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Cellular mechanisms underlying tumor and normal tissue radiosensitivity

Mecanismos celulares subyacentes a la radiosensibilidad tumoral y del tejido normal

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ABSTRACT: This review aims to provide an overview of the main cellular mechanisms that influence the response of healthy and tumor tissues to radiation and, thus, their radiosensitivity. Knowledge of the biological mechanisms that define individual radiosensitivity is the initial path for establishing assays aimed at predicting responses to treatment and is essential to achieve the application of personalized medicine in RT procedures. In this sense, the interest in studying radiosensitivity in the clinical setting is the determination of 1) the individual risk of developing adverse effects to IR treatment (clinical or normal tissue radiosensitivity) and 2) the possible therapeutic benefit of IR (tumor radiosensitivity). The authors conducted an extensive review of articles and resources on radiation biology and cellular mechanisms that affect the response of both normal and cancerous tissues to ionizing radiation (IR) treatment. The review primarily focuses on materials published from 2000 to March 2023 while incorporating select older articles to enrich the discussion. To gather these articles from popular electronic databases such as PubMed, ScienceDirect, Google Scholar, and Cochrane, the authors utilized a search strategy that employed Boolean "AND" and "OR" logic. The different combinations of keywords searched included the following terms: "radiosensitivity", "cellular", "radiation sensitivity", "radioresistance", "ionizing radiation", "radiotherapy", "biological effects", "tumor", "normal tissues", "cellular mechanisms", "oxidative stress", "DNA repair", "immune response", "cell death", "radio induced effects". Conclusions: Radiation therapy (RT) is one of the primary treatment modalities in oncology, along with surgery, chemotherapy, and immunotherapy. RT delivers a precise and sufficient dose to tumor tissues, inducing cell death. However, individual response to IR exposure varies based on the type of therapy used (*i.e*., external RT, radiosurgery, brachytherapy, among others) and the intrinsic heterogeneity between tumor types and subtypes. In addition, variants in genes controlling the cellular response to DNA damage, oxidative stress, cell cycle control, cell death, and the immune response would lead to a spectrum of radiosensitivity. Understanding how radiation impacts normal and tumor cells at a cellular level is essential to develop effective treatment options that account for biological differences among individuals. While many people experience moderate sensitivity to radiation therapy regarding side effects and tumor response, there may be variations in sensitivity. Therefore, acquiring this knowledge is essential to achieve the best clinical outcomes.

KEYWORDS: cellular radiobiology; radiosensitivity; radiotherapy; DNA damage response, ionizing radiation.

INTRODUCTION

RT is one of the primary treatment modalities in oncology. It eliminates cancer cells by delivering a precise and effective dose to the tumoral volume while minimizing exposure to normal tissues (Joiner & van der Kogel, 2019). According to studies, at least half of all cancer patients worldwide are expected to receive RT (Pavlopoulou *et al.*, 2017).

For decades, research to improve RT has focused almost exclusively on the ability of IR to induce cancer cell death and on improving the medical technology used to deliver the prescribed dose to the tumor volume. These advances have provided the ability to customize treatments based on clinical parameters and anatomical information. However, individual responses to RT vary among individuals with apparently the "same type" of neoplastic disease

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(*i.e.,* same tumor subtype). So far, there has not been much advancement in customizing RT to individual biological factors that affect how normal and tumor tissues respond to IR exposure. Accumulated evidence shows that individuals possess varying levels of radiosensitivity, resulting in a wide range of people with either lower or higher degrees of radiosensitivity (Averbeck *et al.*, 2020).

Knowledge of the biological mechanisms that define individual radiosensitivity is the initial path for establishing assays aimed at predicting responses to treatment and is essential to achieve the application of personalized medicine in RT procedures. In this sense, the interest in studying radiosensitivity in the clinical setting is the determination of 1) the individual risk of developing adverse effects to IR treatment (clinical or normal tissue radiosensitivity) and 2) the possible therapeutic benefit of IR (tumor radiosensitivity) (Ferlazzo *et al.*, 2017; Habash *et al.*, 2017; Wisdom & Kirsch, 2019).

This review aims to provide an overview of the cellular mechanisms that influence the response of healthy and tumor tissues to radiation and how these mechanisms affect their radiosensitivity. By delving into the cellular mechanisms that impact sensitivity to IR, we can gain a deeper understanding of their contribution to the development of adverse effects of radiation therapy (AERT) and the response of tumors to radiation therapy.

METHODS

The authors meticulously carried out a review of the latest articles and resources on radiation biology and the cellular mechanisms that influence both normal and cancerous tissues' reaction to ionizing radiation (IR) treatment. The review mainly focuses on materials published from 2000 to March 2023, while also drawing on select older articles to enhance the discussion. To collate these articles from popular electronic databases such as PubMed, ScienceDirect, Google Scholar, and Cochrane, the authors utilized a search strategy that employed Boolean "AND" and "OR" logic. We conducted a scoping search using terms related to biological plausibility or mechanism to identify key references. The different combinations of keywords searched included the following terms: "radiosensitivity," "cellular," "radiation sensitivity," "radioresistance," "ionizing radiation," "radiotherapy," "biological effects," "tumor," "normal tissues," "cellular mechanisms," "oxidative stress," "DNA repair," "immune response," "cell death," and "radio-induced effects." This narrative review provides valuable insights into the cellular response to ionizing radiation and its effects on normal and malignant tissues, enabling a deeper understanding of the biological mechanisms involved and potentially paving the way for more effective treatments.

