The treatment options for cancer include surgery, radiotherapy and chemotherapy. However, the traditional approach of high-dose chemotherapy brings tremendous toxic side effects to patients, as well as potentially causing drug resistance. Drug resistance affects cell proliferation, cell senescence and apoptosis. Cellular senescence refers to the process in which cells change from an active proliferative status to a growth-arrested status. There are multiple factors that regulate this process and cellular senescence is activated by various pathways. Senescent cells present specific characteristics, such as an increased cell volume, flattened cell body morphology, ceased cell division and the expression of β-galactosidase. Tumor senescence can be categorized into replicative senescence and premature senescence. Cellular senescence may inhibit the occurrence and development of tumors, serving as an innovative strategy for the treatment of cancer. The present review mainly focuses on senescent biomarkers, methods for the induction of cellular senescence and its possible application in the treatment of cancer.

1. Introduction

Cancer has high incidence and mortality rates worldwide. Tumor cells can easily develop resistance to traditional treatments, and survive to result in metastasis and invasion. The induction of tumor senescence has been proposed as a potential method for the treatment of tumors. In 1961, Hayflick and Moorhead (1) cultured human fibroblasts and found that normal diploid cells proliferated in vitro for 50-70 generations before entering senescence. This limit to cell proliferation, when cells lose their proliferative ability but maintain stable metabolic activity, is called the ‘Hayflick Limit’. After reaching this limit, the cells enter into a senescent state (2). Senescence is a defensive mechanism that prevents cells from being damaged. When cells are senescent, they do not re-enter the cell cycle when exposed to mitogenic stimuli, but exhibit an enhanced secretory phenotype and are resistant to cell death. It has been hypothesized that cell senescence is an important mechanism that may be used to attack tumorigenic cells. When DNA is damaged, cell senescence becomes the third pathway, in addition to apoptosis and DNA repair, to defend against tumorigenesis (3). Some antitumor drugs have been demonstrated to inhibit tumor cell proliferation by inducing senescence in vitro and in vivo (4,5). Therefore, the induction of cancer cell senescence and the subsequent inhibition of tumorigenesis and recurrence is a focus of research into novel tumor treatments.

Tumor senescence can be divided into two types, namely replicative senescence and premature senescence. Replicative senescence is determined by the number of cell divisions (6). Premature senescence is mainly caused by DNA damage, the loss of tumor suppressor factors, oxidative stress and malnutrition (7,8).
Tumor cells exhibit unique characteristics when senescent, the most notable being the loss of ability to proliferate in an unlimited capacity whilst maintaining metabolic activity (9). Senescent cells are usually arrested in the G0 or G1 phase (10,11). Research has focused on studying the phenotypical characteristics of cells after they have entered senescence, as well as the mechanisms of action that activate the process and the molecular signaling pathways involved (12). In subsequent sections of the present review, the factors that initiate senescence and induce senescent phenotypes are discussed.

2. The phenomenon of tumor cellular senescence

When tumor cells enter into senescence, they exhibit morphological changes, including an increase in volume, flattened shape and increased intercellular space, and they also present with blocked DNA synthesis, heterochromatin foci, lipofuscin accumulation, DNA damage-induced foci, loss of lamin B1, satellite distension, the expression of differentiated embryonic chondrocyte-expressed 1 and decay death receptor 2, the upregulation of certain microRNAs and secretion of numerous factors, including growth factors, cytokines, chemokines and proteases, which are collectively known as the senescence-associated secretory phenotype (SASP) (5,13-17). The SASP has been shown to contribute to the protective effect of senescence, and to induce detrimental effects when the pathological accumulation of senescent cells occurs. One study revealed that cisplatin can induce JegG2 tumor cells to enter into senescence and present senescent phenotypes, even when used at a low dose (18). Such effects of this and other chemotherapeutic agents have been confirmed in numerous cell lines, including HCT-116, H460, H1299, HT1080 and A549 (19,20). For example, Zhang et al (20) treated HCT-116 colon cancer cells with 20 and 50 nM camptothecin for 24 h, and the cells entered into senescence 48 h after the low-dose treatment. Also, when treated with a low level of DNA-damaging agents, such as cisplatin and doxorubicin, JegG2 cells clearly progressed into senescence (18,21,22). At present, several anticancer drugs that are used clinically are known to mediate therapy-induced senescence, including docetaxel, bleomycin, cyclophosphamide, doxorubicin, vincristine, etoposide and cisplatin; all of the aforementioned chemotherapeutic agents have been shown to induce senescence in various cancer cell lines (23).

