Review

Role of the ubiquitin system and tumor viruses in AIDS-related cancer

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Abstract

Tumor viruses are linked to approximately 20% of human malignancies worldwide. This review focuses on examples of human oncogenic viruses that manipulate the ubiquitin system in a subset of viral malignancies; those associated with AIDS. The viruses include Kaposi's sarcoma herpesvirus, Epstein-Barr virus and human papilloma virus, which are causally linked to Kaposi's sarcoma, certain B-cell lymphomas and cervical cancer, respectively. We discuss the molecular mechanisms by which these viruses subvert the ubiquitin system and potential viral targets for anti-cancer therapy from the perspective of this system.

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Introduction

Viruses are etiologically linked to approximately 20% of all human malignancies worldwide and much of what we know today about the molecular mechanisms of onco-genesis has come from the study of tumor viruses. The means by which viruses subvert the ubiquitin proteasome system (UPS) is a relatively new area of inquiry. The study of the interactions between viruses and this system not only furthers knowledge of how viruses work, but also often offers shortcuts to understanding cellular processes in general. Though the infectious nature of viruses distinguishes them from other oncogenic factors, it is the adaptation of tumor viruses, mainly DNA viruses, over millennia of co-evolution with their hosts to persistence within these hosts that make the viruses an ideal focus for study of cellular mechanisms reviewed briefly here. This perspective is valid because the immense array of normal intracellular regulatory mechanisms is for the most part intact in latently infected cells, even when they become

neoplastic. This symbiosis between virus and cell is mirrored by the fact that in most infected individuals tumors do not develop, and in most instances many years pass between initial infection and appearance of a tumor. The host immune system generally keeps viral infection under control; however, conditions such as acquired immune deficiency syndrome (AIDS) elevate the risk of virus-associated malignancies dramatically [1-4].

Although human immunodeficiency virus (HIV), the cause of AIDS, itself does not have oncogenic properties, the profound immunodeficiency it causes creates a favorable environment for the development of cancer. All HIV-infected patients are at increased risk of developing several types of cancer, particularly in the later stages of AIDS. Despite highly active anti-retroviral therapy (HAART) being widely employed in developed countries, malignancy in this population is still a leading cause of morbidity and mortality [2,5,6].

Among the heterogeneous types of cancer associated with AIDS are Kaposi's sarcoma, immunoblastic B-cell lymphomas and an increased incidence of cervical and anal carcinoma [7,8]. Three human oncogenic viruses are involved causally: Kaposi's sarcoma herpesvirus (KSHV), Epstein-Barr virus (EBV) and human papilloma virus (HPV) [9,10].

AIDS-related malignancies represent only a small portion of all virus-associated human cancers. The consistency of association between a given virus and a specific malignancy ranges from essentially 100% to as low as 15% depending on the virus, the cancer and other factors [11]. Since the UPS regulates diverse cellular functions, including transcription, stress responses, cell cycle, cellular differentiation, angiogenesis, antigen processing and DNA repair [12], it is inevitably involved in oncogenesis induced by all the human tumor viruses [13,14].

Here we discuss several examples of how three tumor viruses manipulate the UPS in AIDS-associated viral malignancies, as well as provide perspectives on UPS-directed agents that might offer pathways to therapeutic intervention in these diseases.

Kaposi's sarcoma and KSHV

The search for a transmissible infectious agent as the cause of Kaposi's sarcoma led to the discovery in 1994 of KSHV, so far the newest member of the group of identified human oncogenic viruses [15-17]. Even though the incidence of Kaposi's sarcoma has fallen since the introduction of HAART, it is still the most common cancer associated with AIDS [18-21].

The ability to evade immune responses is crucial for long-term survival of viruses in the host. Oncogenic viruses make use of diverse strategies in achieving survival; one is the down-regulation of major histocompatibility complex (MHC) class I antigen presentation through the UPS [22,23].

KSHV encodes several viral products with oncogenic properties, among them two proteins, K3 and K5 (also known as MIR1 and MIR2), that have ubiquitin ligase activity [24,25]. K3 and K5 recruit E2 enzymes with their N-terminal RING-CH domain [25]. Either direct or indirect interactions between the transmembranes of K3 and K5 and MHC class I molecules ultimately lead to the ubiquitylation of lysine residues present in the MHC class I intracytoplasmic tail [25,26]. Ubiquitylated MHC class I molecules are then endocytosed and degraded by the lysosome [25,27,28]. A recent report indicates that K3, but not K5, can promote down-regulation of MHC class I molecules lacking lysine residues in their intracytoplasmic domains [29]. Another study argues that lysine 63-linked

ubiquitylation of MHC class I molecules is necessary for their efficient K3 ubiquitin ligase-mediated endolysosomal degradation [30].