RADIOSENSITIVITY

The concept of radiosensitivity refers to how prone an organism is to exhibit biological effects from exposure to IR (El-Nachef *et al.*, 2021; Wojcik *et al.*, 2018). However, it is appropriate to understand radiosensitivity from the different levels of organization of biological systems and consider the final effect of exposure. In this sense, it is common to find the use of terms such as cellular radiosensitivity, normal tissue radiosensitivity for acute or chronic deterministic effects (clinical radiosensitivity), tissue radiosensitivity for the risk of carcinogenesis (radiosusceptibility), tumor radiosensitivity, and whole organism radiosensitivity (El-Nachef *et al.*, 2021; Health Protection Agency, 2013). Due to the focus of the present review on the field of radiation oncology, we will detail the concepts of cellular radiosensitivity, clinical radiosensitivity, and tumor radiosensitivity.

Cellular radiosensitivity

The concept of cellular radiosensitivity considers the different mechanisms that occur when cells are exposed to IR and how they can lead to cell death as a possible outcome (El-Nachef *et al.*, 2021). The effect of IR at the cellular level begins with the deposition of energy by the direct interaction of particles or photons with biomolecules or by the formation of free radicals or reactive oxygen (ROS) or nitrogen species (RNS) that are capable of inducing damage in biomolecules, of which DNA is considered to be the main target. The primary forms of DNA damage induced by IR include single-strand breaks (SSB) and double-strand breaks (DSB), modifications of deoxyribose, and nitrogenous bases. Exposure to IR causes a temporary cell arrest due to DNA damage, leading to a decrease in the ability of cells to multiply and the activation of the DNA repair machinery. The cells eventually trigger cell death mechanisms if the damage is too severe to repair. Nevertheless, some irradiated cells may avoid cell death by hyperactivating DNA repair path-

ways in response to genomic damage (Hein *et al.*, 2014; Joiner & van der Kogel, 2019).

The sensitivity of a cell to IR can be significantly influenced by various factors such as its type, specific genetic variations (both pathological and non-pathological), the oxygen level in its environment, and the stage of the cell cycle. These factors can substantially impact the cellular response to DNA damage.

Radiosensitivity of normal tissues or clinical radiosensitivity

AERTs in normal tissues occur between 5% and 20% of treatments. These effects' frequency, severity, and type vary according to fractionation schemes, total dose, dose per fraction, irradiated volume, patient comorbidities, and irradiated anatomical region (Ferlazzo *et al.*, 2017). Clinical radiosensitivity refers to the natural differences among individuals in how they respond to RT, which can lead to different short-term and long-term side effects from similar treatments (Giorgio, 2006). This is partly because of gene variants encoding enzymes responsible for the cellular response to DNA damage caused by RI and oxidative stress (Habash *et al.*, 2017). Other non-genetic factors are determinants of clinical radiosensitivity: physical factors of IR such as dose, dose rate, dose distribution, and treatment volume; additional therapies to RT such as chemotherapy, hormone therapy, and surgery, as well as individual factors such as age, hemoglobin levels, smoking, diabetes, and comorbidities (Barnett *et al.*, 2015).

Deterministic AERTs are either acute or chronic. AERTs that occur within 90 days after treatment are known as acute, whereas those after this period are considered chronic. Additionally, the AERTs manifested vary according to the tissues and organs irradiated during treatment (Dilalla *et al.*, 2020). For example, in the case of IR treatment in head and neck neoplasms, acute effects may include pain in the treated area, fatigue, hair loss, tinnitus, aphonia, xerostomia, nausea, loss of appetite, vomiting, dysphagia, oropharyngeal and esophageal mucositis, slurred speech, difficulty falling asleep, and dermatitis (Falchook *et al.*, 2016; Mohan *et al.*, 2019). Late deterministic AERTs are a broad spectrum of conditions, often permanent, which may include cardiovascular disease, pulmonary and arterial fibrosis, cognitive deficits, and bone fractures.

Tumor radiosensitivity

Tumor response to RT is significantly heterogeneous; it depends on the type of therapy applied, the intrinsic heterogeneity between tumor types and subtypes, and the acquired mutations present in the tumors that influences how vulnerable are cancer cells to IR (Carlos-Reyes *et al.*, 2021). It has been known for decades that the intrinsic radiosensitivity of tumor cells is one of the main determinants of tumor response to IR. Through *in vitro* studies using clonogenic survival assays, it has been discovered that tumor cells from lesion types that respond well to RT display higher radiosensitivity than cells from other tumor types with poor responses (Fertil and Malaise, 1985).