3. Senescence biomarkers

When cells enter senescence, certain markers are expressed, such as senescence-associated β-galactosidase (SA-β-gal). SA-β-gal has been identified as a specific marker for cell senescence, as it is detected by histology in the majority of senescent cells, but not present in non-senescent cells (24). Senescent cells can also be recognized using physiological methods, such as measurement of the formation of senescence-associated heterochromatin foci and SASP-associated factors (25). Another marker commonly used to identify senescent cells is the cyclin-dependent kinase inhibitor 2A (p16\(^{INK4a}\)) tumor suppressor protein, which is expressed at a low level or is undetectable in the majority of healthy cells and tissues, but is notably upregulated in most senescent tumor cells (21,26). The identification of novel markers of senescence may assist in the prognosis of senescence and cancer. Various other biomarkers of senescence have been identified and are listed in Table I (27-41).

4. Cell cycle regulation in tumor senescence

Regulation of the cell cycle is a complex process, which controls basic activities including growth, division and differentiation (42). Cell division genes control the initiation and progression of the cell cycle, and two tumor suppressor genes, namely retinoma inhibitory protein (Rb) and p53, have important roles in cell cycle arrest and the maintenance of senescence (43). The Rb protein (pRb) is critical for the G1/S and G2/M regulatory points of the cell cycle; when activated through dephosphorylation it leads to the transcription of S-phase genes being blocked (44). Tumor cell senescence is also induced by p53 following treatment with chemotherapeutic drugs, which results in cell cycle arrest in the G1/S and G2/M phases (45,46). In addition, some cyclin-dependent kinase (CDK) 4/6 inhibitors, including palbociclib and abemaciclib, have also been demonstrated to induce senescence. Currently, these drugs have been approved for clinical, to be used alone or in combination, for chemotherapy (47-49).

5. Causes of cell senescence

Effects of telomeres and telomerase. Telomere-induced cell senescence is a component of replicative senescence. As the telomeres of normal cells shorten, the cells eventually undergo a stagnation of proliferation or division and reach senescence. By contrast, tumor cells often exhibit unlimited proliferative capacity, because the length of telomeres in tumor cells is stable (Fig. 1) (44,50,51).

Telomerase is a reverse transcriptase, the main function of which is to add the repeat base sequence TTAGGG to the end of chromosomes to increase the length of telomeres and the number of cell divisions (9,52). One study demonstrated that the telomeres of human primary fibroblasts shorten when the cells lose their proliferative capacity (53). However, the cell senescence caused by telomere shortening can be prevented via the activation of telomerase (51). Telomerase serves an important role in the process by which cells escape senescence, as its activation can stabilize the length of telomeres and even prolong the life of tumor cells. Among the 100 immortalized cell lines tested by Kim et al (54), telomerase was highly expressed in 94 tumor-derived cell lines.

Due to the complexity of telomerase, various strategies for its inhibition have been developed as potential treatments for cancer. These include the use of antisense oligonucleotides to target the RNA component of telomerase, chemical telomerase inhibitors, oligonucleotides and nucleosides, small-molecule drugs that target human telomerase reverse transcriptase (TERT), gene therapies, and molecules that target telomeres and telomerase-related proteins (17,55-59). Among these, a non-competitive inhibitor of TERT, BIBR1532, has been demonstrated to shorten telomere length, inhibit cell proliferation and induce senescence in human cancer cells (60). The aforementioned studies have shown that telomerase dysfunction can induce cell senescence,
damage organ functions and shorten the human life span. However, the process of senescence may be reversed by inhibiting telomerase activation (61).

