

The Challenge of Malignancies in HIV-1, Beyond Immune Activation and Back to Decreased Immune Surveillance

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Abstract

The HIV-1 epidemic continues around the world, but also in the United States where we continue to see approximately 50,000 new diagnosis of HIV-1 infection each year. It is estimated that there are currently more than 1.2 million individuals in the United States living with HIV-1 infection, with 12.8% unaware of their infection. Effective therapy for HIV-1 is allowing infected individuals to have greater life expectancies. We now have an older aging population infected with HIV-1, reaching ages where diseases such as malignancy are increased in incidence. Even compared to age matched peers there is clearly an excess of malignancies affecting the HIV-1-infected population. Malignancies are now the most common cause of death for patients in the United States living with HIV-1 infection. B-cell malignancies are the most common malignancy accounting for death in HIV-1 infected patients in the United States. It is not clear that all that we have come to understand regarding B-cell lymphomas applies to the lymphomas developing in the HIV-1-infected population. It is particularly important to understand the factors leading to and molecular disturbances involved in these lymphomas developing in the HIV-1-infected population as they appear to be increasing in frequency and characterized by aggressive courses with short median survival times. Although much attention has focused on the chronic immune activation hypothesis of cancer in HIV-1 infection, this article explores the possible contribution of decreased immune surveillance and exposure to highly active antiretroviral medications to the development of B-cell lymphomas in HIV-1-infected patients.

Keywords: HIV-1; Malignancy; Lymphoma; B-cell; Integrase inhibitor; Protease inhibitor; Non-nucleoside reverse transcriptase inhibitor; HIV-1; HIV

Background

The HIV-1 epidemic continues with 50,000 new diagnosis of HIV-1 infection each year in the United States and is now characterized by an aging population of 1.2 million individuals in the United States living with HIV-1 infection who are reaching ages where diseases such as malignancy are increased in incidence [1-6]. Malignancies, particularly B-cell malignancies, are now the most common cause of death for patients in the United States living with HIV-1 infection, and is a significant factor driving 30 day hospital readmissions [7-10]. Currently available highly active antiretroviral therapy (HAART) is able to suppress viral replication, maintain CD4 T-cell levels and increase life expectancy in the majority of HIV-1-infected individuals [11,12]. B cell lymphoma is the most common of the malignancies responsible for cancer mortality in the current HAART treated HIV-1-infected population [8,13-15]. Although the genetic basis of and heterogeneity of B-cell lymphomas has been extensively studied in the HIV-negative population, much remains to be learned about the genetics of and causes underlying B-cell lymphomas in HIV-1-infected individuals [16]. In addition to a possible oncogenic milieu developing as a consequence of the chronic immune activation present in many HIV-1-infected individuals it is possible that loss of immune surveillance or exposure to certain medications contained in modern HAART regimens is driving the process [17,18].

Malignancies in HIV-1-uninfected patients

Six hallmarks of cancer have been suggested as essential for tumor development and dissemination [19,20] Along with the six suggested pillars of oncogenesis: sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, induction of angiogenesis, acquisition of replicative immortality, and activation of invasion and metastasis, immune evasion may be a critical seventh pillar of oncogenesis [19-21] (Figure 1). In many ways the first six hallmarks

of cancer seem very tumor-centric. From the perspective of the host these are import checkpoints that must be maintained for homeostasis. The host's immune system, however, is the last defense of the host against a cell that has lost the critical controls and transformed into a malignancy [21]. Advances, in the understanding of malignancies, have led to an expanded model with 10 hallmarks of cancer that now includes immune evasion [20].

Advances in the understanding of cancer biology have established the importance of immune evasion as a critical feature of malignancies [19,20]. Immune evasion is critical for the success of all malignancies, including B-cell lymphomas, in HIV-1-uninfected individuals [21]. Without immune evasion malignant cells could be recognized by innate and adaptive cells of the immune system and cleared or destroyed [22]. There is thus a tremendous selective pressure for successful immune evasion placed on evolving tumor cells that is evident in both the genome and in the tumor exome of tumors developing in immunocompetent hosts [23].

Immune evasion by malignancies in HIV-1-infected Patients, the seventh pillar of oncogenesis

Unfortunately early in HIV-1 infection there is a significant and

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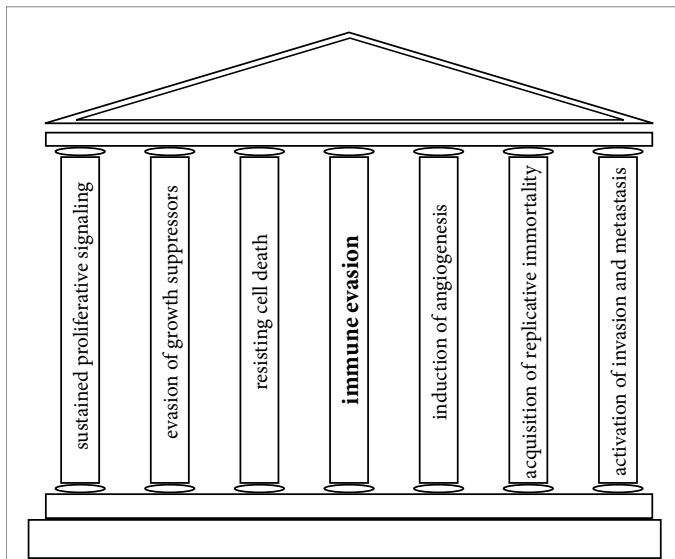


