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Mechanism of Increased Cancer Risk in HIV

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ABSTRACT

Purpose: To critically appraise and explore the underlying mechanisms of increased cancer risk in HIV with a view to revealing novel opportunities in preventing and treating cancer in HIV.

Methodology: Literature search was carried out with the aid of PubMed, Google scholar and New England Journal of Medicine.

Findings: Different articles were reviewed to better understand the synergistic mechanisms of oncogenesis in HIV. Although, some mechanisms are largely unclear, evidences derived from several studies clarified the oncogenic mechanisms of some factors examined in this article. Immunodeficiency appears to be pivotal and fundamental to the proneness to cancer risk in HIV whereas evidence is emerging that a direct pro-oncogenic effect of HIV, chronic immune activation (inflammation), and possible carcinogenic effects of antiretroviral drug may also contribute. Furthermore, increasing age and lifestyle behaviors such as multiple sexual partners, anal sex, intravenous drug use and alcohol use could also contribute.

Unique Contribution to Theory, Practice and Policy: While the role of immunosuppression as a risk factor for malignancy in HIV is well established, other synergistic mechanisms have been in the shadows of clinical practice. This review explores novel mechanisms associated with rise in titre of inflammatory markers, direct effects of HIV tat and vpr molecules and oncogenic effects of anti-retroviral drugs.

Summary: Continued research on the mechanisms of cancer risk in HIV is advocated to better understand how to intervene to mitigate cancer risk. Possible exploration and investigation of the role of tat and vpr inhibitors is recommended as tat and vpr are highly implicated in the direct oncogenic effects of HIV.

Keywords: *HIV, cancer, malignancy, antiretroviral therapy, oncogenesis, inflammation.*

INTRODUCTION

Ever since the outbreak of the Human Immunodeficiency Virus (HIV) in the 1970s, clinicians and researchers have noticed a remarkably higher incidence of malignancies in infected people as compared to the general population. Some specific malignancies were commonly associated with those having low CD4 counts and later formed part of the criteria for the diagnosis of acquired immune deficiency syndrome (AIDS). These were subsequently described as AIDS dependent malignancies (ADM)[1]. These include Kaposi Sarcoma, aggressive B cell lymphoma and invasive cervical carcinoma[1,2]. The close correlation was attributed to the immunodefiency present in AIDS. In the background of AIDS, oncogenic viruses like Ebstein Barr Virus (EBV) and Kaposi Sarcoma Herpes Virus (KSHV) will evade the immune system and cause infection unchecked, leading to sufficient cellular changes that will cause the formation of malignant cells. These malignant cells further proliferate remarkably and accumulate more genetic mutations required for systemic invasion thereby further evading immunosurveillance[1]. In one study, it was shown that ADMs occurred in 30% of HIV patients with AIDS before the development of effective anti-retroviral therapy (ART). This remarkably dropped by around 70% in the United States following the introduction of 3 drug ART regimen[1,3,4]. Such findings subsequently clarified the key role of immunodeficiency for oncogenesis in HIV. With the established and widespread use of ART, general morbidity and mortality from HIV and its complications remarkably decreased leading to better life expectancy and outcomes. Nevertheless, it was noticed that as people living with HIV aged, they were still at higher risk of developing other cancers as compared to the general population[1,5]. These generally known as Non-AIDS dependent Malignancies (NADM) further raised the question of alternative mechanisms of oncogenesis in HIV. Some other mechanisms have been studied, like the role of chronic inflammation stimulation, direct oncogenic effect of HIV and possible oncogenicity of ART.

In this article, we reviewed evidences from different studies to better understand other synergistic mechanisms of oncogenesis in HIV. Considering the increased burden of malignancies in people living with HIV, it has become imperative to explore factors that further increase the risk as these will guide researchers and clinicians on novel opportunities to reduce occurrence amongst this population.

METHODOLOGY

Literature search was carried out with the aid of PubMed, Google scholar and New England Journal of Medicine over a period of 2 months (April and May 2020). Search was done using a combination of the following key words; 'HIV and Cancer','HIV and Increased Cancer risk', 'mechanisms of cancer in HIV', 'oncogenic effects of ART' and 'immunosuppression and cancer'. Prospective and retrospective studies published in peer reviewed journals and equally relevant to purpose of review were selected.

