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A conversation with ChatGPT on contentious issues in senescence and cancer research

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Running title: ChatGPT and senescence

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List of non-standard abbreviations:

AGR2: Anterior gradient protein 2

AI: Artificial Intellegence

AML: Acute myelogenous leukemia

BCL-2: B-cell lymphoma 2

BCL-X_L: B-cell lymphoma-extra large

BET: Bromodomain and extra-terminal domain

CCL5: Chemokine ligand 5

ChatGPT: Generative Pre-trained Transformer

CXCL10: C-X-C Motif Chemokine Ligand 10

D+Q: Dasatinib+quercetin

DAMPs: Damage-associated molecular patterns

DC: Dendritic cells

DEC1: Deleted in esophageal cancer 1

DNA-SCARS: DNA segments with chromatin alterations reinforcing senescence

EVs: Extracellular vesicles

FGF: Fibroblast Growth Factor

HDAC: Histone deacetylase

HSP90: Heat shock protein 90

IFN: Interferon

IFNγ: Interferon gamma

IL-1β: interleukin-1β

MDSC: Myeloid-derived suppressor cells

MHC-I: major histocompatibility complex-I

mTOR: Mammalian target of rapamycin

NK: Natural killer

NKG2D: Natural killer cell activating receptor

OIS: Oncogene-Induced Senescence

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PCNA: Proliferating cell nuclear antigen
PD-1: Programmed cell death protein 1
PD-L1: Programmed death-ligand 1
PGE2: Prostaglandin E2
Rb: Retinonlastoma protein
ROS: Reactive oxygen species
RS: Replicative Senescence
SAGA: Senescence-Associated Growth Arrest
SASP: Senescence-Associated Secretory Phenotype
SA-β-gal: Senescence-Associated β-galactosidase
TIS: Therapy-Induced Senescence
TNF: Tumor necrosis factor
uPAR: Urokinase-type Plasminogen Activator Receptor
VEGF: Vascualr Endothelial Growth Factor

Abstract: Artificial Intelligence (AI) platforms such as Generative Pre-trained Transformer (ChatGPT) have achieved a high degree of popularity amongst the scientific community due to their utility in providing evidence-based reviews of the literature. However, the accuracy and reliability of the information output and the ability to provide critical analysis of the literature, especially with respect to highly controversial issues, has generally not been evaluated. In this work, we arranged a Q/A session with ChatGPT regarding several unresolved questions in the field of cancer research relating to Therapy-Induced Senescence (TIS) including the topics of senescence reversibility, its connection to tumor dormancy, and the pharmacology of the newly emerging drug class of senolytics. ChatGPT generally provided responses consistent with the available literature, while occasionally overlooking essential components of the current understanding of the role of TIS in cancer biology and treatment. While ChatGPT, and similar AI platforms, have utility in providing an accurate evidence-based review of the literature, their outputs should still be considered carefully, especially with respect to unresolved issues in tumor biology.

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Significance Statement

Artificial Intelligence platforms have provided great utility for researchers to investigate the biomedical literature in a prompt manner. However, several issues arise when it comes to certain unresolved biological questions, especially in the cancer field. This work provided a discussion with ChatGPT regarding some of the yet to be fully elucidated conundrums of the role of Therapy-Induced Senescence in cancer treatment and highlights the strengths and weaknesses in utilizing such platforms for analyzing the scientific literature on this topic.

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Introduction

Recently, the release of Generative Pre-trained Transformer (ChatGPT), an artificial intelligence (AI) platform, has attracted substantial interest from the scientific community. This interest in ChatGPT is related largely to its unique capabilities to cover, analyze and provide presumably accurate information in a human-like conversational style, often in the shape of conceptual, factual and technical knowledge, including topics in the biomedical field (Agathokleous et al., 2023). Such large language models can provide avenues for readily accessible navigation through the biomedical literature (Thapa and Adhikari, 2023). For instance, AI was shown to have the capability to capture fundamental concepts in scholarly texts and generate high-quality revisions that improved the clarity of the presentations (Milton and Casey, 2023). The benefits of AI also extend to literature reviews, outlining, and writing different sections of scientific manuscripts (Mojadeddi and Rosenberg, 2023). Furthermore, AI-based programs were able to analyze and predict gene expression profiles from DNA sequences, structure or functions of proteins as well as the molecular properties of drugs (Wang et al., 2023). Moreover, ChatGPT was shown to be capable of resolving questions requiring higher-order thinking in medical biochemistry (Ghosh and Bir, 2023). Clinically, AI platforms, including ChatGPT, can provide accurate answers to commonly asked questions in the public domain in fields such as oncology and cancer treatment (Johnson et al., 2023). Despite the range of benefits that can be integrated into the process of scientific research by ChatGPT, some substantive limitations have been reported including lack of context, failure to provide necessary interactions and engagement with health professionals, and an inability to provide access to external scientific databases (Ashraf and Ashfaq, 2023; Biswas, 2023; Cascella et al., 2023). Furthermore, a major concern for users of ChatGPT can be the accuracy (or lack thereof) of answers to specific molecular biology questions in cases involving highly controversial subjects.

Cellular senescence is an established hallmark of cancer (Hanahan, 2022) and a primary component of tumoral cell stress response to cancer therapy (Saleh et al., 2020a). Originally, senescence was introduced by Leonard Hayflick and Paul Moorhead as an irreversible state of growth suppression in non-transformed fibroblasts (Hayflick, 1965; Hayflick and Moorhead, 1961). However, more recently, senescence has been recognized as a transient but durable form of growth arrest, during which cells remain metabolically active but fail to respond to mitogenic drivers (Saleh et al., 2020b; Sharpless and Sherr, 2015). Three general forms of senescence have been extensively described in the literature, specifically Replicative Senescence (RS), Oncogene-induced Senescence (OIS) as well as the primary focus for this article, therapy-induced or accelerated senescence (Gewirtz, 2009; Saleh et al., 2022c). Therapy-induced Senescence (TIS) is a state of stable growth arrest that is induced in response to different anticancer treatment modalities (Fitsiou et al., 2022). In addition to the Senescence-Associated Growth Arrest (SAGA), the senescent phenotype exhibits a range of related characteristics including enlarged and flattened morphology, increased β-galactosidase (Senescence-Associated β-galactosidase; SA-β-gal) activity (Kurz et al., 2000), accumulation of reactive oxygen species (ROS) (Nelson et al., 2018; Saleh et al., 2022c), chromatin rearrangement known as Senescence-Associated Heterochromatic Foci (SAHFs) (Zhang et al., 2005), persistent DNA damage often described as DNA segments with chromatin alterations reinforcing senescence (DNA-SCARS) (Saleh et al., 2022c), as well as secretion of an abundance of inflammatory mediators implicated in altering the surrounding microenvironment, collectively known as the Senescence-Associated Secretory Phenotype (SASP) (Gorgoulis et al., 2019). The association between TIS and the development of tumor phenotypes that likely interfere with patient responsiveness has been described, suggesting a direct relation between the senescence state and tumor recovery (Finnegan et al., 2022a), therapy resistance (Jo et al., 2023), evasion of apoptosis (Yosef et al., 2016), cellular stemness (Milanovic et al., 2018), as well as metastasis (Kawaguchi et al., 2021). These findings have led to the consideration of the possibility that TIS could serve as a potential target in cancer treatment, and the investigation of various senolytics, senomorphics as well as senostatics, as potential anticancer therapeutics (Nelson et al., 2018; Nelson et al., 2012; Short et al., 2019). Although the evolving viewpoint in the literature views TIS as an unfavorable outcome of cancer treatment, controversial issues remain to be resolved, including whether senescence serves as a component of tumor dormancy, its identification in *in vivo* systems, as well as the most efficient strategy for the targeting of these senescent populations with the least adverse effect profile. For this purpose, we decided to ask ChatGPT carefully selected, and, in some cases, highly controversial questions that involve the role of TIS in cancer therapy, to evaluate

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the reliability of using this technological platform as a tool to help investigators to fully understand the role of TIS tumor response to treatment.

Lastly, while the answers provided were generated largely based on the September 2021 update to the platform, we have made sure that our discussion of the platform's responses is also commensurate with the most recent literature on each topic. We would like to emphasize that the process of evaluating AI's output on various issues in the biomedical field is constantly evolving as these platforms are being further developed, and this work represents only a representative window of interaction between scientists and AI.

