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Cell Cycle Regulators Guide Mitochondrial Activity in Radiation-Induced Adaptive Response

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Abstract

Significance: There are accruing concerns on potential genotoxic agents present in the environment including low-dose ionizing radiation (LDIR) that naturally exists on earth's surface and atmosphere and is frequently used in medical diagnosis and nuclear industry. Although its long-term health risk is being evaluated and remains controversial, LDIR is shown to induce temporary but significant adaptive responses in mammalian cells and animals. The mechanisms guiding the mitochondrial function in LDIR-induced adaptive response represent a unique communication between DNA damage and cellular metabolism. Elucidation of the LDIR-regulated mitochondrial activity may reveal new mechanisms adjusting cellular function to cope with hazardous environmental stress. ***Recent Advances:*** Key cell cycle regulators, including Cyclin D1/CDK4 and Cyclin B1/cyclin-dependent kinase 1 (CDK1) complexes, are actively involved in the regulation of mitochondrial functions *via* phosphorylation of their mitochondrial targets. Accumulating new evidence supports a concept that the Cyclin B1/CDK1 complex acts as a mediator in the cross talk between radiation-induced DNA damage and mitochondrial functions to coordinate cellular responses to low-level genotoxic stresses. ***Critical Issues:*** The LDIR-mediated mitochondrial activity *via* Cyclin B1/CDK1 regulation is an irreplaceable network that is able to harmonize vital cellular functions with adjusted mitochondrial metabolism to enhance cellular homeostasis. ***Future Directions:*** Further investigation of the coordinative mechanism that regulates mitochondrial activities in sublethal stress conditions, including LDIR, will reveal new insights of how cells cope with genotoxic injury and will be vital for future targeted therapeutic interventions that reduce environmental injury and cancer risk. *Antioxid. Redox Signal.* 20, 1463–1480.

Introduction

HUMANS ARE CONSISTENTLY exposed to a certain dose range of low levels of ionizing radiation (IR), which includes natural radiation on earth surface, medical radiation, and industrial radioactive materials (31, 92, 141, 198). In contrast to extensive studies collected from the exposure to high doses of IR that cause acute injury resulting in cell death and carcinogenesis (15, 77, 88, 109, 161), the health risks associated with low level of genotoxic agents, including low-dose ionizing radiation (LDIR) (less or equal to 10 cGy), need to be further investigated (169, 213). In addition to the controversial cancer risks evaluated on long-term consequences (27, 34, 56, 169, 170), mammalian cells exposed to a single dose or accumulated doses of LDIR are shown to be able to induce a temporary but significant resistance to subsequent more severe genotoxic agents, such as high doses of IR (3, 4, 22, 67, 68, 98, 122, 186, 192, 240). Further investigation of LDIR-associated adaptive mechanism may reveal new information on unknown cellular capacities that may allow cells to sense and tolerate hazardous environmental conditions. Such studies may also provide effective approaches or targets to reduce radiation-associated injury and cancer risk. Recent evidence suggests that mitochondria play a key role in the orchestrated response to maintain the homeostasis of the cell and organism (129). IR triggers not only the DNA repair (70) but also the detoxification of reactive oxygen species (ROS) that lasts for many hours or weeks depending on the

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cell or tissue type, and redox imbalance plays a critical role in mitochondria-mediated adaptive response (46, 101, 160, 211, 221, 233). Under IR stress, cells initiate several critical steps to induce an adaptive protection, including the enhancement of free glutathione and superoxide dismutase with a subsequent decrease in lipid peroxidation (65, 80, 201, 242). Additional prosurvival pathways are activated *via* a cross talk between mitochondria and NADPH oxidase (NOX) (53), which is contrasted with the proapoptotic response induced by mitochondrial dysfunction and subsequent Ca^{2+} release to the cytoplasm activating protein kinase C (PKC), mitogen-activated kinases (MAPKs), and c-jun N-terminal kinases (JNKs) (129).

Additionally, mitochondria affect cell fate by interconnecting glycolysis and the pentose phosphate signaling pathways to cell cycle progression and apoptosis (33, 60, 113, 126, 184, 189, 218). Essential nuclear events are shown to be affected by cellular nutrient metabolism *via* the regulation of D type cyclins, cyclin-dependent kinases (CDKs), p53, and B-cell lymphoma 2 (Bcl-2) proteins (19, 26, 43, 95, 176, 190, 205, 234). These results illustrate a unique signaling network that appears to enable the mitochondria to sense and respond to major nuclear events, such as IR-induced DNA damages and repair. In this review, we demonstrate a pattern of radiation-induced cell adaptive response *via* the cell cycle regulator-mediated mitochondrial activity. We will focus the role of Cyclin D1/CDK4 and Cyclin B1/CDK1 in LDIR-induced adaptive response. A conceptual new mechanism is proposed to link the nuclear events, such as IR-induced nuclear DNA damages and G2/M division, with mitochondrial regulation (Fig. 1). The elucidation of the cell cycle regulator-guided mitochondrial metabolism in IR-induced adaptive resistance may shed light on how DNA damage can initiate the reprogramming of mitochondrial metabolism. Since the mitochondria-to-nuclear communication has been reviewed well in the literature, we will focus on the mitochondrial functions triggered by IR-induced mitochondrial protein influx, while keeping in mind the hypothesis that this could represent a paradigm for understanding nuclear-to-mitochondria and mitochondria-to-nuclear cross talk. Further elucidation of these communications in genotoxic conditions may define more abnormalities in cellular metabolism and human diseases.

Features of LDIR-Induced Adaptive Response

Mammalian cells are able to induce an adaptive protective response when exposed to IR with low dose and/or low dose rate. The term of *adaptive radioprotection* is defined as "the ability of low dose radiation to induce cellular changes that alter the level of subsequent radiation induced or spontaneous damage" (Notice 03-07 of Office of Science, DOE, 2003) (29, 31, 122, 141, 186, 202, 230, 240, 247). Radioadaptive responses have been observed in nearly all the species, including *Escherichia coli*, protozoa, algae, higher plants, and insects (12, 35, 143, 185, 192, 246, 247). The most significant phenomena of LDIR-induced radioprotection include the reduction of the lethal and mutagenic effects caused by subsequent exposure to higher doses (105, 154, 173, 193, 204, 227), resistance to subsequent radiation-induced genomic instability (96, 105, 121, 142), and activation of stress-sensitive transcription factors and gene regulators (68, 69, 202, 228). Bhattacharjee and Ito (22) reported that whole-body pre-irradiation of Swiss mice with five repeated exposures to small doses of 1 cGy per day reduces the incidence of thymic lymphoma from 46% to 16% following 2 Gy IR (21). Additionally, IR-induced non-targeted effects from astronaut space exploration were mimicked by cranially irradiated Sprague Dawley rats; the results showed that levels of key proteins involved in mitochondrial fatty acid metabolism were reduced, and proteins involved in various cellular defense mechanisms, including antioxidants, were elevated in both irradiated and nonirradiated tissues (2, 81). An adaptive response of human lymphocytes to IR has long been observed (154, 238) (187), and several reports create a strong case for the existence of cellular radioprotective