Immunodeficiency

After years of research, there is now established evidence between immunodeficiency and increased cancer risk[5,6]. This includes both ADM and infection related NADM[5,6-9]. Based on recent studies, most HIV associated cancers are caused by oncoviruses like KSHV, EBV, high risk HPV, HBV, HCV and Merkel cell Polyoma virus[1]. It therefore becomes clear the paramount role of

optimal viral clearance in preventing HIV related cancers. As copies of HIV increase in infected patients, there is more widespread immune infiltration and subsequent lysis of infected immune cells with release of more viral particles. Unchecked, this leads to a gradual but steady decline in immune cells, most importantly the CD4 lymphocytes. CD4 cells play a pivotal role in immune recognition and response by the recruitment and stimulation of other immune cells like B Lymphocytes and maintaining immunologic memory. Consequently, decline in CD4 cells will cause a defect in immune recognition and response thereby allowing oncogenic viruses to spread unchecked. In addition, there is failure of clearance of both viruses and viral infected cells allowing sufficient cellular changes and consequent pathogenesis of malignancies associated with these viruses[10,11]. Immunodeficiency is a major player as immunosuppression from other causes like inherited immunodeficiency disorders and post-transplant immunosuppression are associated with increased risk of specific cancers caused by viruses[10,12]. Also, as malignant cells accumulate, sufficient mutations become recognized by host immune cells leading to immune clearance. With immunodeficiency, there is reduction in immune surveillance and subsequent clearance of cancers cells fostering resultant growth and spread.

Chronic Immune Activation (Inflammation)

Recent studies have linked the activation of inflammatory and coagulation pathways to increased cancer risk as demonstrated by elevated blood levels of biomarkers. Chronic immune activation is one of the three recognized immunologic hallmarks of HIV. Others are immunodeficiency (previously discussed) and immune senescence/dysfunction and these all contribute to tumor oncogenesis.[5,6]

Chronic inflammation causes the production and release of biomarkers and growth factors which encourage cell proliferation, production of genotoxic reactive oxygen and nitrogen species which facilitates generation, proliferation and metastasis of tumour cells [10, 13, 14]. According to recent studies, interleukin 6 (IL-6), C- reactive protein (CRP) and D-dimer are the most implicated biomarkers with IL-6 having the highest correlation [15-18]. In the Strategies for management of Anti-retroviral Therapy (SMART) Study, structured ART interruptions were associated with higher levels of inflammatory markers and coagulation with consequent increased morbidity and cancer risk[18]. Increased IL-6 and Tumour Necrotic Factor α (TNF α) in plasma of HIV patients leads to increased Cyclogene Oxygenase (COX) and Prostaglandin E_2 synthesis which have been linked to the development of AIDS related cervical cancer. The perceived underlying mechanism for this effect is through the promotion of angiogenesis which is fundamental for tumour growth and spread.[30-32]

Direct Oncogenic Effect of HIV

For many years, the synergistic interplay between immunodeficiency and oncogenic viruses have been considered the major pathways of increased cancer risk in HIV. However, recent studies have shown that there is a direct pro-oncogenic effect of the HIV virus, regardless of CD4 count. This is mainly exerted through the actions of viral trans-activator (tat) and viral protein R (vpr) [19-23]

The cell cycle is a complex well-regulated process experienced by every cell. Tight regulation ensures that various cells exist in various stages of the cell cycle depending on prevailing chemical stimulation in the cellular environment. One method through which the tat protein exerts its

carcinogenic effect is by altering some regulatory pathways of the cell cycle, potentiating the actions of proto-oncogenes, inhibiting the actions of tumour suppressor genes and facilitating angiogenesis which is a milestone for tumour growth and metastasis.[29,30]

Tat is released from HIV infected cells then enter uninfected cells through its protein transduction domain, [30,34,35,36]. Once endocytosed by uninfected cells, it inhibits the function of p53, a major tumour suppressor gene in the cell cycle[22,23]. It has also been implicated in altering DNA repair of host cells, leading to genomic instability and subsequent accumulation of mutations that contribute to oncogenesis. Its direct actions have been documented in inhibition of double stranded break DNA repair. Studies showed that cellular extracts containing tat possess a reduced capacity to rejoin damaged DNA[30,42]. Furthermore, it alters the proliferative capacity and apoptosis sensitivity of EBV- immortalized cells thereby conferring a selective growth advantage, producing clones with enhanced oncogenicity[30,43]. Apart from its direct role in oncogenesis, it also predisposes to cancer through some indirect mechanisms. It has been noticed that in Primary effusion lymphoma (PEL) HIV infection triggers reactivation of KSHV through the direct action of tat[30,33]. Lastly tat has been shown to induce angiogenesis which is an essential process for cancer growth and metastasis[24,25-30]. It therefore becomes clear that HIV through tat alters the regular cellular functions in different ways to predispose to malignancy and further sets in motion process to ensure cancer growth and spread.

