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MINIREVIEWS

Role of senescence induction in cancer treatment

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Abstract

Cellular senescence is a form of permanent cell cycle arrest that can be triggered by a variety of cell-intrinsic and extrinsic stimuli, including telomere shortening, DNA damage, oxidative stress, and exposure to chemotherapeutic agents and ionizing radiation. Although the induction of apoptotic cell death is a desirable outcome in cancer therapy, mutations and/or deficiencies in the apoptotic signaling pathways have been frequently identified in many human cancer types, suggesting the importance of alternative apoptosis-independent therapeutic approaches for cancer treatment. A growing body of evidence has documented that senescence induction in tumor cells is a frequent response to many anticancer modalities including cyclin-dependent kinases 4/6 small molecule inhibitor-based targeted therapeutics and T helper-1 cytokine-mediated immunotherapy. This review discusses the recent advances and clinical relevance of therapy-induced senescence in cancer treatment.

Key words: Cellular senescence; Cancer treatment; Chemotherapy; Ionizing radiation; Cyclin-dependent kinases 4/6 inhibitor; Aurora kinase inhibitor; Immunotherapy; T helper-1 cells; T helper-1 cytokines

Core tip: Both *in vitro* and *in vivo* studies have revealed that senescence induction in human cancer cells is a prominent response to chemotherapy and irradiation. A senescent phenotype has been detected in clinical tumor samples of breast cancer patients following preoperative neoadjuvant chemotherapy. Immunotherapy-induced senescence of cancer cells contributes to tumor regression *in vivo*. The induction of cancer cell senescence appears to be a major mechanism of action of cyclin-dependent kinases 4/6 small molecule inhibitor-based targeted therapy. Collectively, these preclinical and clinical observations have demonstrated an important role for senescence induction in

cancer treatment.

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INTRODUCTION

Cellular senescence is an anti-proliferative program that restrains tumorigenesis *via* limiting the propagation and transformation of aging and damaged cells[1,2]. Senescence can be induced by a variety of cell-intrinsic and extrinsic stimuli, including telomere shortening, DNA damage, oxidative stress, chemotherapeutic agent treatment, radiation exposure, and the activation of oncogenes such as *Ras*[3-6]. Senescent cells are in a state of irreversible cell cycle arrest and are characterized by a flat and enlarged morphology, elevated senescence-associated β-galactosidase activity, and the activation of the p53-p21 and p16-Rb signaling pathways[2,7]. Additional characteristics of senescence cells include the presence of senescence-associated heterochromatic foci and the senescence-associated secretory phenotype[8,9]. Traditionally, senescence induction is considered to be an important mechanism of cancer prevention and cellular aging[10]. However, numerous recent studies have revealed that senescence is a prominent solid tumor response to therapy in which cancer cells evade apoptosis and instead enter into a stable and prolonged cell cycle arrest[3,5]. Furthermore, targeted therapeutics and cancer immunotherapies also have been shown to cause cancer regression *via* the induction of senescence in tumor cells[11,12]. These findings underscore the significant implications of senescence induction in cancer treatment.

INDUCTION OF TUMOR CELL SENESCENCE IS AN IMPORTANT OUTCOME OF CHEMOTHERAPY

Cellular senescence is a state of permanent cell growth arrest that often has been included with apoptosis as one of the terminal outcomes of cancer treatment. It is well-established that different classes of chemotherapeutic agents and ionizing radiation (IR) induce senescent-like phenotypes in tumor cells both *in vitro* and *in vivo*[2,5,11,13]. Our recent studies indicate that resveratrol induces premature senescence in lung cancer cells *via* promoting reactive oxygen species (ROS)-mediated DNA damage[14]. Inactivation of Myc results in tumor regression through induction of senescence but not apoptosis in hepatocellular carcinoma and lymphoma cells[15]. In addition, it has been reported that the restoration of p53 promotes tumor regression *in vivo via* induction of senescence in tumor cells[16,17]. More importantly, Schmitt *et al*[13] showed that senescence induction contributes directly to the outcome of chemotherapy *in vivo*. In agreement with this finding, there is evidence that the senescent phenotype is present in clinical tumor samples of breast cancer patients after undergoing preoperative neoadjuvant chemotherapy[18]. Moreover, our recent studies found that the number of senescent cells is markedly increased in tumor samples of lung cancer patients as compared to normal lung tissues (Figure 1). However, the clinical relevance of the presence of senescent cells in tumor samples has yet to be determined.

