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Ionizing radiation-induced cellular senescence promotes tissue fibrosis after radiotherapy. A review

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ABSTRACT

Ionizing radiation-exposure induces a variety of cellular reactions, such as *senescence* and *apoptosis*. Senescence is a permanent arrest state of the cell division, which can be beneficial or detrimental for normal tissue via an inflammatory response and senescence-associated secretion phenotype. Damage to healthy cells and their microenvironment is considered as an important source of early and late complications with an increased risk of morbidity in patients after radiotherapy (RT). In addition, the benefit/risk ratio may depend on the radiation technique/dose used for cancer eradication and the irradiated volume of healthy tissues. For radiation-induced fibrosis risk, the knowledge of mechanisms and potential prevention has become a crucial point to determining radiation parameters and patients' intrinsic radiosensitivity. This review summarizes our understanding of ionizing radiation-induced senescent cell in fibrogenesis. This mechanism may provide new insights for therapeutic modalities for better risk/benefit ratios after RT in the new era of personalized treatments.

1. Introduction

Ionizing radiation (IR) exposure can induce a variety of cellular reactions, such as *apoptosis* and *senescence*. Cellular senescence plays an important role in embryonic development and in shaping organogenesis, wound healing and tumor suppression (He and Sharpless, 2017). A senescent cell is a potent anti-cancer mechanism that can occur in virtually any cell, including fibroblasts, epithelial cells, melanocytes, endothelial cells, and astrocytes (He and Sharpless, 2017;Chinta et al., 2015). It remains viable and metabolically active even though it does not undergo cell division and permanently arrests cell proliferation (He and Sharpless, 2017; Campisi and d'Adda di Fagagna, 2007).

At the tissue level, cellular senescence increases with age in many renewable tissues which are discovered at sites of age-related diseases, including degenerative disorders, malignant and benign diseases. In addition, researches on senescence biomarkers have to take into account specific contexts and different cell types. In the lung tissue, senescent fibroblasts could trigger fibrogenesis (Schafer et al., 2017), while senescent activated hepatic stellate cells could diminish liver cirrhosis (Krizhanovsky et al., 2008). The impact of cellular senescence in tissue may be beneficial or harmful, which depend on the triggered factors, tissue, and cell type (Schafer et al., 2018). At the cellular level, the long-drawn presence of senescent cells in normal tissues may stimulate potency damage, predominantly due to the persistence of related inflammatory responses (Lasry and Ben-Neriah, 2015). Conversely, cellular senescence can have a beneficial response and prevent the growth of premalignant cells and activate cancer immune surveillance.

IR-induced cellular senescence as a promoter of fibrotic sequelae has been shown in several models recently. In lung, data from Beach et al. have suggested radiation-induced pulmonary fibrosis as a step in progressive fibrosis (Beach et al., 2017). Recently, Schafer et al. showed that IR-induced senescent fibroblasts contribute to lung fibrosis via their profibrotic secretomes (Schafer et al., 2017). Korpela and Liu reported that radiation-induced senescence is involved in endothelial cells (Korpela and Liu, 2014). Hong et al. reported articular

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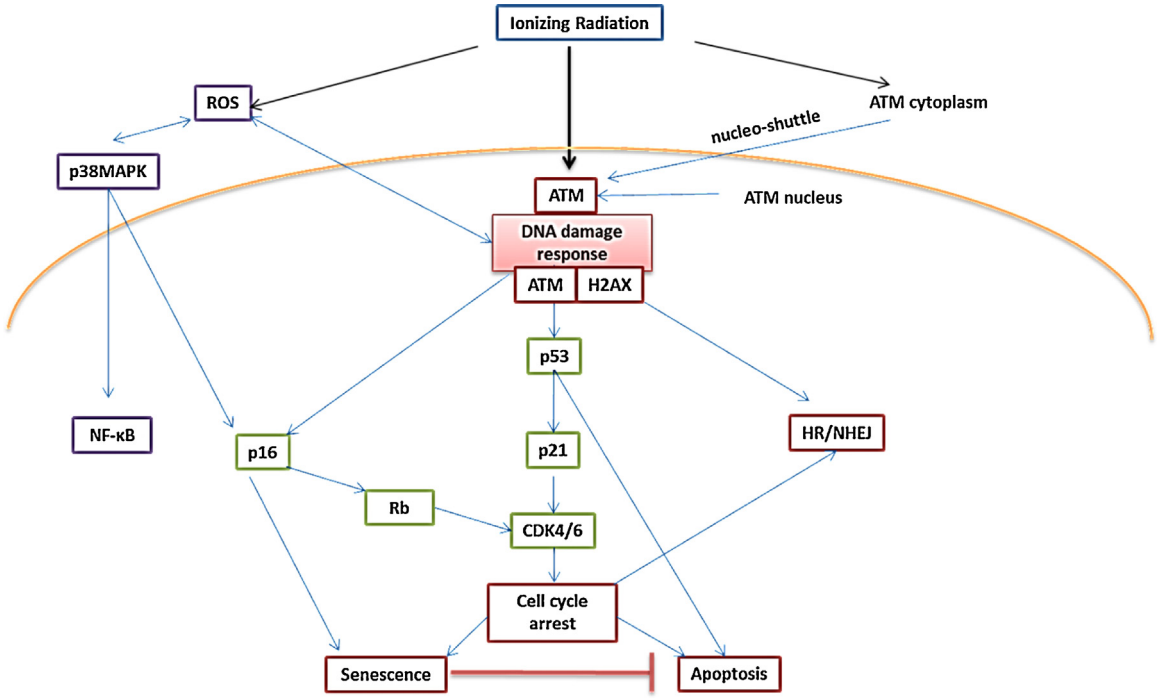

