# Chapter 5
# Senotherapy of Cancer


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**Abstract** Cellular senescence is a stress and repair response that protects us from cancer and contributes to tissue homeostasis by inducing a stable cell cycle arrest and imposing a secretory phenotype. Senescent cells are held in check to avoid their aberrant proliferation while at the same time they serve as new signaling nodes to orchestrate tissue repair and to reestablish homeostasis in damaged tissue. Chemotherapeutic drugs can induce senescence in cancer cells and, although restricting tumor growth, senescence can also have negative consequences for cancer therapy. Senescent cancer cells remaining after chemotherapy might represent a risk of tumor relapse and secrete a huge number of soluble factors known as SASP with detrimental activities that can alter the tumor microenvironment. In addition, induction of senescence in the normal surrounding tissue can produce severe side effects. In recent years, we have deciphered many aspects of the process of cellular senescence that can help us apply this response in our benefit. In particular, we have identified anticancer drugs that can induce a potent senescence response in cancer cells, we are learning how to modulate the SASP to avoid the negative effects, and we have found vulnerabilities in senescent cancer cells that allow their specific cell killing by senolytic compounds. In summary, we are in a position to start considering the possibility of developing effective senotherapies of cancer.

**Keywords** Cellular Senescence · Cancer · Senolytics · Senotherapy

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## 5.1 Cellular Senescence in Cancer

Senescence is a cellular state defined by a stable cell cycle arrest and the acquisition of characteristic molecular and morphological features. Senescent cells are enlarged and flattened, contain numerous lysosomes with increased beta-galactosidase activity, lack proliferation due to the expression of high levels of cell cycle inhibitors, secrete huge amounts of soluble factors, and show heterochromatic foci and DNA damage. It was originally described after prolonged in vitro culture of human normal diploid cells and considered to represent the exhaustion of the predetermined replicative potential of cells (Hayflick and Moorhead 1961). As such, senescence was linked to the process of aging. The accumulation of senescent cells in multiple tissues is associated with pathological and normal aging (Childs et al. 2017; McHugh and Gil 2018). Already in the initial description of cellular senescence it was clear that this process took place in normal non-transformed cells, but not in tumor derived cancer cells, suggesting that cancer cells were not under the control of senescence. This differential response of normal and tumor cells suggested that senescence was a process involved in limiting the indefinite proliferation of cells to avoid the emergence of cells accumulating unrepaired damage.

### *5.1.1 Tumor Suppressive Function of Senescence*

The observation of a sudden induction of senescence in normal primary cells after the introduction of an activated HRAS oncogene led to the notion of cellular senescence as a tumor suppressor mechanism (Serrano et al. 1997). The molecular players involved in this response, p16 and p53, were the same ones described to operate during the so-called replicative senescence on in vitro serially passaged cells, and the morphological change undergone by the RAS-expressing cells was identical to the one experienced after replicative exhaustion. Cells expressing single activated oncogenes do not show any of the typical features of transformed cells and the combination of two (in the case of mouse cells) or more (in human) oncogenic events are required to achieve fully transformed cells (Hahn and Weinberg 2002). Cultures of cells expressing oncogenes tend to show an initial phase of hyperproliferation followed by massive induction of apoptosis and/or senescence. Overcoming these cellular protective responses is a requisite of cancer cells to successfully become a tumor. Indeed, two of the initially recognized hallmarks of cancer in the classical review by Hanahan and Weinberg are the bypass of apoptosis and the acquisition of indefinite replicative potential, highlighting the crucial role played by apoptosis and senescence as barriers against cancer progression (Hanahan and Weinberg 2000). The identification of the senescence response in vivo on mouse models of oncogenic activation and in human samples from preneoplastic tissue, as well as the tumor prone phenotype of animals lacking some of the crucial regulators of senescence (e.g. p16 and p53) clearly established cellular senescence as a robust barrier restricting tumor

development (Braig et al. 2005; Chen et al. 2005; Collado et al. 2005; Lazzerini Denchi et al. 2005; Michaloglou et al. 2005). Oncogene activation in vivo does not lead to the immediate growth of a tumor. After an initial phase of hyperproliferation, oncogenically-damaged cells enter senescence, restricting cancer development. Premalignant lesions are composed of a mixed population of cells undergoing senescence and/or apoptosis and bypass of these defensive responses is absolutely required for tumors to advance on their road to full malignant transformation (Collado and Serrano 2006).