RT rapidly selects the most IR-resistant tumor clones from the more sensitive dominant cells initially present. Following exposure to IR, tumor cells initiate mechanisms to respond to radio-induced damage. The modulated genes can alter multiple biological events, mainly a redistribution of the cell cycle, activation of DNA repair pathways, reconfiguration (global and local) of chromatin, metabolic plasticity, changes in the lipid and protein composition of the plasma membrane, hyperactivation of the antioxidant defense, evasion of apoptosis, epithelial-mesenchymal transition, among others (Carlos-Reyes *et al.*, 2021; Zhao *et al.*, 2023). After radiation exposure, some cells may survive and become radioresistant; these cells may experience changes in the expression of genes that are crucial for tumor growth and progression (Coleman *et al.*, 2020). As a result, they may exhibit behaviors that promote cancer, such as migration, invasion, and metastasis. In this sense, radioresistance results from activating intrinsic mechanisms of tumor cells, such as the response pathways to radio-induced DNA damage, epigenetic mechanisms, and morphological changes. However, resistance to RT may arise not only from selection pressure on the cancer cells themselves but also from changes occurring within the tumor microenvironment, including responses of stromal cells to IR (Berg & Pietras, 2022). Different preclinical studies using *in vitro* tumor models have suggested that RT-induced changes in the tumor microenvironment may favor tumor invasion and dissemination (Barker *et al.*, 2015).

Cancer can develop from any cell type, substantially influencing its behavior and response to available treatments. This diversity is even more

significant when considering the different subtypes within the same type of cancer and the differences between individuals who, in principle, suffer from the same disease (*i.e.,* the same subtype) but carry different (epi)mutations. Thanks to modern technological tools, clinicians are now able to examine neoplastic lesions on a molecular level. As a result, we can take a more objective and practical approach to treating oncology patients based on the presence or absence of specific genetic alterations. This approach is known as precision oncology (Carbone, 2020).

CELLULAR MECHANISMS DETERMINING RADIOSENSITIVITY

When radiation damages DNA, specific pathways are activated to locate the damaged sites, triggering a series of signaling processes that activate various molecules, ultimately determining the cell's fate. Activated effector molecules will belong to different response pathways: 1) DNA repair pathways, 2) Cell cycle control, 3) Oxidative stress, 4) Cell death, and 5) Immune response (Pavlopoulou *et al.*, 2017). Overall, in response to radio-induced DNA damage, these pathways govern the fate of the cell and, by extension, its radiosensitivity.

The range of each pathway evoked in response to IR exposure depends on cellular microenvironment factors such as oxygen partial pressure and radiation-specific factors such as radiation quality, dose, and fractionation scheme (Maier *et al.*, 2016). Additionally, the pathways activated, and the outcome of radio-induced damage depends on intrinsic factors such as cell type and the presence of variants or mutations in genes controlling DNA damage repair, response to oxidative stress and antioxidant defense, cell cycle control, cell death, and immune response (Palumbo *et al.*, 2019).

Detection and repair of radio-induced DNA damage

The first step in the DNA damage response is the detection of DNA damage by ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and RAD3-related protein), which are initiator kinases that phosphorylate and activate several downstream proteins. ATM and ATR belong to the family of phosphatidylinositol 3-kinase-related protein kinases (PIKKs), which are considered master regulators of the response to DNA damage (Blackford and Jackson, 2017); specifically, ATM is the master regulator of DNA damage response and repair of DSB, ATR is mainly activated following SSB formation. The MRN complex composed of MRE11/RAD50/NBS1 proteins also functions as a sensor of RDH and recruits distinct mediators and effector enzymes in the DSB repair pathway by homologous recombination (Maier *et al.*, 2016).

The sensitivity of cells and tissues to IR is linked to specific genes that identify and repair damaged DNA. When these genes are mutated, it can lead to syndromes related to radiosensitivity. These mutations affect the proteins involved in the cellular response to radio-induced damage. Mutations in ATM cause ataxia telangiectasia, the first described syndrome of severe radiosensitivity. Defects of activity in the MRE11A protein (part of the MRN complex) are responsible for the *ataxia telangiectasia-like disorder* characterized by cellular radiosensitivity (Joubert *et al.*, 2008). Ligase 4 syndrome occurs due to mutations in the gene encoding for the Ligase 4 enzyme, which joins the ends of an RDH after repair by non-homologous end joining. This enzyme functions as part of the IV/XRCC4/XLF complex (Rassool & Tomkinson, 2010).

Most of these severe radiosensitivity syndromes are inherited in an autosomal recessive manner. Although rare, specific syndromes related to radiation sensitivity may be considered in clinical radiation oncology. For homozygous patients with recessive radiosensitivity syndromes, radiotherapy is generally not recommended (Lohynská *et al.*, 2022).

The interindividual variability in the AERT is most likely caused by the presence of non-pathological variants that are more widely distributed in populations. The contribution of variants in genes linked to DNA repair is directly associated with the cellular capacity to repair DSB and SSB, and the efficiency of damage repair is one of the main determinants of the radiosensitivity of normal tissues (Figure 1) (Joubert *et al.*, 2008).

