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Cyclin B1/CDK1-regulated mitochondrial bioenergetics in cell cycle progression and tumor resistance

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Abstract

A mammalian cell houses two genomes located separately in the nucleus and mitochondria. During evolution, communications and adaptations between these two genomes occur extensively to achieve and sustain homeostasis for cellular functions and regeneration. Mitochondria provide the major cellular energy and contribute to gene regulation in the nucleus, whereas more than 98% of mitochondrial proteins are encoded by the nuclear genome. Such two-way signaling traffic presents an orchestrated dynamic between energy metabolism and consumption in cells. Recent reports have elucidated the way how mitochondrial bioenergetics synchronizes with the energy consumption for cell cycle progression mediated by cyclin B1/CDK1 as the communicator. This review is to recapitulate cyclin B1/CDK1 mediated mitochondrial activities in cell cycle progression and stress response as well as its potential link to reprogram energy metabolism in tumor adaptive resistance. Cyclin B1/CDK1-mediated mitochondrial bioenergetics is applied as an example to show how mitochondria could timely sense the cellular fuel demand and then coordinate ATP output. Such nucleus-mitochondria oscillation may play key roles in the flexible bioenergetics required for tumor cell survival and compromising the efficacy of anti-cancer therapy. Further deciphering the cyclin B1/CDK1-controlled mitochondrial metabolism may invent effect targets to treat resistant cancers.

Keywords

metabolism; mitochondria; CDK; cell cycle; tumor resistance

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AUTHOR CONTRIBUTIONS

JL conceived the idea for the review. BX, SW, and NJ searched the literature and BX and NJ wrote the manuscript. BX generated the figure panels. BX, NJ and JL edited the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

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1. Introduction

In addition to the functions in signaling transduction, mitochondria in all organisms including singular or multiple cell forms provide the major biofuel in the form of adenosine triphosphate (ATP), the energy currency mainly generated through oxidative phosphorylation (OXPHOS) by coupling of electron transport with proton pumping, for the energy consumption required for cell proliferation and organ development. Instead of its own genome, more than 98% of mitochondrial proteins are transcribed by the genes located in the nuclear genome [1], and only 13 out of ~1500 mitochondrial proteins/factors remain to be encoded by mitochondrial DNA [2, 3]. Such coordinative pattern of two genomes in the same cell illustrates a potential evolution trend in which an organelle is adapted to a host in order to keep the homeostatic cellular functions under the control of the leading genome. It can therefore be assumed that the nuclear genome gradually rules over the mitochondrial functions so as to provide timely and economically energy supply required for different cellular functions and organism regeneration.

This two-way signaling traffic between mitochondria and the nucleus is further illustrated by accumulating evidence including that nucleus-coded proteins control the mitochondrial DNA segregation [4], dynamics, function, and autophagy [5]; whereas mitochondrial dysfunction leads to nuclear genomic instability [6], tumorigenesis [7–9], tumor growth [10, 11], therapeutic resistance [12], and tumor metastasis [13, 14]. Over functional mitochondria are also implied in different stress conditions including the adaptive response to radiation in cancer cells [15–18]. In addition, mitochondria-assisted cell cycle progression is confirmed by blocking mitochondrial fission that damages cell cycle progression and causes apoptosis [19]. Recent results suggest that mitochondria are the key cellular organelle targeted by CDKs (cylcin-dependent kinases) in compensating cell cycle regulation. In such studies, CDK4 is shown to upregulate mitochondrial antioxidant MnSOD [20], cyclin D1 inhibits mitochondrial activity in B cells [21], cyclin B1/CDK1 not only coordinates mitochondrial biogenetics for G2/M progression [22], but also mediates SIRT3 activation to enhance mitochondrial function and tumor radioresistance [23], and phosphorylates mitochondrial antioxidant MnSOD in cell adaptive response to radiation stress [24]. These results further confirm the concept that healthy mitochondria are indeed required for normal cell functions, deficiency or over function will cause different pathological conditions in cells such as cell transformation and tumor aggressiveness.

In this review, we aim to illustrate the cyclin B1/CDK1-modulated mitochondrial activities in cell cycle progression and proliferation. Taking a backward approach, we want to reveal a potential mechanism on how mitochondrial energy metabolism coordinates with cell cycle such as G2/M transition and tumor aggressive phenotype. Further elucidation of the mechanisms underlying mitochondria-regulated cell behaviors will help to understand the network on energy generation and consumption within a cell and define unknown mechanisms in balancing energy consumption in normal and tumor cells.

