Mechanism and Potential of Senolytics in Tumour Microenvironment

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Abstract. Senescent cells (SnCs) produce stress response and enter a state of proliferation arrest under the action of drug radiotherapy and chemotherapy, and secrete senescence related secretory phenotype (SASP), which can participate in the remodeling of tumor microenvironment (TME) through the secretion of inflammatory factors and cancer-promoting factors. The influence of cell senescence on tumors is complex, which has both tumor inhibitory and tumor promoting effects. This study shows that senescent cells are responsible for the tumor promotion mechanism. Senolytics appears as a drug that selectively clears senescent cells. It induces apoptosis by targeting the upregulated anti-apoptotic pathway in senescent cells (such as the BCL-2 family), thereby reducing the accumulation of senescent cells, inhibiting the negative effects of SASP, and improving the TME. Enhance the efficacy of anti-cancer therapy and explore the adverse effects of Senolytics in the TME, aiming to provide new ideas and strategies for future Senolytics therapy optimization and treatment of cancer.

Keywords: Senolytics, cellular senescence, SASP (senescence associated secretory phenotype), immune regulation, tumour therapy.

1. Introduction

Cellular senescence refers to a persistent condition of cell cycle arrest [1], typically induced by stressors like DNA damage, oxidative stress, or signals that promote carcinogenesis. This process results in the development of a senescence-associated secretory phenotype (SASP), characterized by the release of various cytokines, chemokines, and proteases. Studies have shown that senescent cells play a dual role in the tumour microenvironment (TME)： On the one hand, SnCs may play the role of anti-tumour by inhibiting the proliferation of tumour cells. In the stage of tumoure inhibition, SASP can activate the immune surveillance function, promote the infiltration of CD8+ T cells, and enhance the anti-tumoure immune response [2]; But on the other hand, long-existing senescent cells may also promote tumour growth and metastasis through SASP. In the tumour stage, SASP induces chronic inflammation, protease and growth factors by secreting pro-inflammatory factors (such as IL-6), promoting tumour proliferation, migration and invasion. In the meantime, SASP factors can also promote epithelial-mesenchymal transformation and induce enhanced tumour cells invasiveness. In additionThe accumulation of senescent cells converts the tumour microenvironment into cancer-promoting'soil' and enhances the tumour's therapeutic resistance. Senolytics are a class of drugs that selectively eliminate senescent cells. The targeted removal of these cells can help to avoid the buildup of senescent cells, demonstrating significant promise in the realm of cancer therapy in recent years. The tumour microenvironment is a complex ecosystem composed of tumour cells, stromal cells, extracellular matrix and cytokines [3]. The dynamic changes of the tumour have important influence on the aggressiveness, metastasis and treatment response. Senolytics selectively eliminate senescent cells by targeting their anti-apoptotic pathways, thereby reducing the negative effects of SASP, improving the tumour microenvironment and enhancing the efficacy of anticancer therapy. This study aims to explore the mechanism of action of senolytics in TME and how it inhibits SASP and tumoure growth, and explore its application prospects in different cancer types. This will provide a theoretical basis for the development of novel senolytics and tumoure therapeutic strategies, and promote the further development of tumour therapeutic field.

2. Classification and Mechanism of Senolytics

2.1. Classification of Senolytics

2.1.1 Navitoclax

Navitoclax (ABT-263) acts as an inhibitor for BCL-2 and BCL-XL, while MCL-1 remains unaffected. It can notably diminish the interaction between BCL-XL and BAX, demonstrating anti-tumour efficacy in various tumour models. In particular, it was effective in clearing treatment-induced senescent cells. A study has shown that after cisplatin-based chemoradiotherapy induced cellular senescence in head and neck cancer (HNSCC), the use of senolytic drugs can be used to eliminate the aging tumour cells that remain after chemotherapy, potentially delaying disease recurrence in patients with HNSCC. The reason is that after cisplatin treatment, HNSCC cells show the typical characteristics of aging, including increased SA-β-gal (age-related β-galactosidase) activity, cell morphological changes, heterochromatin focus (SAHF) formation, and up regulation expression of secretory phenotypic (SASP) related factors (such as IL-6, IL-8, IL-1, etc.).Moreover, an interaction occurs between BCL-XL and BAX in senescent cells induced by cisplatin, and the compound ABT-263 can notably diminish this interaction while activating the pro-apoptotic activity of BAX [4], consequently inducing apoptosis in tumour cells. Therefore, it is speculated that ABT-263 could serve as a cornerstone for preclinical studies of senolytic drugs, and it shows promise as a treatment for both liquid and solid tumours.

