



## Review

## Mechanisms of radiation-induced sensorineural hearing loss and radioprotection



Mario A. Mujica-Mota<sup>a,e,\*</sup>, Shirley Lehnert<sup>d</sup>, Slobodan Devic<sup>b,c</sup>, Karina Gasbarrino<sup>a</sup>, Sam J. Daniel<sup>a,e,\*</sup>

<sup>a</sup> McGill Auditory Sciences Laboratory, Montréal, QC H3H1P3, Canada

<sup>b</sup> Medical Physics Unit, McGill University, Montréal, QC, Canada

<sup>c</sup> Department of Radiation Oncology, Jewish General Hospital, Montréal, QC H3T1E2, Canada

<sup>d</sup> Department of Radiation Oncology, Montreal General Hospital, Montréal, QC H3H1A4, Canada

<sup>e</sup> Department of Otolaryngology, The Montreal Children's Hospital, Montréal, QC, Canada

## ARTICLE INFO

## Article history:

Received 9 September 2013

Received in revised form

12 February 2014

Accepted 7 March 2014

Available online 18 March 2014

## ABSTRACT

Patients that receive radiotherapy are at risk of late sensorineural hearing loss when the inner ear is included within the radiation field. Preclinical and human temporal bone studies have shown that there is differential damage to cochlear structures depending on the amount of dose delivered to the inner ear. *In vitro* studies have suggested that reactive oxygen species (ROS) are the main initial actors in radiation-induced damage. The interaction of ROS with different cellular components can result in different apoptotic pathways. Therefore, approaches to radioprotection are mainly aimed to reduce ROS production through antioxidants. This review summarizes recent research in the field that can improve the understanding and boost preventive efforts of this adverse effect.

© 2014 Elsevier B.V. All rights reserved.

## 1. Introduction

Radiotherapy (RT) is a valuable component of cancer therapy especially in cerebello-pontine angle, head & neck and brain tumors. Unfortunately, the patients are at a latent risk of developing radiation-induced sensorineural hearing loss (RISNHL) when the inner ear is included within the radiation field (Pan et al., 2005). About one third of the patients subjected to radiotherapy for H&N cancer present with this adverse effect (depending on different reports), which has been characterized as dose-dependent, late, progressive and permanent (Mujica-Mota et al., 2013). It usually

affects the high frequencies of the hearing range and progresses toward lower frequencies when it becomes perceptible by the patient (Bhandare et al., 2010).

Despite the increased interest for this adverse effect, there is little research on the mechanisms involved in it. In this review, we describe the current knowledge on the mechanisms of RISNHL and the interventions that have attempted to reduce this complication. While many of the radiobiology concepts are cancer-biology oriented, this review will present them with a specific orientation toward cochlear damage to help in understanding the effects of radiation on the inner ear.

## 2. Radiation-induced formation of reactive oxygen species

The radiation used in cancer therapy is predominantly X-rays (photons) in the energy range from 6 to 18 MV produced by linear accelerators. While energy deposition in the target (tumor) volume is according to the prescribed dose, in the surrounding tissues or organs (the cochlea in the case of head and neck cancer) the deposition is dependent on the location of the organ with respect to the target and the degree of conformality of the treatment. In any event, the dose received by surrounding structures will be a small part of the 1.8–2.0 Gy daily fraction that is received by the tumor volume.

**Abbreviations:** ABR, Auditory Brainstem Response; DNA, deoxyribonucleic acid; DSB, double-strand breaks; Gy, Gray; kHz, kilohertz; mtDNA, mitochondrial DNA; MV, megavolt; RISNHL, radiation-induced sensorineural hearing loss; RNS, reactive nitrogen species; ROS, reactive oxygen species; RT, radiotherapy; SSB, single-strand breaks

\* Corresponding author. McGill Auditory Sciences Laboratory, 2300 Tupper St. Room B-240, Montreal, QC H3H 1P3, Canada. Tel.: +1 514 412 4304; fax: +1 514 412 4342.