2. CDK1-DRP1 pathway in regulation of mitochondrial dynamics

Mitochondrial proliferation origins from existing mitochondria via complementary fission and fusion events [29], these two opposing processes dynamically and harmoniously coordinated to maintain the average size of mitochondria, plays critical roles in maintaining mitochondria function and cell division, and closely links with human diseases [25–28]. An optimal balance between fission and fusion could be critical in maintaining mitochondrial membrane dynamics and different cellular functions [30, 31]. The fusion events are carried out by a mitochondrial transmembrane GTPase known as Mitofusin (Mfn) [32] whereas dynamin related protein 1 (DRP1) is responsible for mitochondrial fission events [33], which is dependent on the communication between DRP1 and GTPase. It has been shown that DRP1 determines GTPase activity during mitochondrial fission [34, 35]. DRP1 contains at least 5 phosphorylation sites at serine residues including Ser^{585} (in rat cells), Ser^{616}, Ser^{637}, Ser^{656} and Ser^{693} (in human cells), etc. These sites were suggested to be modified by different kinases, in which only Ser^{585} and Ser^{616} can be modified by cyclin B1/CDK1.Taguchi et al. has demonstrated that in addition to chromatid segregation, cyclin B1/CDK1 regulates the mitotic mitochondrial fragmentation, a cell cycle-regulated mitochondrial fission [36]. Interestingly, phosphorylation of DRP1 by cyclin B1/CDK1 at Ser-585 residue during mitosis is found to be required to translocate DRP1 from cytosol to the mitochondrial outer membrane which is required for mitochondrial fission [36, 37]. The activated DRP1 then punctuates spots on the mitochondrial membrane to proceed with membrane constriction and fission directed by Fis1 [38, 39]. The energy-sensing adenosine monophosphate (AMP)-activated protein kinase (AMPK) is also involved in mitochondrial fragmentation when mitochondrial respiration via electron transfer chain is inactivated. Recently, a specific substrate of AMPK is identified as mitochondrial fission factor (MFF) that is identified to be the outer-membrane receptor for DRP1 required for DRP1-mediated fission process [40]. DRP1 mediated mitochondrial fragmentation is believed to allow equal distribution of the mother mitochondria into two daughter cells as the fission events occur during the cell cycle. Deficiency of DRP1 causes elongated mitochondrial filaments with reduced mitochondrial fragmentation [36, 41], and leads to mitochondrial dysfunction, loss of mtDNA and decrease of cellular ATP generation [42, 43]. As such the dynamic equilibrium between fission and fusion in mitochondrial dynamic plays critical roles in maintaining mitochondria function and cell division [44]. The cyclin B1/CDK1-mediated activation DRP-1 and mitochondrial fission contribute to the balance between fission and fusion may coordinate with cyclin B1/CDK1-mediated mitochondrial bioenergetics only in the fused mitochondria which is to be further elucidated.

Another proof in cyclin B1/CDK1-mediated mitochondrial dynamics is supported by Ras-related protein Ral-A (RALA) and its effector RalA-binding protein 1 (RALBP1). The mitotic kinase, Aurora A, phosphorylates RALA at Ser-194 to enhance the translocation of RALA into mitochondria, in which RAPLA concentrates RALBP1 and promotes mitochondrial localization of DRP1 [45]. RALBP1 binds to cyclin B1/CDK1 to enhance DRP1 phosphorylation and activation at Ser-616, which controls the fission and proper segregation of mitochondria during cell division and maintains appropriate mitochondrial and cellular function [45, 46]. However, in addition to DRP1-guided mitochondrial

fragmentation linked with reduced mitochondrial bioenergetics, DRP1 is also required for mitochondrial metabolic activation, supported by the report that ATP production is severely impaired in DRP1−/− deficient cells [43]. Phosphorylation at Ser-637 of DRP1 by cAMP-dependent protein kinase (PKA) blocks its GTPase activity by reducing the intra-molecular interaction that drive GTP hydrolysis [46, 47], which can be lifted by the phosphatase Calcineurin [48]. Data discussed in the following sections on CDK1-mediated mitochondrial bioenergetics in cell cycle progression and tumor cell behavior will highlight the concept that an enhanced mitochondrial bioenergetics is required for G2/M transition and cell proliferation. Further elucidating the precise mitochondrial dynamics linked with metabolic activity may reveal more insights on CDK1/DRP1-mediated mitochondrial functions that drive different cell behaviors.

3. CDK1 regulates mitochondrial functions

A specific subset of CDKs with their corresponding partner cyclins orchestrate the precise cell cycle progression [49]. CDK1, among the well-defined cell cycle check point proteins, is involved in regulation of an array of fundamental cellular functions for cell proliferative growth [50, 51]. Mouse embryos lacking CDK2, CDK3, CDK4, and CDK6 are still able to undergo organogenesis whereas fail without CDK1. CDK1 is able to bind to different cyclins and is sufficient to regulate all the steps required for cell division [52]. This report together with many other results indicates that CDK1 is the most critical cell cycle element for cell proliferation and organ development. CDK1 is involved not only in mitochondrial dynamics as mentioned above [36, 45], but also in mitochondrial protein influx and bioenergetics [22, 54, 55], targeting CDK1 initiates mitochondria-initiated apoptosis [53],. Another cell cycle-related complex, cyclin D1/CDK4 is also found relocating to the mitochondria and phosphorylate the major antioxidant enzyme MnSOD at Serine-106, whereby enhancing MnSOD enzymatic activity to promote mitochondrial homeostasis and prevent cellular genotoxic stress [20]. Further elucidating how mitochondrial bioenergetics is differently regulated by varied complexes of cyclins/CDKs during progression of different cycle phases may reveal more unknown mechanisms underlying cell cycle-related mitochondrial adjustment.

Cyclin B1 and its catalytic partner CDK1 belong to the fundamental kinase machinery regulating the progression from G2 to mitosis. Also known as the mitotic promoting factor (MPF), cyclin B1/CDK1 phosphorylation governs key steps for mitotic entrance featured by the nuclear envelope breakdown, spindle formation, and chromatin condensation [56]. However, the mitochondrial transition of cyclin B1/CDK1 seems to be dependent on the total levels of cellular cyclin B1 and CDK1 [57]. Under normal growth conditions, mitochondrial localization of cyclin B1/CDK1 is attenuated during G_1 phase due to a lack of cyclin B1 accumulation.

3.1 Mitochondrial translocation of CDK1

The mitochondrial matrix localization of cyclin B1/CDK1 complex has recently been identified in multiple human cells, especially shows increase in those experiencing cell cycle transition or exposed to DNA-damaging stress conditions [22, 57]. Under genomic toxic

conditions such as anti-cancer chemotherapy and radiation, cyclin B1/CDK1 expression is induced to cause the cell cycle G2/M arrest, which is believed either to extend the time period for cells figuring and fixing DNA damages to survive or to warrant a time required to initiate and process apoptosis [58, 59]. Following genotoxic stress such as ionizing radiation (IR), mitochondrial translocation of cyclin B1/CDK1 is enhanced [57]. As shown in Figure 1, relocation of cyclin B1/CDK1 to mitochondria could results from an increased overall level of cyclin B1/CDK1 in cytoplasm at the peak time of cell cycle progression during G2/M transition, or leaded by a specific mechanism to allow mitochondria to sense the increased demand of energy consumption needs. Since present and being activated at the prophase of mitosis [60], mitochondrial CDK1 phosphorylates substrates to promote mitosis. The activation of CDK1 in mitochondria is supported by the report that Cdc25c, the phosphatase activator of CDK1 [61], is identified by mapping of the mitochondrial intermembrane space [62]; both reports support that cyclin B1/CDK1 can be fully activated to boost ATP generation whereas the CDK1 proteins in cytoplasm and nucleus remain inactive for progression into prophase although the mechanism causing such segregations is to be revealed.

