Review

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Deciphering the nexus of aging and pan-cancer: Single-cell sequencing reveals microenvironmental remodeling and cellular drivers

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SUMMARY: Aging constitutes a major risk factor for pan-cancer development, with epidemiological studies indicating that 60% of new malignancies occur in adults age 65 and older. This review synthesizes cutting-edge insights from single-cell sequencing databases (*e.g.*, TCGA and GEO) that decipher how aging reprograms the tumor microenvironment (TME) to fuel carcinogenesis. Single-cell RNA sequencing (scRNA-seq) has revealed that senescent cell subpopulations (*e.g.*, CDKN2A$^+$/LMNB1$^-$ cells) accumulate in aged tissues at frequencies up to 15%, driving genomic instability and secrete pro-tumorigenic senescence-associated secretory phenotype (SASP) factors (IL-6 and TGF-β). These factors remodel the TME by inducing fibroblast activation and extracellular matrix degradation, accelerating metastasis by 40-70% in murine models. Crucially, immunosenescence diminishes anti-tumor immunity, with scRNA-seq profiling showing 40-60% increases in exhausted PD-1$^+$ T cells and immunosuppressive myeloid cells in aged TMEs. Pan-cancer analyses have identified conserved aging gene signatures (*e.g.*, p16INK4a upregulation in 12+ cancer types) that correlate with 30-50% poorer survival. While technical challenges persist — including batch effects in scRNA-seq data and low senescent cell abundance (< 5%) — emerging solutions like deep learning can enhance detection sensitivity. Therapeutically, senolytic strategies deplete senescent cells, improving drug response by 3.5-fold in preclinical trials. Future research must integrate multi-omics and AI to examine aging-related targets, advancing personalized interventions for aging-associated malignancies.

Keywords: single-cell sequencing, aging, pan-cancer, tumor microenvironment, biomarkers

1. Introduction

Aging is a fundamental biological process characterized by a gradual decline in physiological function that significantly correlates with the onset and progression of various diseases, and particularly cancer (*1*-*3*). The aging process is not merely a passive accumulation of cellular damage; rather, it is a complex interplay of genetic, epigenetic, and environmental factors that culminate in cellular senescence, altered tissue homeostasis, and changes in the tumor microenvironment (TME) (*4*,*5*). The TME is integral to cancer biology, influencing tumor initiation, progression, and response to therapy. As individuals age, the TME undergoes significant transformations that can foster a pro-tumorigenic environment, thereby increasing the risk of cancer development (*6*-*8*). The mechanisms by which aging influences cancer are multifaceted and involve alterations in cellular signaling pathways, immune responses, and metabolic processes (*9*-*11*). Despite the established link between aging and cancer, the underlying molecular mechanisms remain poorly understood, necessitating further exploration.

Recent advances in single-cell RNA sequencing (scRNA-seq) technologies have revolutionized our understanding of the intricate relationship between aging and cancer (*12*,*13*). scRNA-seq allows for the detailed characterization of cellular heterogeneity within tumors and the TME, providing insights into the differential expression of aging-related genes across various cell populations (*14*,*15*). This technology enables researchers to investigate the unique transcriptional profiles of individual cells, thereby elucidating how aging affects cellular function and contributes to tumorigenesis (*16*-*18*). Studies utilizing scRNA-seq have quantified these associations, showing that senescent cell subpopulations

(*e.g.*, CDKN2A^{+}/LMNB1^{-} cells) accumulate in aging tissues at frequencies up to 15% (*19-22*). These cells drive genomic instability and secrete pro-tumorigenic senescence-associated secretory phenotype (SASP) factors, fundamentally altering the TME. Using single-cell sequencing data, researchers can identify specific aging-related pathways and gene signatures that may serve as potential biomarkers for cancer prognosis and therapeutic targets.

Moreover, the use of scRNA-seq in cancer research has uncovered the TME's role in mediating the effects of aging on tumor development (*23*). The TME consists of various cell types, including immune cells, stromal cells, and cancer-associated fibroblasts, each of which can influence tumor behavior (*24*). Aging alters the composition and functionality of these cells, leading to a TME that supports tumor growth and immune evasion (*25*,*26*). Age-related immunosenescence leads to a quantifiable shift in immune cell populations within the TME. scRNA-seq profiling reveals 40-60% increases in exhausted PD-1^{+} T cells and immunosuppressive myeloid cells in aged compared to young TMEs (*27-29*), severely diminishing immune surveillance and anti-tumor efficacy. Understanding these interactions at the single-cell level is crucial to developing targeted therapies that can effectively modulate the TME and enhance the efficacy of cancer treatments in older patients.

