Molecular Pathways: Harnessing E2F1 Regulation for Prosenescence Therapy in p53-Defective Cancer Cells

Anni Laine and Jukka Westermarck

Abstract

Induction of terminal proliferation arrest, senescence, is important for in vivo tumor-suppressive function of p53. Moreover, p53-mutant cells are highly resistant to senescence induction by either oncogenic signaling during cellular transformation or in response to different therapies. Senescence resistance in p53-mutant cells has been attributed mostly to inhibition of the checkpoint function of p53 in response to senescence-inducing stress signals. Here, we review very recent evidence that offers an alternative explanation for senescence resistance in p53-defective cancer cells: p21-mediated E2F1 expression. We discuss the potential relevance of these findings for senescence-inducing therapies and highlight cyclin-dependent kinases (CDK) and mechanisms downstream of retinoblastoma protein (RB) as prospective prosenescence therapeutic targets. In particular, we discuss recent findings indicating an important role for the E2F1–CIP2A feedback loop in causing senescence resistance in p53-compromised cancer cells. We further propose that targeting of the E2F1–CIP2A feedback loop could provide a prosenescence therapeutic approach that is effective in both p53-deficient and RB-deficient cancer cells, which together constitute the great majority of all cancer cells. Diagnostic evaluation of the described senescence resistance mechanisms in human tumors might also be informative for patient stratification for already existing therapies. *Clin Cancer Res*; 20(14); 3644–50. ©2014 AACR.

Background

Replicative senescence is a cellular phenomenon by which normal cells are induced to terminal growth arrest after multiple replications in vitro (1). Recently, two research groups showed that replicative senescence is not only associated with cellular aging but also contributes to tissue remodeling during embryonic mammalian development (2, 3). In cell culture conditions, senescent cells often show clear morphologic changes characterized by cell flattening, enlargement, and multinucleated appearance (1). In addition to morphologic changes, several biomarkers can be used to detect senescent cells in vitro and in vivo. As comprehensively reviewed by Kuilman and colleagues (1), many of these markers are cell specific and tissue specific, and it has been a challenge to identify markers that would reliably indicate for senescence induction in *in vivo* tissues.

In addition to replicative senescence, another type of senescence can occur in response to different types of stress stimuli, such as DNA damage, oxidative stress, and acute expression of oncogenes or inactivation of tumor suppressors (1). Originally, oncogene-induced senescence (OIS) was identified in mutant oncogenic HRAS–transfected human and mouse fibroblasts (4). Later, OIS and tumor suppressor inactivation–induced senescence were reported to prevent transformation in the context of several different oncogenes and tumor suppressors in many tissue types both in vitro and in vivo (5). For example, in a mutant oncogenic KRAS-driven mouse model, multiple senescent markers are expressed in premalignant lung and pancreas tumors, whereas malignant lung and pancreas adenocarcinomas show robust proliferation (6). These studies clearly indicate that for malignant transformation, cells must become resistant to both apoptotic cell death and senescence induction. In humans, oncogenic mutation in *BRAF* induces senescence in premalignant nevi and arrests malignant melanoma progression (7). Also, senescence has been detected in early-stage human prostate cancer lesions, further indicating that senescence is a restrictive phenomenon during human carcinogenesis (8).

**p53 and its downstream effector pathway in senescence regulation**

The tumor suppressor p53 is involved in senescence induction by various senescence-inducing stimuli (9). Consistent with this, ectopic activation of p53 has been shown to inhibit tumor initiation and tumor maintenance by inducing senescence in *vivo* (10, 11). In fact, most recent studies indicate that even though apoptosis induction is the classical response to acute p53 induction, it may be
senescence, rather than apoptosis induction, that mediates tumor suppressor function of p53 in vivo (12, 13). In early research, both p53 and its downstream RB activity were identified as limiting factors in human cellular transformation by forcing cells into cellular senescence (14). This could be explained by findings that upon oncogene-induced signaling, p53 is stabilized, leading to activation of the p53 downstream pathway, p53/p21/CDK2/RB/E2F1 (Fig. 1; ref. 9). In fact, it has even been demonstrated that p53 activation by a conditional allele in mouse tumors is not sufficient to induce tumor regression in the absence of Ras-driven oncogenic stress (15).