Notably, human tumors may harbor various types of defects in the apoptotic signaling pathways (*e.g*., loss of p53 and overexpression of BCL2) and, as a result, are resistant to apoptosis-based anticancer therapies[19,20]. In these conditions, a senescence-targeted strategy is likely to be a more effective and practical than traditional apoptosis-inducing approaches. A welcome benefit to this approach is that therapy-induced senescence can be achieved using much lower doses of therapy than those required to induce apoptosis[2,14]. Compared to the traditional apoptosis-inducing strategies, this low dose approach would significantly reduce the side effects of anticancer therapy and thus improve the quality of life for cancer patients.

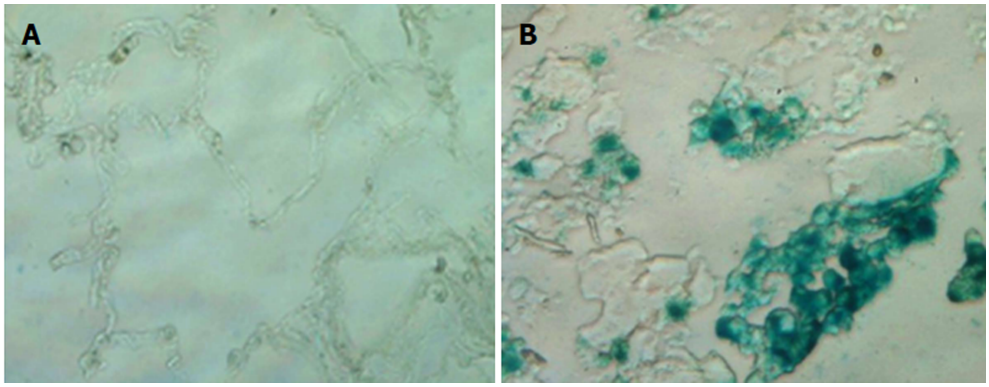

Figure 1 Number of senescent cells is significantly higher in tumor tissues of lung cancer patients than in normal lung tissues. Senescence-associated β-galactosidase staining was performed to analyze senescent cells in normal human lung tissues (A) and tumor tissues of lung cancer patients (B), respectively.

ROLE OF SENESCENCE INDUCTION IN CANCER RADIOTHERAPY

Radiotherapy is used in over 50% of patients during the course of cancer treatment and is effective both as a curative modality and for palliation[21]. However, many epithelial-derived tumors including lung cancer have been shown to be resistant to radiation-induced apoptosis[6,20]. Consistent with these observations, our recent studies have demonstrated that IR primarily induces premature senescence rather than apoptosis in human non-small cell lung cancer (NSCLC) cells[6]. Subsequent mechanistic studies revealed that the p53-p21 signaling pathway plays a critical role in modulating IR-induced senescence in NSCLC cells (Figure 2). More importantly, we showed that pharmacologic activation of p53 by Nutilin-3 sensitizes NSCLC cells to radiation by enhancing IR-induced senescence[6]. These results suggest that pharmacological promotion of senescence induction can be exploited as a novel and effective therapeutic approach to improve the efficacy of lung cancer radiotherapy.

MicroRNA-34a (miR-34a) has been shown to be a p53 responsive miRNA that is involved in regulating senescence induction[22-24]. Our recent studies showed that the expression of miRNA-34a was increased substantially in human NSCLC cells after exposure to IR[25]. Moreover, we found that treatment with synthetic miR-34a mimics enhances the anti-cancer effects of irradiation by promoting senescence induction *via* targeting the Myc oncoprotein in NSCLC cells (Figure 2). These findings not only provide new insights into the mechanisms by which IR induces senescence in lung cancer cells but also support the hypothesis that pharmacological manipulation of senescence induction should be explored as a new therapeutic strategy for improving the outcome of cancer radiotherapy.