Proteins and polypeptides with mitochondrial leading sequences are transported into mitochondria by the translocase of the outer mitochondrial membrane (TOM) complex and translocase of mitochondrial inner membrane 23 (TIM23) complex [63]. However, like many other mitochondrial proteins, CDK1 does not hold the leading sequence for mitochondrial translocation. Many other proteins without mitochondrial leading sequences are translocated to mitochondria by chaperons [64]. The translocation of cyclin B1/CDK1 is possibly conducted with chaperons such as HSP70, HSP-90, and Cdc37 [65–68]. Harbauer et al show that clb3-activated CDK1 is able to phosphorylate the cytosolic Tom6 precursor to enhance the import of Tom6 into mitochondria, which accelerates Tom40 assembly and mitochondrial protein influx [54, 55]. Additionally, 14–3-3 family proteins, well-defined as mitochondrial chaperons with mitochondrial targeting sequences in their ligands [69–71], can dynamically balance cyclin B1/CDK1 inhibition and activation to control G2/M checkpoint maintenance and release [72]. 14–3-3ζ binds and transports Cdc25c to mitochondria to activate CDK1. Both 14–3-3ζ and cyclin B1 are upregulated in radiation-resistant breast cancer cells [16] and knockdown of 14–3-3ζ enhances radiosensitivity and radio-induced apoptosis in CD133 (+) liver cancer stem cells [73]. Further elucidation is appreciated to reveal the mechanistic insight underlying cyclin B1/CDK1 mitochondrial translocation in normal and tumor cells.

3.2. CDK1 substrates in mitochondria

Reversible protein phosphorylation is a fundamental post-translational modification required to guide different mitochondrial functions [74, 75]. CDK1 belongs to the serine/threonine (S/T) kinase family catalyzing the transfer of phosphate from ATP to proline (P)-oriented serine (S) or threonine (T) residues. Its substrates contain either an optimal (S/T*-P-x-K/R; x, any residue) or a minimal (S/T*-P) consensus motif. It is well-defined that in mammals the oscillations in activation of different CDKs govern cell reproduction by catalyzing the transfer of phosphate from ATP to specific protein substrates. Ubersax et al has identified 200 substrates in whole-cell extracts of budding yeast that are directly phosphorylated by

CDK1 [76]. However, CDK1 is shown to phosphorylate mitochondrial proteins isolated from G0/G1 cells that possessed low endogenous cyclin B1/CDK1 activity and dozens of mitochondrial proteins contain at least one consensus site or motif that can be directly phosphorylated by CDK1. These substrates involve in multiple bio-functions including electron transport (CI-CV), tricarboxylic acid cycle, amino acid, and lipid metabolism (Table 1) [22]. A cluster of CI subunits is identified to be the CDK1 substrates in OXPHOS (NDUFV1 at T-383, NDUFV2 at T-164, NDUFV3 at S-530, NDUFS2 at S-364, NDUFAF1 at S-450, NDUFA12 at T-142, NDUFB5 at S-128 and NDUFB6 at S-550), and CIII subunit (UQCRC1 at T-266). Expression of mitochondria-targeted cyclin B1/CDK1 increases CI activity and ATP generation and G2/M-associated mitochondrial enhancement is deficient by expression of mitochondria-targeted mutant CDK1 [22]. MnSOD, the primary mitochondrial antioxidant in detoxifying superoxide for mitochondrial homeostasis is found to contain CDK1 phosphorylation consensus (Serine/Threonine-proline [Ser/ThrPro]) at Ser-106 [24, 77] and cyclin B1/CDK1-mediated MnSOD phosphorylation is required for MnSOD tetrameric conformation, enzymatic activity, and protein stability [24]. Interestingly, another critical substrate of mitochondrial cyclin B1/CDK1 is the tumor suppressor p53 that is identified at Serine-315 [57] which is to be discussed below. Cyclin B1/CDK1 also phosphorylate SIRT3, an essential NAD^+-dependent deacetylase for mitochondrial functions and homeostasis [78], at Thr-150 and-Ser159 [23]. An array of SIRT3-modified proteins including AceCS2 (K642) [79], LCAD (K42) [80], IDH2 (K413) [81], SOD2 (K53/89) [82], FOXO3 (K271/290) [83], and HMGCS2 (K310/447/473) [84] have been identified and suggested to govern mitochondrial metabolism via SIRT3 regulation (Figure 1). The cyclin B1/CDK1-mediated SIRT3 activation is another example how cyclin B1/CDK1 is applied to adjust mitochondrial activity and homeostatic status. Since SIRT3 activity is well-defined to play a key role in for preventing mitochondria-associated carcinogenesis and aging [85], this link between cylcin B1/CDK1 and SIRT further supports the close relation of cell cycle events causing ging and cell transformation.

