulates mTORC1 pathway.By targeting sestrin-2 on mitochondria, AKAP1 relieves the inhibitory constraint of sestrin2 on the mTOR-dependent metabolic pathway and enhances the scavenging system on the organelle, supporting cancer cell growth and survival (Fig. 1 and Fig. 2). As expected, downregulation of AKAP1 increases oxidative stress, inhibits mTOR pathway, and affects tumor growth [8]. This signaling circuitry exemplifies a mechanism of regulation of mitochondria biogenesis by a nuclear oncogene-driven assembly of multi-scaffold complexes on the organelles that controls cancer growth and metabolism.

Mitochondria are removed by mitophagy. This is a highly conserved mechanism that cells adopt to eliminate damaged or unneeded mitochondria, preventing accumulation of dysfunctional organelles that would otherwise inhibit respiration, metabolism and survival [72]. This, in part, explains the absence of damaged mitochondria, or mitochondria carrying genome mutations affecting organelle activity, in cancer cells. Selective pressure induces elimination of damaged mitochondria to preserve the metabolic activities that support cancer cell growth. At the mechanistic level, depolarization of the mitochondrial membrane activates PINK1 (PTEN-induced putative kinase 1 PINK1), which in turn recruits Parkin to the outer mitochondrial membrane. Ubiquitylation of mitochondrial proteins by Parkin activates the mitophagy machinery that incorporates and degrades dysfunctional mitochondria. In addition, PINK1 targeted to mitochondria displaces PKA from AKAP1, impairing the inhibitory phosphorylation of the kinase on Drp1 and promoting mitochondrial fission and mitophagy [43]. Conversely, PKA counteracts the effects of Parkin on mitochondria. Thus, PKA phosphorylation of MIC60 and MIC19, two members of the mitochondrial contact site and cristae organizing system (MICOS) of the inner mitochondrial membrane, prevents recruitment of Parkin to the mitochondrial membrane and suppresses organelle clearance [73].

In addition to the PINK1/Parkin pathway, mitophagy is activated by other regulatory proteins, such as BNIP3, NIX, FUNDC1 and BCL2L13 [72]. The relevance of these pathways in promoting mitophagy in cancer cells and their role in tumor growth and progression is not well defined. Several oncogenes, including K-Ras, induce transcription and accumulation of nuclear factors of the MiTF/TFE family proteins that control the autophagy machinery and lysosome biogenesis. Interfering with the clearance of damaged mitochondria in oncogene-induced tumors severely affects respiration, growth and survival, impairing development and metastasis of the malignant lesions [74].

Mitochondrial dynamics is emerging as an important parameter of cancer cell growth. Fission and fusion regulate mitochondria morphology; mitochondriaassumean elongated shape after fusion or a punctiform pattern after fission [75,76]. Mitochondrial fusion is directed by two distinct GTPase family proteins, mitofusins and OPA1, whereas fission is promoted by the dynamin-related protein 1 (Drp1) and hFis1. Distinct signaling pathways, including the GPCR-cAMP pathway, control the activity of the fusion and fission machinery. It is worth noting that, in rapidly proliferating cancer cells, mitochondria often assume a fragmented pattern, suggesting that fission positively contributes to their metabolic reprogramming. In support of this model, preventing mitochondrial fission by selectively targeting Drp1 expression or activity inhibits cell transformation induced by several oncogenes, including K-Ras, and severely inhibits tumor growth *in vivo* [75,77]. However, other oncogenes, as c-Myc, induce a gene expression program that ultimately leads to mitochondrial fusion [78]. This apparently conflicting evidence clearly suggests that the mechanisms and the role of mitochondrial dynamics in cancer cell growth are more complex than initially postulated and demand further investigation.

