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Pathogen-Driven Cancers and Emerging Immune Therapeutic Strategies

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Abstract

Infectious agents play an etiologic role in approximately 20% of cancer cases worldwide. Eleven pathogens (seven viruses, three parasites, and one bacterium) are known to contribute to oncogenesis either directly via the expression of their protein products or indirectly via chronic inflammation. Although prevention of infection and antimicrobial treatments have helped in reducing infection rates and the incidence of associated malignancies, therapies for these cancers remain limited. The importance of immune control over malignant progression is highlighted by the fact that many cancers, particularly those induced by pathogens, occur more frequently among immunosuppressed patients as compared with healthy individuals. Therefore, therapeutic strategies that can elicit a robust immune response and restore tumor detection may be a beneficial approach for treating these cancers. In addition, the study of immune escape mechanisms used by pathogens and their associated cancers may provide insight into the mechanisms of malignant transformation and improved therapies for cancer more generally.

Pathogen-Mediated Oncogenesis

It is estimated that approximately one in five cancers worldwide is linked to an infectious agent (1). To date, there are seven oncogenic viruses [hepatitis virus B and C (HBV and HCV), human papillomavirus (HPV), Epstein–Barr virus (EBV), human T-cell lymphoma virus 1 (HTLV-1), Merkel cell polyomavirus (MCPyV), and Kaposi's sarcoma virus also known as human herpes virus 8 (KSVH or HHV8)], one oncogenic bacterium (*Helicobacter pylori*), and three oncogenic parasites (*Schistosoma haematobium*, *Opithorchis viverrini*, and *Clonorchis sinensis*) that have been identified (Table 1; ref. 1–4). Four of these agents (HBV, HCV, HPV, and *H. pylori*) each account for approximately 5% of all cancer cases by leading to hepatocellular carcinoma, cervical cancer, and stomach cancer, respectively. Although highly varied in their oncogenic mechanisms, these pathogens can generally be divided into direct and indirect carcinogens (4, 5). Currently, five viruses (HPV, HTLV-1,

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EBV, MCPyV, and KSVH) are classified as direct carcinogenic pathogens and share several similarities (4). At least a critical portion of the viral genome can generally be detected in each cancer cell resulting in the expression of viral oncogenes that disrupt cell-cycle checkpoints, inhibit apoptosis, and contribute to cell immortalization (3, 5). In contrast, the indirect carcinogenic pathogens (HBV, HCV, *H. pylori*, *S. haematobium*, *O. viverrini*, and *C. sinensis*) do not induce expression of oncogenes, but instead their persistent infection leads to a chronic inflammatory state. Persistent inflammation from these pathogens leads to the release of chemokines, cytokines, prostaglandins, and reactive oxygen species, which can result in the deregulation of the immune system and promotion of neovascularization (3–5). Of note, classification of pathogens as direct or indirect carcinogens is simplistic and does not fully capture the likely oncogenic mechanisms of these pathogens. HBV, for example, is an indirect carcinogen that is clonally integrated into almost all HBV-related cancers; however, it is unclear whether persistent viral gene expression is required for continued cancer cell proliferation (5).

Prevention and Eradication of Oncogenic Infectious Agents

Important strategies for reducing the incidence of pathogen-driven cancers have been the prevention of infection or the eradication of infection before the development of cancer. Large-scale vaccination programs for both HBV and HPV have dramatically reduced infection rates. Specifically, within the United States, an 82% decline in HBV infection has been reported since the implementation of the vaccine in 1991 (6). In Taiwan, introduction of the HBV vaccines has also shown remarkable efficacy in reducing infection rates and longitudinal studies have shown a corresponding reduction in the age-specific incidence of hepatocellular carcinoma (7). Since the introduction of HPV vaccines in the United States in 2006, the prevalence of the targeted, high-risk HPV types has decreased from 11.5% to 5.1%, a 56% reduction among teenage girls (8). Of note, only 32% of 13- to 17-year-old girls received all three vaccine doses. Improved administration and access could therefore lead to even greater efficacy. Despite these successes, administration of these vaccines to the developing world remains a challenge due to environmental, cultural, and socioeconomic barriers (7). Vaccinations against the other oncogenic pathogens such as HTLV-1, EBV, HCV, and *H. pylori* are in developmental stages but will face diverse technologic and implementation challenges (7). Infection with these microbes will therefore remain a global problem prompting the need for other treatment modalities.

