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REVIEW

Mitochondrial reactive oxygen species-mediated genomic instability in low-dose irradiated human cells through nuclear retention of cyclin D1

Tsutomu Shimura and Naoki Kunugita

Department of Environmental Health, National Institute of Public Health, Wako, Saitama, Japan

ABSTRACT

Mitochondria are associated with various radiation responses, including adaptive responses, mitophagy, the bystander effect, genomic instability, and apoptosis. We recently identified a unique radiation response in the mitochondria of human cells exposed to low-dose long-term fractionated radiation (FR). Such repeated radiation exposure inflicts chronic oxidative stresses on irradiated cells via the continuous release of mitochondrial reactive oxygen species (ROS) and decrease in cellular levels of the antioxidant glutathione. ROS-induced oxidative mitochondrial DNA (mtDNA) damage generates mutations upon DNA replication. Therefore, mtDNA mutation and dysfunction can be used as markers to assess the effects of low-dose radiation. In this study, we present an overview of the link between mitochondrial ROS and cell cycle perturbation associated with the genomic instability of low-dose irradiated cells. Excess mitochondrial ROS perturb AKT/cyclin D1 cell cycle signaling via oxidative inactivation of protein phosphatase 2A after low-dose long-term FR. The resulting abnormal nuclear accumulation of cyclin D1 induces genomic instability in low-dose irradiated cells.

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Introduction

The main target of ionizing radiation (IR) is thought to be the nuclear DNA (nDNA) in the cell nucleus. Double strand breaks (DSBs) in nDNA generated by IR give rise to chromosomal aberrations. In response to genotoxic stress, mammalian cells activate cellular defense systems, including cell cycle checkpoints, apoptosis, and DNA repair mechanisms.[1,2] Research has therefore focused on the effect of radiation on nDNA to elucidate DNA damage responses (DDR) in mammalian cells. Radiation also affects cell organelles, such as the plasma membrane, cytoskeleton, mitochondria, endoplasmic reticulum, Golgi apparatus, and lysosomes.[3-6] Direct evidence for the effect of IR on the cytoplasmic structures has been obtained as bystander effects after cytoplasmic irradiation with α particles.[7,8] Mitochondria contain their own DNA and can be directly damaged by IR. Although the whole mitochondrial genome, apart from the D-loop control region, consists of genes, only approximately 1% of nDNA encodes genes. Thus, mitochondrial DNA (mtDNA) mutations are more likely to cause functional loss than nDNA mutations. Hence, it is of special importance to maintain mtDNA integrity, particularly under oxidative stress conditions. Mitochondria, along with the nucleus, are therefore likely to be a major target of IR.[6]

Mitochondria regulate energy supply and are shown to be a source of endogenous reactive oxygen species (ROS) generation through oxidative phosphorylation.[9] ROS function as a second messenger of intracellular signaling pathways for physiological processes[10-12] by modifying the cysteine residues within redox-sensitive target proteins leading to reversible modification of enzymatic activity.[13,14] However, ROS accumulation at high levels inflicts oxidative damage on cellular components, such as nucleic acids, proteins, and lipids, and inhibits cell proliferation.[15] IR triggers genomic instability, a hallmark of cancer in irradiated cells as the late effect of IR.[16-18] Changes in the pattern of DNA methylation are associated with cancerogenesis together with genetic mutations.[19,20] Mitochondrial ROS induce genomic instability in irradiated cells.[21-23] To control redox balance, mitochondria contain antioxidants, such as glutathione (GSH) and manganese superoxide dismutase (MnSOD), which scavenge ROS.[24] KRIT1, a gene responsible for cerebral cavernous malformations regulates antioxidant pathway involving FoxO1 and MnSOD to maintain the homeostasis of intracellular ROS.[25] Dismutation of superoxide anions in the mitochondria forms H_2O_2, either spontaneously or through the catalytic function of MnSOD, to maintain redox homeostasis. GSH peroxidases then further reduce H_2O_2 to water using GSH as a ROS receptor.

