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COMMENTARY

Harnessing Senescence for Antitumor Immunity to Advance Cancer Treatment

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Considering the limitations and complexities of the cell-killing-based cancer treatment approaches, one could aim to integrate symbiotic advances in many energy delivery technologies and transformational pieces of evidence in research on senescence and immunomodulators to advance cancer treatment. Although senescent cells contribute to drug tolerance, resistance to therapy, tumorigenesis, maladapting cancer phenotypes, tumor relapse, recurrence, and metastasis, emerging pieces of evidence also demonstrate that acutely induced senescent cells in tumors can elicit a strong and lasting antitumor immune response juxtaposed to the immunologically silent apoptotic cells. This commentary is to help develop an unconventional conceptual framework to advance cancer treatment. Accordingly, it will involve transiently inducing senescent cells in tumors at optimal levels to prime the immune system with radiation, then eliminating senescent cells with senolytics (drugs that specifically eliminate senescent cells) to disrupt their positive feedback accumulation (to prevent tumor maladaptation and adverse effects in healthy cells) and unleash long-lasting antitumor immunity with immunomodulators. The approach is reasonably speculative and will require scientifically rigorous fit-for-purpose, well-controlled preclinical research and development involving dose and schedule optimization of radiation and drugs, using representative in vitro and in vivo cancer models to obtain high-quality data to proceed to clinical studies.

INTRODUCTION

Radiotherapy, chemotherapy, and/or surgery are the mainstays of cancer treatment. Despite decades of research and development, the progress in cancer treatment has been limited. With the added complexities of cancer itself, the problems with current therapeutic approaches, radiotherapy (*1*), and chemotherapy (*2*) include normal tissue toxicities and suppression of natural immunity (*3*, *4*), and with surgery, incomplete excision of the tumor (*5*). These problems are further augmented due to the spatiotemporal heterogeneity in tumor response (*6*), suboptimal quality of preclinical research (*7*), and the need to address differences among patients in their tumor response to treatment (*8*).

Considering the limitations of cancer treatments, one could aim to integrate transformational research in senescence and immunomodulators with radiotherapy to eradicate cancer from both the primary and metastatic sites concurrently. This concept is antithetical to the focus of most cancer treatment approaches, which are mainly based on cell killing by apoptosis and several other mechanisms, including necrosis, necroptosis, ferroptosis, autophagy, and mitotic catastrophe (*9*). Apoptosis is a form of regulated cell death (RCD) with the activation of proteases of the caspase family (*10*), which allows cancer cells to escape immunity because the detection and disposal of apoptotic bodies are typically immunologically silent and tolerogenic (*11*). Therefore, exploiting other cell death mechanisms to improve cancer therapy is also explored, which includes autophagy (*12*), ferroptosis (*13*), necroptosis, and pyroptosis (*14*). Recent evidence suggests that senescent cells (SnCs) in tumors contribute to drug tolerance, resistance to therapy, tumorigenesis, maladapting cancer phenotypes, tumor relapse, recurrence, and metastasis (*15*, *16*). Yet, SnCs can also effectively activate dendritic cells (DC) and antigen-specific CD8 T-cells, eliciting a robust antitumor immune response (*17*).

This commentary discusses an unconventional concept of the potential to exploit the immunomodulatory effects of acutely induced SnCs in tumors to improve anticancer treatment. The purpose of this commentary is not to extensively review the literature but to help develop a conceptual framework to advance anticancer treatment. This approach will involve transiently inducing SnCs in a tumor with radiation at optimal doses to prime the immune system and subsequently eliminate SnCs with senolytics (drugs that

