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AUTHOR'S VIEW

Cellular senescence enhances adaptive anticancer immunosurveillance

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ABSTRACT

Cancer therapy often induces senescence in some cancer cells. Senescent cells, due to their profoundly altered biology, may conceivably interact with the adaptive immune system in novel ways that may boost cancer immunosurveillance, triggering the clearance of both senescent and non-senescent neoplastic cells. In this regard, we have recently reported that senescent cancer cells exhibit potent antigenicity and adjuvanticity and can elicit strong $CD8^+$ T cell-dependent anticancer effects when used as vaccination agents.

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In our recent publication in *Cancer Discovery*, we provide novel insights on the crosstalk between senescent cells and the adaptive arm of host immunity.[1]

The ignition of the "Cancer-Immunity Cycle"[2] (Figure 1) is required to place neoplastic cells under the surveillance of tumor-infiltrating lymphocytes (TILs). This multistep process involves (i) the recruitment of immature dendritic cells (DCs) to the tumor bed, following the release of damage-associated molecular patterns (DAMPs) by dying tumor cells; (ii) the maturation of DCs into professional antigen presenting cells (APCs), endowed with the ability to phagocyte tumor cells and prime T cells; and (iii) the recognition and killing of tumor cells by antigen-specific TILs. While the process can be triggered during normal tumor progression as result of spontaneous apoptosis of tumor cells, a more potent immune response can be elicited through the pharmacological induction of immunogenic cell death (ICD).[3]

Intriguingly, the use of ICD-inducing agents (e.g., doxorubicin) at a lower dose than the one required to promote ICD may switch the fate of cancer cells from death to senescence. The term "senescence" embraces an umbrella of heterogenous cellular states defined by common features that include a stable cell cycle arrest and a prominent secretory phenotype.[4] From a mere cell-intrinsic standpoint, senescence acts as a barrier against the formation of tumors. In addition, senescent cells present a complex combination of immunostimulatory and immunosuppressive signals, whose balance may determine the outcome of antitumor immunosurveillance and the success of cancer therapy.

The modalities through which senescent cancer cells stimulate T cells are multifarious. Regardless of the senescence-inducing stimulus, we show that senescent cells display high processing and presentation of antigens through MHC class I (MHC-I). Mechanistically, we demonstrate that MHC-I overexpression depends on the activation of a paracrine, self-sustained type I interferon (IFN-I) signaling in senescent cells, as indicated by the reduction in MHC-I expression upon JAK inhibition or IFN-I blockade. These results align with existing literature linking elevated IFN-I gene signature and MHC-I levels with improved therapeutic outcome after therapy.[5]

We provide unprecedented indication that senescent cells – regardless of their transformed state – are inherently antigenic, presenting MHC-I-associated self-antigens that can be targeted by CD8 + T cells. Some of these self-antigens are shared with non-senescent cells, but, interestingly, other self-antigens are proprietary of senescent cells. While we did not explore in detail the mechanisms underlying the altered immunopeptidome in senescent cancer cells, it is tempting to speculate that senescence would promote the expression of tumor antigens, possibly via events of aberrant splicing, activation of transposable endogenous retroviral elements and expression of defective ribosomal products (DRiPs).[6]

We found that senescent cancer cells release DAMPs (i.e., ATP and calreticulin) at levels comparable to those detected in cells undergoing ICD. Likewise, both ICD and senescent cells evoked similar levels of $CD11b^+$ and $CD3^+$ cells infiltration after subcutaneous engraftment. However, while ICD cells were undetectable 2 days post-injection, senescent cells were still detectable and viable 11 days post-injection, a circumstance that may favor a stronger immune activation. In co-culture experiments, senescent cells skewed DCs toward an activated phenotype. Furthermore, senescent cells were able to transfer cytosolic and membrane antigens to DCs more efficiently than their ICD counterpart. Accordingly, DCs cultured with senescent B16-F10 melanoma cells expressing ovalbumin (B16F10-OVA) were more effective in activating OT-I CD8 + T cells than DCs cultured with non-senescent B16F10-OVA cells. Altogether, the induction of senescence in tumor cells boosts their adjuvanticity to higher levels than ICD.