Mitochondria regulate apoptosis after high-dose IR in normal cells. Similarly, apoptosis was induced in radiosensitive ATM-deficient cells after low-dose long-term FR.[26] In contrast, the same low-dose long-term FR activates mitochondrial function and causes chronic oxidative stresses due to elevated mitochondrial ROS in normal and complemented cells expressing ATM. So, there are different modes of mitochondrial radiation response according to intrinsic radiation sensitivity of the irradiated cells.[26] This review is focused on our current understanding of a unique radiation response of mitochondria upon repeated low-dose IR. Mitochondrial ROS perturb cell cycle

CONTACT Tsutomu Shimura tsimura@niph.go.jp Department of Environmental Health, National Institute of Public Health, 2-3-6 Minami, Wako, Saitama 351-0197, Japan

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signaling and this is concomitant with genomic instability in human cells after low-dose long-term FR.

Radiation responses of mitochondria

The radiation responses of mitochondria are well reviewed in other study[6] and are summarized in Figure 1. IR increases mtDNA copy number in mammalian cells *in vitro* and *in vivo*.[6] IR stimulates mitochondrial enzyme activity and gene expression to supply energy for radiation responses.[6,27,28] Low-dose IR changes the dynamics of mitochondrial morphology and induces mitochondrial fusion to protect rat neurons.[29] Mitochondrial fusion enables content mixing within a mitochondrial population including both damaged and healthy mitochondria to protect against mitochondrial dysfunction.[30-32] On the other hand, mitophagy refers to the selective removal of damaged mitochondria by autophagy to control mitochondrial quality.[33,34] The E3 ubiquitin ligase Parkin recognizes damaged mitochondria and promotes their clearance by mitophagy.[35,36] Mitochondria are also associated with the non-targeted effects of radiation, including the adaptive response, the bystander effect, and genomic instability.[21,22] Mitochondrial localization of MnSOD is required for radioprotection.[37-39] IR at low doses induces NF-kappaB-mediated activation of MnSOD as a signaling regulator of cell survival pathways in low-dose IR-induced adaptive responses in mammalian cells.[40,41] Constitutive active AKT is associated with induction of NF-kappaB signaling after chronic low-dose IR.[41] Mitochondria-dependent NF-kappaB signaling pathways also implicates in the regulation of radiation-induced bystander.[42] In contrast, IR at high doses results in the breakdown of the mitochondrial membrane potential, opening of the permeability transition pore (PTP), and release of cytochrome c for the induction of apoptosis in irradiated cells (Fig. 1, upper panel).[43]

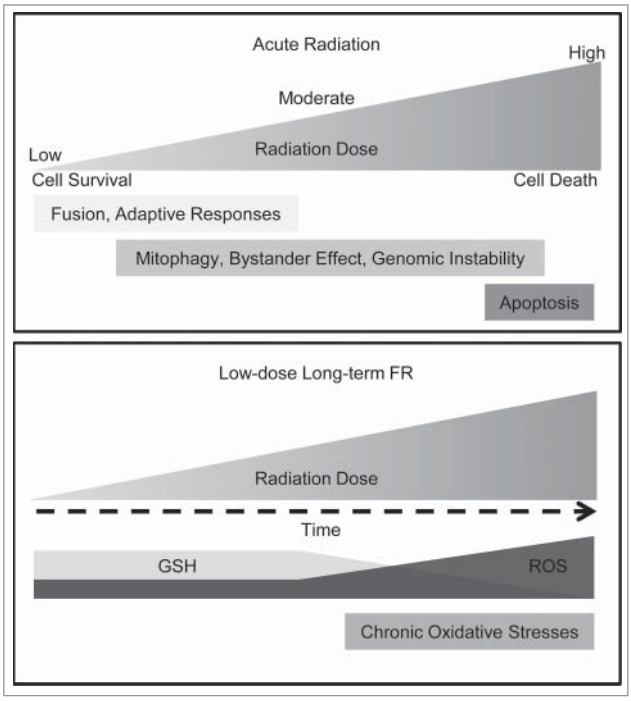

Figure 1. Radiation response of mitochondria The upper panel shows the difference in the radiation response of mitochondria according to the radiation dose after acute single radiation. The lower panel shows the mitochondrial radiation response to low-dose long-term fractionated radiation.