Because persistent infection is a hallmark of oncogenic pathogens, there is a window of opportunity for cancer prevention by treating the pathogen before malignant progression (7). Antiviral therapies including IFNs, nucleoside/nucleotide analogues, and therapeutic vaccines can be used to treat oncogenic viruses before malignant progression. Such antiviral strategies have been successful in reducing HBV- and HCV-associated cirrhosis and hepatocellular carcinoma (9). The combination of zidovudine (a nucleoside analogue) and IFN-α may reduce the incidence of EBV-induced lymphoma, and a worldwide meta-analysis demonstrated a 35% complete response rate and 31% partial response rate in HTLV-1–driven adult T-cell leukemia/lymphoma (ATLL; refs. 10, 11). Another antiviral strategy, currently being tested in clinical trials for HPV treatment, is the use of therapeutic vaccines, which can range from peptide, protein, DNA, RNA, and dendritic cell–based

vectors (12). For the nonviral pathogens, several antimicrobial therapies have been successfully used such as the quadruple therapy approach for *H. pylori* (a proton pump inhibitor, dual antibiotics, and bismuth) and praziquantel for the oncogenic parasites (13–15). Increasing antibiotic resistance, reinfection, and lack of access to available treatments have diminished the potential benefit of these approaches (14, 15). Therefore, while effective strategies are being taken to reduce the incidence of oncogenic agents, these infections will continue to occur, as will their corresponding malignancies.

Pathogen-Driven Cancers Are Uniquely Poised for Immunotherapies

Although infectious agents contribute significantly to the overall global cancer burden, it is important to realize that oncogenesis is actually an uncommon outcome of infection and is a deviation from the normal life cycle of these pathogens. Pathogen-induced oncogenesis, when it does occur, usually arises many years after the initial infection. This delay indicates that additional steps are required beyond infection by the pathogen (5). As one would expect, there are increased rates of pathogen-driven cancers where infection rates are higher, such as in developing countries, underserved communities, and among immunosuppressed populations. A meta-analysis of two immunosuppressed populations (HIV/AIDS patients and transplant patients) demonstrated a significantly increased incidence of several types of cancer, most of which were pathogen-driven (16). Higher rates were reported of EBV-lymphoma/leukemia, HBV- and HCV-hepatocellular carcinoma, HPV-cervical cancer, and *H. pylori*–associated gastric carcinoma, whereas rates of most common epithelial cancers were equivalent or reduced as compared with the general population (16). This pattern of increased cancer risk in two different immunosuppressed populations suggests that immunodeficiency, rather than other risk factors, is responsible for the increased cancer incidence (16). An additional example of immune regulation of pathogen-driven cancers is seen in the setting of Merkel cell carcinoma (MCC). Approximately 10% of patients with MCC have chronic immunosuppression, which is a significant over-representation of the general public (17). In addition, patients with immunosuppressed MCC have a significantly reduced MCC-specific survival rate (40% at 3 years) as compared with patients with nonimmunosuppressed MCC (74% at 3 years; ref. 17). This indicates that immunosuppressed patients are both more likely to develop MCC and more likely to succumb to the disease, underscoring the importance of immune function in regulating this pathogen-driven cancer (17).