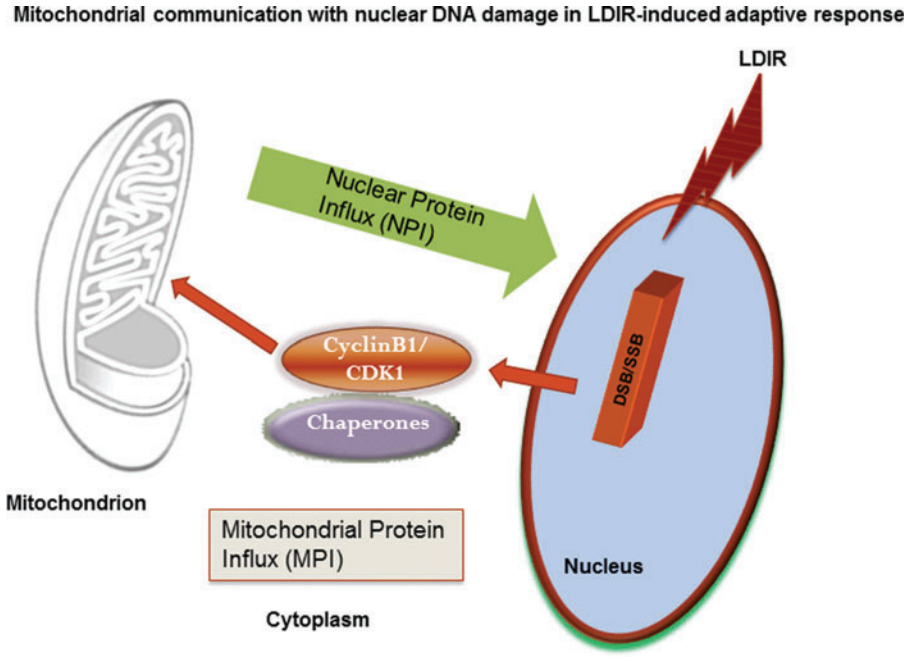

FIG. 1. Hypothesized communication between nuclear DNA damages and mitochondrial activity. Cyclin B1/CDK1, one of the components of the MPI, is delivered with mitochondrial chaperones to mitochondria and potentially cooperated with NPI (not discussed in this review) in the LDIR adaptive response. CDK1, cyclin-dependent kinase 1; LDIR, low-dose ionizing radiation; MPI, mitochondrial protein influx; NPI, nuclear protein influx. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

mechanisms activated in response to IR (3, 105, 154, 173, 193, 204, 227). IR induces the expression of a specific cluster of stress responsive genes to repair damaged biomolecules, including DNA, and enhance overall cell survival (7, 28, 63, 68, 69, 85, 120, 140, 199, 202, 228). Recent studies demonstrate that colon carcinoma cells along with transformed mouse embryonic fibroblasts showed an adaptive response when grown either to confluence *in vitro* or as tumors in the flank of C57BL/6 mice. LDIR-induced survivin expression was linked to the adaptive radioresistance after pre-exposure of 100 mGy or a lower dose. This survivin-mediated adaptive response may affect the outcomes if regularly induced throughout a course of image-guided radiation therapy (82). In another study, the same dose of 100 mGy offered radioprotection to C57BL/6 mice exposed 24 h later to 100 mg/kg of *N*-ethyl-*N*-nitrosourea *via* inducing manganese superoxide dismutase (MnSOD) (83) whose enzymatic activity can be further enhanced by Cyclin B1/CDK1-mediated phosphorylation (36). These results clearly indicate that mitochondria are actively involved in LDIR-induced adaptive response and specific factors that are able to coordinate DNA damages with the mitochondrial activity remain to be identified.

Mitochondrial Activities Guided by Nuclear Genome-Encoded Proteins

Accumulating evidence suggests that mitochondria play an important role in the IR-induced adaptive response *via* the regulation of mitochondrial metabolism (198). The major function of mitochondria in mammalian cells is to generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) to accommodate cellular energy demands (14, 18, 51, 112). The nucleus represents a less oxidizing and hospitable environment for high fidelity storage of large amounts of genetic material necessary to code for the gene products required for organism function (226). Many mitochondrial functions are shown to be regulated by nuclear-encoded proteins and *via* protein phosphorylation (159). For example, despite the presence of mitochondrial DNA (mtDNA), more than 98% of mitochondrial protein components are encoded by the nuclear genome (174) with only 13 of 1465 mitochondrial proteins identified to date transcribed from the mitochondrial genome (48). Such a "foreigner-taking-over" process in the mitochondrion indicates how adopted organelles with its own genome are well integrated evolutionarily into one living system. As a result, the major function of mitochondria is under the control of the central genome in the host cells. Thus, the nuclear genome is able to efficiently and timely guide the activity of mitochondria. This organization of the regulatory hierarchy likely evolved because coordinated control in cellular fuel generation is required for optimal function of cell proliferation and stress response.

Mitochondrial Activities Guided by Radiation-Induced Cyclins and CDKs

Cell cycle progression depends on highly ordered events controlled by a subset of Cyclins and CDKs (139, 146, 191). Cyclin B1/CDK1 complex specifically regulates the entry into mitosis at the G2/M border (61). Through its cytoplasmic, nuclear, and centrosomal localization, Cyclin B1/CDK1 synchronizes the crucial events of early mitosis, such as nuclear envelope breakdown and centrosome separation (76). Accumulating evidence links mitochondrial dynamics (40) and metabolism (54, 107) with cell proliferation and cell cycle regulation (10, 73, 128, 175, 183). Examples include the G1–S arrest caused by mitochondrial dysfunction (156); involvement of Cyclin D1 in coordinating mitochondrial bioenergetics with G1 progression; (118, 176, 178, 223) and Cyclin E in controlling the formation of high energy-charged mitochondria in the G1/S transition (138). Recent identification of the mitochondrial localization of Cyclin B1/CDK1 (149) as well as its role in the integration of mitochondrial fission with the onset of G2/M transition (207) suggests that Cyclin B1/CDK1 activity is involved in mitochondrial morphological dynamics, mitochondrial bioenergetics, and mitochondria-mediated resistance to IR as shown in Figure 2. Numerous studies have examined the effects of IR on the expression of genes involved in cell cycle control (8, 20, 93, 120, 158, 199). Irradiated MCF7 cells showed a rapid reduction in Cyclin D1 levels before p53 stabilization, indicating that the stability of Cyclin D1 was controlled in a p53-independent manner (48). In addition, Cyclin D1 phosphorylation and proteolysis are linked with cell genomic instability and the regulation of Cyclin D1 degradation is involved in cancer development (132, 166). However, specific cyclins induced by varied IR doses may function differently in mitochondria-mediated responses. In *Xenopus* embryos, a high dosage of IR induced apoptotic cell death due to the increased levels of Cyclin A1 and Cyclin A1/CDK2 activity (9). In the following review, we will illustrate the protective functions of two cell cycle complexes, Cyclin D1/CDK4 and Cyclin B1/CDK1, in LDIR-induced adaptive responses (Fig. 2).

Cyclin D1/CDK4-Mediated Adaptive Radioprotection

Cell cycle progression is controlled by highly ordered events *via* Cyclins and CDKs (97, 137, 139, 146, 162). The activity of CDKs is exquisitely controlled by multiple pathways, including the regulation of Cyclins (49), phosphorylation of the catalytic subunits (125), and subcellular localization (209). Cyclins, such as Cyclin D1, is involved in cell cycle arrest in DNA-damage response. A study tested the hypothesis that Cyclin D1 regulates mitochondrial apoptosis. Cyclin D1 was found to complex with chaperon 14-3-3ζ (3). A direct interaction of Cyclin D1 with proapoptotic Bax occurred in LDIR-treated cells and improved mitochondrial membrane potential ($\Delta\psi_m$). These results demonstrate the evidence that cytosolic Cyclin D1 is able to regulate apoptosis by interaction with Bax in LDIR-induced adaptive resistance (105).

The LDIR-induced adaptive response is manifested through changes of total mitochondrial protein translocation rate (160). NF-κB upregulates and translocates mitochondrial antioxidant MnSOD from the nucleus to the cytoplasm in (55) cells exposed to IR (67, 85). According to radiation-induced gene expression profiles (6, 200), cell cycle regulators, such as Cyclin D1, are also required for the IR-induced adaptive response. Cyclin D1 is involved in the IR-induced adaptive response when localized in the cytoplasm, and apoptosis is enforced by nuclear relocation of Cyclin D1 (203). Additionally, 14-3-3 chaperones (14-3-3s) are crucial for cell cycle checkpoint control and cell survival after radiation-induced DNA damage (231). Studies show that inhibition of 14-3-3s renders cancer cells sensitive to IR (171). The radioprotective