3.3. CDK1 enhances OXPHOS in G2/M progression

Metabolic activity and energy supply are believed to be a crucial determinant for cell division and proliferation. However, the exact mechanism how mitochondria sense the increased cellular energy demands by different cycling phases was unknown [86]. ATP is generated in mitochondria by the electron transport chain (ETC) carried by the respiratory chain complexes I–IV transfering electrons i n a stepwise pattern until they finally reduce oxygen to form water. Mitochondria are in charge of processing both the tricarboxylic acid cycle (TCA) and OXPHOS whereby providing the major cellular energy source. OXPHOS supplies more than 90% of cellular ATP required for eukaryotic cells [87], and it is irrefutably critical for the progression of the cell cycle as the level of ATP determines whether cells are ready for division [88]. It is assumed that G1/S and G2/M phases are energy-sensitive processes in which pronounced energy supply is demanded for increasing biomass for cell cycle transition [89]. For this function, all of five large protein complexes (CI-CV) must be functional in the respiration chain [90, 91] and many mitochondrial function-related diseases are linked to the status of OXPHOS [92–95]. CI is the largest complex containing 46 subunits, and serves as the major entry point of electrons into OXPHOS. A functionally efficient CI is required for OXPHOS function [96] and for

successful cell-cycle progression [97]. As reported. the D-type cyclins and CDKs are associated with the metabolic crosstalk [86]. By searching mitochondrial protein databases for the CDK1 consensus phosphorylation motif (S/T*-P-x-K/R) [98] among all the subunits of mitochondrial respiration chain (Complex I – V), interestingly, 12 subunits, inclu ding 8 components from CI (NADH ubiquinone oxidoreductase) [99], can be potentially phosphorylated by cyclin B1/CDK1 (Table 1) [22], indicating that cyclin B1/CDK1 functions as a switcher to control the surge of ATP output. A cluster of other mitochondrial factors are also targeted by cyclin B1/CDK1-phosphorylation that includes proteins in carbohydrate and lipid metabolism of mitochondria including TCA cycle. The dual functions of cyclin B1/CDK1 in both the nucleus and the mitochondria mark a tight connection between cell cycle progression and mitochondrial cooperation, and raise the question of whether this coordination is linked in the different metabolisms in normal and cancer cells.

4. Cyclin B1/CDK1 in mitochondria-associated apoptosis

Mitochondria-regulated apoptosis plays a key role in tumor response to anti-cancer therapies. Although several studies report that cyclin B1/CDK1 is responsible for initiating mitochondria-mediated apoptosis under cell damage conditions by its phosphorylation of several pro- (Bcl-2, BAD and Bcl-xL cytosol [100, 101]) and anti-apoptotic proteins (Mcl1 [102]) in normal and cancer cells, more emerging evidence demonstrate that cyclin B1/CDK1 is pivotal in inhibition of apoptosis in tumors. Cyclin B1/CDK1-mediated phosphorylation of pro-caspase-9 and survivin (BIRC5) lead to inhibition of apoptosis [103, 104] and Intact cyclin B1 with mutant CDK1 is shown to compromise CDK1-mediated substrates phosphorylation, mitochondrial function as well as cell viability [57] [22].. Cyclin B1, as the most important catalytic partner of CDK1, has been unearthed to be abnormally activated and aberrantly expressed in a number of human cancers including esophageal squamous cell carcinoma, laryngeal squamous cell carcinoma, and colorectal carcinomas [105–107]. Besides, cyclin B1 is linked with anti-apoptosis and tumor resistance in head and neck cancer [108, 109], one of the most aggressive cancers [110], triggers tumor proliferation and links with poor prognosis in esophageal squamous cell carcinoma [111], non-small cell lung cancer [112], and colorectal carcinoma [113]. Consistently, deficiency of cyclin B1 causes inhibition of cell proliferation and activation of apoptosis [114] and activated cyclin B1 leads to a pro-survival machinery mediated by the NF- κB signaling network [115]. These different results suggest that mitochondrial energy is required for both cell death and cell cycle. Cyclin B1/CDK1 not only regulates mitochondrial fuel output for normal cell cycle progression but also can initiate mitochondria-mediated apoptosis by modifying several pro-apoptosis proteins and anti-apoptotic proteins when cells exposed to excessive damage stresses.

4.1. CDK1-mediated mitochondrial bioenergetics for DNA repair

Radiation-generated ROS induces mitochondrial and nuclear DNA strand break [116] and potentially leads to cell apoptosis [117]. In this process, cellular energy supply, DNA repair capacity, and apoptosis play important roles in determining cell fate [118]. Timely and efficient DNA repair, ,an energy-consuming process [119–121], is necessary for cell survival [122]. However, it remains unclear how cellular energy supplement is coordinated in DNA

repair. A study in Jurkat cells indicates that both glycolysis and OXPHOS provide the energy supply of apoptosis [123]. A group of stress responsive proteins including MnSOD, cyclin B1/CDK1, cyclin D1/CDK4, and survivin [20, 124, 125] (Figure 2) inflow into mitochondria to induce cellular adaptive protection. The CI in the respiration chain is identified to be a key cyclin B1/CDK1 target in mitochondria [22]. Mitochondrial relocation of cyclin B1/CDK1 and nuclear DNA repair is correlated with oxygen consumption and ATP production in normal human cells after radiation [126]. The basal and radiation-induced mitochondrial ATP generation is reduced significantly in cells harboring CDK1 phosphorylation-deficient mutant CI subunits. Similarly, mitochondrial ATP generation and nuclear DNA repair are also compromised severely in cells harboring mitochondria-targeted, kinase-deficient CDK1 [126]. Together, these results implicate that cyclin B1/CDK1 functions to deliver signals to mitochondria to boost ATP generation for DNA repair and cell survival under genotoxic stress conditions.

