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Review

Age-associated differences in the cancer molecular landscape

Kasit Chatsirisupachai [1,*], Cyril Lagger [1] and João Pedro de Magalhães [1,*]

Cancer is an age-related disease, as incidence and mortality for most types of cancer increase with age. However, how molecular alterations in tumors differ among patients of different ages remains poorly understood. Recent studies have shed light on the age-associated molecular landscapes in cancer. Here, we summarize the main findings of these current studies, highlighting major differences in the genomic, transcriptomic, epigenetic, and immunological landscapes between cancer in younger and older patients. Importantly, some cancer driver genes are mutated more frequently in younger or older patients. We discuss the potential roles of aging-related processes in shaping these age-related differences in cancer. We further emphasize the remaining unsolved questions that could provide important insights that will have implications in personalized medicine.

Highlights

While the age-related increase in cancer incidence and mortality has been widely recognized, studies of how aging shapes the molecular landscape of tumors have only just begun.

Somatic mutations in cancer driver genes are not uniformly distributed across age. Some driver genes are mutated more often in younger or older patients, as revealed by recent pan-cancer studies.

Age-associated gene expression and epigenetic landscapes in cancer relate to diverse biological processes such as immune-related processes, extracellular matrix organization, and angiogenesis.

Age-related differences in tumor immune landscapes should alter therapeutic responses.

Tissue microenvironment changes with age may have a profound impact on cancer.

Do cancers differ according to the patient's age?

Aging (see Glossary) involves a progressive deterioration of physiological functions and an increased risk of numerous diseases [1]. In particular, an exponential increase in cancer incidence and mortality rate with age has long been recognized [2,3]. As the aging population continues to rise, a better understanding of the relationship between aging and cancer is critically needed. In addition, disparities between cancers in young and aged patients have also been observed [4]. For instance, breast cancer in younger patients tends to be more aggressive and is associated with poorer survival [5], while the prognosis is worse in older ovarian cancer patients [6]. Several studies have revealed distinct molecular characteristics of tumors in relation to age in various cancer types, such as breast [7,8], prostate [9], and colorectal [10] cancers. These analyses, however, focused on one cancer type and only a few molecular data types at a time. Recently, four independent studies performed pan-cancer analyses to shed light on the age-associated genomic, transcriptomic, and epigenomic patterns [11–14]. The age-related patterns of molecular alterations might suggest differences in the oncogenic mechanisms concerning the patient's age. Another **pan-cancer study** focused on age-related markers of **immune checkpoint blockade (ICB)** and a shift in immune-cell-type abundance with age, which will be crucial for designing immunotherapy strategies [15]. Here, we summarize the major findings from these pan-cancer and cancer-specific studies (Table S1 in the supplemental information online) and discuss potential aging processes that might contribute to these differences in cancer molecular landscape.

Age-related genomic landscape in cancer

Age-related somatic mutation burden in tumors

Increased age is associated with higher **somatic mutations** (single-nucleotide variants and small insertions/deletions) in most cancer types [11,12,14,16–18], with an estimated increase of 0.077 mutations per megabase per year [12]. The spontaneous deamination of 5-methylcytosine to thymine (C>T) transitions, often referred to as the 'clock-like' mutational signature, dominates this age-related increase in mutation load. Furthermore, DNA damage repair signatures are more

[1]Integrative Genomics of Ageing Group, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L7 8TX, UK

*Correspondence:
k.chatsirisupachai@liverpool.ac.uk (K. Chatsirisupachai) and
jp@senescence.info (J.P. de Magalhães).

likely to be found in older individuals [12]. The mutational signature related to APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like family) cytidine deaminase activity increases with age in melanoma [12] and prostate cancer [9]. In addition to somatic mutations, **somatic copy-number alterations (SCNAs)** also increase as a function of age in the pan-cancer analysis (Figure 1) [11,12]. Cancer-type-specific analyses revealed a significant positive association between SCNA level and age in a few cancer types, including low-grade glioma, endometrial, ovarian, and prostate cancers [11,12]. However, another study found a positive association between SCNAs and age only in sarcoma [14]. This discrepancy might be due to the use of a 50-year-old cutoff to separate young and old patients [14], in contrast to other studies that used age as a continuous variable in their statistical model [11,12]. Tumors from older individuals tend to accumulate more clonal mutations (i.e., mutations that arise earlier in tumor evolution) [12]. This observation could correspond to an accumulation of somatic mutations with age occurring before carcinogenesis, as recently reported in most noncancerous human tissues [19–21]. Further studies are needed to elucidate how age affects clonal and subclonal mutations in cancer to better understand the impact of age on cancer evolution.

