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Immune-based therapeutic approaches to virus-associated cancers

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It is estimated that 60–70% of cancers associated with infectious agents are linked to viral infections. Both RNA and DNA viruses that can establish persistent infection exploit various mechanisms including host cell immortalization through genomic instability, chronic inflammation and immune escape, to promote oncogenic transformation of human cells. Expression of selected viral proteins in malignant cells provides a unique opportunity to employ targeted therapies that can disrupt the cellular proliferation and prevent collateral damage caused by standard clinical therapies. While vaccination can be used to prevent infection before malignant transformation, immune-based therapies based on adoptive transfer of T cells and/or antibodies have emerged as powerful tools for the treatment of virus-associated cancers. Here we discuss recent advances and future prospects of immune-based therapies for virus-associated cancers.

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Introduction

More than one million cases of newly diagnosed cancers worldwide are associated with oncogenic viral infections [1]. Predominantly found in developing nations, virus associated malignancies are present in all geographic locations. Malignancies are currently associated with six distinct viral families that include the Herpesviridae, Papillomaviridae, Polyomaviridae, Hepadnaviridae, Flaviviridae and Retroviridae (Table 1); although not all members of these families are known to be associated with the oncogenic transformation of infected cells. These include both DNA and RNA viruses, with either very complex genomes as in the case of Epstein Barr Virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) that encode in excess of 100 genes, or relatively simple viral genomes in the remaining oncogenic viruses, encoding only four to eight genes. Despite these differences, a clear overlapping feature of oncogenic viruses is their capacity to establish lifelong latent or persistent infection in infected cells, to evade immune recognition and induce the transformation and proliferation of infected cells (Table 2). This immune evasion either via the regulation of antigen expression following the establishment of latency or as a consequence of chronic antigen exposure leading to immune dysfunction is a critical mediator that restricts the control of virally infected malignant cells [2,3]. Restoration of immune control remains a significant goal of current immunotherapeutic approaches for virus-associated malignancies.

Viral immunology in cancer and antigenic targets

Stable long-lived populations of T cells, including both cytotoxic CD8+ T cells and T helper 1 CD4+ T cells, mediate the long-term immunological control of persistent viral infections [4,5]. Following activation and differentiation during primary infection, virus-specific T cell populations are maintained at relatively stable frequencies due to constant antigen exposure during latent infection. These T cell populations can remain at high frequencies in circulation, rapidly trafficking to sites of reactivation, or become tissue resident [4]. The critical role of T cells in mediating the control of virus associated cancers is best exemplified in immunocompromised individuals. Immunosuppressed individuals have an increased susceptibility to malignancies associated with EBV and KSHV, Merkel cell polyomavirus (MCPyV), and the human papillomaviruses (HPV) [6–9]. This increased susceptibility is a direct consequence of the immunosuppression used to prevent organ rejection, and is associated with a deficiency in virus-specific T cell immunity [2,3]. Immunological control in the context of organ transplantation has been most extensively studied in EBV-associated post-transplant lymphoproliferative disease (PTLD), which has also provided the most compelling evidence for the efficacy of virus-specific adoptive cellular therapy for the treatment of cancer.

EBV-establishes a lifelong latent infection characterized by the stable transformation of infected B cells and the intermittent shedding of virus via the oropharyngeal epithelium [10,11]. Infection in B cells is defined by different stages of latency, characterized by the

Table 1

List of virus-associated cancer and immunotherapies

Virus	Malignancies	Immunotherapy studies	Clinical trials identifier
EBV	Post-transplant lymphoproliferative disease (PTLD); nasopharyngeal carcinoma (NPC); gastric carcinoma (GC); hodgkin lymphoma (HL); NK/T lymphoma (NK/TL)	Ongoing ACT studies for PTLD, NPC, GC, HL and NK/TL. Checkpoint inhibition approved for HL. Ongoing studies combining ACT and checkpoint blockade	NCT03394365; NCT02578641; NCT02875613; NCT03427827; NCT02605967; NCT03257163; NCT03044743; NCT02763254
KSHV	Kaposi sarcoma	Ongoing clinical studies of checkpoint blockade	NCT03219671; NCT03316274; NCT03469804;
CMV	Glioblastoma multiforme	Ongoing clinical studies of ACT for CMV-associated GBM	NCT02661282;
HPV	Cervical Cancer; Vaginal Cancer; vulvar cancer; oropharyngeal cancers; anal cancer; penile cancer; squamous cell carcinoma	Ongoing clinical studies of ACT, checkpoint blockade; and combining checkpoint blockade and ACT	NCT02379520; NCT02858310
MCPyV	Merkel cell carcinoma	Ongoing clinical studies of combined ACT and checkpoint blockade	NCT02584829
HBV	Hepatocellular carcinoma	Ongoing clinical studies of ACT and checkpoint blockade	NCT02686372; NCT03419481
HCV	Hepatocellular carcinoma	Ongoing clinical studies of checkpoint blockade	NCT01658878
HTLV	T-cell leukemia-lymphoma	Ongoing clinical studies of checkpoint blockade	NCT03075553

expression patterns of EBV latent genes that influence the immunogenicity of the transformed B cells [12]. Immune control of latent EBV infection is dominated by CD8+ T cells that recognize EBV nuclear antigens (EBNA) 3–6 [13,14]. Subdominant immunity is directed towards EBNA 1–2 and the latent membrane proteins (LMP) 1 and 2. Due to the lack of efficient immunological control because of the broad immunosuppression used in transplant patients, PTLD typically shows no restriction in latent antigen expression. In contrast, the EBV-associated malignancies that arise in otherwise immunocompetent individuals demonstrate a restricted pattern of gene expression (EBNA1 in Burkitt's Lymphoma; EBNA1 and LMP1/2 in Hodgkins lymphoma, NK/T cell lymphoma, nasopharyngeal carcinoma and gastric carcinoma) [15–18].

Gene expression is also restricted in other viral-associated malignancies. Malignant HPV-transformed cells display a preferentially expression of the E6 and E7 genes [19], while MCPyV transformed cells express the T antigens [20]. These genes are typically involved in cell transformation, while the expression of viral replication genes is restricted.

Immunotherapy: adoptive cellular therapy

The presence of well-defined foreign antigens in virus-associated malignancies and our understanding that T cells predominantly mediate the immunological control of persistent viral infections has provided the impetus for the development of adoptive cellular therapy (ACT) approaches using virus-specific T cells. For over 20 years, ACT has been used for the treatment and prevention of PTLD in both hematopoietic stem cell transplant

Table 2

Association between viral gene function and cancer

	Immune evasion and modulation	Cell survival	Cell proliferation	DNA damage and genomic instability
EBV	BARF1, EBNA1 and LMP1	LMP1	LMP1&2 and EBNA2-6	LMP1
KSHV	vIRF, MIR1, MIR2, ORF45, CCPH	vBcl-2, vFLIP, LAMP	vGPCR, LANA, vIL-6 and vCyclin	LANA
HPV	E6 and E7	E6 and E7	E6 and E7	E6 and E7
MCPyV		LTAg	LTAg	LTAg
HBV	HBs and HBx	HBx	HBx	HBx
HCV		NS2, Core, NS3, NS5A	NS5B, NS2, Core, E2, NS3, NS5A	Core, NS5A
HTLV	Tax	Tax	Tax	Tax