Variants in signaling molecule genes such as MDC1, BRCA1, and p53, which activate effector molecule pathways of radio-induced damage repair mechanisms influence radiosensitivity (Erasimus *et al.*, 2016; Lieber, 2010; Pavlopoulou *et al.*, 2017; Sage & Shikazono, 2017). Similarly, at the end of SSB repair by base excision, a basic site is filled by DNA

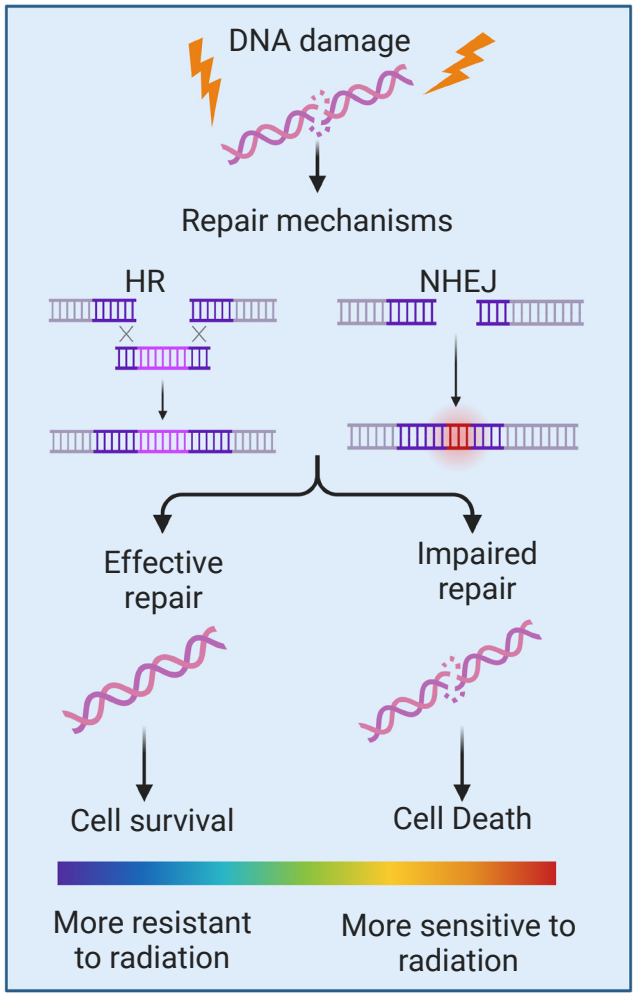

Figure 1. The sensitivity of cells and tissues to IR is linked to specific genes that encode proteins related to DNA repair mechanisms. If the repair mechanisms fail, the cell usually triggers cell death pathways. HR: homologous recombination. Created with BioRender.com.

polymerase beta and sealed by the DNA ligase III/XRCC1 complex (Cannan & Pederson, 2016). Specific variants of XRCC1 are associated with greater cellular sensitivity to radiation and a higher likelihood of developing AERTs (Gong *et al.*, 2021). Other variants in DNA damage and repair genes, including XRCC2, XPD, ERCC1, ZNF24, NBN, Ku70, CHEK1, RAD51C, ERCC2, PMS1, and MLH1 have been linked to acute toxicities caused by RT (Gupta *et al.*, 2021; Li *et al.*, 2013; Ren *et al.*, 2014; Yang & Liu, 2020).

Cell cycle

Cell cycle arrest is an essential part of the DNA damage response, facilitating the action of repair mechanisms by preventing entry into further cycle stages before damage resolution. ATM activates checkpoint regulators that promote cell arrest in G1 or G2; ATR-regulated pathways lead to the phosphorylation of CHK2, p53, KAP-1, and CDC25 proteins. In response to radio-induced damage, the protein p53 plays a crucial role as a tumor suppressor (Maier *et al.*, 2016).

Cellular radiosensitivity varies according to the cell cycle phase, being most radiosensitive between G2 and M, and to a lesser degree during the late S phase (Figure 2) (Yu *et al.*, 2023). During the M phase, all chromosomes are condensed and located in the middle zone of the nucleus, forming large targets; likewise, during this phase, the damage repair mechanisms are less active (Liu *et al.*, 2018). The radioresistance of the S phase is due to the high availability of repair enzymes and the fact that chromosomes are less condensed in the nucleus, facilitating the access of the enzymatic machinery to the sites of damage (Hubenak *et al.*, 2014).

The length of G2 is related to how sensitive different normal cell lines are to radiation. Cell lines that are more resistant to radiation tend to have a longer delay in G2 than those that are more sensitive (Maity *et al.*, 1994). In addition, cells that suffer damage in the late G2 phase terminate their cell cycle more rapidly than cells that receive damage in the early G2 phase (Müllers *et al.*, 2014). Another relevant aspect of cell cycle control concerning cellular radiosensitivity is the ability of IR to induce entry into senescence, usually by inducing permanent arrest in G2 (Li *et al.*, 2018).

Understanding the effect of the cell cycle on response to RT has led to hypotheses about the benefit of radiochemotherapy at the most radiosensitive phases of the cell cycle (Otani *et al.*, 2016). Similarly, since transient cell cycle arrest is a major cause of resistance to RT, pharmaceutical agents that cause premature cell cycle progression toward mitosis may lead to radiosensitization and mitotic catastrophe (Hong *et al.*, 2015).