2.1.2 Dasatinib

Dasatinib can block the function of Bcr-Abl and Src family kinases, along with receptors and non-receptor tyrosine kinases, in addition to signaling protein kinases. It also serves an anti-tumour purpose in numerous aggressive blood cancers and solid tumours. Studies have shown that dasatinib has strong anti-growth, anti-angiogenic, and pro-apoptotic effects on human oral cancer cells [5]. Dasatinib had a concentration-dependent effect on inhibiting the proliferation of different oral cancer cell lines. HIF-1α is highly expressed in YD-38 cells, which plays a crucial role in the oral cancer microenvironment. Dasatinib acts in the microenvironment by reducing HIF-1α stability, inhibiting angiogenesis, regulating apoptosis-related proteins, and blocking important signaling pathways, which in turn restricts the growth and development of oral cancer cells. Oral squamous cell carcinoma (OSCC), recognized as the prevalent form of oral cancer, is generally located in a low-oxygen environment that induces the activation of HIF-1α (hypoxia-inducible factor-1α), a crucial transcription factor that governs the expression of numerous genes linked to tumour growth, angiogenesis and cell viability. In the microenvironment of OSCC, a high level of HIF-1α expression is linked to tumour progression and an unfavorable prognosis. Treated YD-38 cells or human umbilical vein endothelial cells (HUVEC) showed decreased expression and stability of HIF-1α, reduced tumour angiogenesis capacity, and increased expression of GRP78 (endoplasmic reticulum stress marker) and eIF-2α (translation inhibitor), tumour cells proliferation was inhibited and apoptosis was promoted. Dasatinib additionally suppressed the phosphorylation of Src, EGFR, ERK1/2, and various other signaling pathways, which may diminish the proliferation and viability of OSCC cells.

2.1.3 Quercetin

Quercetin is widely found in various vegetables, fruits and liquor, and has significant anti-proliferation and pro-apoptotic activities. Quercetin has the potential to suppress CYP3A activity, leading to a reduction in epoxyeicosatrienoic acids (EETs) derived from arachidonic acid (AA) metabolites, consequently hampering p-Stat3 and nuclear translocation, thus impeding BC development [6]. Furthermore, quercetin could inhibit the progression of BC by inducing apoptosis, inhibiting cell migration and invasion, and regulating immune cells and extracellular matrix in the tumour microenvironment. Breast cancer cells express CYP3A4, a cytochrome P450 enzyme that metabolizes AA to produce EET, and then EETs indirectly affect the phosphorylation and

transcriptional activity of Stat3 through effects on intracellular signalling pathways, thereby promoting breast cancer cell growth. However, quercetin can directly bind to CYP3A4 to inhibit its enzyme activity. This inhibition reduces EETs produced by AA metabolism, further inhibits Stata3 and attenuates the phosphorylation and transcriptional activities of Stata3. (Fig.1)