Effects of reactive oxygen species (ROS). The levels of active oxygen free radicals within living organisms increases over time (62). When free radicals are present in excessive quantities or the antioxidant capacity is inadequate, oxygen free radicals oxidize unsaturated fatty acids in cells, causing lipid peroxidation and biofilm damage, thus damaging the structure and function of organelles (63). The effects of ROS on cells are positively associated with their concentration. ROS attack mitochondrial DNA and accelerate the process of tumor cell senescence. The premature senescence of human fibroblasts occurs in a high-oxygen environment (40-50% O₂), while the cell cycle is extended in hypoxic conditions (2-3% O₂) (64,65). ROS intervene in tumor senescence through processes such as lipid peroxidation, DNA damage and protein destruction (66). Busulfan has been demonstrated to create DNA-DNA and DNA-protein cross-links, and induce the senescence of human fibroblasts in a ROS-dependent manner (67).

Multiple factors causing DNA damage and gene mutation. When tumor cells are exposed to abnormal external conditions but are unable to activate their auto-repair mechanisms, they may undergo senescence or apoptosis (68). Numerous types of antitumor treatment, including cytotoxic chemotherapy drugs, ionizing radiation and topoisomerase inhibitors, are DNA-damaging agents that can induce the senescence of tumor cells and as well as healthy cells (69-72). It has been shown that chemotherapeutic compounds, such as doxorubicin, etoposide and cisplatin, which cause double or single-strand breakages of DNA, can cause healthy human fibroblasts to become senescent prematurely (73,74).

The activation of oncogenes in mammalian cells results in proliferative stress and the induction of senescence, which limits tumor growth. Genetic mutations can occur at any stage of development, usually during DNA replication or the interphase of cell division, and may affect DNA replication, DNA damage repair, carcinogenesis and senescence (75). Severe deficiencies in proteins that contribute to the sensing of DNA damage and its repair have the potential to accelerate senescence, while milder mutations in these same pathways may predispose individuals to develop cancer (76,77). In young human fibroblasts, mutation of the Ras gene has been shown to induce cell cycle arrest in the G₁ phase, a senescence-like phenotype and SA-β-Gal expression (78,79). Thus, senescence is a physiological mechanism of tumor suppression that inhibits the progression from benign tumor lesions to malignant tumors. In addition to the aforementioned factors, certain cellular pathways are also able to induce cell senescence.

6. Senescence induction pathways

Ataxia telangiectasia mutated (ATM), p53 and p21. Genes such as p53, p21 (CDK inhibitor 1A) and Rb play important roles in cell senescence, and determine whether cells are apoptotic or senescent (71). The ATM gene is an important component of the DNA damage checkpoint pathway, which is critical in cell cycle regulation, DNA damage response and repair (80). The loss of ATM leads to telomere shortening and damage. When DNA is damaged, ATM is activated, and induces the phosphorylation of downstream proteins such as checkpoint kinase 1 (Chk1), Chk2 and cell division

Table I. Biomarkers used in the detection of cell senescence.

| Senescence biomarker | Biomarker category | (Refs.) |
|----------------------|-------------------|---------|
| SA-β-Gal            | Senescence-associated β-galactosidase | (5,27-29) |
| SAHF                | Senescence-associated heterochromatic foci | (28,30,31) |
| p21 WAF1/CIP1       | CDK inhibitor | (21,32,33) |
| p16 INK4a           | CDK inhibitor | (21,34,35) |
| γ-H2AX              | Marker of DNA damage and repair | (36,37) |
| ARF                 | CDK inhibitor | (35,38,39) |
| SASP factors        | Senescence-associated secretory phenotype factors | (17,40,41) |

SA-β-gal, senescence-associated β-galactosidase; SAHF, senescence-associated heterochromatic foci; CDK, cyclin-dependent kinase; p21 WAF1/CIP1, CDK inhibitor 1; p16 INK4a, CDK inhibitor 2A; SASP, senescence-associated secretory phenotype; γ-H2AX, γ-H2A histone family member X; ARF, ADP-ribosylation factor.