Oxidative stress

Oxidative stress is the imbalance between oxidative and antioxidant species, favoring oxidation, and represents an increased risk of oxidative damage to lipids, proteins, and nucleic acids (Grether-Beck *et al.*, 2000). The electrons produced by ionization can generate ·H and ·OH free radicals by water

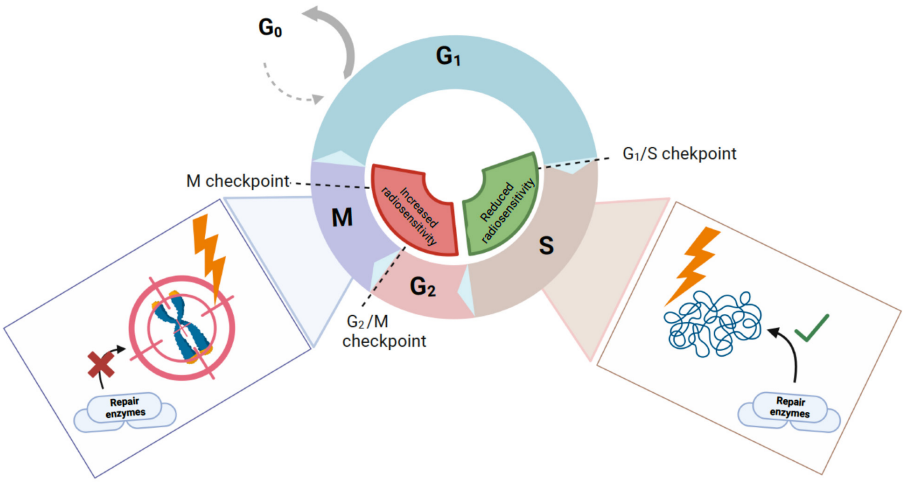

Figure 2. Cells in the G2 and M phases are most sensitive to radiation, while those in the late S phase are less sensitive. During the M phase, chromosomes are condensed, and fewer repair mechanisms are active, making them easier targets for damage. The S phase is more resistant to radiation due to abundant repair enzymes and less condensed chromosomes. Created with BioRender.com.

radiolysis. Through consequent reactions, these radicals can generate and induce the formation of ROS and RNS (Figure 3) (Joiner & van der Kogel, 2019). Additionally, IR exposure stimulates metabolic activation within the mitochondria to provide energy for the DNA damage response. Mitochondrial respiratory chain complexes I and III are the most important intracellular source of ROS during oxidative phosphorylation in eukaryotic cells.

During and after IR exposure, endogenous antioxidant molecules are upregulated and capable of interacting with reactive species and neutralizing oxidation reactions (Joiner & van der Kogel, 2019). Some examples of enzymes that fall under this category include NADPH oxidase, lipoxygenase, nitric oxide synthase, and cyclooxygenase (Wei *et al.*, 2019). Dysregulation or deficiency of antioxidant defenses could contribute to increased radiosensitivity. For example, Yazlovitskaya *et al.*, (2015) observed that knockout mice for the Fus1 enzyme exhibited increased levels of radiosensitivity when exposed to 9 Gy doses of gamma rays. The Fus1 protein is involved in the regulation of mitochondrial homeostasis, including ROS generation. Its Fus1 expression levels vary significantly between individuals in the human species, which could explain some interindividual variability in IR toxicity in normal tissues.

When exposed to IR, mitochondria in eukaryotic cells become metabolically active and provide energy for DNA damage response. The respiratory chain complexes I and III in mitochondria are the primary source of ROS during oxidative phosphorylation (Shimura, 2021). ROS disrupts AKT/cyclin D1 cell cycle signaling via oxidative inactivation of protein phosphatase 2A, a negative regulator of AKT activity. The resulting cyclin D1 nuclear accumulation is associated with cellular senescence and induction of genomic instability in irradiated cells. Therefore, high levels of ROS resulting from mitochondrial dysfunction are linked to radiation-induced genomic instability in cells. This excess of ROS can cause oxidative stress in normal cells and induce apoptosis in radiosensitive cells (Shimura *et al.*, 2016).

Free radical formation induces an inflammatory response associated with the release of cytokines and growth factors, such as transforming growth factor B1 (TGFβ1), tumor necrosis factor-α (TNFα), epidermal growth factor, and interleukins (Rattay & Talbot, 2014). Genetic variants in GSTP1 (glutathione S-transferase P1) and SOD2 (superoxide dismutase 2) are associated with radio-induced fibrosis (Pavlopoulou *et al.*, 2017).

Cell death

The sensitivity of cells to IR-induced cell death, as well as the type of cell death, are determined by the ability to repair and respond to DNA damage, activation of specific groups of genes con-