While mutation load increases with age in most cancer types, lung adenocarcinoma and endometrial cancer show an opposite trend. SCNAs also decrease with age in lung adenocarcinoma. The fact that smokers were diagnosed with lung cancer at younger ages in The Cancer Genome Atlas (TCGA) cohort potentially explains the negative association between age and somatic mutation and SCNA in patients with lung cancer [11,12], although other unexplored causes are likely to contribute as well. For endometrial cancer, tumors from younger patients showed a higher proportion of the high **microsatellite instability** (**MSI**-H) subtype [22]. Furthermore, mutations in DNA polymerase ε (*POLE*) and polymerase δ (*POLD1*) are found more often in younger endometrial cancer patients [11,14,23]. Why the MSI-H and *POLE/POLD1* mutation subtypes occur more frequently in younger patients is, however, still unclear.

How somatic mutations in cancer driver genes differ according to age

Several cancer types display an age-associated mutational landscape in known **cancer driver genes**. In other words, some driver genes are mutated more often in younger or older individuals (Figure 1). A prominent example of this is a much higher frequency of mutations in isocitrate dehydrogenase 1 (*IDH1*), alpha thalassemia/mental retardation syndrome X-linked gene (*ATRX*), and tumor protein p53 (*TP53*) in younger glioma patients. These mutations are associated with the IDH-mutant subtype [11,12,14,24]. One study found that mutations in *ATRX* are an age-dependent prognostic biomarker for low-grade glioma; such mutations are associated with a poor outcome in younger patients but with better survival in older patients [12]. Conversely, the IDH-wild-type subtype associated with copy-number losses of chromosome 10 (*PTEN*) and gains of chromosome 7 (*EGFR*) is higher in older glioma patients [11,14,25]. As another example already mentioned above, younger endometrial cancers are associated with MSI-H and *POLE/POLD1* mutation subtypes with a high mutation load. Thus, younger patients contain a higher percentage of somatic mutations in cancer driver genes, including DNA-repair genes, PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α), and growth factor signaling pathways [13]. However, older endometrial tumors present a very high SCNA burden in several regions, including regions harboring cancer driver genes [11], and are associated with poorer survival than in younger patients [26].

Breast cancer is potentially the most well-characterized cancer in terms of age-associated subtyping. A favorable prognostic estrogen receptor-positive (ER^+) subtype is diagnosed more often in older individuals, while an aggressive human epidermal growth factor receptor 2-positive ($HER2^+$) subtype is more common in younger patients. In the PAM50 subtyping system, younger

Glossary

Aging: while having multiple definitions, aging can be broadly defined as a complex, progressive process associated with a decline in physiological function, leading to increased susceptibility to diseases and increased mortality.
Cancer driver gene: a gene in which mutations are causally associated with cancer progression.
Cellular senescence/senescent cells: a stage of a cell in which irreversible cell cycle arrest occurs in response to different damaging stimuli. Characteristics of senescent cells include flattened and enlarged morphology, resistance to apoptosis, and secretion of cytokines, chemokines, and proteinases [collectively called senescence-associated secretory phenotypes (SASPs)].
Immune checkpoint blockade (ICB): a type of immunotherapy by targeting checkpoint proteins that impair T cell activation. Therefore, immune checkpoint blockade therapy boosts the ability of T cells to kill cancer cells.
Microsatellite instability (MSI): a hypermutable phenotype caused by impaired DNA mismatch repair activity. Cancer types with a high prevalence of MSI-high (MSI-H) tumors include endometrial, colorectal, and stomach cancers.
Multi-omics: the integration of multiple layers of data generated by high-throughput techniques, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics.
Pan-cancer study/analysis: a study that investigates molecular and cellular similarities and differences across several cancer types.
Somatic copy-number alteration (SCNA): a somatic change that results in the gain or loss of copy numbers of the affected chromosomal section.
Somatic mutation: an alteration in the DNA sequence that occurs after fertilization.
Structural variation: a genomic variant that affects a large scale of the genome. Structural variations are generally classified into five major types – deletions, insertions, duplications, inversions, and translocations. Deletions and insertions are commonly referred to as copy-number alterations.
Tissue microenvironment: the set of cellular and noncellular components in a tissue such as fibroblasts, endothelial cells, pericytes, adipocytes, various