Figure 1. Telomere shortening causes cellular DNA damage, which induces cell senescence (replication senescence).

Figure 1. Telomere shortening causes cellular DNA damage, which induces cell senescence (replication senescence).
cycle. This regulates the cell cycle checkpoints, so that DNA damage is repaired (81).

The p53 gene is important in cell carcinogenesis, senescence, apoptosis and gene repair (82). When cells are exposed to external stimuli that induce DNA damage, such as chemotherapy drugs, ionizing radiation, gene mutation or telomerase shortening, the p53 gene is activated (83). p53 activates p21, which inhibits CDK1, causing cells to be arrested in the G1/M phase and decreasing the phosphorylation level of pRb by inhibiting the activity of CDK2 and CDK4. This prevents cells from entering the S phase, and ultimately leads to cell senescence (Fig. 2). In one study, mice that were genetically engineered to express altered isoforms of p53 with increased activity were shown to be resistant to cancer (84). In human and mouse cells, inactivation of the p53-p21 pathway leads to cells escaping senescence (85). The knockdown of p53 or p21 reduced the drug-induced senescence of HCT116 cell line several folds, and the same phenomenon was observed when p53 expression was suppressed in HT1080 fibrosarcoma cells (86,87). Genome-wide analysis has demonstrated that the loss of p16INK4a expression and/or p53 function is the most common genetic event in human cancers, and may enable cancers to evade senescence (88).

p16INK4a and pRb. P16INK4a affects the process of senescence in tumor cells and is recognized as a tumor suppressor and biomarker of senescence (89). p16INK4a is an upstream regulator of pRb, which accelerates the degradation of phosphorylated pRb, activates the E2 factor (E2F) family of transcription factors, arrests cells at the transition from the G1 phase into the S phase and leads to cell senescence and apoptosis (90). Rb is a major tumor suppressor protein that serves a key role in the induction of cellular senescence and is the major substrate of CDK4/6 (91). Rb inhibits E2F regulatory factors by binding to them and shielding their transcriptional activation domains (92). When the cell genome or epigenome is damaged, the DNA damage response system is activated, which leads to the activation of protein kinase C and increased levels of ROS, which ultimately increase the expression level of p16INK4a. p16INK4a activates the pRb tumor suppressor and inhibits cell proliferation (Fig. 3) (94). A study demonstrated that activation of the p16INK4a-pRb pathway was critical for the development of senescence in most human cell lines (95). The expression of p16INK4a is low or undetectable in young, healthy organisms, but increases exponentially in most aged tissues with senescence (96,97).

ADP-ribosylation factor (ARF), double minute 2 (Mdm2) and p53. P14 (ARF) is one of the two proteins encoded by the CDKN2A, the other of which is p16INK4a, and is an important inducer of cellular senescence (39). The p14 (ARF) protein is expressed at low levels in normal cells, but is markedly increased as the cells reach senescence. P14 (ARF) blocks cells in the G1 and G2/M phases mainly through the p53 pathway, leading to cell senescence or apoptosis. It has been shown that when the p16INK4a gene is knocked out, mice are prone to developing tumors (35). It was initially considered that the deletion of p16INK4a was responsible for disturbing the cell senescence pathway; however, it has since been demonstrated that ARF-negative mice with normal expression levels of p16INK4a exhibit the same phenotype as those with p16INK4a deletion (94). Mdm2, also known as Hdm2, is a proto-oncogene in human tissues, which induces the degradation of p53 protein and inhibits its transcriptional activity. In particular, Mdm2 specifically binds to p53, thereby inhibiting its transcriptional activity and promoting its extracellular transport, resulting in the inactivation of the p53 protein (98). Transcription of the Mdm2 gene is regulated by a p53 transcriptional domain and the RAF-MEK-MAP kinase signal transduction pathway. The upregulation of Mdm2 by the RAF-MEK-MAP kinase pathway has been shown to decrease p53-mediated apoptosis (99-101). The exogenous expression of ARF stabilizes p53, promotes p53 transcription, p21WAF1/CIP1 expression and activation of the p53-mediated apoptotic pathway, leading to apoptosis or premature senescence. In the absence of stimulation, p53 can promote the expression of Mdm2 while, conversely, Mdm2 reduces the activity of p53. p21 is downstream of p53, and its expression blocks progression of the cell cycle, promotes apoptosis and increases the sensitivity of tumor cells to chemotherapy (102). Mdm2 promotes the proteasome-mediated degradation of p21 and also reduces the stability of p21 by binding with it. When Mdm2 expression is downregulated, the expression of p21 protein increases (Fig. 4).