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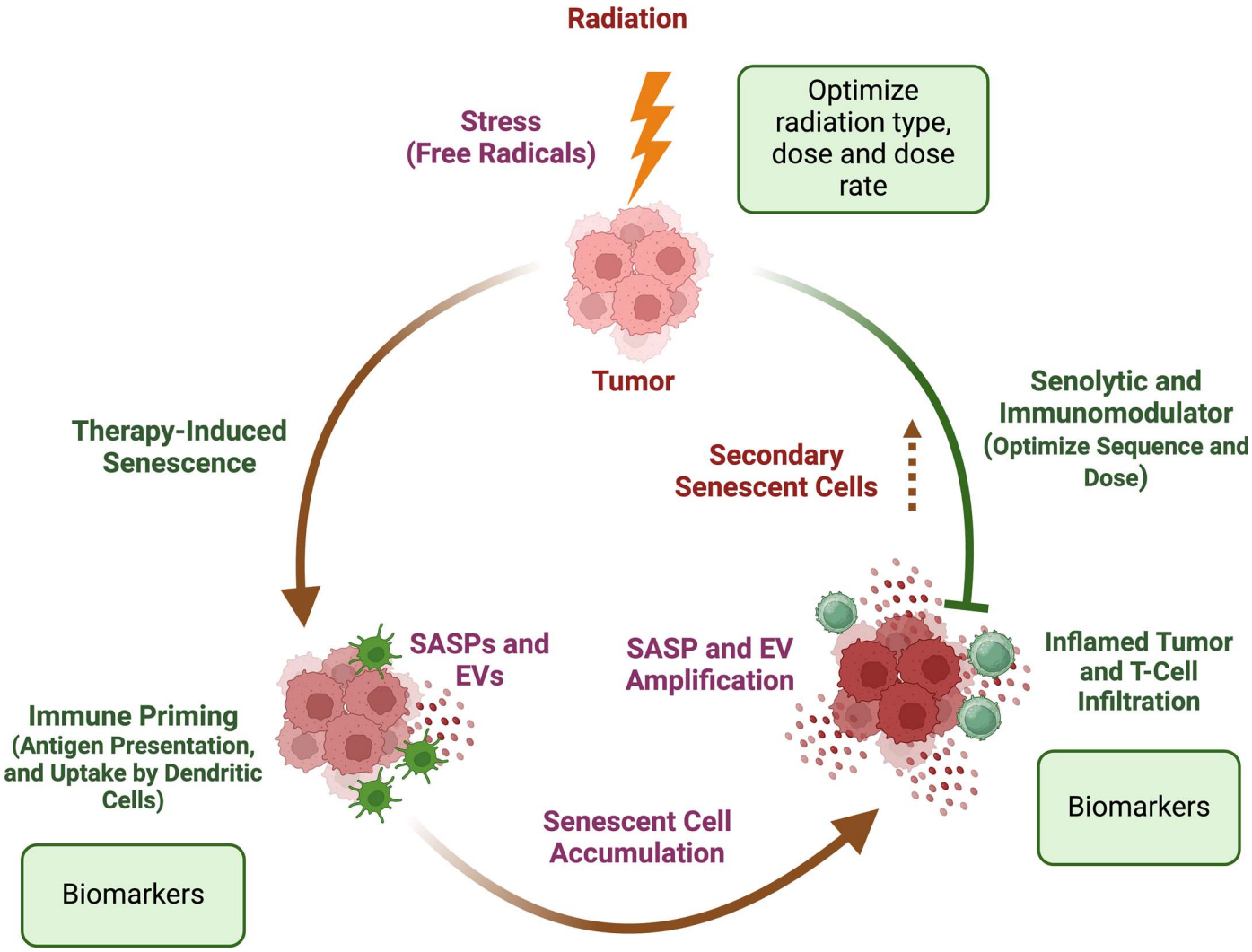

FIG. 1. Graphical abstract of the conceptual framework of harnessing senescent cells (SnCs) in the tumor microenvironment for antitumor immunity to advance cancer treatment. This conceptual approach will involve transiently inducing SnCs in a tumor with radiation, then eliminating them with senolytics (drugs that specifically eliminate SnCs) to disrupt the positive feedback accumulation of SnCs to prevent tumor maladaptation and adverse effects in healthy cells and subsequently unleash T-cell mediated immunity with immunity-enhancing drugs (immunomodulators). Created with Biorender.com.