Besides K3 and K5, another KSHV product, the immediate-early transcriptional transactivator RTA, is reported to encode E3 ubiquitin ligase activity [31]. RTA-dependent ubiquitylation of interferon regulatory factor 7 (IRF7), a key inducer of interferon-stimulated genes (ISGs), could target it for ubiquitin-dependent proteasomal degradation [31], thus dampening innate immune responses to the infection.

B-cell lymphomas and EBV

Several decades of intensive studies on EBV, the first human oncogenic virus discovered, have revealed its association with a variety of malignant diseases [11,32-37], including B-cell lymphomas associated with acquired and innate immunosuppressive conditions [38-42].

The EBV product EBNA1 represents an interesting example of how a virus evades immune system responses. EBNA1 is a nuclear protein that binds to EBV episomes and is required for maintenance of latency by the virus [34]. This viral protein contains repeats of Gly-Ala residues that prevent its proteasomal degradation and, additionally, sequester cleaved viral products in a cytoplasmic compartment, rendering them inaccessible for presentation by MHC class I molecules [43]. Although EBNA1 is not the only viral protein expressed during EBV latency, its resistance to UPS-dependent degradation creates a perfect camouflage to prevent recognition by the immune system [43-45].

Like other tumor viruses, EBV demonstrates its oncogenic potential by redirecting cell signaling pathways. Recent studies reveal ways in which EBV can manipulate different components of the UPS. For example, in B-cells its major oncogenic product, latent membrane protein 1 (LMP1), inhibits Siah-1 ubiquitin ligase to rescue the oncogenic factor β-catenin from proteasomal degradation [46,47]. In contrast, in epithelial cells LMP1 activates the same ubiquitin ligase, the targets of which in this case are prolyl hydroxylases (PHDs) [48]. These enzymes mark hypoxia-inducible factor-1α (HIF1α for degradation by the UPS. The stability of PHD 1 and PHD 3 is regulated by both Siah-1 and Siah-2 ubiquitin ligases [49]. The result of LMP1-dependent Siah up-regulation in epithelial cells is that HIFα levels are increased and become active HIFα-responsive genes [48,50]. These are recent observations and physiological reasons for the distinct functional roles of Siah ubiquitin ligases in the different cell types are unknown.

Another EBV latent membrane protein, 2A (LMP2A), acts as a surrogate B-cell receptor by providing constitutive signaling required for B-cell development and survival [51]. LMP2A signaling appears to be regulated in B-cells by association with members of the HECT domain-containing Nedd4 family of ubiquitin ligases [52,53] and likely utilizes ubiquitin-mediated degradation through the proteasome complex to regulate the strength of its own signal. Such processes could allow LMP2A to modulate B-cell pathways such as differentiation, activation or survival [51].

A further EBV latent antigen, EBNA 3C, targets the tumor suppressor pRb for proteasome-dependent degradation through the well known SCF^{Skp2} ubiquitin ligase in different systems including B-cells [54]. Besides directing ubiquitylation that leads to proteasomal degradation, EBV can also affect the regulatory lysine 63 ubiquitylation of IRF7 (the master regulator of type I IFN responses), which leads to its activation instead of degradation [55].

Cervical carcinoma and HPV

While Kaposi's sarcoma and B-cell lymphoma are the main viral malignancies associated with AIDS, and their connection with HIV infection are hallmarks of the condition, the association between HIV/AIDS and cervical and anal cancer is less obvious [56,57]. However, in 1993 a revised classification system for HIV infection listed invasive cervical cancer as one of the AIDS-defining malignancies [58], and there is growing evidence that HIV infection is associated with increased prevalence and severity of HPV-containing malignant cervical lesions [9,59,60].

