Role of senescence induction in cancer treatment

Shenghui Qin, Bradley A Schulte, Gavin Y Wang

Cellular senescence is a form of permanent cell cycle arrest that can be triggered by a variety of cell-intrinsic and extrinsic stimuli, including telomere shortening, DNA damage, oxidative stress, and exposure to chemotherapeutic agents and ionizing radiation. Although the induction of apoptotic cell death is a desirable outcome in cancer therapy, mutations and/or deficiencies in the apoptotic signaling pathways have been frequently identified in many human cancer types, suggesting the importance of alternative apoptosis-independent therapeutic approaches for cancer treatment. A growing body of evidence has documented that senescence induction in tumor cells is a frequent response to many anticancer modalities including cyclin-dependent kinases 4/6 small molecule inhibitor-based targeted therapeutics and T helper-1 cytokine-mediated immunotherapy. This review discusses the recent advances and clinical relevance of therapy-induced senescence in cancer treatment.

Key words: Cellular senescence; Cancer treatment; Chemotherapy; Ionizing radiation; Cyclin-dependent kinases 4/6 inhibitor; Aurora kinase inhibitor; Immunotherapy; T helper-1 cells; T helper-1 cytokines

©The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Both in vitro and in vivo studies have revealed that senescence induction in human cancer cells is a prominent response to chemotherapy and irradiation. A senescent phenotype has been detected in clinical tumor samples of breast cancer patients following preoperative neoadjuvant chemotherapy. Immunotherapy-induced senescence of cancer cells contributes to tumor regression in vivo. The induction of cancer cell senescence appears to be a major mechanism of action of cyclin-dependent kinases 4/6 small molecule inhibitor-based targeted therapy. Collectively, these preclinical and clinical observations have demonstrated an important role for senescence induction in...
INTRODUCTION

Cellular senescence is an anti-proliferative program that restrains tumorigenesis via limiting the propagation and transformation of aging and damaged cells\[1-2\]. Senescence can be induced by a variety of cell-intrinsic and extrinsic stimuli, including telomere shortening, DNA damage, oxidative stress, chemotherapeutic agent treatment, radiation exposure, and the activation of oncogenes such as Ras\[3-6\].

Senescent cells are in a state of irreversible cell cycle arrest and are characterized by a flat and enlarged morphology, elevated senescence-associated β-galactosidase activity, and the activation of the p53-p21 and p16-Rb signaling pathways\[2,7\]. Additional characteristics of senescence cells include the presence of senescence-associated heterochromatic foci and the senescence-associated secretory phenotype\[8,9\]. Traditionally, senescence induction is considered to be an important mechanism of cancer prevention and cellular aging\[10\]. However, numerous recent studies have revealed that senescence is a prominent solid tumor response to therapy in which cancer cells evade apoptosis and instead enter into a stable and prolonged cell cycle arrest\[3,5\]. Furthermore, targeted therapeutics and cancer immunotherapies also have been shown to cause cancer regression via the induction of senescence in tumor cells\[11,12\]. These findings underscore the significant implications of senescence induction in cancer treatment.

INDUCTION OF TUMOR CELL SENESCENCE IS AN IMPORTANT OUTCOME OF CHEMOTHERAPY

Cellular senescence is a state of permanent cell growth arrest that often has been included with apoptosis as one of the terminal outcomes of cancer treatment. It is well-established that different classes of chemotherapeutic agents and ionizing radiation (IR) induce senescent-like phenotypes in tumor cells both in vitro and in vivo\[2,5,11,13\]. Our recent studies indicate that resveratrol induces premature senescence in lung cancer cells via promoting reactive oxygen species (ROS)-mediated DNA damage\[14\]. Inactivation of Myc results in tumor regression through induction of senescence but not apoptosis in hepatocellular carcinoma and lymphoma cells\[15\]. In addition, it has been reported that the restoration of p53 promotes tumor regression in vivo via induction of senescence in tumor cells\[16,17\]. More importantly, Schmitt et al\[13\] showed that senescence induction contributes directly to the outcome of chemotherapy in vivo. In agreement with this finding, there is evidence that the senescent phenotype is present in clinical tumor samples of breast cancer patients after undergoing preoperative neoadjuvant chemotherapy\[18\]. Moreover, our recent studies found that the number of senescent cells is markedly increased in tumor samples of lung cancer patients as compared to normal lung tissues (Figure 1). However, the clinical relevance of the presence of senescent cells in tumor samples has yet to be determined.