5. Mitochondrial metabolism and signaling in cancer cells

Mitochondria integrate signal inputs from extracellular stimuli to modulate and shape the activity of metabolic enzymes and regulators. In normal cells, interconnections between glycolysis, oxidative phosphorylation, tricarboxylic acid cycle (TCA), beta oxidation of fatty acids (FAO) and the biosynthesis of nucleotides, amino acids, lipids, and other mitochondrial bioproducts provide an efficient system to support survival, growth and differentiation. Modification of this system is critical forthe development of malignant tumors (Fig. 2). Within the tumor lesion, the rapidly dividing cancer cells undergo a profound metabolic reprogramming that primarily involves mitochondria in

order to support their high energetic requirements [65,79–81].

A major metabolic change in cancer cells is the switch to aerobic glycolysis, also known as 'Warburg effect'. This shift allows tumor cells to ferment glucose even in the presence of oxygen. The net effect of the metabolic shift is the production of large amounts of lactate, which was initially considered to result from mitochondrial respiratory defects. However, no functional alteration or enzymatic defects of components of the respiratory chain are detectable in cancer cells. Instead, the activity of the oxidative phosphorylation machinery is fully retained or even increased in certain types of cancers [82]. At the molecular level, upregulation of the glycolytic pathway is supported by HIF-1α, which accumulates within the tumor lesion as consequence of a hypoxic microenvironment and reactive oxygen species (ROS)-mediated inhibition of prolyl hydroxylases (PHDs). The effects of ROS are normally counteracted by the SIRT3-mediated deacetylation and activation of the scavenging enzymes superoxide dismutase SOD2 and IDH2, and by induction of anti-oxidant genes [83–86].

Oncogenic mutations of K-Ras, c-Myc, phosphatidylinositol-3(PI3) kinase, or genetic inactivation of tumor suppressors, as p53 and PTEN (phosphatase and tensin homolog), promote and sustain the high glycolytic rate in cancer cells [87–90]. In particular, K-Ras downregulates mitochondrial respiration by inhibiting the activity of complex I and increasing mitochondrial fission and mitophagy [77,91].

Activation of the PI3K/AKT signaling pathway in cancer cells increases the mTOR-dependent anabolic route and promotes mitochondrial biogenesis [92,93]. mTOR also represses the transcription of SIRT4, leading to increased expression of glutaminase (GLS) and glutamate dehydrogenase (GDH). This enhances theconversion of glutamine to glutamate, and glutamate to α-ketoglutarate (α-KG), which fuels the TCA cycle. A significant amount of α-ketoglutarate can be converted to isocitrate by the isocitrate dehydrogenases (IDHs) to sustain biosynthetic and redox reactions [94,95]. PI3K/AKT/mTOR pathway also stimulates nucleotide synthesis by upregulating the expression of methylentetrahydrofolate dehydrogenase 2 (MTDHD2), the rate-limiting enzyme of the folate pathway [96].

In malignant tumors, activation of AMP-regulated kinase (AMPK), an enzyme activated under nutrient limitation, confers a metabolic advantage to rapidly proliferating cells. Within the tumor context, AMPK promotes mitochondria biogenesis, favours energy production and metabolism, and facilitates elimination of damaged mitochondria (mitophagy) that might otherwise negatively affect cancer cell growth [97,98]. Interestingly, AKAP1 has been identified as a direct target of AMPK; AKAP1phosphorylation by AMPK during increased energy demands stimulates respiration and mitochondrial activity [99]. Thus, as an upstream regulator of mTOR pathway, AKAP1 works at the boundary between the energy sensing/producing system andthe anabolic pathway [8]. This loop may influence mechanisms governing mitochondrial plasticity duringthe course of tumorigenesis, favouring the metabolic switch in cancer cells. Functional interference with mitochondrial activity in the presence of activated oncogenic pathways inhibits the growth and metastatic potential of tumor cells. This supports the concept that metabolic adaptation of mitochondria is a fundamental mechanism to support and sustain tumor growth and widespread dissemination of cancer cells.