Whereas activation of wild-type p53 results in senescence induction, genetic p53 inhibition can overcome oncogenic mutant BRAF-induced senescence in mouse lung leading to tumor progression (16). In addition, p53 inactivation has been shown to occur over Pten inactivation–induced senescence in mouse prostate leading to cancer progression (8). Thus far, the senescence resistance of p53-defective cancer cells has been attributed to inhibition of p53 checkpoint function in response to OIS. However, an alternative explanation for senescence resistance of p53-mutant cancer cells could be that p53 inactivation actively drives mechanisms of senescence resistance. In this review, we discuss the latter explanation and uncover that common between these p53 inhibition–driven senescence resistance mechanisms is that they all feed to E2F1 regulation. We further discuss the potential of these mechanisms as prosenescence therapy targets.

**p21 mediates p53-induced senescence**

Because p53 has a well-established role in senescence induction, it is not a surprise that the downstream targets of p53 are important senescence regulators (9). Activation of p53 results in induction of direct p53 transcriptional target p21, which further inhibits cyclin-dependent kinase 2 (CDK2)/cyclin E complex, leading to RB-mediated E2F1 inhibition (Fig. 1; refs. 17, 18). In turn, and relevant for the model proposed in this review, p53 inhibition in cancer cells leads to increased p21 expression and consequent activation of E2F1. We do realize that other downstream effectors of p53 than p21 may also contribute to senescence regulation, but for the clarity of presentation, those mechanisms are not discussed here. The critical role for p21 in senescence regulation, even independently of p53, was supported by two recent articles describing p21-dependent programmed senescence during mouse development (2, 3). As a further support to the central role for p21 in senescence, recent studies have demonstrated p21-induced senescence in p53-defective cancer cell lines (17, 19–21) and tumors in vivo (22, 23).

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**Figure 1.** Regulation and therapeutic targeting of E2F1-driven cancer cell senescence resistance. Activity and expression of transcription factor E2F1 is regulated by upstream tumor suppressors p53, p16, and RB and by positive feedback loop between E2F1 and its target gene CIP2A. CIP2A inhibits activity of tumor suppressor PP2A resulting in increased E2F1 expression and senescence resistance. Blue color denotes proteins and regulatory connections that in normal cells promote senescence induction (blue enlarged multinucleated cell), whereas regulatory mechanisms driving senescence resistance and increased proliferation in cancer cells are denoted by red color. Left (red), mechanisms by which the depicted proteins are deregulated in cancer cells and thus promote senescence resistance. Right (blue), potential pharmacologic approaches to target the depicted proteins for prosenescence cancer therapies.
RB–E2F1 as a nodal point of senescence sensitivity regulation in p53-defective cancer cells

As mentioned above, CDK2 inhibition mediates senescence signaling from p21 to RB. In support of an important role for CDK2 activity in mediating senescence resistance, inhibition of CDK2 was shown to induce senescence in p53-deficient human leukemic tumor cells and in MYC-driven in vitro and in vivo transformation models (24, 25). Hydbring and colleagues further presented evidence that direct MYC phosphorylation by CDK2 was important for senescence evasion (25). CDK2 phosphorylates tumor suppressor retinoblastoma protein (RB), resulting in release of transcription factor E2F1 from RB/E2F1 complex (Fig. 1; ref. 26). RB protein family proteins, RB (p105), p107, and p130, have overlapping functions in cell-cycle control (26) and have compensatory and complementary roles in senescence regulation (27, 28). For example, in the absence of functional RB, p107 was shown to primarily mediate irradiation-induced senescence in prostate cancer cells (29). On the other hand, the most recent data with human fibroblasts show that RB, but not p107 or p130, has an essential role in oncogene-induced senescence in human cells (30) implicating for a cell type specificity for requirement of different RB family members in senescence regulation in experimental conditions. Importantly, unlike RB, mutations in p107 or in p130 are rare in human cancer, strengthening the important role for RB in tumor suppression among members of the RB protein family (26). Relevant for the model proposed in this review, a tumor suppressor VHL induced RB-dependent senescence in vitro even in the absence of functional p53 (31). In addition, in human cancer cells, including those that are p53 deficient, reactivation of RB induces the senescence phenotype (32).

