

Exploiting Senescence for Cancer Treatment

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Abstract

Senescence is considered as a cellular defensive response evoked by diverse stimuli to combat tumor development and progression. An evolving body of knowledge indicates that tumor cells are capable of undergoing senescence when latent senescence pathways are reengaged. Given the apparent benefits associated with senescence induction as a therapy outcome, targeting of senescence triggering factors is being actively pursued. In this review, we briefly describe modes of senescence induction and discuss therapy approaches being undertaken for the development of pro-senescence anti-cancer therapies.

Keywords: Senescence; Cancer therapy; Induction of senescence

Introduction

Replicative senescence was first described by Hayflick and Moorehead about 40 years ago, when they observed that *in vitro* serial passages of normal human fibroblasts culminates in an irreversible exit from the cell cycle [1,2]. Later conflicting scientific data and arguments surfaced which prompted the scientific experts to refine the original definition of senescence. Cellular senescence is now defined as an irreversible non-proliferative state of cells, characterized by the permanent exit from cell division cycle and non-responsiveness to mitogenic signaling and oncogenic influence [3]. It is important to note that senescent cells remain viable and metabolically active despite undergoing stable proliferation arrest. In addition, senescent cells secrete a multitude of protein factors with diverse physiological function. These cellular secretions are collectively termed as senescence-associated secretory phenotype (SASP) [4,5].

Replicative senescence

Two critical pathways influence the onset of replicative senescence. The first is the DNA Damage Response (DDR) pathway that is triggered upon the exposure of telomeric ends and on attrition of telomeres [6]. In the DDR pathway, Ataxia telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3 related (ATR), Checkpoint kinase 1 (Chk1), and Checkpoint kinase 2 (Chk2) are the main mediators that phosphorylate and activate many proteins including p53 which promote the cellular exit from the cell proliferation cycle [6-9]. It is intriguing to note that in many cancers sustained DDR signaling is observed yet the cells do not manifest senescence phenotype [10]. The second pathway operates via de-repression of cyclin-dependent kinase Inhibitor 2A (CDKN2A) locus which encodes p16 and ARF. p16 protein inhibits G1 phase cyclin dependent kinases, Cdk4 and Cdk6, while ARF regulates p53 through inactivation of its negative regulator, Mouse double minute 2 homolog (MDM2). The molecular mechanisms underlying the de-repression of CDKN2A locus are not completely known, however, it is well-recognized that disengagement of polycomb repression complexes from the CDKN2A locus is critically involved in this process [6,11]. The extent to which these two individual pathways are engaged for senescence induction is greatly influenced by the organism of origin, type of cell and the nature of stress [6,11].

Oncogene induced senescence (OIS)

OIS was first seen in normal fibroblasts as an *in-vitro* cellular response to forced overexpression of oncogenic RAS (G12V) with ensuing phenotype very similar to replicative senescence [12]. Studies demonstrated that this phenotype was a result of DNA hyper-replication which triggered the activation of S phase-specific DDR.

Despite the differences in the mechanism of initiation of DDR, OIS and replicative senescence employ similar primary pathways and effectors of DDR signaling. In congruence with this notion, it is found that the OIS response fails to set in the cells with deficient ATM activity or when the DNA damage sensing machinery is inactivated or DDR signaling to p53 is blocked.