women are diagnosed with more biologically aggressive HER2-enriched and basal-like subtypes [27]. Luminal A tumors that have a better prognosis are more common in older women [4]. Regarding somatic mutations, higher cadherin 1 (*CDH1*) mutations in older patients are observed [7,8,11,13]. The *CDH1* mutation is highly enriched in the invasive lobular carcinoma subtype, which is more common in older patients [28]. Mutations in *PIK3CA* also appear to increase in frequency with age [29,30]. Breast cancer in younger patients is associated with higher *TP53*, GATA binding protein 3 (*GATA3*), and AT-rich interaction domain 1A (*ARID1A*) mutations [7,13,30,31]. Interestingly, a recent report suggests that the age-associated differences in *GATA3*, *ARID1A*, and *PIK3CA* mutations were only found in luminal A but not in other PAM50 subtypes [30].

The identification of age-related driver genes may be clinically relevant. For instance, *PIK3CA* mutations, which are more common in older patients, correlate with a better treatment outcome in early-stage breast cancer [32]. Next, mutations in *GATA3*, a gene encoding transcription factor that acts cooperatively with ER and is mutated more frequently in younger patients, could promote tumor cell growth and associate with endocrine resistance [33]. Furthermore, lower *GATA3* expression is associated with poor prognosis [34]. However, mutations in *GATA3* can be both gain-of-function and loss-of-function [35], and it remains unclear whether *GATA3* acts as a tumor suppressor or as an oncogene [36]. Therefore, further studies are required to better clarify biological and clinical implications of *GATA3* mutations in younger and older breast cancer patients.

For other cancer types, it has been reported that *TP53* and *CTNNB1* mutations are more common in younger colorectal cancer patients, while adenomatous polyposis coli (*APC*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) *V600* mutations are higher in older patients [10,37,38]. By contrast, *BRAF* mutations, especially *BRAF V600*, decrease with age in melanoma [39]. *CDH1* mutations, which are higher in older breast cancer patients, decrease with age in stomach cancer [11]. In prostate cancer, **structural variation** breakpoints were highly enriched near gene regulatory regions such as active enhancers in the early-onset but not late-onset prostate cancer [9].

Overall, somatic mutations in cancer driver genes do not uniformly distribute across age. These age-related somatic mutations appear to be cancer-type specific. In addition, some mutations display opposite trends in different cancers. Typically, mutations in *BRAF V600* decline with age in melanoma and increase in colorectal cancer. Mutations in *BRAF V600* are an example of age-related mutations that are clinically actionable targets with multiple approved drugs [14]. Additional investigation of age-related driver genes could shed light on the underlying biological differences between tumors from younger and older groups and help improve treatment strategy. In addition, further studies are needed to determine if the effectiveness of targeted drugs differs according to patient's age [4]. Besides, older patients often present with comorbidities and may have specific therapeutic challenges [40]. In summary, the identification of age-related somatic driver mutations and further investigation of these drivers could have a profound impact in the clinical setting to improve treatment options for patients of different age groups.

Age-associated gene expression, epigenetic, and immunological landscape in cancer

Age-associated gene expression and DNA methylation patterns

Several studies attempted to investigate age-related gene expression in cancer. In breast cancer, an early study reported a higher expression of cell cycle-related genes in tumors from younger than those from older ER^+ patients [41]. Recently, another work suggested that age-related differentially expressed genes in breast cancer could partly be controlled by age-related changes in estrogen signaling [42]. Pan-cancer studies reported that the amount of age-associated

types of immune cells, and the extracellular matrix and fluid. These components interact to maintain tissue homeostasis.
Tumor immune infiltration: the process of immune cells leaving the bloodstream to migrate towards a tumor and settling in between tumor cells.