INDUCTION OF SENESCENCE IS A MAJOR MECHANISM OF ACTION OF CYCLIN-DEPENDENT KINASES 4/6 INHIBITION-BASED TARGETED THERAPEUTICS

The cyclin-dependent kinases (CDKs) are a large family of serine-threonine kinases that play a pivotal role in regulating cell cycle progression. Commitment to cell cycle entry occurs during the G1 phase, when CDK4 and CDK6 form active complexes with one of the three D-type cyclins (D1, D2, or D3). Cyclin D-CDK4/6 complexes promote G1/S transition by phosphorylating the Retinoblastoma tumor suppressor (Rb), which in turn releases its suppression of the E2F transcription factor, resulting in initiation of E2F-dependent gene transcription and DNA synthesis. CDK4 and CDK6 are overexpressed in the majority of human cancers and they presumably promote tumorigenesis by suppressing senescence in cancer cells[11,26,27]. Both preclinical studies and clinic trials have demonstrated the therapeutic potential of CDK4/6 small molecule inhibitors against several solid tumors[28-31]. Recently, a CDK4/6-specific inhibitor, palbociclib (also known as PD033299[1], was approved by the FDA for the treatment of advanced estrogen receptor-positive breast cancer[32].

It is well established that CDK4/6 inhibitors suppress tumor growth by the induction of senescence in various type of cancer cells[11,26,27,32]. Mechanistic studies have revealed that CDK4/6 suppress tumor cell senescence *via* phosphorylating and activating the Forkhead Box M1 (FOXM1) transcription factor, and that activation of

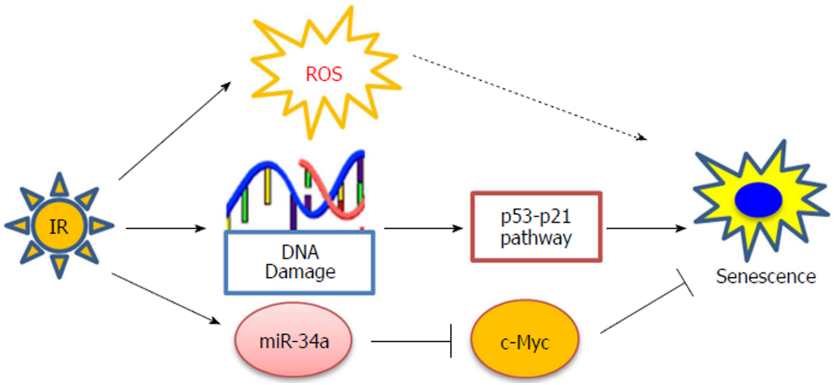

Figure 2 This model summarizes the mechanisms underlying ionizing radiation-induced senescence in non-small cell lung cancer cells. Ionizing radiation (IR) exposure increases the levels of reactive oxygen species in tumor cells and oxidative stress is known to trigger the induction of senescence. IR exposure leads to DNA damage which in turn can activate the p53-p21 senescence pathway. Irradiation up-regulates the expression of miR-34a that inhibits c-Myc, resulting in the induction of senescence. ROS: Reactive oxygen species; IR: Ionizing radiation.

FOXM1 may inhibit the induction of senescence in tumor cells by repressing ROS-mediated oxidative stress[33]. However, the precise mechanisms whereby FOXO1 controls ROS and oxidative stress remain unclear. Promyelocytic leukemia (PML) acts as a tumor suppressor by inducing senescence in response to oncogenic stress[34,35]. Interestingly, Acevedo *et al*[36] showed that CDK4/6 suppress PML-induced senescence in tumor cells, suggesting that CDK4/6 inhibitors such as PD0332991 may induce senescence in cancer cells by blocking CDK4/6-mediated suppression of PML's senescence-inducing function. Moreover, CDK4/6 inhibition has been shown to be efficacious against therapy-resistant HER2 positive breast cancers[37]. These results imply that although some tumors may be resistant to apoptosis-inducing treatments, it is likely that they are still responsive to senescence-targeted therapies.

AURORA KINASE INHIBITION INDUCES SENESCENCE IN TUMOR CELLS BOTH *IN VITRO* AND *IN VIVO*

Aurora kinases are a family of serine/threonine mitotic kinases that regulate a diverse set of mitotic processes including spindle formation, centrosome segregation, checkpoint activation and kinetochore-microtubule connections[38,39]. Aurora A kinase (AurA) is located on 20q13.2, a chromosomal region that is frequently amplified in many human cancers. Overexpression of AurA correlates with poor clinical outcomes in patients with hormone-related cancers[40]. Aurora kinase inhibitors (AKIs) are a promising class of drugs for cancer treatment. Several small molecule AKIs including MK-0457, PHA-739358 and MLN8237 have been investigated in clinical trials for the treatment of human cancers[41-43].