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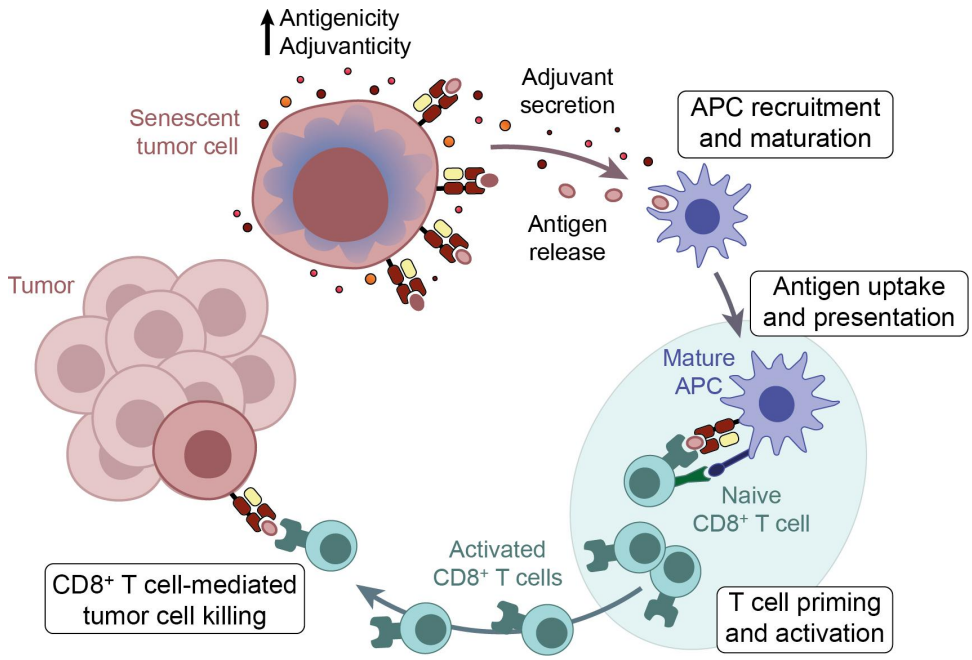

Figure 1. Senescent cancer cells promote superior TIL activation. Anti-cancer immunosurveillance relies upon the efficient activation of the cancer-immunity cycle. Senescent cancer cells boost the ignition of this process via different modalities that include (i) the enhanced expression of MHC-I and MHC-I associated antigens; (ii) the secretion of immunostimulatory alarmins and (iii) the efficient transfer of antigens to Dendritic Cells (DCs), which in turn prime and unleash the cytotoxic action of TILs against tumor cells.

We then decided to explore the putative immunostimulatory activity of senescent cells in an ectopic environment to avoid the immunosuppressive factors present in the intratumoral microenvironment. In line with a previous report,[7] we show that (doxorubicin-treated) senescent melanoma B16-F10 and pancreatic cancer Panc02 cells transplanted into immunocompetent hosts prevented the appearance of tumors when mice were re-inoculated with proliferating B16-F10 and Panc02 cells, respectively. Interestingly, senescent cells outperformed cells undergoing ICD (also doxorubicin-treated) in mediating this effect. Future experiments will clarify whether senescent cell-based vaccines would extend the protection to other cancer types. We also report that the immunostimulatory effect of senescent cell-based vaccines was lost when $CD8^+$ or $CD11b^+$ cells were depleted, suggesting that these immune subtypes are required for the cancer preventive action of senescent cells.

It is worth noting that in experimental settings of therapeutic vaccination immunization with senescent cells significantly delayed – but did not completely halt, the progression of already established tumors. This effect was mirrored by an augmented infiltration of $CD11c^+$ DCs in the tumor bed along with enhanced activation of TILs. Prospectively, it will be interesting to assess whether the pharmacological induction of senescence in established tumors would synergize with therapeutic senescent vaccines in restraining tumor progression. Also, it is tempting to speculate about the potential synergistic effect of those cancer vaccines when combined with immune-checkpoint blockers (ICB).

Finally, we validated our findings in primary human neoplasias. We show that the induction of senescence in four different patient-derived primary cancer cell lines promoted the hyperstimulation of their autologous tumor reactive TILs in an antigen-specific manner, as further corroborated upon enrichment of a population of TILs specific for a tumor neoantigen previously identified in one of the cell lines. To our knowledge, this is the first demonstration that induction of senescence in human tumors evokes superior antigen-specific $CD8^+$ T cell-dependent anticancer effects.

Taken together, the results presented in this study (and further supported by studies by Lowe and colleagues[8] and Di Micco and colleagues[9] indicate that the activation of senescence strongly enhances the immunogenicity of cancer cells. On the one hand, activation of senescence may unmask and promote expression and presentation of neoantigens on MHC-I, while counteracting cancer cell immune evasion mediated by MHC-I downregulation. On the other hand, the induction of senescence in tumors surgically resected from patients or tumor biopsies may be harnessed to create live cancer vaccines, also to potentiate the transfer of antigens to autologous DCs and hence increase the efficacy of DC-based vaccines,[10] or even as a tool for boosting TIL activation in TIL-based cell therapies.

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Disclosure statement

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