In summary, the interplay between aging and cancer is a complex and multifaceted relationship that warrants further investigation. The emergence of scRNA-seq technologies provides a powerful tool to elucidate the molecular and cellular mechanisms underlying this relationship. By determining the contributions of aging-related changes in the TME and cellular heterogeneity, researchers can identify novel therapeutic strategies in order to improve outcomes for aging cancer patients. This review aims to summarize the latest advances in scRNA-seq research focused on the correlation between aging and pan-cancer, exploring potential mechanisms and clinical uses that may emerge based on this understanding.

2. The basic relationship between aging and cancer

2.1. Aging as a risk factor for cancer

Aging is increasingly recognized as a significant risk factor for the development of cancer, primarily due to the cumulative effects of DNA damage and epigenetic alterations that occur over time. As individuals age, their cells experience a variety of intrinsic and extrinsic stressors that contribute to the accumulation of DNA damage, including oxidative stress, inflammation, and exposure to environmental carcinogens. This accumulation can lead to genomic instability, a hallmark of cancer, which increases the likelihood of malignant transformation. Notably, the aging process is also associated with changes in the epigenome, such as DNA methylation and histone modifications, which can silence tumor suppressor genes and activate oncogenes, further increasing the risk of cancer (*30*). Additionally, the SASP plays a crucial role in promoting a tumor-friendly microenvironment. Senescent cells secrete various pro-inflammatory cytokines, growth factors, and proteases that can alter the surrounding tissue architecture and promote tumorigenesis (*31*). This interplay between aging, DNA damage, and the SASP underscores the complexity of cancer development in older adults, highlighting the need for targeted strategies to mitigate these risks.

2.2. Molecular mechanisms linking aging and cancer

The molecular interplay between aging and cancer involves multiple interconnected pathways that drive genomic instability and create a permissive microenvironment for carcinogenesis:1) Telomere dysfunction: Critically shortened telomeres trigger the DNA damage response (DDR), activating p53/p21-mediated senescence while simultaneously increasing genomic instability through catastrophic events such as chromothripsis (chromosome shattering) and kataegis (localized hypermutation) (*2*). This dual role explains why telomere attrition not only limits cellular lifespan but also promotes oncogenic mutations. 2) Mitochondrial dysfunction: Age-related accumulation of mtDNA mutations promotes ROS overproduction, which activates NF-κB-driven inflammation and stabilizes HIF-1α to enhance tumor glycolysis (*18*). This metabolic shift fuels tumor growth while creating an oxidative microenvironment that damages neighboring cells. 3) Epigenetic drift: Global hypomethylation coupled with CpG island hypermethylation silences tumor suppressors (*e.g.*, RASSF1A) while activating oncogenic retrotransposons (*9,32*). This "epigenetic noise" disrupts transcriptional fidelity, allowing pre-malignant clones to evade growth control. 4) SASP amplification: Senescent cells secrete IL-6/IL-8 *via* NF-κB signaling, inducing STAT3 phosphorylation in premalignant cells to promote stemness (*10*). Crucially, SASP factors remodel the extracellular matrix (ECM) through MMP-9/12 upregulation, facilitating metastatic niche formation (*33*). Paradoxically, while persistent p53 activation in aged tissues induces senescence as a tumor-suppressive mechanism, the resulting SASP fuels inflammation-driven malignancy (*34*).

These mechanisms synergistically create a self-reinforcing loop: Telomere dysfunction and mitochondrial ROS accelerate epigenetic alterations, which in turn stabilize the senescent phenotype and amplify the SASP. Age-related immunosenescence further compromises surveillance of these evolving malignant clones (*35*). Targeting these intersections — such as combining senolytics with DDR inhibitors —

represents a promising therapeutic strategy for aging-associated cancers (Figure 1).