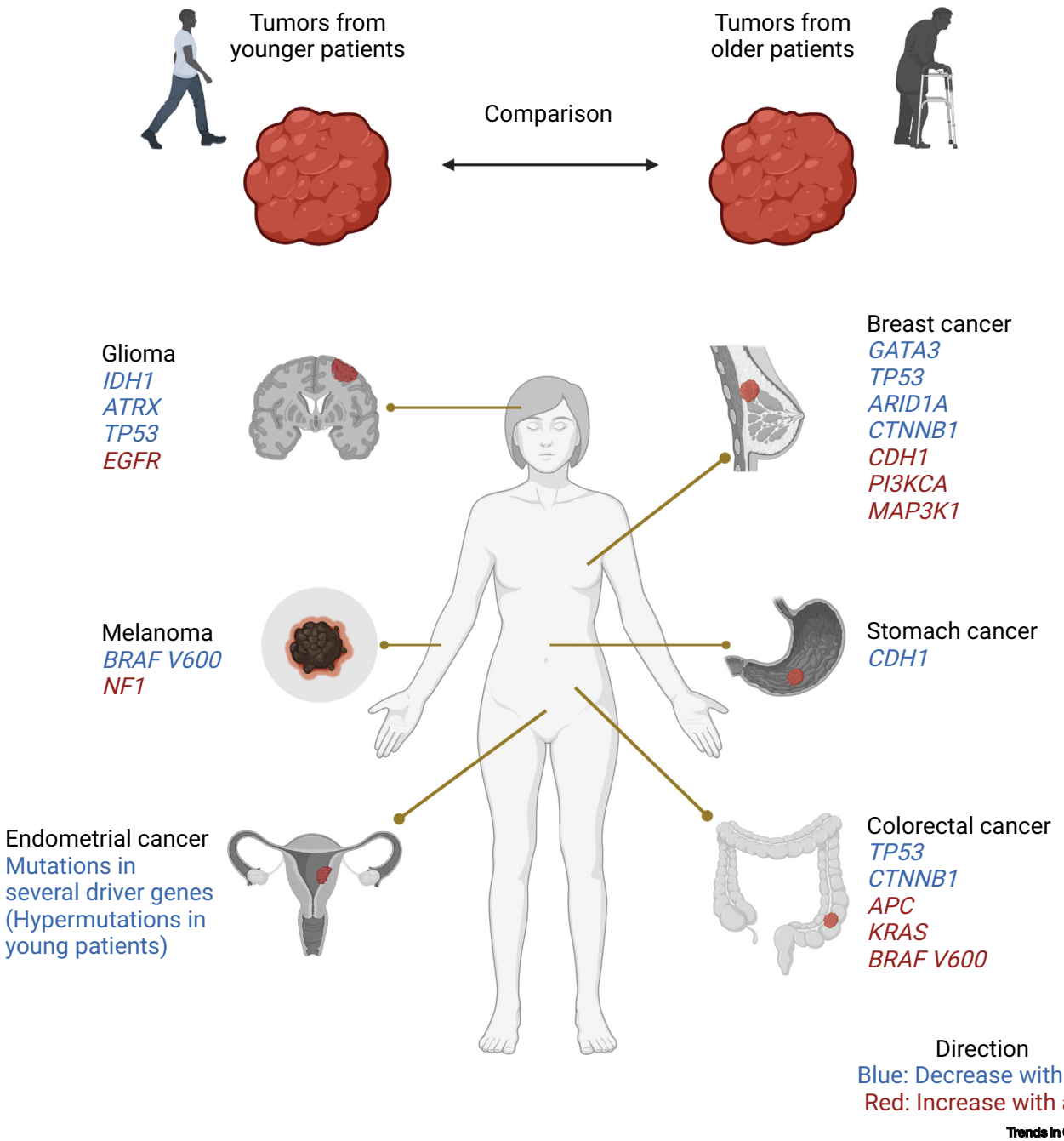

Figure 1. Age-associated differences in the cancer genome. Examples of cancer driver genes that display age-associated patterns in somatic mutations are shown in the figure. Driver genes in blue represent genes that are mutated more frequently in younger patients, while those in red denote genes that are mutated more frequently in older patients. Please note that this is not a comprehensive list of age-related somatic mutations in cancer driver genes. For more complete data, we refer to Table S1 in the online supplemental information online. Figure created with BioRender.com.