More than 95% of all cervical carcinomas contain at least one copy of one of the HPV genotypes 16 & 18 as well as other types that pose a high risk for the malignancy [61]. The HPV *E6* and *E7* genes are the only viral genes that are retained and expressed in tumor tissue, and their role in HPV-induced carcinogenesis is well established [61-63]. Both proteins cause down-regulation of crucial tumor suppressors; E6 inhibits p53 [64-68] and E7 inactivates the retinoblastoma family proteins (pRb) [69-72]. Both E6 and E7 utilize the UPS to target these proteins for degradation and thus inactivation [73]. These interactions are recognized as classic oncogenic mechanisms; they operate in place of mutation of p53 and pRb.

HPV E6 recruits E6-associated protein (E6-AP), now recognized to be an E3 ligase; this E6-E6-AP complex then binds to p53, resulting in E6-AP-mediated ubiquitylation and proteasomal degradation of p53 [67,74,75]. From the perspective of cancer cell biology, this interaction is of interest because the virus product alters endogenous substrate specificity; normally, p53 is a target for Mdm2 ubiq-

uitin ligase-mediated ubiquitylation and degradation [76,77].

The mechanism of E7-induced proteasomal degradation of pRb is still unclear [73,78]. One possibility is that E7 recruits a cellular ubiquitin ligase that targets pRb for ubiquitylation and subsequent degradation. This model is supported by the finding that co-expression of pRb with the Rb-binding-deficient E7 mutant causes a consistent increase in pRb-induced contact-inhibited cell growth in culture [79]. Another possibility is that E7 could function as an adaptor between pRb and the proteasome, thereby targeting pRb directly to the proteasome without prior ubiquitylation, since it has been reported that E7 interacts with the ATPase subunit of the 19S regulatory complex of the 26S proteasome [80].

Disease models, knockouts and assays

Animal models that mimic human cancers caused by viruses are obviously important for understanding the tumor biology of AIDS-associated malignancies, as well as for evaluating the effect of potential anti-tumor and anti-viral drugs. Although there is currently still no animal model that accurately represents KSHV, EBV or HPV pathogenesis, mouse models have been established that attempt to address specific factors known to contribute to the development of the diseases. For example, murine gammaherpesvirus 68 (γHV-68) is used as a rodent model to help understand the pathogenesis of EBV and KSHV. Several reviews of γHV-68 have documented advances made toward understanding the pathogenesis of AIDS-associated malignancies in the context of these two human viruses [81-83].

Another approach is the transplantation of human tumor tissue to mice with severe combined immunodeficiency disease (SCID), which provides valuable models for viral carcinogenesis and also demonstrates the strict species barrier for infection by human viruses [84-87].

As for the roles of the UPS in virus-related cancers, cultured cell lines are still the primary model used at present to study the relations between viral oncogenes and the components of the UPS.

Crucial proof of the transforming potential of KSHV came from *de novo* infection of cultured bone marrow (microvascular) endothelial cells and human umbilical vein endothelial cells (HUVECs). KSHV infection conferred long-term survival of both cell types and anchorage-independent growth of HUVECs [88]. Continuous KSHV infection and also conditional, productive viral replication in cells cultured from primary effusion lymphoma (PEL) (a rare B-cell non-Hodgkin's lymphoma) [89] provide additional models.

The ability of EBV to immortalize normal human B-lymphocytes *in vitro* and to transform them into lymphoblastoid cell lines (LCLs) generates a cell-culture model of AIDS-associated EBV lymphomas [90]. Virus-containing B-lymphoblastoid cell lines that have been derived from primary tumors are also suitable as *in vitro* model systems [91].

Numerous cell lines infected with HPV serve as model cell culture systems to study different aspects of tumorigenesis, but perhaps the most relevant system for evaluating the transforming potential of the HPV oncoproteins is immortalization of primary human keratinocytes, which are the natural host cells of this virus *in vivo*[92]. HPV-immortalized cells are not tumorigenic in nude mice, although they display altered growth and differentiation.

Due to the oncogenic properties of HPV E6 and E7, these proteins have been the focus of most studies on cervical carcinogenesis [64,93-95]. Although the majority of the studies have been performed using cell culture models, several *in vivo* mouse model systems have been developed for the study of HPV-dependent carcinogenesis [96].

Disease targets and ligands

Both HPV E6 and E7 dysregulate the UPS so that there is down-regulation of the tumor suppressors p53 and pRb. Since both E6 and E7 are immunogenic, these viral products present potential targets for therapeutic vaccines [97-101].