The target of RB, E2F1, is a transcription factor whose expression is increased in many human cancers (33). The E2F protein family consists of 8 transcription factors (E2F1–8) that are important regulators of the cell cycle and cell fate (33). Even though E2F proteins have overlapping cellular functions, they differ in their biologic roles, for instance, in mammary development and in mammary carcinogenesis (34, 35). Excellent recent reviews underline specific functions of E2F family members (36, 37), but hereafter, we only concentrate in discussing the role of E2F1 in regulating senescence induction in cancer cells. Related to the role of E2F1 in regulating OSIs, several publications have reported downregulation of E2F1 in senescent cells (38, 39). More importantly, inhibition of E2F1 induces the senescence phenotype in cancer and in immortalized cells (17, 33, 40, 41). Recent studies have characterized E2F1 target genes relevant for senescence regulation (30, 42). However, despite RB proteins, the mechanisms by which E2F1 expression and activity are regulated during senescence regulation have been elusive. Recently, we demonstrated a previously unidentified positive feedback loop between E2F1 and another human oncoprotein CIP2A (43, 44) and demonstrated that this feedback mechanism promotes tumorigenesis by suppressing senescence induction in breast cancer cell lines and in a HER2-driven breast cancer mouse model (17). Rescue experiments demonstrated that senescence induction either by p53 activation, or by direct adenoviral overexpression of p21, was fully dependent on the capacity of these stimuli to downregulate CIP2A expression (17). Importantly, CIP2A depletion also induced senescence in breast cancer cells with impaired p53 or RB function (17). Moreover, CIP2A was identified as a novel direct target gene for E2F1, explaining how high E2F1 expression in p53-mutant cancer cells drives senescence resistance (17). In line with these results, also ectopic expression of E2F1 rescues the senescence phenotype in cancer cells (38, 39, 41) and similarly to CIP2A, E2F1 knockout mouse shows reduced tumorigenesis in MMTV-neu model (17, 35). In addition to breast cancer, loss of CIP2A has been reported to induce the senescent phenotype in gastric cancer and in esophageal squamous cell carcinoma cell lines (45, 46). Importantly, high CIP2A expression predicts for poor patient survival in more than a dozen different human cancer types (44). Together these results indicate that a senescence-inhibiting role for CIP2A may be generalized to the majority of human cancer types.

The molecular function of CIP2A is to inhibit phosphatase activity of a tumor suppressor phosphatase complex PP2A (44, 47). Different PP2A complexes regulate serine/threonine phosphorylation of numerous cellular targets implicated in a variety of physiologic and cellular processes (48). Although the role of PP2A is not thus far widely studied in the context of senescence, the emerging evidence does indicate that certain PP2A complexes do promote senescence (49). Related to the role of PP2A in CIP2A-mediated senescence resistance, inhibition of the B55α subunit of PP2A was identified to promote stability of E2F1 phosphorylated on serine 364 and to prevent p53-induced downregulation of E2F1 (17). Together these results indicate that E2F1–CIP2A interplay involving PP2A (Fig. 1) is an important novel mechanism regulating senescence sensitivity of human cancer cells. Notably, these results do not exclude the possibility of a role for other PP2A and CIP2A targets than E2F1 in the regulation of senescence resistance in cancer cells.

Clinical–Translational Advances

Notably, although traditionally considered as apoptosis-inducing agents, many of the currently used chemotherapies most probably exert their therapeutic effect, at least partly, by senescence induction (50). For example, significant induction of several senescence-associated gene expression was detected in prostate tumors after mitoxantrone chemotherapy, and senescence-associated β-galactosidase positivity was reported in 41% of breast tumors after neoadjuvant chemotherapy, including cyclophosphamide, doxorubicin, and 5-fluorouracil (50–52). On the basis of these and other studies suggesting an important role for senescence induction in cancer therapy responses, an increasing interest has been expressed in development of prosenescence cancer therapeutic strategies (9, 50). The rationale of driving cancer cells to senescence, rather than
apoptosis, is that there is increasing evidence that apoptosis-inducing regimens increase the risk for secondary malignancies and mutational evolution of those cancer cells that are spared from apoptosis. However, it should be noted that a recent mouse study indicated that p53-driven senescence induction in tumors might actually protect tumor cells from chemotherapy-induced apoptosis (53). This can be explained by the fact that senescent cells persist in tumors but are not sensitive to DNA-damaging therapies due to cell-cycle arrest (9, 50). On the other hand, clearance of senescent cells from tumors by innate immune cells has been shown repeatedly (9, 10). On the basis of these findings, it is evident that further studies are needed to clarify the therapeutic potential of prosenescence strategies separately in each cancer therapy setting.