Notably, human tumors may harbor various types of defects in the apoptotic signaling pathways (e.g., loss of p53 and overexpression of BCL2) and, as a result, are resistant to apoptosis-based anticancer therapies\[19,20\]. In these conditions, a senescence-targeted strategy is likely to be a more effective and practical than traditional apoptosis-inducing approaches. A welcome benefit to this approach is that therapy-induced senescence can be achieved using much lower doses of therapy than those required to induce apoptosis\[2,14\]. Compared to the traditional apoptosis-inducing strategies, this low dose approach would significantly reduce the side effects of anticancer therapy and thus improve the quality of life for cancer patients.
ROLE OF SENECESSCENCE INDUCTION IN CANCER RADIOTHERAPY

Radiotherapy is used in over 50% of patients during the course of cancer treatment and is effective both as a curative modality and for palliation\(^{[21]}\). However, many epithelial-derived tumors including lung cancer have been shown to be resistant to radiation-induced apoptosis\(^{[6,20]}\). Consistent with these observations, our recent studies have demonstrated that IR primarily induces premature senescence rather than apoptosis in human non-small cell lung cancer (NSCLC) cells\(^{[6]}\). Subsequent mechanistic studies revealed that the p53-p21 signaling pathway plays a critical role in modulating IR-induced senescence in NSCLC cells (Figure 2). More importantly, we showed that pharmacologic activation of p53 by Nutlin-3 sensitizes NSCLC cells to radiation by enhancing IR-induced senescence\(^{[6]}\). These results suggest that pharmacological promotion of senescence induction can be exploited as a novel and effective therapeutic approach to improve the efficacy of lung cancer radiotherapy.

MicroRNA-34a (miR-34a) has been shown to be a p53 responsive miRNA that is involved in regulating senescence induction\(^{[22-24]}\). Our recent studies showed that the expression of miRNA-34a was increased substantially in human NSCLC cells after exposure to IR\(^{[25]}\). Moreover, we found that treatment with synthetic miR-34a mimics enhances the anti-cancer effects of irradiation by promoting senescence induction via targeting the Myc oncoprotein in NSCLC cells (Figure 2). These findings not only provide new insights into the mechanisms by which IR induces senescence in lung cancer cells but also support the hypothesis that pharmacological manipulation of senescence induction should be explored as a new therapeutic strategy for improving the outcome of cancer radiotherapy.

INDUCTION OF SENECESSCENCE IS A MAJOR MECHANISM OF ACTION OF CYCLIN-DEPENDENT KINASES 4/6 INHIBITION-BASED TARGETTED THERAPEUTICS

The cyclin-dependent kinases (CDKs) are a large family of serine-threonine kinases that play a pivotal role in regulating cell cycle progression. Commitment to cell cycle entry occurs during the G1 phase, when CDK4 and CDK6 form active complexes with one of the three D-type cyclins (D1, D2, or D3). Cyclin D-CDK4/6 complexes promote G1/S transition by phosphorylating the Retinoblastoma tumor suppressor (Rb), which in turn releases its suppression of the E2F transcription factor, resulting in initiation of E2F-dependent gene transcription and DNA synthesis. CDK4 and CDK6 are overexpressed in the majority of human cancers and they presumably promote tumorigenesis by suppressing senescence in cancer cells\(^{[11,26,27]}\). Both preclinical studies and clinic trials have demonstrated the therapeutic potential of CDK4/6 small molecule inhibitors against several solid tumors\(^{[28-31]}\). Recently, a CDK4/6-specific inhibitor, palbociclib (also known as PD0332991), was approved by the FDA for the treatment of advanced estrogen receptor-positive breast cancer\(^{[32]}\).