### *5.1.2 Pro-Tumor Activity of Senescence*

Despite being growth arrested, senescent cells are metabolically active and are characterized by a particular secretory phenotype known as SASP (Senescence-Associated Secretory Phenotype) (Coppé et al. 2008). Among the different molecules released by senescent cells there are a great number of pro-inflammatory cytokines and chemokines (e.g. IL6, IL8, CXCL1…), matrix remodeling enzymes (e.g. MMP1, MMP3, PAI-1…), and growth promoting factors (e.g. HGF, Epiregulin, Amphiregulin…). The putative pro-tumoral nature of these secreted factors seemed perplexing when considering the known antitumor effect of senescence. Reports from different laboratories have confirmed this pro-tumorigenic activity of the SASP (Krtolica et al. 2001; Angelini et al. 2013). Already when SASP was first identified, it was shown that premalignant epithelial cells exposed to SASP factors from genotoxic-induced senescence experienced an epithelial-mesenchyme transition and enhanced invasiveness, both hallmarks of malignant tumor cells (Coppé et al. 2008). Similarly, stromal senescent cells that accumulate during aging seem to be capable of conditioning the niche in the bone through secreted factors to promote metastasis development (Luo et al. 2016). This is in contrast with other reports showing induction of paracrine senescence in cells exposed to secretions of senescent cells (Acosta et al. 2008). We should be cautious when considering the putative role of SASP regarding tumor promotion or prevention; these relative effects could be influenced by cell type, senescence-inducing stimulus or time scale at which the different SASP factors are produced (Chan and Narita 2019). As already mentioned, the SASP is a complex and dynamic phenotype that evolves in composition with time from immunosuppressive and profibrotic to proinflammatory and fibrolytic activities, affecting surrounding cells in a beneficial or detrimental fashion according to the nature of these signals and the state of the recipient cells (Ito et al. 2017).

## 5.2 Chemotherapy-Induced Senescence

Even though cancer cells require bypassing the senescence barrier on their road to malignant transformation to achieve unlimited proliferative potential, the cellular senescence response can still be engaged if cancer cells receive the appropriate stimulus. This is evidenced for example using mouse models of inducible oncogenic activation in which shutting off the oncogene in an already established tumor leads to the control of tumor progression through induction of senescence (Wu et al. 2007). Similarly, tumors developed in the absence of crucial tumor suppressor genes such as p53 are restricted and even disappear after induction of senescence (Xue et al. 2007; Ventura et al. 2007). Interestingly, this senescence response is triggered only on the tumor cells and not in normal cells that are also deficient in p53. This potent tumor restrictive activity of senescence induction on tumor cells led many to consider the possibility of developing a prosenescence therapy of cancer (Serrano 2007).

### *5.2.1 Drugs Inducing Senescence Limit Tumor Growth*

We now know that senescence can account for the beneficial response of cancer cells to chemotherapy. Establishing a senescence index by measuring a set of senescence markers on samples obtained at the time of colorectal cancer diagnosis demonstrated that the presence of senescence in the tumor lesion, previous to the treatment, correlated with a better therapeutic response (Haugstetter et al. 2010). On the other hand, the identification of senescence markers in vitro using cellular models of chemotherapy-induced senescence was further corroborated on samples derived from tumors from cancer patients that had been subjected to chemotherapy prior to surgery (te Poele et al. 2002; Roberson et al. 2005). In support of these data, the reevaluation of the effects on senescence of classic chemotherapeutic agents using mouse models of cancer revealed that this was a crucial component of the therapeutic effects of these drugs (Schmitt et al. 2002). This pro-senescence response was not intended when these anticancer drugs were originally developed because chemotherapy of cancer has traditionally been designed with the basic idea of killing tumor cells in the most effective way, and as selective as possible.

