all mutations in the same gene yield the same biologic phenotype (Chakravarty et al., 2017; Hanrahan et al., 2020). Furthermore, the pattern of co-alteration, tumor lineage, interaction with the host immune system, and other factors, many of which are not easily assayed using current methods, are also critical in modulating therapeutic responses. Exceptional responder studies should therefore be coordinated with laboratory studies designed to elucidate biologic differences among individual mutant alleles and with translational research designed to determine the influence of cellular and comutational context on drug response. Finally, the NCI Exceptional Responder study highlights the importance of analyzing the epistatic interactions between multiple lesions in functionally redundant pathways and tumor microenvironmental factors including the host immune response as the basis for the variability of clinical outcomes observed in patients.

In sum, exceptional responder studies can inform future biologic and clinical research. Clinicians and researchers should seek to facilitate *N* of 1 analyses by ensuring appropriate patient consent and optimized tissue collection protocols to facilitate bedside-to-bench collaborative science.

DECLARATION OF INTERESTS

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The Jekyll and Hyde of Senescence in Cancer: TIMP1 Controls the Switch from Tumor-Controlling to Tumor-Promoting Senescence

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Cellular senescence is a response with two faces in cancer: it restricts tumor proliferation, but it can also promote cancer progression and metastasis. In this issue of *Cancer Cell*, Guccini et al. uncover the role of TIMP1 in prostate cancer allowing a switch from tumor-controlling to tumor-promoting senescence.

Oncogenic signaling activation leads to a defensive response mounted by the cell known as cellular senescence, characterized by a stable cell cycle arrest, accumulation of macromolecular damage, altered metabolism, and a secretory phenotype (Gorgoulis et al., 2019). Together with apoptosis, cellular senescence represents a fundamental tumor-suppressor mechanism that prevents the emergence of hyperproliferative, aberrant cells (Collado et al., 2007). Disabling senescence is a pre-requisite for cancer cells to grow and form a tumor. This led many to suggest the possibility of developing a

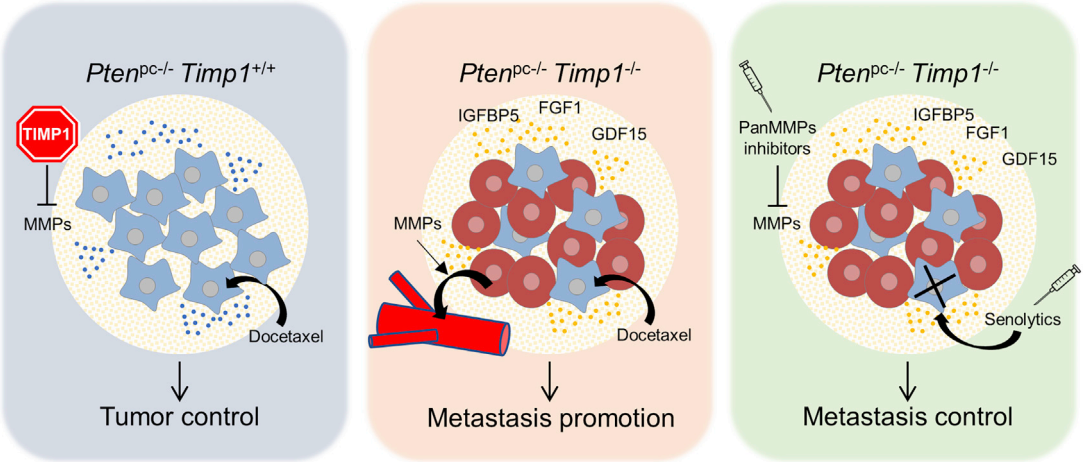

Figure 1. TIMP1 Controls the Pro-metastatic Activity of Secreted Factors from Senescent Cells
Mice with *Pten* inactivation in the prostate (*Pten*$^{pc-/-}$) develop localized indolent tumors composed of cells showing features of senescence. Among the factors secreted by senescent cells, Timp1 restricts the activity of other secreted factors such as the MMPs, acting as a break for metastatic growth. A similar situation is elicited by chemotherapeutic treatments such as Docetaxel, which helps control tumor growth by inducing senescence in prostate tumors (left). Co-deletion of *Timp1* leaves pro-metastatic factors produced by senescent cells free to act, resulting in metastasis promotion. Induction of senescence in the absence of *Timp1* by Docetaxel now has a negative effect, promoting metastasis (middle). Acting therapeutically through inhibition of the pro-metastatic factors secreted by senescent cells, with chemical inhibitors of the MMPs for example, or inducing senescence specific cytotoxicity to remove the senescent cells producing these factors can control efficiently metastasis growth (right).

pro-senescence therapy of cancer by identifying drugs that could reengage the senescence machinery to activate its tumor-restrictive function (Nardella et al., 2011).

Traditional cytotoxic chemotherapy, despite having been designed to induce tumor-cell killing, has the potential to induce senescence in some tumors and at certain particular conditions. Although initially this was seen as a beneficial response, evidence gathered at various laboratories raised the concern of potential detrimental secondary effects derived from the induction of senescence in cancer cells (Wang et al., 2020). The complex mixture of pro-inflammatory cytokines, growth-factor molecules, and matrix-remodeling enzymes (collectively known as SASP, senescence-associated secretory phenotype) released by senescent cells to the tumor microenvironment represents a potential pro-tumorigenic cocktail. Indeed, recent evidence demonstrates that chemotherapy-induced senescence can promote metastasis through the SASP by stimulating survival and migration of tumor cells (Wang et al., 2020). Understanding the relative contribution of cell senescence to cancer restriction or metastatic growth is fundamental to develop more effective and safer anti-cancer therapies.