It is well established that CDK4/6 inhibitors suppress tumor growth by the induction of senescence in various type of cancer cells\(^{[11,26,27,32]}\). Mechanistic studies have revealed that CDK4/6 suppress tumor cell senescence via phosphorylating and activating the Forkhead Box M1 (FOXM1) transcription factor, and that activation of
Figure 2 This model summarizes the mechanisms underlying ionizing radiation-induced senescence in non-small cell lung cancer cells. Ionizing radiation (IR) exposure increases the levels of reactive oxygen species in tumor cells and oxidative stress is known to trigger the induction of senescence. IR exposure leads to DNA damage which in turn can activate the p53-p21 senescence pathway. Irradiation up-regulates the expression of miR-34a that inhibits c-Myc, resulting in the induction of senescence. ROS: Reactive oxygen species; IR: Ionizing radiation.

FOXM1 may inhibit the induction of senescence in tumor cells by repressing ROS-mediated oxidative stress[33]. However, the precise mechanisms whereby FOXO1 controls ROS and oxidative stress remain unclear. Promyelocytic leukemia (PML) acts as a tumor suppressor by inducing senescence in response to oncogenic stress[34,35]. Interestingly, Acevedo et al[36] showed that CDK4/6 suppress PML-induced senescence in tumor cells, suggesting that CDK4/6 inhibitors such as PD0332991 may induce senescence in cancer cells by blocking CDK4/6-mediated suppression of PML’s senescence-inducing function. Moreover, CDK4/6 inhibition has been shown to be efficacious against therapy-resistant HER2 positive breast cancers[37]. These results imply that although some tumors may be resistant to apoptosis-inducing treatments, it is likely that they are still responsive to senescence-targeted therapies.

AURORA KINASE INHIBITION INDUCES SENESCENCE IN TUMOR CELLS BOTH IN VITRO AND IN VIVO

Aurora kinases are a family of serine/threonine mitotic kinases that regulate a diverse set of mitotic processes including spindle formation, centrosome segregation, checkpoint activation and kinetochore-microtubule connections[38,39]. Aurora A kinase (AurA) is located on 20q13.2, a chromosomal region that is frequently amplified in many human cancers. Overexpression of AurA correlates with poor clinical outcomes in patients with hormone-related cancers[40]. Aurora kinase inhibitors (AKIs) are a promising class of drugs for cancer treatment. Several small molecule AKIs including MK-0457, PHA-739358 and MLN8237 have been investigated in clinical trials for the treatment of human cancers[41-43].

Alisertib (MLN8237) is an orally bioavailable, second-generation selective inhibitor of Aurora kinases which binds to AurA and prevents its phosphorylation and activation[44]. It has been shown that senescence is likely a terminal outcome of AurA inhibition and that pharmacological inhibition of AurA induces senescence in colon cancer cells both in vitro and in vivo[45]. AurA is overexpressed in gliomas and treatment with Alisertib induces senescence and differentiation in glioblastoma cells[46]. Moreover, recent studies have revealed that p53 and p73 tumor suppressors play a critical role in modulating tumor cell responses to AKIs. Tentler et al[47] reported that Alisertib treatment resulted in apoptosis in human triple-negative breast cancer (TNBC) cells with functional p53 and p73, whereas it induced senescence in cells lacking p53 and p73. These findings suggest that AKI may induce growth arrest in TNBC through a p53- and p73-independent mechanism. Nevertheless, further studies are warranted to better understand the in-depth mechanisms whereby AKIs induce senescence in human tumor cells.

INDUCTION OF CANCER CELL SENESCENCE CONTRIBUTES TO IMMUNOTHERAPY-INDUCED TUMOR REGRESSION
Immunotherapy has shown promising efficacy against human cancers both in preclinical studies and in clinical trials. T helper-1 (Th1) cells play a critical role in mediating the antitumor adoptive immune response. Th1 T-cell infiltration is associated with better outcomes and Th1 cytokines are more effective at promoting the antitumor functions of CD40L-activated macrophages as compared to Th2 cytokines. Moreover, Müller-Hermelink et al. showed that treatment with T antigen (Tag)-specific Th1 cells induced tumor dormancy and doubled the survival of tumor-bearing mice by arresting tumor growth, without detectable evidence of tumor cell cytotoxicity, necrosis or apoptosis. These findings suggest that other alternative non-cytotoxic mechanisms are likely involved in Th1- and Th1 cytokine-mediated immunotherapy. In agreement with this idea, it has been shown that treatment with Th1 cytokines, IFN-γ and tumor necrosis factor (TNF) induces senescence in cancer cells.

