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Human Oncogenic Viruses

ABSTRACT

Human Oncogenic Viruses (HOVs) cause 17% of all cancer in humans. Most of these viruses cause common infections and their associated malignancy is only a rare end result. Their oncogenic mechanisms are diverse and complex, but research into these mechanisms is identifying new insights which have the potential to be translated into new strategies to treat viruses and their cancer.

INTRODUCTION

It was in 1842 that the Italian surgeon from Asiago, Domenico Rigoni-Stern[1] suggested that a 'transmissible agent' might be responsible for some types of human cancer. Of course, at that time there was no knowledge of viruses, but from epidemiological analysis of death certificates he observed that nuns had less cervical cancer when compared to married females and prostitutes. He also proposed that cervical cancer was connected to sexual contact.

Currently, there are seven well established Human Oncogenic Viruses (HOVs). Table 1 lists them with their year of discovery and their associated human malignancy.

Table 1. List of the seven HOVs.

Virus	Discovery	Virus Classification	Malignancy
Epstein–Barr virus (EBV)	1964	Herpesviridae dsDNA	Burkitt's lymphoma Diffuse large B-cell lymphoma Hodgkin lymphoma Undifferentiated nasopharyngeal carcinoma Gastric adenocarcinoma Leiomyosarcoma Post-transplant lymphoproliferative disease
Hepatitis B virus (HBV)	1965	Hepadnaviridae dsDNA-RT	Hepatocellular carcinoma
Human T-lymphotropic virus-1 (HTLV-1)	1980	Retroviridae ssRNA-RT, positive strand	Adult T-cell leukaemia (ATL)
Human genital papillomavirus (HPV)	1983	Papillomaviridae dsDNA	Cervical carcinoma Squamous cell head and neck carcinoma Squamous cell anal cancer Vulvar cancer
Hepatitis C virus (HCV)	1989	Flaviviridae ssRNA-RT, positive strand	Hepatocellular carcinoma Marginal zone lymphoma Diffuse large B-cell lymphoma Follicular lymphoma
Kaposi sarcoma herpesvirus (KSHV/HHV8)	1994	Herpesviridae dsDNA	Kaposi's sarcoma Primary effusion lymphoma Multicentric Castleman disease
Merkel cell polyomavirus (MCV)	2008	Polyomaviridae dsDNA	Merkel cell carcinoma

The malignancies that are associated with HOVs reflect the viruses' ability to target specific cells which they infect, the so-called 'viral cell tropism'. Specifically, HBV and HTLV-I are very restricted as they cause only one cancer, HBV causing primary hepatocellular carcinoma while HTLV-I causing adult T-cell leukaemia. HPV is restricted to squamous epithelial cancers but these occur in various body locations like the cervix, head, neck and anus. In contrast, EBV and KSHV infect a variety of tissues. EBV shows the highest 'viral cell tropisms' and is linked to various cancer types (nasopharyngeal carcinoma, gastric adenocarcinoma, lymphomas, and leiomyosarcoma). KSHV infect endothelial and post-germinal B cells causing respectively, Kaposi's sarcoma and primary effusion lymphoma and a B-cell lympho-proliferative syndrome.

As can be seen from Table 1, HOVs belong to different families of viruses. And yet they share common features enabling them to cause cancer by seizing pivotal cellular pathways of cell growth and metabolism. The molecular mechanisms involved are complex and this essay briefly highlights the main ones.

MECHANISMS OF VIRAL PERSISTENCE AND ONCOGENESIS

HOVs can perturb a plethora of cellular pathways that can lead to viral persistence and, at a later stage carcinogenesis. The following are some of them.

Attenuation of Host Immunity

When a virus infects the cells of the host, it exploits their molecular machinery to propagate itself. But the host is not passive and tries to keep its cellular integrity. Both have evolved mechanisms to settle this conflict of interest. These mechanisms involve pathways that govern genome upkeep, cellular growth, and immune surveillance. During the asymptotic persistent period of infection by HOVs, a friable equilibrium to settle this conflict is reached. It is proposed that when this fragile equilibrium is broken, oncogenesis is triggered since the viral tactics that sustain infection start causing uncontrolled proliferation of cells, circumvention of antitumour immunity, and build-up of mutations. The fragile equilibrium can be broken by outside factors that cause immune suppression or damage in the DNA. Endogenous factors can also be responsible, like ageing which is associated with cumulative genetic mutations and suppression of immunity.

Indeed, advanced ageing, host genetic mutations, exposure to certain environmental factors and status of immunity are determinants or co-factors of oncogenesis in hosts harbouring HOVs. For example, cancers induced by EBV, HPV, MCV, KSHV and HTLV-I have an increased incidence in persons who are immuno-suppressed (like patients with AIDS and solid-organ transplants). Also advanced age is a cofactor because it is associated with some immune dysfunction and accumulation of genetic mutations in the host along the years. Furthermore, certain environmental exposures elevate the risk of oncogenesis. For example, mycotoxins, like aflatoxin in food, are connected with HBV-associated hepatocellular carcinoma,[3] and malaria infection is connected with Burkitt's lymphoma in children.[4]

Perturbations of Host Metabolism

Cancer cells often show the 'Warburg effect', whereby cancer cells generate their energy not through the normal Krebs cycle and oxidative phosphorylation in the mitochondria, but through the process of aerobic glycolysis. The latter is less efficient (generates less adenosine triphosphate (ATP)), and occurs in the cytosol.[5] In a similar way, HOVs shift the metabolism of cells, when they infect and transform them.