Research has focused on investigating the involvement of the ARF-Mdm2-p53-p21 pathway in natural states as well as those involving premature senescence (103). Notably, one study showed that the loss of p14 (ARF) expression in patients with prostate cancer was positively associated with an increased risk of disease recurrence and metastatic disease (104).

S-phase kinase-associated protein 2 (Skp2) and p27. Skp2 is a member of the F-box family, which mediates cell cycle regulation and cell proliferation by degrading cell cycle regulatory proteins, including p27, p21, p53, cyclin A, cyclin E and cyclin D. The Skp2 gene is an important regulator of the cell cycle, which interacts with the S-phase kinase cyclin A-CDK2 (cyclin dependent kinase 2) complex. The expression levels of Skp2 are very low in the G1/G0 phase, but increase markedly in the S phase. An important substrate of Skp2 in the cell division cycle is p27 (105). p27 is an important member of the CDK family; p27KP1 is a protein encoded by the CDKN1B gene. As a negative regulator of the cell cycle, p27KP1 inhibits the activity of CDK complexes to coordinate the cell cycle, DNA replication and DNA repair (106,107). In a study in which 68 cases of non-small cell lung cancer tissues were compared with normal bronchial epithelial cells using tissue microarrays and immunohistochemistry, the results revealed that Skp2 was only expressed in the lung cancer tissues while p27KP1 was expressed in both normal bronchial epithelial cells and lung cancer cells (108). In addition, the expression of p27KP1 was found to be significantly downregulated in Skp2-positive cells and negatively correlated with Skp2 expression. In another study, Shapira et al (109) analyzed the expression of Skp2 and p27KP1 in the tissue sections of 80 patients with colorectal tumors using immunohistochemistry, and found that Skp2 overexpression was significantly associated with the loss of p27KP1 expression and cell differentiation.

Skp2 may contribute to a malignant phenotype, and the overexpression of Skp2 protein results in the accelerated hydrolysis of p27 and deterioration of tumor cells (110). Since
Skp2 can degrade p27kip1 and promote tumor development, interference with the Skp2-p27kip1 pathway may induce tumor senescence (111).

**Lamin B receptor (LBR).** The LBR is an integral membrane protein of the interphase nuclear envelope. Its N-terminus protrudes into the nucleoplasm where it binds to lamin B and heterochromatin; these interactions are disrupted during...
mitosis (112). A number of studies have indicated that chromatin and chromatin proteins are involved in cellular senescence (113,114). For example, the altered expression of lamins A/C and B, which form the nuclear lamina, as well as altered heterochromatin structures have been observed in senescent cells (115,116). In addition, the expression of lamin B1 (LB1) in WI-38 cells was found to decrease during cellular senescence, and the silencing of LB1 slowed the proliferation of these cells and induced premature senescence. These effects were accompanied by a reduction in p53-dependent ROS, which was repaired by growth under hypoxic conditions (15).

In addition to the aforementioned senescent pathways, studies have demonstrated that inhibition of the ERK and AKT pathways can reduce the number of senescent cells, with ERK and AKT potentially acting through the ETS variant transcription factor 6 and forkhead box O1 genes (117-120). As such, drugs that target and disrupt downstream effectors of ERK and AKT have been proposed as new therapeutic methods. It has also been demonstrated that oxytocin can alleviate cell senescence through ERK/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling; this implies that interference with the ERK/Nrf2 pathway may induce cell senescence (121). Furthermore, the inhibition of mTORC1 has been shown to prolong the lifespan of yeast, worms, fruit flies and some mice, suggesting that mTORC1 may also be a novel target for inducing cell senescence and treating various types of cancer (122).