It has been reported that cancer immunotherapy causes tumor growth arrest and regression without any clear evidence of tumor cell death or cellular toxicity. Moreover, it has been shown that immunotherapy-induced tumor growth arrest was associated with an increase in interferon (IFN)-γ-producing CD4+ Th1 cells, but not CD8+ cytotoxic T lymphocytes. These observations suggest that senescence induction may contribute to the outcome of immunotherapy. In agreement with this, Braunmüller et al. showed that Th1 immunotherapy arrests tumor progression through IFN-γ- and TNF-induced cancer cell senescence in vivo. Their subsequent mechanistic studies revealed that TNFR1 signaling is required for Th1 immunotherapy-induced tumor cell senescence and that activation of the p16-Rb pathway is involved in senescence induction. In line with these findings, it has been shown recently that CDK4/6 inhibition-induced tumor cell senescence promotes antitumor immunity in preclinical models. Furthermore, there is evidence that IL-12 inhibits the growth of human sarcoma cells by senescence induction. Taken together, these results highlight a novel link between cancer immunotherapy and the induction of senescence in tumor cells.

CONCLUSION

Given the fact that many human cancers may harbor different defects in the apoptotic signaling pathways, and thus are inherently resistant to chemotherapeutics-induced apoptosis, there is a critical need for the development of innovative apoptosis-independent approaches for cancer therapeutics. The induction of tumor cell senescence has been well-established as a prominent therapeutic response of cancer cells to chemotherapy, radiation, small-molecule inhibitor-based targeted therapeutics and immunotherapy. These results underscore the important implications of senescence induction in cancer treatment. Although senescent cells were detected in clinical tumor samples of cancer patients, the clinical significance and applications of therapy-induced senescence remain incompletely understood. It is still unclear if senescence markers in patient tumor samples will be useful for prognosis prediction and/or therapeutic efficacy evaluation in the clinic. In addition, further studies, particularly clinical investigations, are necessary to better elucidate the clinical relevance and significance of therapy-induced senescence in the treatment of cancer.

REFERENCES

1. Muñoz-Espin D, Serrano M. Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol 2014; 15: 482-496 [PMID: 24954210 DOI: 10.1038/nrm3623]
2. Ewald JA, Desotelle JA, Wilding G, Jarrard DF. Therapy-induced senescence in cancer. J Natl Cancer Inst 2010; 102: 1536-1546 [PMID: 20858887 DOI: 10.1093/jnci/djp364]
3. He S, Sharpless NE. Senescence in Health and Disease. Cell 2017; 169: 1000-1011 [PMID: 28575665 DOI: 10.1016/j.cell.2017.05.015]
4. Hydbring P, Bahram F, Su Y, Tromp et al. von der Lehr N, Sharifi HR, Lilschikias R, Hein N, Wu S. Phosphorylation by Cdk2 is required for Myc to repress Ras-induced senescence in cotransformation. Proc Natl Acad Sci USA 2010; 107: 38-63 [PMID: 19966300 DOI: 10.1073/pnas.0901213107]
5. Chang BD, Swift ME, Shen M, Fang J, Broude EV, Roninson IB. Molecular determinants of terminal growth arrest induced in tumor cells by a chemotherapeutic agent. Proc Natl Acad Sci USA 2002; 99: 389-394 [PMID: 11768208 DOI: 10.1073/pnas.0260259]
6. Luo H, Yount C, Lang H, Yang A, Ziemer EC, Lyons K, Vaneck KN, Silvestri GA, Schulte BA, Wang GY. Activation of p53 with Nutlin-3a radiosensitizes lung cancer cells via enhancing radiation-induced premature senescence. Lung Cancer 2013; 81: 167-173 [PMID: 23683497 DOI: 10.1016/j.lungcan.2013.04.017]
7. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O. A biomarker that identifies senescent human cells in culture and in aging skin, WJCO https://www.wjgnet.com December 20, 2018 Volume 9 Issue 8
Qin S et al. Senescence in cancer treatment

in vivo. Proc Natl Acad Sci USA 1995; 92: 9363-9367 [PMID: 7568133 DOI: 10.1073/pnas.92.20.9363]