4.2 CDK1- p53 pathway in anti-apoptosis

The p53 protein is well-characterized to regulate mitochondria-mediated apoptosis at protein and mRNA levels [127, 128]. p53 initiates the apoptotic cascade by inducing the expression or interacting directly with cytoplasmic Bcl-2 family proteins [129]. Mitochondrial function of p53 has been associated with mtDNA transcription, DNA repair, mitochondrial bioenergetics [130–132], as well as ATP production since p53 also regulates mitochondrial respiratory gene, SCO2 and GLS-2 [133]. It is generally believed that localization of p53 to mitochondria resembles a major starting signal for mitochondria-mediated apoptosis [134]. However, it has been proposed that mitochondrial p53 may not necessarily induce apoptosis [135]. Activation of CDK via Spy1 is indicated for the anti-apoptotic response via p53 induced by intrinsic DNA damage response such as in cell division [136]. Mice that lack of critical effectors of p53-induced apoptosis do not develop tumors spontaneously [137]. Therefore, the role of mitochondria-localized p53 should be considered broadly, depending on its cooperative and differential phosphorylation in addition to its apoptotic signal [138]. p53 can also be phosphorylated by mitochondrial cyclin B1/CDK1 [57]. Mitochondrial p53, cyclin B1 and CDK1 are elevated after radiation treatment, enhancing the phosphorylation of mitochondrial p53 at Ser-315, the only putative site for cyclin B1/CDK1 phosphorylation [139]. In contrast with p53-mediated pro-apoptotic signaling, this phosphorylation suppresses the mitochondrial apoptosis by sequestering p53 from binding to Bcl-2 and Bcl-xL [57]. This finding reinstates the role of cyclin B1/CDK1 in non-cell cycle functions. The pattern of cyclin B1/CDK1-mediated p53-apoptotic inhibition demonstrates a feedback signaling pathway for mitochondria-initiated apoptosis. The decision of pro- or anti-apoptotic response may be made based on the degree of DNA damage in the nucleus and the length of period cell arrested.

5. Mitochondrial bioenergetics in reprogramming energy metabolism in tumor cells.

Increasing interests have been attracted in cancer energy metabolism [140]. The high acidity in tumor tissues due to enhanced lactate generation even under oxygenated condition suggests that tumor cells generate ATP via glycolysis (aerobic glycolysis, Warburg Effect).

Although ATP generation via glycolysis is less efficacious compared to OXPHOS, glycolysis generates fundamental elements for cellular function and proliferation such as pyruvate and NADPH that are required for ribose production and protein glycosylation [141–143]. The Warburg assumption is that mitochondria are damaged, and glycolysis is primarily used as the major energy-supply for cellular proliferation and survival even under oxygenated conditions. However, this theory was challenged by a series of evidence since 1950s [144–148], which indicate that mitochondria in some cancer cells remain intact structure and function [149], and mitochondria are actively involved in tumor response to anti-cancer therapy. This apparent contradiction between glycolysis-dominated energy reprogramming and the OXPHOS-activated bioenergetics in tumor cells may reflect unknown dynamics of the flexible re-/deprogramming energy metabolism in cancer cells which is required to adapt and survive under different genotoxic conditions.

5.1. Mitochondria are still active and have potential role in tumor cells.

Contrasted to the prevailing thoughts of aerobic glycolysis, increasing results demonstrated functional mitochondria exist in tumors. Heat-shock-protein-90 (HSP90)-involved mitochondrial protein folding is required for cellular bioenergetics in tumor cells [150]. By using the isotopically labeled glucose, lactic acid, and palmitic acid, Weinhouse et al show that oxidation of glucose and fatty acid in tumor is similarly to normal tissues [147]. Similarly, Wenner et al observe that enzyme activities of the TCA cycle in tumor cells are at a similar active level in normal tissues [148]. Upon vivo experiment, Whitaker-Menezes report that epithelial cancer cells enhance OXPHOS for generation of high amounts of ATP. The transcriptional upregulation of genes in mitochondrial OXPHOS is identified in a report with over 2,000 breast cancer patients [151]. Others also report that mitochondrial bioenergetics may be reactivated to provide additional energy supply in the maintenance and function of cancer stem cells [18, 152–155], hematopoietic cells, as well as lymphoma and leukemia cells [155, 156]. However, the exact mechanism guiding such mitochondrial activation is yet to be elucidated. Other studies also reveal that cancer cells remain OXPHOS capacity to provide the vital amount of cellular fuels for energy consumption required for the fast proliferation of cancer cells [157, 158] and adaption of metabolic stress such as nutrient deficiency and hypoxia [159, 160]. On the other hand, pharmacological glycolysis inhibitors such as 2-DG, fail to provide significant therapeutic benefits in vivo test [161, 162]. These results together suggest that mitochondria in cancer cells can dynamically activate or inactivate its functions with different cellular energy consumption conditions and in different cancer types. Such plasticity in adjusting mitochondrial bioenergetics of tumor cells challenges the anticancer modalities that aim to inhibit tumor growth by blocking glycolysis.

5.2. Mitochondrial bioenergetics in tumor resistance to therapy

Mitochondrial metabolism has been linked with tumor therapeutic resistance [18, 150, 163–169]. Mitochondrial bioenergetics is enhanced when cellular energy demand is increased for repairing DNA damages to allow cancer cells to survive from therapeutic genotoxicity [23, 167]. Overexpressing MnSOD, a key enzyme for maintaining mitochondrial homeostasis, induce radioresistance in breast cancer MCF7 cells [16, 170]. The mammalian target of rapamycin complex 1 (mTORC1) that serves as an sensor of extracellular nutrient levels and intracellular bioenergetics [171], maintains cellular bioenergetics under glucose deficiency

[172]. mTOR, as the core element in mTORC1 enhances OXPHOS with reduced glycolysis for tumor cells to survive IR [167]. The apparent “quiet” mitochondria in tumor cells can function as a backup line to boost up cellular fuel supply under genotoxic anticancer modalities such as ionizing radiation and chemotherapy (Figure 2 legend). This “backing-up” mechanism proposed here is to demonstr ate a flexible feature in the energy metabolism of cancer cells under genotoxic and “normal” growth conditions. In addition, mitochondrial metabolism is identified in tumor cells and actively involved in tumor metastasis [173–175]. These observations are further supported by findings that reprogramming the mitochondrial trafficking can help to fuel the tumor cell invasion [14, 176]. Most importantly, mitochondrial energy metabolism is recently linked with the aggressive phenotype of triple-negative breast cancer (TNBC) [174]. Therefore, further elucidation on the dynamic alterations in mitochondrial energy metabolism in tumor cells especially IR-associated energy dynamics will provide critical information on invention of effective metabolic targets to treat cancer cells.