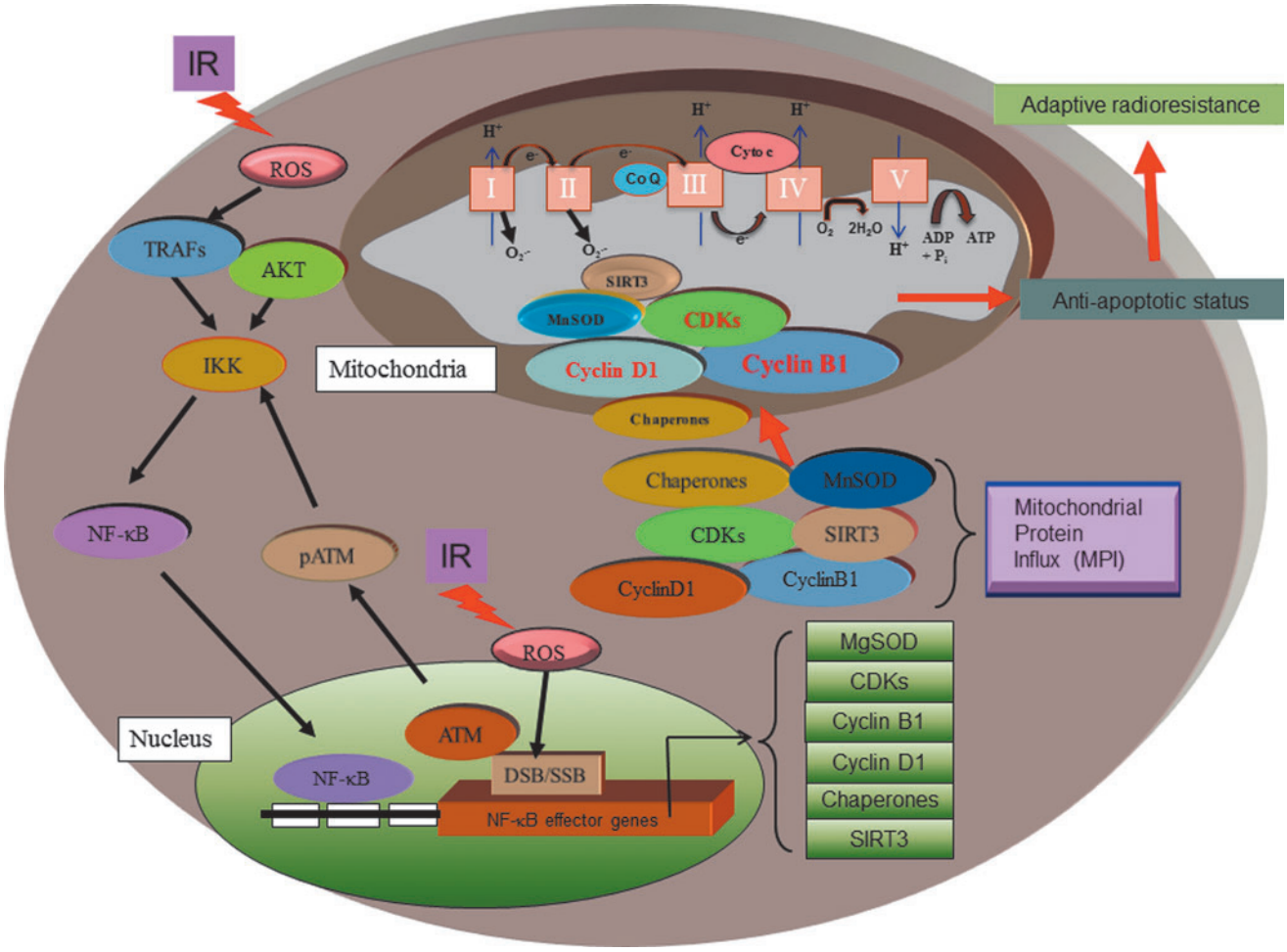

FIG. 2. Schematic presentation of mitochondrial signaling network in cellular adaptive response to IR. IR generates reactive oxygen species (ROS) to induce nuclear DNA damages and mitochondrial ROS level by accumulating cells in the G2/M phase (235). NF-κB can be activated *via* the ROS in cytoplasm and damaged DNA in nucleus *via* the regulation of IκB kinase (IKK). NF-κB in turn regulates an array of IR-responsive effector genes, including mitochondrial antioxidant MnSOD, Cyclins, and CDKs (marked as red color). These effector genes are shown to localize to mitochondria and to regulate the mitochondrial activity to induce the adaptive response after exposure to IR. IR, ionizing radiation; MnSOD, manganese superoxide dismutase.

effect of 14-3-3s in normal cells is from both interaction and inhibition of proapoptotic Bcl-2-associated X protein (Bax) (151), relocation of apoptosis-promoting fork-head transcription factor (FKHRL1) to the cytoplasm (32), and sequestration of cytoplasmic c-Abl (237). The mitochondrial proapoptotic Bax and antiapoptotic Bcl-2 are major factors involved in mitochondrial apoptosis and $\Delta\psi_m$ (103). Bcl-2 antagonizes the proapoptotic activity of Bax through the formation of Bcl-2/Bax heterodimers, and the Bcl-2 to Bax ratio is associated with alterations of $\Delta\psi_m$ and cell death (243). Bax activity is decreased in cells with enhanced $\Delta\psi_m$ preventing cell death. An antiapoptotic pathway was induced by Ataxia telangiectasia mutated (ATM)/NF-kB-mediated Cyclin D1 expression after treating human skin keratinocytes with LDIR (5- or 10-cGy X-ray) and mice with whole-body IR. Exposure of normal cells to 5 Gy IR caused nuclear translocation of Cyclin D1, whereas LDIR decreased 14-3-3/Cyclin D1 complex formation resulting in free cytoplasmic Cyclin D1. Higher levels of free cytoplasmic Cyclin D1 further sequestered Bax from mitochondria maintaining $\Delta\psi_m$. siRNA-mediated Cyclin D1 inhibition ablated LDIR-induced Cyclin D1/Bax complex formation and decreased $\Delta\psi_m$. Thus, the formation of Cyclin D1/Bax in LDIR is able to inhibit mitochondria-mediated cell death (Fig. 3).

Mitochondrial Relocation of Cyclin B1/CDK1 in Adaptive Radioprotection

Cyclin B1 and its catalytic partner protein CDK1 belong to the fundamental kinase machinery regulating cell cycle progression from G2 to mitosis (61, 164). The cytoplasm-, nucleus- and centrosome-localized Cyclin B1/CDK1 synchronizes critical subcellular events, such as nuclear envelope breakdown and centrosome separation to ensure even segregation of chromosomes into two daughter cells (76). Cyclin B1/CDK1 was not activated in G2 phase until nuclear envelope breakdown, thereby initiating the events of prophase and different levels of Cyclin B1/CDK1 activity required to trigger different mitotic events (76). Mass spectrometry analysis identified a cluster of MnSOD protein–protein interactions in an array of cellular and mitochondrial proteins (63). Cyclin B1/CDK1 regulates the MnSOD activity through reversible