specifically eliminate SnCs) (*15*) to disrupt the positive feedback accumulation of SnCs to prevent tumor maladaptation (*18*) and then unleash lasting antitumor immunity with immunity-enhancing drugs (immunomodulators) (Fig. 1). SnCs elimination after surgery will also improve cancer outcomes by preventing local recurrence and distant metastasis. Nevertheless, this reasonably speculative approach will require scientifically rigorous "fit-for-purpose" preclinical research and developmental efforts involving dose and schedule optimization of radiation and drugs, using several representative in vitro and in vivo cancer models to obtain high-quality data to proceed to clinical studies.

INDUCING SENESCENT CELLS

The goal of most cancer therapies is cell-killing. Thus, radiation, drugs, and their dose levels and delivery sequences are not designed to specifically induce SnCs in tumors. However, an optimum SnCs burden will be necessary to inflame the tumor for immune priming. Thanks to decades of advances in radiation dose delivery and its distribution within a tumor, dosimetry, and onboard imaging, precise and focused delivery using several radiation types at different dose rates, ranging from several cGy/min to Gy/s, are available (*19*). All radiation types induce SnCs in tumors; however, their efficacy will vary depending on radiation type, dose, cell types, and schedule. Therefore, any transformational approach to using radiation as a "drug" should consider the biological perturbations with unique and exploitable mechanisms of action (*20*).

Focused delivery of radiation to a tumor to induce SnCs circumvents several problems associated with cytotoxic drug delivery, including systemic toxicities and immune suppression. Of note, with advances in image guidance,

tumor-focused radiation delivery has not been a problem in general. Yet, their role in inducing various modes of cell death, including SnCs and/or priming the immune system, has not been systematically investigated but is needed.

The inability to detect tumors early compromises the ability to treat them with radiation and surgery due to local spread and metastasis, which results in treatment failures. Systemic administration of antibody-drug conjugates (ADC) for delivering cytotoxic drug payloads (*21*) and radiopharmaceutical therapy (RPT) to spatially target cancer cells (*22*) are also rapidly emerging research areas. Of note, chemotherapeutic agents (e.g., doxorubicin) are routinely used to induce SnCs (*17*). Unlike radiotherapy or surgery, which are localized, ADCs and RPT can target cancers both in primary and metastatic sites to induce SnCs. However, their efficacy will depend on absorption, distribution, metabolism, excretion, toxicity, and time after administration.

SENESCENCE

Despite the primary goal of cell-killing, cancer therapies induce SnCs in tumors and healthy tissue to some extent (*15*), but not at a level to inflame the tumor for antigen presentation for DCs to induce immunogenicity. Acutely induced SnCs are strongly immunogenic because of several features, including their longer persistence in vivo, interferon (IFN) signaling activation, efficient antigen transfer and activation of antigen-presenting cells, and altered immunopeptidome (*17*). SnCs are also found to release alarmins, enhance MHC class I machinery, and present senescence-associated self-peptides to activate CD8 T cells (*17*). Senescence-associated secretory phenotypes (SASPs) of tumor cells can recruit and activate CD4 and CD8 T cells (*23*). In addition, SnCs secrete extracellular vesicles (EVs), which were once thought to be cellular "debris" but are now recognized as vital mediators of cell-cell communications and have a role in the immune response. EVs carry immunogenic inflammatory cytokines, chemokines, and matrix metalloproteinases (*24*).