5.3. CDK1-mediated mitochondrial bioenergetics in cancer cells plays a pivotal role in tumor radiation response.

As discussed above, in addition to cyclin B1/CDK-mediated morphological alterations via DRP1 regulation and mitochondrial fission [36,177], CDK1 is able enhance mitochondrial metabolism in cell cycle progression of normal cells and in radiation-induced stress. Cyclin B1/CDK1 promotes the activity of OXPHOS to induce anti-apoptotic response in human colon cancer HCT116 cells via cyclin B1/CDK1-mediated SIRT3 activation together with phosphorylation of p53 at Ser-315 leading to an increased mitochondrial ATP production and reduced mitochondrial apoptosis [23, 57]. Besides, cyclin B1/CDK1 are found to specifically modify MnSOD that can enhance resistance of breast cancer cells in genotoxic conditions such as IR [15, 16] and increase mitochondrial homeostasis, biosynthesis, and signaling aggressive phenotype of cancer cells [10, 178–180]. MnSOD, located in mitochondria, is important in balancing the ROS (reactive oxygen species) and protecting mitochondrial function [116]. Down-regular of MnSOD expression or inhibit of its enzymatic activity in normal cells have been proven leading to a high risk of cell transformation [181,182]. Increased expression of MnSOD may be beneficial to cancer cells to survive from radiation therapy [183], as well stimulate metastatic behavior [184–187]. When exposed under ionizing radiation, mitochondria recruit cyclin B1/CDK1 in cancer cells enhancing MnSOD activity and stability along with improved mitochondrial function and cellular adaptive response [24]. Similarly, CDK4, the key kinase for G1/S progression, activates MnSOD to improve mitochondrial function and serve as an important pathway in cellular adaptive protection [20]. Therefore, a cluster of mitochondrial proteins post-transcriptionally modified by cyclin B1/CDK1 can instantly upregulates mitochondrial energy output for tumor cell survival under genotoxic cancer therapy (Figure 2). However, it is currently unknown how such cyclin B1/CDK1-boosted mitochondrial energy supply could be mechanistically associated with specific tumor cells such as cancer stem cells under anti-cancer therapy. Future exploring in cyclin B1/CDK1-mediated mitochondrial bioenergetics in different therapeutic modalities may invent effect targets to timely block the cellular energy reprogramming to eliminate resistant tumor cells.

6. Concluding remarks

We illustrate here that mitochondrial energy metabolism is critically regulated in cell proliferation and tumor growth [188–190]. Beside their direct functions in regulation of cell cycle progression, the complex of cyclin B1/CDK1 is able to coordinate the cell cycle events with enhanced mitochondrial bioenergetics. Such cyclin B1/CDK1 regulated mitochondrial metabolism is highlighted in this review to demonstrate how the two genomes are functionally cooperated to control the balance of energy supply with the timely demanded cellular fuel consumption. However, it remains unclear how cyclin B1/CDK1-mediated mitochondrial homeostasis orchestrates different cell cycle phases. It is also to be further elucidated whether the mitochondrial bioenergetics is required for tumor cell survival under anti-cancer treatments such as chemotherapy and radiation. In addition to mitochondrial targets, cyclin B1/CDK1-controlled cytoplasmic components for cell cycle progression must coordinate timely with mitochondrial functions, and way around, the oscillation for mitochondrial bioenergetics should meet the specific requirements of cell division and proliferation. To define specific metabolic targets in tumor cells, outstanding questions still need to be addressed. First, it remains unclear if a specific cluster of cyclin B1/CDK1-regulated metabolic enzymes is required for the different metabolic status in normal and cancer cells [86, 191, 192]. Second, cross-talking among the cyclin B1/CDK1-targeted proteins may guide the mitochondrial bioenergetics based on the different stages of cell cycle progression and tumor growth status such as tumor metastasis. Since different CDKs are required in transition of each cell cycle stage, it would be highly appreciated if mitochondrial energy metabolism can be precisely oscillated with each cycle phase. In addition, the mechanistic insights guiding the signaling traffics between the nucleus and mitochondria under physiological and pathological conditions needs to be further deciphered. These studies will help to understand the flexible mitochondrial bioenergetics in cancer cells under different stress conditions and thus to invent new metabolic targets to treat cancer.

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HIGHLIGHTS

- Two genomes located in the nucleus and mitochondria coordinate to achieve homeostasis.
- Such two-way signaling traffics present an orchestrated dynamics between energy metabolism and consumption.
- Cyclin B1/CDK1 regulates mitochondrial bioenergetics for cell cycle progression and tumor response to therapy.
- Deciphering the cyclin B1/CDK1-controlled mitochondrial metabolism may invent effect targets to treat resistant cancers.