differentially expressed genes in cancer varies across tumor types. These genes are partly regulated by age-associated DNA methylation changes [11,13,43]. One study used survival data and the number of differentially expressed genes to classify cancers as age-associated and non-age-

associated [13]. Age-associated cancer types include low-grade glioma, lung squamous cell carcinoma, thyroid adenocarcinoma, and cancers of female reproductive organs (breast, ovarian, and endometrial). Notably, tumors from younger patients of age-associated cancers are associated with increased age acceleration as measured by the epigenetic clock. This was not observed in non-age-associated cancers [13]. Nevertheless, the molecular mechanisms behind this observation, and why such a feature is limited to only age-associated cancers, are unclear.

The observed age-related gene expression changes in tumors are associated with numerous biological processes, such as extracellular matrix (ECM) organization, metabolism, development, signaling pathways, and immune-related processes across various cancer types [7,8,11,13,14,43,44]. For instance, the expression of genes from immune-related pathways was lower in younger sarcoma, low-grade glioma, and head and neck cancer [14]. As these results have been derived from bulk RNA sequencing (RNA-seq) analyses, they likely incorporate changes not only from cancer cells themselves but also from the aging **tissue microenvironment** [45]. The ever-increasing data generated from single-cell RNA-seq (scRNA-seq) hold a great promise to resolve this issue. For example, a recent study in mouse mammary gland revealed age-dependent alterations in cell proportions and gene expression. These changes are potentially associated with pro-tumorigenic microenvironment properties, such as loss of ECM integrity, compromised endothelial barrier, and increased production of proinflammatory cytokines [46]. Yet, to date, the comparison of gene expression between tumors as a function of patient's age using scRNA-seq is still lacking.

Another critical question is how age-related somatic mutations in cancer driver genes alter age-related transcriptional programs in cancer. Indeed, copy-number alterations usually correlate with the expression of the affected genes [11,12]. However, the precise interplay between age-related omic landscapes in cancer has not been comprehensively examined. We expect recently designed single-cell dual- and tri-omics sequencing methods (e.g., G&T-seq [47], scTrio-seq [48]) or Genotyping of Transcriptomes (GoT) [49] to shed new light on such questions in the near future. For instance, although not in the context of aging, scTrio-seq was able to measure simultaneously the SCNAs, methylome, and transcriptome of individual hepatocellular carcinoma cells and predict malignancy and metastasis potentials of different cell subpopulations [48].

Age-related changes of the immunological landscape in cancer

Aging is associated with a decline in immune system function (immunosenescence) and chronic and persistent inflammation (inflammaging) [50,51]. Immunosenescence is linked with a decrease in immune cell ability to eliminate cancer cells, while inflammaging is associated with carcinogenesis and cancer progression [52,53]. Thymic involution, the shrinkage of the thymus with age, could partly be responsible for immunosenescence, by reducing T cell production and altering T cell antigen receptor (TCR) diversity. Thus, thymic involution is thought to contribute to the rise of cancer incidence with age [54]. Age-related changes in immune cell populations also contribute to a shift of the immune landscape, notably via myeloid-bias differentiation, increase of natural killer cells, decrease of naive T cells, and increase of memory T cells [55].

Immune-related pathways are enriched in age-related differentially expressed genes in several cancers [11,13,14,43]. Although an increasing number of studies use scRNA-seq to explore tumor immune landscape (e.g., [56]), the comparison of immune cell population between cancer from younger and older patients has not been performed. To bridge this gap, a recent study used deconvolution approaches to examine the relationship between age and immune cell proportions in cancer from bulk RNA-seq data [13]. They suggested older age is associated with decreased $CD4^+$ and $CD8^+$ T cells in breast and ovarian cancers and increased M2 macrophages in breast and thyroid cancers. Furthermore, naive B cells decline, while plasma cells increase with age in

breast cancer. Some of these patterns were also discovered by another study [14]. In addition, immune gene signature analysis reported lower transforming growth factor (TGF)-β and elevated interferon (IFN)-γ responses with age, corresponding to a better response in immunotherapy in cancer from older patients [14]. Another recent deconvolution analysis reported a decrease in T cell abundance, together with increased macrophage abundance in tumors from older patients [15]. This study also investigated ICB biomarkers in relation to age across cancer types. Overall, tumors from older patients have a higher mutation burden, increased expression, and decreased promoter methylation of immune checkpoint genes. Therefore, older patients are more likely to benefit from immunotherapy based on these biomarkers. By contrast, a decline in T cell abundance with age might be related to reduced ICB efficiency. Future large-scale studies are needed to shed light on the effects of age-related tumor immune landscape on ICB therapy.