The idea that the immune system has the capacity to control malignancy is not a new concept. In the 1890s, a New York bone surgeon, William B. Coley, documented complete regression of a sarcoma lesion in a patient who had a high fever following the development of a concurrent bacterial infection. He went on to treat many more cancer patients with bacteria or bacterial products (which became known as "Coley's toxins") to induce an immune reaction and saw some responses (18). However, this technique was highly criticized and immunotherapeutic approaches remained in the background until other studies documented improved cancer outcomes via nonsurgical manipulation of the immune system. One example was the discovery that interleukin (IL)-2 administration had efficacy against melanoma and renal cell carcinoma (19). Specifically, 15% to 20% of the patients exhibited objective regression of tumors following treatment with high dose IL-2, with half of the

responding patients experiencing complete tumor regression despite bulky metastatic disease (19). The mechanism for this observed effect is likely due to the expansion of antitumor lymphocytes. Indeed, it has been shown in several cancer types that T-cell intratumoral infiltration can positively influence survival outcomes, indicating that a cellular rather than humoral response mediates cancer progression (20). As a result, enhancing cell-mediated immunity using antigen-specific T lymphocytes has received significant attention and has emerged as an increasingly effective treatment for patients with advanced cancer (19, 21).

Adoptive T-cell transfer therapy involves the collection and expansion of antigen-specific T cells and the subsequent infusion of these cells back into the patient, where they can traffic to the tumor and promote targeted tumor cell death. Tumor-specific antigens presented on MHC class I molecules provide an excellent target for discriminating malignant from normal cells. T cells targeting melanoma-associated antigen recognized by T cell 1 (MART-1) were first proved effective in the treatment of metastatic melanoma (22). This method has since been applied to lymphomas associated with EBV. Specifically, posttransplant lymphoproliferative diseases (PTLD) arise following the administration of immunosuppressive agents, which can lead to a reactivation of latent EBV. PTLDs encompass a range of disorders from reactive, polyclonal hyperplasia to aggressive non-Hodgkin lymphomas (NHL; ref. 23). The highly immunosuppressed state in these patients allows for immune escape despite the expression of highly immunogenic viral latency proteins (EBNA3 family proteins) on the surface of tumor cells (23, 24). Targeting of these EBV-specific proteins using T-cell therapy resulted in complete responses in 10 of 24 patients with PTLD (23). The expression of EBV-specific antigens on malignant cells provides an example of how tumor-specific antigens can make such cancers particularly suited for targeted cellular therapies.

This immunotherapeutic approach also has been used prophylactically in transplant patients and in the treatment of other EBV-related malignancies such as nasopharyngeal carcinoma (NPC) and Hodgkin lymphoma. Responses in the treatment of NPC and Hodgkin lymphoma using T-cell therapies were not as successful as responses in PTLD, perhaps due to the reduced expression of the EBNA3 family proteins, the expression of cytokines promoting Th2 responses, and a higher expression of T-regulatory cells (23). Targeting another EBV protein, LMP2, which is expressed on several EBV-associated tumors, has been shown to mediate successful resolution of some Hodgkin lymphoma and NHL and of severe chronic active EBV infection in patients (23), whereas the use of polyclonal CTL lines resulted in several complete and partial remissions in NPCs. Unfortunately, these results were often short-lived most likely due to a lack of persistence and proliferation of the infused cells *in vivo*. Adoptive T-cell strategies are being investigated for the treatment of patients with MCC. Of note, 80% of MCC tumors require the persistent expression of the immunogenic polyomavirus tumor-antigen oncoproteins. Thus, MCC has highly desirable tumor-specific antigens for T-cell therapy.

The shortcomings of treating EBV- and MCPyV-associated malignancies with virus-specific T cells highlight some of the challenges currently faced in this approach, including the insufficient persistence of infused T cells, downregulation of antigen presentation, and T-cell exhaustion. One method to enhance the persistence of transferred T cells is to administer

