

COMMENTARY



## Senescent cells: New target for an old treatment?

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### ABSTRACT

Many genotoxic chemotherapies have debilitating side effects and induce cellular senescence in normal tissues. Senescent cells acquire a pro-inflammatory phenotype which contributes to local and systemic inflammation. Eliminating senescent cells reduce several short- and long-term effects of the drugs, providing a new target to reduce the toxicity of anticancer treatments.

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Genotoxic and cytotoxic drugs are widely used as anticancer treatments and act by non-specifically targeting proliferative cells through different mechanisms. The toxicity of chemotherapies for many types of dividing cells leads to a number of adverse reactions, which include immunosuppression, pain, fatigue, anemia, nausea, gastrointestinal distress, and hair loss.<sup>1</sup> Moreover, clinical studies of cancer survivors treated during childhood suggest that chemotherapy causes a range of diseases normally associated with aging.<sup>2</sup>

Many chemotherapeutic drugs induce changes of cellular states in the tumor microenvironment, including cellular senescence.<sup>3</sup> Cellular senescence is a complex stress response whereby cells irreversibly lose the capacity to proliferate due to induction of the *CDKN2A* gene (from now on p16<sup>INK4a</sup>), a potent Cyclin-Dependent Kinases (CDK) 4/6 inhibitor. Moreover, senescent cells are characterized by numerous changes in gene expression, including the activation of the Senescence-Associated Secretory Phenotype (SASP).<sup>4</sup> We and others have suggested that the secretory phenotype associated with senescent cells (SASP) can serve several biological functions, either beneficial or deleterious.<sup>5</sup> Among the deleterious effects, the excessive persistence of senescent cells can disrupt tissue homeostasis and drive the onset or progression of several diseases, particular age-related pathologies.<sup>6</sup> Accordingly, therapy-induced senescence (TIS) is thought to have both positive and negative roles in the body: on one side, senescent cells and the SASP can stimulate immunosurveillance to eliminate tumor cells; on the other side, the prolonged presence of senescent cells can potentially be a source of chronic inflammation and drug resistance.<sup>7</sup>

Using a mouse model (*p16-3MR*) in which p16<sup>INK4a</sup>-positive senescent cells can be detected in living animals and eliminated upon treatment with an otherwise benign drug,<sup>8</sup> we have recently shown that TIS cells contributed to a number of

chemotherapy-associated side effects.<sup>9</sup> First, senescent cells promoted the increased expression of pro-inflammatory and SASP-related factors in tissue and sera observed in chemotherapy-treated mice. Second, elimination of senescent cells contributed to the functional re-activation of Haematopoietic Progenitor Cells (HPCs), thus accelerating the recovery from bone marrow suppression. Third, endothelial cells were induced to senescence in the heart and, together with higher levels of circulating pro-inflammatory factors, induced the development of cardiac dysfunction. Fourth, senescent non-tumor cells were an important component for cancer relapse after chemotherapy, and their elimination also dramatically reduced the number of metastasis in a model of breast cancer. Fifth, clearing senescent cells improved the spontaneous physical activity and overall strength in the presence or absence of cancer. In order to validate these effects in a human cohort, we measured p16<sup>INK4a</sup> expression in peripheral T-cells of human patients with breast cancer. Strikingly, we observed a strong direct correlation between high level of p16<sup>INK4a</sup>-positive senescent cells and the severity of chemotherapy-induced fatigue. These data are in accordance with recent findings showing that aging is the major risk factor for long-term (>2 or >5 years) fatigue after chemotherapy treatment.<sup>10</sup>

These results show that a variety of DNA-damaging agents potentially and rapidly increase the in vivo burden of senescent cells in humans and mice, and the accumulation of such cells causes a number of adverse reactions. Considering that some of the chemotherapy-induced and senescence-dependent side effects, such as bone marrow suppression and cardiac dysfunction, are major limiting factors for the drug dosage in cancer patients, it is conceivable to consider the development of therapies that can selectively target senescent cells (senolytics) and/or the SASP. In our work, we showed that the administration of a senolytic agent, ABT-263, efficiently eliminated senescent

cells, improved physical activity, and reduced cancer relapse in mice treated with chemotherapy. Thus, pharmacological removal of senescent cells might be an innovative combinatorial approach to limit some toxicity associated to chemotherapies, with consequent improvements in the health span and possibly life span of cancer patients.

However, these interventions will need to carefully consider any beneficial effects of TIS, including promotion of tissue repair and of tumor immunosurveillance.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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