Altogether, recent studies have investigated the age-related tumor immune landscape. Further research using scRNA-seq to compare immune cell population and gene expression between young and old tumors would complement existing studies. The interaction between cancer

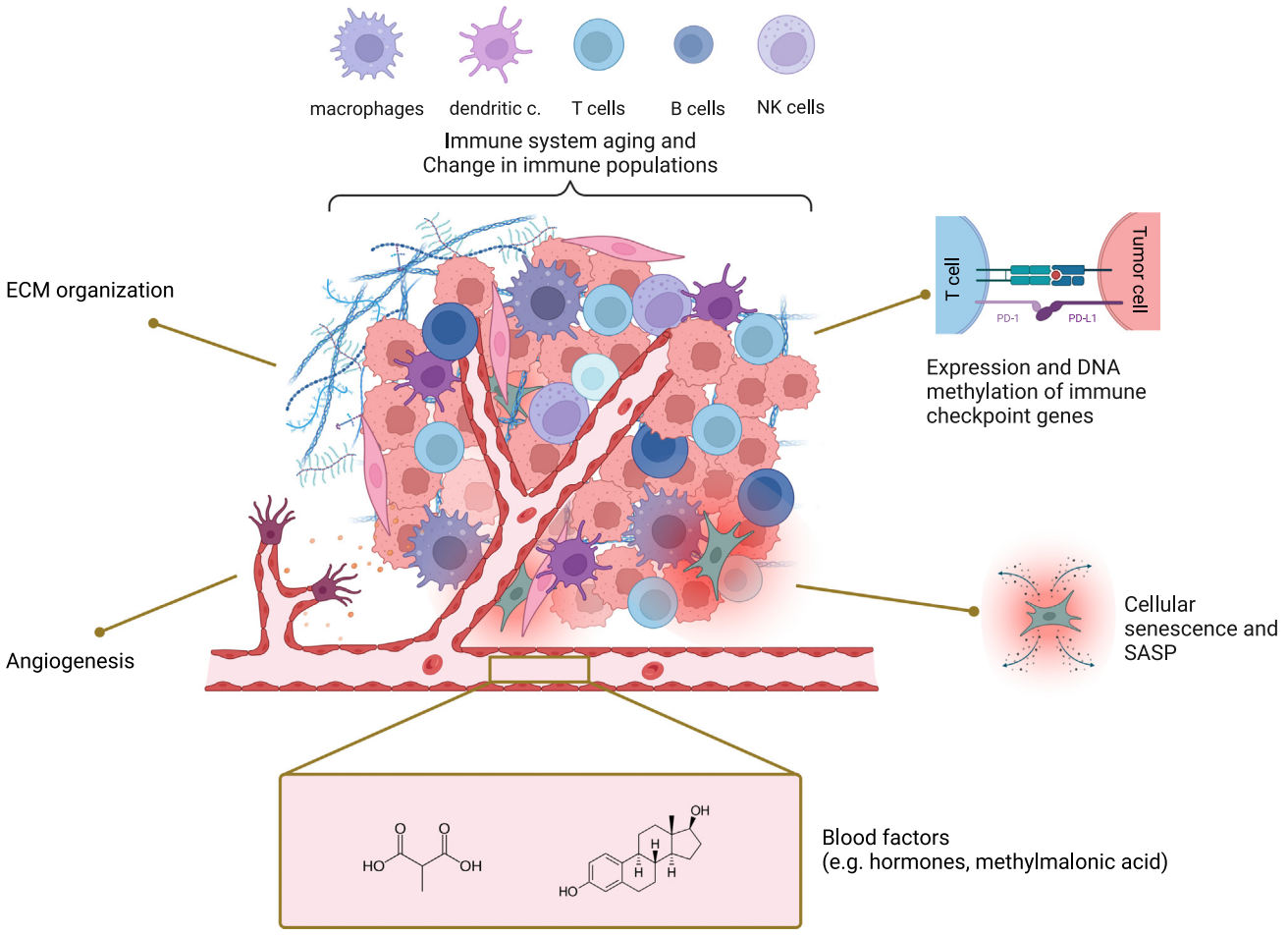

Figure 2. The contribution of the aging tissue microenvironment to cancer. Aging is associated with diverse alterations in the tissue microenvironment, many of which have been shown to promote cancer progression. These processes include, but are not limited to, immune system aging, accumulation of senescent cells which secrete inflammatory cytokines, reorganization of the extracellular matrix (ECM), and changes in circulatory factors such as hormones. Figure created with BioRender.com. Abbreviations: NK cells, natural killer cells; SASP, senescence-associated secretory phenotype.

cells and other cell types in the tumor microenvironment, including immune cells, could also be different in patients of different ages. The advent of tools to analyze intercellular communication and spatial transcriptomic is expected to advance our understanding of age-associated immune-cancer crosstalk in tumors [57–59]. Finally, a better understanding of age-related **tumor immune infiltration** is needed to prioritize cancer patients who will benefit from specific immunotherapy [15,55].

How may aging processes contribute to age-related features of cancer?

The studies mentioned above clearly show that age does impact the molecular landscape of cancer. In addition to somatic mutation accumulation with age, tissue microenvironment changes during aging can contribute to cancer progression (Figure 2), as evidenced by mathematical modeling and experimental studies [45,60–63]. Tumor microenvironment may have a profound impact on the cancer genome landscape. For example, a recent study showed an association between breast cancer microenvironment and genomic features [64]. Notably, shifts in ECM organization and angiogenesis might have considerable effects on carcinogenesis and tumor progression [45]. ECM organization-related genes are upregulated with age in normal kidneys but are downregulated with age in clear-cell renal cell carcinoma (ccRCC) [44]. In addition, the expression of angiogenesis-related genes also decreases with age in ccRCC. However, one study found that angiogenesis-related genes are upregulated with age in glioblastoma [65], again highlighting cancer-type-specific gene expression differences with age. It is possible that age-related alterations in the tissue microenvironment might provide different selective advantages for cancer cells containing distinct molecular alterations (Figure 3). This hypothesis is, however, waiting for experimental evidence.