In the context of cancer, immunization with SnCs elicits strong antitumor protection mediated by DCs and CD8 T cells, and therefore, inducing SnCs in tumor cells may be a promising approach to elicit immune response. Although SnCs and immunogenic cell death (ICD, an RCD that can drive an inflammatory response and culminate with the activation of cytotoxic T-lymphocyte (CTL)-driven adaptive immunity) produce similar levels of alarmins, their production is limited in time in the case of ICDs (less than a day). At the same time, alarmins are maintained over several days in SnCs (*17*), triggering the adaptive immune response involving the capture of antigens by DCs and DC activation and maturation (*25*). In addition, SnCs may also contribute to the tumor mutational burden (TMB), which is believed to be a key driver in the generation of immunogenic peptides displayed on MHC complexes on the tumor cell surface that influence patient response to immune checkpoint inhibition (ICI) therapy (*26*). Further, the observations that immunization with viable senescent cancer cells can promote a tumor prophylactic and therapeutic CD8 T cell-dependent antitumor immune response support the notion that therapeutic vaccination with SnCs is feasible (*17*).

SENOLYTICS

Since this concept proposes to specifically exploit SnCs in a tumor to elicit an innate immune response, once the immune system is primed, it is crucial to eliminate them from the tumor to prevent them from entering a chronic state and causing drug resistance, tumor maladaptation, plasticity, recurrence, and metastasis (*15*, *16*). While acutely induced SnCs can attract various types of immune cells into the tumor microenvironment (TME), their progression to a chronic state in healthy tissue can lead to accelerated aging, age-related diseases (*27*), and other adverse effects such as fibrosis (*28–30*), stem cell aging (*31*), and peripheral neuropathy (*32*). Therefore, eliminating SnCs with a senolytic is necessary after immune priming. The concept of inducing SnCs in tumors followed by their selective elimination using a senolytic is called "one-two punch" cancer therapy (*15*, *18*), and its integration with personalized adaptive cancer therapy was discussed earlier in a workshop at NCI (*15*). Many senolytics are now at various stages of development, including some in clinical trials (*15*, *18*, *33*). Acutely induced SnCs can have beneficial effects as they recruit immune cells for removal, in contrast to chronic SnCs that secrete pro-inflammatory, pro-tumorigenic SASPs (*27*, *34*). Current senolytic therapies can function to eliminate SnCs, inhibit the secretion of SASPs, and enhance immune clearance (*34*). Thus, it is reasonable to expect that at least some senolytic therapies such as those specifically enhance immune clearance via ICD, will likely amplify the immunogenic potential/load of the TME while concurrently reducing the SnCs burden.

Detection and quantification of SnScs have been a problem due to tissue-specific spatial-temporal heterogeneity and the availability of only a few biomarkers. The research on EVs is advanced with the guidelines for their separation and characterization (*35*), an enhanced understanding of their biogenesis, and their ubiquitous involvement in immune mechanisms and diseases (*36*, *37*). The EV release dynamics and their cargo may be investigated to serve as senescence biomarkers (*38*, *39*), and they can also serve as therapeutic targets (*36*). Further, with advances in fluorescent imaging for monitoring biomolecules in living systems, providing real-time, non-invasive, high-resolution spatial and temporal resolution, it may be possible to develop tools for detecting and monitoring enzymes (e.g., beta-galactosidase, hydrolases, oxidases, etc.), proteins, and peptides associated with SnCs, and develop non-invasive fluorescent "off-on" and/or ratiometric biosensors

that are capable of deep tissue penetration with low-background interference (*40*).

Several recent advances by the SenNet through NIH's common funds (*41*), NCI's SBIR Development Center (*42*), and elsewhere can be leveraged to test this concept. These advances include building a multimodal and multidimensional SnCs atlas, identifying a panel of reliable biomarkers, imaging and visualizing SnCs (including artificial intelligence tools to identify SnCs), establishing experimental model systems and validation experiments, and developing senolytics (*41*, *42*). Nevertheless, many knowledge gaps must be critically filled to develop next-generation senolytics that work best with immunomodulators to unleash long-lasting antitumor immunity. However, rigorous and well-controlled preclinical efficacy testing is critical before proceeding to clinical studies.

