Cancer Heterogeneity and Plasticity
https://doi.org/10.47248/chp2502030013

Perspective

The Three Barriers Senescent Tumor Cells Must Overcome to Relapse

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Abstract

Tumor cells that enter senescence as a response to treatment can be permanently arrested or removed by the immune system, resulting in favorable patient outcomes. Alternatively, many studies have now shown that, in some tumors, the senescent program enables tumor cell survival, persistence, and eventually relapse, resulting in poor patient outcomes. Whether senescence is a positive or negative factor is dependent on a clonal population of cells overcoming three critical barriers. First, senescence must enable survival from the initial stress of treatment, such as DNA damage, by preventing apoptosis and/or mitotic catastrophe. Senescent cells are also frequently immunogenic, thus, a second barrier is the activation of programs of immune evasion, such as PD-L1 expression, that outweigh the immunogenic properties. Third, senescent cells must escape their rigid arrest to proliferate again. Studies over the years have experimentally addressed challenging questions related to relapse and senescence, but more research is needed, particularly *in vivo*. Here, we discuss critical studies investigating how tumor cells that enter senescence as a response to treatment overcome barriers to relapse.

Keywords: Senescence; relapse; cell cycle arrest; immunotherapy; immune evasion; p53; PD-L1

Cite This Article:
Jackson JG. The Three Barriers Senescent Tumor Cells Must Overcome to Relapse. Cancer Heterog Plast 2025;2(3):0013. https://doi.org/10.47248/chp2502030013

Received: 28 May 2025
Accepted: 27 Jul 2025
Published: 4 Aug 2025

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1. Introduction

Cancer cells can respond to treatments in a variety of ways. Clearly, the most beneficial to the patient will be activation of extensive intrinsic cell death pathways coupled with surveillance by the immune system, resulting in complete tumor eradication and durable cure. This can and does occur in many tumors in response to therapies that induce cell death (such as chemotherapies) and/or activate the immune system (e.g., immune checkpoint inhibitors, or ICI). Of course, conventional and targeted therapies and the immune system frequently fail to eradicate the tumor, and surviving cells cause relapse and patient mortality.

Tumor cells rely on different strategies to survive and persist post treatment [1], including primary pharmacological resistance such as that mediated by drug efflux pumps [2]. Among strategies for cells that become stressed and damaged by treatments are various states of cell cycle arrest, including a diapause-like state [3,4] and, frequently, programs of senescence [5]. Both would result in a pathological stable disease or partial response [6]. Tumor volume decreases minimally and residual disease is frequently extensive. The senescence response to treatment occurs in breast and other cancers and has been investigated in animal models, and is the subject of this article.

Senescence response is best identified in cancers that are treated with neoadjuvant therapy, where the systemic treatment such as chemotherapy is given before the surgery, and thus the response to treatment can be characterized by molecular, transcriptomic, and immunohistochemical techniques in the surgical specimen. This has allowed senescence to be identified as a primary response in breast cancers that fail to undergo complete pathological response [7-10], and this has been followed up and studied in controlled experiments in animal models [10-12]. These studies have identified senescent cells using various means, including RNA expression data showing elevated cell cycle inhibitors, loss of Lamin B1 and cyclins/cdks, induction of p53 target genes as well as genes related to the senescence associated secretory phenotype, or SASP [10,12,13]. Studies have used staining for many of these same genes in histological sections of tumors, pre- and post-treatment, including Ki67, p21, p16, SASP genes, and Lamin B1 loss [7-9]. Lastly, studies have shown extensive positive staining for senescence marker SAβGal [14] when feasible [9,12]. In addition to breast, various reports have demonstrated therapy-induced senescence in patient samples or mouse models for prostate [15,16], pancreas [17], lung [18-20], mesothelioma [21], rectal [22], leukemia/lymphoma [23-25], head and neck squamous [26], and ovarian cancer [27]. As other tumor types are examined in the post-treatment period preceding relapse or eradication, it is likely that cells in a senescent-like state would be detected.

2. Induction of Senescence as A Favorable Treatment Response

In between eradication and primary resistance is stable disease or partial response, where a tumor has responded to treatment, but viable cells remain. The tissue, cell, and stimulus specific regulation of senescent phenotypes will ultimately determine the fate of the tumor cell and the patient. One potential outcome is that any tumor cells that might remain after surgery are rigidly arrested, never proliferating again at a rate to produce a detectable relapse. It is also possible that these senescent cells may interact with the immune system to facilitate their removal over time, and it is known that senescent cells become immunogenic [10,16,28-30]. Lastly, entering a senescent state can introduce vulnerabilities to a second “senolytic” therapy. This strategy, particularly the targeting of the BCL2 family of antiapoptotic proteins, has had varying success [11,31-33], depending on the state of apoptotic priming of the senescent cells [34-36]. Thus, induction of senescence as a majority response in a tumor can effectuate a cure if the arrest is rigid, the immune system is activated, and/or senolytic drugs can be used to remove them.