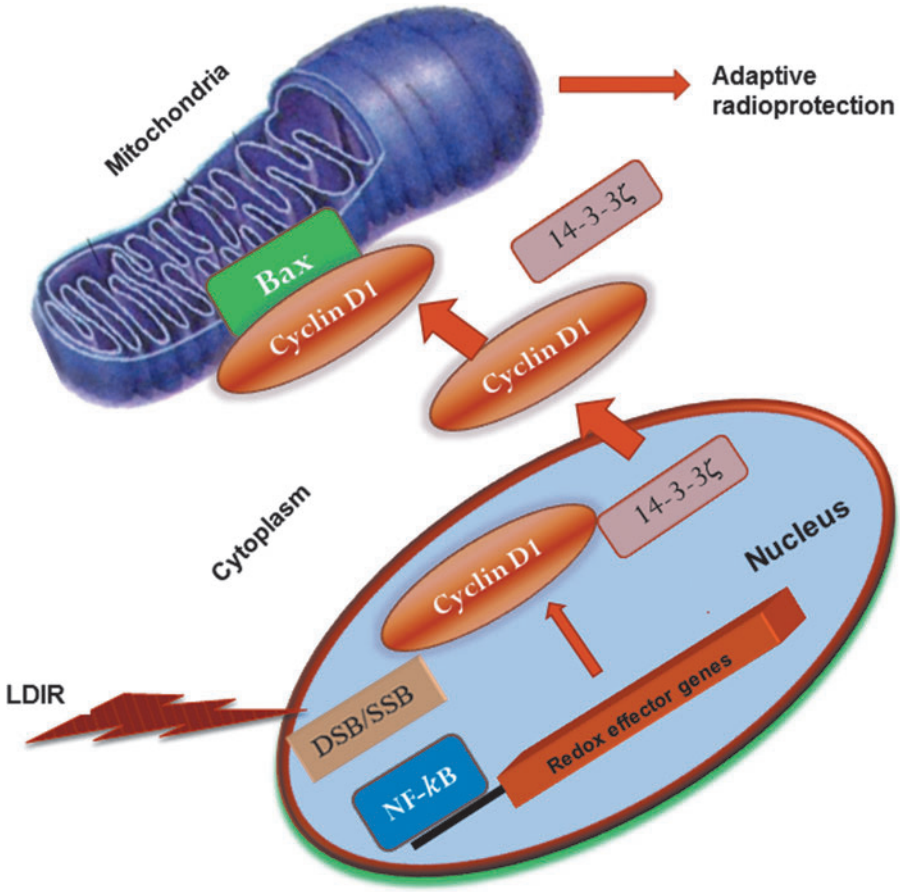

FIG. 3. Cyclin D1 interacts with Bax in the LDIR-induced adaptive response. LDIR (10 cGy X-ray) induced Cyclin D1 *via* NF-κB regulation is conjugated with the chaperon 14-3-3 protein in the cytoplasm. Cyclin D1 then interacts and forms a complex with Bax in mitochondria of human karotinocytes and skin tissue from whole-body irradiated mice (3). The NF-κB-Cyclin D1-Bax signaling pathway is critical to the regulation of the level of 14-3-3/Cyclin D1 complex in the LDIR adaptive response. Bax, Bcl-2-associated X protein; 14-3-3ζ, chaperones. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

serine 106 phosphorylation both *in vivo* and *in vitro*, enhancing the MnSOD enzymatic activity and protein stability to improve mitochondrial function in LDIR-induced adaptive protection (36). Also known as the mitotic promoting factor, Cyclin B1/CDK1 phosphorylation governs key steps for mitotic entrance featured by the nuclear envelope breakdown, spindle formation, and chromatin condensation (75). However, the mitochondrial transition of Cyclin B1/CDK1 is hypothesized to be dependent on the total levels of cellular Cyclin B1 and CDK1 (149). Abundance of Cyclin B1 was found to regulate γ-ray radiation-induced apoptosis (167). Under normal growth conditions, mitochondrial localization of Cyclin B1/CDK1 is attenuated during G1 phase due to a lack of cellular Cyclin B1 before gradually accumulating in the mitochondria. Upon entering S/G2 phase, Cyclin B1 expression reaches a maximum level at the G2/M phase, and this will be discussed in the following sections. Upon DNA-damage conditions, such as chemotherapy and IR, induced Cyclin B1/CDK1 expression can delay the cell cycle causing the G2/M border arrest to enable DNA damage repair or initiate apoptosis (147). Following DNA-damaging agents and radiation, at least a fraction of the induced Cyclin B1/CDK1 is translocated to mitochondria and Cyclin B1/CDK1 may phosphorylate mitochondrial targets under both normal and DNA-damaging stress conditions (149). As shown in Figure 4A, mitochondrial localization of Cyclin B1/CDK1 appears to be proportional with the overall expression levels of cellular Cyclin B1/CDK1 throughout the cell cycle phases. Since Cyclin B1/CDK1 is activated in the prophase stage of mitosis (99), the mitochondrial CDK1 may be activated causing the phosphorylation of mitochondrial substrates in prophase. In Figure 4B, mitochondrial ATP generation and ROS production are linked with G2/M transition phase, indicating that mitochondrial Cyclin B1/CDK1 may participate in mitochondrial bioenergetics in DNA damage-associated adaptive response. This is supported by the fact that cell division cycle 25c (Cdc25c), the phosphatase activator of CDK1, is also present in mitochondria and therefore may further enhance the mitochondrial CDK1 kinase activity. We assume that mitochondrial Cdc25c may allow Cyclin B1/CDK1 to function in this particular compartment of cells, whereas the cytoplasmic and nuclear Cyclin B1/CDK1 may remain inactive until the cells progress into prophase. Thus, the mitochondrial Cdc25c may also play a critical role in radiation-induced adaptive protection, which remains to be elucidated.

Redox and Mitochondrial Cyclin B1/CDK1 in the Adaptive Response

Cells under genotoxic stress, such as IR, induce an imbalance in redox reactions caused by altered mitochondrial function, metabolism, and adaptive responses leading to short- or long-term effects in the cells (9, 49, 56, 57, 71–73, 100, 175, 214). A topic on redox reactions in cellular responses to IR has been well reviewed (199). Recent studies revealed that normal stem cells alter their redox homeostasis to adapt to adverse conditions, and radiation-induced oxidative stress in

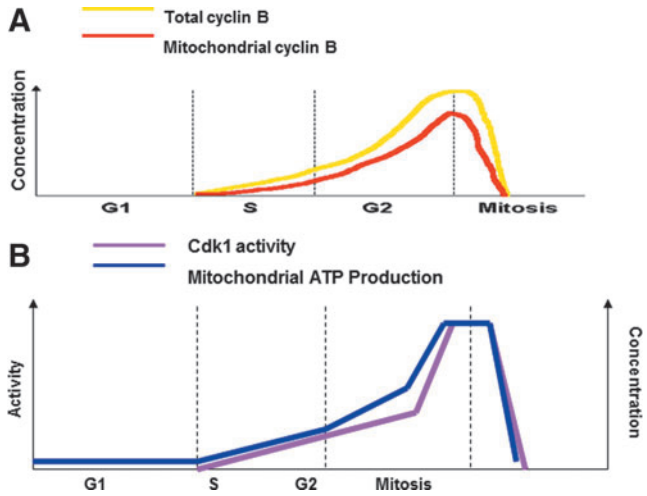

FIG. 4. Correlation between mitochondrial Cyclin B1/CDK1 activity and mitochondrial bioenergetics in cell cycle progression. (A) Cyclin B1 is expressed at the beginning of S phase, accumulated during the G2 phase, peaked at the late G2/early M-phase before advancing into mitosis, and is rapidly degraded during anaphase (86, 92). Cyclin B1 is not expressed throughout G1 phase. **(B)** The activity of mitochondrial CDK1 correlated with the level of mitochondrial Cyclin B1 and IR induces Cyclin B1/CDK1-mediated phosphorylation of mitochondrial p53 to mediate the adaptive response. An enhanced mitochondrial ATP generation (149) and mitochondrial ROS are accompanied by upregulation of mitochondrial electron transport chain function, and mitochondrial content is under control of cell cycle checkpoints (235). ATP, adenosine triphosphate. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

the pluripotent and multipotent human stem cells plays a crucial role in regulating the function and fate of stem cells within tissues compromised by radiation injury (72, 78, 110). IR-mediated ROS generation can directly alter the activity of kinases and transcription factors indirectly modulating cysteine-rich redox-sensitive proteins exemplified by thioredoxin and glutathione *S*-transferase. ROS-related redox changes in key signaling pathways have been well addressed (1, 11, 79, 86, 199).

Mitochondrial Ca^{2+} release to the cytoplasm causes the activation of multiple signaling pathways, including PKCs, MAPKs, and JNK (129). Herein, we illustrate two other major lines of evidence supporting mitochondria-centered redox signaling pathways in IR-induced adaptive response. The first is NOX. Under IR stress, NOX-derived ROS can activate MAPKs (extracellular signal-regulated kinase, p38) and JNK, which both participate in the adaptive response signaling network that cross talk with mitochondria (53). Acetylation of MnSOD directs the enzymatic activity responding to cellular nutrient status or oxidative stress (157). JNK-mediated repression of MnSOD and catalase occur *via* mitochondrial complex I and NOX I (104). Among the main factors involved in the redox balancing in adaptive response to IR (119), ATM, NF-κB, and pre-inflammatory factors (134, 135, 224) may also be regulated *via* NOX (220). In addition, plasminogen activator inhibitor-1 is a redox-regulated factor involved in the induction of profibrogenic mediators in acute or chronic oxidative stress after exposure to IR or H_2O_2 (244). A second redox-regulated factor is Dynamin-related protein 1 (DRP1), a guanosine triphosphate hydrolase enzyme (GTPase) regulating mitochondrial fission during cell cycle progression (236). A recent study reported that excessive nitric oxide could also lead to S-nitrosylation of Drp1 at cystine 644 (130). S-nitrosylation of Drp1 (resulting in SNO-Drp1) induces Drp1 dimerization, which functions as fundamental elements for higher order structures of Drp1 to activate Drp1 GTPase (148). Hypoxia-inducible factor-1α (HIF-1α) activation leads to mitochondrial fission by Cyclin B1/CDK1-dependent phosphorylation of DRP1 at serine 616 (130). These results together with the identification of mitochondria-localized Cyclin B1/CDK1 (36, 149) indicate that Cyclin B1/CDK1 cooperates with the redox-mediated signaling network to regulate the mitochondrial activity (Fig. 5).