However, cytotoxic chemotherapy might be limited by the extend of cancer cell death achieved with the use of these drugs, the heterogenous state at which cancer cells are present within the tumor, and many other factors influencing chemotherapy success. The induction of cancer cell senescence could represent an alternative approach with beneficial effects for cancer therapy. For this, we would need to identify drugs inducing a potent cellular senescence response or develop new ones selected for their senescence-inducing potential (Fig. 5.1). Although there are a number of known chemotherapeutic agents that have been identified as capable of inducing cellular senescence in cancer cells, such as doxorubicin, etoposide, bleomycin, etc. (Liu et al. 2019), we still lack in depth information regarding the mechanisms involved

and the clinical relevance of inducing senescence in the context of cancer treatment. Reevaluating known anticancer drugs for their potential senescence-inducing activity could also provide clues about their potential use on a prosenescence therapy of cancer. This is the case, for example, of recently developed CDK4/6i (Palbociclib and Abemaciclib) (Llovet et al. 2016; Torres-Guzmán et al. 2017). These drugs have been shown to elicit a senescence response in pre-clinical and clinical settings (Llovet et al. 2016; Gong et al. 2017). A more recent example is provided by poly (ADP-ribose) polymerase 1 inhibitors (PARPi). These drugs have been developed and are in clinical use for ovarian and breast cancer and have been recently shown to induce a strong senescence response in cancer cell lines of these tumor types (Fleury et al. 2019).

To discover new drugs inducing cancer cell senescence we will need to screen for compounds with this activity or identify potential targets that can be drugged to trigger senescence in cancer cells. There are some recent elegant examples of high-throughput genetic and compound screenings to develop cancer cell senescence-inducing drugs. Using a CRISPR library targeting enzymes involved in remodeling of chromatin and in the modulation of epigenetic marks it was possible to show that suppression of SMARCB1, a component of the SWI/SNF nucleosome remodeling complex, induces senescence of melanoma cells (Wang et al. 2017). Similarly, a CRISPR library targeting kinases identified several kinases required for proliferation of p53-mutant liver cancer cells. Among them, inhibition of CDC7 using a chemical inhibitor induced cellular senescence specifically in liver cancer cells, suggesting that this kinase could be used as a potential target to develop a senogenic cancer therapy (Wang et al. 2019). On the other hand, using compound screening, multiple aurora kinase inhibitors were shown to possess strong senescence inducing activity on RAS mutant lung cancer cell lines (Wang et al. 2017).

### *5.2.2 Senescent Cancer Cells Fuel Malignant Growth*

Apart from the proposed non-cell autonomous negative effect of senescence over premalignant or malignant cells in their vicinity by SASP factors, tumor cells can also be fueled by the senescence program when they escape from the tight cell cycle control (Milanovic et al. 2018; Achuthan et al. 2011). Chemotherapy-induced senescence of cancer cells has been shown to induce pathways similar to those that are typical of a stemness state. When these cells escape the control of senescence, they manifest an increased malignancy with respect to their parental tumor cells. This reinforced tumorigenic potential seems to be related with the activation of the Wnt pathway during chemotherapy-induced senescence and, accordingly, inhibition of Wnt leads to a reduced tumorigenicity of these “cancer stem cell-like” escapees. A similar pro-stemness activity of senescence cells has been linked to the SASP. Senescence induction alters surrounding cells increasing their plasticity and promoting their regenerative potential and cell reprogramming to pluripotency (Rhinn et al.

2019; Mosteiro et al. 2016). This state can be triggered by chemotherapeutic drugs but can also result from oncogenic induction (Rhinn et al. 2019; Ferreirós et al. 2019).