Alisertib (MLN8237) is an orally bioavailable, second-generation selective inhibitor of Aurora kinases which binds to AurA and prevents its phosphorylation and activation[44]. It has been shown that senescence is likely a terminal outcome of AurA inhibition and that pharmacological inhibition of AurA induces senescence in colon cancer cells both *in vitro* and *in vivo*[45]. AurA is overexpressed in gliomas and treatment with Alisertib induces senescence and differentiation in glioblastoma cells[46]. Moreover, recent studies have revealed that p53 and p73 tumor suppressors play a critical role in modulating tumor cell responses to AKIs. Tentler *et al*[47] reported that Alisertib treatment resulted in apoptosis in human triple-negative breast cancer (TNBC) cells with functional p53 and p73, whereas it induced senescence in cells lacking p53 and p73. These findings suggest that AKI may induce growth arrest in TNBC through a p53- and p73-independent mechanism. Nevertheless, further studies are warranted to better understand the in-depth mechanisms whereby AKIs induce senescence in human tumor cells.

INDUCTION OF CANCER CELL SENESCENCE CONTRIBUTES TO IMMUNOTHERAPY-INDUCED TUMOR REGRESSION

Immunotherapy has shown promising efficacy against human cancers both in preclinical studies and in clinical trials[48-50]. T helper-1 (Th1) cells play a critical role in mediating the antitumor adoptive immune response[51,52]. Th1 T-cell infiltration is associated with better outcomes and Th1 cytokines are more effective at promoting the antitumor functions of CD40L-activated macrophages as compared to Th2 cytokines[53]. Moreover, Müller-Hermelink *et al*[54] showed that treatment with T antigen (Tag)-specific Th1 cells induced tumor dormancy and doubled the survival of tumor-bearing mice by arresting tumor growth, without detectable evidence of tumor cell cytotoxicity, necrosis or apoptosis. These findings suggest that other alternative non-cytotoxic mechanisms are likely involved in Th1- and Th1 cytokine-mediated immunotherapy. In agreement with this idea, it has been shown that treatment with Th1 cytokines, IFN-γ and tumor necrosis factor (TNF) induces senescence in cancer cells[12].

It has been reported that cancer immunotherapy causes tumor growth arrest and regression without any clear evidence of tumor cell death or cellular toxicity[55,56]. Moreover, it has been shown that immunotherapy-induced tumor growth arrest was associated with an increase in interferon (IFN)-γ-producing $CD4^+$ Th1 cells, but not $CD8^+$ cytotoxic T lymphocytes[55-57]. These observations suggest that senescence induction may contribute to the outcome of immunotherapy. In agreement with this, Braumüller *et al*[12] showed that Th1 immunotherapy arrests tumor progression through IFN-γ- and TNF-induced cancer cell senescence *in vivo*. Their subsequent mechanistic studies revealed that TNFR1 signaling is required for Th1 immunotherapy-induced tumor cell senescence and that activation of the p16-Rb pathway is involved in senescence induction[12]. In line with these findings, it has been shown recently that CDK4/6 inhibition-induced tumor cell senescence promotes antitumor immunity in preclinical models[58,59]. Furthermore, there is evidence that IL-12 inhibits the growth of human sarcoma cells by senescence induction[60]. Taken together, these results highlight a novel link between cancer immunotherapy and the induction of senescence in tumor cells.

CONCLUSION

Given the fact that many human cancers may harbor different defects in the apoptotic signaling pathways, and thus are inherently resistant to chemoradiotherapy-induced apoptosis, there is a critical need for the development of innovative apoptosis-independent approaches for cancer therapeutics. The induction of tumor cell senescence has been well-established as a prominent therapeutic response of cancer cells to chemotherapy, radiation, small-molecule inhibitor-based targeted therapeutics and immunotherapy. These results underscore the important implications of senescence induction in cancer treatment. Although senescent cells were detected in clinical tumor samples of cancer patients, the clinical significance and applications of therapy-induced senescence remain incompletely understood. It is still unclear if senescence markers in patient tumor samples will be useful for prognosis prediction and/or therapeutic efficacy evaluation in the clinic. In addition, further studies, particularly clinical investigations, are necessary to better elucidate the clinical relevance and significance of therapy-induced senescence in the treatment of cancer.

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