Q1: Is Senescence in Cancer Cells Reversible?

ChatGPT: Senescence in cancer cells can be complex, and its reversibility depends on several factors, including the type of senescence, the underlying genetic and molecular context of the cancer cells, and the specific treatments being utilized. There are two main types of cellular senescence: replicative senescence and stress-induced senescence. Replicative Senescence: This type of senescence is triggered by a gradual shortening of telomeres (the protective caps on the ends of chromosomes) during each cell division. Eventually, when telomeres become critically short, cells enter a state of replicative senescence and cease to divide. This process is generally considered irreversible. Stress-Induced Senescence: This form of senescence is triggered by various stressors, such as DNA damage, oxidative stress, or cellular insults. In the context of cancer, treatments like chemotherapy and radiation therapy can induce stress-induced senescence in cancer cells. While stress-induced senescence is initially intended to halt cell proliferation, it can sometimes be reversed under certain conditions. The potential for senescence reversal in cancer cells is an active area of research and remains a topic of debate. Some studies suggest that stress-induced senescence can be reversible if the underlying stressors are removed. However, the degree of reversibility and the conditions under which it occurs are not fully understood. It is important to note that the concept of "reversing senescence" does not necessarily mean that senescent cells revert to a fully functional, healthy state. Reversal may involve a partial restoration of certain cellular functions, but these cells might not regain their full proliferative capacity. Researchers are investigating various strategies to target and manipulate senescence in cancer cells, including approaches to selectively eliminate senescent cells, alter the SASP, or induce the clearance of senescent cells by the immune system. However, these approaches are still in the experimental stages, and their clinical applicability is being explored. As of my last knowledge update in September 2021, the field of senescence research is rapidly evolving, and new insights might have emerged since then. For the latest information, I recommend consulting recent scientific literature and resources in the field of cancer biology and cellular senescence.

Discussion: First, ChatGPT starts by indicating that the senescent response is more complex when induced in tumor cells which is something generally agreed upon, taking into account the highly unsettled genetic background of cancer (Hanahan, 2022). Subsequently, ChatGPT provides a distinction between RS, which is often precipitated by telomere dysfunction (Karlseder et al., 2002), and stress-induced senescence, which can be triggered by the exposure to various cancer therapies (Fitsiou et al., 2022). In fact, the most frequent form of senescence often observed in tumor cells is TIS (Saleh et al., 2020a). ChatGPT indicates that RS is an irreversible state of growth arrest which reflects the consensus in the literature. However, some examples have been reported previously that indicate that even RS induced in non-transformed cells can be evaded. These examples, of course, show evidence that RS can be overcome following certain experimental manipulations that involve, for instance, suppression of p53 or $p16^{INK4a}$ functions (Beauséjour et al., 2003; Bond et al., 1994; Dirac and Bernards, 2003). It is noteworthy that the escape from senescence occurs in rare occasions, such as during transformation when OIS is bypassed by several mutational events which facilitates the evasion of the tumor suppressor barrier imposed by the growth arrest, and the progression towards malignancy (Kolodkin-Gal et al., 2022). Escape from OIS, which is observed as a component of premalignant lesions, has provided the basis for the proposition that pharmacological elimination of senescence might be a use therapeutic approach to mitigate cancer progression (Saleh and Carpenter, 2021).

Importantly, ChatGPT acknowledges that senescent tumor cells can revert into a proliferative state, albeit conservatively, which reflects the current debate in the literature with regard

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to the reversibility of TIS in tumor cells. Recent evidence has supported the possibility that a fraction of TIS senescent cells can, in fact, escape the SAGA and recover their proliferative capacity. For example, irinotecan-induced senescence in breast and colorectal tumor cells is reversed following a period of growth stagnation for 7 days that was accompanied by the manifestation of several senescence-associated hallmarks (Guillon et al., 2019). The reversibility of irinotecan-induced senescence was also demonstrated in immune-compromised mice, where senescent tumor cells were able to form viable tumors (Guillon et al., 2019). In confirmation, we have previously utilized cell sorting techniques to demonstrate that the observed recovery from TIS originates from an enriched senescent tumor cell population rather than only from a proliferating, non-senescent cell group that managed to avoid senescence induction after exposure to chemotherapy (Saleh et al., 2019). These observations were confirmed in primary tumor cells derived from patients diagnosed with acute myelogenous leukemia (AML), where their exposure to chemotherapy *ex vivo* results in the development of classical signs of TIS, including the SAGA, which are then reversed within a consistent time scale (Duy et al., 2021). More importantly, persistent leukemic cells in AML patients who completed their chemotherapeutic treatment exhibit transcriptomic profiles consistent with TIS and its secretory phenotype, indicating that a similar phenomenon can also be detected *in vivo* (Duy et al., 2021).

More recent evidence has suggested that the ability of tumor cells to escape the SAGA is dependent on key molecular players including c-Myc and the anterior gradient protein 2 (AGR2) (Afifi et al., 2023; Maarouf et al., 2022). For this to be the case, it is necessary for senescent tumor cells induced into senescence by exposure to chemotherapy to upregulate proliferative drivers, such as c-Myc, in order to overcome growth stagnation, as the persistent degradation of these drivers commits tumor cells in a persistent state of growth arrest. Only tumor cells with a non-degradable form of c-Myc can then repopulate following the display of senescence-associated markers including a prominent cell cycle arrest (Afifi et al., 2023). Similarly, only senescent tumor cells that exhibit an upregulation of AGR2 can resume cell division after a period of senescent cell cycle arrest (Maarouf et al., 2022). Moreover, it seems that the escape from the senescent growth arrest is accelerated under hypoxic conditions, as the suppression of antioxidant scavengers such as catalase and glutathione peroxidase-1 further enforces the growth arrest of chemotherapy-exposed senescent colon cancer cells (Borkowska

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et al., 2022). In this regard, ChatGPT seems to have missed a more recent proposition in the literature that provides a distinction between escape from senescence, which is characterized by the restoration of the proliferative capacity and resolution of senescence-associated markers such as dysregulated lysosomal biogenesis, and senescence bypass, which describes a state where senescence is evaded as part of malignant progression, where proliferation is accelerated in response to pro-tumorigenic stimulation (Evangelou et al., 2023).

ChatGPT also alludes to the fact that the reversion from TIS is not complete, and the senescence escapees do not exhibit molecular profiles identical to that prior to senescence induction. While this is true, in part, ChatGPT continues to suggest that reversion from senescence yields phenotypes that are not healthy and probably incapable of proliferating effectively. This conclusion might not be fully accurate as some of the rigorous reports in the literature unequivocally show that tumor cells that escape TIS are often aggressive and acquire more malignant phenotypes. For example, B-cell lymphoma cells induced into TIS by Adriamycin manage to escape the SAGA upon loss of p53 or Suv39h1 and exhibit wide-spectrum reprogramming that favors the development of stem cell-like characteristics leading to the formation of rapidly progressive tumors upon their implantation in immune-competent mice (Milanovic et al., 2018). Evidently, the genetic reprogramming that accompanies escape from senescence is associated with increased invasive and migratory potential of tumor cells (Palazzo et al., 2022; Yang et al., 2017b). These observations not only support the fact that escape from senescence is not an uncommon occurrence but also indicate that it is overall an unfavorable event.

While ChatGPT mentions that escape from TIS is still poorly understood, several mechanisms have been previously proposed to explain this phenomenon. These mechanisms include loss of the growth inhibitory functions of key cell cycle regulators that enforce the SAGA including p16^{INK4a} (Beauséjour et al., 2003), p21^{Cip1} (Hsu et al., 2019), upregulation of cell cycle drivers such as Cdc2/Cdk1, Cdk4, cyclin D1, cyclin B1 and c-Myc (Afifi et al., 2023; Le Duff et al., 2018; Pandey et al., 2020), nuclear relocalization of p65 (Salunkhe et al., 2021), polyploidy-driven endoduplication (Mosieniak et al., 2015; Saleh et al., 2022b), enhanced autophagic drive (Bojko et al., 2020), overcoming metabolic distress (Lee et al., 2012), cellular cannibalism

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(Tonnessen-Murray et al., 2019), and SASP-driven pro-growth stimulation (Zhang et al., 2021). While it is apparent that none of these mechanisms can alone fully explain the reversibility of senescence, it appears that escaping senescence would require extensive reprogramming before a tumor cell can escape the SAGA.