### *5.2.3 Secondary Effects of Cancer Therapy Mediated by Senescence Induction*

Chemotherapy and radiotherapy of cancer is unfortunately associated with devastating secondary effects due to the unspecific targeting of normal cells. Tissues subjected to the harsh action of anticancer therapies frequently accumulate damaged cells that have undergone apoptosis or senescence. There is now mounting evidence that these senescent cells contribute to the adverse effects of chemotherapy and radiotherapy. The analysis of p16INK4A expression levels, a classical marker of cellular senescence, in CD3+ lymphocytes in the blood of breast cancer survivors revealed that adjuvant chemotherapy of breast cancer promotes aging by inducing cellular senescence (Sanoff et al. 2014). Similarly, irradiation of normal tissues is known to induce cellular senescence and to cause for example pulmonary fibrosis or loss of salivary gland function during radiotherapy of lung or head and neck tumors (He et al. 2019; Marmary et al. 2016). These negative effects are considered to be mediated by the secretion of pro-inflammatory factors present in the SASP that cause a low level chronic inflammatory environment. Transgenic mice that allow visualization of senescent cells revealed the induction of senescence after treatment with the anthracycline Doxorubicin (Demaria et al. 2017). These animals suffer from systemic inflammation that results in bone marrow suppression, cardiac dysfunction, fatigue and even cancer recurrence. All these adverse effects derive from senescence induced by chemotherapy on normal cells and model the response of cancer patients to treatments (Fig. 5.1).

## 5.3 Senolytics as Antitumor Adjuvant Therapy

Senescent cells present a particular expression profile, part of which consists on the secreted factors that form the SASP and on the expression of cell cycle regulators responsible for the cell cycle arrest. Apart from these typical hallmarks of the process, cellular senescence is characterized by an increased resistance to apoptosis (Childs et al. 2014). This seems to rely, at least in some settings, on an upregulated expression of the BCL-2 family of antiapoptotic proteins (Wang 1995). The use of chemical inhibitors of these antiapoptotic proteins, for example using ABT-263 or ABT-737, demonstrated the feasibility of inducing selectively the killing of senescent cells (Chang et al. 2016; Zhu et al. 2016; Yosef et al. 2016). There are other compounds with this activity, now collectively known as senolytics. Senolytic compounds such as Quercetin and Dasatinib are also thought to work by disarming senescent cells (Zhu

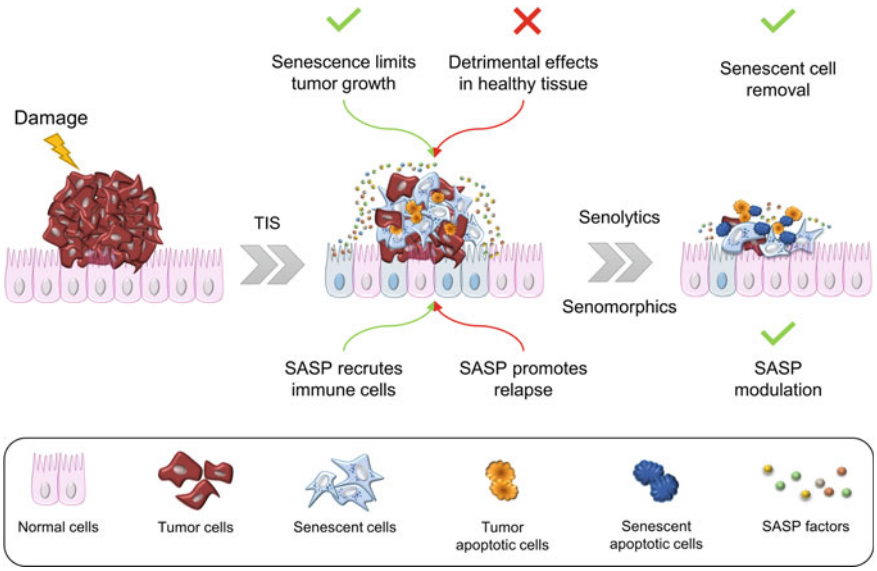


**Fig. 5.1 Senotherapy of cancer**. Chemotherapy and radiotherapy can induce cellular senescence as part of their action on tumor cells and this can have positive and negative impacts on cancer therapy derived from the cell cycle arrest and the SASP. Using senolytics to kill specifically the tumor and normal senescent cells, and senomorphics to modulate the SASP can contribute to the success of the therapy while reducing the secondary effects at the same time. TIS: Therapy-Induced Senescence. SASP: Senescence-Associated Secretory Phenotype

et al. 2015). In contrast, a novel family of broad spectrum senolytic compounds, the Cardiac Glycosides, seem to induce senescent cell killing by taking advantage of an acquired vulnerability of senescent cells derived from their membrane depolarization and disbalanced electrochemical gradient (Guerrero et al. 2019; Triana-Martínez et al. 2019).