As the UPS is closely involved in the regulation of numerous signaling pathways in tumor cells, it has in the last several years become an attractive target for anti-cancer therapy. The use of proteasome inhibitors to block the final stage in the UPS, proteolysis in the proteasome, presents the opportunity to manipulate intracellular processes in cancer cells for tangible benefit [102-106]. Yet, the functional activity of the UPS is crucial for normal cell function; blockade of protein degradation by proteasome inhibitors causes accumulation of misfolded or damaged proteins, which in turn leads to cell death [107,108]. At the same time, there is much evidence that some proteasome inhibitors are more cytotoxic to proliferating malignant cells than to normal quiescent cells [109].

The first of this new proteasome-inhibiting class of drugs to be on the market, bortezomib (Velcade, formerly known as PS-341), shows promising results in clinical trials with different types of cancer specifically by inhibiting the oncogenic NF-κB signaling pathway [110,111]. Since UPS-dependent degradation of IκB leads to NF-κB activation (as observed in most known malignancies including those that are AIDS-related [112]), bortezomib could be a candidate for the treatment of the virus-related cancers. In *in vitro* studies, bortezomib has demonstrated activity against a variety of malignancies by inducing apoptosis in cancer cells and increasing sensitivity of tumor cells to radiation or chemotherapy [113]. Since bortezomib is proving to be highly efficient for treatment of multiple myeloma and also shows promise for lymphoid cancers [113,114], it could be useful in the treatment of EBV-induced B-lymphomas, which are the second most common AIDS-related malignancy.

Since latent infection with these three DNA viruses is the basis for tumorigenesis, induction of the viral lytic cycle, leading to death of virus-infected malignant cells, is a potential antiviral strategy [115,116]. Recent study shows that bortezomib induces KSHV lytic gene expression *in vitro* in two latently KSHV-infected lymphoma cell lines [117]. This result suggests that the UPS regulates viral reactivation and that proteasome inhibitors could have similar effects on other latently infected virus-associated malignant cells.

Also, targeting of other steps of the UPS, such as specific ubiquitin ligases or deubiquitylating enzymes, could produce more selective effects since ubiquitylating and deubiquitylating complexes specifically bind to potential substrates. KSHV ubiquitin ligases K3 and K5 could be good examples of such targets.

Next frontiers

The effect of bortezomib and other proteasome inhibitors in virus-associated malignancies needs to be defined further. Viral products themselves are closely involved in UPS-dependent regulation and therefore the effects of proteasome inhibitors can be unexpected. For instance, it has been shown on one hand that proteasome inhibitors inhibit HIV budding [118] and on the other hand that inhibition of proteasome function can enhance HIV-1 infection [119].

Generally, present knowledge of how UPS modulators affect AIDS/HIV-associated or other virus-related malignancies is very limited and calls for further investigation. Recent information on the relations between tumor viruses and the host cell system is summarized in Table 1.

Despite the limitations of *in vivo* model systems for virus-related human malignancies, some (for example, human peripheral blood lymphocytes (hu-PBL) engrafted in SCID mice) could facilitate screening and preliminary testing of proteasome inhibitors.

Finally, there is no doubt that in the broader panorama of other cancers associated with viruses, such as human T-cell lymphotropic virus-1 (HLTV-1: leukemia), hepatitis B and C viruses (HBV and HCV: hepatocellular carcinoma),

Table 1: Viral products manipulate the ubiquitin system in AIDS-related cancers. Summarized here is recent information on the relations between tumor viruses and host cell systems. The general strategy through which the ubiquitin system is manipulated, the effector proteins and the host target proteins are indicated for KSHV, EBV and HPV.

Malignancies	Kaposi's sarcoma (KSHV)	Immunoblastic B-cell lymphomas (EBV)	Cervical cancer (HPV)
Strategy	Virus-encoded ubiquitin ligases	Dysregulation of host ubiquitin system	Dysregulation of host ubiquitin system
Viral Effectors	KSHV K3, K5 and RTA	EBV LMP1	HPV E6 and E7
Cellular Targets	MHC class I, IRF7	β-catenin, PHD/HIFa, IRF7	p53, pRb

as well as EBV (nasopharyngeal and gastric carcinomas, Burkitt's and Hodgkin's lymphomas) and HPV (cervical cancer) in non-immunocompromised patients, many aspects of the UPS are at work and will offer targets for therapy.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements

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Publication history