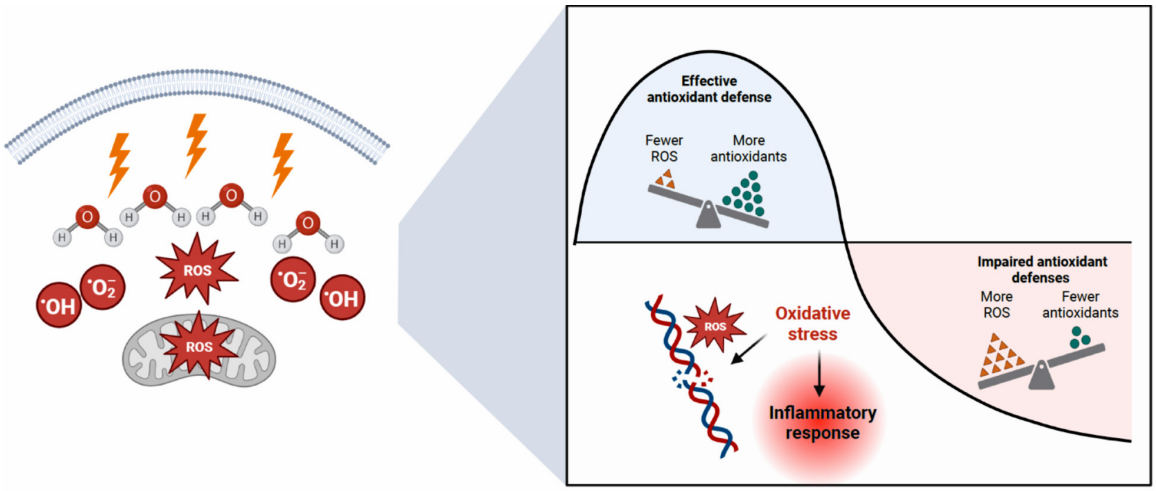

Figure 3. During water radiolysis, free radicals such as ·H and ·OH are formed. These free radicals react to produce reactive oxygen species (ROS) like superoxide (·O2-). Oxidative stress is caused by an imbalance between oxidative and antioxidant species, which favors oxidation and leads to protein, lipid, and DNA damage. When exposed to ionizing radiation, mitochondria become active and produce energy for DNA damage response. High levels of ROS resulting from mitochondrial dysfunction cause genomic instability and cell apoptosis. Free radical formation triggers an inflammatory response, leading to the release of cytokines and growth factors. Created with BioRender.com

trolling cell cycle checkpoints, inhibition of replication and transcription, induction of apoptosis, or an adaptive immune response (McKelvey *et al.*, 2018).

Cell death will occur if the radio-induced damage is significant, and repair is not possible. Cell survival and, therefore, their ability to resist cell death has been a widely used indicator in experimental radiobiology to study the *in vitro* resistance of different cell types to IR. Classically, radio-induced cell death can be classified as interphasic or proliferative. The former occurs in irradiated cells before they enter mitosis, occurs soon after exposure, and has been observed in specific cell types such as peripheral lymphocytes, thymocytes, and small intestine cryptic cells. On the other hand, proliferative death is the loss of the cell's ability to divide and cannot give rise to progeny; it occurs in most cell types and is observed after several cycles (Kondo, 2012). Although practical and widely used, this classification ignores the various mechanisms involved in cell death and its final effects.

The mechanisms in which radio-induced cell death occurs have been an avid subject of research; currently, multiple types of programmed cell death are recognized, such as apoptosis, necroptosis, autophagy, senescence, pyroptosis, ferroptosis, and cuproptosis; unscheduled cell death such as different forms of necrosis; as well as non-lethal processes such as mitotic catastrophe and senescence (Chen *et al.*, 2022).

Although different cell types have different sensitivities to IR, the pattern of cell death after exposure is usually dose-dependent. Apoptosis is more likely to occur at lower doses, while cell necrosis is more common at higher doses. However, clinically relevant doses of IR also promote mitotic catastrophe, immunogenic cell death, autophagy, and senescence (Li *et al.*, 2021).

The BCL-2 family of proteins is critical in regulating and carrying out intrinsic apoptosis. This family includes members that promote apoptosis (pro-apoptotic) and those that prevent it (pro-survival or anti-apoptotic). Balancing the two groups of BCL-2 proteins is crucial in determining cell fate decisions between life and death (Singh *et al.*, 2019).

Also, the p53 protein plays a crucial role in determining a cell's fate after IR-induced DNA damage, whether it undergoes senescence, apoptosis, or non-apoptotic death. In p53-deficient cells, despite severe radio-induced damage, the cell does not undergo arrest and continues into mitosis, accumulating genetic damage, which over several divisions, leads to death by mitotic catastrophe. The ability

of p53 to regulate both senescence and apoptosis makes it an essential protein in tumor suppression, as is confirmed by the fact that it is mutated in about 50% of all cancers (Liu *et al.*, 2014). Cell fate decisions still need to be fully understood. However, they are considered to be the result of the interplay of many different factors, probably with p53 still at the center of an intricate network.

Cells containing functional p53 may be more sensitive to stress and more prone to senescence in response to IR. I*n vitro* and *in vivo* experiments have shown that *wild-type* p53 expression is linked to greater radiosensitivity than defective variants of this gene. In addition, IR-sensitive tissues tend to have higher p53 expression and are more prone to produce apoptosis-inducing responses to IR exposure, indicating that IR may promote cellular apoptosis by activating p53-dependent pathways (Ruiter *et al.*, 1999).

Xu *et al.*, (2018) studied differential radiosensitivity among small-cell lung cancer cells in p53 competent and p53 deficient cells. They observed that radiosensitivity was higher in p53 competent cells than in the p53 deficient cell line and that this differential sensitivity was not a consequence of apoptosis or autophagy. Radiosensitivity appeared to be more closely related to senescence, which occurred earlier and to a greater extent in the p53-deficient cells.