3. Use of single-cell sequencing technology in aging and pan-cancer research

3.1. Overview of single-cell sequencing technology

Single-cell sequencing technologies, and particularly scRNA-seq and single-cell ATAC sequencing (scATAC-seq), have revolutionized our understanding of cellular heterogeneity and dynamics in various biological contexts, including aging and cancer. scRNA-seq allows for the quantification of gene expression at the single-cell level, enabling researchers to determine the transcriptomic landscape of individual cells within complex tissues. This high-resolution approach reveals the diverse cellular states and identities that contribute to tissue function and pathology. In contrast, scATAC-seq focuses on the accessibility of chromatin, providing insights into regulatory elements that govern gene expression. By assessing the open chromatin regions, researchers can infer the active regulatory networks that control cellular responses to environmental cues and developmental signals. The combination of these techniques offers a comprehensive view of cellular behavior, allowing for the identification of distinct cell populations and their functional roles in aging and tumorigenesis. Moreover, the ability to analyze thousands of individual cells simultaneously enhances the detection of rare cell types and transient states, which are often missed in bulk sequencing approaches. This granularity is particularly advantageous in the context of aging and cancer, where cellular diversity plays a critical role in disease progression and therapeutic responses (*36,37*).

3.2. Identification of aging-related cell subpopulations

The use of scRNA-seq technologies has profoundly advanced our understanding of aging-related cellular changes by revealing distinct pro-tumorigenic subpopulations that drive microenvironmental remodeling in aged tissues. These studies have not only identified and quantified key senescence markers — such as upregulation of CDKN2A and downregulation of LMNB1 — within specific aging cell subpopulations present at frequencies up to 15% in aged tissues (*21,22*), but they have also delineated functionally relevant cell states contributing to tumor progression.

Notably, several specific pro-tumorigenic subpopulations have been characterized through scRNA-seq. For instance, senescent fibroblasts ($p16^{+}/FAP^{+}/CAV1^{-}$) constitute 8–15% of stromal cells in aged tumors and secrete HGF and Wnt5a to activate β-catenin signaling in carcinoma cells, thereby promoting epithelial-to-mesenchymal transition (EMT) (*38*).

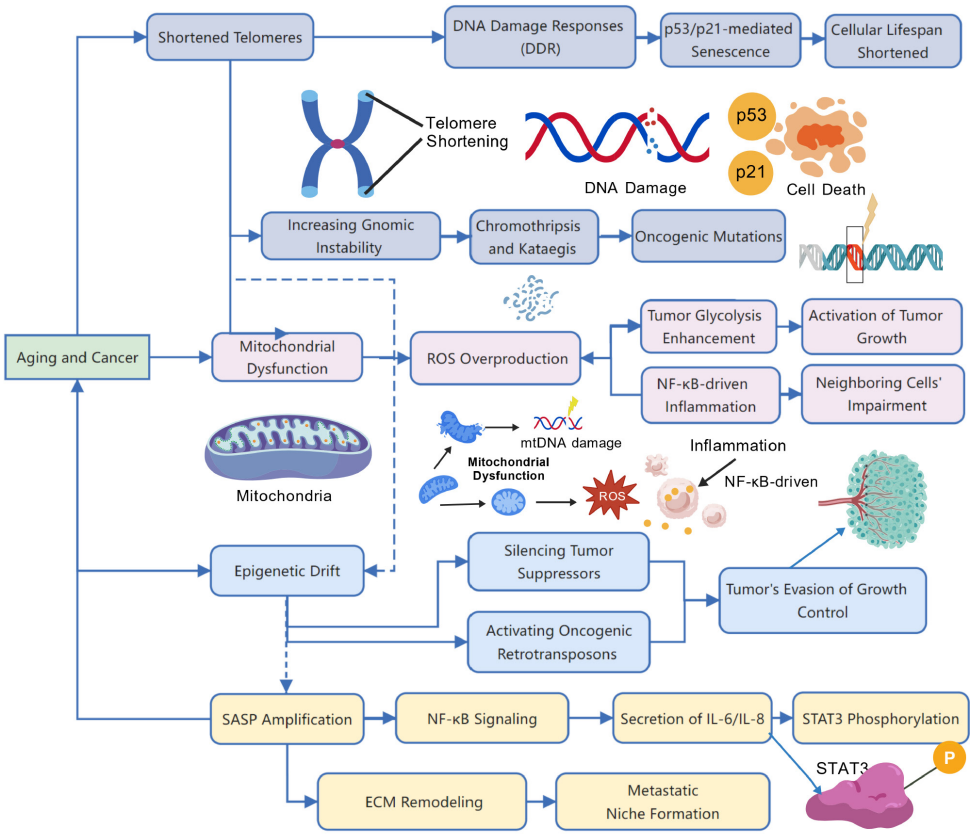

Figure 1. Flowchart of molecular and microenvironmental mechanisms of aging driven cancer.