Fig. 1. DNA damage response induced senescence by ionizing radiation.
IR induced nucleo-shuttling of ATM. The ATM kinase activated, permit accurate phosphorylation of H2 AX and other DNA repair protein by two main repairs NHEJ, HR. The DNA damage response (DDR) after IR leads to stimulate p38 mitogen-activated protein kinase (MAPK) through ROS, ROS also produced after radiolysis of water, in turns activate transcription factor nuclear factor kappa-B, in turn production of p16INK4A, p16 INK4A activates the pRb tumor suppressor, which block certain proliferative genes, ultimately induces durable cell-cycle arrest. DDR activates not only p16/Rb but also p53 tumor suppressor, then turns on the p21 WAF1 gene transcription, ultimately causes senescence permanent growth arrest. Both the p53/p21 and p16INK4a/pRb pathways are clearly of major importance in cellular senescence by inhibiting the cyclin-dependent kinase (CDK) to exit from cell division cycle, thus involve in cellular arrest and oncogene-induced senescence, which is characterized by overexpression of p16, p53 or p21 proteins and resistant to apoptosis. (ATM: Ataxia Telangiectasia Mutated protein; CDK: cyclin-dependent kinase; DNA: Deoxyribonucleic acid; H2 AX: histone H2 A family; IR: Ionizing radiation; NF-κB: nuclear factor kappa-B; NHEJ: non-homologous end joining; p38MAPK: p38 mitogen-activated protein kinase; pRb: retinoblastoma protein ROS: Reactive Oxygen Species).

chondrocytes damage after radiation via the senescence pathway (Hong et al., 2010). In the heart, Liu et al. recently reported that radiation can induce myocardial fibrosis after RT for thoracic tumors (Liu et al., 2017). However, the authors have not shown that IR-induced senescence promotes a fibrotic myocardium.

In this review, we aimed to focus on IR-induced senescence accelerated tissue fibrosis. We hypothesize that this mechanism may provide new insights into novel therapeutic modalities in RT to prevent or cure radiation-induced fibrosis in patients who have a long-term outcome after irradiation.

2. Methods

2.1. Data sources

We searched for relevant studies by using the electronic resources of the “Pubmed” database from 1977 to 2018. The search language was limited to publications written in English and French.

2.2. Search strategy

A literature search strategy involving the keywords “radiation-induced toxicity”, “radiotoxicity” “radiation-induced senescence”, “radiation-induced fibrosis”, “radiotherapy-induced toxicity”, “radiosensitivity AND radioresistance”, “radiation AND senescence”, “senescence AND fibrosis”, “radiation AND fibrosis”, “senescence AND senotherapeutics”, “senescence AND senolytics”, “senescence AND senomorphics”, and “senescence AND SASP inhibitors” was used. We screened keywords, titles and abstracts of all retrieved articles and selected significant articles for full text. Electronic links to related articles and references of selected articles were hand-searched. Eligible articles included meta-analyses, prospective studies, multicenter studies, clinical trials, reviews and systematic reviews.

3. Results

3.1. Radiation-induced senescent cells mechanisms

Exposure to IR can lead to many cellular responses, including a modification of gene expression as well as deoxyribonucleic acid (DNA) damage which occurs either as a direct effect of radiation on DNA molecules or by an indirect action by the free radicals genesis and reactive oxygen species (ROS). DNA double-strand breaks (DSBs) are one of the most genotoxic lesions in the genome, with 5% unable to be repaired. Unrepaired DSBs after irradiation can lead to cell death, such as apoptosis, senescence, mutation or genomic instability. IR induces cell apoptosis and senescence via multiple pathways (Islam, 2017; Liauw et al., 2013a; Santivasi and Xia, 2014).

Several authors have shown that radiation can lead to the oxidation of ataxia telangiectasia mutated (ATM) protein dimers converted into ATM monomers. The resulting ATM monomers are nucleo-shuttled, to allow DSB recognition via the phosphorylation of H2 AX (γ-H2 AX) and execute DSBs repair by two main repair pathways non-homologous end joining (NHEJ), prevalent throughout all phases of the cell cycle and homologous recombination (HR), prevalent during late S-phase and G2-phase (Islam, 2017; Santivasi and Xia, 2014; Belkacemi et al., 2016; Bodgi et al., 2013; Bodgi and Foray, 2016; COPERNIC project investigators et al., 2016). The DNA damage response (DDR) after IR leads to stimulating p38 mitogen-activated protein kinase (p38 MAPK) and protein kinase C (PKC), activating transcription factor nuclear