Metastatic tumor growth is the most devastating form of cancer and for which in most cases we lack effective means of control. Prostate cancer is the most frequent cancer in men, with more than 160,000 new cases each year in the United States alone. Fortunately, in localized and advanced prostate tumors, surgery and radiation are curative treatments. For metastatic disease, however, despite advances in chemotherapeutic drugs and the use of androgen deprivation, acquired resistance ultimately leads to the death of patients. Understanding the molecular basis of metastatic prostate tumor growth would allow the development of more effective treatments and to identify those patients at higher risk of suffering from the deadly form of the disease.

In this issue of *Cancer Cell*, Guccini et al. (2020) use a mouse model of conditional ablation in the prostate of tumor suppressor *Pten* that produces indolent tumors with features of senescence. The authors reason that the SASP produced by *Pten* deficiency either lacks pro-metastatic activity or contains a factor that restricts metastatic growth. They profile the secretome of senescent prostatic tumors lacking *Pten* and compare it with non-senescent prostate tumors developed by *Pten*/*Trp53* doubly deficient mice (*Trp53* being essential for senescence induction). Among the factors that they identify, the most upregulated one independently of the induction of senescence is Timp1, a matrix metalloprotease inhibitor and known regulator of cell invasion and migration in cancer.

To further test the role of Timp1 in restricting metastatic growth promoted by senescent prostate tumors, the authors combine deficiency in *Pten* and *Timp1*. Genetic inactivation of *Timp1* induces metastatic growth of senescent tumors but not of the non-senescent ones obtained in the context of *Trp53* deficiency. This suggests that Timp1 might be restricting a SASP factor released by senescent cells to the tumor microenvironment. To test whether senescent cells were responsible for the metastatic tumor growth observed in the doubly deficient *Pten*/*Timp1* animals, the authors use a senolytic agent. Senolytics are compounds with specific senescent-cell-killing activity (Dolgin, 2020). Removing senescent cells from *Pten*/*Timp1* double *null* animals impairs metastatic potential without affecting the growth of non-senescent tumors.

These data imply that senescent tumors have the potential to promote metastatic growth, but Timp1, produced and released by senescent cells, blocks this

activity. The implications for prostate cancer therapy are relevant because some of the treatments currently given to patients could be inducing cancer cell senescence. This is the case of the taxane Docetaxel. Animals treated with this drug exhibit tumor regression in *Timp1*-proficient tumors but conversely accelerated metastases formation in the absence of *Timp1*. The same results are observed with human prostate cancer cells manipulated or not to express *TIMP1* and are implanted into recipient mice treated with Docetaxel. In contrast, concomitant treatment with the senolytic drug avoids the accumulation of senescent tumor cells and prevents metastatic growth of *TIMP1*-deficient human prostate cancer cells (Figure 1). This is a crucial result because it is telling us that the genetic background in which tumors are produced would determine a radically different response to chemotherapeutic treatment, either restricting tumor growth or promoting metastatic progression.

These observations are reinforced by interrogation of public databases of human cancer and the analysis of patient-derived samples. Loss of *TIMP1* and *PTEN* correlate in more advanced and metastatic prostate tumors. Importantly, patients with tumors showing low levels of PTEN and TIMP1 respond poorly to Docetaxel treatment and experience a shorter disease-free survival.

From the mechanistic point of view, the authors tested the activity of the senescent secretome lacking Timp1. Cell culture media in which senescent cells lacking Timp1 have been growing promote cell invasion and migration of cells that lacked these abilities, implying a paracrine effect is responsible. Proteome profiling of the secretome of senescent cells lacking TIMP1 and treated with Docetaxel identifies some putative factors that could be responsible for the increased cell migration, GDF15, FGF1, and IGFBP5, three known regulators of cell migration (Suyama et al., 2002). Interestingly, TIMP1 is a matrix metalloprotease (MMP) inhibitor, and, accordingly, chemical inhibitors of MMPs can compensate the absence of TIMP1 and block the pro-invasive and pro-migratory paracrine activity of senescent cells (Figure 1).

These results provide an explanation for how the senescence response can switch from tumor suppressive to metastasis promoting, helping reconcile what might be seen as contradictory results. They should also send a note of caution when considering the development of senescence-inducing therapies to cancer patients. In particular, these observations could be used to stratify prostate cancer patients and could help guide therapeutic interventions in the future based on the status of TIMP1. It would be very interesting to know whether the same or a similar situation might be operating in other tumor types affecting different tissues and bearing diverse genetic defects.

Another interesting message from this paper is the increasingly recognized potential utility of senolytics for the treatment of cancer (Picallos-Rabina et al., 2020). Originally considered as anti-aging treatments, these and other results prove the relevance of considering the administration of senolytic drugs to cancer patients. Removing senescent cells could decrease the negative side effects derived from their secreted factors. But for all this, it would be essential to develop efficient tools to assess the senescence response in a clinical setting during cancer therapy. Getting a deeper knowledge of how cellular senescence operates in cancer might provide us with safer and more efficient anti-cancer therapeutic opportunities.

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