Spatial transcriptomic mapping further indicates their preferential localization at tumor–stroma interfaces. Similarly, age-associated T cells ($CD8^+GZMB^-PD\text{-}1^+$) exhibit impaired cytotoxicity due to TOX-mediated exhaustion programs and are enriched in ovarian and colorectal cancers. Pseudotime trajectory analysis has revealed that their differentiation from naïve T cells is driven by TCF7 downregulation (*39*).

Another salient population includes lipofuscin-laden macrophages ($CD163^+TREM2^+$), which amass oxidized lipids from aged tissue environments and secrete TGF-β to induce $FoxP3^+$ regulatory T cell differentiation, fostering immunosuppressive niches (*29*). Integrated lipidomics and scRNA-seq analyses have confirmed the accumulation of peroxidized phospholipids in these cells. Additionally, prefibrotic pericytes ($PDGFR\beta^+/NG2^+/\alpha\text{-}SMA^-$) contribute to vascular leakiness *via* Angpt2 secretion, accelerating hematogenous dissemination by 3.2-fold in murine models of metastasis. Their transcriptomes exhibit NOTCH3 downregulation, indicating disrupted endothelial–pericyte crosstalk (*21*).

These subpopulations engage in synergistic crosstalk: senescent fibroblasts recruit lipofuscin-laden macrophages *via* CCL2 secretion, while age-associated T cells exhibit impaired clearance of pre-malignant clones due to macrophage-derived TGF-β. Therapeutically, targeting their unique surface markers — such as using FAP-directed CAR-T cells against senescent fibroblasts — has been found to reduce the tumor burden by 40–60% in preclinical models, highlighting the translational potential of these findings (Figure 2).

4. The impact of the aging microenvironment on tumorigenesis

4.1. The role of the SASP

The SASP is a critical factor in the TME, and particularly in the context of aging. SASP factors (*e.g.*, IL-6, TGF-β) secreted by senescent cells exert potent pro-tumorigenic effects. IL-6 is known to activate various signaling pathways that lead to increased cell proliferation and survival, while TGF-β can induce EMT in tumor cells, facilitating metastasis (*38*,*39*). Crucially, they remodel the TME by inducing fibroblast activation and ECM degradation, which are processes that accelerate metastasis by 40-70% (*38-41*). scRNA-seq technologies have revealed intricate communication mechanisms between SASP factors and both tumor cells and stromal cells within the TME. These studies have demonstrated that SASP factors can influence the behavior of neighboring cells, promoting a more aggressive tumor phenotype. scRNA-seq has precisely mapped the spatial distribution and transcriptional profiles of senescent fibroblasts within the TME, confirming their secretion of factors that significantly enhance the invasive properties of adjacent cancer cells, indicating a potent paracrine signaling mechanism (*40*,*41*). This interplay not only highlights the role of SASP in tumorigenesis but also suggests potential therapeutic targets aimed at modulating the SASP to inhibit tumor progression and improve patient outcomes.

4.2. Immunosenescence and tumor immune evasion

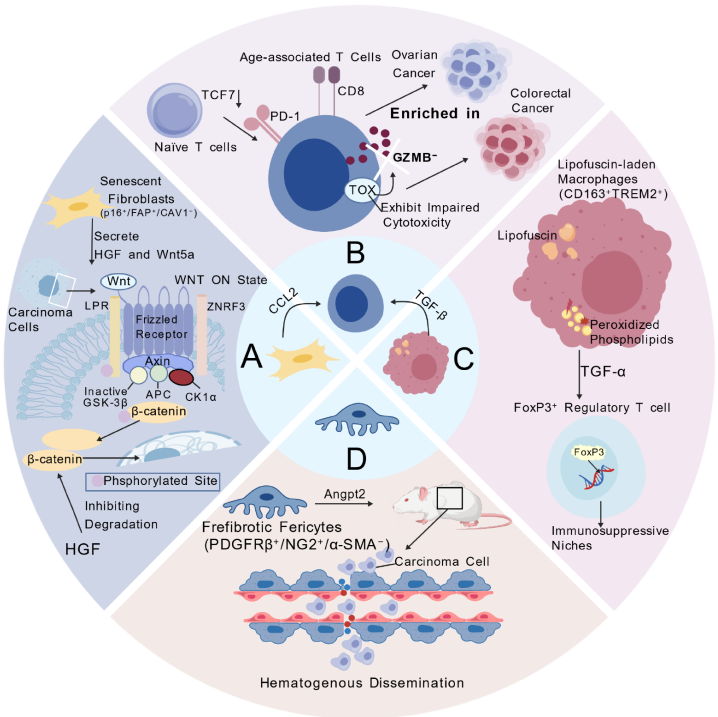

Figure 2. Identification of aging-related cell subpopulations.