Several aging-related processes might contribute to creating a fertile ground for cancer. For instance, **senescent cells** release proinflammatory cytokines, chemokines, and growth factors, collectively known as senescence-associated secretory phenotypes (SASPs) [66]. The gene expression signatures of **cellular senescence** increase with age in various human tissues [67]. Although the SASP has been suggested to promote cancer initiation and progression [66,68], how this process contributes to the progression of cancer cells harboring diverse molecular landscapes is unknown. Likewise, systemic changes in circulating factors during aging, such as hormones, can also influence cancer. A recent study suggested that a majority of age-related differentially expressed genes in breast cancer are potentially regulated by age-dependent estrogen signaling [42]. Another study showed that metabolic alterations with age increase methylmalonic acid (MMA) in blood and promote cancer progression [69]. It remains to be investigated how these aging-related processes affect the cancer molecular landscape in addition to their role in facilitating cancer progression.

Concluding remarks and future perspectives

In addition to an increase in cancer incidence and mortality with age, tumors arising from patients of different ages also show distinct characteristics and may relate to age-associated subtypes of cancer. The studies mentioned above relied heavily on only a few large-scale datasets, primarily TCGA [70], Genomics Evidence Neoplasia Information Exchange (AACR GENIE) [71], and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) [72] (Table S1 in the supplemental information online). Furthermore, the lack of consistency regarding age cutoffs between studies impairs the reproducibility of the findings. Whereas the meaning of 'young' and 'old' groups may vary between analyses, other studies choose to analyze age as a continuous variable. Thus, careful consideration should be taken when interpreting these data. Moreover, current datasets usually have limited numbers of samples from extreme age groups, particularly from those 20–30 and 80–90 years old, obscuring the findings of the molecular

Outstanding questions

What drives the differences in cancer molecular landscape according to patient's age?

How do age-related changes in the microenvironment, such as cellular senescence, shape the age-related molecular landscape of cancer? And how does it relate to clinical outcomes?