Chaperones for Cyclin B1/CDK1 Mitochondrial Influx

Although mitochondria possess their own transcriptional machinery, merely 1% of mitochondrial proteins are synthesized inside the organelle; thus, the transportation of the nuclear-encoded proteins into mitochondria is an indispensable process alluding to multiple cross talk signaling pathways resulting in the nuclear to mitochondrial translocation of proteins. For proteins containing mitochondrial targeting sequences (MTS), the chaperone Translocase of Inner Mitochondrial Membrane 23 complex located on the mitochondrial membrane mediates their mitochondrial translocation to the matrix of the mitochondria (217). However, few mitochondrial proteins, including Cyclin B1 and CDK1, are identified to contain an MTS. Thus, specific chaperone proteins are required to assist their mitochondrial translocation. Although chaperone proteins, such as heat shock protein (HSP)60, HSP10, and HSP70, are suggested to be involved in mitochondrial translocation of many proteins (38, 150), the exact mechanism and the chaperones responsible for trafficking the cell cycle regulators to mitochondria remains largely unknown. Both 14-3-3ζ, a well-defined chaperon for mitochondrial protein flux, and Cyclin B1 are activated by radiation (67, 85), indicating the possibility that 14-3-3ζ may be the vehicle responsible for delivering Cyclin B1/CDK1 to the mitochondria under genotoxic stress. Interestingly, 14-3-3ζ is known to bind to Cdc25c (74) and thus may also be responsible for transporting Cdc25c to mitochondria to activate the mitochondrial CDK1 activity. Taken together, although the exact mechanism underlying mitochondrial relocation of Cyclin B1/CDK1 is unknown, current data implicate that chaperone proteins, including 14-3-3ζ, are involved in facilitating Cyclin B1/CDK1 mitochondrial relocation. In addition to the 14-3-3s, Cyclin B1/CDK1 is shown to interact with other chaperone proteins, such as HSP70-2, HSP90, and cell division cycle 37 (144, 214, 248). These chaperones should be able to assist Cyclin B1/CDK1 mitochondrial translocation. The specific pathways involved in a timely fashion of Cyclin B1/CDK1 mitochondrial transportation, especially under cell cycle progression and nuclear DNA damaged conditions, remain to be elucidated.

Cyclin B1/CDK1 in Mitochondrial Fission

Cyclin B1/CDK1 may regulate mitochondrial fission and fusion in radiation-induced adaptive responses. Mitochondria

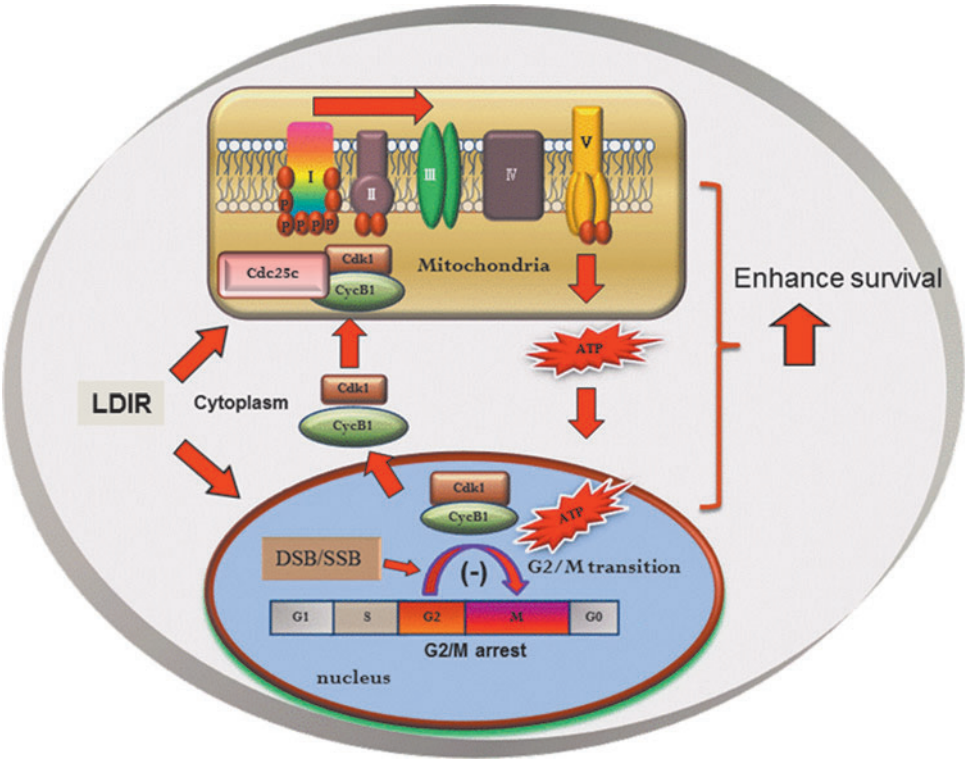

FIG. 5. NADPH oxidase redox reaction imbalance in IR-induced adaptive protection. Cyclin B1/CDK1 phosphorylation of the ubiquinone-binding site of core complex I confers transition of G2 to M phase. ATP mitochondrial generation mediates cell division by G2 to M phase transition.

proliferate only from existing mitochondria (168) *via* complementary fission and fusion events. A balance between these opposing processes contributes to mitochondrial membrane dynamics (152, 225). In mammalian cells, the fusion events are carried out by a mitochondrial transmembrane GTPase known as mitofusin (66), whereas Drp1 is responsible for mitochondrial fission events (195). The post-translational modification on Drp1 is shown to play a critical role in determining the GTPase activity during mitochondrial fission (179). The contribution of Cyclin B1/CDK1 in the regulation of mitochondrial functions is not limited to directing the kinase targeting to mitochondria but also is involved in the morphological regulation. It has long been recognized that the mitochondrial number coordinates with the cell cycle phase with a 50% increase during S phase due to fission (58). However, the mechanism connecting cell cycle and regulation of mitochondrial fission and fusion remains obscure. Taguchi *et al.* demonstrated that in addition to chromatid segregation, Cyclin B1/CDK1 is the kinase regulating the mitotic mitochondrial fragmentation, also known as mitochondrial fission during mitosis (207). Interestingly, phosphorylation of Drp1 by Cyclin B1/CDK1 at serine 585 residue during mitosis was found to be required to translocate Drp1 from cytosol to the mitochondrial outer membrane, which is necessary for mitochondrial fission (Fig. 6) (194, 207). Cyclin B1/CDK1 coordinates mitochondrial fission with the onset of G2/M transition *via* phosphorylation of Drp1 by Cyclin B1/CDK1 (207). Activated Drp1 then punctuates holes on the mitochondrial membrane to proceed with membrane constriction and fission directed by mitochondrial fission 1 protein (Fis1) (41, 111). Drp1 reportedly assembles into rings and spirals that encircle and constrict the mitochondria during fission (57). The separation of mitochondria during cytokinesis is essential to the survival of the two daughter cells, and the mitochondrial fragmentation modulated by Drp1 allows equal distribution of the mother mitochondria into two daughter cells as the fission events occur during the cell cycle. Exogenous expression of unphosphorylated mutant Drp1S585A leads to reduced mitotic mitochondrial fragmentation (207). In addition to morphological alterations, the Drp1 activity has shown to be essential for mitochondrial bioenergetics supported by the fact that ATP production is severely impaired in $Drp1^{-/-}$ deficient cells (17). On the contrary, phosphorylation at serine 637 residue by cyclic adenosine monophosphate-dependent protein kinase on Drp1 has been shown to suppress its GTPase activity by decreasing the intramolecular interaction that drives GTP hydrolysis (42, 108), which can be removed by the phosphatase calcineurin (52). Mutation in Drp1 also leads to the highly elongated mitochondrial filaments and reduction in mitotic mitochondrial fragmentation (24, 207). This hypothetic pathway is illustrated in Figure 6. Further definition of the relationship between Cyclin B1/CDK1 and Drp1 during mitochondrial fission may reveal a new role of mitochondrial Cyclin B1/CDK1 in regulating Drp1 to prepare mitochondria for a successful cell division, which may be interrupted or enhanced under different doses of genotoxic agents.

