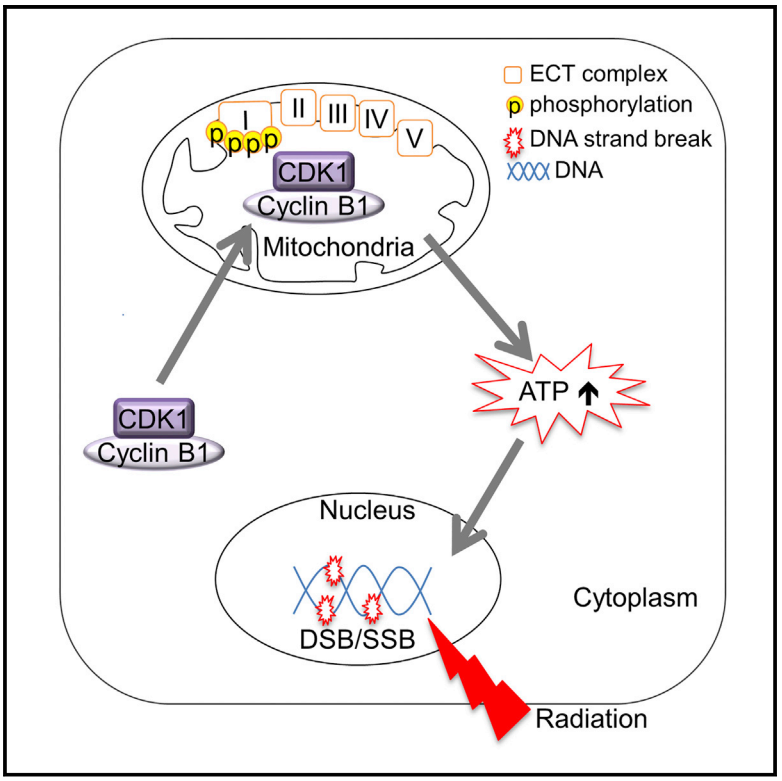
Report

Cell Reports

CDK1 Enhances Mitochondrial Bioenergetics for Radiation-Induced DNA Repair

Graphical Abstract



Highlights

- Oxygen consumption and mitochondrial ATP generation are enhanced in irradiated cells
- Upon radiation, CDK1 relocates to mitochondria
- Mitochondrial CDK1 boosts ATP generation via CI phosphorylation
- CDK1-regulated mitochondrial ATP generation favors DNA repair and cell survival

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In Brief

Qin et al. identify communication between mitochondrial bioenergetics and nuclear DNA repair. Upon radiation, the mitotic kinase CDK1 relocates to mitochondria and activates mitochondrial complex I. The resulting ATP generation is required for efficient DNA repair.

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CDK1 Enhances Mitochondrial Bioenergetics for Radiation-Induced DNA Repair

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SUMMARY

Nuclear DNA repair capacity is a critical determinant of cell fate under genotoxic stress conditions. DNA repair is a well-defined energy-consuming process. However, it is unclear how DNA repair is fueled and whether mitochondrial energy production contributes to nuclear DNA repair. Here, we report a dynamic enhancement of oxygen consumption and mitochondrial ATP generation in irradiated normal cells, paralleled with increased mitochondrial relocation of the cell-cycle kinase CDK1 and nuclear DNA repair. The basal and radiation-induced mitochondrial ATP generation is reduced significantly in cells harboring CDK1 phosphorylation-deficient mutant complex I subunits. Similarly, mitochondrial ATP generation and nuclear DNA repair are also compromised severely in cells harboring mitochondrially targeted, kinase-deficient CDK1. These results demonstrate a mechanism governing the communication between mitochondria and the nucleus by which CDK1 boosts mitochondrial bioenergetics to meet the increased cellular fuel demand for DNA repair and cell survival under genotoxic stress conditions.

INTRODUCTION

It is well known that radiation induces cell death because of nuclear DNA damage. To survive, cells need to maintain their genomic stability via checkpoint activation and a rapid DNA repair process. Lack of or an insufficient repair mechanism could lead to apoptosis or abnormal cell proliferation and cancer risk (Hoeijmakers, 2009; Kastan and Bartek, 2004). DNA repair has long been believed to be a highly energy-demanding process, consuming a large amount of cellular ATP (Bakkenist and Kastan, 2004; Hopfner et al., 2000; Paull and Gellert, 1999; Ward and Chen, 2004). As the powerhouse of mammalian cells, mitochondria provide the major cellular fuel for many critical processes in cell proliferation and survival (Pagliarini and Dixon, 2006; Scheibye-Knudsen et al., 2015). Inhibition of the respiration chain suppresses the spontaneous and H_2O_2-induced DNA damage repair in peripheral blood mononuclear cells (Gafter-Gvili et al., 2011). Mutations of mitochondrial genes encoding respiration chain subunits sensitize B-lymphoblastoid cells to radiation with decreased ATP generation and DNA repair gene expression (Kulkarni et al., 2011). However, the exact mechanism regulating mitochondrial bioenergetics to coordinate the nuclear DNA repair capacity under genotoxic stress conditions remains unknown.

Recent findings have revealed that Cyclin B1/CDK1, a well-defined cell-cycle kinase governing key steps of cell-cycle progression (Gautier et al., 1990; Hochegger et al., 2008), functions in the communication between mitochondrial activity and cell-cycle progression. CDK1 is involved in the integration of mitochondrial fission during G2/M transition through phosphorylation of mitochondrial fission proteins (Taguchi et al., 2007; Yamano and Youle, 2011). Cyclin B1/CDK1 has also been found to be able to phosphorylate and activate MnSOD and p53 in mitochondria to enhance cell survival (Candas et al., 2013; Nantajit et al., 2010). Recent data have also revealed that a fraction of mitochondrially relocated Cyclin B1/CDK1 can assist G2/M transition by boosting mitochondrial ATP generation via phosphorylation of mitochondrial respiration chain complex I (CI) subunits (Wang et al., 2014) and that CDK1-mediated Tom6 phosphorylation enhances the mitochondrial protein influx required for mitochondrial biogenesis and activity (Harbauer et al., 2014). Here we report that Cyclin B1/CDK1 mitochondrial relocation and mitochondrial ATP generation are enhanced in parallel with nuclear DNA repair in irradiated cells. Expression of CDK1 phosphorylation-deficient CI subunits or mitochondrially targeted kinase-deficient CDK1 inhibits radiation-induced mitochondrial ATP generation and DNA repair. These results provide evidence indicating communication between mitochondrial bioenergetics and nuclear DNA repair in which CDK1-mediated phosphorylation and activation of mitochondrial CI enhances mitochondrial ATP production to