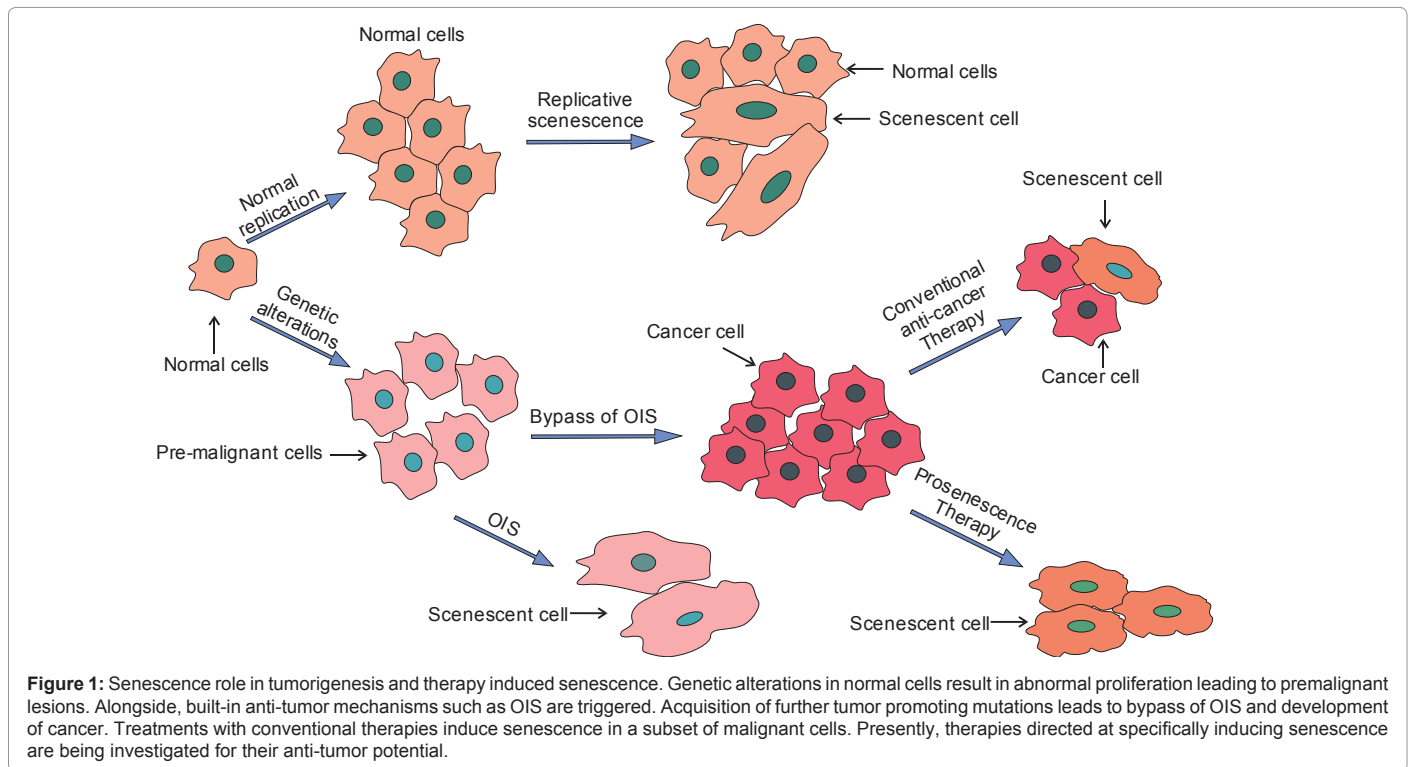
The presence OIS was detected in various human and mouse premalignant lesions by many independent groups, however, their advanced tumors lacked OIS features [13-16]. Examples of premalignant lesions in which OIS was observed include nevi, benign precursor lesions to melanoma, early stage lung and pancreatic cancer, serrate colon cancer models, 7,12-dimethylbenz-(a) anthracene (DMBA) and Tissue plasminogen activator (TPA) induced skin papilloma [14,17,18]. Furthermore, inactivation of tumor suppressor genes was also seen to evoke senescence phenotype. For example, loss of Phosphatase and tensin homolog (PTEN) in mouse prostate, Nuclear Respiratory Factor 1 (NRF1) loss in neurofibromas, von Hippel-Lindau (VHL) loss in renal cancer and Rb in thyroid cancers all resulted in premalignant lesions with senescence markers [6,19-21]. There is now abundant evidence to support that oncogenic activation spark the appearance of premalignant lesions but also could alongside initiate senescence program. Abrogation of this senescence program is essential for progression of tumor (Figure 1). For instance, development of melanomas can be strikingly accelerated upon inactivation of p53 or p16 in nevi lesions induced by oncogenic BRAF expression [6]. Similarly, p53 ablation in PTEN (-/-) prostate neoplastic lesions can accelerate the development of advanced metastatic prostate cancer [22]. It is clear from these examples that if mutations deactivating senescence program occur, then it could lead to the reversal of OIS and promote tumor progression (Figure 1). A corollary to this inference is that senescence triggered in the paraneoplastic lesions serves as an effective barrier against tumorigenesis and that it needs to be breached for tumor progression.

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Therapy induced senescence (TIS)

Senescence induction as a form of therapy outcome has achieved active clinical interest due to the observations that some tumor cells are capable of undergoing senescence in response to genotoxic treatments. These therapy outcomes indicate that senescence program is intact, nevertheless latent inside many tumor cells and that therapies aimed at reviving senescence may unleash pathways critical to senescence induction. p16INK4a and p53 tumor suppressor pathways are critical to the induction of therapy induced senescence (TIS). Inactivation of either of these two pathways confers resistance to cancer treatment which suggests that ability to actuate a strong senescence response governs the therapy outcome in cancer cells. It has also been reported that the dose strength of genotoxic therapy influences the choice of cellular response pathways in cancer cells. For example, we have shown that supraphysiological dose of cisplatin leads to apoptosis in head and neck squamous cell carcinoma (HNSCC) cells regardless of p53 status; however, a physiological cisplatin dose leads to robust senescence response in wild type p53 HNSCC cells [23]. Advanced malignancies frequently harbor epigenetic silencing, losses, or mutations in the genes critical for TIS pathway induction. Indeed, it is not surprising to see that conventional therapy resistances often arise from the same genetic alterations critical for tumor progression.