Mitochondrial Cyclin B1/Cdk1 in Cell Cycle Progression

Dynamic alterations in mitochondrial mass and $\Delta\psi_m$ together with cellular ATP levels were detected during cell cycle progression (206). Depletion of nutrients induced mtDNA replication but not nuclear DNA replication during the development of *Dictyostelium discoideum* cells (188). Mitochondrial regulation of cell cycle progression during development was revealed by the permanent mutation in *Drosophila*, which caused a reduction of intracellular ATP that was still sufficient

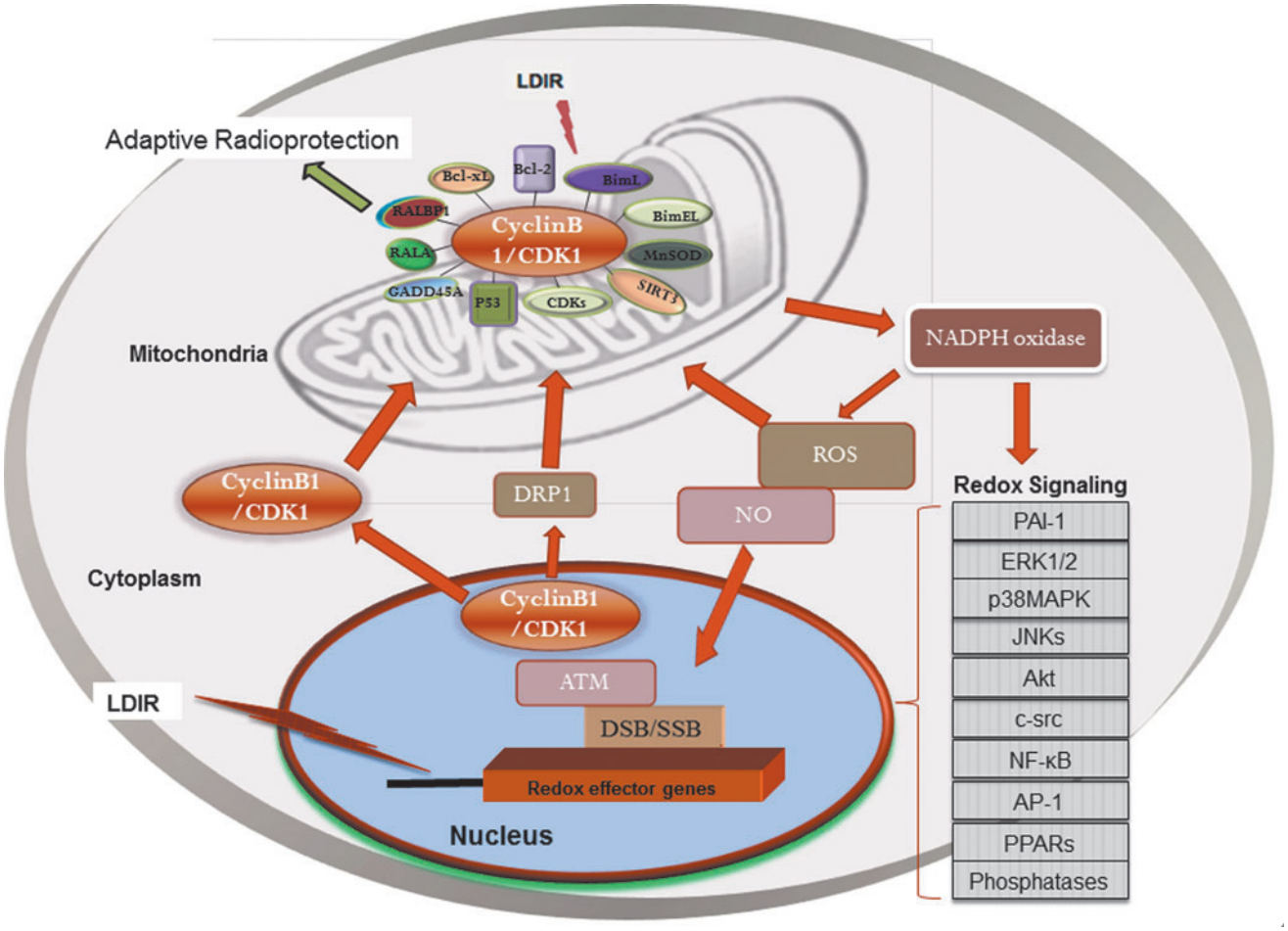

FIG. 6. Phosphorylation of Drp1 by Cyclin B1/CDK1 at the serine 585 residue during mitosis is required to translocate Drp1 from cytosol to the mitochondrial outer membrane during mitochondrial fission. Activated Drp1 results in membrane constriction and fission directed by Fis1. Drp1, dynamin-related protein 1. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

to maintain cell survival, growth, and differentiation, but not adequate for progression through the cell cycle (128). This suggests that a group of mitochondrial proteins were regulated during cell cycle progression. We have identified mitochondrial protein targets of Cyclin B1/CDK1 in an array of cancer cells that were treated with high-dose IR (5 Gy) (149). As shown in Figure 7, a model of Cyclin B1/CDK1-mediated mitochondrial function in cell cycle progression is proposed for the IR-induced adaptive response. In this model, adaptive response-inducing DNA damage, such as those triggered by LDIR, stimulates the translocation of Cyclin B1 and CDK1 to mitochondria where the kinase activity of Cyclin B1/CDK1 is activated by cdc25 to phosphorylate the cluster of subunits in the OXPHO machinery. This leads to increased mitochondrial respiration, ATP production, and $\Delta\psi_m$, which facilitates DNA repair and cell cycle progression. This may be significant for rapidly growing cells, and radiation may block cellular mitosis by causing G2/M arrest.

Specific Cyclin B1/CDK1 Targets in OXPHO

Mitochondria, the powerhouse in mammalian cells, derive energy from both the tricarboxylic acid cycle and OXPHOS. Although the metabolic activity is believed to be a crucial determinant for cell proliferative growth, the exact pathways linking mitochondrial energy output and cell cycle regulation are unknown (7). During division, cells require additional amounts of ATP to enter mitosis at the G2/M phase (206). OXPHOS supplies more than 90% of cellular ATP required for eukaryotic cells (91), and the mitochondrial OXPHOS is irrefutably critical for the progression of the cell cycle as the level of ATP determines the fate of cell division (133). A mitochondrial protein database for the CDK1 consensus phosphorylation motif (S/T P×R/K) (196, 215) reveals 12 OXPHOS subunits that can be potentially phosphorylated by CDK1 on the mitochondrial respiration chain (Complex I–V) (Fig. 8). This phosphorylation has the potential to modulate the activity of the protein complexes thereby regulating energy production. The majority of those subunits are the components of the mitochondrial Complex I (nicotinamide adenine dinucleotide-ubiquinone oxidoreductase), the essential complex in the OXPHOS system (180, 216). The potential targets of phosphorylation by Cyclin B1/CDK1 are the ubiquinone-binding sites located on the core of the complex I facing the matrix side of the mitochondria (Fig. 8). Since the ubiquinone of complex III and an unknown component of complex I functions as the major sites of ROS generation (25, 62, 127), the mitochondrial Cyclin B1/CDK1 may regulate