8 Narita M, Nînêz S, Heard E, Narita M, Lin AW, Hearn SA, Spector DL, Hannon GJ, Low SW. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. Cell 2003; 113: 703-716 [PMID: 12880602 DOI: 10.1016/S0092-8674(03)00401-X]

9 Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest 2013; 123: 966-972 [PMID: 23454759 DOI: 10.1172/JCI64098]

10 Briaq M, Lee S, Loddankeremper C, Rudolph C, Peters AH, Schlegelberger B, Stein H, Dörken B, Jenuwein T, Schmitt CA. Oncogene-induced senescence as an initial barrier in lymphoma development. Nature 2005; 436: 660-665 [PMID: 16079837 DOI: 10.1038/nature03841]

11 Rader J, Russell MR, Hart LS, Nakazawa MS, Belcastro LT, Martinez D, Li Y, Carpenter EL, Attiyeh EF, Diskin SJ. Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. Clin Cancer Res 2013; 19: 6173-6182 [PMID: 24045179 DOI: 10.1158/1078-0432.CCR-13-1765]

12 Baumüller H, Wiedler T, Brenner E, Aßmann S, Hahn M, Alkhaled M, Schiblich K, Essmann F, Knelling M, Griessinger C. T-helper-1 cell cytokines drive cancer into senescence. Nature 2013; 494: 363-365 [PMID: 23376950 DOI: 10.1038/nature12184]

13 Schmitt CA, Fridman JS, Yang M, Lee S, Baronov E, Hoffman RM, Low SW. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. Cell 2002; 109: 335-346 [PMID: 12101983 DOI: 10.1016/S0002-9440(02)00734-1]

14 Luo H, Yang A, Schulte BA, Wagrowski MJ, Wang GY. Resveratrol induces premature senescence in lung cancer cells via ROS-mediated DNA damage. PLoS One 2013; 8 e60065 [PMID: 23533664 DOI: 10.1371/journal.pone.0060065]

15 Wu CH, van Riggelen J, Yetil A, Fan AC, Bachrieddy P, Felsher DW. Cellular senescence is an important mechanism of tumor regression upon c-Myc inactivation. Proc Natl Acad Sci USA 2007; 104: 13028-13033 [PMID: 17644422 DOI: 10.1073/pnas.0701953104]

16 Xue W, Zender L, Mathcing C, Dickins RA, Hernando E, Krizhanovsky V, Cordon-Cardo C, Low SW. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature 2007; 445: 656-660 [PMID: 17251933 DOI: 10.1038/nature05529]

17 Ventura A, Kirsch DG, McLaughlin ME, Tuveson DA, Grimm J, Lintault L, Newman J, Reczek EE, Weissleder R, Jacks T. Restoration of p53 function leads to tumour regression in vivo. Nature 2007; 445: 661-665 [PMID: 17251932 DOI: 10.1038/nature05541]

18 te Poele RH, Okorokov AL, Jardine L, Cummings J, Joel SP. DNA damage is able to induce senescence in tumour cells in vitro and in vivo. Cancer Res 2002; 62: 1876-1883 [PMID: 11991216]

19 Mori S, Ito G, Usami N, Yoshioka H, Ueda Y, Kodama Y, Takahashi M, Fong KM, Shimokata K, Sekido Y, p53 apoptotic pathway molecules are frequently and simultaneously altered in nonsmall cell lung carcinoma. Cancer 2004; 100: 1673-1682 [PMID: 15075286 DOI: 10.1010/cancer.2004.30]

20 Yin DX, Schimke RT. BCL-2 expression delays drug-induced apoptosis but does not increase clonogenic survival after drug treatment in HeLa cells. Cancer Res 1995; 55: 4922-4928 [PMID: 7885331]

21 Ngiof SF, McArthur GA, Smyth MJ. Radiotherapy complements immune checkpoint blockade. Cancer Cell 2015; 27: 437-438 [PMID: 25873170 DOI: 10.1016/j.ccell.2015.03.015]

22 Heremek H. p53 enters the microRNA world. Cancer Cell 2007; 12: 414-418 [PMID: 17966451 DOI: 10.1016/j.ccr.2007.10.028]

23 Tazawa H, Tsuchiya N, Izumiya M, Nakagama H. Tumor-suppressive miR-34a induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells. Proc Natl Acad Sci USA 2007; 104: 15472-15477 [PMID: 17875987 DOI: 10.1073/pnas.0701751104]