Another caveat in ChatGPT's answer to this question is the lack of any commentary on the fate of oncogene-induced senescent cells, and whether OIS is also an escapable event. As noted above, overcoming OIS is now considered a hallmark of cancer and a prerequisite for transformed cells to progress into a full-blown malignancy. This argument is supported by observations indicating that the inactivation of p53, $p16^{INK4a}$, or Rb, all important senescence-regulatory players, in premalignant cells, accelerates malignant transformation via senescence evasion (Carrière et al., 2011; Harajly et al., 2016). More specifically, Rb loss-of-function has been implicated in allowing the transformation of oncogene-induced senescent astrocytes into glioma cells (Seoane et al., 2008). An additional, highly relevant, observation demonstrated that the genetic suppression of $p27^{Kip1}$ function is permissive for Ras-induced, senescent prostatic cells to escape the SAGA, and to progress into prostatic cancer (Majumder et al., 2008). Interestingly, more recent evidence has demonstrated that the reversal from OIS can be tracked by identifying stable chromatin (epigenetic) changes that persist in the senescence escapees, collectively termed the Senescence-associated Chromatin Scars (SACSs) (Martínez-Zamudio et al., 2023). Identifying these epigenetic signatures in cancer lesions might reveal the role of senescence as an escapable tumor suppressor mechanism during malignant transformation.

Lastly, ChatGPT seems to consider that reversibility from TIS provides a strong rationale for the use of senescence-eliminating therapy. The use of compounds that selectively kill senescent tumor cells, collectively referred to as senotherapeutics, has generated wide interest (Wang et al., 2022a). Despite certain limitations that might complicate the use of senotherapeutics for cancer treatment (discussed below), many studies now favor their potential use as adjuvant therapy (Short et al., 2019). Preclinical evidence has confirmed the ability of different senotherapeutics in culling senescent tumor cells induced into senescence by various forms of anticancer treatment including conventional chemotherapy (Saleh et al., 2020b), ra-

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diotherapy (Huart et al., 2022), targeted therapy (Estepa-Fernández et al., 2023), and hormonal therapy (Saleh et al., 2020a). While further investigation is required to establish the utility of these compounds in the clinic, the use of senotherapeutics seems to be a promising strategy to eliminate the likelihood of senescent tumor cells escaping and also mitigating some of the drug-related adverse effects that might arise from the accumulation of therapy-induced senescent cells (Demaria et al., 2017). Consistent with the work of Ashraf et al. (Ashraf and Ashfaq, 2023), ChatGPT mentioned the inability to provide more information beyond September 2021, highlighting a major limitation of the current technological platform to provide the latest knowledge in the scientific literature, and as demonstrated by the discussion of some of the most recent evidence on the topic.

Q2: Is Senescence Considered a Form of Tumor Dormancy?

ChatGPT: No, senescence and tumor dormancy are not the same concepts. They refer to different biological processes, although they both relate to cell behavior. Senescence: Cellular senescence is a state in which cells cease to divide and undergo various molecular and morphological changes. It's often considered a form of permanent cell cycle arrest. Senescence can be triggered by factors such as DNA damage, telomere shortening, or oncogene activation. It's a protective mechanism that prevents damaged or potentially cancerous cells from continuing to replicate. Senescent cells are typically metabolically active but do not proliferate. They can also secrete various molecules, which is known as the senescence-associated secretory phenotype (SASP), which can have both beneficial and detrimental effects on surrounding tissues. Tumor Dormancy: Tumor dormancy refers to a situation in which cancer cells remain in a state of quiescence, where they neither proliferate nor undergo programmed cell death (apoptosis). This can occur after cancer treatment or as a natural occurrence in some cancer types. Dormant cancer cells are not actively dividing and do not contribute to tumor growth. However, they can potentially become active again and start proliferating under certain conditions, leading to disease recurrence. While both senescence and tumor dormancy involve cells that are not actively dividing, they have different underlying mechanisms and implications. Senescence is often a response to cellular stress or damage and is considered a protective mechanism against

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cancer development, whereas tumor dormancy is a phenomenon where cancer cells are temporarily inactive and can potentially contribute to cancer recurrence.

Discussion: As indicated above, ChatGPT responded to this question with a definitive answer wherein senescence and tumor dormancy were described as two, completely independent, cellular responses to different external stimuli. Moreover, ChatGPT adopts the prevailing hypothesis that cellular dormancy takes the form of cellular quiescence and largely attributes the ability of a tumor cell to recover from the state of growth arrest to be considered dormant. This is likely to apply to a quiescent cell, rather than a senescent cell. However, and as discussed earlier, senescence can still fit into the current paradigm of cellular dormancy since senescent tumor cells can, under specific circumstances, escape the SAGA (particularly in the form of TIS) as demonstrated in a variety of research papers assessing different types of cancer (Afifi et al., 2023; Duy et al., 2021; Saleh et al., 2019). Interestingly, ChatGPT refers to tumor cell senescence as a "protective", and somewhat beneficial cell stress response since it is characterized by a more stable growth stagnation in response to therapy. Despite the fact that senescence plays several useful physiological roles (mostly in somatic cells, e.g., in the context of wound healing or embryonal development (Zeng, 2007)), and acknowledging that therapy-induced growth arrest, even if transient, can prolong patient survival, it recognizes that TIS provides an avenue whereby tumor cells persist, evade apoptosis, resist cytotoxic therapy, and then escape and recover proliferative capacity (DeLuca and Saleh, 2023). It is also worth mentioning that while generating this response, it seems that ChatGPT based its answer on established research that describes the stability of the SAGA solely in the context of replicative senescence. Moreover, several opinion and review articles have recently argued quite convincingly that senescence could represent a form of tumor dormancy leading to cancer relapse, which have been overlooked by ChatGPT (Kirkland, 2023; Truskowski et al., 2023)(Chiu et al., 2023).

ChatGPT continues by providing the definition of tumor dormancy which aligns with the general consensus in the field, as it describes it as a state of reversible growth arrest with minimal metabolic activity and emphasizes the fact that, in this state, tumor cells can begin

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replicating again under favorable conditions leading to disease recurrence (Páez et al., 2012). ChatGPT concludes by demonstrating that senescence and tumor dormancy occur through different cellular pathways, in response to different stimuli and for different purposes. However, several recent studies that investigated possible similarities between components of the senescence phenotype and hallmarks of dormancy suggest the existence of a link between the two processes (Chiu et al., 2023); more specifically, potential connections between hallmarks of senescence and angiogenic, immunogenic and cellular forms of tumor dormancy have been proposed. With respect to angiogenic dormancy, it is hypothesized that in a poorly vascularized, hypoxic area of a tumor, cells undergo both quiescence and senescence; in such cases, the SASP could contribute to the angiogenic switch required by tumor cells to escape the dormant state through the release of certain cytokines such as VEGF, IL-6, and FGF, which was observed in both *in vitro* and *in vivo* studies that investigated the role of the SASP in the formation of blood vessels in tumors (Mikuła-Pietrasik et al., 2016). In addition, for tumor cells to be considered dormant, it is essential to have the ability to escape immunosurveillance and remain undetected until they can replicate again, which is often representative of immunogenic dormancy. Interestingly, cells in a senescent state have been shown to evade immunosurveillance through two fundamental process: either by directly suppressing the immune system, for example by the up-regulation of programmed death-ligand 1 (PD-L1) (Shahbandi et al., 2022) or by creating an immunosuppressive microenvironment, for instance by interfering with macrophage polarization, favoring their differentiation into M2 macrophages with reduced or suppressed anti-tumor effects (Sen et al., 2022). Finally, senescence can also fit into the cellular dormancy paradigm. Firstly, it was demonstrated that both cancerous and non-cancerous senescent cells contribute to the emergence of cancer stem cell phenotypes (Muñoz-Galván et al., 2019), which are permissive for more invasive and resistant tumor behavior (Al-Hajj et al., 2003; Talukdar et al., 2019). Secondly, the role of autophagy in maintaining the survival of dormant cells (Zhang et al., 2009) had been documented and observed in senescent cells as well (Milczarek et al., 2018), which was also shown to have a role in facilitating the escape from growth arrest in both states (Lazova et al., 2012; Was et al., 2017). Thirdly, polyploidy, a predominant feature of senescent tumor cells, has been shown to contribute to the emergence from suppressed growth and acquisition of stemness in dormant tumor cells (Zhang et al., 2014) and senescence (Mosieniak and Sikora,

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2010; Saleh et al., 2022b) leading to features of tumor cell re-emergence in preclinical models of both states. Recent unpublished data has also suggested that melphalan-exposed multiple myeloma cells that display features of TIS share common dormancy signatures. Interestingly, in a mouse model of intracerebral B16F10 melanoma tumors that existed in a dormant phase following radiation, molecular analysis revealed that these tumors exhibit senescence-associated signatures including upregulated $p16^{INK4a}$, $p21^{Cip1}$, SA-β-gal, and reduced Ki-67, strongly suggesting that residual tumor cells in a dormancy-like state might also be in a senescent state (Ridwan et al., 2023).