E-mail addresses: [mario.mujicamota@mail.mcgill.ca](mailto:mario.mujicamota@mail.mcgill.ca) (M.A. Mujica-Mota), [shirley.lehnert@mcgill.ca](mailto:shirley.lehnert@mcgill.ca) (S. Lehnert), [slobodan.devic@mcgill.ca](mailto:slobodan.devic@mcgill.ca) (S. Devic), [karina.gasbarrino@mail.mcgill.ca](mailto:karina.gasbarrino@mail.mcgill.ca) (K. Gasbarrino), [sam.daniel@mcgill.ca](mailto:sam.daniel@mcgill.ca) (S.J. Daniel).

Traditionally it has been described that radiation exerts its effects through direct or indirect damage to the deoxyribonucleic acid (DNA) (Sharma et al., 2008), which results mainly in DNA single-strand breaks (SSB) or double-strand breaks (DSB) (Powell and McMillan, 1990). For ionizing radiation, the largest component of DNA damage (approximately 2/3) results from indirect damage mediated by free radicals generated by the interaction of radiation with water molecules (Sharma et al., 2008). It has been proposed that, in the presence of oxygen, damage initiated by free radicals is propagated by the production of reactive oxygen species (ROS) in the cytoplasm, which are particularly damaging to the oxygen-rich mitochondria (Mikkelsen and Wardman, 2003).

Intra-cellular ROS produced under physiologic conditions serve as essential signaling molecules that regulate numerous cellular processes and homeostatic cellular functions; therefore, the cell requires tight control of the redox environment. The level of excess ROS produced by ionizing radiation is low compared with ROS produced during normal oxidative metabolism processes (Ward, 1994); however, this radiation-induced and inhomogeneous overproduction can disrupt homeostasis resulting in oxidative stress. Radiation can also stimulate the inducible nitric oxide synthase, which reacts with superoxide dismutase to form peroxynitrite anions (Azzam et al., 2012). These anions are highly reactive nitrogen species (RNS) that can further damage cell membranes and DNA. One interpretation of this evidence is that ROS/RNS production is a continuous process that in the long run promotes cell damage, inflammation and other long term effects following radiation (Azzam et al., 2012) (see Fig. 1).

### 3. Cell death after irradiation

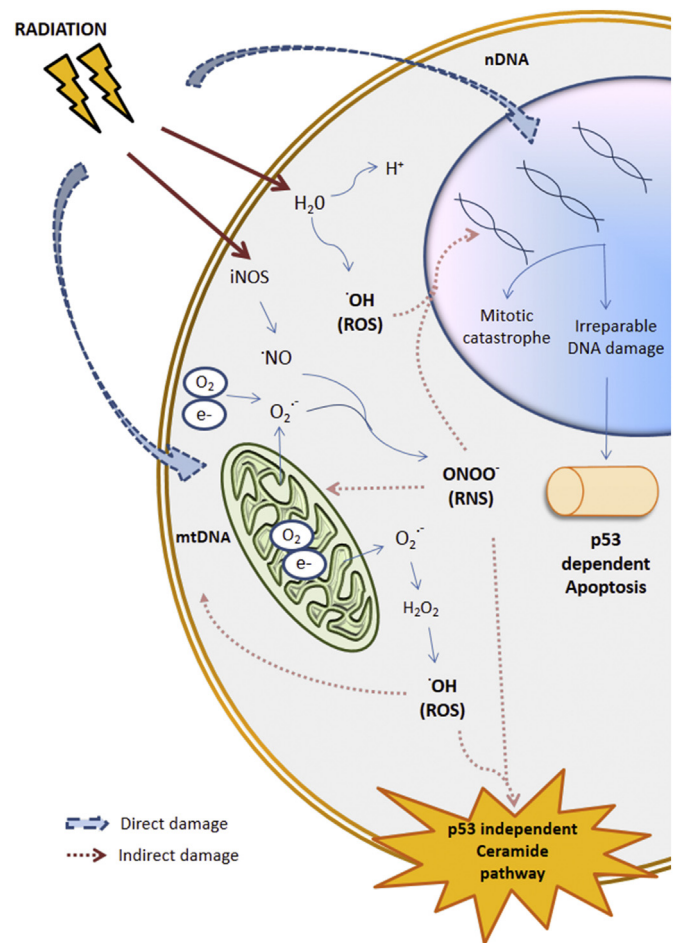
When the damage caused by irradiation is not repaired, the cell can have different responses to radiation. The function of an organ that depends on cell division is at risk when the cells can no longer divide as a result of an acute apoptotic response (Gudkov and Komarova, 2003), mitotic catastrophe or prolonged cell cycle arrest. The choice between these pathways depends on the cell type, the severity of the damage (Offer et al., 2002) and the integrity of p53 (Song and Lambert, 1999). On the basis of *in vitro* evidence, epithelial auditory hair cells, which do not divide, are most likely to die as a result of apoptosis (Low et al., 2006).