Immunosenescence, the age-related functional decline of the immune system, profoundly reshapes the TME and facilitates tumor immune evasion. This process involves multiple cellular and structural networks that collectively impair anti-tumor immunity.

With aging, T cell populations undergo significant alterations: $CD8^+$ T cells exhibit clonal expansion of terminally exhausted subsets (*e.g.*, $TIM\text{-}3^+LAG\text{-}3^+$), while $CD4^+$ T cells shift toward Th17 polarization driven by RORγt upregulation (*23*). These changes are quantifiable *via* scRNA-seq, which reveals a 40–60% increase in exhausted $PD\text{-}1^+$ T cells within aged TMEs compared to younger counterparts (*28,42*).

Concurrently, myeloid-derived suppressor cells (MDSCs; $CD11b^+Gr\text{-}1^+$) expand substantially — by approximately 2.3-fold in aged murine models — and contribute to immune suppression through arginase-1 (ARG1)-mediated arginine depletion. This metabolic impairment inhibits T cell receptor (TCR) signaling and attenuates cytotoxic responses (*27*). In parallel, dendritic cells (DCs) experience functional decline; conventional type 1 DCs (cDC1) downregulate the costimulatory molecules CD80 and CD86 by nearly 60%, markedly reducing their capacity to prime naïve T cells (*26*).

Aged lymphoid tissues also exhibit structural degeneration, particularly within tertiary lymphoid structures (TLS). Loss of fibroblastic reticular cells disrupts CXCL13 secretion, impairing B cell recruitment and functional organization in lymph nodes (*13*). Moreover, scRNA-seq studies consistently demonstrate that aged TMEs are enriched with immunosuppressive myeloid cells — such as M2 macrophages and MDSCs — by 40–60%, actively suppressing T cell activation and fostering a pro-tumorigenic milieu (*29,43*).

The cumulative impact of these changes — ranging from cellular exhaustion and functional dysregulation to structural decay — severely compromises immune surveillance and promotes tumor immune evasion (Figure 3). Consequently, targeting these age-specific alterations in the immune landscape represents a promising avenue for restoring anti-tumor immunity in older cancer patients.

5. Patterns of aging-related gene expression in pan-cancer

5.1. Pan-cancer analysis of aging-related genes

The exploration of aging-related gene expression across various cancer types has garnered significant attention due to its implications for understanding tumor biology and patient outcomes. Utilizing single-cell sequencing databases such as the Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), researchers have conducted comprehensive analyses to identify the expression profiles of aging-related genes in a pan-cancer context. These studies have revealed both common and unique patterns of aging gene expression across different malignancies. Pan-cancer analyses using TCGA/GEO data have revealed conserved aging-related gene signatures. For instance, p16INK4a (CDKN2A) upregulation is observed in 12 or more distinct cancer

