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Short Communication

Beyond Immunosuppression: Reframing the HIV–Cancer Interface in the Era of Precision Medicine

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Abstract

The relationship between Human Immunodeficiency Virus (HIV) and cancer has traditionally been framed through the lens of immunosuppression and opportunistic oncogenesis. However, with the advent of effective antiretroviral therapy (ART), people living with HIV are experiencing longer lifespans, revealing a more complex and evolving cancer landscape. This article presents a new perspective on the HIV–cancer interface, emphasizing the interplay of chronic inflammation, immune dysregulation, viral co-infections, and accelerated aging. It highlights the transition from AIDS-defining malignancies to non-AIDS-defining cancers and explores emerging insights from molecular oncology and immunotherapy. By integrating advances in precision medicine, this article argues for a paradigm shift—from viewing HIV merely as a risk factor to understanding it as a dynamic modifier of cancer biology. This evolving perspective has significant implications for screening, prevention, and tailored therapeutic strategies in HIV-associated malignancies.

Introduction

The intersection of HIV and cancer has undergone a profound transformation over the past three decades. Initially, cancers associated with HIV—such as Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer—were primarily attributed to severe immune suppression. However, the widespread use of antiretroviral therapy (ART) has dramatically altered this narrative. Today, individuals living with HIV are more likely to develop non-AIDS-defining cancers, prompting a re-evaluation of the underlying mechanisms linking HIV and oncogenesis

. The Shift in Cancer Spectrum

In the pre-ART era, AIDS-defining cancers dominated the clinical landscape. With immune restoration achieved through ART, their incidence has significantly declined. Conversely, non-AIDS-defining cancers—including lung, liver, anal, and Hodgkin lymphoma—have emerged as leading causes of morbidity and mortalityThis shift suggests that factors beyond immunodeficiency are at play. Chronic immune activation, persistent inflammation, and co infections with oncogenic viruses (such as HPV, EBV, and HBV/HCV) are now recognized as central contributors.

Chronic Inflammation: The Silent Driver

Even with effective viral suppression, HIV infection is characterized by a state of chronic low-grade inflammation. This persistent immune activation creates a pro-tumorigenic environment by:

- Promoting DNA damage
- Enhancing cellular proliferation
- Inhibiting apoptosis
- Facilitating angiogenesis

Unlike traditional models of cancer development, where a single mutation may initiate disease, HIV-associated cancers often arise from a sustained inflammatory milieu that accelerates oncogenic processes

HIV as a Modulator of Tumor Biology

A novel perspective is to view HIV not just as a predisposing factor but as a modulator of tumor biology. HIV proteins such as Tat and Nef may directly influence cellular pathways involved in cancer progression. Additionally, immune exhaustion and altered cytokine profiles reshape the tumor microenvironment, potentially affecting tumor growth and response to therapy.

This conceptual shift opens new avenues for research, particularly in understanding how HIV alters cancer behavior at a molecular level.

Accelerated Aging and Cancer Risk

People living with HIV often exhibit features of accelerated aging, including earlier onset of age-related diseases such as cancer. Telomere shortening, mitochondrial dysfunction, and epigenetic changes contribute to this phenomenon As a result, cancer screening guidelines for HIV-positive individuals may need to be adapted to account for earlier risk onset and increased susceptibility.

Implications for Immunotherapy

The rise of immunotherapy has revolutionized cancer treatment, but its application in HIV-positive patients presents unique challenges and opportunities. Historically excluded from clinical trials, these patients are now being reconsidered as evidence suggests that immune checkpoint inhibitors can be both safe and effective in this population.

Understanding the interplay between HIV-related immune dysregulation and immunotherapeutic response is critical for optimizing treatment outcomes

Precision Medicine and Future Directions

Advances in genomics and personalized medicine are paving the way for more targeted approaches to HIV-associated cancers. Molecular profiling can identify unique mutations and pathways influenced by HIV, enabling tailored therapies

Future strategies should integrate:

- Early and aggressive cancer screening
- Management of co-infections
- Anti-inflammatory interventions
- Inclusion of HIV-positive individuals in clinical trials

Conclusion

The relationship between HIV and cancer is no longer defined solely by immunosuppression. It is a multifaceted interaction involving chronic inflammation, immune modulation, viral co-infections, and accelerated aging. Recognizing HIV as an active participant in cancer biology rather than a passive risk factor marks a critical paradigm shift.

As the population of people living with HIV continues to age, a deeper understanding of this evolving interface will be essential for improving cancer prevention, diagnosis, and treatment. Embracing this new perspective will ultimately lead to more effective and equitable healthcare strategies

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