Vpr have been shown to affect not only the function of p53 but also p21 and other regulatory proteins in the cell cycle[5,21]. In addition, it inhibits the action of telomerase[21]. Telomerase is an enzyme. Its activity is essential in cellular aging and senescence. Modulation of its activity is a routine mechanism of conferring immortality to malignant cells.

Evidence currently exist to show that HIV replication products may also directly contribute to lymphoma induction. HIV envelop protein gp120 has the ability to directly activate B-cells through its interaction with DC-SIGN. This leads to changes in immunoglobulin class-switch gene, increased interleukin secretion and induction of cytokine deaminase expression thereby causing inflammatory dysfunction which has been shown to increase cancer risk.[31,44]

Pro-oncogenic effects of Antiretroviral Therapy

Unarguably, since the advent of antiretroviral drugs, the therapeutic outcome as well as the quality of life of HIV patients have significantly improved over the years. Furthermore, patients can now live for many years and still maintain some level of efficiency and effectiveness at work and maintain good relationships and family life. However, recent studies have shown the potential oncogenic effects of some antiretroviral drugs thereby provoking more research into the development of new and better drugs without any cancer risk. Studies have shown that Zidovudine could be potentially carcinogenic especially to off-springs of pregnant women taking the drug. From two animal studies conducted, the pro-oncogenic effect was found to be due to it's ability to potentially induce a gain-of-function mutation in kras gene and a loss-of-mutation in Tp53 gene. Furthermore, the probable mechanism of the pro-oncogenic effects of Zidovudine as explained from two human studies revealed the damaging effect of Zidovudine on GYPA gene encoding the glycophorin A protein, which is a major sialoglycoprotein of human erythrocyte membrane. The mechanism is not exactly clear but it was noticed that people with GPA mutations had an increasing number of cancers.[45] Additionally, the mutation in GPA could lead to mutations in some

tumor suppressor genes like Tp53 thereby contributing to the development of cancer.[46] Hence, the ongoing research to investigate GPA assay in ascertaining cancer risk.[47]Besides Zidovudine, other antiretroviral drugs have been linked to the causation of different types of cancer. Although the mechanism is still unclear, studies have shown that protease inhibitors could potentially lead to anal cancer whereas Efavirenz could lead to Hodgkin lymphoma. The integrase inhibitor, Raltegravir, have been shown to contribute to cancer development by inducing host DNA rearrangements. Furthermore, studies have explained that CCR5 inhibitors could lead to cancer by reducing the immunological surveillance of malignant cells.[5]

Others

In addition to the above elucidated mechanisms, there are some other factors that have been linked to increased cancer risk. A major risk factor for cancer in both people with and without HIV is increasing age. With the use of effective ART regimen and subsequent increase in both life expectancy and quality of life of people living with HIV, there have also been a rise in number of aged population thus increasing the relative incidence of cancers in HIV. This is most frequently associated with Non AIDS dependent malignancies(NADM).[1,2] Lastly people with HIV are more likely to have some lifestyle behaviors which predisposes them generally to cancers. Such factors include multiple sexual partners, anal sex, intravenous drug use and alcohol use. The first 3 predispose to infection by some oncogenic viruses like human papilloma virus, hepatitis B virus and hepatitis C virus. Consumption of large volumes of alcohol is a known predisposing factor to oral, oesophageal, gastric and hepatic cancers.

Conclusion and Recommendation

It is clear from this review that the increased risk of cancer among people with HIV is a result of close synergism between several factors. Immunodeficiency, chronic inflammation, oncogenic effects of HIV, pro-oncogenic effects of ART, advancing age and life style factors all work hand in hand. It therefore becomes imperative for direct actions to be taken to mitigate these factors to reduce the risk of cancer in HIV. Ensuring early commencement and compliance to ART will maintain the CD4 cells at levels that will ensure effective immune surveillance thus tackle oncogenic viruses and mount necessary response against the formation, growth and spread of cancers.

Specific therapies can also be developed to alter the actions of HIV tat and vpr consequently mitigating the major oncogenic mechanism of the HIV. Multi-national meta-analysis can be done to review the relative pro-oncogenic effect of some currently implicated ART regimen to empirically clear out the doubts, with outlook towards safer and equally effective regimen. Lastly, a wholistic approach involving life style counselling in addition to pharmacologic treatment is essential. Counselling against high risk possible oncogenic behavior prevalent in people living with HIV will play a fundamental role in reducing the overall risk. Offering smoking and alcohol cessation support and guidance to ensure safer sexual practices will also reduce the risk of cancer associated with such practices.

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