Immune and inflammatory response

IR induces various forms of tumor cell death, among which necroptosis, pyroptosis, ferroptosis and caspase-independent apoptosis are considered immunogenic forms of cell death (Demuynck *et al.*, 2021). A common feature of these types of cell death is the release of damage-associated immunostimulatory molecular patterns (DAMPs); key molecules for initiating innate and adaptive immune responses (Figure 4) (de Andrade-Carvalho & Villar, 2018; Zhu *et al.*, 2021).

IR significantly boosts antitumor immunogenicity by releasing adenosine, ATP, proinflammatory cytokines, chemokines, tumor antigens, ROS, and

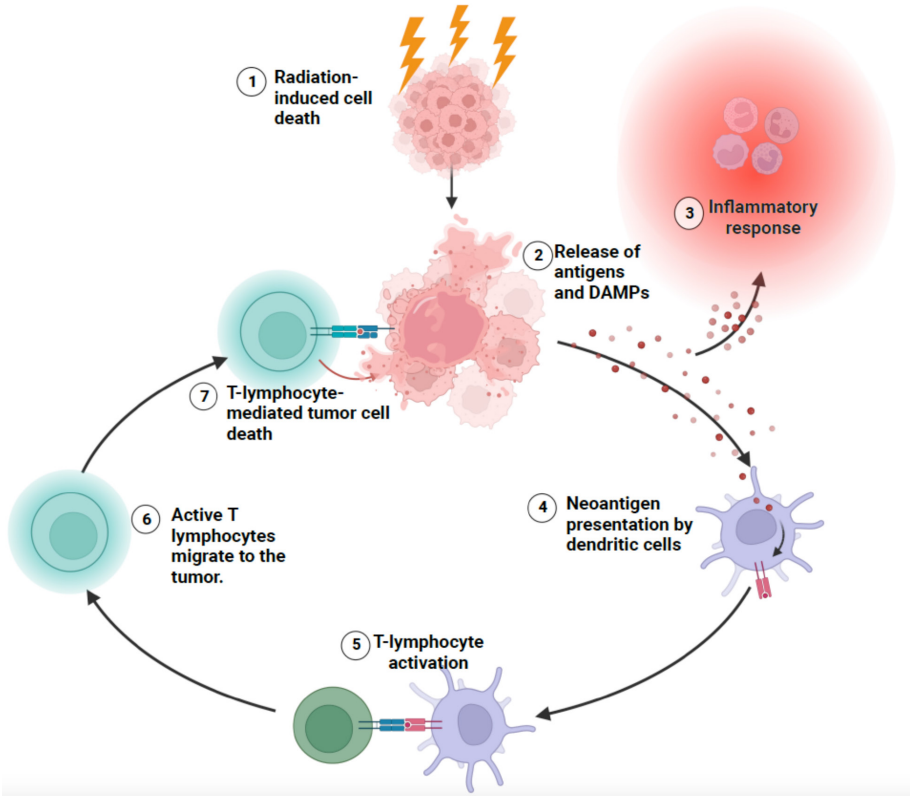

Figure 4. Radiation can cause cell death in tumors, releasing DAMPs and tumor neoantigens. These trigger antitumor immune responses in the body. Created with BioRender.com.

other DAMPs (de Andrade Carvalho & Villar, 2018). These non-targeted effects can be of two types. First, the bystander effect refers to the additional regression of surrounding non-irradiated tumor areas after local radiotherapy. On the other hand, the abscopal effect refers to the ability of localized IR to induce an antitumor response throughout the whole organism, including regions or sites not exposed to the RT field (Craig *et al.*, 2021; Wang, 2021).

A critical step for non-targeted effects is the ability of the immune system to process and present tumor neoantigens presented on MHC molecules of professional antigen-presenting cells. Differences in the processing capacity and antigen presentation by professional cells may influence the efficiency of the antitumor immune response and, therefore, could correlate with the clinical response to radiotherapy (Cui *et al.*, 2018).

The effects of immunogenic cell death on the tumor microenvironment after the death of the cancerous cells have not been thoroughly investigated. On the one hand, RT can inhibit tumor proliferation by inducing cell death and triggering the antitumor immune response via apoptosis, ferroptosis, necroptosis, and pyroptosis. However, it can also lead to an inflammatory response, resulting in tumor development and possible adverse effects in normal tissues (Gao *et al.*, 2022).

For instance, radiation-exposed cancer cells generate cytokines that trigger inflammation. These cytokines, namely IFN, IL-1, IL-6, IL-8, VEGF, EGFR, and TNFα, are usually released within minutes to hours post-exposure. This is associated with the production of ROS and cytokines that will participate in the creation of a proinflammatory microenvironment. Post-RT inflammatory responses can cause secondary effects in normal tissues, such as pneumonitis, myocarditis, and fibrosis (Walle *et al.*, 2018).

Recent studies have found that specific gene variants are closely linked to inflammation and play a crucial role in pain and other adverse effects after RT. These genes, such as TNF-α, STING1, HLA-DQB1, GHRL, IFNG, IL12, NF-κβ, among others, are activated in immune cells following RT, leading to the release of inflammatory cytokines and chemokines that cause cellular damage and inflammation. This, in turn, activates nociceptors, resulting in pain (Brzozowska *et al.*, 2018; Lee *et al.*, 2019; Liu *et al.*, 2018; Reyes-Gibby *et al.*, 2018; Schack *et al.*, 2022).