6. ROS production and oncometabolites

Reactive oxygen species (ROS) are important byproducts of mitochondrial respiration. Although they have been considered as toxic, their role as second intracellular messengers has been recently documented. The physiological production of mitochondrial ROS is counterbalanced by a regulated antioxidant system, represented by superoxide dismutases (SOD1/2), glutathione, thioredoxin and peroxiredoxins [100–102]. In cancer cells, ROS accumulation may have dual functions, as drivers of oncogenic mutations, and as cytotoxic agents. This is especially relevant under stress or hypoxic conditions, where ROS levels dramatically increase, stabilizing HIF1-alpha and supporting survival and mitogenic pathways of cancer cells (Fig. 2). As example, ROS-mediated oxidation of the active site of PTEN, a negative regulator of PI3K-AKT pathway, decreases phosphatase activity and leads to overstimulation of the anabolic pathway and cell survival. Similarly, ROS-mediated inactivation of the tyrosine phosphatase PTP1B, a negative regulator of most tyrosine kinase receptors (RTKs), sustains the mitogenic pathways induced by growth factors [103]. Moreover, ROS-induced oxidation of Src tyrosine kinase at its catalytic cysteine site promotes and supports metastatic dissemination of cancers [104]. Interestingly, stimulation of ROS synthesis can also intersect AMPK-dependent metabolic pathways. Thus, ROS activation of AMPK stimulates a PGC-1α-dependent antioxidant circuitry that supports mitochondrial homeostasis and cellular metabolism. Interfering with this control system in cancer cells leads to accumulation of HIF-1α and to a metabolic reprogramming [105–108]. Stress conditions and hypoxic microenvironment can also affect the mitochondrial membrane permeability transition (MMPT), causing defects of the apoptotic pathway and giving rise to tumor cell populations that escape programmed cell death. The most common example is the overexpression of BCL2 in many malignant lesions that enhances the resistance of tumor cells to apoptosis [109]. These findings suggest that tumor cells can balance pro-oxidant and anti-oxidant systems that favours accumulation of ROS to levels adequate to support tumor cell proliferation and metabolic activities, and to prevent cytotoxic effects and apoptosis.

In addition to ROS, tumor cells accumulate several mitochondrial metabolites that directly contribute to different aspects of tumor cell biology. Thus, activating mutations of the isocitrate dehydrogenase enzymes (IDH1/2), in gliomas and in other human cancers, leads to accumulation of the α-ketoglutarate-derived oncometabolite 2-hydroxyglutarate (2-HG) [110] (Fig. 2). This by-product interferes with the activity of chromatin remodeling enzymes (TET and JHDM), exerting major effects on gene expression [111,112]. These compounds also inhibit prolyl hydroxylases (PHD) and stabilize HIF-1α, enhancing the HIF-1α-induced Warburg effect [113,114]. In some human tumors, inactivating mutations of the trycarboxylic acid cycle (TCA) enzymes succinate dehydrogenase (SDH) and fumarate hydratase (FH) lead to accumulation of two intermediates, fumarate and succinate. High levels of fumarate also lead to increased cysteine succinylation and consequent inhibition of the Kelch-like ECH-associated protein 1 (KEAP1), a negative regulator of Nrf2 [115,116]. By removing the inhibitory constraint of KEAP1, fumarate enhances the Nrf2-mediated anti-oxidant response pathway that supports cell proliferation and tumor growth.

7. Targeting mitochondria in cancer therapy

The cellular energy production required for anabolic and catabolic reactions in cancer cells primarily relies within mitochondria. Mitochondria are also the principal source of reactive oxygene species (ROS) production that contributes to cancer cell growth and metastasis. However, high levels of ROS often result in tumor cell death. Accordingly, excessive enhancing of ROS production can be a valuable tool to kill cancer cells (Fig. 3). Thus, treatment with 2-methoxyestradiol (2-ME), with the microtubule-disrupting agent (CYT997) or with metformin increases ROS levels and promotes tumor cell apoptosis [117,118]. However, in some cancers, the apoptotic machinery is defective due to overexpression of anti-apoptotic proteins (Bcl-2 or IAP family members) or to suppression of pro-apoptotic proteins, as BAX and BAK. Furthermore, tumor cells can develop resistance to treatment based on the induction of apoptosis. For these reasons, novel strategies have been developed to target members of the apoptotic machinery. In particular, Venetoclax, an inhibitor of Bcl-2, or small molecules mimicking the function of the IAP inhibitor Smac/Diablo have been used in clinical trials of cancer patients [119,120].