24 Wang Y, Scheiber MN, Neumann C, Calin GA, Zhou D. MicroRNA regulation of ionizing radiation-induced premature senescence. Int J Radiat Oncol Biol Phys 2011; 81: 839-848 [PMID: 21093163 DOI: 10.1016/j.ijrobp.2010.09.048]

25 He X, Yang A, McDonald DG, Riemer EC, Vanek KN, Schulte BA, Wang GY. MiR-34a modulates radiation-induced premature senescence in lung cancer cells. Oncotarget 2017; 8: 69797-69807 [PMID: 29050242 DOI: 10.18632/oncotarget.19267]

26 Yoshida A, Lee EK, Diehl JA. Induction of Therapeutic Senescence in Vemurafenib-Resistant Melanoma by Extended Inhibition of CDK4/6. Cancer Res 2016; 76: 2990-3002 [PMID: 26988987 DOI: 10.1158/0008-5472.CAN-15-2931]

27 Klein ME, Dickson MA, Antonescu C, Qin LX, Dooley SJ, Barlas A, Manova K, Schwartz GK, Crako AM, Singer S. PDLIM7 and CDH18 regulate the turnover of MDM2 during CDK4/6 inhibitor therapy-induced senescence. Oncogene 2018; 37: 5066-5078 [PMID: 29798718 DOI: 10.1038/s41388-018-0332-y]

28 Jansen VM, Blaha NE, Bauer JA, Formisano L, Lee KM, Hutchinson KE, Witkiewicz AK, Moore PD, Estrada MV, Sánchez V. Kinome-Wide RNA Interference Screen Reveals a Role for PDK1 in Acquired Resistance to CDK4/6 Inhibition in ER-Positive Breast Cancer. Cancer Res 2017; 77: 2488-2499 [PMID: 28249008 DOI: 10.1158/0008-5472.CAN-16-2653]

29 Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375: 1925-1936 [PMID: 27995613 DOI: 10.1056/NEJMoa1609785]

30 Finn RS, Crown JP, Lang I, Börk K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus placebo alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015; 16: 25-35 [PMID: 25932478 DOI: 10.1016/S1470-2045(14)71391-7]

31 Vijayraghavan S, Karacas B, Doostan I, Chen X, Bui T, Yi M, Raghavendra AS, Zhao Y, Bashour SI, Ibrahim NK. CDK4/6 and autophagy inhibitors synergistically induce senescence in Rb positive cytoplasmic cyclin E negative cancers. Nat Commun 2017; 8: 15916 [PMID: 28653662 DOI: 10.1038/ncomms15916]

32 Sherr CJ, Beach D, Shapiro GI. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov 2016; 6: 353-367 [PMID: 26608964 DOI: 10.1158/2159-8290.CD-15-0894]
Qin S et al. Senescence in cancer treatment

33 Anders L, Ke N, Hydbring P, Choi YJ, Widlund HR, Chick JM, Zhai H, Vidal M, Gygi SP, Braun P. A systematic screen for CDK4/6 substrates links FOXM1 phosphorylation to senescence suppression in cancer cells. Cancer Cell 2011; 20: 620-634 [PMID: 22094250 DOI: 10.1016/j.ccr.2011.10.003]

34 Ferbeyre G. PML is a target of translocations in APL and is a regulator of cellular senescence. Leukemia 2002; 16: 1918-1926 [PMID: 12357343 DOI: 10.1038/sj.leu.2402722]

35 Pearson M, Carbone R, Sebastiani C, Ciocca M, Fagioli M, Saito S, Higashimoto Y, Appella E, Minucci S, Pandolfi PP. PML regulates p53 acetylation and premature senescence induced by oncogenic Ras. Nature 2000; 406: 207-210 [PMID: 10590134 DOI: 10.1038/35051827]

36 Acevedo M, Vemuri M, Migliaccio L, Lessard F, Huot G, Moiseeva O, Bourdevé V, Ferbeyre G. A CDK4/6-Dependent Epigenetic Mechanism Protects Cancer Cells from PML-induced Senescence. Cancer Res 2016; 76: 3252-3264 [PMID: 27728849 DOI: 10.1158/0008-5472.CAN-15-2347]