How do cell–cell communications in the tumor microenvironment, such as through ligand–receptor interactions and through small vesicles like exosomes, differ according to age?

What are the differences in tumor immune landscape according to age, and how do these differences affect response to immunotherapy?

How does age influence metastatic patterns of cancer?

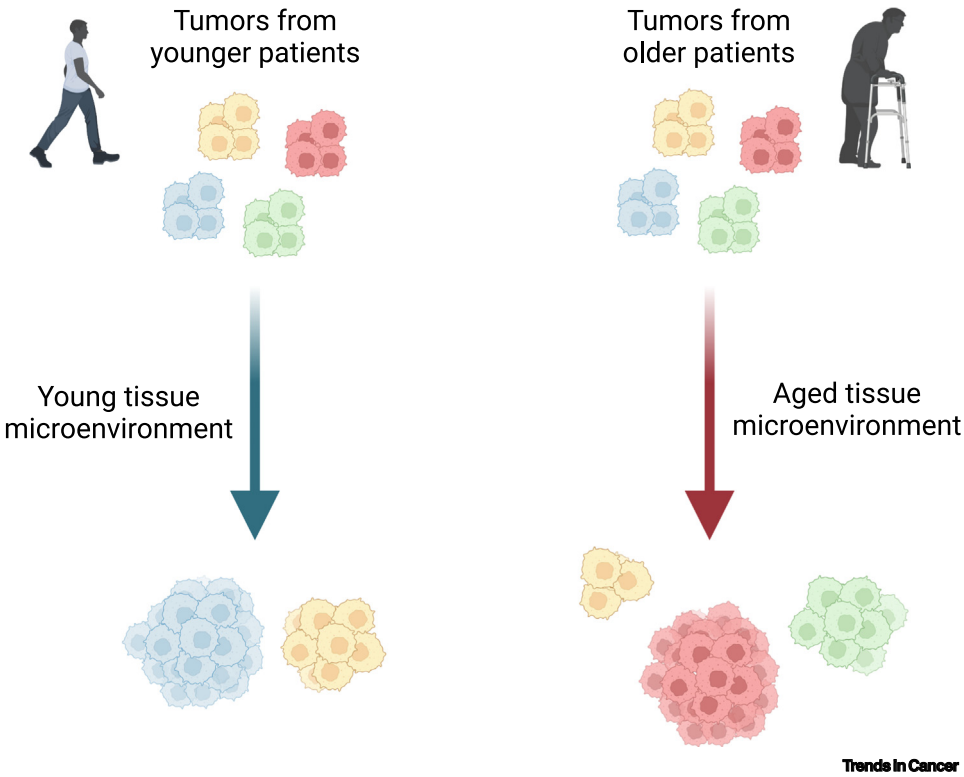

Figure 3. Tissue microenvironment changes with age may contribute to the selection of cancer clones with distinct phenotypes (hypothesis). What drives the age-associated differences in the cancer molecular landscape is unknown. One potential explanation is that tissue microenvironment changes during aging might alter local selection pressures to favor tumor clones driven by different oncogenic driver events (tumor clones with different colors in the figure). This hypothesis is yet to be proven, however. Figure created with BioRender.com.

alterations specific to these age ranges. While results from the current studies are informative, there is an urgent need for new **multi-omic** cancer datasets to both validate previous findings and discover novel information.

Current studies have identified the differences in molecular landscape between cancer in younger and older patients. Therefore, the logical next step is to understand why such differences emerge. Indeed, it is also possible that we may still be missing unknown layers of biological and genomic regulation that could be significant in aging and cancer. In addition, several important questions remain to be elucidated (see Outstanding questions). For example, age-dependent metastatic patterns have not been investigated. Novel experimental strategies, such as the use of mouse models of different ages carrying cancer clones with distinct genotypes, and advances in single-cell genomics, spatial omics, and statistical methods, are expected to improve our understanding of the impact of age on the cancer molecular landscape. This knowledge will, ultimately, be helpful to inform treatment strategies for patients of different ages.

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Declaration of interests

J.P.d.M. is an advisor/consultant for the Longevity Vision Fund, NOVOS, YouthBio Therapeutics, and the founder of Magellan Science Ltd, a company providing consulting services in longevity science.

Supplemental information

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