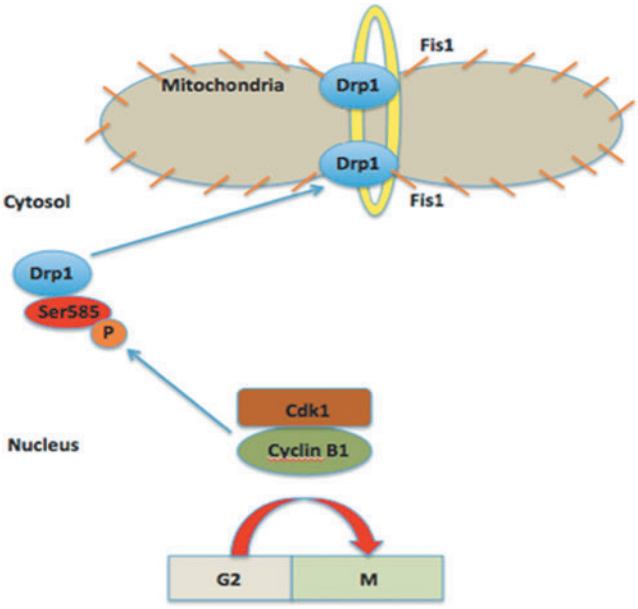

FIG. 7. Cyclin B1/CDK1 phosphorylation of the ubiquinone-binding site of core complex I confers transition of G2 to M phase. DNA-damage IR stimulates the gene expression and translocation of Cyclin B1 and CDK1 from the nucleus to the mitochondria. Mitochondrial Cyclin B1 and CDK1 form a complex to phosphorylate the ubiquinone-binding site of core complex I, which leads to increased ATP production and inhibition of mitochondria-mediated apoptosis. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

the surge in mitochondrial ATP production required for the critical boost of cellular energy reserves to repair DNA damage. In addition, radiation-induced Cyclin B1/CDK1 is also required for many cellular functions, such as DNA repair in the nucleus. Therefore, a cooperation of events occurring in the nucleus and mitochondria by the same regulator highlights a tight connection of cell cycle progression with mitochondrial activity.

Cyclin B1/CDK1 in Mitochondria-Mediated Apoptosis

It has been generally accepted that the initiation of apoptosis is a unique function of mitochondria in mammalian cells (64, 84, 115–117, 165). Cyclin B1/CDK1 is known to be responsible for initiating mitochondria-mediated apoptosis under cell damage conditions by phosphorylation of several pro- and antiapoptotic proteins (37, 219, 229). CDK activity is involved in the mitochondrial translocation of Bax, which plays an important role in the mitochondrial membrane permeability transition during apoptotic progression (47). Under different levels of genotoxic stresses, including IR, the phosphorylation of several Bcl-2 family proteins, such as Bcl-2, Bcl-2-associated death protein, and B-cell lymphoma-extra large (Bcl-xL) by Cyclin B1/CDK1 can alter mitochondrial membrane permeability resulting in loss of cytochrome c to the cytosol (100, 149, 212, 219, 232). Cyclin B1/CDK1 thus may be the determining factor in deciding cell apoptosis. Abnormal activities and aberrant expression of Cyclin B1 have been observed in a number of human cancers, including esophageal squamous cell carcinoma (145), laryngeal squamous cell carcinoma, nonsmall cell lung cancer (197), and colorectal carcinoma (59, 114, 208, 222). Most importantly, Cyclin B1 also potentially causes chemo- and radioresistance in cancer cells (89, 90). Deficiency of Cyclin B1 leads to profound inhibition of cell proliferation and activation of apoptosis (241). Activated Cyclin B1 is linked with the prosurvival pathway regulated by NF-κB (158). Therefore, Cyclin B1/CDK1 serves as an important component in NF-κB-induced cellular resistance to genotoxic insults. However, Cyclins and CDKs appear to have dual functions in both promoting and suppressing apoptosis in mammalian cells. Examples include that phosphorylation on pro-caspase-9 by Cyclin B1/CDK1 or survivin (Baculoviral inhibitor of apoptosis repeat-containing

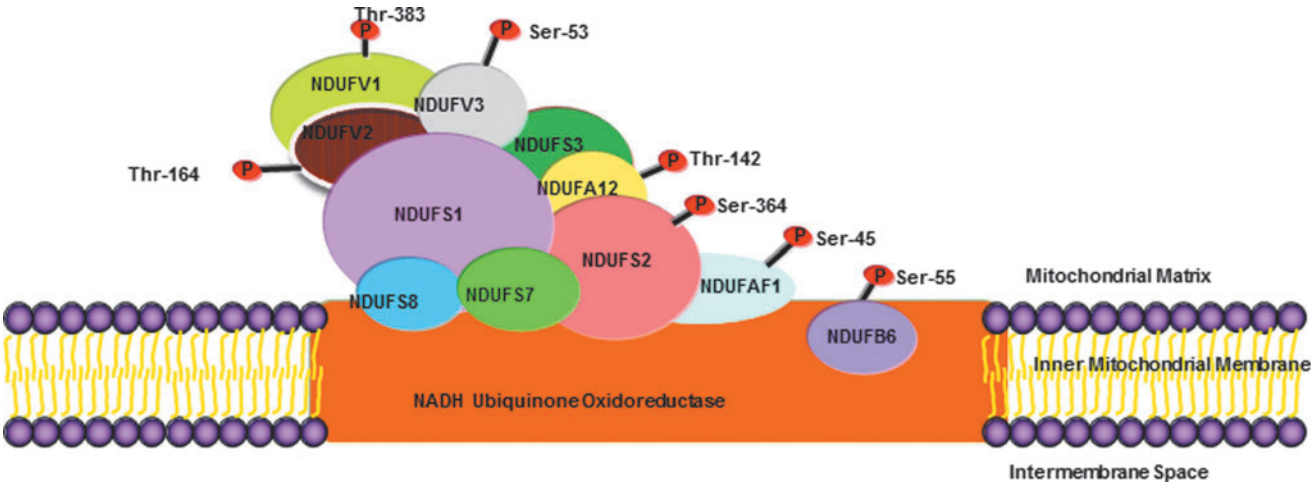

FIG. 8. The location of potential Cyclin B1/CDK1-targeted mitochondrial complex I subunits corresponding to the structure of complex I (NADH-ubiquinone oxidoreductase) in the mitochondrial inner membrane. Three of the phosphorylation targeted subunits are the central subunits for NADH reduction (30). The phosphorylation on these subunits leads to the enhanced function of the complex I, particularly during the G2/M phase when Cyclin B1 expression is at the peak level (Fig. 3). The model structure is derived from Sazanov and Hinchliffe (181). NADH, nicotinamide adenine dinucleotide. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

5) by p34cdc2 leads to inhibition of apoptosis (5, 153). These results suggest that although Cyclin B1/CDK1 is a key factor determining the fate of an irradiated cell, cell survival appears to be dependent on not only the degree of genomic injury and instability but also Cyclin B1/CDK1-associated mitochondrial targets of phosphorylation with the end result of increased or decreased energy production.

Cyclin B1/CDK1-Mediated Antiapoptotic Pathway

Tumor suppressor p53 is well characterized to regulate mitochondria-mediated apoptosis at protein and mRNA levels (45, 136). p53 initiates the apoptotic cascade by inducing expression or interacting directly with cytoplasmic proteins in the Bcl-2 family (44). Localization of p53 to mitochondria conventionally resembles a major starting signal for mitochondria-mediated apoptosis (245). However, mitochondrial p53 may not necessarily induce apoptosis (71). Vital functions of mitochondrial p53 have been reported, including mtDNA transcription, DNA repair, mitochondrial biogenesis (13, 177, 239), as well as in ATP production since p53 also regulates mitochondrial respiratory genes, synthesis of cytochrome c oxidase (SCO2), and phosphate-activated mitochondrial glutaminase (GLS-2) (131, 205). Therefore, the role of mitochondria-localized p53 should be considered broadly, depending on its cooperative and differential phosphorylation in addition to apoptotic signals (102). Although several kinases reportedly phosphorylate 17 residues on p53, the regulation of phosphorylation on mitochondrial p53 is not yet known. In an attempt to identify kinases for mitochondrial p53, our group recently reported direct evidence showing Cyclin B1/CDK1 phosphorylation on mitochondrial p53 (149). Upon stress stimulus, the levels p53, Cyclin B1, and CDK1 in mitochondria were all elevated leading to the phosphorylation of mitochondrial p53 at serine 315 residue, the only putative site for CDK1 phosphorylation (23). This phosphorylation, together with the phosphorylation of other Cyclin B1/CDK1 targets in the mitochondria and elevated OXPHO, could compromise the proapoptotic function of mitochondrial p53 by sequestering it from binding to Bcl-2 and Bcl-xL (Fig. 9). As a result, its proapoptotic potential is reversed into the prosurviving function by maintaining mitochondrial integrity and increasing ATP production as a possible supplement for the DNA repair processes. The finding of Cyclin B1/CDK1-phosphorylated mitochondrial p53 reinstates the prosurvival function of Cyclin B1/CDK1, an important insight in the nuclear-guided mitochondrial functions.