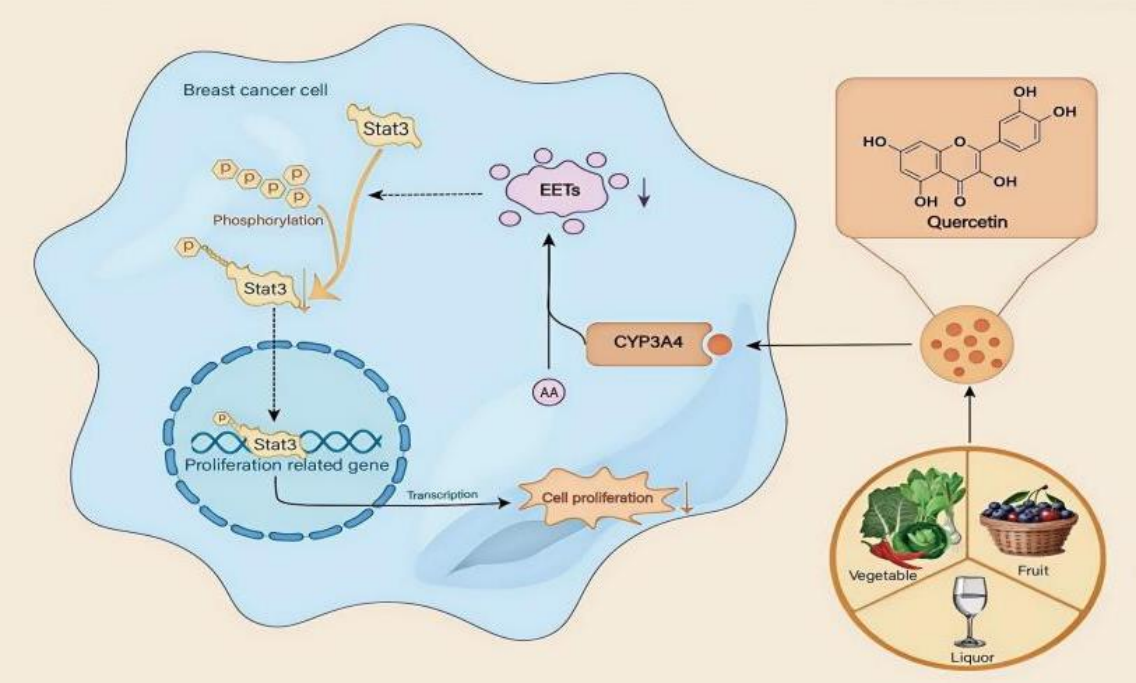

Fig. 1. Schematic diagram of the molecular mechanism of quercetin inhibiting breast cancer progression by inhibiting CYP3A4 activity [6].

Quercetin can also suppress the polarization of tumour-related macrophages (TAMs) and reduce the number of immunosuppressive cells (like regulatory T cells), and improve the anti-tumoure immune response and inhibit the expression of MMP2 and MMP9. Reducing the degradation of extracellular matrix and regulating the tumour microenvironment may impede tumour cells' ability to migrate and invade, which can be speculated to achieve the purpose of treating BC.

2.1.4 Fisetin

Fisetin is a natural flavonoid that inhibits tumour cells proliferation and induces apoptosis by targeting a variety of signaling pathways to inhibit tumour growth [7]. In pancreatic ductal adenocarcinoma (PDAC) cell lines, fisetin inhibits CDK1 by inhibiting CDK1-STAT3 signaling pathway, and may regulate the metabolic process of tumoure cells, reduce the number of pancreatic cancer stem cells, and ultimately suppress PDAC growth. Pancreatic cancer stem cells (CSCs) are a cell subgroup with high self-renewal ability and multidirection differentiation potential in pancreatic ductal adenocarcinoma, and they are crucial in the occurrence, progression, drug resistance, metastasis and relapse of PDAC. CDK1 is crucial in preserving the self-renewal and multidirectional differentiation capabilities of pancreatic cancer stem cells through cell cycle regulation and tumour cell proliferation promotion. Research indicates that fisetin can suppress CDK1's expression and activity of CDK1 by directly binding to the kinase pocket domain of CDK1, consequently hindering its subsequent STAT3 signaling route, diminishing the arid traits of pancreatic cancer stem cells. In addition to this, fisetin regulates the metabolic process of pancreatic ductal adenocarcinoma cells, affecting the supply of nutrients and the accumulation of metabolites in the microenvironment, thereby improving the acidic environment in the microenvironment, inhibiting the production and growth of pancreatic cancer stem cells, and ultimately potentially treating pancreatic ductal adenocarcinoma.

3. The Role of Senolytics in the Tumour Microenvironment

3.1. Regulate SAPS and Reshape the Mcroenvironment

Senescent cells remodel TME by secreting SASP. The composition of SASP is highly heterogeneous, including IL-6, IL-8, VEGF, etc. The secretion of SASP is affected by cell type, aging inducement and microenvironment. SASP has a bidirectional effect: The short-term direction promotes tissue repair and immune surveillance, but long-term accumulation leads to chronic inflammation, fibrosis and fosters the proliferation and emergence of diverse tumour cells. Furthermore, SASP is capable of recruit myeloid suppressor cells (MDSCs) and regulatory T cells (Tregs), thereby inhibiting the immune response against tumours, and form a tumoure-promoting microenvironment. For example, in HNSCC and OSCC, SASP activates NF-κB and other signaling pathways by secreting IL-6, IL-8 and other inflammatory factors, promotes the dry maintenance of tumour stem cells, enhances chemotherapy resistance and metastasis potential, and promotes the progress of tumour. However, the combination of dasatinib and quercetin in senolytics can reverse immunosuppression and enhance chemotherapy sensitivity by clearing senescent fibroblasts (CAFs) and tumour cells and reducing the release of SASP factors IL-6 and IL-8 [8]. In addition, navitociax can target BCL-2 family proteins to inhibit SASP-mediated MDSCs recruitment and T cell function, forming an inhibitory tumour environment. Also in breast cancer, the core factors of SASP, IL-6 and IL-8, enhancing cancer stem cells self-renewal and promote tumour recurrence and metastasis by activating STAT3 and NF-κB signaling pathways, but fisetin in senolytics, by clearing aged tumour cells and CAFs, promotes tumour recurrence and metastasis. Reduce IL-6 and IL-8 levels, inhibit the dryness of cancer stem cells and restore immune surveillance function, inhibit the growth of BC cells.