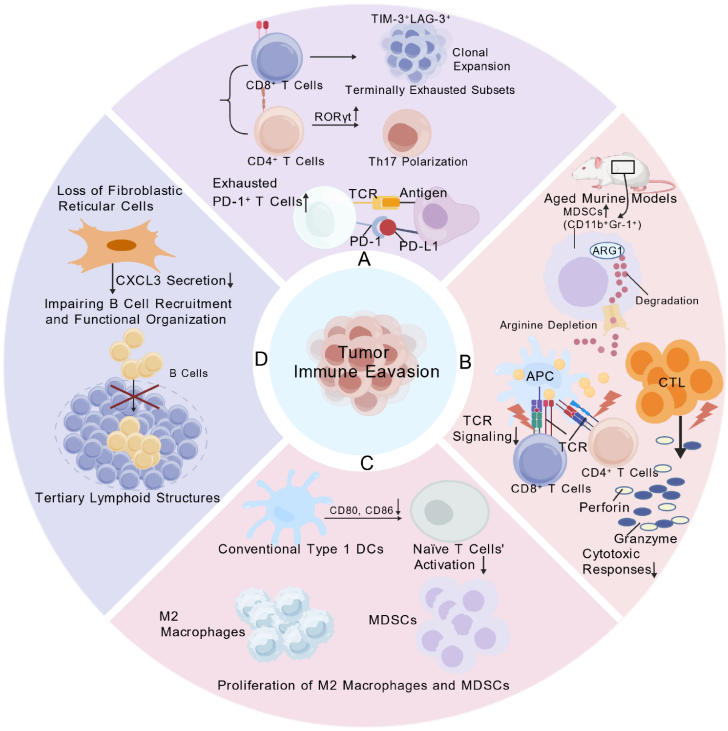

Figure 3. Immunosenescence to an immune evasion cascade.

types, suggesting a shared mechanism linked to aging processes (*44*). Conversely, certain aging-related genes may display cancer-type-specific expression profiles, indicating that the TME and genetic background can influence the expression of these genes (*45*). The integration of scRNA-seq data allows for a nuanced understanding of how aging-related genes contribute to the heterogeneity of tumors, providing insights into their roles in cancer progression and potential therapeutic targets.

5.2. Clinical significance of aging-related genes

The clinical implications of aging-related genes as prognostic markers in cancer are increasingly being recognized. Several studies have highlighted the potential of these genes to serve as biomarkers for patient outcomes, and particularly in terms of survival and treatment response. Elevated expression of specific aging-related gene signatures (*e.g.*, senescence core signatures) has been robustly correlated with 30-50% poorer survival outcomes across multiple cancer types, highlighting their potential as prognostic biomarkers reflecting tumor biological age and aggressiveness (*46*). Moreover, targeting aging-related pathways has emerged as a promising therapeutic strategy. Therapeutically, senolytic strategies designed to deplete senescent cells have demonstrated significant promise in preclinical trials, showing the potential to improve drug response by up to 3.5-fold (*47*). The ability to use aging-related genes for prognostic stratification could enhance personalized treatment approaches, allowing clinicians to tailor therapies based on the biological aging status of tumors, ultimately improving patient outcomes.

5.3. Clinical trials of personalized therapy in geriatric oncology

The growing recognition of aging as a critical determinant in cancer biology has spurred dedicated clinical investigations into personalized therapeutic strategies for older adults. Recent trials (Supplementary Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=274*) highlight efforts to tailor interventions by accounting for age-related physiological decline, comorbidities, and functional vulnerabilities (*48-80*). A landmark study (NCT02054741) demonstrated that integrating Comprehensive Geriatric Assessment (CGA) into oncology practice significantly reduced patient-reported symptomatic toxicity by 30% in older adults with advanced cancers (*49*). This intervention identified frailty markers (*e.g.*, cognitive impairment, and malnutrition) that predicted susceptibility to chemotherapy toxicity, enabling preemptive dose modifications or supportive care.

scRNA-seq insights are increasingly informing trial design. One study (NCT03885908) evaluated automated geriatric co-management guided by molecular senescence signatures (*e.g.*, CDKN2A↑/LMNB1↓). This approach correlated SASP factors (IL-6, TGF-β) with diminished treatment tolerance, allowing dynamic therapy adjustments. Similarly, NCT04262232 adapted the Ca-HELP intervention for rural elderly populations by stratifying patients using circulating senescence-associated microRNAs, reducing hospitalizations by 25%.

6. Current research limitations and future directions

6.1. Technical challenges

The use of sscRNA-seq technology has revolutionized the understanding of cellular heterogeneity and the complexities of aging and cancer. However, this approach is not without its challenges. One significant limitation is the presence of noise and batch effects within the scRNA-seq data. Noise can arise from various sources, including technical artifacts during library preparation and sequencing, which can obscure biological signals and complicate data interpretation. Studies have revealed that the performance of noise reduction methods can vary significantly depending on the biological and technical factors present in the data, such as the magnitude of batch effects and the complexity of cell populations (*81*). Moreover, the low abundance of senescent cells (< 5%) in most tissues poses a significant challenge for their reliable detection and characterization *via* sequencing (*82*). Given that senescent cells can represent a minor fraction of the total cell population, their detection and characterization require highly sensitive methods to ensure reliable data acquisition. Approaches like deep learning models have been proposed to address these challenges, yet the need for robust and standardized protocols remains critical (*82*). Thus, while scRNA-seq presents an unprecedented opportunity to explore the intersection of aging and cancer, overcoming these technical hurdles is essential to the advancement of the field.