Conclusion

Citing a model of cellular adaptive response to LDIR, this review discussed a new feature of nuclear-to-mitochondrial communication mediated by the cell cycle G2/M regulator Cyclin B1/CDK1. A myriad of Cyclin B1/CDK1 protein targets remain to be characterized (94, 124, 215). Promising novel mitochondrial targets of Cyclin B1/CDK1 may play an important role in coordinating cellular respiration related to cell cycle progression and the adaptive response to genotoxic stress. Thus, Cyclin B1/CDK1 may be considered one of the key harmonizers for the regulation of mitochondrial functions in cellular adaptive response under genotoxic stress, including LDIR.

The variation in cellular energy at different stages of the cell cycle requires the precise control and communication with mitochondria that produces the major resource of ATP for proliferation. The production of ATP from a glucose molecule is ~13-fold higher with aerobic respiration compared to anaerobic metabolism (172). The targets of mitochondria regulated by Cyclin B1/CDK1 may serve as one of the many mechanisms for cells to communicate with mitochondria under different growth or stress conditions. Since the function of this kinase complex varies at different stages of the cell cycle and can be induced by IR, Cyclin B1/CDK1 seems to synchronize mitochondrial energy production in concomitant with the nuclear DNA repair. In addition, the Warburg effect, described as cancer cells utilizing energy produced from glycolysis rather than OXPHOS (106), may be perturbed or

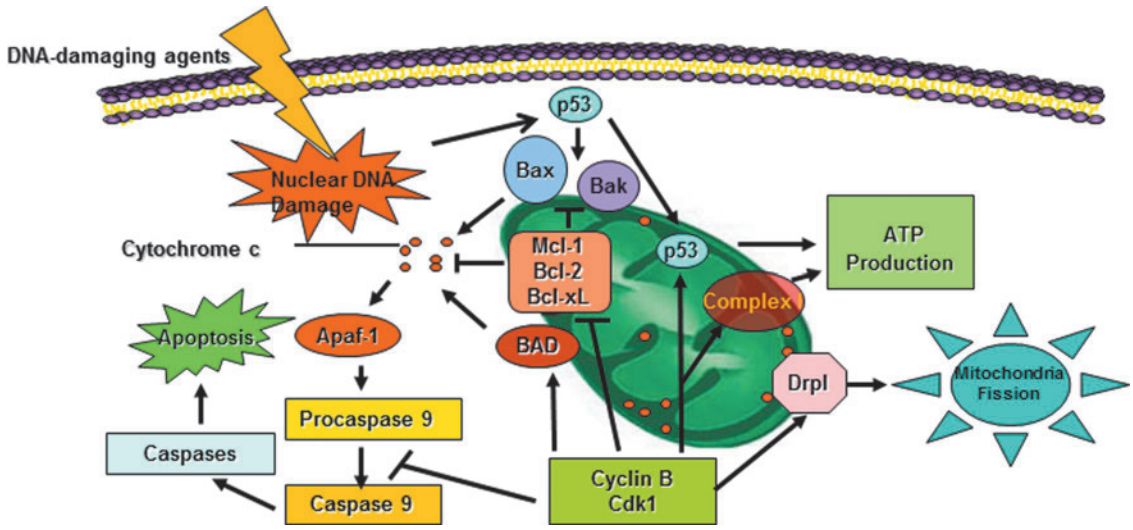

FIG. 9. Schematic representation of signaling transduction for Cyclin B1/CDK1 in mitochondria. Cyclin B1/CDK1 serves as a kinase on several mitochondria-translocated proteins involved in bioenergetics and apoptotic functions. The Cyclin B1/CDK1 complex also serves as a direct link between cell cycle and mitochondrial responses in response to stress signals. During the G2 phase, the Cyclin B1/CDK1 serves as an apoptotic suppressor when the cells undergo a G2 checkpoint and repair DNA damage. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

reversed under stress conditions leading to mitochondrial metabolism reprograming. Unknown mechanisms remain to be elucidated to understand why cancer cells avoid utilizing mitochondrial machinery for its major energy source and how it is adjusted under anticancer radiotherapy. A potential critical mechanism involving sirtuin3 (SIRT3), a mitochondrial sirtuin protein (50), was proposed to guide mitochondrial energetics in normal cells *versus* glycolysis in tumor cells described as the Warburg effect (16, 39, 123, 155, 163, 182). A recent study showed that tumors from SIRT3-deficient mice have high levels of ROS that induce genomic instability and elevate HIF-1α protein levels (87). Importantly, the acetylation/deacetylation status of MnSOD was found to regulate the MnSOD enzymatic activity responding to cellular nutrient status or oxidative stress (157). Thus, an integration of signals between Cyclin B1/CDK1-mediated MnSOD phosphorylation (36) and SIRT3-mediated MnSOD acetylation status (210, 249) may coordinate the radiation-induced adaptive response at the subcellular level.

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Abbreviations Used

$\Delta\psi_m$ = mitochondrial membrane potential
14-3-3ζ = chaperones
Apaf-1 = apoptotic peptidase activating factor 1
ATM = ataxia telangiectasia mutated
ATP = adenosine triphosphate
BAD = Bcl-2-associated death protein
Bak = Bcl-2 homologous antagonist/killer
Bax = Bcl-2-associated X protein
Bcl-2 = B-cell lymphoma 2
Bcl-xL = B-cell lymphoma-extra large
BIRC5 = Baculoviral inhibitor of apoptosis repeat-containing 5
cAMP = cyclic adenosine monophosphate
Cdc25c = cell division cycle 25c
Cdc37 = cell division cycle 37
CDK = cyclin-dependent kinases
CDK1 = cyclin-dependent kinase 1
DRP1, Drp1 = dynamin-related protein 1
ERK = extracellular signal-regulated kinase
FKHRL1 = apoptosis-promoting fork-head transcription factor
GLS-2 = phosphate-activated mitochondrial glutaminase
GTPase = guanosine triphosphate hydrolase enzyme
HIF-1α = hypoxia-inducible factor 1
HSP = heat shock protein
IR = ionizing radiation
JNKs = c-jun N-terminal kinases
LDIR = low-dose ionizing radiation
MAPKs = mitogen-activated kinases
Mfn = mitofusin
MnSOD = manganese superoxide dismutase
MPF = maturation promoting factor
MPI = mitochondrial protein influx
mtDNA = mitochondrial DNA
MTS = mitochondria targeting sequence
NADH = nicotinamide adenine dinucleotide
NDUFA12 = NADH dehydrogenase ubiquinone 1 alpha subcomplex subunit 12
NDUFB6 = NADH dehydrogenase ubiquinone 1 beta subcomplex subunit 6
NDUFS2 = NADH dehydrogenase ubiquinone iron-sulfur protein 2
NDUFV1 = NADH dehydrogenase ubiquinone flavoprotein 1
NDUFV3 = NADH dehydrogenase ubiquinone flavoprotein 3
NOX = NADPH oxidase
NPI = nuclear protein influx
OXPHOS = oxidative phosphorylation
PAI-1 = plasminogen activator inhibitor-1
PKA = cAMP-dependent protein kinase
PKC = protein kinase c
SCO2 = synthesis of cytochrome c oxidase
sirtuin3 = SIRT3
Thr = threonine (T)
Tyr = tyrosine (Y)