SYMPOSIUM OUTLOOK

Cancer mortality and senescence: Is redox therapy an option?

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Patient genomics and mouse functional genetics have revealed that senescence is a barrier to metastatic progression of prostate cancer. Many efforts focus on eliminating senescent cells, whereas others aim to elucidate distinct characteristics that set them apart from normal and aging cells. Here, we discuss how exploration of the redox state of senescent cells could help define new markers and prooxidant vulnerabilities, drawing analogy to what is known about the redox sensitivity of proliferating cancer cells.

Senescence as a barrier to lethal prostate cancer

With some 313,000 expected new cases in the United States in 2025, prostate cancer (PC) is the most common male cancer diagnosed. Although therapeutic options for localized PC are effective, metastatic PC is a yet incurable disease. Standard of care antiandrogen therapies invariably result in fatal disease relapse.

Comprehensive human sequencing initiatives have unveiled substantial structural complexity and subclonal branching both within and between cells at metastatic sites. The ability to study terminal PC genomes was introduced through rapid autopsy programs, which revealed that metastatic cells that have evolved from a truncal clonal origin present with highly complex genome rearrangements that reflect the pressures of overcoming major bottlenecks of metastasis and antihormonal therapy (Robinson et al. 2015). A separate bottleneck was discovered in genetically engineered mouse (GEM) models of PC exactly 20 years ago: Loss of *Pten* in prostate epithelium triggers *PTEN* loss-induced senescence (PICS) (Chen et al. 2005). This phenomenon is an extension of oncogene-induced senescence (OIS). However, unlike OIS, it introduced the discrete nature of gene dosage: PICS is only induced by loss of both *PTEN* alleles. Conceptually, it further suggested a conditional and cooperative relationship between p53 and PTEN function in the prostate. Although loss of p53 on its own does not trigger a noticeable phenotype in this tissue, loss of PTEN alone is growth-restricted by p53-dependent senescence. Loss of both genes, however, does unleash lethal and metastatic PC (Cho et al. 2014).

When comparing gene alterations found in patients with primary PC with those found in metastasis, Armenia et al. (2018) found that *PTEN*/*TP53* loss clearly stands out as a distinctive feature of metastatic PC. The human and mouse data thus collectively establish these two tumor suppressors as the primary drivers of PC mortality.

In spite of this genetic predominance, however, terminal PC is unfortunately in no way constricted to PTEN/PI3 kinase signaling. Instead, metastatic tumors evolve to acquire a plasticity that allows for resistance to all known cancer treatment regimens. Consequently, inhibitors of the PI3 kinase pathway have not made it into standard of care and are not part of an FDA-approved regimen against lethal PC. This prompted us to revisit the features of men who died of metastatic PC using single-cell genomics analysis. At the Symposium, we presented results from this approach, which strongly suggest that senescence is a barrier to metastatic disease progression and prostate cancer mortality, findings that emphasize the need for development of effective strategies targeting senescent cancer cells.

Targeting senescence: selectivity and specificity

An overarching challenge of senolytic therapy is the issue of achieving selectivity and specificity when targeting cancer-associated senescence. For instance, it is unclear whether senescent cells that arise during metastatic evolution possess characteristics similar to those induced by therapeutic intervention. Furthermore, distinctions between tumor cell-intrinsic senescence and senescence in the tumor microenvironment—or even senescence in aging organs—warrant further exploration. A more comprehensive molecular understanding of these diverse senescent contexts is important for the development of potent therapies (Colucci et al. 2025). One approach to

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meet this need has been to identify metabolic features that are hallmarks of senescent cancer cells. Recent discoveries include the finding that retinoids promote arrest and subsequent immune clearance of senescent cells or the persistent accumulation of iron in senescence (Maus et al. 2023; Colucci et al. 2024).

Pro-oxidants as senolytic agents: Is the lysosome a target?

