The importance of aging in cancer research

Cancer is a disease of aging, but it is rarely studied in aged animal models and older adults are often insufficiently represented in cancer clinical trials. To further our understanding of cancer and find better treatments, more research is needed on the role of biological aging in cancer and clinical trials must enroll larger numbers of older patients.

Cancers are a collection of diseases in which normal cells acquire specific 'driver' mutations that lead to their transformation into highly mitotic malignant cells that form tumors and that eventually spread to other tissues in the body. Treatments exist that can increase patient survival but cancer remains the second leading cause of death worldwide, after cardiovascular diseases. Although cancers affect children, adolescents and young adults, most individuals are diagnosed after the fifth or sixth decade of life (Fig. 1). This age dependency is also reflected in mortality statistics. Globally, individuals aged 70 and older bear half of the cancer mortality burden (about 5 million deaths each year), with another 40% borne by 50-to-70-year-old individuals. As such cancer is considered an aging-related disease. Interestingly, many of the biological processes that underlie the hallmarks of cancer[1] overlap with the hallmarks of aging[2], including genomic instability, abnormal proteostasis, telomere attrition, heightened inflammation and increases in cellular senescence, thus pointing to the existence of biological connections.

Despite the clear epidemiological statistics and similarities between aging and cancer biology, most preclinical studies on cancer ignore the aging dimension of the disease. Typically, mouse studies use young animals of 6–8 weeks of age[3], the equivalent of approximately 15–20-year-old humans. There also appears to be disconnect in clinical research, as older adults — in particular, those over 75 years old — are underrepresented in clinical trials[4]. This is an important issue as older patients tend to have more aging-related physiological decline conditions, such as frailty and sarcopenia, and more comorbidities (often leading to polypharmacy) than younger patients. All of these factors can influence the safety, toxicity and effectiveness of treatments. Encouragingly, this important gap has just been formally recognized by the FDA, who recently issued guidelines on the inclusion of older adults in cancer clinical trials. Although trends are changing, the study of aging in cancer is still very much in its infancy.

A root cause of cancer is the acquisition of somatic driver mutations in proto-oncogenes or tumor-suppressor genes. The fact that somatic mutations drive tumorigenesis is often perceived as the explanation for why the onset of most cancers takes place in middle and old age: if somatic mutations accumulate with the passage of time, getting older progressively increases the risk of reaching the oncogenic mutation threshold necessary for cancer initiation. Although there is some truth to this, this passage-of-time explanation is too simple. Long-lived species, such as the naked mole rat, some species of bats, elephants and blue whales, are cancer-resistant[5] and large mammals do not have higher rates of cancers than small ones[6], despite comprising much larger numbers of cells (something known as Peto's paradox). This points to the fact that animals have evolved various tumor-suppressing mechanisms, many of which remain to be identified. Interestingly, a recent study has also shown that somatic mutations tend to accumulate more slowly in long-lived mammalian species, suggesting that somatic mutation rates themselves are subject to evolutionary constraints[7]. Altogether, these observations suggest that the age dependency of cancer incidence is not simply the result of the passage of time, but that it is also partly determined by biological forces (which themselves are probably affected by aging).

Another piece of the age-dependency puzzle in cancer comes not from the biology of cancerous cells but from their aged environment. There has been accumulating evidence that the 'tumor microenvironment' has a deterministic role in the acquisition of cancer hallmark traits[1,3]. Several types of nonmalignant cell (including fibroblasts, and endothelial, immune and stem cells) in the tumor stroma and its vicinity are not simply bystanders, but instead interact with precancerous and cancerous cells to contribute to the initiation and progression of tumorigenesis. There is increasing evidence that biological changes associated with aging shape the influence of tumor-associated stromal cells on the course of the disease[3]. For instance, it was recently discovered that inducing cellular

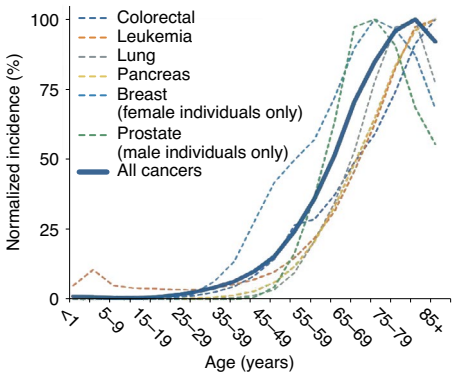

Fig. 1 | Normalized incidence of cancer as a function of age in humans in the USA (2015–2019). Data source, SEER (https://seer.cancer.gov/statistics-network/); inspiration for this figure comes from figure 1b in ref. [11]. See ref. [11] and other interesting related works on the concept of 'adaptive oncogenesis' that propose an explanation for the age-dependency of cancer incidence in the context of evolution.

senescence specifically in the stroma to mimic biological aging creates a chronically inflamed tumor-permissive environment[8]. It was also recently found in a mouse model of melanoma that aged fibroblasts can drive lung metastasis and therapy resistance[9], as well as the awakening of dormant metastatic cells. Beyond the tumor microenvironment, the systemic environment also changes with age in ways that can promote tumor progression[10]. Thus, it is becoming increasingly clear that many factors linked to the biology of aging and the age of the host contribute to an environment that not only can promote tumor initiation but also influence tumor progression and metastasis, and even affect resistance to cancer treatments.

If we are to understand cancer in all its complexity and develop new and better therapeutic approaches to help patients with cancer, it is essential to better understand the role of the aged environment in cancer development and in the response to treatment. It is also important to collect more clinical data on therapeutic outcomes in older patients so as to better inform clinical

practice in a geriatric context. *Nature Aging* is interested in recognizing and supporting all these efforts. We encourage researchers who study the intersection of aging and cancer in the laboratory (as exemplified above), in the clinic or in societal contexts to consider submitting their work to the journal. ❐

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