Therapy approaches for senescence induction

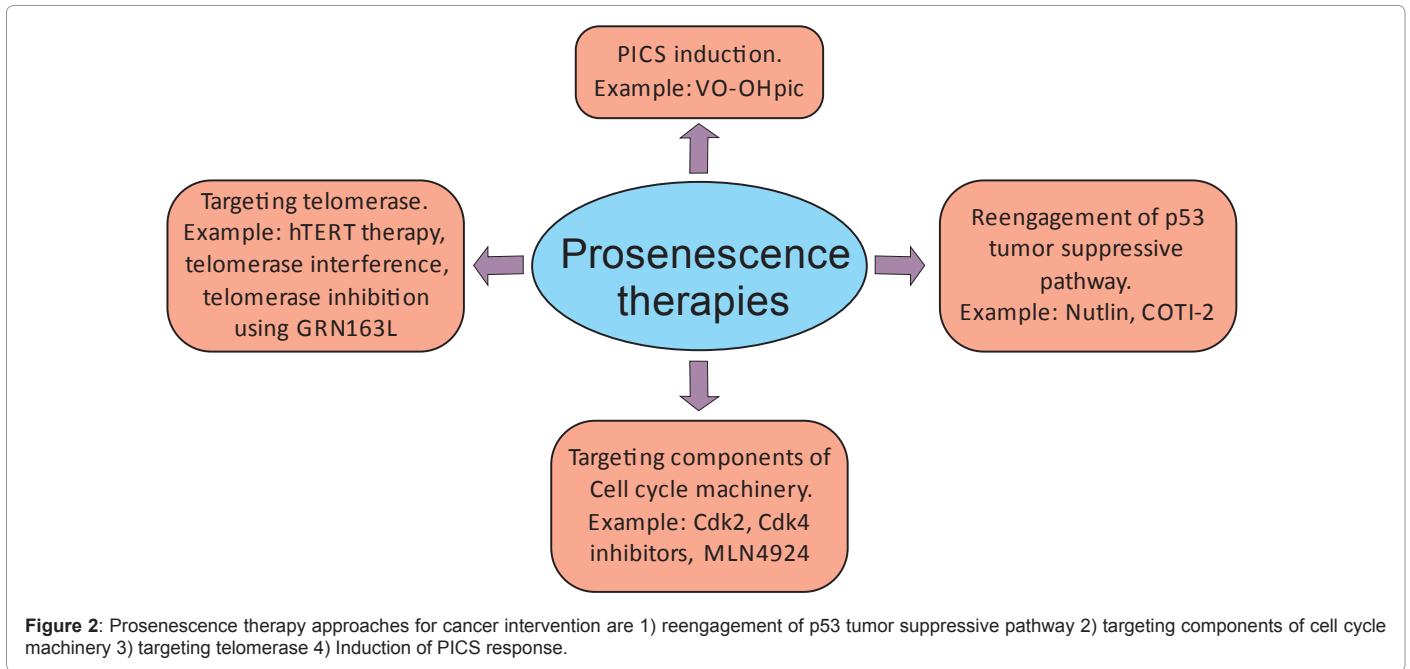
Due to the recognized complications arising out of untoward side effects, the genotoxic therapies for cancer management are utilized less enthusiastically. Drug therapies designed to selectively induce senescence in cancer cells, i.e., prosenescence therapies, have been proposed as a novel strategy for cancer treatment. In line with this approach, several drug therapies positively influencing senescence induction or targeting pathways operating antithetically to senescence program have emerged recently (Figure 2). We seek to present a brief overview of these therapy approaches and the rationale behind their application.

Reengagement of p53 tumor suppressor networks

Incipient tumors frequently inactivate p16/Rb and p53 tumor suppressive networks to escape OIS and progress into malignancy. Therefore, reengagement of these tumor suppressor networks could reinstate senescence program and arrest tumor growth [9]. While this strategy may be ineffective in tumor harboring p53 deletions, therapeutics augmenting p53 function via MDM2 inhibition or those capable of restoring normal p53 function in p53 mutant tumors could be beneficial [24-27]. Evidences supporting this approach have come from mouse models of lymphoma, sarcoma and hepatocellular carcinoma [6]. In lymphoma, restoration of p53 activity lead to induction of apoptosis and tumor regression, while in sarcomas senescent features with cell cycle arrest were grossly evident [28]. Oncogenic HRASG12V driven HCC exhibited senescent features with negligible apoptosis when p53 was reactivated [29]. Examples of investigational drugs operating through the mechanism of action involving p53 modulation include Nutlin and PRIMA1 [24,26,27]. Recently, COTI-2, a novel small molecule inhibitor with purported p53 based mechanism of action has entered phase I clinical trial [30].