Figure 1: The seven pillars of oncogenesis. The current six pillars of oncogenesis sustained proliferative signaling, evasion of growth suppressors, resisting cell death, induction of angiogenesis, acquisition of replicative immortality, and activation of invasion and metastasis with the addition of the critical seventh pillar of immune evasion.

permanent loss of mucosal immune cells and permanent damage to the immune system despite rebound of CD4 counts from initial nadirs [24]. It is thus not surprising that, in addition to malignancies driven by oncogenic pathogens, there is an increased incidence of many malignancies not associated with oncogenic pathogens in HIV-1-infected patients [6]. The barrier posed by the immune system in HIV-1-uninfected individuals may be less formidable in the HIV-1-infected population.

Immune evasion may be accomplished through avoidance of detection by the immune system, neutralization of immune cells, induction of tolerance, and/or modulation of the immune response. In many malignancies immune evasion involves reduction in the surface expression of antigen presentation molecules [25]. Avoidance of detection by the immune system can be accomplished by a decrease in the antigen presentation by MHC class I antigens. This may be due to defects in the machinery that processes aberrant proteins and delivers MHC class I molecules with contained peptides to the cell surface [26,27]. An interesting aspect of B cell malignancies is that the malignant cells also serve as professional antigen presenting cells with inherent expression of MHC class-II molecules [28]. Decreased class II expression is associated with decreased immune response and poor prognosis [29]. Diffuse large B-cell lymphoma (DLBCL) is also often characterized by down regulation of MHC-II molecules, HLA-DR and HLA-DR, which correlates with T cell infiltration and is likely a strategy for immune evasion [30].

Malignancies may avoid destruction by the immune system by neutralizing host immune cells. B-cell lymphomas have been demonstrated to express elevated levels of Fas ligand (FasL) which can trigger Fas mediated apoptosis of cytotoxic T lymphocytes [31]. Malignancies may also accomplish neutralization of host immune cells through expression of programmed death ligand 1 (PDL1) or programmed death ligand 2 (PDL2), which reduces the proliferation of host T-cells [32].

Certain malignancies, such as B-cell lymphomas, both Hodgkins

and non-Hodgkins lymphomas, also appear to have the ability to influence the surrounding tumor microenvironment and induce proliferation of tumor tolerant CD4⁺ CD25⁺ FoxP3⁺ T-regulatory cells [33-35]. Although it remains unclear how these T-regulatory cells are induced, they do appear to secrete IL-10 and interfere with the generation of anti-tumor Th17 cells. Myeloid derived regulatory cell induction appears to be another critical component of the B-cell lymphoma immune evasion strategy and is associated with poor overall survival [36-38]. Not only are malignant cells modulating immune cells toward an immune-tolerant phenotype but they are also attracting immunosuppressive cells to the tumor microenvironment with chemo-attractant chemokines such as CCL2/MCP-1, CXCL12, CCL22, CCL5, CCL17/TARC, and fractalkine/CX3CL1 [21].

Malignancies also have the ability to express immune modulatory molecules and produce a number of secreted or soluble factors that facilitate their immune evasion. Through malignant cell expression of Galectin-1, T cells are polarized toward a Th2 phenotype and T cell proliferation and IFN- γ production is decreased [39]. Prostaglandin E2 can also be produced by certain lymphomas and can influence both CD4⁺ T-cells and B-cells [40,41]. Malignancies are able to evade natural killer (NK) cells by the secretion of the decoy protein NKG2D which prevents activation through a surface NK cell receptor [42,43]. Serum sIL-2R α may be produced and interfere with IL-2 mediated T cell activation in certain contexts [44,45].

In addition to the induction of suppressive cells that secrete immunosuppressive cytokines, certain malignancies are often capable of secreting immunosuppressive cytokines such as IL-10 and IL-6 themselves [46]. Some B-cell lymphomas may in fact be developing from subsets of B cells that spontaneously or with appropriate stimulation secrete IL-10 [47,48]. Analysis of B-cell chronic lymphocytic leukemia cells has demonstrated similarities to IL-10 producing regulatory B10 cells and innate IL-10 spontaneously secreting B cells [49-53]. TGF- β is another immunomodulatory molecule produced in both membranes bound and secreted forms by malignancies as part of their immune evasion [54].