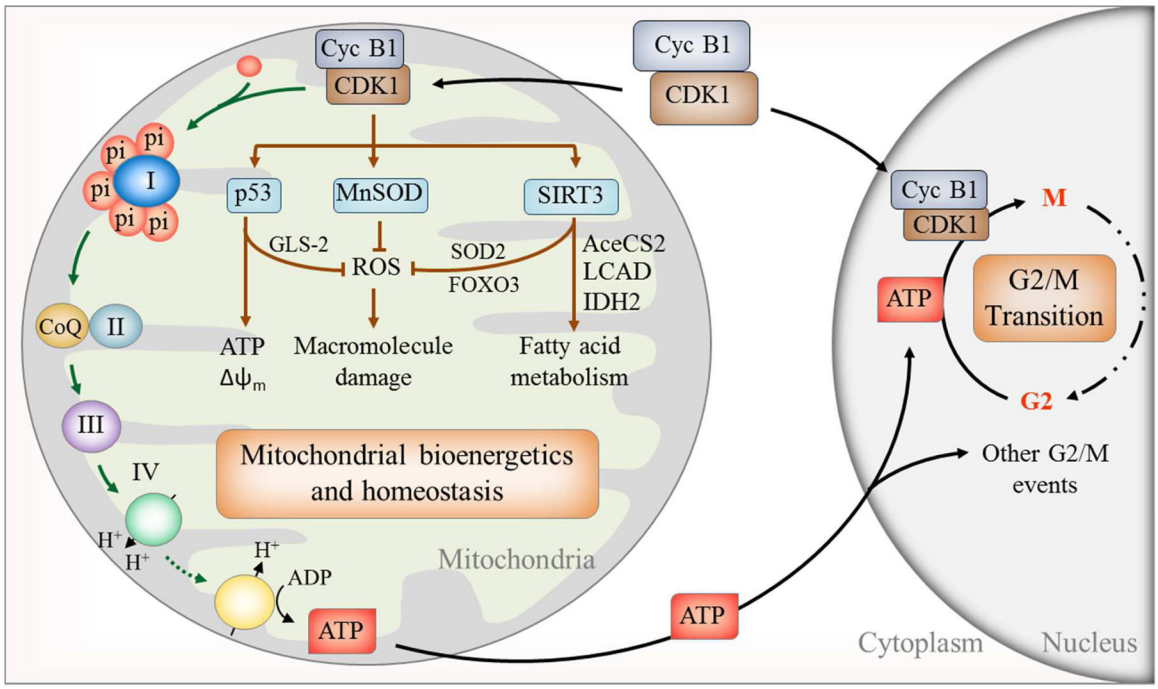

Figure 1. A model of nuclear and mitochondrial cooperation in regulating mitochondrial bioenergetics for G2/M transition.

Cyclin B1/CDK1 relocates to mitochondria during G2/M phase to phosphorylate and activate an array of substrates including multiple subunits of mitochondrial CI to enhance mitochondrial function and energy production which drives energy-sensitive G2/M transition. In addition, cyclin B1/CDK1 activates p53, MnSOD, and SIRT3 to eliminate ROS and protect and maintain mitochondrial homeostasis. CDK1-SIRT3-mediated fatty acid metabolism and mitochondrial homeostasis remain to be further elucidated. Cyc B1, cyclin B1. Also see other mitochondrial substrates of cyclin B1/CDK1 in Table 1.

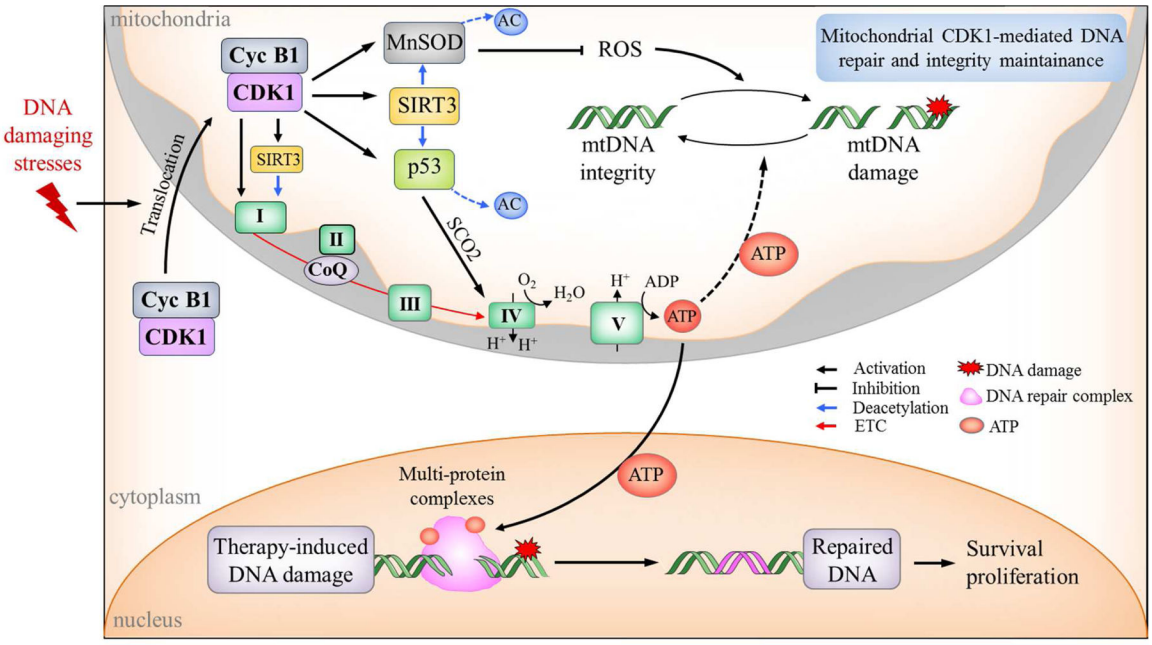

Figure 2. Cyclin B1/CDK1-mediated mitochondria bioenergetics in DNA repair and tumor resistance.

DNA-damaging agents including chemotherapy and radiotherapy enhance the translocation of cyclin B1/CDK1 to mitochondria causing phosphorylation and activation of OXPHOS leading to enhanced ATP output required to repair DNA damages for cell survival. CDK1 also directly phosphorylates MnSOD to eliminate ROS, activates p53 to promote energy generation and maintain mitochondrial DNA integrity, or indirectly enhances the activity of MnSOD and p53 via SIRT3-mediated deacetylation, which as a whole improve mitochondrial homeostasis and function. NDUFA9, one of the subunits of CI, can also be deacetylated by SIRT3 to promote OXPHOS. Thus, our model applies to the situation in which under non-stressful conditions tumor cells may relay on the energy generated by predominant oxidative glycolysis, whereas under genotoxic crisis such as chemotherapy and radiation, cyclin B1/CDK1-mediated OXHPOS is activated to meet the extra energy demands for repairing damages and enhancing cell survival.