Targeting cyclin dependent kinase activity

Cyclin dependent kinase (CDK) inhibitors can promote selective prosenescence response in tumor cells harboring appropriate genetic alterations. For example, c-myc driven tumor cells underwent senescence after inhibition of Cdk2 [31]. Likewise, genetic targeting of cdk4 in oncogenic K-RASG12V driven lung adenomas resulted in induction of senescence and tumor regression [32]. A similar senescent phenotype was observed in advanced lung adenocarcinomas upon cdk4 inactivation. Induction of senescence and suppression of tumorigenesis was also observed upon treatment with skp2 inhibitor MLN4924 in mouse models of various cancers that harbored PTEN loss [33].



Targeting telomerase function

Around 90% of tumors acquire telomerase activity to overcome the replicative barrier imposed due to eroded telomeres. Conforming to these findings, genetically engineered mouse models deficient in telomerase were found less susceptible to cancer [6]. Unsurprisingly, therapies aimed at inhibiting telomerase activity are now being evaluated for their anticancer potential. A host of therapeutic strategies targeting telomerase are currently under active investigation. These include direct enzymatic inhibition of telomerase, hTERT therapy, telomerase interference, telomere locking or stabilizing approaches, and telomerase vaccines [34,35]. Among the different drugs developed based on these approaches, GRN163L, a telomerase inhibitor, with promising anti-tumor activity has progressed into later stages of clinical trial [9]. It remains to be seen to what extent senescence would contribute to these therapy outcomes as gross aneuploidies and apoptosis are frequently reported consequences of telomerase inhibition [6].

Inducers of PICS response

While it is counterintuitive to think that inhibition of tumor-suppressor could have any beneficial outcomes, VO-OHpic based inhibition of PTEN in hemizygous PTEN tumors (+/-) resulted in senescence response solely in PTEN -/+ cells with no disastrous consequence on the surrounding homozygous PTEN +/+ cells. This senescence response was labelled as PTEN loss Induced Senescence (PICS) [6,9]. Augmented PTEN levels or inhibition of PI3K can also give rise to senescence, nevertheless, slight changes in opposite direction can elicit undesirable effects suggesting that PTEN/PI3K pathway are tightly regulated in cells. These findings highlight that application of prosenescence therapies should be undertaken judiciously with proper regard to the genetic context.

Senescence secretome – an untapped avenue for prosenescence therapy development

Although permanently non-proliferative, senescent cells manage to influence their surrounding through the release of soluble factors

and extracellular proteins. These secreted factors termed as SASP or senescence secretome was initially investigated for protumorigenic properties, however, their role in tumor suppression have also come to light [7,8]. The senescence secretome exerts tumor suppressive function through stable maintenance of cell cycle arrest and signaling to and engaging the immune system. Examples of secretome components supporting senescence phenotype include IL-6, IL-8 and TGF- β [4,6,9]. Thus, approaches aimed at modulating components of senescence secretome to reinforce senescence phenotype may offer therapeutic benefit. However, it is worthy to note that the same components may discharge protumorigenic actions in a different context. For instance, both IL6 and IL8 display protumorigenic function in tumor models driven by oncogenic RAS [4]. It is unclear what determines this reversal from tumor suppressive function to protumorigenic, but the presence of p16/Rb and p53 pathways are thought to be involved [4,6]. Although we have been equipped with considerable knowledge on senescence secretome and bear collection of reagents of small molecules and antibodies targeting SASP components, no study as yet has sought to evaluate the utility of prosenescence therapies targeting senescent secretome. We hope that future research in this area of investigation will give us insight on the utility of such approaches.

Conclusion

Accumulating evidences have highlighted the significance of senescence as an initial physiological response to tumor development. The observations of senescence induction in various cellular models after treatment with current conventional therapies suggest that therapeutic benefits imparted due to senescence have been incompletely harnessed. Nevertheless, such exploration may be viewed with skepticism because senescence as an anti-tumor therapy results in permanent exit from cell cycle whereas other outcomes such as apoptosis or necrosis ensure complete elimination of affected cells. However, examples of senescent cell elimination through immune system recruitment by secretome network indicate that prosenescence therapies may offer two-fold advantage, by inducing irreversible proliferation arrest and engagement of immune system to clear off premalignant as well as malignant cells. We envisage that a detailed mapping of molecular pathways directing

senescence and identification of senescence regulators by screening experiments from *in vitro* cellular models may be critical to develop novel pro-senescence therapies. Given the state of current knowledge, we predict that constituents of senescent secretome and drugs aimed at modulating epigenetic regulators of senescence could furnish opportunities for development of pro-senescence therapies.

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