low-dose IL-2 following T-cell infusion, although this approach can induce T-regulatory cells (25, 26). Another approach, called lymphodepletion, has been used in combination with IL-2 (27). Lymphodepletion involves the destruction of host lymphocytes using cyclophosphamide or anti-CD45 before T-cell infusion. This approach eliminates host T-regulatory cells, improves access to cytokines such as IL-7 and -15, and thus promotes the ability of infused T cells to persist *in vivo* (23, 27). The necessity of lymphodepletion, however, remains unclear as some studies have shown that with sufficient numbers of infused T cells, complete regression of a tumor can occur in either lymphodepleted or lymphoreplete hosts (27). Another challenge for the adoptive strategies is the downregulation of HLA-I molecules on the surface of tumor cells, thereby obscuring the intended target of the infused tumor-specific T cells. HLA downregulation in patients can be reversed by the treatment with either IFN or single-fraction radiation (28, 29). These strategies are currently being tested in conjunction with T-cell therapy for patients with MCC. In addition, epigenetic modulators such as the histone deacetylase inhibitors and a methyltrasferase inhibitor (5-aza-2′-deoxycytidine) have been shown to upregulate HLA and cancer-testis antigen expression on tumor cells (30, 31).

These agents are under active investigation and could significantly increase tumor immunogenicity and clinical responses to concurrent immunotherapies (31). Besides increasing immunogenicity, ensuring that tumor-specific T cells retain their effector function is another essential component of T-cell therapy. Studies of chronic infection have shown that upon persistent exposure to a specific antigen, T cells can progressively lose their ability to kill target cells, in part through a process known as T-cell exhaustion. T-cell exhaustion has been best described in LCMV (lymphochoriomeningitis virus)-infected mice. Over the course of chronic LCMV infection, virus-specific T cells lost effector function most significantly when viral burden was high and $CD4^+$ Th cells were lacking (32). Markers of T-cell exhaustion have been investigated extensively, and coinhibitory molecules such as PD-1 and CTLA-4 have been shown to be upregulated and contribute to this phenotype, although through different mechanisms (32, 33). CTLA-4 attenuates early activation of naïve and memory T cells, whereas PD-1 interaction with PD-L1 serves to modulate T-cell activity in peripheral tissues including the tumor microenvironment (34). Importantly, antibodies targeting CTLA-4 and PD-1/PD-L1 reverse exhaustion and mediate clinical activity against melanoma, renal cell carcinoma, and non–small cell lung cancer (34, 35). In 2011, ipilimumab (anti-CTLA-4) was approved by the U.S. Food and Drug Administration (FDA) for treatment of unresectable malignant melanoma. Because these two molecules act in a nonredundant fashion, combined blockade may achieve enhanced antitumor activity (34). It is plausible that the combination of antigen-specific T-cell infusion with agents that activate T cells and prevent their exhaustion may be a particularly effective approach to treating pathogen-associated cancers.

Although therapies targeted to specific tumor antigens have shown success in the treatment of some cancers, immunotherapies that aim to stimulate a more general cellular response against malignancies may prove beneficial. A promising therapeutic cytokine is IL-12, which is considered to be a highly potent trigger of antitumor immune responses (36). IL-12 is required for optimal differentiation of naïve CD4 T cells into type I Th cells and promotes

cell-mediated immunity, making it an ideal candidate for immunotherapies. Subcutaneously injected IL-12 as a monotherapy has shown a 71% response rate in patients with Kaposi sarcoma and a 43% response rate in patients with various NHLs; however, minimal responses were observed in several other cancer types (36). Localized low-level production of IL-12 following intratumoral electroporation of plasmid DNA has shown benefit in the treatment of malignant melanoma (37).