Importantly, in vivo senolytic treatment has proved to provide therapeutic benefit in a number of age-related diseases and ultimately to lead to improved physical function and increased lifespan in mice (Brooks et al. 2018; Xu et al. 2018). The successful reports of in vivo use of senolytic compounds in the context of aging and age-related diseases open the possibility for a potential use as adjuvant therapy of cancer. In this sense, it is worth noting that some of these senolytics have been or are currently used in clinical trials for different neoplastic pathologies: ABT-263 was originally developed as an anti-cancer drug that failed to advance further due to the toxicity shown in patients during the early stages of clinical trials; Dasatinib, is a drug approved for clinical use in Chronic Myeloid Leukemia as an alternative to Imatinib; Cardiac Glycosides and Quercetin are currently being investigated as anti-cancer drugs in a number of neoplastic diseases in combination with other chemotherapeutic agents.

These potential treatments could be further improved by the specific targeting of senescent cells. Development of functionalized nanocarriers and formulations could increase the efficacy of the cytotoxic effect of senolytics while reducing their potential secondary effects. A nice example on this direction was provided recently with the encapsulation of senolytic compounds on mesoporous silica nanoparticles coated with galactose-based polymers to direct their delivery to senescent cells (Muñoz-Espín et al. 2018). This strategy also proved useful to label and monitor the fate of senescent cells in vivo.

### *5.3.1 A One-Two Punch Strategy Against Cancer*

Since current chemotherapy for cancer has been shown to induce a potent senescence response in tumor cells in many cases, several laboratories reasoned that it should be possible to induce senolysis of the senescent tumor cells as a strategy to remove these damaged tumor cells to avoid tumor relapse and to reduce the undesired secondary effects that could potentially derive from the SASP. This led to the proposal of a one-two punch therapeutic strategy for cancer based on the use first of a compound inducing senescence in cancer cells followed by a senolytic drug that would specifically kill these cells (Fig. 5.1). With this idea in mind, several laboratories have addressed the issue using different systems. Initially, it was shown that treatment of cancer cells with aurora kinase inhibitors such as Alisertib and Barasertib, previously identified on genetic and compound screenings as potent senescence inducers, sensitizes the tumor cells in vitro to a BCL-2 family inhibitor and senolytic compound, ABT-263, leading to their specific killing (Wang et al. 2017). A similar strategy has been followed more recently after identifying the kinase CDC7 as a potential target to induce senescence of p53-deficient liver cancer cells using a genetic screening. The use of XL413, a specific inhibitor of CDC7 (Koltun et al. 2012), proved that targeting this kinase induces senescence in the tumor cells (Wang et al. 2019). However, this induction of senescence does not sensitize the cancer cells to known senolytics such as ABT-263 or Dasatinib. Further investigation on the molecular mechanisms involved in senescence induced by CDC7 inhibition revealed that blocking the mTOR pathway selectively triggered apoptosis in the XL413-treated cancer cells. The combination of the senogenic XL413 with the mTOR inhibitor AZD8055, acting as a specific senolytic agent, proved more effective than monotherapy in xenograft models of cancer growth as well as in a genetic model of hepatocellular carcinoma, providing an elegant example of the combined use of genetic and compound screenings to identify vulnerabilities of specific cancer cells (Wang et al. 2019).