37 Goel S, Wang Q, Watt AC, Tolaney SM, Dillon DA, Li W, Ramm S, Palmer AC, Yuzugullu H, Varadan V. Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. Cancer Cell 2016; 29: 255-269 [PMID: 26997875 DOI: 10.1016/j.ccel.2016.02.006]

38 Liouatas A, Vernois I. Aurora A kinase and its substrate TACC3 are required for central spindle assembly. EMBO Rep 2013; 14: 829-836 [PMID: 23987685 DOI: 10.1038/embor.2013.109]

39 Marumoto T, Honda S, Hara T, Nitta M, Hirota T, Kohmura E, Saya H. Aurora-A kinase maintains the fidelity of early and late mitotic events in HeLa cells. J Biol Chem 2003; 278: 51786-51795 [PMID: 14523060 DOI: 10.1074/jbc.M307153200]

40 Das K, Lorena PD, Ng LK, Shon L, Lim D, Siow WY, Narasimhan K, Teh M, Choolani M, Putti TC. Aurora-A expression, hormone receptor status and clinical outcome in hormone related cancers. Pathology 2010; 42: 540-546 [PMID: 20854072 DOI: 10.1111/j.1440-1827.2010.01879.x]

41 Falchook GS, Bastida CC, Kurzrock R. Aurora Kinase Inhibitors in Oncology Clinical Trials: Current State of the Progress. Semin Oncol 2015; 42: 832-848 [PMID: 26615120 DOI: 10.1053/j.seminoncol.2015.09.002]

42 Dickson MA, Mahoney MR, Tap WD, D’Angelo SP, Keohoon ML, Van Tine BA, Agulnik M, Horvath LE, Nair JS, Schwartzk GR. Phase II study of MLN8237 (Alisertib) in advanced/metastatic sarcoma. Ann Oncol 2016; 27: 1855-1860 [PMID: 27507208 DOI: 10.1093/annonc/mdw281]

43 Fathl AT, Wander SA, Blongquist TM, Brunner AM, Amrein PC, Supko J, Hernandez NM, Manning AL, Radzadeh H, Ballen K. Phase I study of the aurora A kinase alisertib with induction chemotherapy in patients with acute myeloid leukemia. Haematologica 2017; 102: 719-727 [PMID: 28034960 DOI: 10.3324/haematol.2016.158394]

44 Manfredi MG, Esedey JA, Meezeha K, Balani SK, Burenkova O, Chen W, Galvin KM, Hoar KM, Huck JJ, LeRoy PJ. Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase. Proc Natl Acad Sci USA 2007; 104: 4106-4111 [PMID: 17360485 DOI: 10.1073/pnas.0608789104]

45 Huck J, Zhang M, McDonald A, Bowman D, Hoar KM, Stringer B, Esedey J, Manfredi MG, Hyer ML. MLN8054, an inhibitor of Aurora A kinase, induces senescence in human tumor cells both in vitro and in vivo. Mol Cancer Res 2010; 8: 373-384 [PMID: 20917280 DOI: 10.1158/1541-7786.MCR-09-0300]

46 Lehman NL, O’Donnell JP, Whiteley LJ, Stapp RT, Lehman TD, Roszka KM, Schultz LR, Williams CJ, Mikkelson T, Brown SL. Aurora A is differentially expressed in gliomas, is associated with patient survival in glioblastoma and is a potential chemotherapeutic target in gliomas. Cell Oncol 2012; 35: 489-502 [PMID: 22274399 DOI: 10.1007/s10432-011-9281-y]

47 Tengler JJ, Ionkina AA, Tan AC, Newton TP, Pitts TM, Ciglovask M, Kbabs P, Sartorius CA, Sullivan KD, Espinosia JM. p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer. Mol Cancer Ther 2015; 14: 1117-1129 [PMID: 25878333 DOI: 10.1158/1535-7163.MCT-14-0581]

48 Dobrzenski MJ, Rowers-Fellins KA, Quinlin IS, Samad KA, Phillips CA, Robinson W, Dickson MA, Mahoney MR, Tap WD, D’Angelo SP, Keohoon ML, Van Tine BA, Agulnik M, Horovath LE, Nair JS, Schwartzk G. Phase II study of MLN8237 (Alisertib) in advanced/metastatic sarcoma. Ann Oncol 2016; 27: 1855-1860 [PMID: 27507208 DOI: 10.1093/annonc/mdw281]