Adjustments of the Cellular Micro-environment

Human cells that are infected with HOVs and their respective cancer cells are adapted to live in an inhospitable micro-environment, where oxygen is low (hypoxia), pH tends to be acidified, and Warburg metabolism occurs.[6,7] This harsh cellular micro-environment selects these adapted cells over cells which are not infected or not transformed.

One way how hypoxia and the Warburg effect help is by helping these cells escape immune attack.[8,9] For example in EBV infected cells, hypoxia upregulates genes that inhibit interferon production.[10]

In Kaposi's Sarcoma oncogenesis, hypoxia is also fundamental because it activates a cluster of genes which benefit the cells though their modulatory functions.[11,12]

Apoptosis Inhibition

When a virus infects a cell, the innate immunity responds by arresting the cell-cycle and initiates apoptosis.[13] HOVs can inhibit apoptosis via several diverse mechanisms. For example, EBV encodes BHRF1 (BamHI fragment H rightward open reading frame 1) and BALF1 proteins that inhibit Bcl2 (B-cell lymphoma 2) pro-apoptotic factors. EBV also encodes various micro-RNA that inhibit BIM (Bcl-2 Interacting Mediator of cell death) and Puma (p53 upregulated modulator of apoptosis)[14] and this promotes the survival of host cells. Similar strategies are seen with the other HOVs.

Induction of Chronic Inflammation

Chronic inflammation is also blamed as a mechanism of oncogenesis. It is proposed that chronic inflammation causes cells to continuously die and as they are replaced by new cells, these cells over time slowly acquire mutations associated with oncogenesis. It is believed that such chronic inflammation in HBV and HCV induces hepatocellular carcinoma. Similarly chronic inflammation has been proposed as a very important driving force in HPV-related oropharyngeal carcinogenesis.[15]

Epigenetic Perturbations

One of the epigenetic perturbations associated with persistent viral infections is DNA hypermethylation of several viral and cellular genes.[16] This hypermethylation is associated with the formation of condensed heterochromatin and thus the 'switching off' of genes. For example, EBV infection activates DNA methyltransferases that cause hypermethylation of genes that code E-cadherin (epithelial cadherin),[17-19] p16 and p21 (latter two being tumour suppressor genes).[20,21] CDH1 (Cadherin 1) gene codes E-cadherin which is a protein in cell membranes of epithelial cells whose function is to keep these cells adhered together.

Another epigenetic perturbation caused by viral infection is histone epigenetic modification resulting in the remodelling of nucleosomes. For example, HPV infection besides causing DNA hypermethylation also causes post-translational modifications of histone tails. These include histone acetylation, methylation, phosphorylation, sumoylation, and ubiquitination, all impacting on the physical state and the transcriptional state of the chromatin.[22]

Non-coding RNA alterations are also found with persistent viral infections. For example, the long non-coding RNA (lncRNA) HOTAIR (HOX transcript antisense intergenic RNA) is down-regulated in cervical cancer[23] leading to up-regulation of HOXD10(Homeobox D10). Other lncRNAs are discussed in greater detail by Hull et al.[24]

Transcriptional Perturbations

HOVs also target and perturb transcription factors and their networks. For example, p53 and Rb-family complexes of host's cells are perturbed by E6, E7 and T-antigens (viral nuclear factors). Other factors repress tumour suppressor genes, like p16 and BIM (Bcl-2 interacting mediator of cell death).[25]

MEDICAL APPLICATIONS OF RESEARCH ON HOVS

Over the years research and knowledge on oncogenic viruses and viral cancers have been translated into the clinical setting.

Increased Knowledge on Fundamental Cellular Processes

Research on HOVs (and other tumour viruses) has played pivotal roles in the investigation and discovery of many fundamental processes of the cell, like signal transduction, immune regulation, transcriptional enhancers, messenger RNA splicing, and cell cycle control.

Identification of Oncogenes and Tumour Suppressor Genes

Research of virus-induced cancers also revealed the functions of various oncogenes and tumour suppressor genes. Currently and specifically HPV is proving valuable in studies of the epigenome of cancer.

Anti-cancer Vaccines

The fact that viruses could cause cancer was translated into the clinical setting by the development of anti-cancer vaccines, specifically against HPV and HBV. With their advent the incidence of human cancers associated with these viruses has already started to decrease. One might think that similar research-driven knowledge and its clinical application will also prevent and even cure other virus-associated cancers. But unfortunately the transition from bench to clinic for specific viruses faces huge challenges given that the pharmaceutical industry might view the 'relatively low burden' of disease they cause to be not cost-effective.