Although still awaiting definitive proof, correlative evidence points to a potential connection and a phenotypical overlap between senescence and tumor dormancy, a proposition that is overlooked by ChatGPT. These reservations and limitations aside, ChatGPT did, in fact, provide a fairly accurate reflection of the overall sense in the field, where senescence is not yet accepted as a form of tumor dormancy, and is only gradually receiving recognition. Lastly, and in support of the utility and relevance of ChatGPT's analysis, a recent viewpoint article by several respected scientists in the field of tumor dormancy insisted on the exclusion of senescence as a possible dormancy mechanism (Agudo et al., 2024). These authors argued that alternative hypotheses to the reversible quiescence theory, especially in the context of re-emergence of leukemic stem cells, are still nascent (Agudo et al., 2024).

Q3: What Markers Are Utilized to Detect Senescent Tumor Cells in Patients?

ChatGPT: Detecting senescent tumor cells in patients can be a challenging task, as these cells often exhibit complex and heterogeneous characteristics. Researchers have been developing various markers and techniques to identify senescent cells within tumors. Some of the markers and methods used for detecting senescent tumor cells include:

1. Senescence-associated beta-galactosidase (SA-β-gal): SA-β-gal is a commonly used marker for senescent cells. It is detected using a histochemical assay, and senescent cells typically exhibit increased SA-β-gal activity, which results in a blue staining pattern. However, SA-β-gal

staining alone may not be specific to senescence and may require additional markers for confirmation.

2. Senescence-associated secretory phenotype (SASP): Senescent cells often produce and secrete various molecules collectively known as the SASP. Components of the SASP, such as cytokines, chemokines, and growth factors, can be detected in patient samples using techniques like ELISA (enzyme-linked immunosorbent assay) or RNA sequencing.
3. $p16^{INK4a}$ expression: Increased expression of the $p16^{INK4a}$ protein is a characteristic feature of many senescent cells. Immunohistochemistry or immunofluorescence staining can be used to detect $p16^{INK4a}$ expression in tumor tissues.
4. DNA damage markers: Senescent cells often have DNA damage, and the presence of DNA damage markers such as γ-H2AX (phosphorylated histone H2AX) can be used to identify senescent cells within tumors through immunostaining.
5. Ki-67 and PCNA: Ki-67 and PCNA (proliferating cell nuclear antigen) are markers of cell proliferation. Senescent cells typically show reduced Ki-67 and PCNA staining, as they have exited the cell cycle. Therefore, a decrease in the expression of these markers can suggest the presence of senescent cells.
6. Telomere-associated markers: Senescent cells often have shortened telomeres. Techniques such as fluorescence in situ hybridization (FISH) or quantitative PCR (qPCR) can be used to measure telomere length in tumor cells, and short telomeres may indicate senescence.
7. Cell cycle arrest markers: Senescent cells are typically in a state of cell cycle arrest. Detection of markers associated with cell cycle arrest, such as $p21^{Cip1}$ or $p27^{Kip1}$, through immunohistochemistry or Western blotting, can provide evidence of senescence.
8. Senolytic markers: Senolytic drugs selectively kill senescent cells. By administering senolytics and monitoring the reduction in senescent cell markers in response, researchers can indirectly detect the presence of senescent tumor cells.

It's important to note that a combination of multiple markers and techniques is often used to identify senescent tumor cells more accurately. The choice of markers and methods may also depend on the specific context and type of cancer being studied. Additionally, the field of senescence research is continually evolving, and new markers and detection methods may emerge in the future.

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Discussion: The identification of the development of TIS in tissues obtained from patients receiving various forms of cancer therapy is essential for understanding its role in dictating the tumor cell response to therapy and overall treatment outcomes. In agreement with ChatGPT's response, identifying TIS in patient's samples is a challenging task. This is primarily due to technical difficulties in obtaining and processing patients' samples and the inability to define a characteristic molecular signature to identify senescence *in vivo* (Saleh et al., 2023). While many classical markers of senescence are routinely used to detect TIS in cell culture or animal tissue, some seem to have limited utility when applied to human tissue. ChatGPT accurately describes some of the markers that have been used to detect TIS in clinical human tissue. Of course, many of the listed markers are also frequently utilized for the investigation of TIS in tumor cell models in the preclinical setting.

ChatGPT first mentions that the utilization of the classical senescence marker SA-β-gal to detect senescence in human tissue, and then indicates that its use can be limited by lack of specificity (Severino et al., 2000). In addition, SA-β-gal requires the use of freshly frozen tissues which makes it applicable only to clinical scenarios where the histopathological diagnosis of cancer can be made using non-fixed tissue. Unfortunately, formalin-fixed paraffin-embedded samples that are most routinely used for cancer diagnosis are not applicable for SA-β-gal staining. Moreover, the burden of SA-β-gal positive cells increases with age in human tissue, and thus, the utilization of SA-β-gal staining in human samples should be carefully matched with the patient's age (Yang and Hu, 2005). ChatGPT proposes that senescence-associated proteins such as $p16^{INK4a}$, $p21^{Cip1}$, PNCA, Ki67, and γH2AX can be used to identify TIS in human tissue using immunohistochemical techniques. In agreement, the utilization of all these markers has been reported previously. However, the measurement of protein expression of these markers can be complicated by difficulty determining the baseline expression of each before exposure to the senescence-inducing chemotherapy, lack of a universal scoring and reporting methods that characterize their measurement, and their lack of expression due to mutational deletion (Saleh et al., 2023). For example, homozygous deletion of $p16^{INK4a}$ is very common among several types of cancer which precludes its routine use to identify TIS in human

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cancer samples (Zhao et al., 2016). Furthermore, the changes in the expression level of p16^{INK4a} and p21^{Cip1} that reflect the development of TIS can be affected by the time of tumor sample collection relative to onset of anticancer treatment, thereby leading to false-negative results (Kohli et al., 2021). Moreover, these markers, which are often reliable in *in vitro* systems to reflect the induction of senescence, can be of limited value *in vivo* (Saleh et al., 2021), as for instance, p21^{Cip1} was shown to be induced in response to DNA damage in the absence of additional senescence-associated hallmarks (Karimian et al., 2016). Other markers of senescence that have been investigated in patients' cancer samples include: p53 (Bascones-Martínez et al., 2012), p14^{ARF} (Pare et al., 2016), p27^{Kip1} (Lehners et al., 2018), γH2AX (Lehners et al., 2018), H3K9Me3 (Saleh et al., 2021), Lamin B1 (Saleh et al., 2022a), Ki67 and PCNA (Seebauer et al., 2016), DEC1 (Zhu et al., 2013), and SASP factors IL-6 (Lee et al., 2017) and IL-8 (Tato-Costa et al., 2016). Of note, proposing the investigation of Lamin B1, DEC1, and the heterochromatic foci formation has been overlooked in this ChatGPT's response.