Mitochondrial metabolism is fundamental for tumor growth, and

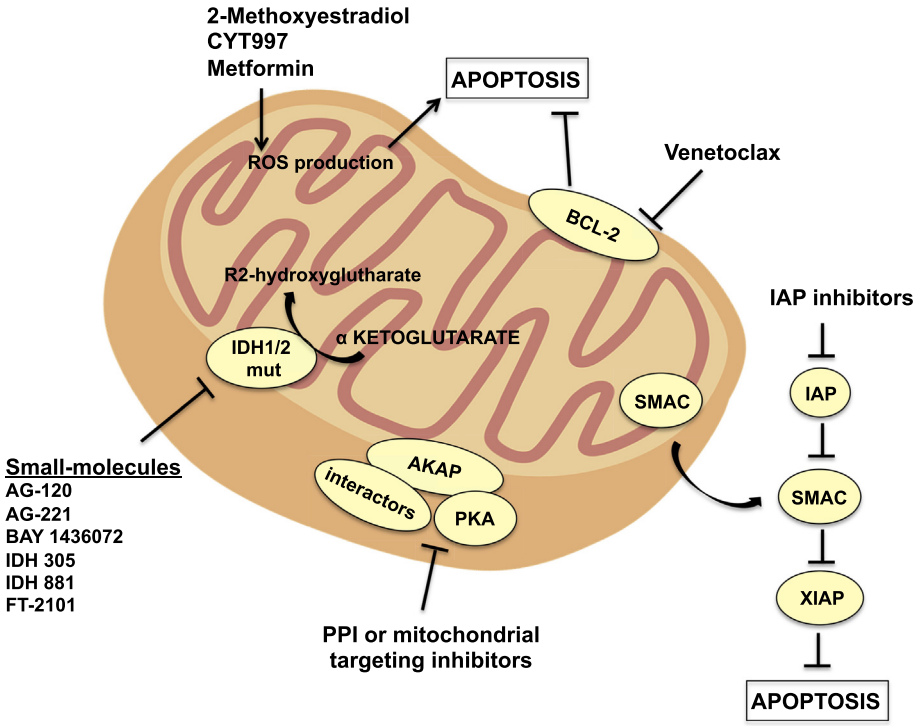

Fig. 3. Targeting mitochondria activity for cancer therapy. To selectively kill cancer cells, different experimental approaches have been designed to inhibit mitochondrial metabolism. Thus, forced overeproduction of mitochondrial ROS by treatment with 2-methoxyestradiol (2-ME), microtubule-disrupting agents (CYT997) or anti-diabetic drugs (metformin) efficiently enhances tumor cell killing. Similarly, inhibiting the anti-apoptotic machinery of cancer cells using bcl-2 antagonists (Venetoclax) or IAP inhibitors have been successfully used as cancer chemotherapeutics. Moreover, highly selective inhibitors of mutated IDH1/2 have been recently developed and are currently being used as chemotherapeutics in several clinical trials. Finally, targeting compartmentalized cAMP signaling at mitochondria using protein-protein interaction (PPI) inhibitors or small molecules interfering with mitochondrial localization of AKAP complexes have potential relevant implications as novel anti-cancer chemotherapeutics.

mutations of metabolic enzymes, as IDH1 and IDH2, have been causally linked to the development and progression of gliomas and leukemia. Accordingly, selectiveinhibitors of mutated IDH1/2 have been developed and are currently being used as chemotherapeutics in clinical trials (Fig. 3). Similarly, chemical interference with the glycolytic pathway, with OMM permeability or with respiratory chain activitymay open novel therapeutic windows [121–123].