Although the health risks associated with low-dose radiation are currently under intensive investigation, the influences of low-dose long-term radiation remain unclear because of a lack of sufficient studies. We recently reported that low-dose long-term FR induces mitochondria-mediated oxidative stresses by increasing the generation of mitochondrial ROS in human cells (Fig. 1, lower panel).[44] Thus, mitochondrial radiation responses change according to the radiation dose, duration of radiation exposure. The antioxidant GSH protects cells against oxygen toxicity mediated by mitochondrial ROS.[44] However, GSH becomes exhausted after repeated low-dose IR. The accumulation of mitochondrial ROS owing to a GSH deficiency would activate oxidative stress responses and DDR over a prolonged period (Fig. 1, lower panel).

The role of ATM on radiation response of mitochondria

In ataxia-telangiectasia (AT), a disease characterized by high levels of radiosensitivity and neurodegeneration, ATM is mutated.[45] ATM is a damage sensor kinase is essential for maintaining genome stability in response to various stresses. It has also been identified as a redox sensor and is activated by oxidization at a cysteine residue independent of DSBs under oxidative stress.[46,47] Lower antioxidative capacity is reported in AT patients.[48] Biogenesis of mitochondria in response to IR was investigated in radiosensitive human ATM-deficient cells compared with that in ATM-complemented cells. Consistent with the results in normal fibroblasts, low-dose long-term FR stimulated mitochondrial biogenesis with elevated ROS levels in ATM-complemented cells. In contrast, mitochondrial biogenesis was not triggered by the same radiation treatments in ATM-deficient cells.[26] Thus, ATM is required for the radiation response of mitochondria. In response to DSB, ATM is shown to phosphorylate AMP-activated protein kinase (AMPK), which senses the cellular AMP/ATP ratio to induce mitochondrial biogenesis.[49] ATM is associated with the induction of mitophagy in response to IR and oxidative stresses.[50] ATM loss leads to defective mitophagy and increased frequency of abnormal mitochondria with decreased mitochondrial membrane potential.[50] Severe mitochondrial damage, assessed from mitochondrial fragmentation, was induced by low-dose long-term FR in ATM-deficient cells, which showed highly radiosensitive phenotypes when subjected to low-dose long-term FR; cell death was through mitochondria-mediated apoptosis.[26] Consequently, it became clear that the mitochondrial radiation response influences radiation sensitivity in human cells.

Mitochondria as target organelles for low-dose radiation

mtDNA is located at the inner mitochondrial membrane close to the sites of ROS production via the electron transport chain and suffers more oxidative damage than nDNA.[51,52] Because mtDNA lacks histone protection and the efficient DNA repair system of nDNA, mtDNA damage due to IR is thought to be more extensive and persistent over time than nDNA damage. Mitochondria

harbor base excision repair, but nucleotide excision repair is absent.[53] DNA polymerase γ (Pol γ) is the enzyme for replication and repair of mtDNA. Although Pol γ exhibits high base substitution fidelity with exonucleolytic proofreading,[54] it has low frameshift fidelity for repetitive sequences longer than 4 nucleotides.[55] ROS-induced DNA lesions, such as abasic sites and single- and double-strand breaks, generate mutations upon DNA replication. mtDNA mutations induced by ROS-mediated oxidative modifications lead to progressive electron transport chain dysfunction and further increases in ROS production.[56-58] IR permanently impairs mitochondria by induction of mtDNA mutations, leading to overproduction of mitochondrial ROS, which are implicated in many toxicities and disease processes as mediators of tissue injury.[15] mtDNA mutations are frequently observed in various human cancers.[59-62] Mutations in the nuclear-encoded mitochondrial gene have also been correlated with an increased cancer risk.[63,64] mtDNA validation affects the radiotherapy and chemotherapy outcomes in cancer patients.[63] Metabolic alterations associated with mitochondrial dysfunction increase tumorigenesis. Mitochondrial genomic instability is closely related to vascular disease, neurodegeneration, aging, and carcinogenesis.[21,22,65,66] Therefore, mtDNA mutation and mitochondrial dysfunction can be used as markers to assess the effect of low-dose long-term FR. N-acetyL-cysteine, a glutathione precursor, increases the intracellular levels of GSH[67] and suppresses the accumulation of mitochondrial ROS.[44] Thus, increasing antioxidant capacity can prevent radiation toxicity induced by low-dose long-term FR.