Despite the limitations mentioned previously, there is a fairly strong body of evidence in support of the capability to identify TIS in tumor samples obtained from cancer patients. Of these, the most robust evidence arises from studies that measured multiple senescence-associated markers simultaneously, which is suggested by ChatGPT as a methodological necessity in this response. For example, a three-marker signature of Lamin B1, Ki67, and p16^{INK4a}, showed that TIS is evident in roughly 40% of breast tumor samples exposed to neoadjuvant chemotherapy (Al Shboul et al., 2023; El-Sadoni et al., 2023). It is logical that this approach was missed by ChatGPT due to its availability only after the last update of the AI platform. A signature of lipofuscin, p16^{INK4a}, p21^{Cip1} and Ki67 also demonstrated the existence of senescence as a primary component of tumor biology in a set of lung cancer samples (Domen et al., 2022). In cancers where intraoperatively obtained frozen samples were available, SA-β-gal staining/SA-β-gal expression was coupled with downregulated expression of Ki67 and Lamin B1, supporting the development of senescence in human malignant tissue (Cotarelo et al., 2016). Other evidence, although utilizing a smaller sample number or single or individually tested markers of senescence, has demonstrated the existence of senescence in tumor samples of rectal cancer (Tato-Costa et al., 2016), hepatocellular carcinoma (Lee et al., 2017), bladder cancer (Aljabery et al., 2018), and sarcomas (Giatromanolaki et al., 2020). Lastly, ChatGPT suggests that the use of senolytics to confirm the senescent status of tumor cells can be used as an additional means to test for senescence. While this indirect method to confirm senescence whereby tumor cells that are amenable to senolysis are likely to be senescent has been used in cell culture models, it is unlikely to be of utility clinically since compounds with senolytic activity have not yet been approved for that purpose.

Overall, ChatGPT has provided an accurate delineation of the possible, and currently utilized, approaches for the identification of TIS in human cancer samples and acknowledged the challenges frequently encountered for this purpose. Despite overlooking some complexities, ChatGPT's answer to this question appears to be relatively thorough and reliable.

Q4: Is Senolytic Therapy a Useful Approach for The Treatment of Cancer?

ChatGPT: Senolytic therapy is not a standard or primary treatment for cancer. Senolytics are a class of drugs that target senescent cells, which are cells that have stopped dividing and can accumulate in tissues as we age. These cells are associated with various age-related diseases and conditions, but their role in cancer is more complex. In cancer treatment, the primary approach is to target and eliminate cancer cells, which are actively dividing and spreading. Traditional cancer treatments such as surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapies are designed to kill or remove cancer cells and control the growth of tumors.

Senolytics may have some potential in cancer treatment as an adjuvant therapy, meaning they could be used in combination with standard cancer treatments. The rationale is that senescent cells can influence the tumor microenvironment, potentially making it more favorable for cancer progression. By removing senescent cells, senolytics might help improve the effectiveness of standard cancer therapies and reduce side effects associated with senescent cell accumulation. However, it's essential to note that the use of senolytics in cancer therapy is still an area of ongoing research, and their safety and efficacy in this context are not well-established. Additionally, the relationship between senescent cells and cancer is not fully

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understood, and the effects of senolytics on cancer cells themselves are complex and may vary depending on the specific cancer type.

For cancer treatment, it's crucial to follow established guidelines and protocols recommended by oncologists and healthcare professionals. If you or someone you know is dealing with cancer, it's essential to consult with a healthcare provider who specializes in oncology to determine the most appropriate and evidence-based treatment plan. Senolytics, if proven effective and safe, may become a complementary therapy in the future, but they are not a standalone treatment for cancer at this time.

Discussion: ChatGPT begins by defining senolytics as drugs that selectively kill senescent cells. These compounds have now been extensively investigated in aging-associated disease models and their positive effects in the mitigation of some of these processes has been confirmed, including in models of Alzheimer's disease (Zhang et al., 2019), osteoarthritis (Dai et al., 2020), heart failure (Redgrave et al., 2023), and diabetes (Palmer et al., 2021). However, their utility in cancer treatment is still under evaluation as an element of the larger question of whether senescence is or is not a favorable outcome in cancer treatment.

ChatGPT proceeds by suggesting that senolytics are effective in improving the prognosis and side effect profile of cancer therapy. Although mentioned briefly and without further explanation, the answer is nevertheless consistent with the results demonstrated by most preclinical evidence on the capability of senolytics to eliminate senescent tumor cells and delay tumor recurrence in different tumor models, including those of breast cancer (Yang et al., 2021), prostate cancer (Carpenter et al., 2021a), and head and neck cancer (Ahmadinejad et al., 2022), in addition to their ability to alleviate some chemotherapy-associated adverse effects (Acklin et al., 2020; Demaria et al., 2017; Saleh et al., 2024), (Baar et al., 2017; Budamagunta et al., 2024). In addition to inducing apoptosis selectively in senescent cells, senolytics have also been shown to modify the tumor microenvironment in a manner that makes it more hostile to tumor cells. This is largely driven by reducing the number of regulatory T lymphocytes and thus increasing the infiltration of immune cells into the tumor (He et al., 2020; Kolb et al., 2021). Another potential use of senolytics is their role in preventing the progression of precancerous

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lesions as supported by some initial studies (Chang et al., 2016; Saleh et al., 2022c), although this is fairly recent, and likely to be missed by ChatGPT based on its last update.

Next, ChatGPT alludes to the lack of comprehensive information about how exactly senescent and cancer cells can react with and affect each other, indicating a concomitant scarcity of knowledge on how senolytics affect cancer progression; here, ChatGPT concludes by mentioning that senolytics might serve as add-on drugs with chemotherapeutics when their potential actions are revealed and fully understood. Recently, the effectiveness of senolytic therapy in the killing of cancer cells evident from laboratory studies has led to the suggestion for a new therapeutic approach in cancer treatment, specifically a "one-two punch", in which senescence-inducing chemotherapy is administered to promote TIS, followed by the delivery of senolytics to eliminate the accumulating senescent tumor cells. Promising finding have been reported in both *in vivo* and *in vitro* models of T cell malignancies (Qing et al., 2021), malignant meningioma (Yamamoto et al., 2021), and head and neck carcinoma (Ahmadinejad et al., 2022), opening doors to the possibility of a new strategy in cancer treatment.

In this context, several pharmacological agents have now been extensively investigated as senolytics. The prototypical family of compounds that showed the most reliable senolytic activity against senescent cells of various forms, including TIS, are the BH3 mimetics. Of those, navitoclax (ABT-263), provided the most universal senolytic effect against a wide variety of senescent tumor cells models. Navitoclax, which non-selectively inhibits BCL-2, BCL-X_L, and BCL-w, exploits the dependence of therapy-induced senescent tumor cells on BCL-X_L for their survival, to exert a pro-apoptotic effect (Bharti et al., 2022; Selt et al., 2023; Skwarska and Konopleva, 2023). In comparison, the role of BCL-2 and BCL-w in the survival of senescent tumor cells, and thus, their susceptibility to BH3 mimetics that selectively target these molecules, is not well established. For example, while venetoclax, a selective BCL-2 inhibitor (ABT-199), has been shown to exert a senolytic activity in models of senescent breast tumor cells (As Sobeai et al., 2022; Softah et al., 2023), its senolytic effect is restricted to tumor cell models where BCL-2 appears to play a critical role in the survival of senescent tumor cells (Rahman et al., 2022; Saleh et al., 2020b). ABT-737, which inhibits both BCL-2 and BCL-X_L, has also shown effective senolytic potential in TIS models in a somewhat similar fashion to

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navitoclax, primarily due to its capacity for BCL-X_L-targeting (Rysanek et al., 2022). In addition to BCL-2 targeting drugs, MCL-1 inhibitors have also emerged as powerful senolytics in senescent tumor cell models, especially in those variants that exhibit resistance to BCL-X_L targeting (Troiani et al., 2023), as well as in systems where other pro-apoptotic proteins, such as NOXA, play a more direct role in conferring sensitivity of senescent tumor cells to BH3 mimetics (Shahbandi et al., 2020) (Al Shboul et al., 2023).

In addition to pharmacological agents that interfere with apoptosis resistance of senescent tumor cells, an array of other agents, although not thoroughly investigated, have shown similar senolytic potential in eliminating senescent tumor cells. These agents include the BET degrader ARV825 (Wakita et al., 2020b) (Finnegan et al., 2022a) (Elshazly et al., 2023a), the Na^+/K^+ ATPase blockers digoxin and ouabin (Guerrero et al., 2019), the mTOR inhibitors temsirolimus and AZD8055 (Fung et al., 2009) (Wang et al., 2019)), and the natural flavonoid fisetin (Zhu et al., 2017). Others that have shown modest potential to serve as reliable senolytics to eliminate senescent tumor cells include the HDAC inhibitor panobinostat (Samaraweera et al., 2017) and the HSP90 inhibitor DMAG-17 (Fuhrmann-Stroissnigg et al., 2017). Newer agents that are showing promising potential as senolytics in various senescence models include UBX-1325 (Quarta and Demaria, 2024), PROTAC 753B (Jia et al., 2023), and CUDC-907 (Al-Mansour et al., 2023). As a component of clinical trials, several senolytics are being investigated, although none in the context of TIS and cancer treatment. Efforts currently are focused on testing these senolytics for the mitigation of several aging-related pathologies. For example, D+Q is being investigated for its ability to improve Alzheimer's disease-associated cognitive, functional, and physical dysfunction (Gonzales et al., 2022). Moreover, D+Q is being investigated for the mitigation of chronic kidney disease and pulmonary fibrosis [NCT02848131, NCT02874989]. Preliminary data have indicated that D+Q can, in fact, reduce the accumulation of senescent cells in vivo (Hickson et al., 2019). In addition, D+Q improved physical function in a subset of patients with idiopathic lung fibrosis, although this effect appeared to be independent of senescence modulation (Hickson et al., 2019).