IMMUNOMODULATORS

SnCs are routinely cleared by natural immunity in a healthy individual (*43*). Cancer and cancer therapies both suppress this immunity (*44*). Harnessing SnCs for cancer treatment may provide an immune-supportive environment to work with immunomodulators that can provide targets for DC and T-cell mediated systemic antitumor immunity to unleash an immune response against reminiscent and secondary SnCs, recurring, and metastatic cancer cells.

Key challenges facing cancer immunotherapy range from a lack of confidence in translating preclinical findings to identifying optimal combinations of immunotherapies (*45*). The most critical challenge in cancer immunotherapy appears to be determining the dominant molecular and cellular drivers defining TME immune contexture and escape (*45*). While the tumor immunity continuum includes inflamed, immune excluded, and immune desert phenotypes, characteristics of inflamed tumors (so-called "hot") include interferon signals with high PD-L1 expression, interferon signal, genomic instability, and a high TMB (*45*). Since some of these features are also expressed in SnCs (*17*, *26*, *46*), it is reasonable to posit that SnCs in the TME can be exploited to potentiate antitumor immunity. Because of their capacity for antigen-directed cytotoxicity, T-cells have become the focus of cancer immunotherapies (*47*); however, the onset and maintenance of T-cell responses and the development of long-lasting memory depend on innate immune responses (*48*). Recent findings that SnCs upregulate MHC-I antigen presentation, efficiently activate DC, and stimulate CD8 T-cells may allow harnessing them to trigger efficient and long-lasting CD8 T-cell dependent antitumor immune response (*17*). Using an immune-competent liver cancer model, it has been demonstrated that SnCs can remodel the cell-surface proteome and render tumor cells more visible to the adaptive immune system by type II interferon (IFNγ) (*46*). Further, endogenous DCs and using engineered T-cells to secrete DC growth factors are promising strategies to overcome the clinical problem of antigen-negative tumor escape (*49*). An evaluation of a regimen of FLT3 ligands to increase DCs and other antigen-presenting cells in high-risk melanoma patients showed significant and durable increases in the activation of DCs, natural killer cells, and humoral and T-cell responses (*50*).

A vision of inducing SnCs in the TME for antitumor immunity to advance cancer treatment is illustrated in the example of breast-to-lung metastasis in Fig. 2. Therapies to overcome treatment resistance in metastatic settings are actively pursued. Recent progress examining the clinical benefit of treating HER-2-positive breast cancers targeted with CDK4/6 inhibitors has been summarized (*51*). The immunomodulatory activities of approved CDK4/6 inhibitors (such as ribociclib, palbociclib, and abemaciclib to treat HER-2-positive and negative metastatic breast cancers), their impact on the cell's metabolic state and the effect on the decision of the cell to undergo quiescence or senescence are also discussed (*52*). In vitro studies using breast cancer cell lines demonstrated that abemaciclib specifically inhibits CDK4 kinase activity versus CDK6 (*53*).

Because of the limited success of immunotherapy [e.g., immune checkpoint blockade therapy (*54*, *55*)], the current focus for using immunotherapy has been to stratify patients based on biomarkers of immune status or response (*56*), but not to answer why such immune responses do not occur in all patients. Is it due to insufficient immune priming of the TME, immune exclusion, or immune suppression by cancer therapies? Harnessing SnCs for antitumor immunity can also help address this scientific curiosity – is unleashing one's immune system by inducing SnCs in TME to eradicate maladapting cancer cells at the primary site and eradicate distant metastasis feasible?

CAVEATS

Of note, the approach is to work with a different cell fate (senescence) vs. inducing cell death (apoptosis) from cancer therapy. Many gaps that need to be addressed include optimizing the dose and sequence of administration for a given cancer type, along with molecular determinants of senescence induction for immune response, understanding the role of EVs released from SnCs in metastasis and immune response, determining the immune status and response, non-invasive detection and tracking SnCs.