Cyclin D1 as the molecular target associated with mitochondrial ROS-mediated genomic instability

Mitochondrial dysfunction can be communicated to the cell nucleus via mitochondrial ROS acting as signaling molecules. Elevated ROS generation stimulates stress-activated kinases and stress-signaling in cancer cells.[68] Thus, ROS have multiple roles in tumor initiation, progression, and maintenance. We recently identified a target molecule associated with mitochondrial ROS-induced genomic instability in low-dose long-term FR cells.[44] Figure 2 depicts a link between mitochondrial ROS and cell cycle perturbation in low-dose irradiated human cells. ROS damage to the molecules affects cell cycling, oxidizing PP2A on cysteine residues, and downregulating PP2A activity in long-term FR cells. This loss of PP2A activity can thus lead to a loss of negative feedback control of the AKT pathway,[69] resulting in persistent AKT activity in cells after long-term FR. Consequently, constitutive AKT activation causes stabilization of nuclear cyclin D1 by inhibiting the nuclear export and subsequent GSK3β-mediated degradation of cyclin D1 (Fig. 2).[70,71] Nuclear cyclin D1 accumulation was observed by low-dose long-term FR in most of PCNA-positive S-phase cells.[70,71] Abnormal nuclear cyclin D1 accumulation during the S phase perturbs DNA replication including DNA re-replication and suppression of replication fork progression leading to DSBs.[72,73] Perturbation of cyclin D1 expression is associated with cellular senescence and induction of genomic instability in irradiated cells.[70,72,74,75] Aberrant cyclin D1 expression provides a driving force behind the development of tumorigenesis and is often detected in premalignant and malignant tissues. Collectively, cyclin D1 is thought to be the molecular target associated with mitochondrial ROS-mediated genomic instability.

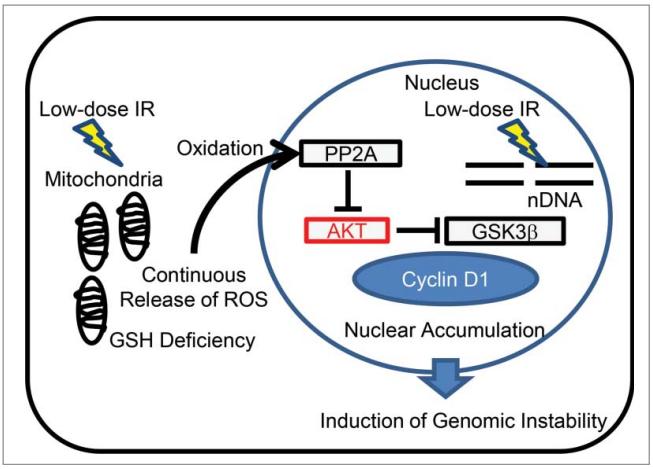

Figure 2. Nuclear retention of cyclin D1 by mitochondrial ROS. ROS are released from the mitochondria after low-dose long-term FR. Mitochondrial ROS inactivate PP2A, which in turn causes a loss of negative feedback control of the AKT pathway, leading to nuclear cyclin D1 accumulation. Perturbation of cyclin D1 expression causes genomic instability in irradiated cells.

Conclusion

This review assesses the role of the radiation response of mitochondria in radiation-induced genomic instability. Mitochondria ROS are primarily responsible for low-dose long-term radiation and affect AKT/cyclin D1 cell cycle signaling. Oxidative stress persists for prolonged periods after low-dose long-term FR. Oxidative damage will accumulate in mtDNA and result in mutagenesis, carcinogenesis, accelerated senescence, and cell death. Antioxidants may therefore be useful agents for radioprotection against mitochondrial damage induced by low-dose long-term FR.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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