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Despite their promise, the potential utilization of senolytics is associated with several limitations. First, a major problem with senolytic therapy is lack of universality, in that senolytic agents show variable effectiveness depending on the type of tumor cell model and the modality that triggered TIS (Carpenter et al., 2021b). For example, navitoclax showed reduced effectiveness when used against androgen-deprivation induced prostate senescent cells compared with radiation induced senescent cells (Malaquin et al., 2020). Moreover, the most frequently tested senolytic cocktail D+Q shows minimal effect against senescent tumor cell and other cell models (Kovacovicova et al., 2018) (Torrance et al., 2023). This variability in the senescence-killing potential of senolytics was also observed among different tumor cell lines of the same malignant origin, exposed to the same senescence inducer under the identical conditions, as seen in breast cancer cell lines treated with navitoclax (Shahbandi et al., 2020). Specifically, the *TP53*-WT breast tumor cell lines SKBR7, Cal51, 4226 were sensitive to navitoclax following induction into TIS doxorubicin, while HCC1428, ZR75-30, and MPE-600 cells were resistant or showed no selective seno-sensitivity to navitoclax (Shahbandi et al., 2020). One possibility to explain this is that, as mentioned previously, some tumor cells show higher dependence on proteins other than the navitoclax targets, BCL-2 and BCL-X_L, for their survival, such as MCL-1 (Troiani et al., 2022).

In addition, senolytics are associated with adverse effects because of their lack of selectivity. For instance, navitoclax, which has been shown to be the most effective senolytic in tumor cell models undergoing TIS, is associated with significant thrombocytopenia, impaired osteoblast function and neutropenia (de Vos et al., 2021; Karnewar et al., 2023; Sharma et al., 2020). Subsequently, the development of novel senolytic drugs as well as the identification of different senolytic targets is an area of active research, and various alternative agents are continuously being identified and tested for their efficacy and specificity against senescent tumor cells and their normally dividing counterparts.

Overall, ChatGPT provided a useful summary of the established view on the possible utility of senotherapeutics in cancer therapy and provided some relevant insights that are commensurate with the current consensus in the field.

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Q5; What Is the Connection Between Senescence and Autophagy as Responses to Cancer Therapy?

ChatGPT: Senescence and autophagy are two cellular processes that play important roles in the response to cancer therapy, although they can have different and sometimes opposing effects.

Senescence: Cellular senescence is a state in which cells lose their ability to divide and proliferate. It is often triggered by various stresses, including DNA damage caused by cancer therapies such as chemotherapy and radiation. Senescence is considered a tumor-suppressive mechanism because it prevents damaged cells from continuing to divide and potentially becoming cancerous. Senescent cells can be eliminated by the immune system, which contributes to their role in cancer therapy. In the context of cancer treatment, the induction of senescence in cancer cells is a desirable outcome. It can lead to the arrest of tumor growth and potentially long-term control or even regression of the cancer. Senescence is particularly important when cancer cells are resistant to apoptosis (programmed cell death), as it provides an alternative means to stop their growth.

Autophagy: Autophagy is a cellular process that involves the degradation and recycling of cellular components, including organelles and proteins. It can be both pro-survival and pro-death, depending on the context. In the context of cancer therapy, the relationship between autophagy and treatment response can be complex:

Pro-survival autophagy: In some cases, cancer cells can activate autophagy as a survival mechanism in response to stress induced by therapy. This allows cancer cells to degrade damaged molecules and organelles, promoting their survival and resistance to treatment. In this scenario, inhibiting autophagy can sensitize cancer cells to therapy.

Pro-death autophagy: On the other hand, autophagy can lead to cell death, known as autophagic cell death, especially when it is excessive or when key autophagic regulators are disrupted. Some cancer therapies are designed to induce this form of cell death in cancer cells.

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So, the connection between senescence and autophagy in the context of cancer therapy is somewhat intertwined. Senescence is generally seen as a way to suppress tumor growth, whereas autophagy can either promote cell survival or contribute to cell death. The specific outcome depends on the type of cancer, the therapeutic approach, and the cellular context. Researchers are actively studying these processes to better understand their roles in cancer therapy and to develop more effective treatments by targeting them selectively.

Discussion: ChatGPT started by defining both senescence and autophagy. However, the senescence definition provided by ChatGPT has limited accuracy as we mentioned earlier and that senescence induction in tumor cells may be not a desirable outcome as it limits the therapeutic benefits of various chemotherapeutic agents (Carpenter et al., 2021b; DeLuca and Saleh, 2023; Finnegan et al., 2022a; Saleh et al., 2020b; Saleh and Gewirtz, 2022). Then, ChatGPT discussed the autophagic process, which occurs in the cytoplasm, where damaged organelles and misfolded proteins are degraded and recycled in order to maintain cellular homeostasis, and survival, in part via energy generation (Rangel et al., 2022). This recycling machinery is triggered in response to a variety of cellular insults including ER-stress, unfolded proteins, starvation as well as nutrient deprivation (Xu et al., 2022). The autophagic flux involves phagophore nucleation, autophagosome formation, and autophagosome-lysosome fusion, generating autophagolysosomes in which the degradation of the cytoplasmic cargos take place (Finnegan et al., 2022b; Lamb et al., 2013).

The role of the autophagic machinery continues to attract attention in the cancer biology field, as tumor cells can induce autophagy for their survival, with many pre-clinical and clinical studies assessing whether targeting the autophagic flux could serve as adjuvant therapy (Elshazly and Gewirtz, 2023a; Elshazly and Gewirtz, 2023c; Pasquier, 2016). Furthermore, anti-neoplastic agents can induce different forms of autophagy in tumor cells (Sharma et al., 2014b). ChatGPT mentioned that autophagy may have different roles, however omitting the non-protective and cytostatic roles (Elshazly and Gewirtz, 2023c; Elshazly and Gewirtz, 2023d; Sharma et al., 2014b). ChatGPT highlighted that the specific autophagic response is based on the tumor/cell line, and the chemical nature of the compounds being utilized, which is widely accepted in the scientific literature (Elshazly and Gewirtz, 2023a; Elshazly and Gewirtz, 2023d;

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Elshazly et al., 2022). In non-protective autophagy, autophagy induction or targeting does not significantly contribute to tumor cell survival (Elshazly et al., 2023b; Xu et al., 2022); for instance, non-protective autophagy is induced by a combination of fulvestrant plus palbociclib in ER^+ breast cancer cell lines, where autophagy targeting genetically or pharmacologically does not affect the cells viability (Finnegan et al., 2022a; Finnegan et al., 2022b). Alternatively, autophagy induction may be responsible for a growth arrested state, a form known as cytostatic autophagy (Elshazly and Gewirtz, 2023b; Sharma et al., 2014a). This form of autophagy is usually accompanied by senescence induction; for instance, encorafenib, a BRAF-targeted therapy (Davis and Wayman, 2022; Li et al., 2016), induced a cytostatic form of autophagy, in addition to senescence in melanoma cells (Elshazly and Gewirtz, 2023a; Li et al., 2016).