However, this is an opportune time to harness SnCs to improve cancer treatment outcomes, to start with at least focusing on a few organ/sites. Many advances have occurred in localized radiation delivery, distribution, and imaging technologies (*19*, *57*, *58*). Similarly, the fields of senescence (*15*, *33*, *41*, *42*) and immunomodulators (*50*, *56*) have also been rapidly progressing. Many senolytics drugs have advanced to clinical testing (*15*, *33*). Several advances in the fields of bioengineering and biosensors have provided us with the ability to track and monitor SnCs to some extent (*59*).

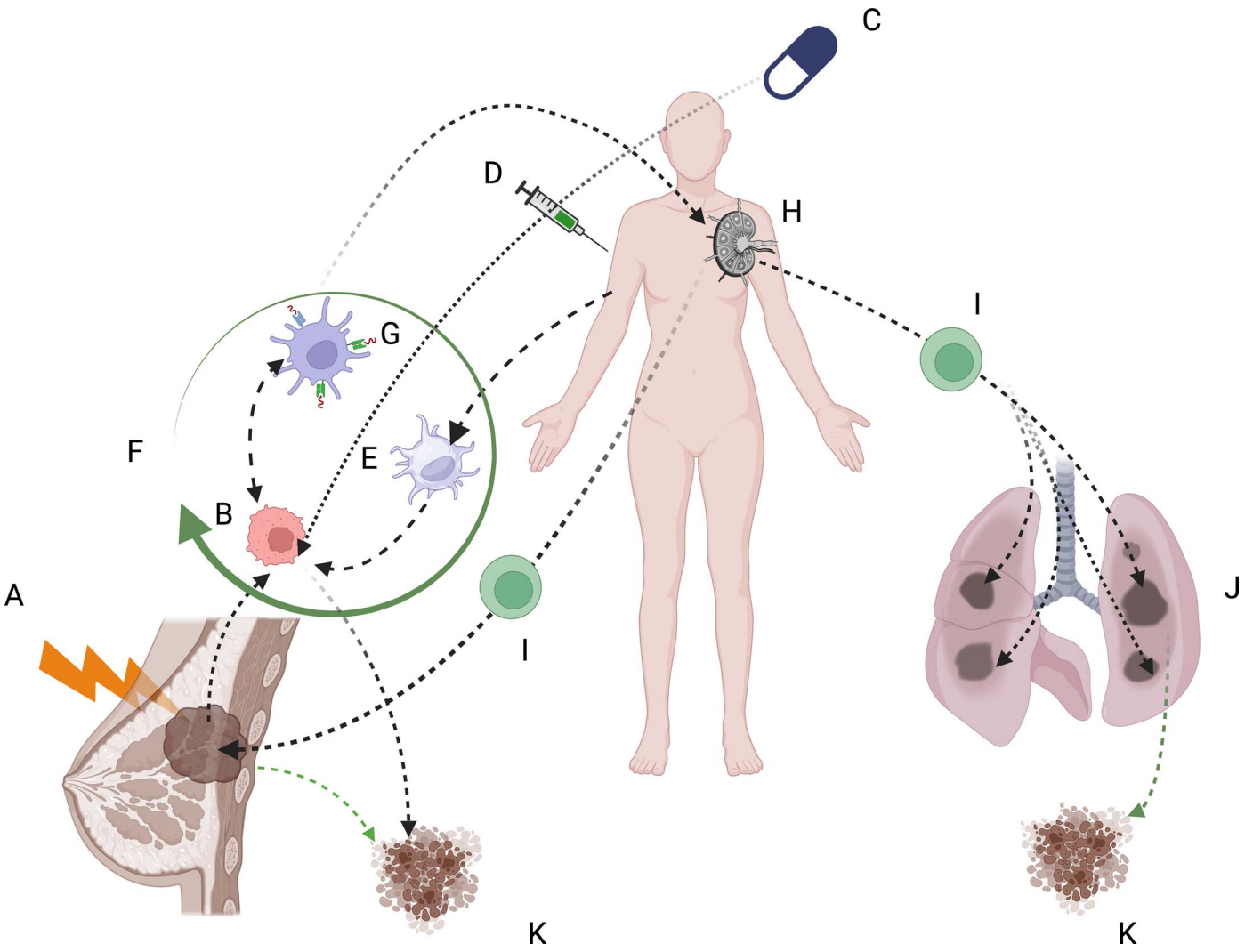

FIG. 2. Illustration of an envisioned example of harnessing senescent cells (SnCs) to advance cancer treatment. Accordingly, delivery of an optimal radiation dose (A) to the breast tumor location induces senescent cells to prime the tumor microenvironment (TME) with specific antigens (B). Administration of a senolytic (a single treatment or a course) (C) will cause the SnCs to die and amplify the immunogenic load and tumor mutational burden. Dying SnCs and the antigen-primed TME will prepare the dendritic cells (E) niche to infiltrate TME following an immunomodulator (D) administration. An immunomodulator will stimulate the differentiation of bone marrow progenitor cells into dendritic cells (E). These dendritic cells will attack both SnCs (B) and reminiscent cancer cells at the primary site, causing their death (B and G) and resulting in a positive feedback loop (F). Antigen-primed dendritic cells (G) will also migrate to the lymph nodes (H) to activate T-cells. Activated T-cells (I) migrate to infiltrate the primary and metastatic tumor sites (J), where they recognize and destroy cancer cells (K). Certain SnCs burden is crucial to provide an initial immunogenic priming load via radiation (A). SnCs death from subsequent administration of senolytics (C) is essential to amplify and synergize the immune response with an immunomodulator (D) from antigen presentation from dying cells. The figure is created with Biorender.com.