Table 1.

Substrates of CDK1 in mitochondria detected by in vitro kinase assay

Function	Gene symbol	Protein	Nucleus/ Mitochondria-encoded	Optimal phsphorylation site and position	Minimal phosphorylation site number
OXPHOS (complex I)	NDUFV1, UQOR1	NADH dehydrogenase [ubiquinone] flavoprotein 1	Nucleus	T^{383} P C R	0
	NDUFV2	NADH dehydrogenase [ubiquinone] flavoprotein 2	Nucleus	T^{164} P D K	4
	NDUFV3	NADH dehydrogenase [ubiquinone] flavoprotein 3	Nucleus	S^{530} P P K	1
	NDUFS2	NADH dehydrogenase [ubiquinone] iron-sulfur protein 2	Nucleus	S^{364} P P K	1
	NDUFB5	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5	Nucleus	S^{550} P W R	2
	NDUFB6	NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6	Nucleus	S^{550} P W R	2
	NDUFA12, DAP13	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	Nucleus	T^{142} P Y K	1
	NDUFAF1, CIA30, CGI-65	Complex I intermediate-associated protein 30	Nucleus	S^{450} P G K	1
OXPHOS (complex III subunit 1)	UQCRC1	Cytochrome b-c1 complex subunit 1	Nucleus	T^{266} P C R	3
OXPHOS (complex III subunit 5)	UQCRFS1	Cytochrome b-c1 complex subunit Rieske	Nucleus	0	6
OXPHOS (complex V)	ATP5A1, ATP5F1A ATP5A, ATP5AL2, ATPM	ATP synthase subunit alpha	Nucleus	0	1
	ATP5B, ATP5F1B, ATPMB, ATPSB	ATP synthase subunit beta	Nucleus	0	1
Amino acid metabolism	GLUD1, GLUD	Glutamate dehydrogenase 1	Nucleus	T^{144} P C K	2
	GATM, AGAT	Glycine amidinotransferase	Nucleus	0	3
	GOT2	Aspartate aminotransferase	Nucleus	0	2
	ABAT, GABAT	4-aminobutyrate aminotransferase	Nucleus	0	1
	BCKDHB	2-oxoisovalerate dehydrogenase subunit beta	Nucleus	0	5
	AGMAT	Agmatinase	Nucleus	0	4
	OTC	Ornithine carbamoyltransferase	Nucleus	0	3
	SHMT2 Serine	Serine hydroxymethyltransferase	Nucleus	S^{266} P F K	3
Carbohydrate metabolism	ALDH1B1, ALDH5, ALDHX	Aldehyde dehydrogenase X	Nucleus	S^{91} P W R	4

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Function	Gene symbol	Protein	Nucleus/ Mitochondria-encoded	Optimal phsphorylation site and position	Minimal phosphorylation site number
Lipid metabolism	ALDH4A1, ALDH4, P5CDH	Delta-1-pyrroline-5-carboxylate dehydrogenase	Nucleus	S^{44} P E R	3
	ALDH6A1, MMSDH	Methylmalonate-semialdehyde dehydrogenase [acylating]	Nucleus	0	2
	ALDH2, ALDM	Aldehyde dehydrogenase	Nucleus	S^{91} P W R	3
	HMGCS2	Hydroxymethylglutaryl-CoA synthase	Nucleus	T^{6} P V K	4
	SUCLG2 Succinyl-CoA	Succinate--CoA ligase [GDP-forming] subunit beta	Nucleus	0	4
	ACADSB Short/ branched	Short/branched chain specific acyl-CoA dehydrogenase	Nucleus	0	1
	ACADM medium-chain	Medium-chain specific acyl-CoA dehydrogenase	Nucleus	0	1
	ACOT1, CTE1	Acyl-coenzyme A thioesterase 1	Nucleus	0	2
	ACAT1, ACAT, MAT	Acetyl-CoA acetyltransferase	Nucleus	0	5
	SUCLG2	Succinate--CoA ligase [GDP-forming] subunit beta	Nucleus	0	4
	ACADS	Short-chain specific acyl-CoA dehydrogenase	Nucleus	0	2
Lipid metabolism	HSD17B10, ERAB, HADH2, MRPP2, SCHAD, SDR5C1, XH98G2	3-hydroxyacyl-CoA dehydrogenase type-2	Nucleus	0	1
	HSD17B8, FABGL, HKE6, RING2, SDR30C1	Estradiol 17-beta-dehydrogenase 8	Nucleus	0	1
	ECH1	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase	Nucleus	0	1
	ACSL1, FACL1, FACL2, LACS, LACS1, LACS2	Long-chain-fatty-acid --CoA ligase 1	Nucleus	0	1
Redox	SOD2	Superoxide dismutase [Mn]	Nucleus	0	1
	PRDX3, AOP1	Thioredoxin-dependent peroxide reductase	Nucleus	T^{128} P R K	3
	MPST, TST2	3-mercaptopyruvate sulfurtransferase	Nucleus	0	2
	TST Thiosulfate	Thiosulfate sulfurtransferase	Nucleus	0	2
	NNT	NAD(P) transhydrogenase	Nucleus	S^{400} P D K T^{467} P F R	4
TCA cycle	PCK2, PEPCK2	Phosphoenolpyruvate carboxykinase [GTP]	Nucleus	0	7
	MDH2	Malate dehydrogenase	Nucleus	0	4
	FH, FH1	Fumarate hydratase	Nucleus	0	1
Protein targeting	HSPD1, HSP60	60 kDa heat shock protein	Nucleus		4

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Function	Gene symbol	Protein	Nucleus/ Mitochondria-encoded	Optimal phsphorylation site and position	Minimal phosphorylation site number
	14–3-3 epsilon	14–3-3 protein epsilon	Nucleus	S^{187} P D R	0
Protein synthesis	TUFM	Elongation factor Tu	Nucleus	0	2