With the importance of evading a competent immune system demonstrated and our understanding of how this is achieved, the appearance of an increased incidence not associated uncontrolled activity of an oncogenic virus starts to seem more expected than surprising. Currently, however, little is known about whether the decreased immune pressure present in an HIV-1-infected patient is evident in the degree and type of immune evasive changes. Further investigation is needed in order to discover how much decreased immunity contributes to the excess frequency of cancers and cancer related mortality.

The impact of antiretroviral therapy on immune surveillance and malignancy development

In addition to the fact that lower levels of CD4⁺ T cells and decreased competence of the immune system change the environment in which tumors develop, there are also a number of chronic medications that most HIV-1-infected individuals are currently taking. There are now a large number of antiretroviral medications in use for the treatment of HIV-1 infection [55]. Although these medications are available and effective, a growing percent of HIV-1-infected individuals are dying due to malignancies despite suppressed HIV-1 viral load and preservation of CD4 count and percentage [8,9,15]. It is usual and necessary for a number of these medications to be used together in a 'cocktail' to successfully treat HIV-1 infection [55].

The classes of medications used to treat HIV-1 infection are; nucleoside/nucleotide reverse transcription inhibitors (NRTIs), non-nucleoside reverse transcription inhibitors (NNRTIs), protease inhibitors, integrase inhibitors, fusion inhibitors, and entry inhibitors [55]. A concern with the use of these different medications is how they impact different cellular mechanisms in the context of the immune activation present at therapy initiations and the chronic immune activation that continues in a large percentage of HIV-1-infected persons despite being on HAART [17,18]. It may be that certain medications are best used during the induction phase and in patients with chronic immune activation while others have a safety profile making them more suited for the chronic therapy of HIV-1 patients without immune activation [56]. It is possible that exposure to particular medications may correlate with specific genetic lesions that are critical to the development of malignancies in HIV-1-infected patients.

Protease inhibitors (PIs) have been suggested to be agents that prevent malignancy and may even be ripe for repositioning as cancer therapeutics [57]. A number of studies have demonstrated the ability of currently used PIs to inhibit cancer cell growth, and improve sensitivity to chemotherapy and radiation therapy [57]. Protease inhibitors have been demonstrated to promote regression of Kaposi's Sarcoma, lymphomas, fibrosarcomas, multiple myeloma, prostate cancer and several cancer cell lines [58-65]. Despite the encouraging data presented in some in vitro systems and these demonstrations of tumor regression, several studies have reported increased rates of malignancies in patients on PI containing regimens [66,67]. It has also been observed that the aspartyl protease inhibitors used to treat HIV-1 have negative impacts on human immune cells that might be critical for successful immune surveillance such as dendritic cells [68]. Currently used protease inhibitors may also interfere with T cell function preventing their efficacy in tumor surveillance [69].

Non-nucleotide reverse transcriptase inhibitors (NNRTIs) have also been shown to have anti-proliferative effects on cancer cells [70]. It was therefore unexpected when HIV-1-infected patients on HAART regimens containing NNRTIs containing regimens were observed to have increased rates of cancer [71]. NNRTIs may also have immune-suppressive effects on monocyte derived dendritic cells [72]. It may be that the suppression of dendritic cells and other highly proliferating immune cells is enough to overcome the antiproliferative effect on cancer cells.

Integrase inhibitors have been shown to achieve the highest rates of virological control in HIV-1-infected patients [73]. Integrase inhibitors are suggested to be ideal agents due their limited drug interactions. With this class of drugs being one of the newest options available for patients infected with HIV-1 there is much less information about their potential role in preventing or promoting cancer. One publication that followed a cohort of approximately 2000 patients did describe an increase rate of cancer in patients on integrase inhibitors versus those on HAART regimens not containing integrase inhibitors, but this may reflect a preference by treating physicians to change prior regimens to integrase inhibitor containing regimens to avoid drug interactions when initiating chemotherapy [9]. With there being no clear host homologue to the targeted HIV-1 integrase it may be that this class of medications lacks any negative impacts on host immune tumor surveillance.

Conclusion

With over 1 million patients in the United States infected with HIV-1 being and new diagnoses each year, we are still unfortunately in the midst of an ongoing epidemic. A current challenge facing

the aging HIV-1 positive population is malignancies, in terms of prevalence, morbidity and mortality. Although awareness of the increased prevalence and associated mortality and morbidity of cancer in the HIV-1-infected population is growing, the mechanisms driving this problem are currently unknown. The chronic immune activation present in many HIV-1-infected patients may be involved in increasing the risk of cancer, but the role of decreased immune surveillance and the effects of antiretroviral medication on this surveillance may be critical. Large cohort studies of the relative incidence of cancer in patients on integrase inhibitor therapy compared to those on PI or NNRTI based regimens are currently underway. Further basic science investigation will be critical to understanding the molecular features of these cancers and the impact of various antiretroviral agents on their development.

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