Preclinical studies can improve using better models (e.g., immunocompetent small and large animal models, humanized animal models, etc.) to perform "fit-for-purpose" studies (*7*, *60*). Unequivocal preclinical data on efficacy and safety will be critical for confidently supporting novel and rationally designed evidence-based clinical studies. Dedicated efforts on the delivery of radiation to induce SnCs, the development, optimization of dose- and scheduling, and translation of non-invasive biomarkers (e.g., imaging, EVs, circulating SnCs, biosensors), senolytics, and immunomodulators leading to clinical studies are necessary. Similarly, early engagement of the FDA for guidance will also be crucial. This is a unique and new opportunity for researchers in academia and industry to collaborate to evaluate senescence for immunity to advance cancer treatment.

However, many essential steps to success include drug development, regulatory, clinical translation, and commercialization. Since this is a cross-disciplinary area, not all fields may advance together. There will be some pitfalls, and alternative approaches may be needed. Lowering the radiation dose or using radiation as a drug to treat cancers may not appeal to many researchers, patients, and physicians alike. Thus, testing these concepts should focus initially on preclinical studies before proceeding to clinical studies. High-quality, convincing data will be critical to design and inform clinical studies. Nevertheless, harnessing SnCs for

antitumor immunity can also lead to other applications that could advance healthcare in many disease settings.

Improvements in patient outcomes for different cancer types are the ultimate measure of success. However, this will take years, if not decades. Nevertheless, intermediate success should be evident from preclinical research. Indications of such success include filing intellectual property (IP) rights, stakeholders' interest in commercializing IPs, co-development interests from potential partners, and commercial potential. However, some misperceptions are inevitable when proposing to deviate from decades of established norms of treatment (i.e., modifying the dose and schedule from "intent to kill" cancer cells to "not to kill"). Therefore, high-quality data and public trust are indispensable for the ultimate success of this approach, which is akin to any transformative science.

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