Harnessing p53 downstream effectors for prosenescence therapy

Several mouse models have indicated that p53 reactivation would be an efficient prosenescence therapeutic strategy (10–13). However, p53 is mutational inactivated in a very large fraction of human cancers, and therefore therapeutic strategies to activate senescence via wild-type p53 are unlikely to be efficient in most human tumors. To overcome this serious shortcoming, several strategies to reactivate mutated p53 have been developed, and these strategies have been reviewed recently (54). Importantly, an alternative therapeutic strategy to induce senescence in p53-compromised tumor cells would be to target the mechanisms that promote senescence resistance due to p53 inactivation (Fig. 1). Potential such strategies are discussed below.

Senescence induction in cancer cells with compromised p53 function by targeting of p21 and CDKs

As described above, ectopic activation of p21 in p53-mutant cells drives cancer cells effectively to senescence and this is dependent on downregulation of E2F1–CIP2A feedback loop (Fig. 1; refs. 17, 19–21). Previously, an inhibitor of guanylate cyclase, LY8583, was demonstrated to increase p21 expression 2-fold and to induce senescence in p53-compromised 2 cancer cells in vitro (19). Similarly, two chemical compounds inhibiting SCF-Skp2 complex, MLN4924 and SZL-P1–41, were recently identified to induce p21 expression followed by senescence in p53-deficient cancer cells in vitro (22, 23). MLN4924 and SZL-P1–41 were further shown to significantly inhibit tumor growth of preformed human prostate and lung cancer xenografts (22, 23), suggesting that Skp2 inhibitors may represent a promising novel class of prosenescence therapeutics in p53-deficient cancer cells.

CDK2 activity is increased in p53-mutant cancers due to p21 inhibition, and either genetic or pharmacologic CDK2 inhibition drives senescence in various cell types, including a p53-null human cancer cell line in vitro (24, 25). Thereby, pharmacologic inhibition of CDK2 could be an attractive approach for prosenescence therapy. Notably, a novel CDK inhibitor, dinaciclib (MK-7965), most potently inhibiting CDK2 and CDK5, is under clinical trials for several cancer types, such as leukemia, melanoma, and breast cancer (55). Dinaciclib does induce apoptosis in tumor cell lines, and this could be explained by its activity toward multiple CDKs (56). However, dinaciclib also reduces phosphorylation of RB in vitro in osteosarcoma cells and in vivo in ovarian cancer cell xenografts (56, 57), and therefore it would be important to validate whether it has senescence-inducing activity in human tumors.

Whereas CDK2 mediates the effects of p21 in senescence regulation, CDK4 and CDK6 are important mediators of senescence resistance in cancer cells with inactivated tumor suppressor p16 (Fig. 1; ref. 58). A common feature of all these CDKs is that they regulate RB and thus they have a common target relevant for E2F1 and senescence regulation. In a mouse model, inhibition of CD4, but not CDK6 or CDK2, induces senescence in advanced KRAS-driven non–small cell lung carcinoma (NSCLC; ref. 59). Another CDK inhibitor in clinical trials, palbociclib (PD-0332991), inhibits CDK4 and CDK6 downstream of p16 and induces senescence in melanoma and glioblastoma cells in vitro (60, 61) and very efficiently suppressed growth of preformed intracranial glioblastoma xenografts (61). The importance of p16-mediated senescence regulation in tumorigenesis is supported by a fact that p16-encoding gene INK4A is frequently mutated in human cancer (1).

Importantly, in glioblastoma cells, depletion of RB conferred senescence resistance to palbociclib, further demonstrating a requirement of RB for sensitivity to CDK4/6 inhibition (61). Instead, in melanoma cells, CDK4/6 inhibition was shown to inhibit phosphorylation of FOXM1, which was shown to be partly independent of RB and was critical for CDK4/6 inhibitor–induced senescence (60). However, a recent study demonstrated that FOXO transcription factors directly stimulate E2F1 expression (62), further suggesting that despite differences in upstream regulation, E2F1 has a critical role in senescence sensitivity regulation by CDK inhibitors. On the basis of these results, CDK inhibitors seem to present a promising prosenescence therapy option in several types of cancers with compromised p53 function.

Senescence induction in cancer cells with compromised p53 and RB function by targeting of E2F1–CIP2A feedback loop

Similar to p53, RB is also inactivated in a large fraction of human cancers, and on the basis of recent functional analysis, this leads to resistance to senescence induction by either RAS-driven replicative stress or by inhibition of CDK4/6 or VHL (30, 31, 61). Importantly, Chicas and colleagues recently demonstrated that senescence resistance in RB−/− cells was associated with selective dysregulation of E2F1 target genes involved in senescence regulation (30). Together with very recent data that ectopic activation of E2F1–CIP2A feedback loop can rescue senescence phenotype in cancer cells (17, 38, 39, 41), these results indicate that targeting of this feedback loop could provide a prosenescence therapy approach that is effective in both
p53-deficient and RB-deficient cancer cells, which together constitute the great majority of all cancer cells.