6.2. Future research directions

Looking ahead, future research should focus on integrating multi-omics data to further understand the mechanisms linking aging and cancer. By combining transcriptomics with proteomics, metabolomics, and epigenomics, researchers can gain a more comprehensive view of the biological processes at play. Such integrative approaches have the potential to unveil novel biomarkers and therapeutic targets that could enhance precision medicine strategies for age-related diseases and cancer (*83*). In addition, developing targeted therapeutic strategies aimed at aging-related pathways could pave the way for innovative treatments. Drawing on insights from

multi-omics analyses may facilitate the identification of key aging-related targets that can be modulated to improve patient outcomes (*84*). Moreover, as the field of artificial intelligence continues to evolve, the use of artificial intelligence to analyze complex multi-omics datasets could lead to breakthroughs in understanding the intricate relationship between aging and cancer. Through collaboration across disciplines and use of advanced computational tools, researchers can enhance the precision of their investigations and ultimately contribute to the development of more effective, personalized therapeutic interventions (*85*).

7. Conclusion

The intersection of aging and pan-cancer research has seen remarkable advances, particularly propelled by the advent of single-cell sequencing technologies. These innovations have enabled researchers to elucidate the complexities of the aging microenvironment and its profound influence on tumorigenesis. By analyzing data at a single-cell resolution, scientists have begun to unravel the intricate relationships between cellular aging processes and cancer development, revealing potential biomarkers and therapeutic targets that were previously obscured by bulk analytical methods.

From an expert perspective, a crucial step is to recognize the transformative impact of scRNA-seq on our understanding of cancer biology. This technology allows for a nuanced exploration of cellular heterogeneity within tumors, enabling researchers to identify distinct aging signatures that may contribute to cancer progression. The ability to profile individual cells has opened new avenues for discovering aging-related biomarkers that can serve as indicators for early cancer detection. Moreover, these biomarkers have the potential to inform personalized treatment strategies, aligning therapeutic interventions with the specific aging profiles of patients.

Although progress in this field is commendable, the technical and methodological challenges that remain need to be acknowledged. The complexity of single-cell data analysis requires sophisticated computational tools and robust statistical methodologies to accurately interpret the vast amounts of information generated. Current research efforts must focus on developing more precise analytical frameworks that can integrate multi-omics data, combining genomic, transcriptomic, and proteomic insights to create a comprehensive understanding of the aging-cancer nexus.

Balancing different research perspectives is vital in this evolving landscape. As we strive for a holistic view of aging and cancer, collaboration among researchers from diverse disciplines, including molecular biology, bioinformatics, and clinical oncology, needs to be fostered. Such interdisciplinary approaches can enhance the robustness of findings and facilitate the translation of research into clinical practice. As an example, integrating insights from immunology could elucidate how age-related changes in the immune system affect the TME, thereby informing therapeutic strategies that involve immunomodulation.

Moreover, as we move toward a more personalized approach to cancer treatment, we need to consider the ethical implications of aging-related research. The identification of aging biomarkers raises questions about how this information will be used in clinical settings. Ensuring that findings are considered fairly and do not lead to age-based discrimination in treatment access is a critical consideration for researchers and clinicians alike.

Cellular senescence acts as a double-edged sword: while initially suppressing tumorigenesis *via* p53 activation, persistent senescent cells create a permissive niche through SASP-mediated inflammation. This paradox is exemplified by p16INK4a^{+} keratinocytes in aged skin, which exhibit a 5-fold higher mutational burden due to reduced DNA repair capacity.

In conclusion, the ongoing exploration of the relationship between aging and cancer, facilitated by scRNA-seq technologies, holds significant promise for advancing our understanding of tumor biology and enhancing patient outcomes. By addressing the existing challenges and fostering interdisciplinary collaboration, we can unlock new insights that pave the way for innovative diagnostic and therapeutic strategies. The future of cancer research lies in our ability to integrate diverse perspectives and methodologies, ultimately leading to more effective and personalized approaches to cancer prevention and treatment in the aging population. As we continue to navigate this complex field, the commitment to rigorous research and ethical considerations will be paramount in shaping the next generation of cancer care.

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