However, senescence induction is not limited to an association solely with cytostatic autophagy. For instance, Wakita et al (Wakita et al., 2020a) showed that ARV-825, a BET inhibitor/degrader (Finnegan et al., 2022a; Wu et al., 2021), induced senolysis in various senescence models primarily through autophagy induction, where autophagy targeting suppressed ARV-825's senolysis abilities (Elshazly and Gewirtz, 2023b). Our lab has also shown that non-protective autophagy may be accompanied by senescence induction, in the case of fulvestrant plus palbociclib in ER^+ breast cancer cells (Finnegan et al., 2022a). Furthermore, senescence may be induced together with cytoprotective autophagy as reported by Yang et al. (Yang et al., 2013), where knockdown of ROC1 E3 ubiquitin ligase induced both responses in liver carcinoma. Of note, autophagy induction is not always accompanied by senescence, as shown by our own studies where tamoxifen in combination with ARV-825 triggered the autophagic machinery without senescence induction in ER^+ breast cancer cells (Elshazly et al., 2023a). Overall, autophagy and senescence usually occur in parallel as both are stress responses (Gewirtz, 2009; Gewirtz, 2013); the relation between these cellular responses is complex and shares various signaling pathways, highlighting the need for further investigation to fully understand their connection(s). For this question, ChatGPT's response was relatively sufficient to demonstrate some of the established connections between therapy-induced senescence and autophagy but lacked a more accurate discussion of some of the complexities.

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Q6: Does the induction of Therapy-Induced Senescence (TIS) in cancer facilitate the removal of the tumor cells by the immune system?

ChatGPT: Therapy-Induced Senescence (TIS) is a phenomenon where cancer cells exposed to certain cancer therapies, such as chemotherapy or radiation, enter a state of cellular senescence. Senescence is a state in which cells lose their ability to divide and grow, essentially becoming "dormant" rather than undergoing programmed cell death (apoptosis). This process is thought to be a cellular defense mechanism against unchecked cell growth. While TIS can potentially have benefits in cancer treatment, it doesn't necessarily guarantee the immune system's removal of tumor cells on its own. TIS can influence the immune response in several ways:

1. Immunogenicity: Some senescent cells release signals and molecules that can attract immune cells to the tumor site. This can potentially lead to an immune response against the tumor.

2. Antigen Presentation: Senescent cells may present tumor-specific antigens, which can activate the immune system to recognize and attack cancer cells.

3. Senescence-Associated Secretory Phenotype (SASP): Senescent cells often secrete a mix of cytokines and chemokines known as SASP. Some of these factors can recruit immune cells, such as cytotoxic T cells and natural killer cells, to the tumor microenvironment.

However, TIS isn't always sufficient for complete tumor clearance by the immune system. Several factors come into play:

1. Immunosuppression: Tumors can develop ways to evade the immune system, creating an immunosuppressive microenvironment that hinders immune cell function.

2. Tumor Heterogeneity: Tumors are often composed of a mix of different cell types, some of which may not undergo senescence, making them resistant to immune-mediated clearance.

3. Tumor Progression: Even if the immune system initially responds to TIS, cancer cells may evolve and develop resistance to the immune attack over time.

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In some cases, combining therapies that induce TIS with immunotherapies, which enhance the immune response against cancer, can be more effective in achieving tumor clearance. For example, checkpoint inhibitors (e.g., PD-1 or PD-L1 inhibitors) can be used to enhance the immune response against senescent cancer cells. In summary, while Therapy-Induced Senescence can potentially enhance the immune system's ability to target and eliminate cancer cells, its success depends on various factors, and it may not lead to complete tumor clearance on its own. Combining TIS-inducing therapies with immunotherapies is an area of active research to improve cancer treatment outcomes.

Discussion: ChatGPT provided an overview of the relationship between TIS and the immune system by presenting three primary mechanisms that can affect the immune response to TIS. First, immunogenicity is indeed a critical part of how senescent tumor cells can regulate the immune response; the cells can release various molecules (via the SASP) that can attract immune cells to the tumor site leading to anti-tumor or pro-tumor response depending on a variety of factors. For example, Marin *et al*, demonstrated that doxorubicin-induced senescence (in cancer and non-cancer cells) upregulated damage-associated molecular patterns (DAMPs) markers along with MHC-I, resulting in the activation and accumulation of dendritic cells (DCs) and natural killer (NK) cells leading to an anti-cancer effect accompanied by an efficient delivery of antigens to DCs (Marin et al., 2023). Furthermore, Borrelli *et al.*, reported that doxorubicin and melphalan induced senescence in multiple myeloma cells could lead to up-regulation of IL15/IL15RA complex, thus stimulating NK cell activation, proliferation, and maturation, possibly contributing to anti-tumor effects (Borrelli et al., 2018). In a non-cancer context, Extracellular vesicles (EVs) released from radiation-induced senescent cholangiocytes upregulated IL-1β and TNF expression levels and induced the migration and activation of human monocytes, creating a proinflammatory environment which might promote anti-tumor effects (Al Suraih et al., 2020). On the other hand, EVs released from senescent cells can also have pro-tumorigenic effects and reinforce cancer cell proliferation (Wang et al., 2022a). The SASP produced by senescent tumor cells has also been shown to include components of the complement system, although the role of the complement system in mediating the immune response against senescent tumor cells has not been elucidated yet (Abu-Humaidan et al., 2024).

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Secondly, it was shown that senescent cells exhibit an altered immunopeptidome (Marin et al., 2023), resulting in the presentation of unique subsets of antigens that are neither expressed by their normal counterparts nor identified in the Mouse Immunopeptidome Atlas (Marin et al., 2023). These senescence-associated self-peptides (derived from the altered proteome of senescent cells) can activate CD8+ T cells, further contributing to the immune response against the tumor (Marin et al., 2023). Muti-omics analyses of several human and mouse fibroblasts and various cancer cell lines induced into senescence by various agents *in vitro* and *in vivo* settings showed upregulation of IFN transcriptional signatures, including MHC-I molecules. These events would lead to the activation of CD8+ T and the recruitment and activation of DCs, suggestive of anti-tumor activity and the possible utilization of senescent cancer cells for 'immunization' intervention (Marin et al., 2023). Another recent *in vivo* study reported complementary findings where senescence induction could lead to enhanced immune recognition, upregulation of the IFNγ receptor and its downstream signaling pathway, accompanied by the activation of CD8+ T lymphocytes and macrophages (Chen et al., 2023).

The relationship and the interaction between the SASP and the immune cells are highly context dependent and tissue specific (Kale et al., 2020; Takasugi et al., 2022). The SASP comprises cytokines, chemokines, and various factors that influence immune cells. These components can have a dual role in either facilitating or impeding the removal of senescent cells (Wang et al., 2022a). Early evidence of how SASP factors promote clearance of senescent cells by the immune system came from liver fibrosis and liver carcinoma mouse models in which senescence was induced *in vivo* leading to upregulation of a ligand for an NK cell activating receptor (NKG2D); this promotes NK cell-mediated cytotoxicity to eradicate senescent cells (Iannello et al., 2013; Krizhanovsky et al., 2008). Another *in vivo* liver carcinoma model showed that restoration of functioning p53 could lead to tumor regression resulting from differentiation and the upregulation of various SASP-related inflammatory cytokines mediated by infiltrating macrophages and NK cells (Xue et al., 2007).

SASP-induced immunosuppression tends to support tumor growth, particularly in the later stages of tumor progression. However, in the early stages of tumorigenesis, SASP can act as a tumor suppressor (Eggert et al., 2016). As ChatGPT suggested, the SASP can indeed recruit and attract immune cells to the tumor microenvironment; however, it is not necessarily exhibiting an anti-tumor profile. For example, senescent thyroid cells released a SASP that was able to skew macrophage polarization to the M2 phenotype under PGE2 regulation (Mazzoni et al., 2019), a prominent SASP factor (Kale et al., 2020). On the other hand, senescent hepatic stellate cells secrete various chemokines and cytokines, including IL-8 and IL-6, that attract macrophages and have the ability to convert them from a pro-tumorigenic, anti-inflammatory M2 phenotype to the proinflammatory-cytotoxic M1 phenotype (Irvine et al., 2014). The removal of these $p16^{INK4a}$/SA-β-gal (+) macrophages (M2 phenotype) resulted in the resolution of the inflammatory process (Hall et al., 2017). Furthermore, it was shown that naive and effector T cells can be induced into senescence and exhibit cytokine profiles indicative of potent suppressive and pro-tumorigenic functions (Ye et al., 2012). Adding another layer of complexity to how senescence interacts with the immune system, it was shown that murine macrophages exhibited features of senescence such as increased expression of $p16^{INK4a}$, reduced proliferation, SA-β-gal activation, and increased mRNA expression of the SASP, indicating that these cells a subclass of macrophages rather than senescent cells (Hall et al., 2016; Liu et al., 2019). Paradoxically, Lujambio *et al.*, utilized an *in vivo* model to demonstrate that ablation of p53-dependent senescence program in hepatic stellate cells skewed macrophage polarization towards a tumor-inhibiting M1-state capable of targeting senescent cells (Lujambio et al., 2013). However, whether immune cells, including NK cells and macrophages and their polarization, undergo senescence is an active field of research and will deepen our understanding of the immune-senescence relationship (Antonangeli et al., 2019; Zhou et al., 2021).