Future Directions

Because of their high prevalence, the development of treatments for pathogen-driven cancers is an important goal. Immunotherapies may offer particularly appealing therapeutic options for many such cancers due to their expression of microbial products. In addition, development of immunotherapies targeting pathogen-driven cancers may provide insight into targeted immune therapies for other cancers. However, it is important to note that while antigen-specific T-cell therapy shows promise in treating pathogen-driven cancers, several challenges limit the efficacy of this approach, including the inability to treat patients who do not have the particular HLA types compatible with the therapy. One approach that does not limit which patients can be treated on the basis of their HLA type is the use of cytokine-induced killer (CIK) cells. These cells are $CD3^+CD56^+$ T cells that express both the natural killer (NK) and T-cell markers and target stress-inducible molecules including MIC A/B that are expressed on many tumor types but usually are not present on normal tissues (38). This method has shown promise in the treatment of several cancers (38). Interestingly, CIK therapy for the treatment of hepatitis B–associated hepatocellular carcinoma has been shown to significantly reduce viral DNA levels in addition to the eradication of residual cancer cells, the prevention of recurrence, and the improved progression-free survival rates (38, 39). Suboptimal persistence of infused cells remains a challenge and will require further investigation (38). Another therapy that is not limited to patients with particular HLA types is the use of chimeric antigen receptors (CAR), which combine the specificity of an antibody with the effector function of CD8 T cells. B-cell malignancies expressing CD19 were the first malignancies treated with CARs and these demonstrated several complete responses, however, their effect on solid tumors has been less encouraging (40). Although the challenges facing the development of treatments of pathogen-driven cancers are significant and diverse, there is ample reason for optimism. Moreover, it is likely that the mechanisms of immune escape used by pathogen-driven cancers will continue to provide valuable clues in the treatment of cancer more generally.

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Table 1

Prevalence and characteristics of pathogens known to promote cancer development

Pathogen	Prevalence of infection[a]	No. of new pathogen-attributable cancers worldwide in 2008 (2)	Notable cancers	% Attributable to infection (2)	Oncogenic mechanism/ oncogenes expressed (7, 41)
Direct carcinogens					
HPV	~10% (ref. 42; in women by cytology)	610,000	Cervical carcinoma	100	Viral integration/E6 and E7
			Penile	50	
			Anal	88	
			Vulva	43	
			Vaginal	70	
			Oropharynx	13–56	
HTLV-1	~5–10 million infected (ref. 43; by serology)	2,100	ATLL	100	Viral integration/Tax
EBV	>90% (by serology)	110,000	BL (Sub-Saharan Africa)	100	Viral integration/EBNA1, EBNA2, EBNA3C, LMP1, LMP2 + EBER (oncogenic RNA)
			BL (Other regions)	20–30	
			NPC	80–100	
			HL (developing-children)	90	
			HL (developing-adults)	60	
			HL (developed)	40	
MCPyV	60%–80% (ref. 44; by serology)	1,600 (United States)	MCC	80	Viral integration, deletion of C-terminus of LT/LT
KSHV	<10% (Northern Europe, United States, Asia)	43,000	Kaposi sarcoma	100	No integration/LANA, vFLIP
	10%–30% Mediterranean				
	>50% Sub-Saharan Africa				
Indirect carcinogens					
HBV	240 million infected worldwide, with highest incidence in Sub-Saharan Africa (ref. 45; by serology)	380,000	Hepatocellular carcinoma	23–59	Viral integration, inflammation/HBX
HCV	2.2% (by serology)	220,000	Hepatocellular carcinoma	20–33	Uncertain/NS3, NS5A
H. pylori	~50% (by serology)	660,000	Noncardia gastric cancer	90	Oncoprotein injection/Cag A
			NHL of gastric location	86	Oncogene insertion/mutated core protein

Pathogen	Prevalence of infection[a]	No. of new pathogen-attributable cancers worldwide in 2008 (2)	Notable cancers	% Attributable to infection (2)	Oncogenic mechanism/ oncogenes expressed (7, 41)
S. haematobium	200 million infected in Africa, less common elsewhere	6,000	Bladder cancer	40	Irritation, inflammation, immunomodulation
O. viverrini	~10 million infected	2,000	Cholangiocarcinoma	NA	Irritation, inflammation, immunomodulation
C. sinensis	~45 million infected				

NOTE: See text for details.

Abbreviations: ATLL, Adult T-cell lymphoma/leukemia; BL, Burkitt lymphoma; HL, Hodgkin lymphoma; MCC, Merkel Cell carcinoma; NA, not applicable, NHL, non-Hodgkin lymphomal; NPC, nasopharyngeal carcinoma.

[a]Data for infection prevalence derived primarily from the World Health Organization (WHO; ref. 4).