7. Conclusions

Cellular senescence and apoptosis are two equally important endpoints when cells respond to stress. As senescence acts as a major tumor suppressor mechanism, it has a number of advantages over apoptosis when dealing with damaged cells. While apoptosis permanently removes cells, senescence arrests them in a functional but non-dividing state, which may provide a persistent signal of oncogenic stress and thereby promote immune surveillance (123). The absence of senescence or apoptosis leads to treatment failure. A number of pathways have been found to activate senescence; however, the phenomenon is interesting in that although chemotherapeutic drugs induce tumor cell senescence, they also promote tumor progression by inducing the secretion of certain matrix metalloproteinases, growth factors and cytokines (12), which may lead to tissue remodeling, organ senescence and many age-related diseases. Processes such as cellular senescence and telomere shortening, which protect against cancer, may accelerate the aging process. Various diseases have been found to have an association with cell senescence, including tumors, idiopathic pulmonary fibrosis, hypertension, Parkinson's disease and diabetes.

A number of pathways are shared between the initiation of cell senescence and tumorigenesis in wound healing and cancer development, such as the activation of proto-oncogenes (124). Cell senescence and tumorigenesis have incidence rates that increase with age. The transient presence of senescent cells is beneficial during normal tissue repair, but the accumulation of these cells can have an adverse effect on local tissue homeostasis due to their pro-inflammatory properties (125-130). Even though senescence strongly inhibits tumorigenesis when initially induced (131-135), the prolonged presence of senescent cells is often associated with malignant cells and supports the expansion of tumors (69). Therefore, whether cell senescence promotes or inhibit tumors varies according to the stage of occurrence, the genetic background and the tissue. Cellular senescence prevents the development of tumors in the early stages of life, but also results in the deterioration of bodily processes. At later life stages, cellular senescence drives the occurrence of a senescence phenotype and age-associated diseases, including various degenerative diseases and a range of hyperplastic diseases. SASP-associated proteins have conflicting effects on cells within the body, indicating that cellular senescence has both favorable and unfavorable consequences during the development of cancer (69,136,137). These proteins inhibit the development of tumor cells and remove abnormal and damaged cells from the body. In addition, senescent cells induce paracrine senescence in neighboring cells through the SASP, which acts as a barrier against tumor growth. By contrast, the SASP promotes the occurrence and development of tumors under certain physiological conditions, by making tumor cells tolerant to chemotherapeutic drugs (138). Further studies are required to investigate how the senescence of tumor cells can be induced or inhibited during treatment. However, the production of WNT16B and secreted frizzled related protein produced in an aged or genotoxin-treated tumor microenvironment has been found to protect cancer cells from chemotherapy in a paracrine manner (139,140).

Although the inhibition of telomerase activity and induction of tumor cell senescence is a theoretically feasible approach for the treatment of tumors, certain issues must be overcome for its practical application. In particular, the telomerase activity in certain tumors is very low, and thus the inhibition of telomerase activity may not be effective for these tumors. Conversely, some normal cells possess telomerase activity (141,142). In such cases, the inhibition of telomerase activity may cause adverse effects and undesirable results.

Senescence serves as a new strategy for the prevention tumors and their treatment. However, it would be beneficial to identify means for inhibiting the senescence of normal cells and prolonging life span whilst also promoting the senescence of tumor cells to treat cancer. In addition, the achievement of an effective balance between the reduction of abnormal proliferation and slowing down of senescence is important, to make good use of the double-edged sword of cellular senescence.

Acknowledgements

Not applicable.

Funding

This review was supported by Yunnan Fundamental Research Projects (grant no. 202001AU070141) and Yunnan Key Laboratory of Pharmacology for Natural Products Open grant (grant no. 2019G005).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.
Authors’ contributions

GW, YJ and CQ designed and conceived the review and contributed to critical reading of the manuscript and editing. XC, YL and JZ participated in drafting the manuscript and performed the literature review. GW and YJ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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