Antioxidant-based strategies firmly dominate antiaging interventions, aiming to suppress aging and senescence by mitigating oxidative damage. This concept has spilled over into approaches for cancer control and led to extensive human trials. However, these demonstrated the opposite: For example, antioxidant supplements significantly promote the risk of developing prostate cancer (Klein et al. 2011). Conversely, our own research recently showed how pro-oxidant therapy is effective against metastatic PC in GEM models because it triggers an oxidative cell death, which we termed triaptosis (Swamynathan et al. 2024).

The rationale for using pro-oxidants lies in their ability to broadly exploit the cancer cell dependency on effective ROS detoxification in light of their heightened dysregulated metabolic activity. Cancer cells are thus poised to be closer to the threshold of oxidative stress-induced cell death modalities, such as ferroptosis or triaptosis, compared with normal cells.

A critical unresolved question is how redox stress changes in a cancer cell during senescence induction, maintenance, and escape. A better understanding of redox stress across cells of a tumor and its microenvironment would help us explore new targeting strategies. Thus, mapping the trajectory of redox dynamics throughout tumor initiation, senescence, and cell cycle re-entry would provide an invaluable conceptual framework. Beyond illuminating novel therapeutic strategies, this could shed light on how existing therapies known to induce ROS are impacting senescence.

Emerging data from our laboratory and others suggest that many pro-oxidants (such as paraquat, menadione, and auranofin) do not indiscriminately affect the cell and its proteome. Instead, they can cause targeted changes that impinge on discrete pathways in ways that are still being deciphered. As a result, many pro-oxidants can induce distinct types of cell death that are often characterized by strict compartmentalization: the cell's (plasma) membrane for ferroptosis, the endosome for triaptosis, and the nucleus for DNA damage-inducing agents.

So, what about senescent tumor cells? Are they subject to a specific redox stress, and can it be pinned down to a cell structure or biological process?

Intriguingly, two reports presented at the Symposium point toward a role for redox stress at the lysosome. The results independently suggested control of cell cycle re-entry after quiescence, a process that is intimately linked to cell cycle re-entry of senescent cancer cells.

Although senescence is a major limiting factor for tumorigenesis, it does not represent an irreversible state. Cell cycle re-entry via alterations in *TP53* or *CDKN2A* is a hallmark of oncogenic transformation. Although mechanisms underlying the bypass of senescence and the transition to cell cycle re-entry are well established, the mechanisms by which senescent cells preserve metabolic fitness and survival during prolonged periods of growth arrest and cellular stress remain ill-defined. Understanding these metabolic requirements could help design therapies that either eliminate cells in the arrested state or ensure that they will not re-enter cell cycle and relapse into their oncogenic program.

Robust metabolic plasticity in stem cells ensures timely and effective switching between quiescence and cell cycle activation. Now, two studies using the *Caenorhabditis elegans* model organism in different contexts of nutrient deprivation highlight the importance of lysosomal signaling in maintaining quiescent cell homeostasis and reactivation efficacy (Murley et al. 2025; Nonninger et al. 2025). Surprisingly, autophagy takes a backseat in this process, whereas instead the lysosomal signaling and transcriptional modulator TFEB takes precedent. Cumulative damage as a result of intrinsic and environmental insults, including oxidative stress, hampers the efficiency of growth-arrested cells to re-enter the cell cycle. Specifically, the work of Murley et al. (2025) suggests that accumulation of protein aggregates in lysosomes drives the lysosomal dysfunction that restricts cells to quiescence. Interestingly, many of these features are conserved in senescence. Senescent cells accumulate lysosomal membrane damage, resulting in decreased proteolytic capacity, but compensate this defect via TFEB-mediated lysosomal biogenesis (Rovira et al. 2022).

Targeting of a TFEB-mediated survival response of senescent cells could serve as a potential senolytic strategy. Although quiescence is characterized by nutrient regulation of TFEB, its regulation in senescent cells may be under the control of signaling mechanisms that remain to be identified. This could also unearth attractive targets. Thus, ancient growth control pathways that are conserved across the animal kingdom may point to novel therapy because these principles resurface in senescent cancer cells.

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