Another good example of the potential use of this one-two punch strategy against cancer was reported recently, when the reevaluation of the effect caused by PARPi on ovarian cancer cells revealed that they can induce senescence (Fleury et al. 2019). Using Olaparib and other PARPi in combination with ABT-263 proved synthetic lethality in vivo leading to a more effective anticancer treatment. PARPi treatment of cancer cells however results in an incomplete cellular senescence response. Stopping

PARPi treatment allows the resumed proliferation of the cancer cells. Interestingly, this unstable senescent-like state provides a window of opportunity for therapeutic treatment with senolytics since this transient growth arrest is sufficient to sensitize the cancer cells to the effect of ABT-263.

Finally, Cardiac Glycosides (CGs) have been reported to have broad-spectrum senolytic activity causing cytotoxicity on a wide range of tumor cells after exposure to different senescence-inducing chemotherapeutic agents (Guerrero et al. 2019; Triana-Martínez et al. 2019). Interestingly, CGs had been previously proposed as cooperating antitumor compounds in combination with classic chemotherapeutic agents. It is tempting to speculate that perhaps the repeatedly observed antitumor activity of CGs could be, at least in part, the result of their senolytic activity.

### *5.3.2 Alleviation of Secondary Effects by Targeting Senescence Cells*

As already exposed, chemotherapy of cancer can trigger the induction of senescence not only of the tumor cells but also of the normal surrounding tissue. Accumulation of these senescent cells actively secreting SASP factors could have detrimental consequences for the correct function of treated tissues (Demaria et al. 2017). The efficient elimination of these senescent cells could result on less toxic therapies by removing these damaged cells (Fig. 5.1). This possibility has been elegantly tested on a recent report in which they eliminated senescent cells produced by chemotherapy using a transgenic mouse model to target these cells or by treating animals with the senolytic ABT-263 (Chang et al. 2016; Zhu et al. 2016; Yosef et al. 2016). In both cases, removing normal senescent cells after treatment considerably decreased different parameters traditionally linked with secondary effects of chemotherapy, such as bone marrow suppression, cardiac disfunction, cancer relapse, and physical activity and strength. Furthermore, examining a senescence marker in T cells from cancer patients prior to chemotherapy showed that higher levels of the senescence marker correlated with increased risk of chemotherapy-induced fatigue.

Radiotherapy of cancer can also lead to secondary effects which have also been attributed to the induction of cellular senescence. For example, radiation-induced loss of salivary gland function or lung fibrosis after thoracic radiation have been shown to occur as a result of induction and accumulation of normal cells induced to senescence by radiation. In the case of the salivary glands it was possible to point to the SASP as responsible for this detrimental effect since IL6 modulation prevented the damage (Marmary et al. 2016). In the case of lung fibrosis, treatment of irradiated mice with ABT-263 after development of fibrosis reduced the number of senescent cells and reversed the disease (Pan et al. 2017).

## 5.4 Modulating the SASP to Improve Senotherapy

The composition and dynamics of the SASP are highly complex. Different molecules are released from senescent cells depending on the nature of the inducer, the cell type and the microenvironment (Coppé et al. 2010). Understanding this complexity is required to tease apart the different activities of SASP factors. The identification of key regulatory elements in the production of SASP factors could give us clues on how to modulate its activity to maximize the positive effects while avoiding the detrimental activities. This could lead to develop novel therapeutic compounds, known as senomorphics, that could be used to obtain therapeutic benefit by controlling the SASP in the context of cancer therapy (Fuhrmann-Stroissnigg et al. 2017) (Fig. 5.1).

There are now a number of reports showing how it is possible to alter the SASP without affecting the senescent cell cycle arrest. The first SASP regulator to be studied was NFkB (Chien et al. 2011). Chromatin proteomics identified p65 (also known as RelA), a member of the NFkB family, as an abundant protein associated with chromatin and regulating multiple genes during senescence, and among them, prominently SASP factors. When p65 is suppressed in vitro, senescent cells escape from immune recognition by natural killer cells and, when combined with p53 inactivation, senescence is bypassed. In vivo, using a mouse model of lymphoma development, inactivation of p65 leads to resistance to chemotherapy-induced senescence and reduced survival. These results demonstrate that NFkB controls cell intrinsic as well as cell extrinsic aspects of senescence and at least for some of these activities, it does so through its control of SASP production.

