Editorial

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The complex interplay between aging and cancer: unraveling the clues

https://doi.org/10.1515/mr-2024-0014

Throughout our life journey, two unstoppable forces shape our existence: the specter of aging and cancer. Seemingly unrelated, these phenomena are more intertwined than we might think [1]. The incidence and mortality rates of cancer increase exponentially with age, and their underlying causes are both related to cellular dysfunction. Studying these commonalities is not only key to unlocking cancer therapies, but it may also inspire us to find interventions that delay the aging process itself. Let us delve deeper into the complex factors that bind them together.

A two-way influence

Aging is a natural process, and over time, our cells and tissues gradually degenerate. Meanwhile, cancer emerges as a formidable opponent, disrupting the delicate balance within our bodies. But the paradox lies in this: aging itself is a risk factor for adult cancer, while some cancer treatments may accelerate the aging process. This relationship is bidirectional, a complex, system-level entanglement where both sides influence each other.

Shared clues

Accumulation of DNA defects

Like old shoelaces, the telomeres at the ends of our DNA wear down [2]. As we age, our cells accumulate mutations – tiny spelling errors in the genetic code. While these errors are usually benign, they can lead to a gradual loss of cellular fidelity and may also tip the balance towards malignancy. Cancer cells also bear these genetic scars, fueling their relentless growth.

The accumulation of genetic mutations makes cellular senescence (a state of permanent growth arrest) more prevalent. These senescence markers mirror the hallmarks of cancer [3], suggesting a fundamental overlap in their underlying biology. For example, oncogenes that promote cell growth are dysregulated in both aging and cancer, such as vascular endothelial growth factor (VEGF) [4]. The inactivation of the tumor suppressor gene p53 [5] allows uncontrolled proliferation of abnormal cells. These molecules stimulate cell growth and proliferation. Dysregulation of growth factors like IGF-1 and TGF-β is seen in both aging and cancer, contributing to tissue degeneration and tumor development, respectively.

Altered metabolic activity

Aging cells change their metabolic rhythm. Energy production starts to decline, and the cellular machinery starts to malfunction. First, mitochondria are the cellular powerhouses, responsible for generating energy through oxidative phosphorylation. With age, mitochondrial function declines, leading to decreased ATP production and increased generation of reactive oxygen species (ROS), which can damage DNA and other cellular components. Cancer cells often exhibit similar mitochondrial dysfunction and utilize alternative metabolic pathways to compensate for decreased energy production [6]. Second, both aging and cancer cells often exhibit insulin resistance [7], meaning they take up less glucose from the bloodstream. This can lead to elevated blood sugar levels (hyperglycemia) and decreased energy

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availability for normal cellular functions. The Warburg effect, a hallmark of cancer, involves increased reliance on aerobic glycolysis, even in the presence of oxygen, to generate energy and support rapid cell growth. This process is also observed in some aged tissues.

Cell-to-cell communication and chronic inflammation

Aging cells release molecules that regulate the environment, shaping the landscape around them. Cancer cells also participate in this clandestine dialogue. Cytokines are immune signaling molecules released by various cells, including immune cells, fibroblasts, and even cancer cells. In aging, chronic low-grade inflammation (inflammaging) is characterized by elevated levels of certain cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) [8]. Similarly, tumors in cancer patients secrete various cytokines to create a pro-tumorigenic environment. Chemokines attract immune cells to specific tissues. While some chemokines promote immune responses, others can contribute to chronic inflammation. Both aging and cancer involve a complex interplay of chemokines and their receptors, influencing immune cell infiltration and inflammation patterns.

Mechanisms and shared targets

However, the precise mechanisms are still unclear. How do aging-related processes conspire to increase cancer risk? How do they affect treatment outcomes? Several promising drug targets are shared between aging and cancer, reflecting the overlapping biological processes involved in both. Here are some key examples:

mTOR pathway

This pathway regulates cell growth, proliferation, and metabolism. Its hyperactivation is associated with both aging and cancer [9]. As we accumulate years, mTOR activity gradually declines. This decrease is thought to be beneficial, promoting cellular stress resistance, autophagy (cellular cleanup), and lifespan extension. However, overly suppressed mTOR can lead to impaired protein synthesis and tissue maintenance, potentially accelerating certain age-related frailty syndromes. In contrast, cancer cells hijack mTOR, hyperactivating it to fuel their relentless growth and survival. This dysregulation allows them to evade cell cycle checkpoints, resist apoptosis (programmed cell death), and adapt to metabolic demands. Consequently, mTOR inhibitors have emerged as powerful anti-cancer weapons, effectively targeting various tumor types. mTOR inhibitors, originally developed as immunosuppressants, are now being tested for their potential to delay aging and treat various cancers [10].

AMPK pathway

AMP-activated protein kinase (AMPK) is a crucial regulator of cellular energy metabolism and stress response pathways. It is also implicated in both aging and cancer. This pathway plays a crucial role in cellular energy metabolism and stress response. AMPK activity declines with age, leading to cellular dysfunction and associated age-related diseases. It has been shown to influence various aging-related processes, including metabolic dysfunction, cellular senescence and inflammation. AMPK hyperactivation is also associated with cancer development and progression. It can promote cell growth and proliferation, metabolic reprogramming and resistance to apoptosis. Its activation is beneficial for lifespan extension and cancer prevention. Our study found that the AKT inhibitor forskolin has a very good effect on extending lifespan [11], and can extend the lifespan of mice by 85 days. Forskolin has known anti-cancer effects.

Epigenetic modifications

Changes in DNA methylation and histone modifications are involved in both aging and cancer development. As we age, epigenetic modifications accumulate like off-key notes. DNA methylation, which silences genes, exhibits an increase in certain regions while decreasing in others, resulting in the disruption of crucial cellular processes. Histone modifications, loosening or tightening DNA access, also change, leading to silencing of beneficial genes and activation of harmful ones. This epigenetic discordance contributes to age-related diseases like Alzheimer's and cardiovascular issues [12]. In cancer, epigenetic modifications are hijacked, creating a distorted melody. Tumor suppressor genes are often silenced through hypermethylation, while oncogenes, promoting cell growth, are activated through hypomethylation. Additionally, altered histone modifications favor unrestrained cell division and metastasis. This epigenetic manipulation fuels the cancer's

chaotic progression. Drugs targeting these epigenetic mechanisms, like DNA methyltransferase inhibitors and histone deacetylase inhibitors, hold promise for both areas.

Collaborative endeavors

Scientists across the globe join hands. They explore the impact of aging on cancer, dissect the secrets of mammary cancer-initiating cells, and unravel the cognitive and physical repercussions faced by esophageal cancer survivors. These collaborative endeavors forge new strategies, bridging the gap between aging and cancer. It is expected to find suitable and effective general strategies for the prevention and treatment of cancer in the future.

Acknowledgments: Not applicable.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Research funding: This work was supported by NSFC (32170756) and National Key R&D Program of China (2023YFF1205103).
Data availability: Not applicable.

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