Although targeting of the E2F1–CIP2A feedback loop appears to be an attractive approach for prosenescence therapy, tools to target this loop selectively are currently limited. Inhibitors targeting the E2F family of proteins have been generated; however, they are not specific for certain E2F proteins (63, 64). Interestingly, one of the traditional classes of chemotherapies, vinca alkaloids, inhibits E2F1 expression and effectively induces senescence in human breast cancer cells in vitro (17, 65). Although the exact mechanism by which vinca alkaloids inhibit E2F1 remains to be determined, it occurs at the level of mRNA expression and does not involve either p53 or p21 (17). Vinca alkaloid vinorelbine-induced senescence was preceded by downregulation of both E2F1 and CIP2A expression, and CIP2A deficiency further enhanced the E2F1 inhibition by vinorelbine (17). Furthermore, low CIP2A expression in human breast tumors predicted for favorable survival in patients treated with vinorelbine ($P \leq 0.019$; ref. 17). These results identify vinca alkaloids as potential clinical inhibitors of E2F1-mediated senescence resistance and use of CIP2A diagnostics for patient stratification to vinca alkaloid–based prosenescence therapy.

Notably, CIP2A is one of the most frequently overexpressed oncoproteins across human cancer types, and inhibition of CIP2A by siRNA results in significant reduction of xenograft growth of cervical cancer, head and neck squamous cell carcinoma, breast cancer, and bladder urothelial cell carcinoma cells in vivo (44). Thereby, and encouraged by recent success in a clinical lipid nanoparticle (LNP)-formulated RNAi therapy trial targeting VEGF and kinesin spindle protein (KSP) in patients with hepatic and extrahepatic tumors with Alynlam (66), RNAi therapy against CIP2A or E2F1 could be proposed as a future approach for prosenescence therapy in various cancer types. Naturally, development of a small-molecule inhibitor against CIP2A or CIP2A–E2F1 interaction, if feasible, could provide an opportunity for prosenescence therapy. Moreover, targeting upstream regulators of CIP2A expression could be another alternative for prosenescence therapy. Of thus far identified regulators of CIP2A expression (Chk1, ETS1, JNK2, or MYC; ref. 44), checkpoint kinase Chk1 could be the most promising candidate to be targeted for prosenescence therapy, as Chk1 inhibitors are already in clinical trials (55). We recently demonstrated that inhibition of constitutive Chk1 activity in various cancer cell lines reduces CIP2A expression resulting in PP2A reactivation and potent inhibition of malignant cell growth (67), whereas increased Chk1 expression was shown to protect against oncogene-induced replicative stress and to promote transformation (68). Finally, as different PP2A complexes mediate senescence induction and regulate E2F1 (49), testing of efficacy of small-molecule activators of PP2A (17, 47) as novel prosenescence therapeutic agents might be warranted.

Future Directions

In sum, the literature reviewed here reveals that senescence resistance in p53-defective cancer cells results from at least two different mechanisms: (i) loss of checkpoint function of p53 in response to senescence inducing signals and (ii) activation of the E2F1–CIP2A feedback loop due to inhibited p21 function. On the basis of these findings, further development of small-molecule activators of p21 and inhibitors of CDKs may provide opportunities for development of prosenescence therapies against p53-mutant tumors. Moreover, the emerging indications for the essential role for E2F1 and CIP2A in mediating senescence resistance in both p53- and RB-compromised tumors should boost development of therapeutics against these previously undruggable proteins. This could involve modern drug development approaches, such as allosteric protein–interaction inhibitors, or RNAi therapy. Finally, the presented evidence suggests that diagnostic evaluation of the RB, E2F1, and CIP2A status of newly diagnosed cancers might help stratification of patients for therapies with already existing therapeutic agents with demonstrated prosenescence activity, such as vinca alkaloids (17, 65).

Disclosure of Potential Conflicts of Interest

J. Westermarck has ownership interest (including patents) in CIP2A RNAi therapy. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A. Laine, J. Westermarck
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Laine
Writing, review, and or revision of the manuscript: A. Laine, J. Westermarck
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Laine

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