#### 3.1. p53-dependent apoptotic pathway

The activation of p53 is known to induce cell cycle arrest facilitating DNA repair or initiation of the apoptotic pathway if irreversible damage has occurred (Chao et al., 2000). Dose-dependent radiation induced apoptosis has already been described in several cell systems and is accepted as a mechanism of cell death *in vivo* (Shinomiya, 2001; Verheij and Bartelink, 2000). However, few studies have specifically investigated apoptosis in auditory hair cells. Organ of Corti-k3 cell lines (immature mice auditory hair cells) were used by Low et al. (Low et al., 2006) to study post irradiation apoptosis (using the TUNEL assay) and reactive oxygen species production. This study showed that ROS production was increased 1 h after irradiation, while the activation of p53 started 72 h after irradiation. In addition, consistent with the clinical experience of RISNHL, the process was dose-dependent. These results suggest that in the irradiated cell ROS production precedes and acts as a trigger of the programmed cell death pathway.

#### 3.2. p53-independent apoptotic pathway

Another pathway possibly involved in RISNHL is the sphingomyelin-ceramide pathway, a p53-independent apoptotic pathway. This pathway usually presents in epithelial cells 24 h



**Fig. 1.** Radiation has direct and indirect effects on auditory hair cells. Direct damaged is caused to mitochondrial (mtDNA) and nuclear DNA (nDNA). Indirect damage is due to the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) derived from water radiolysis, induction of nitric oxide synthase (iNOS) in the cytoplasm and mitochondrial damage. These cellular stressors can cause irreparable DNA damage causing mitotic arrest or lead to apoptosis by p53 dependent or independent pathways.

following radiation-induced DNA damage (Lehnert, 2007b). Studies have shown this pathway to be a dose dependent response involving the interaction of ROS with the plasma membrane (Kolesnick, 2002). It is believed that this response is mainly present in pluripotential cells involved in the recovery of epithelial tissues from damage, as it was observed in epithelial organs such as the intestine (Hendry et al., 1997) and testis (Hasegawa et al., 1998). Given their resting and highly specialized state, it is unlikely that the outer and inner hair cells present this metabolic pathway as a response to radiation.

One type of cell where this pathway is known to be important, at least after high doses of radiation, are vascular endothelial cells, which are well represented in the stria vascularis. The sphingomyelin-ceramide pathway has been observed in the endothelium of gastrointestinal tissue subjected to high doses of radiation (Paris et al., 2001), and it is possible that the damage seen in endothelial cells of the stria vascularis after large radiation doses is due to the same type of response (Kim and Shin, 1994).

In the case of supportive and connective tissue cells where minimal regeneration has been reported after cochlear stress (Yamasoba and Kondo, 2006), the contribution of this pathway is currently unclear. Further research is needed to determine the implications of this pathway in the response to clinically relevant fractionated radiotherapy.

Download English Version:

<https://daneshyari.com/en/article/6287390>

Download Persian Version:

<https://daneshyari.com/article/6287390>

[Daneshyari.com](https://daneshyari.com)