3.2. Senolytics can Reduce Treatment-Related Adverse Reactions

Recent studies have shown that chemotherapy and radiotherapy induce senescence of tumoure cells and normal tissue cells, and these senescent cells exacerbate tissue injury and inflammation by secreting SASP. Senolytics reduces tissue damage and inflammatory responses caused by chemotherapy and radiotherapy by clearing treatment-induced senescent cells. Navitoclax selectively clears chemotherapy-induced SnCs by inhibiting the BCL-2/BCL-XL anti-apoptotic protein family [9]. In mouse models, navitoclax significantly reduced radiotherapy-induced adverse reactions such as intestinal epithelial damage and pulmonary fibrosis, and enhanced the anti-tumour effect of chemotherapy agents such as cisplatin. Fisetin (natural Senolytic) has been shown to reduce doxorubicin-induced cardiotoxicity in breast cancer models. Doxorubicin (DOX) has been used as a chemotherapy agent in a variety of solid tumours and malignant tumours of the hematological system. However, the severe dose-dependent adverse reactions of DOX on the heart greatly limit its clinical application [10]. DOX induces cardiotoxicity through a variety of mechanisms, including iron overload, oxidative stress, inflammation and apoptosis. Fisetin can regulate the intake, storage and output of iron by activating SIRT1/Nrf2 signaling pathway to reduce iron overload. At the same time, fisetin can reduce the damage to cardiac cells caused by oxidative stress, protect the integrity of cell membrane and alleviate DOX-induced cardiotoxicity by scavenging free radicals and inhibiting the production of ROS.

4. Research Status of Senolytics

4.1. Progress of Senolytics Preclinical Research

Oncogene-induced senescent cells in precancerous lesions can inhibit the early tumour, but their long-term accumulation may drive malignant transformation through paracrine tumour promoting factors. Preclinical studies have shown that senolytics (such as ABT-263) can clear B-Raf mutation-induced nevus cells and senescent cells in pancreatic prelesions, reducing the risk of their transformation into aggressive cancer, and may become a new strategy to prevent malignant

transformation. Additionally, in older mouse models, Senolytics (such asa combination of dasatinib and quercetin) significantly improved physical fitness, reduced muscle atrophy, and extended healthy lifespan. In animal studies on vascular dysfunction and pulmonary fibrosis, senolytics has been shown to reverse pathological changes caused by the accumulation of SnCs. Idiopathic pulmonary fibrosis (IPF), a lethal condition, is marked by changes in the interstitial space [11], resulting in impaired lung function. The cellular senescencemarker was detected in IPF lung tissue, and studies have shown that fibrotic lung disease is partly senescent cell mediated. Senolytics (e.g. dasatinib, quercetin, ABT-263) clearing senescent cells has demonstrated efficacy in diminishing pulmonary fibrosis in mouse models and is currently entering to clinical trials. Senescent cells in IPF affect neighboring fibroblasts by secreting a variety of cytokines, chemokines, matrix remodeling proteases and other factors, making them more susceptible to aging and activation, thus promoting the development of fibrosis.Moreover, the accumulation of SnCs further aggravates the disturbance of microenvironment. Senolytic (such as dasatinib) in microenvironment, Bcl-2 family proteins are usually highly expressed, protecting normal cells from apoptosis while selectively eliminating senescent cells. Dasatinib can inhibit the anti-apoptotic function of the BCL-2 family, making senescent cells more prone to apoptosis, reduce cell accumulation, improve the microenvironment, and thus alleviate fibrosis.

4.2. Combination Therapy Strategy Based on Senolytics

4.2.1 "One-Two Punch" therapy

"One-Two Punch" therapy is a phased treatment strategy in which the tumour cellular senescence is induced using pro-aging drugs such as CDK4/6 inhibitors, and the SnCs is eliminated using senolytics. The accumulation of senescent cells caused by conventional chemotherapy can be avoided. Clinical doses of cancer therapy can induce tumour and normal tissue aging while completing tumour cells killing (first punch), selective elimination of treatment-induced SnC with subsequent hit-and-run administration of senolytics (second punch) prevents tumour recurrence, metastasis and drug resistance to treatment, which has been validated in multiple tumour models [12]. For example, tumour cellular senescence induced by chemotherapy for lymphoma is followed by the use of metabolically senolytic drugs to block glucose utilization or autophagy to clear senescent cells. Through this combination therapy, chemotherapy-induced SnCs accumulation can be reduced. This reduces the risk of tumour recurrence and metastasis. Similar strategies have also been used to enhance the anti-tumour effect after radiation or chemotherapy.