CONCLUSIONS

Advances in RT medical technology and treatment techniques have made it possible to optimize clinical outcomes. However, a significant proportion of cases do not show a therapeutic response, and current evidence suggests that the variability of response to different treatments is due to the heterogeneity of tumor lesions. Tumor heterogeneity and its differential response to treatment are partly due to genetic and epigenetic factors.

In addition, clinical radiosensitivity, the probability of experiencing some acute or delayed toxicity to IR treatment, is a multidimensional phenomenon involving demographic factors, clinical history, and physical aspects of IR but also being “intrinsically” determined in part at the genetic level. Genetic variability among individuals in a population generated by polymorphisms in genes linked to the cellular capacity to respond to radio-induced damage would lead to a spectrum of radiosensitivity where we find a distribution towards lower or higher degrees of radiosensitivity.

Accurately predicting radiosensitivity is paramount for effectively implementing personalized medicine in the field of radiation oncology. That is the treatment adjustment based on the individual’s biological characteristics. As part of the implementation of personalized medicine in radiation oncology, it is essential to detect, a priori, those individuals with higher degrees of radiosensitivity and identify the tumor characteristics that allow predicting their response to treatment.

Understanding the cellular mechanisms of resistance and sensitivity to IR is fundamental for implementing treatment strategies considering the biological differences between individuals that explain the different treatment responses.

There are different assays for the evaluation of radiosensitivity that allow the study of this phenomenon from different angles, such as the use of clonogenic survival assays, the formation of chromosomal aberrations, DNA repair mechanisms, and at the genomic level by assessing gene expression, the detection of single nucleotide polymorphisms or by techniques such as massive sequencing (Averbeck *et al.*, 2020). Currently, no test is routinely used in the clinical setting for the assessment of individual radiosensitivity.

DECLARATION OF INTEREST

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RESUMEN: Esta revisión tiene como objetivo proporcionar una visión general de los principales mecanismos celulares que influyen en la respuesta de los tejidos sanos y tumorales a la radiación y, por tanto, en su radiosensibilidad. El conocimiento de los mecanismos biológicos que definen la radiosensibilidad individual es el camino inicial para establecer ensayos dirigidos a predecir respuestas al tratamiento y es fundamental para lograr la aplicación de la medicina personalizada en los procedimientos de RT. En este sentido, el interés en estudiar la radiosensibilidad en el ámbito clínico es la determinación de 1) el riesgo individual de desarrollar efectos adversos al tratamiento con IR (radiosensibilidad clínica o de tejido normal) y 2) el posible beneficio terapéutico de la IR (radiosensibilidad tumoral). Los autores realizaron una revisión extensa de artículos y recursos sobre biología de la radiación y mecanismos celulares que afectan la respuesta de los tejidos normales y cancerosos al tratamiento con radiación ionizante (IR). La revisión se centra principalmente en artículos publicados desde 2000 hasta marzo de 2023, al tiempo que incorpora artículos seleccionados más antiguos para enriquecer la discusión. Para recopilar estos artículos desde bases de datos electrónicas populares como PubMed, ScienceDirect, Google Scholar y Cochrane, los autores utilizaron una estrategia de búsqueda que empleaba lógica booleana “Y” y “O”. Las diferentes combinaciones de palabras clave buscadas incluyeron los siguientes términos: “radiosensibilidad”, “celular”, “sensibilidad a la radiación”, “radiorresistencia”, “radiación ionizante”, “radioterapia”, “efectos biológicos”, “tumor”, “tejidos normales”, “mecanismos celulares”, “estrés oxidativo”, “reparación del ADN”, “respuesta inmune”, “muerte celular”, “efectos radioinducidos”. Conclusiones: La radioterapia (RT) es una de las principales modalidades de tratamiento en oncología, junto con la cirugía, la quimioterapia y la inmunoterapia. La RT administra una dosis precisa y suficiente a los tejidos tumorales, induciendo la muerte celular. Sin embargo, la respuesta individual a la exposición a IR varía según el tipo de terapia utilizada (es decir, RT externa, radiocirugía, braquiterapia, entre otras) y la heterogeneidad intrínseca entre los tipos y subtipos de tumores. Además, las variantes en los genes que controlan la respuesta celular al daño del ADN, el estrés oxidativo, el control del ciclo celular, la muerte celular y la respuesta inmune conducirían a un espectro de radiosensibilidad. Comprender cómo la radiación afecta las células normales y tumorales a nivel celular es esencial para desarrollar opciones de tratamiento efectivas que tengan en cuenta las diferencias biológicas entre los individuos. Si bien muchas personas experimentan una sensibilidad moderada a la radioterapia en cuanto a los efectos secundarios y la respuesta del tumor, puede haber variaciones en la sensibilidad. Por tanto, adquirir este conocimiento es fundamental para lograr los mejores resultados clínicos.

PALABRAS CLAVE: radiobiología celular; radiosensibilidad; radioterapia; Respuesta al daño del ADN, radiación ionizante.

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