49 Nitshino M, Ramaiya NH, Hatabu H, Hodi FS. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. Nat Rev Clin Oncol 2017; 14: 655-668 [PMID: 28653677 DOI: 10.1038/nrclinonc.2017.88]

50 Rosembli C, Datta J, Lowenfeld L, Xu S, Basu A, Kodumudi K, Wiener D, Czerniecki BJ. Oncodriver inhibition and CD4+ T cells cooperate through Stat1 activation to induce tumor senescence and apoptosis in HER2+ and triple negative breast cancer: implications for combining immune and targeted therapies. Oncotarget 2018; 9: 23058-23077 [PMID: 29796172 DOI: 10.18632/oncotarget.25208]

51 Datta J, Xu S, Rosembli C, Smith JB, Cintolo JA, Powell DJ Jr, Czerniecki BJ. CD4(+)-T-Helper Type 1 Cytokines and Trastuzumab Facilitate CD8(+) T-cell Targeting of HER2/neu-Expressing Cancers. Cancer Immunol Res 2015; 3: 445-463 [PMID: 25791067 DOI: 10.1158/2326-6066.CIR-14-0288]

52 Thakur A, Schalk D, Sarkar SH, Al-Khadimi Z, Sarkar FH, Lum LG. A Th1 cytokine-enriched microenvironment enhances tumor killing by activated T cells armed with bispecific antibodies and inhibits the development of myeloid-derived suppressor cells. Cancer Immunol Immunother 2012; 61: 497-509 [PMID: 21971887 DOI: 10.1007/s00262-011-1116-1]

53 Luhesni N, Davies G, Poon E, Wiggins K, McCourt M, Legg J. Th1 cytokines are more effective than Th2 cytokines at licensing anti-tumour functions in CD40-activated human macrophages in vitro. Eur J Immunol 2014; 44: 162-172 [PMID: 24114604 DOI: 10.1002/eji.201343351]

54 Müller-Hermelink N, Btunmülher H,ピヒル B, Wieder T, Maalhammer R, Schak K, Goreschi K, Yazdi A, Haubner R, Sander CA. TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multistage carcinogenesis. Cancer Cell 2008; 13: 507-518 [PMID: 18585784 DOI: 10.1016/j.ccr.2008.04.001]

55 Kenter GG, Welters MJ, Valentin AJ, Lowik MJ, Berends-van der Meer DM, Vloon AP, Essahhsh F, Fathers LM, Offerling R, Drijhout JW. Vaccination against HPV-16 oncoproteins for
56 Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassell JC. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-723 [PMID: 20525902 DOI: 10.1056/NEJMoa0810097]

57 Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, Jungbluth A, Gnjatic S, Thompson JA, Yee C. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med* 2008; 358: 2698-2703 [PMID: 18565862 DOI: 10.1056/NEJMoa0800251]

58 Deng J, Wang FS, Jenkins RW, Li S, Dries R, Yates K, Chhabra S, Huang W, Liu H, Aref AR. CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-cell Activation. *Cancer Discov* 2018; 8: 216-233 [PMID: 29101163 DOI: 10.1158/2159-8290.CD-17-0915]

59 Goel S, DeCristo MJ, Watt AC, BrinJones H, Sceney J, Li BB, Khan N, Ubellacker JM, Xie S, Metzger-Filho O. CDK4/6 inhibition triggers anti-tumour immunity. *Nature* 2017; 548: 471-475 [PMID: 28913415 DOI: 10.1038/nature23465]

60 Schilbach K, Alkhaled M, Welker C, Eckert F, Blank G, Ziegler H, Sterk M, Müller F, Sonntag K, Wieder T. Cancer-targeted IL-12 controls human rhabdomyosarcoma by senescence induction and myogenic differentiation. *Oncoimmunology* 2015; 4: e1014760 [PMID: 26140238 DOI: 10.1080/2162402X.2015.1014760]

P- Reviewer: Chiang TA, Wei HF
S- Editor: Wang XJ  L- Editor: A  E- Editor: Bian YN