The extent of senescence within the tumor is a critical factor in the response. Senescence can vary in depth and expression of other various phenotypes [37]. If a tumor loses only a small amount of volume post-treatment but then remains stable, the extent of the senescent arrest is likely widespread. If the tumor growth stalls briefly and then resumes, it is fair to speculate that senescence was either not induced in many cells that also resisted cell death, or that the arrest was shallow and easily exited [37]. Too frequently, this is the case, and the senescence response by a tumor actually prevents realizing a cure, ultimately promoting relapse and patient mortality. This is glaringly evident in breast cancer, where p53 wild-type tumors are the most difficult to eradicate with chemotherapy [38-40] and survival of these patients is much shorter than those with p53 mutant tumors that are far less likely to enter senescence after treatment [41-44]. Thus, the induction of senescence is heterogeneous across the population of tumor cells, with some cells sustaining more or less damage, during different phases of the cell cycle, and in different immune and tumor microenvironment contexts. This heterogeneity allows selection of the fittest clones over the next phases toward relapse.

Here, we discuss three layers of selection that a tumor cell that has entered senescence must overcome to cause eventual relapse.

3. The Three Layers of Selection in Relapse of Senescent Tumor Cells

3.1 Avoid intrinsic cell death

The first requirement for the survival of a tumor cell post-treatment is avoiding cell death in response to toxic stresses, including DNA damage, mitotic spindle poisons, and therapies that target oncogenic drivers (**Figure 1A-B**). The state of senescence can facilitate and enable this survival by multiple mechanisms. Mouse models of breast cancer have shown that *TP53* mutant tumor cells that fail to arrest following DNA damaging chemotherapy continue through S-phase and mitosis, ultimately undergoing mitotic catastrophe, and perhaps other modes of cell death [12]. *TP53* wild type breast tumors, however, enter senescence and are not eradicated by the chemotherapy [12,38-40]. In fact, in many tumors, a majority of cells will not be eliminated by the initial chemotherapy, and instead, senescence is the primary outcome [45-47]. This is not necessarily a case of rare persisters. In breast cancers, p53 transactivates many genes related to apoptosis, but cell cycle arrest and senescence is the outcome for many cells. Cell types that are inherently resistant to apoptosis are not “primed” to undergo apoptosis following p53-mediated expression of pro-apoptotic genes such as Puma, Noxa, and Bax [48,49]. Residual disease is often quite extensive in patients or models systems with *TP53* wild-type tumors [12,38-40].

As mentioned above, reliance on BCL2 family members such as BCL-XL to survive, however, does create a vulnerability to “senolytic” agents that block BCL2 family members [11,31,34]. Thus, these agents might be used to improve response to treatment by throwing cells into apoptosis that are surviving in senescence [50]. Pre-clinical data suggest that indeed, some fraction of the cells in the tumor can be eliminated, improving response and survival in mouse models, but there remain enough cells in the heterogeneous population that

resist and survive [11, 51]. Further, cell lines exhibit an array of sensitivities to the various BCL2 family targeting drugs [11,51]. One mechanism employed by cells that resist BCL-XL inhibition is activity of another BCL2 family member, MCL-1, shown initially in breast [11] and then prostate [32] and melanoma [52]. MCL1 can be targeted by a second drug, and more senescent cells in the population can be killed, but this combination is probably too toxic to provide clinical benefit.

Breast and other tumor cell types that have survived treatment by entering senescence express an array of genes related to macrophages and dendritic cells, and acquire the ability to engulf and break down various large targets, including apoptotic cells, healthy proliferating cells, and other senescent cancer cells [53,54]. Further, senescent tumor cells have increased capacity for autophagy [55]. It is reasonable to hypothesize that the ability to acquire nutrients via engulfment or autophagy would enhance survival of senescent cells, but more research is needed to understand this definitively, especially *in vivo* where very little is known.