Additional evidence as to how the SASP can serve a paradoxical role in the context of the immune system in relation to cellular senescence was reported by Di Mitri *et al*, (Di Mitri et al., 2014). On one hand, the SASP can impede tumor growth by strengthening autocrine senescence and triggering paracrine senescence in adjacent tumor cells through the release of IL-1α. However, the SASP can also exhibit immunosuppressive properties, attracting a substantial influx of myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment. Such an effect will cause the immunosuppression of infiltrating immune cells such as natural killer cells (NK) and T cells (Salminen et al., 2018). Sagiv *et al.*, reported that NK cells were able to clear

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senescent human fibroblasts; however, this effect was abolished by the MDSC suppressive functions (Sagiv et al., 2016). Additionally, it was shown that doxorubicin induced senescence in breast cancer cells resulted in increased sensitivity to cytotoxicity of activated CD4+ T cells and by cytotoxic natural killer cells (Inao et al., 2019); similar to Sagiv *et al.,* the clearance of breast senescent cancer cells would be suppressed by the MDSCs. Nevertheless, the extent of these effects and precise mechanisms of how MDSCs interact with senescent tumor cells requires further investigation in both *in vitro* and *in vivo* settings.

Over the last few years, the cGAS-STING pathway has begun to attract significant attention in the cellular senescence field, particularly in terms of its interaction with and influence of the immune response and the concepts of immunosenescence and immunosurveillance (Chen and Xu, 2023) (Lian et al., 2020)); however, ChatGPT neglected todiscuss this aspect. Senescent cells, regardless of the inducing moiety, are known to lose their nuclear envelope integrity (characterized by Lamin B1 degradation), which makes the cells a source of chromatin fragments, micronuclei and mitochondrial DNA, all of which are considered activators of the cGAS-STING signaling pathway. Indeed, it was demonstrated that cGAS/STING signaling is critical to the promotion of paracrine senescence via the SASP (Glück et al., 2017) and that loss of cGAS leads to abrogation of the SASP, at least in cell culture settings (Yang et al., 2017a). The interaction between the cGAS/STING pathway and cellular senescence/SASP was also reported in various animal models. For example, Paffenholz *et al.,* reported that the cGAS/STING pathway induced both the SASP and immune infiltration, particularly T cells, into the tumor mass (Paffenholz et al., 2022). Another colorectal cancer model was utilized to show that recruitment of CD8+ T cells is mediated by upregulation of CCL5 and CXCL10 chemokines that was a result of DNA damage that would lead to the activation of the cGAS/STING pathway and type I IFN signaling (Mowat et al., 2021). In summary, the cGAS-STING pathway plays a key role in regulating the immune response against senescent cells, as demonstrated in both *in vitro* and *in vivo* settings, and orchestrates immune responses, shedding light on its multifaceted role in the complex landscape of senescent cell biology and cancer microenvironments.

Tumor heterogeneity is considered one of the primary reasons for the failure of many anti-cancer treatments and the consequent disease recurrence (Mirzayans and Murray, 2022). As noted above, the effect of the SASP is highly dependent on context and cell type and can vary during different stages of cancer progression and their response to anti-cancer therapeutics (Jochems et al., 2021; Ruhland and Alspach, 2021). Therefore, not all tumors will develop TIS and not even all different cells within the tumor microenvironment will undergo growth arrest. The presence of these non-senescent cells within a heterogeneous tumor can contribute to its resistance to immune-mediated clearance, as these cells may not be affected by the immune response targeting senescent cells (Park et al., 2021). Senescent cancer cells that are not re-moved by the immune system can, in theory, spontaneously escape proliferation arrest under certain circumstances and re-enter the cell cycle leading to more aggressive disease recurrence (Saleh et al., 2020a).

Combining therapies that induce TIS with immunotherapies can be more effective in achieving tumor clearance. As mentioned earlier, senescent cells can express PD-L1, which can inhibit T cell activity, expansion, and cytotoxic activities (Lee et al., 2022; Prieto et al., 2023). However, PD-L1 inhibition was also shown to be a strong senescence inducer (Lee et al., 2022). Checkpoint inhibitors (e.g., PD-1 or PD-L1 inhibitors) can be used to enhance the immune response against senescent cancer cells (Wang et al., 2022b). The SASP of senescent tumor cells can modulate the TME either as an anti-tumor effect via inducing growth arrest or can have immunosuppressive properties via MDSCs activity (Di Mitri et al., 2014; Salminen et al., 2018). A combination treatment of a senescence inducer and a senolytic nanoparticle selectively eliminates senescent cells (Galiana et al., 2020). A recent study by Ruscetti *et al.* utilized a KRAS-mutant pancreatic ductal adenocarcinoma mouse model to demonstrate a direct senolytic effect of the immune checkpoint inhibitor anti-PD1 antibody. Furthermore, the au-thors showed that pro-angiogenic and pro-inflammatory SASP profiles resulted in an increase of CD8+ T cell infiltration into tumors, thus improving the efficacy of anti-PD1checkpoint blockade (Ruscetti et al., 2020). The problem of tissue specificity, the senescence inducer and how SASP can could exhibit dual roles in immune regulation was partially addressed using chimeric antigen receptor (CAR) T cell therapies with chimeric receptors that recognize cell surface proteins upregulated in senescence. Such an approach was shown to be feasible with urokinase-type plasminogen activator receptor (uPAR) as a cell surface membrane protein broadly upregulated during senescence; uPAR-specific CAR T cells effectively eliminated

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senescent cells in vitro and in a lung cancer mouse model (Amor et al., 2020; Wang et al., 2022a).

Overall, the interaction between TIS and the immune system is incredibly complex, as acknowledged by ChatGPT. It outlined the immunogenicity of senescent tumor cells and their potential impact on various immune signals. Additionally, ChatGPT discussed the altered immunopeptidome of senescent cancer cells and highlighted the highly variable nature of SASP, contingent upon the senescence inducer's context. Moreover, ChatGPT touched upon the association between senescence and macrophage polarization, as well as the role of MDSCs in inflammatory contexts—areas necessitating further investigation, especially within the cancer context. These insights underscore ChatGPT's utility in pinpointing gaps in current literature and offering pathways for novel cancer-senescence research. Finally, ChatGPT highlighted tumor heterogeneity and proposed using immunotherapy as a neoadjuvant approach to induce TIS for more effective tumor elimination.

Concluding Remarks

Investigating the role of TIS in cancer biology remains an active area of research in which a number of questions are unresolved. The contribution of TIS to overall cancer therapy, tumor dormancy, interaction with the immune system, and connection to autophagy represent major areas of interest. The utility of AI platforms, such as ChatGPT, in the biomedical field is evolving to provide a reliable source for literature review and analysis. In this work, we were able to validate and discuss some of the key points provided by ChatGPT in response to selected and highly relevant questions related to TIS and cancer treatment. Overall, ChatGPT was accurate and reliable in presenting the predominent viewpoint(s) in the field regarding fundamental issues related to our understanding of senescence such as its possible reversibility and the potential utilization of senotherapy for cancer. Moreover, ChatGPT provided an accurate description of the currently availble approaches to investigate the development of TIS in cancer patients in the clinical setting. However, ChatGPT was severely limited in elucidating some complexities regarding the contribution of senescence to tumor dormancy or its connection to various forms of autophagy. Of course, the output delivered by ChatGPT is

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largely dependent of the way these questions were constructed and formulated, and alternative answers could have been provided if those questions were shaped differently. We also selected these questions based on our own understanding of the current issues in the field of TIS and cancer, where others might benefit from formulating different inquiries. Furthermore, ChatGPT's answers are certainly not static and can change as the body of literaure evolves and as new updates of its access to the scientific archive are incorporated. Collectively, and based on this work, it does appear that ChatGPT provides a relatively high degree of accuracy in viewing the scientific literature, even with respect to topics that are controversial and debatable. Nevertheless, a certain degree of caution is warranted when considering its output, as some relevant observations are likely to be overlooked.

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