4.2.2 In Combination wth Paclitaxel

Paclitaxel inhibits the tumour cell by interfering the dynamic balance of microtubules, such as the proliferation and induction of apoptosis of colorectal cancer [13]. However, drug resistance is an important issue faced by paclitaxel in the treatment of colorectal cancer. Natural senolytics (such as fisetin, quercetin) can increase the sensitivity of colorectal cancer cells to the drug paclitaxel through the regulation of intracellular signalling pathways. Meanwhile, fisetin can block the proliferation and epithelium-mesenchymal transformation of colorectal cancer cells by inhibiting the PI3K/AKT/mTOR and WNT/β-catenin pathways. In animal studies, fisetin significantly reduced tumour load in liver metastatic models of colorectal cancer. In addition, paclitaxel often causes intestinal mucosal damage, while quercetin can reduce oxidative stress through antioxidant effects, and fisetin can inhibit the accumulation of intestinal senescent cells, which may alleviate diarrhea and inflammation.

5. The Sortcomings of Snolytics

5.1. Specificity and Side Effects of Senolytics

Although senolytics shows significant potential in cancer treatment, its specificity and side effects remain questions to be addressed. At present, first-generation senolytics (such as navitoclax, dasatinib+quercetin combination) have shown some side effects in early clinical trials due to improper

dosage, including thrombocytopenia, lung complications, and gastrointestinal reactions. Animal studies have shown that the dose-specificity of senolytics is critical for efficacy, with dasatinib requiring a dose of 5mg/kg to clear senescent cells in retinal ganglion cells (RGCs) in mouse models, while the human equivalent dose is only about 0.4 mg/kg. These differences suggest that the metabolic differences between species may affect the targeting efficiency of the drug, and the dose should be carefully adjusted in clinical application. Therefore, the adverse reactions should be closely monitored during treatment, and the development of senolytics with lower toxicity and more targeted is one of the future research directions.

5.2. Long-term Effects of Senolytic Drugs and Drug Resistance

The long-term effects of senolytic drugs and drug resistance are also concerns. Current senolytics research is mainly based on animal models or short-term human trials, and the effects of long-term use are still unclear. For example, fisetin has shown anti-inflammatory and senescent cell clearing effects in experiments, but its long-term safety, especially in the elderly or those with chronic diseases, has not been fully validated. Research indicates that senolytics markedly decrease senescent cell count, improve TME, and inhibit tumoure growth in the short term. However, long-term single use of senolytics may lead to the generation of drug resistance [14], affecting its therapeutic effect. Future studies could also further explore the use of senolytics in combination with other therapeutic strategies to optimize its clinical application strategy.

6. Discussion

Here, the study describes the therapeutic effect of senolytics on tumour types and the impact on SASP, and presents the shortcomings of senolytics and the regimen of combination medication. Future studies should first focus on optimizing the drug design of senolytics to improve its targeting and safety. This study proposes that senolytics based on nanotechnology can first be developed to improve the targeting and bioavailability of drugs. For example, functional magnetic nanoparticle loading senolytic drugs that have been developed can be utilized [15]. Targeted enrichment of senescent cells in the microenvironment by enhancing osmotic and retention effects (EPR effects). Moreover, the combined application of senolytics with other anticancer drugs is a hot research topic in the future. Studies have shown that senolytics (such as ABT-263) can remover chemotherapy-induced senescent cells in pancreatic cancer models. Thus enhancing the efficacy of gemcitabine and other chemotherapy drugs. Ultimately, large-scale clinical trials will be critical to validate the safety and efficacy of senolytics in cancer treatment, emphasis should be placed on meticulously designed clinical trials to assess how senolytics perform in different cancer typ. It is helpful to develop a personalized senolytics treatment plan by analyzing the characteristics of senescent cells and TME status of patients.

7. Conclusion

In recent years, selective tumour removal senescent cells on senolytics have shown promising results in preclinical studies, and they show significant therapeutic potential in tumour microenvironment. The tumour microenvironment was improved and tumour growth and metastasis were inhibited by removing SnCs, regulating SASP and enhancing immune surveillance. However, the application of senolytics still faces many challenges, such as drug side effects, drug resistance, long-term effects and lack of clinical trials. Future studies should further explore the mechanism of action of senolytics, carry out extensive clinical trialsto assess senolytics' safety and effectiveness in cancer therapy, optimize its clinical application strategies, and provide new ideas and methods for cancer therapy. It is committed to the exploitation, cure and improvement of drug resistance of novel senolytics, focusing on optimizing the targeting and combination therapy strategies of senolytics to fully realize its potential in cancer therapy.

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