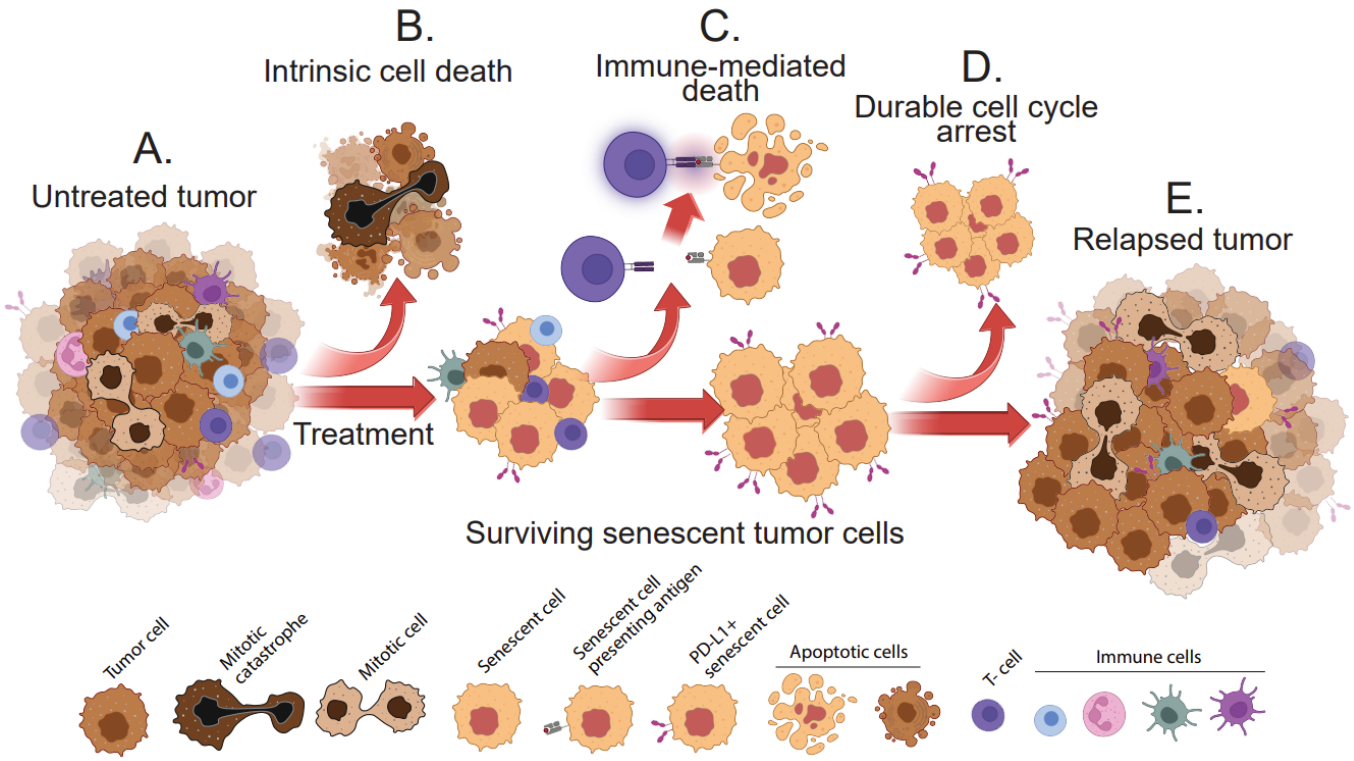

Figure 1. Three layers of selection must be overcome for senescent tumor cells to cause relapse. (A) An untreated, growing tumor is comprised of dividing tumor cells and various stromal/immune cell types. (B) Following treatment, such as with a chemotherapy drug, apoptosis or mitotic catastrophe will result in intrinsic cell death, but cells that enter senescence frequently survive. C) The cells that survive apoptosis must then evade the immune system, including cytotoxic T-cells. (D) Senescent tumor cells that remain viable and persist, can be permanently arrested. (E) Some tumor cells that expressed senescent phenotypes can re-enter the cell cycle, begin proliferating again, and cause relapse.

3.2 Avoid immune mediated cell death

Among the large population of tumor cells that become senescent after treatment are those that express differing levels and combinations of immune modulatory genes [56]. These include cytokines and chemokines of the SASP [57], as well as checkpoint ligands and other immune co-stimulatory or

inhibitory genes [46,58]. This creates a next layer of selection for tumor cells that will reach relapse: evade the immune system (**Figure 1C**).

Recent studies make clear that genes that promote immune surveillance are expressed by senescent cells. These include antigen presentation genes and various cytokines and chemokines that can attract and activate T-cells [10,28,29,59] and NK cells [20,60-62]. For a tumor cell to survive, these immunity promoting phenotypes must be counteracted by immune inhibitory pathways, and, indeed, senescent tumor cells simultaneously express an array of genes that suppress the immune system. These include clinically important genes such as PD-L1, PD-L2, and Galectin 9 [10,63,64]. In some tumor types such as breast, it is clear the ultimate outcome for tumors that enter senescence is relapse. In these cancers, the balance of immune regulation must be tilted toward evasion. Expression of PD-L1/PD-L2 and other suppressive pathways "wins" over antigen presentation and immunogenicity, thus the tumor survives to relapse.