The SASP is also controlled by the inflammosome-mediated IL1 signaling (Acosta et al. 2013). Activation of this pathway during senescence leads to the production of SASP factors that can trigger senescence in a paracrine manner, extending the senescence response to neighboring cells, and activates and recruits the immune system to sites of senescence induction. In this manner, the SASP contributes to tumor suppression, as demonstrated in vivo using IL-1a inhibitors on a model of oncogene activation in liver. Blocking the SASP in this context leads to liver tumor progression in the presence of a defective immune surveillance. In contrast, other authors have reported that IL-1a inactivation impairs tumor progression by decreasing the SASP without affecting the senescent cell cycle arrest (Lau et al. 2019).

Another crucial regulator of the SASP is mTOR. Inhibition of mTOR or its effectors blocks the SASP in the context of cancer, revealing both its tumor suppressive and tumor promoting activity (Herranz et al. 2015). In particular, reducing a specific subset of SASP factors by mTOR inhibition decreases EMT induction and the invasive properties of cancer cells elicited by conditioned media derived from senescent cells. In vivo, co-injection of tumor cells with senescent cells enhances tumor growth but this pro-tumorigenic activity is lost when senescent cells express an shRNA targeted against mTOR. In contrast, the paracrine induction of senescence mediated by SASP factors present in conditioned media is clearly reduced when mTOR signaling is blocked in senescent cells. At the same time, senescence induction by oncogene expression in the liver of mice treated with rapamycin, an mTOR inhibitor, shows

a defective immune surveillance activity that results in decreased tumor suppressive function of senescence. Livers of mice treated with the mTOR inhibitor showed reduced infiltration of T cells, B cells, NK cells and macrophages, immune cells in charge of the clearance of senescent cells and contributing to the tumor suppressor activity of senescence.

Finally, another important player regulating the SASP is the Bromodomain-containing 4 (BRD4), a member of the BET (bromodomain and extra terminal domain) family of transcriptional regulators. Inhibition of BRD4 in senescent cells does not result in bypass of senescence but decreases the SASP resulting in poor paracrine senescence activity, impaired macrophage polarization, and reduced NK cytotoxic activity (Tasdemir et al. 2016). As a result, BRD4 inhibition leads to a disruption in immune surveillance and elimination of senescent cells in vitro and in vivo, a crucial tumor suppressive activity of senescent cells mediated by the SASP.

## 5.5 Concluding Remarks and Future Perspectives

The recent development of compounds with specific cell killing activity against senescent cells, known as senolytics, has provided strong evidence of the possibility of removing senescent cells with therapeutic consequences. This idea has been initially applied to aging and age-related diseases. Selectively eliminating senescent cells improves the healthspan of premature and naturally aged mice while providing the beneficial tumor suppressive function of senescence (Childs et al. 2017). This has led many to consider the possibility of using this strategy in the context of cancer therapy. Chemotherapy-induced senescence of cancer encountered opposition when the potentially harmful effects of the SASP were first described. Besides, leaving damaged tumor cells hanging around in cancer patients represent a potential risk of relapse due to escape of senescent tumor cells from the growth arrest. Developing strategies to modulate the SASP, through senomorphics, and combining senescence-inducing drugs with senolytics could represent novel approaches to treat cancer more effectively. The induction of a senescent phenotype in cancer cells, even a partial one, might provide a therapeutic window of opportunity. As part of the process of senescence, cancer cells might acquire novel vulnerabilities that could make them susceptible to the cytotoxic activity of senolytics. On top of that, the possibility of removing non-tumor senescent cells generated by the unspecific targeting of normal cells by chemotherapy or radiotherapy offers the promise of reduced secondary effects. There are now a number of known chemotherapeutic drugs that can induce senescence in tumor cells. We need to identify more and to decipher their mode of action to potentially use them in the clinic. In addition, we also need to identify more powerful and specific senolytic compounds and try to understand the molecular basis of their action.

Understanding the molecular basis of the process that make us grow old could remarkably provide us with the key to develop more effective and less toxic treatments against cancer.

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