Targeting compartmentalized cAMP signaling is becoming of interest in translational medicine and several approaches have been tested and experimentally validated. As an example, peptides spanning the amphipathic helical wheel of AKAPs have been successfully employed to delocalize and inhibit cAMP-dependent events at a given target organelle, both in cell cultures and *in vivo*, offering potential applications for disease treatment [124–129]. However, the high conservation of the amphipathic helical wheel among different families of AKAPs may generate off-target effects of the displacing peptides, thus limiting its clinical value. As an alternative approach, we envisage the design of competitor molecules targeting unique domains of AKAPs that are employed in tethering relevant interactors and/or regulators of the scaffold complex. In particular, AKAP1 binds and targets PTPD1/src complex to mitochondria, which promotes oxidative phosphorylation. AKAP1 also binds and inhibits sestrin2, a physiological inhibitor of mTOR pathway. By inhibiting sestrin2, AKAP1 positively regulates the anabolic pathway [8]. Accordingly, peptides or molecules targeting the sestrin2 or PTPD1 interaction domains could interfere with mitochondrial respiration and anabolism in cancer cells. Moreover, strategies aimed to delocalize an entire AKAP complex, *e.g.*, the AKAP1 complex from the mitochondrial compartment, could be even more efficient in inhibiting oncogenic pathways and metabolic activities, ultimately leading to cancer cell death (Fig. 3). This approach has been experimentally tested to induce oxidative stress and apoptosis in cardiomyocytes, both in cell cultures and *in vivo* [130]. An alternative strategy to modulate AKAP-regulated oncogenic pathways is to downregulate AKAP expression. The use of small RNA molecules (siRNAs and miRNAs) targeting specific regions of AKAP mRNAs can be employed to inhibit the growth and progression of AKAP-addicted cancers. Proof-of principle of the validity of this strategy has been recently provided in an orthotopic mouse model of human glioblastoma [8,131]. However, the stability, the biodistribution and the delivery of small RNAs to target tumor tissues, and possible unacceptable side effects in disrupting of AKAP complexes, represent a major limitation for these treatments.

8. Concluding remarks

Mitochondria are essential organelles for eukaryotic cells. They are the sites at which cell respiration, survival signals and metabolic pathways converge and integrate. In the last decade, the role of mitochondria in signal transduction in addition to their role in cell respiration and metabolism has come to be recognized. A wide array of signaling relays, adapter proteins, receptors, chanels, transcription factors and regulators have been isolated from, and are part of the mitochondrial compartment. Mitochondria now unambiguosly appear as a cellular hub where metabolism and respiration integrate with signaling pathways that support cell growth and survival. This is especially relevant for the development and progression of cancers. Tumor cells undergo a profound metabolic reprogramming that ultimately provides all the energetic needs to fuel a wide variety of cellular activities and to support the production of the building blocks for rapidly proliferating cancer cells. Mutations of mitochondrial metabolic enzymes have been mechanistically linked to the development and progression of several types of human cancers. For these reasons, mitochondrial metabolism represents a valuable target for novel, more efficient therapeutic strategies for cancer treatment. The identification of compartmentalized signaling platforms assembled by AKAPs at mitochondria and involved in critical aspects of metabolism and survival, offers the possibility to design novel tools able to interrupt the trophic signals by oncogenic pathways that are directed to mitochondria. Mitochondrial AKAPs may, thus, constitute the Achille's heel of chemoresistant cancers. Interfering with signaling events regulated by AKAPs, and preventing signal-induced metabolic switch at mitochondria, will likely provide novel valuable targets for cancer therapy.

Author contributions

AF wrote the manuscript with contributions from LR, RDD, DB and LI.

Competing financial interests

The authors declare no competing interests.

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