Antiviral Therapy

Antiviral therapy can be effective in clearing chronic viral infections and so prevent associated cancers. For example, sofosbuvir (a nucleotide analogue inhibitor of HCV NS5B polymerase) is one such effective anti-viral which clears HCV infection and thus prevents hepatocellular carcinoma.[26]

Potential Diagnostic Biomarkers

High performing diagnostic biomarkers can detect cancer at an earlier stage resulting in a better prognosis because of earlier treatment and small cancer burden. Specifically, micro-RNAs (miRNAs) are potential biomarkers in cancers induced by HOVs (Table 2). Indeed, miRNA profiling can differentiate between pathological and physiological states.

Table 2. miRNAs as potential biomarkers of HOVs

HOV	Cancer	miRNA	Level of Expression	Reference
EBV	Nasopharyngeal carcinoma	BART7, 13	Decreased	27
HBV	Hepatocellular carcinoma	miR-885-5p,122,21	Increased	28
HCV	Hepatocellular carcinoma	miR-29a, 146, 149, 221, 222 miR-192a	Increased Decreased	29,30
HPV	Cervical carcinoma	miR-21, 146a, 224, 182 miR-218	Increased Decreased	31-33
MCV	Merkel cell carcinoma	MCV-miR-5p, 23	Decreased	34
KSHV/HHV8	Kaposi sarcoma/B-cell lymphoma	miR-143, 145, 126-3p and 13 miR-221, 222	Increased Decreased	33,35
HTLV-1	T-cell leukaemia	miR-93, 155 miR-126	Increased Decreased	36

Hull et al.[24] also discusses lncRNAs as potential biomarkers and as therapeutic anti-cancer targets. They propose that since lncRNAs expression profile is different as a cancer develops and progresses, it can be used for diagnosis, and to stratify patients vis-a-vis cancer stage and its treatment.

Re-Activation of the Lytic Cycle

Recently, oncolytic viruses have been tested as anti-cancer agents and such interventions are promising. In a similar beneficial way, theoretically, HOVs can be activated into their lytic cycle (thus breaking their latency) and kill the infected cancer cells. Such a reactivation would also mean that viral antigens are generated and this could promote an immune response. Such a conception has spurred research to investigate it.[37] However, it must be pointed out that such reactivation could also mean replication and further spread of the virus.

Re-activating 'Cold' Tumours

Some of the viral tumours are defined as 'cold' (or non-T-cell-inflamed) because there is little or no immune infiltrates in the tumour micro-environment. Viral factors contribute to this diminished immune response. Thus, reinstating an immune activity in such 'cold' tumours is a possible therapeutic approach. Indeed, credence to this principle has resulted in promising achievements in some viral cancers.

A typical example is the successful use of anti-PD1-PDL1 (anti-Programmed cell death protein 1 - Programmed death-ligand 1) immune checkpoint blockade in advanced MCPyV (Merkel cell polyomavirus) associated with MCC (Merkel-cell carcinoma).[38,39] Extrapolating further, if the viral factors that repress immunity are specifically targeted, better targeted immunotherapies can be developed.

ONGOING RESEARCH

Research on human oncogenic viruses is still ongoing. Specifically, it is resolving better the dynamics at the molecular level between the virus and the host during persistent infection and oncogenesis. This promises new therapeutic targets, sensitive biomarkers or prevention strategies. Also, this interest is being extended toother possible HOVs and other tumours that might be virally induced or where the viral infection is a triggering determinant or co-factor. For example, there is already convergent evidence that in cases of long-Covid-19 infections there is long-term suppression of p53 function, the latter being a tumour suppressor. Therefore, this might be itself a trigger to oncogenesis or worsen any already oncogenic processes.[40-42] It has already been shown that SARS-CoV-2 has hijacking strategies that control p53 similar to those used by the EBV and HBV.[43,44] If SARS-CoV-2 is confirmed to be oncogenic, this will definitely and hugely impact negatively on human health into the future.

RESEARCH ON HUMAN ONCOGENIC VIRUSES IS STILL ONGOING. SPECIFICALLY, IT IS RESOLVING BETTER THE DYNAMICS AT THE MOLECULAR LEVEL BETWEEN THE VIRUS AND THE HOST DURING PERSISTENT INFECTION AND ONCOGENESIS

Other viruses are also under scrutiny to see and confirm if they have the status of oncogenic viruses. Known oncogenic viruses are also being incriminated with other carcinomas. In 2022 Afzal et al. identified associations between EBV, HPV and Bovine Leukaemia Virus (BLV) and breast cancer,[45] and between BKPyV (BK Polyoma Virus) and renal cell carcinoma and urothelial carcinoma.[45]

CONCLUSION

Worldwide there is large interest in using -omics to undermine the HOV-host interactions in persistent infection and oncogenesis. Their use is being exploited in identifying viral molecular signatures, biomarkers and dysregulated cellular pathways. Biomarkers that are highly specific would enable clinicians in the theranostic management of cancer caused by these viruses. Specifically, they would aid in cancer theranostics like diagnosis (preferably early) and prognosis. Also, the dysregulated cellular pathways could offer insights of new targets for cancer treatment.

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