Mechanisms of immune evasion, however, can be targeted by immunotherapies such as immune checkpoint inhibitors (ICI), including anti PD-L1 and PD-L2 antibodies [10,64], as well as strategies to increase immunogenicity of tumor cells [65]. The blocking of the negative signal transmitted from PD-L1 and/or PD-L2 on tumor cells to the PD1 expressed on T cells, combined with the expression of antigen presentation and costimulatory genes, can result in a robust response to ICI by senescent tumor cells [10,64]. There is also, however, redundancy in the system. Senescent cells can express many immune modulatory genes, including various checkpoint ligands and cytokines [10]. Thus, blocking one may not be enough to overcome the sum of negative signals being generated by the senescent cell.

3.3 Emerge from the senescent arrest to proliferate again

The final layer of selection in the path to relapse is the ability of a cell to emerge from senescent arrest to proliferate again and create a growing tumor (**Figure 1D-E**). Relatively little is known about these cells for reasons of intractability in their study and characterization. Cells with an evident senescent morphology have been observed to restart proliferation *in vitro* [51,66-69]. *In vivo* studies have correlated the presence of senescent cells in a tumor at one time point with proliferating cells at a later time point, but the question of whether the proliferating cell had at one time harbored some number of senescence properties is not clear. This conundrum was recently addressed in a model of tumor suppression, not therapy induced senescence. The authors generated hepatocytes with a *Cdkn1a* promoter driving Cre recombinase that could convert a tdTomato expressing allele to a GFP allele. This, in effect, would permanently mark with GFP any cell that had expressed the p53 target and senescence gene *Cdkn1a*. They found that hepatocytes that expressed *Cdkn1a* in response to metabolic stress indeed proliferated again as transformed carcinoma cells [70]. This is a powerful model for testing emergence from senescence, however, the *Cdkn1a* promoter is activated by p53 within hours after stress, long before cells become senescent. It is possible these *Cdkn1a* positive cells did not co-express various other markers and effectors of senescence.

In another recent report, *in vitro* experiments showed that in a population of cells that were treated, the surviving cells were mostly positive for senescence markers and morphology, and these cells did begin dividing again. The "repopulating" cells were sensitive to further treatment, and were very similar to untreated cells in gene expression and single cell population composition [51]. It is not entirely clear from the study design the precise origin or nature of these repopulating cells. This would include characterization of the specific cells from which the repopulating cells were derived or if their program of arrest had any defining characteristics such as chromatin structure [71,72] or cytoplasmic chromatin activating c-GAS/Sting [73], which both can regulate the depth and quality of senescence in normal cells such as fibroblasts. In another recent study, the authors showed that chemotherapy treated, immortalized mammary epithelial cell line MCF-10A expressed many typical markers of senescence with graded intensity rather than a binary state. The more intensely positive for features such as SAβGal, the longer the duration before cell cycle re-entry [74].

In vivo evidence that a "previously therapy-induced senescent cell" (how this is defined varies, and is important) can proliferate again to repopulate the relapsed tumor, has not been rigorously demonstrated. It is possible that in some tumor types senescence is more rigid, more locked into a chromatin state. As discussed recently, it is likely that in a heterogeneous tumor cell population, various cells display a continuum across the arrest spectrum that includes cells that readily escape and proliferate again and those that are permanently arrested [37,74].

4. Conclusions

Whether the senescence response to treatment is favorable or detrimental to the patient's outcome is dependent on the ability of senescent cells to overcome three barriers to relapse: apoptosis, immune surveillance, and durable cell cycle arrest (**Figure 1**). Tumor cells in a heterogeneous population will vary widely in the degree to which each senescent phenotype is expressed. Ultimately, as selective pressures are placed on this population by the treatment, the immune system, and the depth of the arrest, it will take only a small number of cells to survive and emerge to cause relapse. Targeting these cells at any of these 3 selection bottlenecks, such as by using senolytics or immunotherapies, will likely provide benefit.

Declarations

Ethics Statement

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Not applicable.

Funding

National Institutes of Health (R01CA259001).

Competing Interests

James G. Jackson is a member of the Editorial Board of the journal *Cancer Heterogeneity and Plasticity*. The author was not involved in the journal's review of or decisions related to this manuscript. The author has declared that no other competing interests exist.

Acknowledgements:

The author acknowledges BioRender was used to create the figure.

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